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Vinood B. Patel
Victor R. Preedy
Editors

Eating Disorders

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Eating Disorders

With 147 Figures and 125 Tables

Springer

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Preface

Eating disorders can profoundly affect the individual, family unit, and local community. Changes in the individual include disturbances in body perception, organ damage, and increased risk factors leading to ill-health in later years. The family unit is affected by the psychological burdens imposed by eating disorders, including increased anxiety and depression in siblings or spouses. There is also the cost burden to consider: for example, in some countries, without a free health service, family members or insurance underwriters are expected to pay for treatments. Local communities are saddled with poor productivity, reduced attainment, and discordant interactions with colleagues and friends. There is thus a fundamental requirement to adequately diagnose, treat, and manage those individuals with eating disorders. However, this is problematic as there are many types of eating disorders, which the American Psychiatric Association have recently categorized (DSM-5) into Anorexia Nervosa, Bulimia Nervosa, Binge Eating Disorder, Other Specified and Unspecified Feeding or Eating Disorders. The categorization of Binge Eating Disorders is new and the previous category of Eating Disorders Not Otherwise Specified has been removed from DSM-5. Nevertheless, in some circumstances, there is continual usage of old terminology, and some groups use their own categorizations.

There are numerous types of instruments and questionnaires which are used for categorizing or studying eating disorders. Some have been rigorously scrutinized and tested, whereas others are new and may eventually become "gold standard" instruments. Treatment regimens are also varied as there are complex relationships between physiological, nutritional, and psychological facets of eating disorders. Treatment protocols can include nutritional supplements or psychobehavioral modifications but will of course depend on the consequences of the eating disorder. In some cases, organs are directly affected, growth is impacted, and fetuses compromised in utero. Treatment regimens can address the multiple concerns, involving both psychiatry and dietetics.

It is thus apparent that there is a wide range of eating disorders, methods of diagnoses, and treatments. The impact of eating disorders are extensive. Thus, finding all the relevant information in a single coherent publication has hitherto

been problematic since there is a wide range of material. This, however, is comprehensively addressed in *Handbook of Eating Disorders* which embraces a holistic approach. It has six main parts:

1. **General Aspects, Overviews, and Setting the Scene**
2. **Anorexia Nervosa**
3. **Bulimia Nervosa**
4. **Binge Eating Disorder**
5. **Other Specified and Unspecified Feeding or Eating Disorders**
6. **Diagnosis, Delective Questionnaires, and Resources**

There are unique features in each chapter, with sub-sections on the following:

- **Applications to Other Eating Disorders**
- **Key Facts**
- **Mini-Dictionary of Terms**
- **Summary Points**

Applications to Other Eating Disorders is particularly important as it highlights the translational aspect of research into eating disorders; their causes, impact, and treatments. **Key Facts** give important information about individual components in each chapter. The **Mini-Dictionary of Terms** is suited for both the non-expert and also those working in other fields or areas. **Summary Points** encapsulate the entire chapter in brief sets of simple sentences.

Handbook of Eating Disorders is designed for dieticians, nutritionists, psychologists, healthcare workers, and research scientists. The audience is multi-intellectual: from undergraduates, masters, and doctoral students to research scientists, lecturers, professors, and heads of groups. Contributions are from leading national and international experts including those from world renowned institutions.

London, UK

Vinood B. Patel
Victor R. Preedy
The Editors

Contents

Volume 1

Part I General Aspects, Overviews, and Setting the Scene 1

1 **Enhanced Cognitive Behavior Therapy for Eating Disorders** 3
Riccardo Dalle Grave

2 **Eating Disorders During Pregnancy** 25
Maria G. Grammatikopoulou, Konstantinos Gkiouras, Tonia Vassilakou, and Dimitrios G. Goulis

3 **Eating Habits During Pregnancy** 37
Irene Cetin, Chiara Bianchi, and Arianna Laoreti

4 **Stress and Disordered Eating Patterns** 51
Fotini Tsofliou, Chloe Casey, and Christina Hughes

5 **Gene Variants Involved in the Etiopathogenesis of Eating Disorders: Neuropeptides, Neurotransmitters, Hormones, and Their Receptors** 75
Maria Rachele Ceccarini, Matteo Bertelli, Elisabetta Albi, Laura Dalla Ragione, and Tommaso Beccari

6 **Genes and Eating Disorders** 95
Beatriz Camarena and Sandra Hernández-Muñoz

7 **Eating Disorders in Athletes** 111
Melda Pelin Yargic and Faik Ozdengul

8 **Eating Disorders in Children and Adolescents with Attention Deficit Hyperactivity Disorder** 123
Zahra Saif and Haitham Jahrami

9 **Insomnia in Eating Disorders** 145
Kara A. Christensen, Ellen Klaver, and Nicole A. Short

10 Uric Acid Levels and Eating Disorders 167
Tanya Goltser Dubner, Ruth Giesser, Amit Shalev, Shikma Keller, Ronen Segman, and Esti Galili-Weisstub

11 The Virtually Delivered Body Project (vBP): A Viable Option for Large-Scale Prevention of Eating Disorders 181
Ata Ghaderi

12 Time-Related Changes in Eating Disorders 199
Tomoko Harada, Dai Miyawaki, and Tsuneo Yamauchi

13 The Connection Between Eating Disorders and Substance Use Disorders 223
Kimberly Claudat, Courtney C. Simpson, Brittany K. Bohrer, and Gina M. Bongiornio

14 Fluid Restriction in Eating Disorders 249
Elizabeth Hamlin

15 Features of Medical Consultations Before the Onset of Eating Disorders 269
Francisco Ruiz Guerrero, Leticia Castro Fuentes, Carla Cobo Gutierrez, Cristina Hernández Jimenez, and Andrés Gómez del Barrio

16 The Role of Parents and Other Caregivers in the Early Detection of Eating Disorders 283
Anna Ciao, Summer Pascual, and Gabbrielle Hodges

17 Alexithymia in Eating Disorders: A Narrative Review 313
Cecilia Serena Pace, Stefania Muzi, and Wanda Morganti

18 Eating Disorder and Quality of Life 353
Jelena Milic, Dunja Stankic, and Dona Stefanovic

19 The Role of Denial in Eating Disorder Development, Assessment, and Treatment 367
Lindsay M. Howard, Anna K. Olson, Brianna N. Pitz, and Kristin E. Heron

20 The Role of the Dietitian 385
Caitlin M. McMaster, Janet Franklin, Melissa Hart, Kylie Matthews-Rensch, Kirrilly Pursey, and Susan Hart

Part II Anorexia Nervosa **411**

21 A Research Approach to Self-Report and Objective Measurements of Physical Activity in Eating Disorders 413
Olivia Wons, Elizabeth Lampe, Laura Boyajian, Anna Gabrielle Patarinski, and Adrienne Juarascio

22 Body Mass Index and Body Fat in Anorexia Nervosa 439
Marwan El Ghoch

23 Modeling Anorexia Nervosa 451
Maria Scherma, Roberto Collu, Simona Dedoni, Walter Fratta, and Paola Fadda

24 Anorexia Nervosa and Impact After Three Decades 469
Elisabet Wentz

25 Linking Anorexia Nervosa with the Gut Microbiota 487
Radka Roubalova, Petra Prochazkova, and Hana Papezova

26 Gender Aspects of Anorexia Nervosa: the Male 513
Hiral Kotadia

27 The Biology of Anorexia Nervosa 537
Kamil Skowron, Magdalena Kurnik-Łucka, and Krzysztof Gil

28 The Hippocampus in Anorexia Nervosa 555
Enrico Collantoni, Valentina Meregalli, Elena Tenconi, Meneguzzo Paolo, and Angela Favaro

29 Endocrine Disturbances in Anorexia Nervosa 569
Magnus Sjögren

30 Anorexia Nervosa and Eye Movements 585
Andrea Phillipou

31 Anorexia Nervosa: Reproduction and Consequences for Mother and Child 603
Ängla Mantel and Angelica Lindén Hirschberg

32 Anorexia Nervosa in the Acute Hospitalization Setting 623
Matteo Martini, Marta Lepora, Paola Longo, Laura Amodeo, Enrica Marzola, and Giovanni Abbate-Daga

33 Anorexia Nervosa and Comorbidities 641
Antonia Parmeggiani and Jacopo Pruccoli

34 **The Electrocardiogram in Anorexia Nervosa** 655
Mikyla Janzen, Julia Raudzus, and Andrew Krahn

35 **Anorexia Nervosa and Concurrent Psychiatric Comorbidity** 673
Gennaro Catone

Volume 2

Part III Bulimia Nervosa 699

36 **The Growth Hormone-IGF-1 Axis in Anorexia Nervosa** 701
Anamil Khiyami and Pouneh K. Fazeli

37 **Relationship Between Bulimia Nervosa and Psychological Problems in Period of Adolescence** 723
Gordana Stankovska, Imran Memedi, and Nexhibe Nuhii

38 **Visuospatial Abilities in Eating Disorders** 747
Elena Tenconi, Valentina Meregalli, Paolo Meneguzzo, Enrico Collantoni, and Angela Favaro

39 **Androgens and Their Role in Bulimia Nervosa and Eating Disorder Not Otherwise Specified of Purging Type (EDNOS-P)** 767
Sabine Naessén

40 **Bulimic Symptomatology** 785
Ana Paula Hermont, Isabela Almeida Pordeus, and Sheyla Márcia Auad

41 **Emotion Regulation in Bulimia Nervosa and Purging Disorder** 805
Danielle E. MacDonald, Shauna Solomon-Krakus, Rachel Jewett, Rachel E. Liebman, and Kathryn Trottier

42 **Pharmacology Options for Bulimia Nervosa** 821
Aaron Keshen, Susan Gamberg, Sara Bartel, Victoria Taylor, Shannon Smith, Victoria Brown, and Anastasia Harris

43 **Linking Embodiment Disorder and Bulimia Nervosa** 843
Livio Tarchi, Eleonora Rossi, Marco Faldi, Emanuele Cassioli, Valdo Ricca, and Giovanni Castellini

44 **Treating Adolescent Bulimia Nervosa** 863
Sasha Gorrell, Leigh Brosof, Lisa Hail, and Daniel Le Grange

45 A Narrative Review on the Dual Pathway Model of Bulimic Pathology 887
Isabel Krug, Francis Puccio, Jade Potingale, and An Binh Dang

46 Bulimia Nervosa: Reproduction and Consequences for Mother and Child 923
Ängla Mantel and Angelica Lindén Hirschberg

Part IV Binge Eating Disorder **939**

47 Long-Term Outcome of Inpatients and Outpatients with Bulimia Nervosa 941
Norbert Quadflieg

48 Parental Care and Binge-Eating Disorder 957
Federico Amianto and Benedetto Vitiello

49 DeltaFosB and Preclinical Binge Eating 981
Richard Quansah Amissah and Igor Timofeev

50 Characterization of Binge Eating Days in Daily Life 1003
Julia Reichenberger, Ann-Kathrin Arend, and Jens Blechert

51 Cancer and Binge Eating 1025
Anna Dolgon-Krutolow and Tyler B. Mason

52 Fat Mass and Obesity-Related Gene (FTO) and Binge Eating Disorder in Adults and Adolescents 1043
Luzia Jaeger Hintze, Éric Doucet, and Gary S. Goldfield

53 Neuroimaging in Binge Eating Disorder 1063
Serkan Turan

54 Binge Eating 1083
Fabiana Salatino Fangueiro and Patrícia Colombo-Souza

55 Linking Sleep Deprivation and Binge Eating: Empirical Evidence and Underlying Mechanisms 1103
Silvia Cerolini

56 The Criterion B Binge-Eating Symptoms 1121
Brianne N. Richson, Kayla A. Bjorlie, Danielle A. N. Chapa, and Kelsie T. Forbush

Part V Other Specified and Unspecified Feeding or Eating Disorders **1141**

57 Cognitive-Behavioral Therapy and Purging Disorder 1143
Zaida Agüera, Isabel Baenas-Soto, and Fernando Fernández-Aranda

58 Purging Disorder 1157
Sarrah I. Ali, Sophie R. Abber, and Pamela K. Keel

59 Purging Disorder 1173
Rachel E. Liebman, Vincent A. Santiago, Sarah Mccomb, Danielle E. MacDonald, and Kathryn Trottier

60 Body Weights and Mass and Links with Nighttime Eating 1191
Cigdem Koroglu and Leslie J. Baier

61 Night Eating Syndrome and Network Analysis of Features 1207
Marshall T. Beauchamp

62 Avoidant/Restrictive Food Intake Disorder in Children 1235
Yaara Shimshoni and Eli R. Lebowitz

63 The Brain in Prader-Willi Syndrome 1261
Kenichi Yamada

64 Behavioral Phenotype of Patients with Prader-Willi Syndrome 1287
Maja Krefft and Maria Libura

65 Body Dysmorphic Disorder: Links with Eating Disorders and Gender-Related Factors 1305
Amy Malcolm

66 Orthorexic Eating and Addictions: Links with Substance Use, Behavioral Addictions, and Research Gaps 1327
Jana Strahler, Lillith Moser, and Hanna Wachten

67 Linking Orthorexia and Obsessive-Compulsive Symptoms 1353
Lut Tamam and Hamdi Yılmaz

68 Cardiac Vagal Imbalance and Emotional Eating 1381
Nerkis Fuentes, Gabriela Nazar, and Miguel Enrique Sánchez-Hechavarría

69 Biologic Aspects of Rumination Syndrome, Eosinophils, and Beyond 1399
Hunter J. Friesen, Jennifer V. Schurman, and Craig A. Friesen

70 Picky Eating in Normally Developing Children and Young Adults 1417
Ada H. Zohar

Part VI Diagnosis, Delective Questionnaires, and Resources **1433**

71 Assessing Orthorexia Nervosa by Questionnaires 1435
Melda Pelin Yargic and Murat Cenk Celen

72 The Eating Disorder Quality of Life (EDQoL) Scale 1451
Paolo Meneguzzo, Enrico Collantoni, Valentina Meregalli, Elena Tenconi, and Angela Favaro

73 Binge Eating Scoring Systems 1465
Natália Luiza Kops and Rogério Friedman

74 Conceptualizing and Evaluating the Healthy Orthorexia Dimension 1479
Wanderson Roberto da Silva, Angela Nogueira Neves, Giovanna Soler Donofre, Steven Bratman, Paula Costa Teixeira, and Juliana Alvares Duarte Bonini Campos

75 The Binge Eating Scale 1503
Sagar Karia, Shorouq Motwani, and Avinash Desousa

76 Health-Related Quality of Life Questionnaires 1517
Jelena Milic, Dunja Stankic, and Dona Stefanovic

77 Resources in Eating Disorders 1529
Rajkumar Rajendram, Daniel Gyamfi, Vinood B. Patel, and Victor R. Preedy

Index 1541

About the Editors

Vinood B. Patel, BSc, PhD, FRSC, is currently Reader in Clinical Biochemistry at the University of Westminster. He presently directs studies on metabolic pathways involved in liver disease, particularly related to mitochondrial energy regulation and cell death. Research is being undertaken to study the role of nutrients, antioxidants, phytochemicals, iron, alcohol, and fatty acids in the pathophysiology of liver disease. Other areas of interest are identifying new biomarkers that can be used for the diagnosis and prognosis of liver disease and understanding mitochondrial oxidative stress in Alzheimer's disease and gastrointestinal dysfunction in autism. Dr. Patel graduated from the University of Portsmouth with a degree in Pharmacology and completed his PhD in protein metabolism from King's College London in 1997. His postdoctoral work was carried out at Wake Forest University Baptist Medical School studying structural-functional alterations to mitochondrial ribosomes, where he developed novel techniques to characterize their biophysical properties. In 2014, he was elected as a Fellow to The Royal Society of Chemistry. Dr. Patel is a nationally and internationally recognized researcher and was involved in several NIH-funded biomedical grants related to disease. Dr. Patel has edited biomedical books in the area of diet, nutrition, and health prevention. He has published over 150 articles.

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Part I

General Aspects, Overviews, and Setting the Scene

Enhanced Cognitive Behavior Therapy for Eating Disorders

1

Riccardo Dalle Grave

Contents

Introduction 4
The Origins of CBT-E 5
Transdiagnostic Theory 8
Overview of CBT-E 9
Goals of CBT-E 12
General Treatment Strategy 13
Forms of CBT-E 14
Versions of CBT-E 15
The Status of CBT-E 18
Implications for Clinical Services 19
Remaining Challenges 19
Applications in Other Eating Disorders 20
Mini-Dictionary of Terms 20
Key Facts of Enhanced Cognitive Behavior Therapy for Eating Disorders 21
Summary Points 21
References 22

Abstract

Enhanced Cognitive Behavior Therapy (CBT-E) is a psychological treatment specifically designed for eating disorders. Based upon the original cognitive behavior therapy for bulimia nervosa (CBT-BN), it has been termed "enhanced" because it uses various innovative strategies and procedures to maximize its effectiveness. It addresses flexibly and individually the transdiagnostic processes maintaining the eating-disorder psychopathology. CBT-E was initially designed for adult outpatients with eating disorders, but has subsequently been adapted for adolescents, intensive settings of care (i.e., intensive outpatients and inpatients), and complex cases featuring medical and psychiatric comorbidities. CBT-E has been trialed in both research and real-world clinical settings, and is recommended

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as the most effective treatment for all clinical presentations of eating disorders in adults, and the most valid alternative to Family-Based Treatment for the management of eating disorders in adolescents. Future challenges are to further establish the validity of CBT-E, increase its effectiveness, improve its promotion, and maximize its availability.

Keywords

Cognitive behavior therapy · Treatment · Eating disorders · Anorexia nervosa · Bulimia nervosa · Binge-eating disorder

Abbreviations

AN	Anorexia nervosa
BED	Binge-eating disorder
BMI	Body mass index
BN	Bulimia nervosa
CBT-BN	Cognitive Behavior Therapy for Bulimia Nervosa
CBT-E	Enhanced Cognitive Behavior Therapy
FBT	Family-Based Treatment
IPT	Interpersonal therapy
MANTRA	Maudsley Model Anorexia Nervosa Treatment for Adults (MANTRA)
SSCM	Specialist Supportive Clinical Management

Introduction

Enhanced Cognitive Behavior Therapy (CBT-E) is a form of cognitive behavior therapy (CBT) specifically developed for eating disorders (Fairburn et al. 2003). Based on the original CBT for Bulimia Nervosa (CBT-BN) it is a transdiagnostic treatment designed to address in a flexible and individualized way the key cognitive and behavioral processes maintaining eating-disorder psychopathology, rather than targeting a single diagnostic classification. In other words, it is equally suitable for treating anorexia nervosa, bulimia nervosa, binge-eating disorder, or "other eating disorders" (a broad term used to encompass the eating disorders that do not fit neatly into the above).

CBT-E is termed *"enhanced"* because it introduces a variety of innovative, evidence-based strategies and procedures specifically developed to enhance the effectiveness of the original CBT-BN. Though designed initially for adult outpatients with eating disorders (Fairburn et al. 2003; Fairburn 2008), it has now been adapted to be suitable for adolescents (Dalle Grave and Calugi 2020; Dalle Grave 2019; Dalle Grave and Cooper 2016), day-hospital patients and inpatients (Dalle Grave et al. 2008; Dalle Grave 2012, 2013), and complex cases involving medical and psychiatric comorbidities (Dalle Grave et al. 2021a). CBT-E has been assessed in numerous clinical trials, and is recommended as both the most effective treatment for

all clinical eating-disorder presentations in adults (National Guideline Alliance 2017), and the most valid alternative to Family-Based Treatment (FBT) for the management of eating disorders in adolescents (National Guideline Alliance 2017).

This chapter begins by describing the origin of CBT-E. It goes on to provide an overview of transdiagnostic cognitive behavior theory and treatment and its current status, and then concludes by discussing the main challenges that still remain to be addressed.

The Origins of CBT-E

The rationale behind CBT-E is closely linked with early reports describing recurrent objective binge-eating episodes and self-induced vomiting in normal-weight persons. This abnormal eating behavior pattern, initially called "bulimarexia" (Boskind-Lodahl and White 1978), was proposed as a specific eating disorder diagnosis by Gerald Russell in his landmark 1979 paper *Bulimia nervosa: An ominous variant of anorexia nervosa* (Russell 1979). In this, Russell described 30 normal-weight patients who, in addition to a fear of becoming fat, displayed recurrent binging and purging behavior. He gave the name "bulimia nervosa" to the disorder, and, intriguingly, claimed that the disorder was "intractable."

In the same period, Christopher Fairburn, a young psychiatrist working in Oxford, started to see cases with similar features to those described by Russell, and observed that these patients had three specific behaviors and concerns, specifically:

1. Unusual form of dieting, characterized by sustained attempts to follow extreme, rigid dietary rules
2. Recurrent episodes of loss of control over eating (binges) followed by self-induced vomiting or laxative misuse (purging); the binges tended to be triggered by dietary rule-breaking
3. Extreme concerns about shape and weight (which he termed "overvaluation of shape, weight and their control")

He noted that these three common features appeared to interact, serving to reinforce, or "maintain," the eating disorder, which led him to propose a theory focused on the psychology "maintaining," rather than causing, bulimia nervosa (illustrated in Fig. 1). He then developed a psychological treatment designed to address each of the maintenance mechanisms described in the theory. The outpatient treatment, called "CBT-BN," consisted of 20 sessions over 20 weeks, focused on addressing binge-eating episodes, dietary restraint and concerns about shape and weight, and achieving a full and lasting response (Fairburn 1981, 1985).

Multiple studies evaluated the efficacy of CBT-BN, and by 2004 over 30 randomized control trials had been conducted. These demonstrated that CBT-BN is more effective than all the treatments with which it had been compared, including a wide range of psychological therapies (e.g., supportive psychotherapy, focal

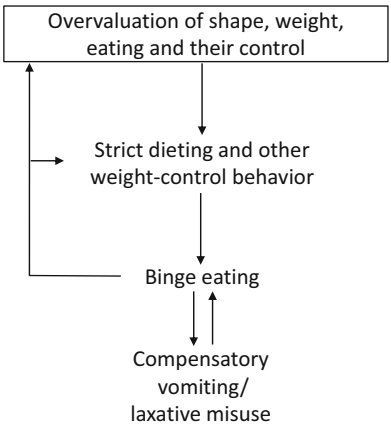


Fig. 1 The cognitive-behavioral theory of bulimia nervosa. (From Fairburn et al. (2003). Reprinted with the permission of Elsevier)

psychotherapy, supportive-expressive psychotherapy, hypnobehavioral treatment, stress management, nutritional counseling, and behavioral versions of CBT-BN), as well as various forms of exposure with response prevention, and pharmacological treatments (Wilson and Fairburn 2002). The only treatment with comparable effects to CBT-BN was interpersonal psychotherapy (IPT), but that was much slower to act (Agras et al. 2000; Fairburn et al. 1993). Summarizing the findings, 40–50% of adult patients with bulimia nervosa treated with CBT-BN displayed a complete response, which appeared to be well maintained over time. These results led the National Institute for Health and Clinical Excellence to recommend CBT-BN for adults with bulimia nervosa – a grade A recommendation (i.e., strong empirical support from well-conducted randomized trials) (National Collaborating Centre for Mental Health 2004).

Despite this, the research into the efficacy of CBT-BN made clear that the treatment is not effective enough as, at best, only half of the patients achieve full and lasting remission. Analysis of the reasons for this yielded two main clinical observations (Fairburn et al. 2003):

1. *Many of the clinical features present in bulimia nervosa are also present in anorexia nervosa and the other eating disorders* (i.e., eating disorders share a specific psychopathology – see Table 1), *and many patients' eating disorder diagnosis shifts from one to another* (e.g., from anorexia nervosa to bulimia nervosa or vice versa, the so-called "diagnostic migration" – see Fig. 2). This observation led to the idea that many of the processes that maintain bulimia nervosa, and are targeted by CBT-BN, also maintain the other eating disorders.
2. *There were consistent reasons for a lack of response to CBT-BN.* A case-by-case analysis of non-response led to the conclusion that the efficacy of CBT-BN might be extended to more patients in two main ways:

Table 1 Eating disorders share the same features

	AN	BN	OEDs
Overvaluation of shape, weight, and eating control	+++	+++	++
Strict dieting	+++	++	++
Binge eating	+	+++	++
Self-induced vomiting	+	++	+
Laxative misuse	+	++	+
Diuretic misuse	+	+	+
Excessive exercising	++	+	+
Food checking	+++	+	+
Body checking	+++	+++	++
Body avoidance	+	++	++
Feeling fat	+++	+++	+++
Low weight and starvation syndrome	+++	+	+

AN anorexia nervosa, *BN* bulimia nervosa, *OEDs* other eating disorders

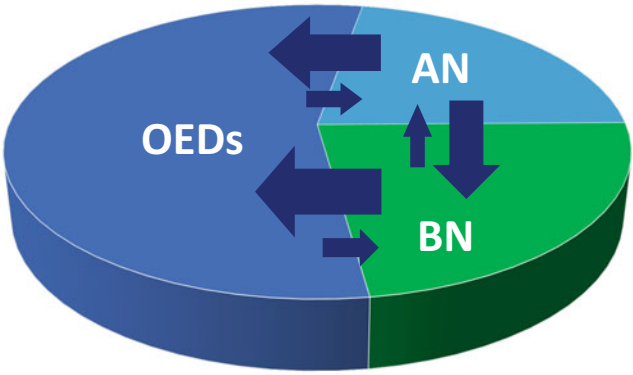


Fig. 2 Diagnostic migration of the eating disorder diagnosis. *AN* anorexia nervosa, *BN* bulimia nervosa, *OEDs* other eating disorders

a) By developing more effective strategies and procedures to address not only extreme concerns about shape and weight, but also ambivalence to change.
b) By addressing the co-existing psychopathology that appeared to maintain some patients' eating disorders (identified as clinical perfectionism, core low self-esteem, marked interpersonal difficulties, and/or mood intolerance).

Accordingly, a "transdiagnostic" theory of the maintenance of eating disorders was proposed, and a transdiagnostic treatment based on this theory, called "CBT-E," was developed (Fairburn et al. 2003).

Transdiagnostic Theory

The transdiagnostic theory accounts for the range of processes that maintain any eating disorder diagnosis, irrespective of its presentation. According to this theory, a distinctive self-evaluation scheme, termed the *overvaluation of shape, weight, eating and their control* is the "core," or central feature maintaining eating disorders. People who display this trait judge their self-worth mainly, or even exclusively, on their shape, weight, and ability to control them. This psychopathological preoccupation with eating, weight, shape, and control seems to drive the other clinical features characteristic of eating disorders, including extreme weight-control behaviors (e.g., *dietary restraint and restriction, purging* and *excessive exercising*), *feeling fat,* and various forms of *body checking and avoidance*. From the transdiagnostic perspective, these features of eating disorders are expressions of an individual's belief that controlling their weight, shape, and eating is vital to their self-evaluation.

The one behavior that is not a direct expression of this core eating disorder feature is *binge eating*. A large subgroup of people with eating disorders experience binge-eating episodes, which seem to stem indirectly from the overvaluation of shape, weight, and eating through the following mechanisms:

1. *Severe undereating*. The overvaluation of shape, weight, eating and their control can lead an individual to undereat. Doing so produces several neuroendocrine signals that control food intake, messaging hunger over satiety.
2. *Extreme and rigid dietary rules.* People with eating disorders tend to react in a negative and extreme (often all-or-nothing) way when these extreme and rigid dietary rules are, almost inevitably, broken, and even small transgressions tend to be interpreted as evidence of a personal failing and lack of self-control. This often results in a temporary abandonment of the effort to restrict the diet, triggering a binge-eating episode. In turn, this episode intensifies concerns and beliefs regarding their lack of control over shape, weight, and eating, and encourages further dietary restriction, thereby increasing the risk of subsequent binge-eating episodes.
3. *Self-induced vomiting or other compensatory behaviors*. The false belief that purging behaviors effectively prevent calorie absorption removes a major deterrent (i.e., the fear of gaining weight) to relaxing the dietary rules and binge eating.
4. *Events and associated mood changes.* These seem to maintain binge-eating episodes through three main mechanisms:
    a) It is more difficult to maintain a high level of dietary restriction when life difficulties and associated emotional changes inevitably occur, and such events facilitate the breaking of extreme and rigid dietary rules.
    b) Binge eating distracts from problems and temporarily improves mood. It may therefore be adopted as a dysfunctional means of coping with life's difficulties and uncomfortable emotions.
    c) Binge eating may be used to gratify and reward oneself (a common process reported by people with binge-eating episodes and obesity).

In persons with the anorexia nervosa presentation, binge-eating episodes are usually subjective or absent, while undereating and being underweight predominate. These lead to the development of several *starvation symptoms*, such as hunger, dizziness, weakness, feeling cold, early sense of fullness, irritability, mood swings, social withdrawal, reduced sexual desire, and preoccupation with food (Keys et al. 1950). These, like undereating, binge-eating and the other eating-disorder features, perpetuate the preoccupation with and overvaluation of shape, weight, and eating control, ensuring that the *eating-disorder mindset* becomes locked in place. This occurs through several mechanisms (see Table 2).

This vicious and debilitating cycle can be conceptualized and illustrated to patients via a transdiagnostic *formulation*, featuring the core processes involved in the maintenance of eating disorders according to transdiagnostic cognitive-behavioral theory (Fig. 3). This can be adapted to reflect any diagnostic category of eating disorders, or rather individual manifestations of the eating-disorder psychopathology, with minimal changes. For example, the formulation of a person with bulimia nervosa does not contain the box "low weight and starvation symptoms," but may include all the other characteristics described in the array of possible eating disorder symptoms. In contrast, the formulation of a patient with anorexia nervosa restricting type will always include the box "low weight and starvation symptoms," but not the "binge-eating" and "self-induced vomiting and "misuse of laxatives" boxes. A patient with anorexia nervosa of the binge-eating/purging type will display the greatest number of maintenance processes, while those with binge-eating disorder will have the smallest number.

As mentioned briefly above, in addition to the core eating-disorder maintenance processes, transdiagnostic cognitive behavioral theory proposes that one or more of the following additional mechanisms may be operating in some patients (Fig. 4) (Fairburn et al. 2003): (i) clinical perfectionism, (ii) core low self-esteem, (iii) marked interpersonal difficulties, and (iv) mood intolerance. If present and marked, these "external" maintenance mechanisms interact with the core processes, perpetuating the eating disorder and hindering its treatment (see Table 3).

Overview of CBT-E

CBT-E is a specialized psychological treatment for eating disorders based on the transdiagnostic cognitive behavioral theory described above. It was initially devised by Fairburn and colleagues at the Centre for Research on Eating Disorders at Oxford (CREDO) to treat eating disorders in adults with a body mass index (BMI) of between 15.0 and 39.9 (Fairburn et al. 2003; Fairburn 2008). It was then adapted by Dalle Grave and colleagues at the Villa Garda Hospital Department of Eating and Weight Disorders, Italy, to be suitable for both adolescents of at least 12 years of age (Dalle Grave and Calugi 2020; Dalle Grave 2019) and more intensive settings of care (Dalle Grave 2012, 2013), such as day-hospital and residential units, where patients with severe eating disorders and or BMI <15.0 are generally treated. The

Table 2 Principal maintaining mechanisms of eating disorders

Dietary restraint and dietary restriction
• Increase the preoccupations with eating
• Cause anxiety every time one eats
• Restrict the way one eats
• Contribute to binge-eating episodes
• Are the major cause of becoming and remaining underweight
• Can be used to manage events and associated mood changes in a dysfunctional way
• Impair interpersonal relationships
Objective and subjective binge-eating episodes
• Increase concerns about shape and weight
• Intensify dieting to compensate for the calories consumed during the binges
• Favor the use of compensatory behaviors (e.g., self-induced vomiting, laxative, and/or diuretic misuse)
• Can be used to manage events and associated mood changes in a dysfunctional way
Excessive exercising
• Increases the preoccupations about weight and body shape
• Promotes binge eating (when used as a compensatory behavior)
• Is a cause of becoming and remaining underweight
• Can be used to manage events and associated mood changes in a dysfunctional way
Purging (self-induced vomiting, laxative, and diuretic misuse)
• Relax the control of diet as the individuals think incorrectly that they are able to eliminate all the ingested calorie through purging
• The prolonged use of laxatives can lead to chronic constipation, which can in turn increase general concern with eating and stomach shape and perpetuates the perceived need to use more of these drugs
• Some people think that if they do not evacuate regularly, they will gain weight
Underweight
• Some starvation symptoms are interpreted by individuals with an eating disorder as a threat to their control over eating (e.g., hunger potentially prompting them to eat more than they had planned) or as their failure to control their food intake (e.g., the early sense of fullness being seen as a sign that they have overeaten)
• Other starvation symptoms, such as social withdrawal, induce individuals to isolate from external "normal" experiences that could serve to reduce their overvaluation of shape, weight, and eating control by introducing/reinforcing other self-evaluation domains
• Some starvation symptoms (e.g., hunger, dizziness, weakness, and feeling cold) are interpreted in a positive light, seeing them as signs of their success in controlling eating and weight
Body checking
• Frequent weighing leads to misinterpreting the minimal variation of body weight – generally due to change of body hydration – as "having gained weight" and encourages the intensification of dieting or the adoption of other extreme weight control behaviors
• Repetitively scrutinizing disliked parts of the body amplifies the perceived flaws and intensifies the body dissatisfaction, which encourages the intensification of dietary restriction
• The superficial and rapid observation of body parts of a filtered subgroup of thin and attractive people or with distinct physical features confirm that one's body shape is wrong, and maintain body dissatisfaction

(continued)

Table 2 (continued)

Body avoidance
• Allows concerns and fears about body weight and shape to persist in the absence of an objective reflection of what one looks like (false beliefs regarding body weight and shape remain unchallenged)
• Denies the possibility of receiving positive comments from others and therefore maintains negative beliefs about their bodies
• Restricts interests, does not allow an intimate life, and leads the persons to isolate themselves focusing more and more on the control of their body shape and weight
• Avoiding weighing maintains the fear of weight gain and facilitates weight gain or loss, as it prevents the use of measures to address the changes in weight
Feeling fat
• It tends to be equated with "being fat" by both underweight and non-underweight individuals with an eating disorder

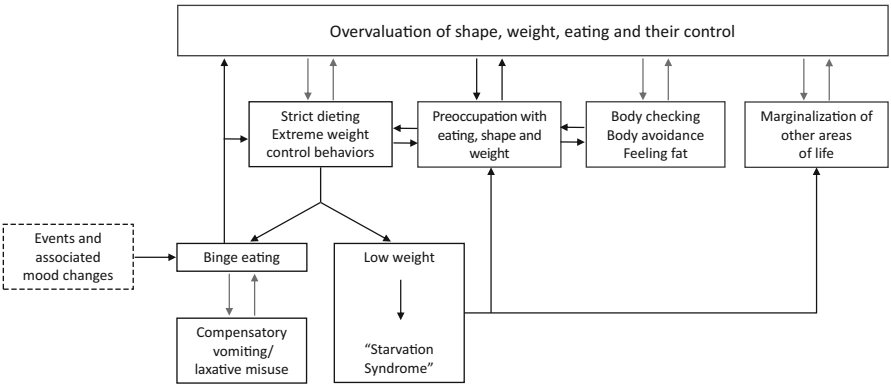


Fig. 3 The core processes involved in the maintenance of eating disorders, according to transdiagnostic cognitive-behavioral theory

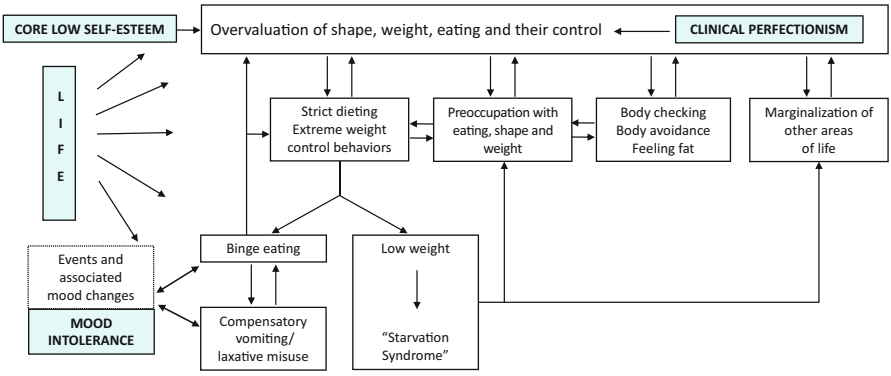


Fig. 4 Composite transdiagnostic formulation of eating disorders featuring additional maintenance processes. "Life" is shorthand for interpersonal life

Table 3 "External" mechanisms operating in a subgroup of persons with eating disorders

Clinical perfectionism This refers to overvaluation of achievement and achieving demanding personal standards, despite the adverse consequences. It maintains the eating-disorder psychopathology through two main mechanisms:
1. The individual's self-evaluation system focuses on the commitment to trying to achieve "perfect" control of shape, weight, and eating, as well as in pursuing demanding standards in other domains of life (e.g., work or sport performance)
2. It intensifies some aspects of the psychopathology of eating disorders (e.g., dieting and/or excessive exercising), making this more difficult to treat
Core low self-esteem This is characterized by a pervasive negative valuation of self-worth which is not affected by either events or changes in the state of the eating disorder. It maintains the eating-disorder psychopathology through two main processes:
1. It creates a sense of helplessness and a lack of confidence in the ability to change, negatively influencing treatment adherence
2. It encourages the individual to pursue success in some areas that are judged important for improving their self-esteem (e.g., control of shape, weight, and eating) with determination, thereby making it even more difficult to enact change in these areas
Marked interpersonal difficulties These maintain eating-disorder psychopathology through various mechanisms. Examples include:
• Family tensions may intensify dietary restriction, especially in younger patients. A process that reflects the intensification of their need to have a sense of control is shifted to control over eating
• Some interpersonal environments (e.g., school and family) intensify concerns about control over shape, weight, and eating
• Adverse interpersonal events and associated emotional changes can affect eating control and promote binge-eating episodes
• Persistent interpersonal difficulties may undermine self-esteem and prompt patients to struggle even harder to achieve certain "positive" goals such as success in controlling shape, weight, and eating
Mood intolerance This is defined as an inability to tolerate intense moods, or excessive sensitivity to mood states, which are managed using "dysfunctional mood-modulation behaviors," such as excessive alcohol intake, substance misuse, or self-harming behaviors (e.g., cutting or burning the skin). It maintains the eating-disorder psychopathology through the following mechanism:
• Binge-eating, self-induced vomiting, and excessive exercising are used as means to modulate mood

management of patients with eating-disorder psychopathology and a BMI equal to or greater than 40 has also been described (Dalle Grave et al. 2018).

Goals of CBT-E

CBT-E has four general goals:

1. To engage the patient in treatment by motivating them to recover and involving them actively in the process of change
2. To help them overcome their eating-disorder features (e.g., dietary restraint and restriction, low weight, self-induced vomiting, laxative misuse, excessive exercising, and preoccupation with shape, weight, and eating)
3. To correct the mechanisms maintaining the eating-disorder features
4. To ensure lasting change and prevent relapse

General Treatment Strategy

CBT-E is a time-limited, personalized psychological treatment designed to treat an individual's psychopathology. It does so by addressing the behavioral and cognitive processes maintaining their eating-disorder features through a flexible and personalized set of strategies and procedures. It has been developed as a comprehensive, standalone treatment, and is therefore not to be combined with other forms of therapy. It is equally well suited to males and females, and is designed to involve the patient actively in all phases of treatment, from the decision to start to the choice of which problems to address and how. This fosters a sense of personal control, as does the progressive education a patient receives to help them make informed decisions.

At the very beginning, patients are taught about the two main ways of understanding eating disorders, namely the so-called "disease" and "psychological" models, and the treatment approaches based upon them. Specifically:

1. The *disease model* postulates that the psychopathological features displayed by the patient are the result of a specific disease – in this case anorexia nervosa or bulimia nervosa, etc. – and are therefore outside their control. As such, they are told not to trust their thoughts about shape, weight, and eating, as these are symptoms of their disease, and asked to adopt a passive role in the treatment of their illness. In other words, the disease model is the grounds for a traditional prescriptive approach to treatment, in which the patient must simply follow the instructions of their doctors, psychologists, and dietitians to recover.
2. The *psychological model* adopted by CBT-E, on the other hand, is based on a psychological explanation of the patient's eating disorder; specifically, the affected person has difficulties seeing dieting and low weight as a problem because their self-evaluation scheme has become skewed, and is predominantly based on shape, weight, eating and their control. This explains why being able to diet and achieving a low weight is associated with a sense of triumph and realization, despite its negative consequences. However, according to this stance, patients can be helped to understand the psychological mechanisms maintaining their eating disorder and that their self-evaluation system is dysfunctional. They can actively decide to find other, more functional solutions for reaching a stable and balanced self-evaluation scheme, and therefore recover from their illness.

The psychological model explains why CBT-E never uses "prescriptive" or "coercive" procedures. Indeed, asking a patient to do things that they are unwilling to is only likely to increase their resistance to change. For example, in underweight patients one of the first major goals is not weight regain itself, but instead to decide whether or not to actively address weight regain by helping them understand how their eating problem operates and is maintained. If they do not conclude that they have a problem to address, the treatment cannot start or must be postponed for a time, but this is seldom the outcome. This "informed decision-making" approach is also used to address other egosyntonic features of eating-disorder psychopathology, like dietary restraint and/or excessive exercising. To this end, a key CBT-E strategy is to collaboratively create with the patient a personalized formulation (or set of hypotheses) of the main mechanisms maintaining their individual eating-disorder psychopathology, which they will actively decide to target one by one during treatment.

Once the patient is engaged in the process of change, their eating-disorder psychopathology is addressed via a flexible set of cognitive, behavioral, and interpersonal treatment strategies and procedures, integrated with ongoing education. Patients are encouraged to observe how the processes illustrated in their formulation operate in real life, and to monitor their eating, and the events, thoughts, and feelings that have influenced their eating, in real time. They are asked, if they agree, to make gradual behavioral changes, and analyze the effects and implications of each change on their way of thinking. By empowering the patient to disrupt the main eating-disorder maintenance mechanisms, this approach usually produces a gradual reduction in their preoccupation with shape, weight, eating and their control. In the later stages of treatment, when patients report experiencing periods free from such concerns, CBT-E focuses on helping them to recognize the early warning signs of eating-disorder mindset reactivation, and to de-center from it quickly, with a few to averting relapse.

If the patient is an adolescent, their parents are actively involved in creating an optimal home environment for change and, with the young person's consent, providing support as they address the main mechanisms maintaining their eating problem. A similar strategy is used with adult patients if both the therapist and the patient agree that involving their significant other(s) might aid their recovery.

Forms of CBT-E

CBT-E can be administered in two forms:

1. *Focused form*, which only targets their eating-disorder psychopathology
2. *Broad form*, which focuses on both their eating-disorder psychopathology and one or more of their external maintenance mechanisms (i.e., clinical perfectionism, core low self-esteem, mood intolerance, or marked interpersonal difficulties), if deemed necessary

The focused form is indicated for most patients, whereas the broad module(s) are introduced if the external psychopathology is pronounced, appears to reinforce the eating disorder, and interferes with the treatment. The decision to use the broad form is taken in a review session held after 4 weeks in not-underweight patients, or one of the review sessions later on in underweight patients.

Versions of CBT-E

Outpatient CBT-E for Adults

The outpatient version of CBT-E lasts 20 weeks in non-underweight patients and 40 weeks in underweight patients. It is recommended for most adult patients with an eating disorder (Fairburn 2008), and can in some cases be shortened, for example, in patients with binge-eating disorder whose binge eating rapidly ceases and who have little other psychopathology to address. More often, however, there is a case for extending treatment. Examples include when the treatment has been disrupted (e.g., by the onset of clinical depression or an interpersonal crisis), or when a patient is benefitting from the treatment but is still underweight. Under these circumstances, the treatment should be continued for some additional months, with a detailed review of progress every 4 weeks to ensure continuation is justified.

Outpatient CBT-E for Adolescents

CBT-E has been adapted for adolescents based on the consideration of two factors that distinguish them from adults, namely physical health concerns and the need for parental involvement. Indeed, some medical complications associated with eating disorders, e.g., osteopenia and osteoporosis, may be severe in this age range and have lifelong repercussions. Therefore, regular medical assessment and a lower threshold for hospital admission are integral parts of CBT-E for adolescents. The treatment lasts 20 weeks in non-underweight patients, but in underweight patients, the "standard" 40 weeks may be shortened to about 30 weeks, as the evidence shows that adolescents tend to return to normal body weight faster than adults (Calugi et al. 2015).

In the great majority of cases, parental involvement is beneficial to treatment. Parents are asked to participate alone in an interview lasting approximately 90 min during the first week, and subsequently the patient and parents are seen together for 15–20 min immediately after the fourth to sixth sessions (in patients who are not underweight) or the eighth to tenth sessions (in patients who are underweight). Table 4 describes the core elements of the adolescents' version of CBT-E for underweight patients.

Intensive Outpatient CBT-E

This version of treatment is designed for patients who may need more professional input than outpatient CBT-E can provide, but whose conditions are not sufficiently severe to warrant hospitalization. This adaptation of CBT-E incorporates all of the

Table 4 The core elements of the focused CBT-E version for not-underweight adolescent patients

Step one – starting well and deciding to change The aims are to engage the patient in treatment and change, including addressing weight regain The appointments are twice weekly for 4 weeks and involve the following:
• Jointly creating a formulation of the processes maintaining the eating disorder
• Establishing real-time self-monitoring of eating and other relevant thoughts and behaviors
• Educating about: body weight regulation and fluctuations, the adverse effects of dieting, and, if applicable, the ineffectiveness and physical complications of self-induced vomiting and laxative misuse as a means of weight control
• Introducing and establishing weekly in-session weighing, and becoming proficient in interpreting and coping with weight fluctuations
• Introducing and adhering to a pattern of regular eating, with planned meals and snacks
• Thinking about addressing weight regain
• Involving parents to facilitate treatment
Step two – addressing the change The aim is to address weight regain and the key mechanisms that are maintaining the patient's eating disorder The appointments are twice a week until the rate of weight regain stabilizes, at which time they are held once a week. This step involves the following CBT-E modules:
• Underweight and undereating: creating a daily positive energy balance of about 500 kcal to achieve a mean weekly weight regain of about 0.5 kg
• Overvaluation of shape and weight: providing education on overvaluation and its consequences; nurturing previously marginalized domains of self-evaluation; reducing unhelpful body checking and avoidance; re-labeling unhelpful thoughts or feelings such as "feeling fat"; exploring the origins of the overvaluation and learning to identify and control the eating-disorder mindset
• Dietary restraint: changing inflexible dietary rules into flexible guidelines, and introducing previously avoided foods
• Events and mood-related changes in eating: developing proactive problem-solving skills to tackle such triggering events, and developing skills to accept and modulate intense moods
• Setbacks and mindsets: providing education about setbacks and mindsets; identifying eating-disorder mindset reactivation triggers; spotting setbacks early on; displacing the mindset; exploring the origins of the overvaluation
Review sessions These are held 1 week after Step One and then every 4 weeks, for the purposes of:
• Collaboratively reviewing treatment compliance and progress
• Identifying barriers to change, both general (e.g., school pressures) and features of the eating disorder itself (e.g., difficulties in weight regain, presence of dietary restraint)
• Adjusting the initial formulation in light of progress and/or emerging issues
• Deciding to continue with the focused form of CBT-E rather than the broad form[a]
Step 3 – ending well The aims are to ensure that progress made during treatment is maintained, and that the risk of relapse is minimized. There are three appointments, 2 weeks apart, covering the following:
• Addressing concerns about ending treatment
• Devising a short-term plan for continuing to implement changes made during treatment (e.g., reducing body checking, introducing further avoided foods, eating more flexibly, maintaining involvement in new activities) until the post-treatment review session
• Phasing out treatment procedures, in particular self-monitoring and in-session weighing
• Education about realistic expectations and identifying and addressing setbacks

(continued)

Table 4 (continued)

• Devising a long-term plan for maintaining body weight, and averting and coping with setbacks
Post-treatment review session
• Reviewing the long-term maintenance plan around 4, 12, and 20 weeks after treatment has finished

[a]The broad form of CBT-E includes four additional modules (i.e., clinical perfectionism, low self-esteem, interpersonal difficulties, and mood intolerance), one of which may be added to the focused modules in Step Two. This form of treatment is indicated if clinical perfectionism, low self-esteem, interpersonal difficulties, or mood intolerance are marked, and appear to be maintaining the disorder and obstructing change

strategies and procedures of outpatient CBT-E, but includes several additional features developed specifically for this new approach (Dalle Grave 2012, 2013).

Intensive outpatient CBT-E can be flexibly adapted to both the clinical needs of the patient and the logistical characteristics of the clinical service that delivers it. However, it should include the following procedures on weekdays: (i) supervised daily meals; (ii) individual CBT-E sessions; (iii) sessions with a CBT-E-trained dietitian to plan and review weekend meals; and (iv) regular reviews with a CBT-E-trained physician. Intensive outpatient treatment lasts for a maximum of 12 weeks, but may be shorter if patients successfully progress in the areas in which they were struggling in outpatient CBT-E (e.g., lack of progress in weight regain, reducing binge eating, and/or eating regular meals). Toward the end of intensive treatment, patients who have responded well are gradually encouraged to eat meals outside the unit, thereby allowing the treatment to evolve into conventional outpatient CBT-E.

Inpatient CBT-E

Inpatient CBT-E is indicated as a first-line option for patients who require close medical supervision, or for those who are not responding well to the less intensive versions. The treatment features all the main strategies and procedures of outpatient CBT-E, which are delivered in group format as well as individual sessions, but has three main features that set it apart (Dalle Grave 2012, 2013). First, the treatment is delivered by a non-eclectic multidisciplinary team, rather than a sole therapist. This will comprise physicians, psychologists, dietitians, and nurses who have all been fully trained in CBT-E. Second, assistance with eating is provided in the early weeks of treatment. This is to help patients overcome their difficulties in real time. Third, adolescent patients are given the opportunity to continue their studies during hospitalization with the aid of on-site educators. Inpatient CBT-E also includes the following additional elements, designed to reduce the high rate of relapse typically seen after discharge from hospital (Dalle Grave et al. 2008):

- The inpatient unit is open, with patients being free to go outside. This is so they are not sheltered from the environmental stimuli that tend to trigger their eating-disorder mindset and behaviors, but can rely on professional support.

- Before the scheduled discharge, the CBT-E team will work with the patient to identify likely environmental setback triggers. These will then be addressed during the individual CBT-E sessions in the final weeks of inpatient treatment.
- Toward the end of treatment, parents are helped to create a positive, stress-free home environment in readiness for the patient's return.

Post-inpatient Outpatient CBT-E

In order to capitalize on and reinforce the progress made during inpatient treatment, this is generally followed with 20 sessions of outpatient treatment over 20 weeks. Post-inpatient outpatient sessions are held twice weekly in the first month after discharge, and thereafter less frequently. The main objectives of these sessions are to help patients to consolidate the changes they have achieved during their residential treatment, to provide them with strategies for dealing with the difficulties that occur once they return home, and to identify and address any residual maintenance and control mechanisms, with a view to preventing relapse.

The Status of CBT-E

CBT-E has been tested in England, Australia, Denmark, Germany, Italy, and the USA on patients from all diagnostic categories of eating disorders. Focusing on the studies in which CBT-E was delivered well, the evidence suggests that about 80% of patients who are not significantly underweight complete treatment. Among these, about two-thirds achieve full remission, which appears stable over time. Many of the remaining patients improve, but do not achieve remission. The remission rate is similar with underweight patients, but treatment is only completed by about 65% of such patients.

In general, the research findings can be summarized as follows:

- CBT-E is suitable for treating all diagnostic categories of eating disorders in adult (Fairburn et al. 2009, 2013, 2015; Byrne et al. 2017) and adolescent patients (Le Grange et al. 2020; Dalle Grave et al. 2013b, 2015, 2019). This is not true of any other treatment (Dalle Grave et al. 2021b).
- In bulimia nervosa, CBT-E for adults has proven to be superior to all the psychological treatments it has been compared with, including psychoanalytic psychotherapy (Poulsen et al. 2014) and interpersonal therapy (IPT) (Fairburn et al. 2015).
- In anorexia nervosa, outpatient CBT-E has demonstrated promising results in adult patients (Fairburn et al. 2013). It was found to be more effective than Specialist Supportive Clinical Management (SSCM) and Maudsley Model Anorexia Nervosa Treatment for Adults (MANTRA) in helping patients achieve a physically healthy weight (in 59%, 47.5%, and 44% of participants, respectively), albeit not significantly so (Byrne et al. 2017).
- In inpatient settings, CBT-E has good outcomes in both adolescents and adults. Eighty-five percent complete the treatment, and among completers, about 50%

still display a full response at 60-week follow-up (Dalle Grave et al. 2013a, 2014, 2020).

- CBT-E has also displayed efficacy in patients with severe and extreme anorexia nervosa, who are seldom included in clinical trials due to their supposed intractability. A completion rate of 66% has been reported in such outpatients, and about 50% of these exhibited a full response at 60 weeks of follow-up (Calugi et al. 2021). In another sample, 85% completed inpatient CBT-E, and 33% of completers displayed a full response at 12-month follow-up (Calugi et al. 2017).
- In adolescent patients with anorexia nervosa, about 72% completed outpatient CBT-E, and among completers about 62% displayed a full response at follow-up (Dalle Grave et al. 2013b). These outcomes were similar to FBT at 6- and 12-month follow-up (Le Grange et al. 2020). Comparably encouraging results have also been achieved when delivering the treatment in real-world clinical settings (Dalle Grave et al. 2019).

Implications for Clinical Services

The results obtained through CBT-E in both research and real-world settings have important implications for clinical services providing treatment for eating disorders. CBT-E is the logical first-line treatment for all eating disorders, as patients can be treated via a single, well-delivered, evidence-based treatment, rather than the common evidence-free "eclectic" approach.

To achieve optimal outcomes, therapists need to be adequately trained in CBT-E. However, clinicians only have to learn a single psychological treatment to treat most adults and adolescent patients with any eating disorder, with substantial clinical and financial benefits. Moreover, multistep implementation of CBT-E, by offering outpatient, intensive outpatient, inpatient, and post-inpatient treatment (Dalle Grave 2013), minimizes the problems associated with transitions from outpatient to intensive treatment. In a unified multistep service, patients avoid the confusing and counterproductive changes in therapeutic approach that commonly accompany such transitions.

Remaining Challenges

Several research and clinical challenges will need to be addressed in the future in order to make the treatment more effective, efficient, and available. Future studies should: (i) clarify the relative effectiveness of CBT-E and FBT in the treatment of younger patients; (ii) identify moderators of the effects of CBT-E; (iii) assess the effects of the broad form of CBT-E; and (iv) develop and test specific modules to address comorbidities (e.g., obesity, post-traumatic stress disorder). It is also crucial to study how to increase the effectiveness of CBT-E, identifying, for example, the reasons for non-response and the mediators of the effects of CBT-E, and then modify the treatment accordingly.

To maximize CBT-E availability, currently under investigation are two strategies, specifically (i) how best to train more therapists via digital training while offering supervision by experts in CBT-E; and (ii) how to make CBT-E more scalable via innovative forms of digital treatment (Fairburn and Patel 2017). It will also be important to improve the promotion of CBT-E via social networks and other modern communication strategies. To this end, a website (www.cbte.co) devoted to the treatment has been recently created for the general public, therapists, and patients.

Applications in Other Eating Disorders

This chapter reviewed "enhanced" cognitive behavioral therapy (CBT-E) for eating disorders. CBT-E is a "transdiagnostic" treatment for all forms of eating disorders, including anorexia nervosa, bulimia nervosa, binge-eating disorder, and other similar states. CBT-E was developed as an outpatient treatment for adults, but is available as an intensive version for day patients and inpatients. There is also a version for younger people. CBT-E addresses common eating disorder maintenance mechanisms, reflecting their shared and evolving psychopathology, rather than the specific diagnosis. The treatment is highly individualized, and the therapist creates a specific version of CBT-E to suit the individual issues of the person receiving treatment. CBT-E is effective in all forms of eating disorders encountered in adults and adolescents. Therapists need to receive training in CBT-E to obtain optimal effects.

Mini-Dictionary of Terms

- **Body checking:** repeated and frequent checking of one's body weight and shape
- **Core psychopathology:** the overvaluation of shape, weight, and eating control characteristic of most eating disorders
- **Dietary restraint:** attempts to limit the amount of food eaten
- **Dietary restriction:** undereating in the physiological sense
- **Dietary rules:** highly specific rules on what, when, and how to eat, etc.
- **Enhanced**: a term used to highlight that the treatment uses various innovative strategies and procedures to enhance the effectiveness of the original cognitive behavior therapy developed for bulimia nervosa
- **Objective binge eating:** episodes of eating characterized by the following: (1) eating a large amount of food given the circumstances, and (2) a sense of lack of control during such episodes
- **Overvaluation of shape, weight, eating and their control:** judging self-worth largely, or even exclusively, in terms of one's shape, weight, and ability to control them
- **Starvation symptoms:** the physical and psychosocial symptoms that occur secondary to dietary restriction and undereating

- **Transdiagnostic:** a mechanism that is present across disorders, irrespective of the specific diagnosis

Key Facts of Enhanced Cognitive Behavior Therapy for Eating Disorders

- Enhanced Cognitive Behavior Therapy (CBT-E) is a specific form of therapy for eating disorders.
- It is focused on the eating disorder psychopathology operating in the patient (not the eating disorder diagnosis).
- It uses strategies and procedures sequentially but flexibly to treat each patient's individual psychopathology.
- Developed as an outpatient treatment for adults, it is now available for younger people and as an intensive version for day patients and inpatients.
- About two-thirds of those who begin treatment make a full recovery with CBT-E. Although fewer patients who are substantially underweight complete treatment, their response rate is similar.

Summary Points

- Enhanced cognitive behavior therapy (CBT-E) is a specialized psychological treatment for eating disorders.
- It was initially devised to treat eating disorders in adults with eating disorders, but has since been adapted for adolescents of at least 12 years of age and intensive settings of care.
- CBT-E is designed to treat the patient's psychopathology. It does so by addressing in a flexible and personalized way the behavioral and cognitive processes maintaining the eating-disorder features of the patient.
- CBT-E can be administered in two forms: (i) the focused form, addressing only the eating-disorder psychopathology; or (ii) a broad form, also incorporating modules for one or more of the following external psychopathologies, as indicated: clinical perfectionism, core low self-esteem, and marked interpersonal difficulties.
- About 80% of not-underweight patients complete treatment, and among them, about two-thirds achieve full remission, which appears well maintained over time. In underweight treatment is completed in about 65% of cases, but the remission rate is similar.
- Future challenges to address are: (i) to further validate CBT-E; (ii) to study how to increase the effectiveness of CBT-E; (ii) to improve the promotion of CBT-E; and (iv) to maximize CBT-E availability, training more therapists and making the treatment more scalable.

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Eating Disorders During Pregnancy

2

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Contents

Introduction 27
EDs and Fertility 27
EDs in Pregnancy 28
Gestational AN 29
Gestational BN 29
Binge Eating Disorder (BED) in Pregnancy 30
Pica in Pregnancy 30
Pregorexia 31
Bottlenecks for the Management of EDs and OFSED Before Fertility Treatment and During Gestation 31
Application to Other EDs 32
Mini-dictionary of Terms 32

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Key Facts of EDs During Pregnancy 33
Summary Points 33
References 34

Abstract

During pregnancy, women might improve their diet and adopt a healthier eating behavior. However, this is not the case for women suffering from eating disorders (ED), who experience comorbidities such as depression, anxiety, binge eating, and increased concerns about weight gain. EDs, especially anorexia nervosa (AN), might interfere with fertility due to weight loss. Furthermore, maternal (impairments in fluid and electrolyte metabolism, miscarriages, cesarean deliveries) and fetal (wheezing in the offspring, prematurity, small head circumference) complications are apparent. The birth weight of the infants is positively associated with maternal pregravid bodyweight (BW). Although bulimic behaviors ameliorate during pregnancy, they resurface postpartum. Bulimia nervosa (BN) has been associated with low-birth-weight infants, fetal abnormalities, prematurity, and complications at delivery. On the other hand, women with binge eating syndrome tend to deliver heavier and larger babies. Other EDs present in pregnancy include orthorexia nervosa (ON) and pica. A multidisciplinary approach is recommended for the treatment of EDs during pregnancy, emphasizing adequate intake of nutrients and BW gain.

Keywords

Pregnancy · Trimester · Prenatal · Pica · Vomiting · Fertility · OFSED · Disordered eating · Binge eating · Orthorexia · Obsessions · Pregorexia · Small for gestational age · Feeding disorders

Abbreviations

AN	Anorexia nervosa
BED	Binge eating disorder
BMI	Body mass index
BN	Bulimia nervosa
BW	Bodyweight
ED	Eating disorders
GWG	Gestational weight gain
IDA	Iron deficiency anemia
IUGR	Intrauterine growth retardation
LGA	Large for gestational age
NINFEA	Nascita e INFanzia gli Effetti dell'Ambiente
ON	Orthorexia nervosa
SGA	Small for gestational age
TfR	Transferrin receptor
U/OSFED	Unspecified or other specified feeding or eating disorder

Introduction

For developing a healthy fetus, pregnancy is characterized by various maternal physiological and psychological adaptations. In particular, proper nutrition is important for meeting the high perinatal energy demands and assuring the provision of all essential nutrients to the fetus. Women may use pregnancy as an opportunity for change (Olander et al. 2018) by improving diet quality (Tsigga et al. 2011), abandoning unhealthy eating habits, and increasing the levels of physical activity (Wise et al. 2020). According to Olander (Olander et al. 2018), the behavioral change during pregnancy is explained by psychological and social terms: behavioral change is inextricably linked to the promotion of the maternal-fetal relationship (Bergh and Simons 2009), and the increased motivation for the latter is both innate-driven and facilitated by the community's expectations.

Nevertheless, eating behaviors may reach extremes, introducing eating disorders (EDs). Numerous systematic reviews have pointed out a high prevalence of EDs or unspecified/other specified eating and feeding disorders (U/OSFED) in pregnant women, associated with symptoms of binge eating, anxiety, depression, and concerns regarding bodyweight (BW) (Dörsam et al. 2019; Martínez-Olcina et al. 2020). Many women enter pregnancy with a history of EDs, and others tend to develop an ED/OFSED during pregnancy. Pregnancy can complicate an underlying ED or trigger the development of a new one. Two mechanisms lead to the development or exacerbation of ED/OFSED during pregnancy, the first being the gestational weight gain (GWG) associated with body dissatisfaction and increased appetite and the second stemming from the need for adopting a more "controlled" and "healthy" diet.

EDs and Fertility

For women with EDs/OFSED, fertility is an issue of concern as many are experiencing sexual dysfunction and miscarriages (Boutari et al. 2020). In anorexia nervosa (AN), women are often anovulatory secondary to reduced body fat (Burke and Vangellow 1990). Nevertheless, there are occasional women with AN who ovulate and become pregnant. As many women may have mistaken beliefs regarding pregnancy, in both AN and bulimia nervosa (BN), unplanned pregnancies are common (Morgan et al. 1999), as they do not take any contraceptive measures (Easter et al. 2011). Time-to-conception is generally longer in women with Eds compared to the general population, with the majority seeing fertility specialists (Easter et al. 2011). When women with a history of AN diagnosis were examined, they exhibited a delayed first birth age and lower parity compared with those with a history of BN, the general population, and their sisters of similar age (Tabler et al. 2018). This finding indicates that the degree of weight loss, which is greater in AN compared with BN, is positively associated with fertility.

EDs in Pregnancy

A previous ED may be triggered again by gestation, as approximately 22% of women are relapsing during the perinatal season (Koubaa et al. 2005). The severity of the ED is important concerning maternal, pregnancy, and fetal outcomes, with women who were hospitalized being at a higher risk for adverse events (Sollid et al. 2004). Women with EDs in remission during the time of conception exhibit greater GWG and deliver babies with higher birth weights and 5-min Apgar scores than those who conceived while demonstrating ED symptomatology (Stewart et al. 1987). According to a systematic review (das Neves et al. 2021), obstetrical and fetal outcomes are dependent on the type of underlying ED: AN and BN have been associated with low birth weight and slow fetal growth and binge eating with the delivery of children with increased birth weight. Figure 1 details the maternal-fetal effects of EDs and OFSED during gestation. EDs are associated with vomiting, hyperemesis, bleeding, anemia, impaired hydration, acute fluid and electrolyte shifts, and a decrease in circulating plasma volume, all of which may increase the risk for

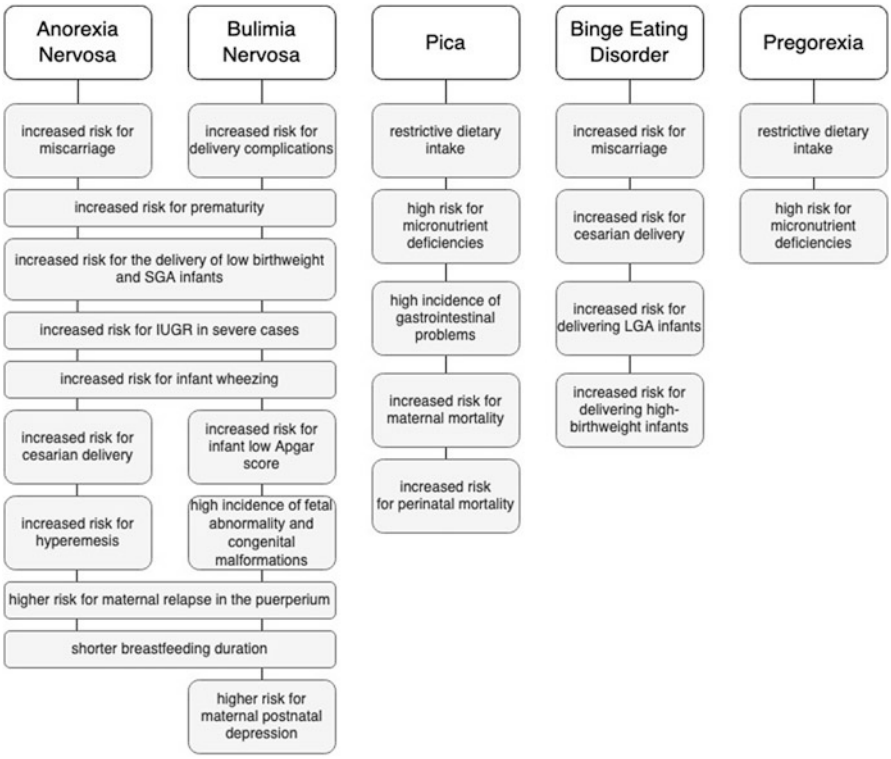


Fig. 1 Results of EDs and OFSED during gestation, on maternal, obstetrical, and fetal outcomes. *IUGR*, intrauterine growth retardation; *LGA*, large for gestational age; *SGA*, small for gestational age

maternal, obstetric, and fetal complications (Burke and Vangellow 1990; das Neves et al. 2021). In severe ED states, intrauterine fetal growth retardation (IUGR) cases have been reported (Burke and Vangellow 1990).

According to the Nascita e INFanzia gli Effetti dell'Ambiente (NINFEA) Internet cohort, infants born to mothers with lifetime EDs exhibit a greater risk of developing wheezing, and this risk is multiplied when the disorders were active during gestation (Popovic et al. 2018). Moreover, previous or active ED diagnoses during pregnancy are associated with several risk factors for the offspring, including wheezing, low birth weight (double risk), prematurity (70% higher), smaller head circumference, microcephaly, small for gestational age (SGA) (80% increase), and a shorter breastfeeding duration (Sollid et al. 2004; Koubaa et al. 2005; Linna et al. 2013; Popovic et al. 2018). Many mothers return to their prepregnancy eating behaviors and thoughts during the postnatal period (Fogarty et al. 2018).

Gestational AN

AN is a complex situation, often encountered among pregnant women (Dinas et al. 2008). Women with underlying AN tend to report negative attitudes toward pregnancy (Easter et al. 2011). Those who achieve conception face a greater burden of miscarriages, cesarean deliveries, prematurity, infant wheezing, and low birth weight (Bulik et al. 1999; Popovic et al. 2018). Moreover, the offspring of women with AN exhibit an even lower birth weight when the mothers have a history of BN (Bulik et al. 1999). These lower birth weights in the offspring of women with AN result from lower pregravid body mass index (BMI) (Micali et al. 2007).

On the other hand, recovery from AN, as indicated by body weight restoration, appears to normalize reproductive function, including fertility, pregnancy, and childbirth rates. According to a recent meta-analysis (Chaer et al. 2020), the pooled odds of childbirth rate between women recovered from AN and the general population was not different. Subsequently, the management of EDs in fertility clinics encompasses the full remission of the patient before any fertility treatment can be initiated (Norré et al. 2009).

Gestational BN

BN during gestation is associated with an approximately doubled risk of induced abortion compared with healthy women (Linna et al. 2013). Prospective studies of untreated, normal BW pregnant women with BN revealed that pregnancy progression induces a need to eat in a healthy way, tampering down bulimic symptoms (Lacey and Smith 1987; Morgan et al. 1999). Thus, with each ascending trimester of gestation, the frequency of binge eating and self-induced vomiting is sequentially reduced. By the last trimester, approximately 75% of the women cease any bulimic behavior, with the remaining 15% exhibiting a less severe disturbed eating pattern than the beginning of pregnancy. Interestingly, the existing literature agrees that BN

symptoms tend to relapse during the puerperium, with approximately 50% of the women exhibiting abnormal eating in a more disturbing severity postnatal than before conception (Lacey and Smith 1987; Morgan et al. 1999; Morrill and Nickols-Richardson 2001). Only one-third of women recover entirely after delivery (Morgan et al. 1999). Relapse is predicted by behavioral persistence, previous co-existence of AN ("type II" BN), unplanned pregnancies, and a diagnosis of gestational diabetes mellitus (Morgan et al. 1999).

Concerning fetal and obstetrical outcomes, BN is associated with a high incidence of fetal abnormality (cleft palate, cleft lip) and congenital malformations, low birth weight, prematurity, increased risk for wheezing, low Apgar scores, and delivery complications, including breech presentation and need for surgical intervention (Lacey and Smith 1987; Morrill and Nickols-Richardson 2001; Popovic et al. 2018). Maternal postnatal depression is also high, particularly among those with BN and AN, alcohol misuse, and increased symptom severity and persistence (Morgan et al. 1999).

Binge Eating Disorder (BED) in Pregnancy

BED diagnosis during pregnancy affects birth outcomes directly or indirectly via maternal body weight and GWG (Bulik et al. 2009; Nunes et al. 2012). BED during pregnancy is associated with disturbed sleep patterns (Ulman et al. 2012), possibly due to the night-eating syndrome. Compared with healthy controls, pregnant women with BED have an approximately triple risk for miscarriage, complicating the conception process (Linna et al. 2013). Concerning pregnancy outcomes, pregnant women with BED tend to give birth to babies with high birth weight, low risk of SGA babies, and a higher risk for large-for-gestational-age (LGA) babies and cesarean section (Bulik et al. 2009; Linna et al. 2014).

Pica in Pregnancy

Pica is the continued consumption of nonnutritive substances that are considered inappropriate according to the developmental level and do not consist of a culturally supported or socially normative practice (Mishori and McHale 2014). This behavior must have a duration of 1 month at least.

The most common nonfood items reported during pica bouts include soap (including laundry detergent), pagophagia (ice and freezer frost), geophagy (earth, soil, dirt, clay, chalk), amylophagy (raw starch), or other substances (Horner et al. 1991; Young et al. 2010; Young 2010; Ezzeddin et al. 2015; Epler et al. 2017). Proposed etiologies of pica include cultural expectations, maternal psychological stress, increased appetite and hunger, micronutrient deficiencies (in particular Fe), dyspepsia, and protection against toxins and pathogens (Young 2010). Depending on the region studied, the prevalence of pica among pregnant women varies between 8.3% (Ezzeddin et al. 2015) and a greater prevalence among less industrialized

countries. Other researchers suggest an overall prevalence of 20%, which manages to go undetected by health-care professionals (Horner et al. 1991). The prevalence of pica appeared on the treadmill during the World War period, demonstrating a decline after that (Horner et al. 1991).

Research has associated pica practices during gestation to low maternal educational attainment, African-American or non-Caucasian background, childhood or family history of pica, living in rural areas, experiencing unwanted pregnancies and pregnancy complications, and experiencing food insecurity, with low levels of economic satisfaction, while receiving iron supplementation during pregnancy (Horner et al. 1991; Ezzeddin et al. 2015; Roy et al. 2018).

The research appears unanimous that pica is associated with iron deficiency anemia (IDA) or low iron scores (Young et al. 2010; Young 2010; Epler et al. 2017), although it is not known which one (pica or IDA) is preceding the other. Pica practices have been associated with high concentrations of the transferrin receptor (TfR) (Roy et al. 2018) and hemoglobin levels (Young et al. 2010). The condition usually represents itself with esophagitis, gastritis, gastrointestinal distress, nausea, abdominal pain, and IDA (Young et al. 2010; Epler et al. 2017), and, if undiagnosed, it can often lead to maternal and perinatal mortality (Horner et al. 1991). A parenteral iron infusion may result in the resolution of all cravings acutely (within hours), suggesting that possibly IDA or low iron stores are triggering the cravings (Epler et al. 2017).

Pregorexia

Orthorexia nervosa (ON), an unhealthy obsession for healthy eating (Bratman and Knight 2000), is often encountered during gestation, under the term "pregorexia." In a Turkish study (Taştekin Ouyaba and Çiçekoğlu Öztürk 2021), high levels of nutritional information and motivation were associated with a healthy eating obsession, propelling ON tendencies in a pursuit for improved health outcomes. Despite the limited evidence, approximately 26.6% of pregnant women demonstrate ON tendencies (Taştekin Ouyaba and Çiçekoğlu Öztürk 2021). However, the lack of a consensus regarding the diagnosis and the subsequent lack of diagnostic tools according to the diagnostic criteria result in a wide variation in this prevalence. Moreover, some OFSED, like ON, merit further investigation during pregnancy.

Bottlenecks for the Management of EDs and OFSED Before Fertility Treatment and During Gestation

Although research unanimously propagates the need for early screening to detect disturbed eating behaviors, this is rarely the case in clinical practice (Morrill and Nickols-Richardson 2001). According to Palaskis and de Zwaan (2019), clinical algorithms for the management of EDs for gynecologists and fertility specialists are practically inexistent. Moreover, the care of women with EDs who become pregnant

requires coordination between various health professionals. The latter must attain a high level of understanding of the complex pathophysiology of EDs/OFSED, including these patients' psychological and physiological characteristics (Burke and Vangellow 1990). Treatment must be multidisciplinary, emphasizing adequate energy and nutrient intakes and appropriate GWG, all aiming to achieve improved pregnancy outcomes (Morrill and Nickols-Richardson 2001). Pregnancy can be seen as an opportunity for intervention, acceptance of body image changes, and developing long-term healthy eating habits (Morrill and Nickols-Richardson 2001; Fogarty et al. 2018). Finally, postnatal treatment interventions should primarily focus on avoiding relapse and diagnosis and managing postnatal depression (Morgan et al. 1999).

Application to Other EDs

This chapter reviewed the literature regarding complications of EDs in pregnant women. Pregnant women suffering from EDs have co-morbidities such as depression, anxiety, and increased concerns about weight gain (Martínez-Olcina et al. 2020). The most common EDs are AN, BN, and BED. However, other less common disorders can occur during pregnancy. Unspecified or other specified feeding and eating disorders (U/OSFED) are often mental disorders in pregnant women. Obsessions with healthy eating, which can reveal ON in the general population, can occur in pregnant women as "pregorexia." These obsessive tendencies might afflict as many as 25% of pregnant women (Taştekin Ouyaba and Çiçekoğlu Öztürk 2021). However, the lack of proper screening should be considered in evaluating their prevalence. Furthermore, consuming substances other than foods (pica) might afflict 20% of pregnant women. Pica has been associated with iron deficiency, and iron infusion might resolve abnormal cravings (Epler et al. 2017). In addition, the prevalence of night eating in pregnant women ranges from 15% to 45%, and the potentially disturbing circadian rhythms might affect the metabolic outcomes (Loy et al. 2020). Night-eating syndrome has been associated psychologically with depressed mood and sleep disturbances and metabolically with higher insulin and lower high-density lipoprotein (HDL) concentrations and insulin resistance (Allison et al. 2012; Deniz et al. 2019).

Mini-dictionary of Terms

- **Binge eating disorder**: A DMS-5 disorder in which recurrent episodes of binge eating occur. During these episodes, the individual might rapidly consume its foods and in larger-than-usual proportions.
- **Orthorexia nervosa**: Often encountered during gestation and is also known as "pregorexia" and is characterized by an obsession to follow a healthy diet. It is not classified in the DSM-5.

- **Other specified feeding or eating disorders**: In the Diagnostic and Statistical Manual of Mental Disorders Version 5 (DSM-5), this category includes eating and feeding disorders not meeting the diagnostic criteria of other classified disorders, and the clinician communicates a reason for this. Along with the unspecified feeding or eating disorders, it replaced the category of EDs not otherwise specified.
- **Pica**: A DSM-5 disorder characterized by consuming substances other than foods such as soap, ice, and soil.
- **Small for gestational age**: Infants weighing at birth lower than the tenth percentile for their gestational age.
- **Unspecified feeding or eating disorder**: A disorder not falling under any other DSM-5 category.

Key Facts of EDs During Pregnancy

- Mechanisms for developing EDs during pregnancy include concerns about GWG and the need to adopt a healthy diet.
- A previous diagnosis of an ED might lead to relapse during pregnancy; many women relapse to disordered behaviors or thoughts postpartum.
- Recovery from AN ameliorates reproductive complications and the childbirth rate.
- Postnatal depression is prevalent in mothers with anorexia or BN.
- Fetal complications of AN include wheezing, prematurity, small head circumference, and low birth weight.
- Fetal complications of BN include cleft lip and palate, congenital malformations, wheezing, low birth weight, and low Apgar scores.
- Pica might be associated with nutrient deficiencies; for iron deficiency, iron infusions result in ameliorating the cravings.

Summary Points

- EDs during pregnancy are accompanied by comorbidities such as depression, anxiety, binge eating, and increased concerns about weight gain.
- Complications affect both the mother and the child.
- In AN, low maternal pregravid body weight is associated with low offspring birth weight.
- Bulimic behaviors decrease during pregnancy but resurface after delivery.
- BED is associated with the delivery of heavy and large babies.
- ON and pica are apparent during pregnancy.
- Treatment of EDs should set appropriate weight goals, provide adequate nutrition, and deal with postpartum depression.

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Eating Habits During Pregnancy

3

Irene Cetin, Chiara Bianchi, and Arianna Laoreti

Contents

Introduction 38
Role of Maternal Anthropometrics and Nutrition on Short- and Long-Term Outcomes 38
Current Maternal Nutrition Is Inadequate Even in Industrialized Countries 41
Dietary Patterns and Feto-maternal Outcomes 42
Conclusion 44
Mini-Dictionary of Terms 45
Summary Points 45
References 46

Abstract

Nutrition and lifestyle during pregnancy and preconceptional period represent a major public health challenge, influencing the development of the embryo, fetus, and placenta, with considerable potential to influence not only maternal health but also that of future generations.

However, the risk of inadequate maternal nutrition is high both in underdeveloped and in industrialized countries, especially for selected groups of women of childbearing age: those following exclusion diets, women affected by eating disorders, underweight or overweight/obese, smokers, and adolescents.

These dietary inadequacies are due to complex sociocultural and economic interacting factors, and it is mandatory to incorporate in clinician's appointment brief nutrition discussions to propose simple and personalized multidisciplinary interventions.

Understanding the relationship between maternal nutrition, pregnancy, and birth outcomes may provide a basis for developing nutritional interventions that will improve maternal well-being, birth outcomes, and long-life health of the

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newborn, improving the quality of life and reducing mortality, morbidity, and health-care costs.

Keywords

Pregnancy · Maternal nutrition · Dietary pattern · Malnutrition · Maternal and neonatal outcomes · Supplementation

Introduction

Pregnancy and infancy comprise the most critical stages for conditioning an individual's health, with a number of implications for subsequent risks of morbidity, mortality, and reproductive health.

Maternal nutrition is recognized as one of the major environmental factors influencing the development of the embryo, fetus, placenta, and maternal tissues. Poor maternal nutritional status and lifestyle, along with maternal body composition, metabolism, and placental nutrient supply, are the main factors that can negatively or positively influence fetal development, affecting the growth trajectory and immune system of the fetus and infant, and have been strictly related to adverse pregnancy outcome and expression of fetal genetic potential.

Understanding the link between maternal nutrition and birth outcomes may provide a basis for developing nutritional interventions and optimizing the "window of opportunity" offered by pregnancy to improve long-term maternal and infant health.

Role of Maternal Anthropometrics and Nutrition on Short- and Long-Term Outcomes

Pregnancy, from conception to birth, is a period when women undergo important metabolic and physiological changes.

According to the "Developmental Origin of Health and Disease" or "Early Metabolic Programming" paradigm, environmental factors including nutrition during pre- and postnatal phases of human development have a significant impact on health in adult life (Barker 2007; Koletzko 2014; Mandy and Nyirenda 2018; Farias et al. 2020). This has been the basis of increasing focus on "the first thousand days" of life – arbitrarily defined as the time between conception and the end of a child's second year – as a period of significant "development plasticity." During this period, phenotypic development is more susceptible to change in response to environmental factors (Koletzko et al. 2014; Lorite Mingot et al. 2017) (Fig. 1).

First of all, an adequate body mass index (BMI) is crucial even in the periconceptional period (Moshe et al. 2019; Adair and Adair 2014): a preconceptional BMI <18.5 kg/m^2 increases the risk of intrauterine growth restriction (IUGR), preterm birth, and iron deficiency anemia (Cetin et al. 2013), while a preconceptional

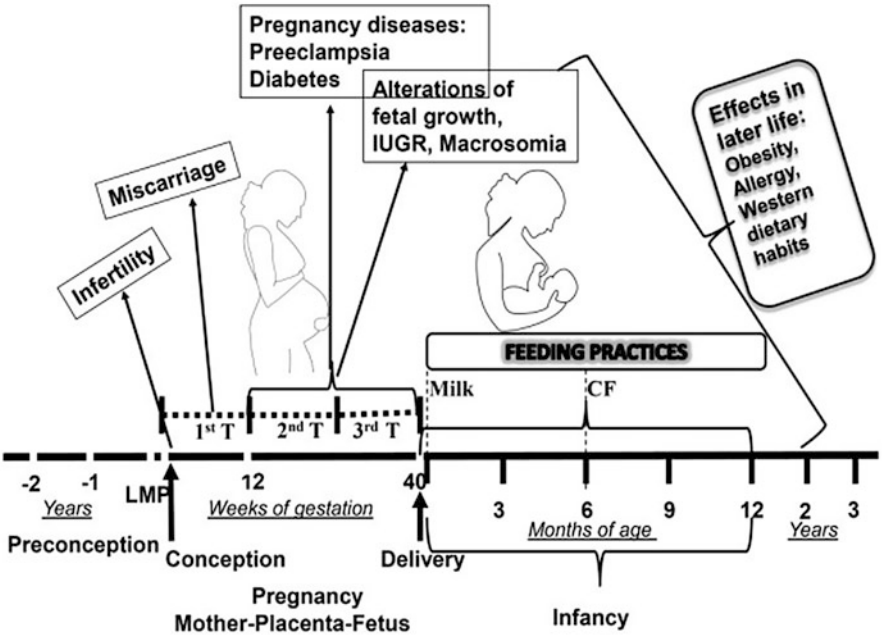


Fig. 1 Role of maternal nutrition on short- and long-term outcomes. The continuum of interplay between a woman of reproductive age, the nutritional environment, and the offspring's lifelong health from conception, through pregnancy, until the cessation of breastfeeding. (Country of Berti et al. 2017)

BMI >25 kg/m^2, and especially obesity, increases the risk of infertility, hypertensive disorders of pregnancy, gestational diabetes mellitus (GDM), structural anomalies, large-for-gestational-age infants or IUGR, preterm birth, fetal and neonatal death, caesarean delivery, and non-communicable diseases in offspring, including obesity, metabolic syndrome, cardiovascular disease, and type 2 diabetes mellitus (Samuels-Kalow et al. 2007; Chu et al. 2007; Delhaes et al. 2018; Black et al. 2013; McDonald et al. 2010; Kristensen et al. 2005; Reynolds et al. 2013).

Moreover, during pregnancy, it is mandatory to obtain an adequate gestational weight gain (GWG) (IOM 1990): a lower GWG is associated with decreased birth weight and failure to initiate breastfeeding, while an excessive GWG is associated with increased birth weight, caesarean delivery rate, and postpartum weight retention. In addition, excessive GWG is associated with subsequent obesity and long-term comorbidity, with the odds of overweight in offspring at age of 7 years old increased by 3% for every 1 kg of gestational weight gain (Tanentsapf et al. 2011; Siega-Riz et al. 2009).

Several studies have demonstrated that imbalances in both macronutrient and micronutrient intakes may affect pregnancy and birth outcomes.

Negative effects in terms of weight and length of the newborn at birth could be associated with insufficient protein, folate, iron, and vitamin D intake

(Blumfield et al. 2012a; Prentice 2011; Parisi et al. 2017a; Peña-Rosas et al. 2015), while excessive weight of the newborn, insulin resistance, glucose intolerance, and inadequate weight control are associated with an excessive amount of high glycemic index carbohydrates (Walsh et al. 2012, 2014).

The risk of stillbirth and fetal growth restriction could be associated with inadequate protein or vitamin D or folate intake (Ota et al. 2012; Ji et al. 2019; Mirzakhani et al. 2016), while the risk of preterm birth could be associated with inadequate protein intake or with low n-3 PUFA or iron intake (Middleton et al. 2018).

Fetal brain and retinal development are influenced by n-3 PUFAs: DHA is the major n-3 polyunsaturated fatty acid contained in the human brain and retinal rods and, thus, is essential for brain and retinal development of the fetus during pregnancy, and it plays a major role in the psychomotor neurodevelopment also in the first months of life (Koletzko et al. 2011; Massari et al. 2020a).

Iodine intake is critical for maternal and fetal thyroid function and fetal neurological development, leading, in case of maternal untreated hypothyroidism, to "iodine deficiency disorders" (abortion, congenital anomalies, deafness, neurological cretinism, neurocognitive delay, mental retardation, as well as attention-deficit/hyperactivity disorders) (Trumpff et al. 2015).

It has been recently demonstrated that periconceptional folate intake and status significantly correlate with embryo growth (Parisi et al. 2017), birth weight, and adverse pregnancy outcomes; folate inadequate intake can cause megaloblastic anemia, leukopenia and thrombocytopenia, and hyperhomocysteinemia and can increase the risk in the offspring of neural tube defects, congenital heart disease, and placental vascular disorders (de Regil et al. 2015; Fekete et al. 2012; Burdge and Lillycrop 2012).

In addition, it is demonstrated that low calcium or vitamin D intake, especially when a deficient status coexists, increases the risk of developing hypertensive disorders of pregnancy (WHO 2013; Hofmeyr et al. 2014; Robinson et al. 2010).

With regard to long-term outcomes, nutrients are involved in enzymes, signal transduction, transcription pathways, oxidative stress, and epigenetic modifications, since the periconceptional period (Cetin et al. 2009). Macro- and micronutrients affect the availability of methyl donors, substrates, and transcription factors which are direct regulators of DNA stability and gene expression. By this mechanism, nutrients are able to influence the complex biological pathways involved in gametogenesis, in embryogenesis, as well as in placental and fetal growth, permanently modulating gene expression and altering developmentally plastic systems, with implications in terms of predisposing or not the fetus to noncommunicable diseases (NCDs) in later life by influencing physiological thresholds of energy balance regulation. This is of fundamental importance considering that NCDs, including obesity, metabolic syndrome, cardiovascular disease, and type 2 diabetes mellitus, represent the leading causes of illness and mortality in the world.

Current Maternal Nutrition Is Inadequate Even in Industrialized Countries

The caloric requirements for healthy, normal weight women with a moderately active lifestyle undergo a moderate increase during pregnancy (dependent on pregnancy stage), which can be met by slightly increasing energy intakes, in a balanced equilibrium between macronutrients within the recommendations of nutritional guidelines (proteins (10–35%), carbohydrates (45–60%), and fats (20–35%)). On the other side, micronutrient requirements increase more than those of macronutrients during pregnancy, and inadequate intakes (and, thus, a low nutritional quality of the diet) can have significant consequences for both the mother and the developing fetus (Marangoni et al. 2016).

Good nutrition is defined as a well-balanced diet that provides all essential nutrients in optimal amounts and proportions, whereas malnutrition is the state produced by an inadequate intake of a good-quality diet, and this can refer to an inadequate intake of macronutrients such as calories and protein (i.e., undernutrition), to an inadequate intake or increased losses of specific or multiple vitamins and minerals (i.e., micronutrient malnutrition) because of an unbalanced diet or to an intake of too many macronutrients (i.e., overnutrition), or to an excessive amounts of inappropriate substances (i.e., alcoholism) (Cetin et al. 2009).

Nutritional deficiencies often coexist among women of reproductive age in low- and middle-income countries, and they are exacerbated in pregnancy due to these increased demands of the developing fetus. Despite the availability of economic and nutritional resources, most women fail to meet the right energy, macronutrient, and micronutrient needs also in industrialized countries, where dietary patterns, typified by fast foods, snacking, breakfast skipping, soft drinks, and energy-dense convenience foods rich in sugars and oils, are nutritionally unbalanced (Parisi et al. 2014).

A large meta-analysis by Blumfield, comparing the dietary intakes of pregnant women with the adult national dietary guidelines in each respective country or geographical region, showed that food intakes among pregnant women in developed countries (the United States/Canada, the United Kingdom, Europe, Australia/NZ, Japan) did not meet national dietary intake recommendations for folate, iron, or vitamin D, while calcium intakes in Japan were lower than those in other developed regions and were below Japanese recommendations (Blumfield et al. 2013). In addition, energy and macronutrient recommendations did not match with reported intakes of pregnant women: energy and fiber intakes were consistently lower than recommendations, total fat and saturated fat intakes were generally above recommendations, and carbohydrate and PUFA intakes were either lower or borderline low compared to recommendations (Blumfield et al. 2012).

Among the deficient micronutrients, iron, iodine, folate, zinc, and vitamin A are the most widespread since they commonly contribute to growth, and in their absence, perinatal complications, intellectual disorders, and increased risk of morbidity-mortality are observed (Bailey et al. 2015).

A recent Cochrane review suggests a positive impact of multiple micronutrient supplementation with iron and folic acid on several birth outcomes, such as preterm births, low birth weight, and small for gestational age (Keats et al. 2019).

Evidence suggests that optimal mineral supplementation can significantly reduce a wide range of pregnancy complications (including anemia, gestational hypertension, gestational diabetes, hyperthyroidism, miscarriage, and preeclampsia) and infant health problems (including anemia, asthma/wheeze, autism, cerebral palsy, hypothyroidism, intellectual disability, low birth weight, neural tube defects, preterm birth, and rickets) (Adams et al. 2021).

Single micronutrient and vitamin supplementation also show improvements for specific outcomes, such as calcium on the risk of preeclampsia/eclampsia, iron on maternal anemia, vitamin D on preterm births, and vitamin A on serum/plasma retinol concentration in mothers (Oh et al. 2020). These findings highlight that micronutrient-specific supplementation should be tailored to specific groups or needs for maximum benefit.

Dietary Patterns and Feto-maternal Outcomes

When evaluating maternal diet and associated outcomes, it is clear that identifying the potential influence of single substances is often difficult. Therefore, the use of dietary patterns, a measure of overall dietary behavior, has become widespread in nutrition research in recent years as an alternative approach to studying individual components of the diet.

Dietary patterns are population specific, since they are influenced by sociocultural factors and food availability, but strictly related to adverse pregnancy outcome and expression of fetal genetic potential (Cetin and Laoreti 2015).

A predominantly "Mediterranean" dietary pattern characterized by joint intakes of fruit, vegetables, vegetable oil, alcohol, fish, legumes, and cereals and low intakes of potatoes and sweets has been associated with a decreased risk of spina bifida in the offspring, with higher levels of serum folate and serum vitamin B12 and lower plasma homocysteine (Vujkovic et al. 2009), and in general, fetus from women with a "prudent dietary pattern" were at lower risk of neural tube defects (NTDs) and some heart defects (Sotres-Alvarez et al. 2013). In addition, a low adherence to the Mediterranean diet has been associated with several adverse outcomes, both in pregnancy (e.g., birth defects, gestational diabetes mellitus, hypertensive disorders, preterm birth) and childhood (e.g., atopy, cardiovascular risk profile, body composition) (Amati et al. 2019; Raghavan et al. 2019; Timmermans et al. 2012; Karamanos et al. 2014; Zhang et al. 2019; Castro-Rodriguez et al. 2010; Garcia-Marcos et al. 2013; Schoenaker et al. 2015). Even in the preconceptional period, the Mediterranean diet has been demonstrated to contribute to enhanced fertility in couples seeking to conceive (Toledo et al. 2011; Vujkovic et al. 2010; Salas-Huetos et al. 2017): most reproductive failures originate during the periconceptional period and may be influenced by the lifestyle of the parents-to-be. In particular, inadequate

pre-pregnancy diets may impact the overall reproductive and/or pregnancy cycle (Steegers-Theunissen et al. 2013).

Lately, maternal dietary patterns have been associated with embryonic growth and congenital anomalies: a recent study conducted on Rotterdam cohort showed that the "high fish and olive oil and low meat" and the "high vegetables, fruit and grain" dietary pattern were associated with accelerated embryonic development in spontaneously conceived pregnancies (Parisi et al. 2018; Parisi et al. 2017).

Data derived from the MoBa cohort (Norwegian Mother and Child Cohort Study) demonstrated that women with high scores on a pattern characterized by high intake of vegetables, plant foods, and vegetable oils were at decreased risk of preeclampsia, whereas a dietary pattern characterized by high consumption of processed meat, sweet drinks, and salty snacks increased the risk of hypertensive disorders of pregnancy (Meltzer et al. 2011; Brantsaeter et al. 2009; Torjusen et al. 2014).

Several authors showed that great adherence to the New Nordic Diet, based on consumption of Nordic fruits, root vegetables, potatoes, salad, onion, garlic, whole-grain cereals, fiber-rich bread, wild fish, milk, and water, was associated with a lower risk of developing preeclampsia and spontaneous preterm delivery among nulliparous women (Hillesund et al. 2014; Englund-Ögge et al. 2014). Similarly, a study from the DNBC (Danish National Birth Cohort) reported that Western-type diet, high in meat and fats and low in fruits and vegetables, is associated with increased odds of induced preterm birth (Rasmussen et al. 2014).

Data from the Nurses' Health Study II showed that a high consumption of red and processed meat was also positively associated with the risk of GDM, contrary to a prudent dietary pattern high in fruit, green vegetables, fish, and protein and fat from vegetable food sources (Zhang et al. 2006; Bao et al. 2014).

In addition, many studies have also specifically evaluated the importance of fish consumption during pregnancy. Fish is of particular importance for the content in long-chain ω-3 fatty acids like DHA. Dietary intake of ω-3 FAs during pregnancy and lactation has biologically important effects on gestational length and the risk of preterm delivery and may have an effect on other pregnancy outcomes such as fetal growth, preeclampsia, and postpartum depression. Similarly, DHA supply to the fetus and the neonate is associated with beneficial effects on later cognitive development and visual function (Leventakou et al. 2014; Cetin and Koletzko 2008; Koletzko and Cetin 2007). For these reasons, women of reproductive age should achieve an average dietary intake of DHA at least 200 mg/day (Massari et al. 2020). However, due to potential presence of contaminants such as mercury and dioxins, the advice is to eat fish on average 2 times per week avoiding fish with higher contaminant levels such as tuna and swordfish.

Studies conducted in different population from Mexico and Brazil to Europe, Japan, and New Zealand found a positive association between dietary pattern and birth weight, with a decreased rate of small-for-gestational-age (SGA) infant and fetal growth restriction in healthy diet (Saunders et al. 2014; Colon-Ramos et al. 2015; Wolff and Wolff 1995; Okubo et al. 2012; Thompson et al. 2010; Coelho et al. 2015).

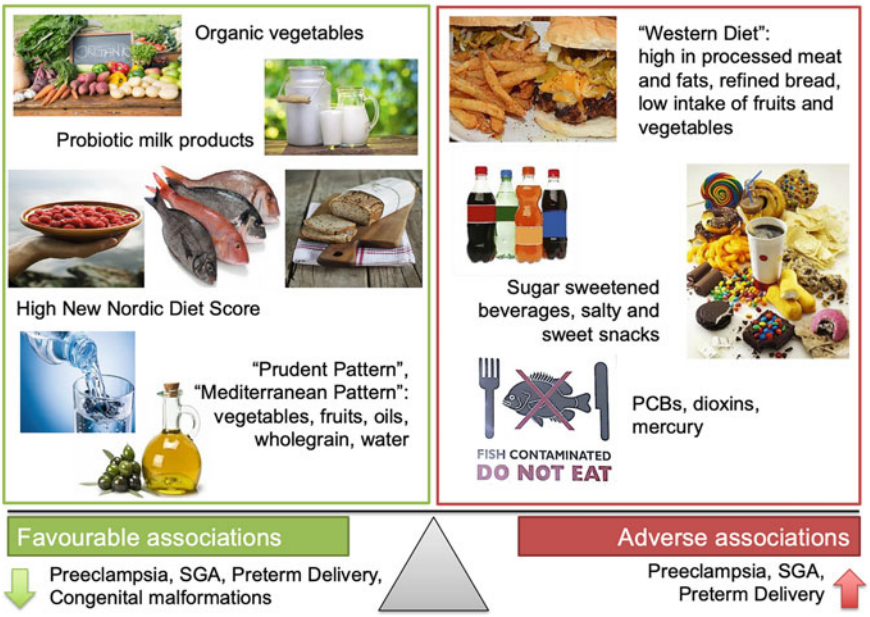


Fig. 2 Maternal dietary patterns and pregnancy and infant outcomes. Matenal dietary patterns of cohorts' population studies and associated pregnancy and infant outcomes. (Adapted from Cetin and Laoreti 2015)

Lastly, caffeine intake has been consistently associated with lower birth weight and higher odds of small-for-gestational-age offspring, not only when consumption exceeds the World Health Organization's recommendation (300 mg/die) but also when it exceeds the recommendation in Nordic countries and the United States (maximum 200 mg/die), which suggests a risk of small-for-gestational-age infants even at very low intakes of caffeine (Sengpiel et al. 2013).

Figure 2 summarizes some of the main results for the investigated dietary patterns of cohorts' population studies.

Conclusion

In conclusion, evidence derived from studies clearly suggests that unhealthy maternal diet during the periconceptional period and throughout pregnancy significantly contributes to impaired pregnancy and offspring outcomes, influencing individual health even before birth, with long-life consequences.

Unfortunately, most women during reproductive age, as well as during pregnancy, fail to meet the right energy, macronutrient, and micronutrient needs also in

industrialized countries, where the recent drop in the adherence to dietary patterns with better micronutrient intakes (green leafy vegetables, fruits, whole-grain breads/cereals, oily fish, etc.) has been demonstrated to have a negative influence on pregnancy outcome and fetal development.

During pregnancy, women may be more motivated to make diet or lifestyle changes: pregnant women welcome diet-, weight-, and nutrition-related discussions and show desire for nutrition to be addressed as "part of the process" in antenatal care, considering diet as one of the factors that are in their control and that can help protect their health and that of the future child. Therefore, clinicians have the responsibility to incorporate brief nutrition and weight discussions as part of their standard appointment, proposing simple but personalized multidisciplinary interventions, and have the ability to improve the health of their patients and that of future generations.

Mini-Dictionary of Terms

- **BMI:** Body mass index
- **GDM:** Gestational diabetes mellitus
- **IUGR:** Intrauterine growth restriction
- **GWG:** Gestational weight gain
- **PUFAs:** Polyunsaturated fatty acids
- **NCDs:** Non-communicable diseases
- **NTDs:** Neural tube defects
- **DHA:** Docosahexaenoic acid
- **SGA:** Small for gestational age

Summary Points

- Nutrition during pregnancy represents a major public health challenge, influencing the development of the embryo, fetus, and placenta and affecting not only women's health but also that of future generations.
- Healthy maternal nutrition, along with adequate body mass index (BMI), is crucial even already in the periconceptional period.
- The risk of dietary inadequacies is high both in underdeveloped and in industrialized countries, and it is due to complex sociocultural and economic interacting factors.
- It is mandatory for clinicians to incorporate in routine preconceptional and antenatal appointments brief nutrition discussions to recognize possible inappropriate habits or nutritional deficiencies and to propose simple and personalized multidisciplinary interventions, leading to healthful dietary practices prior to conception and eventually to tailored supplementation.

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Stress and Disordered Eating Patterns

4

Fotini Tsofliou, Chloe Casey, and Christina Hughes

Contents

Introduction 53
Stress Responses 53
Physiology of Stress 54
Role of the HPA Axis and Glucocorticoids in Eating Behaviors 55
HPA Axis and Dopamine Reward Pathway 57
Hedonics and Addictive Properties of Food 58
Stress and Eating Patterns 59
The Impact of Eating Patterns on Stress and Mood 59
Individual Differences and Disordered Eating 62
Stress and Undereating 63
Stress and Overeating 64
Coping Strategies 66
Applications to Other Eating Disorders 67
Mini-Dictionary of Terms 67
Key Facts 68
Summary Points 68
References 69

Abstract

This chapter provides a review of the relationship between stress and eating behavior, with emphasis on aspects of altered eating patterns in the presence of stress, and the physiological and psychological underpinning of this. This chapter does not focus on clinically diagnosed eating disorders; however, the eating behaviors discussed could be a precursor to their development. It encompasses the different forms of stress and explores the biological consequences such as endocrine and metabolic changes and increased inflammation and oxidative

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stress. The social determinants of eating patterns are also discussed, such as socioeconomic status, culture, and environment. In contrast, the bidirectional effect of nutrition and stress is debated, providing recommendations for the intake of specific nutrients or adherence to dietary patterns that may reduce the physiological and psychological consequences of stress. Individual differences and the two-way relationship of stress on food intake are also explored, outlining how some individuals increase their energy intake, while others reduce their consumption. Finally, the chapter recommends how an individual can be encouraged to cope with stress in more adaptive ways.

Keywords

Stress · Eating behavior · Eating/dietary patterns · Disordered eating · Stress-related illness · Autonomic nervous system · Hypothalamic-pituitary-adrenal axis · Glucocorticoids · Chronic inflammation · Pro-inflammatory cytokines · Overeating · Undereating · Mediterranean diet · Coping strategies

Abbreviations

ACTH	Adrenocorticotropic
AGRP	Agouti-related peptide
AMPK	AMP-activated protein kinase
ANS	Automatic nervous system
CRF	Corticotropin-releasing factor
GC	Glucocorticoid
Gen Z	Generation Z
GL	Glycemic load
GR	Glucocorticoid receptors
HPA	Hypothalamic-pituitary-adrenal axis
IFN	Interferon
IL	Interleukin
MD	Mediterranean diet
MR	Mineralocorticoid receptors
n-3	Omega-3
n-6	Omega-6
NAcc	Nucleus accumbens
NPY	Neuropeptide Y
PFC	Prefrontal cortex
PUFA	Polyunsaturated fatty acids
PVN	Paraventricular nucleus
RA	Receptor antagonist
SCFA	Short-chain fatty acids
SNS	Sympathetic nervous system
TNF	Tumor necrosis factor
VTA	Ventral tegmental area

Introduction

The experience of stress has always been part of life in mankind, and in prehistoric times our progenitors relied on the adaptive response to stress, known as the "fight-or-flight" pattern, in order to escape a dangerous life-threatening situation, defend themselves from a predator, and survive in harsh environmental conditions (Price 2003). But high stress levels can damage health when they become chronic and are not resolved. In this case, increased stress has been associated with a broad range of adverse health outcomes such as cardiovascular disease, hypertension, stroke, obesity and related metabolic disorders, immune impairment, and mental illness (O'Connor et al. 2021). Most modern societies show a common problem: the concomitant experience of stress and ill health related to noncommunicable diseases such as diabetes, cardiovascular disease, and cancer. Recent stress prevalence statistics, from an online study undertaken in the United Kingdom on 4619 adults, found that 74% of participants were feeling stressed and unable to cope because of stress (Mental Health Foundation 2017). Predominately this is more common among younger individuals known as Generation Z (Gen Z) teens (ages 13–17) and Gen Z adults (ages 18–24) than all other generations. In the United States, a recent stress survey among 3409 adults highlighted a mental health crisis. The reported stress levels were significantly elevated in young adults (Gen Z), and declining mental health affected all Americans broadly (*American Psychological Association* 2020). Recent research suggests that stress is a key element in developing mental health problems such as depression and anxiety if people are not coping with stress well and are unaware of management approaches.

People's mental health deteriorated during the coronavirus pandemic worldwide, and evidence showed that there was a concurrent increase in obesity, consumption of unhealthy diet, and physical inactivity (Melamed et al. 2022). There are various self-management approaches that people can use to moderate stress and the risk of stress-related mental illness efficiently. Lifestyle strategies are of primary importance and can include healthy eating, physical activity, and enough sleep (Firth et al. 2019). Eating a healthy, high-quality diet is becoming increasingly significant for mental well-being, and evidence-based recommendations have strongly advocated the role of high-quality eating patterns for reducing stress and low mood (Sarris et al. 2015). The present chapter will aim to provide a review of the evidence regarding the relationship between stress and eating behavior, with emphasis on aspects of altered eating patterns in the presence of stress.

Stress Responses

In 1950, Hans Selye (1950) published an influential manuscript and critically stated that "anything that causes stress endangers life, unless it is met by adequate adaptive responses; conversely, anything that endangers life causes stress and adaptive responses. Adaptability and resistance to stress are fundamental prerequisites for life, and every vital organ and function participates in them." It means that there are

adaptive intelligent responses which help people to deal and balance stress so that they can function and live a healthy everyday life. Stress can be caused by various situations which cause an emotional or physiological challenge. These can be broadly divided into environmental or psychological stressors.

There are three main forms of stress: acute and current, acute and episodic, or can be ongoing on daily basis and chronic. Acute stress can be caused by short-term event such as a threat to personal safety or getting involved in an interpersonal conflict (Yau and Potenza 2013). The acute episodic stressors are frequent brief events such as work deadlines, and the chronic stressors are experienced with job pressures, unemployment, family struggle, and mistreatment of physical or psychological nature (Torres and Nowson 2007). These stressors, particularly when they become prolonged and intense, will dampen the adaptive response to stress (stress-related homeostasis) and contribute to disease predisposition such as increased risk and delayed recovery of infectious conditions (Yau and Potenza 2013). It has been shown that chronic stress and mental illness can increase inflammation via biological pathways of automatic nervous system sympathetic activity, oxidative stress, transcription factor nuclear factor-κB activation, and pro-inflammatory cytokines (Kiecolt-Glaser 2010). This type of observations has triggered a vast scientific interest to explore further and get an insight into the relationship between stress, health, and well-being across the life span.

Physiology of Stress

Stress can disrupt the physiological homeostasis of our bodies and brains, ensuing activation of neural and endocrine mechanisms to re-establish homeostasis. This stress response is highly adaptive, with two primary interacting pathways: the autonomic nervous system (ANS) and the hypothalamic-pituitary-adrenal (HPA) axis. During periods of acute stress, the sympathetic branch of the ANS (known as the sympathetic nervous system (SNS)) is commonly activated. Signals are sent through the autonomic nerves to the adrenal glands, which responds by releasing catecholamine's epinephrine (adrenaline) and norepinephrine (noradrenaline) into the circulatory system. These hormones then circulate the body and bring on several physiological changes, such as increased heart rate, and adjust blood vessel diameters to redirect blood flow to the muscles, heart, and brain. The HPA axis, a group of hormone-secreting glands from the nervous and endocrine systems, stimulates the production of glucocorticoids (GCs) during times of stress. Corticotropin-releasing factor (CRF) is secreted from the paraventricular nucleus (PVN) of the hypothalamus, which in turn occupies receptors at the anterior pituitary, releasing adrenocorticotropic hormone (ACTH). ACTH triggers the production of GCs such as cortisol (or corticosterone in rodents) in the adrenal cortex. These GCs have numerous effects that help the body to deal with stress, primarily mobilizing energy by promoting gluconeogenesis in the liver. This increased supply of glucose, with the increased blood flow to the muscles due to SNS activation, aid survival. Together, the ANS and HPA axis interact to produce a state of preparedness, known as the

"fight-or-flight" reaction. Activities which conflict with this evolutionarily adaptive response to survive are typically inhibited. These include food intake, digestion, and reproduction. For instance, elevated levels of noradrenaline are known to result in reduction of appetite in obese patients (Lean and Finer 2006). Additionally, the physiological responses to acute stress such as slowed gastric emptying and inhibition of blood from gastrointestinal tract to muscles might be related to reduce food intake in the short term (O'Connor et al. 2021). Thus, explaining the stereotypical stress response of suppression of appetite and food intake.

Stress can therefore activate both physiological and behavioral responses which influence health outcomes; however, a stress-eating paradox emerges. As discussed, by producing a physiological response to homeostasis, there is a disruption of eating behavior in terms of inhibition, but this is counterintuitive given that increased eating is also associated with the stress (Torres and Nowson 2007). In humans, individual differences in food intake response are similarly noted, with stress leading to both under and overeating; this will be discussed further later in the chapter. Though the relationship between stress and eating behavior is complex, and little is known about what determines the direction of eating, physiological changes appear to be an underling mechanism. The HPA axis has shown to have a particular role in this relationship due to sharing the same neuroanatomy (structure and function of the nervous system) with the pathways that regulate food intake. Thus, each system can influence each other in stimulating a response.

Role of the HPA Axis and Glucocorticoids in Eating Behaviors

The HPA axis is an integrated system where GCs negatively feedback to the areas of the brain such as the hypothalamus and hippocampus, inhibiting the continued production. This effectively shuts down the stress response, thus keeping concentration stable and limiting the duration of GC exposure. GCs also act on the hypothalamus to stimulate appetite by interacting with several appetite regulators (Dallman et al. 2004). Therefore, a GC-mediated stimulation of eating behavior during stress recovery serves to replace the energy used when dealing with the stressful event (Sominsky and Spencer 2014). However, under conditions of chronic stress, where there is repeated or sustained activation of this physiological stress response, there are elevated basal and stress-evoked GC levels. Indeed, high circulating cortisol levels have been found in people who live with chronic stress. It is these high levels of GCs which have been linked to disordered eating behaviors, affecting the amount of food eaten, as well as the types of foods that are chosen, with heightened preference to hyperpalatable energy-dense foods.

In terms of increased appetite, GCs upregulate neuropeptide Y (NPY) and agouti-related peptide (AGRP) by increasing AMP-activated protein kinase (AMPK) signaling (Shimizu et al. 2008). These neuropeptides are considered orexigenic, stimulating appetite (Luo et al. 2011). The increase in GCs has been additionally implicated in dysregulation of appetite-related hormones such as leptin. While Leptin is known as an appetite suppressant which GC stimulates to be

released from adipose tissue; GCs also reduce the brain sensitivity to leptin, contributing to leptin resistance (Jéquier 2002). This therefore results in the converse effect by limiting appetite suppression. Furthermore, the loss of leptin signaling increases the expression of NPY and AGRP. This disruption in the balance between leptin and NPY, enhancing the activity of the latter, increases appetite and food intake especially in overweight and obese people (Björntorp 2001).

Additionally, GCs also influence the insulin, a metabolic hormone which acts at the hypothalamus by inhibiting orexigenic and exciting anorexigenic neurons. While at acute levels GCs stimulate insulin secretion from the pancreas (Strack et al. 1995), and therefore have an appetite-suppressant effect, during chronically activated levels, GCs have been shown to exert diabetogenic effects by interfering with number of mechanisms leading to GC-mediated insulin resistance. Namely, GCs promote proteolysis, lipolysis, free fatty acid production, and in the liver increased steatosis (Ferris and Kahn 2012). Much like leptin, GCs therefore have an intermediate role between insulin sensitivity and increased appetite by contributing to a reduced ability of insulin to inhibit NPY and AGRP. As a result, elevated stress-induced GCs lead to impaired sensitization of satiety signals.

GC relationship with insulin can also offer an explanation to the increase in preference for energy-dense palatable foods. Evidence from experimental animal studies shows that when given a choice, under stressed conditions rats prefer foods that are high in fat and sucrose, suggesting energy-dense food intake is relative to a corticosterone-insulin interaction (la Fleur et al. 2004; Warne et al. 2009). Corticosterone was shown to dependently provoke dose-related increases in total energy intake, while the food source choice the energy was derived from was influenced by insulin levels. Therefore, working both independently and interactively to regulate energy balance and intake. Humans similarly make stress-related changes in food choice to high fat and sugary foods (Oliver et al. 2000) even in the absence of hunger (Rutters et al. 2009). It is also suggested that the "hunger" hormone ghrelin potentiates the motivation for food reward and wanting for high-calorie foods which can be induced by stress (Liu 2015). There is some preliminary evidence to suggest that higher chronic stress, cortisol levels, and higher ghrelin levels were predictive of food cravings and weight gain over 6 months in overweight people. Future rigorous studies are needed that can measure concurrently stress hormones (catecholamines and cortisol), appetite-related hormones (ghrelin, leptin, insulin), and eating behavior in randomized controlled trials to elucidate the causal relationship of stress and eating behavior to fully understand their interactive role in obesity and related metabolic and mental illness. Furthermore, more research is needed to investigate whether diet-based interventions targeting reduction of stress and maintenance of normal cortisol response might be useful strategies in prevention of stress in high-risk groups in the community.

Overall, GCs have a significant influence on neurons and hormones in homeostatic regulation of hunger, chronic stress leading to increased appetite and an impaired capacity to inhibit eating. Additionally, chronic stress has been related to heighted preference for hyperpalatable, energy-dense foods, high in sugar and fat.

HPA Axis and Dopamine Reward Pathway

The mesolimbic dopaminergic system is a key component of reward processing, in which the neurotransmitter dopamine is used to communicate to the different regions in the brain involved in reward and pleasure. When exposed to or expect to receive a rewarding stimulus, dopamine neurons in the ventral tegmental area (VTA) are activated. These project to the nucleus accumbens (NAcc), amygdala, prefrontal cortex (PFC), and other forebrain regions. The NAcc is associated with motivation and reward, the amygdala with emotion, and the PFC with decision-making. The HPA axis has been linked to this system having direct and indirect effects on dopamine neurons, overriding the homeostatic regulation of appetite and food intake (Schellekens et al. 2012).

High GC levels, through administration of corticosterone in rats, significantly increased brain stimulation reward and positively correlated to dopamine transporters binding in the NAcc shell (Barr et al. 2000). A GC and dopamine interrelationship is also seen in humans where stress-induced cortisol levels proportionally enhanced dopamine release in the ventral striatum, which contains the NAcc (Wand et al. 2007). Activation of dopamine neurons in this region associated with motivation and "wanting" has been implicated in behavioral guidance toward natural rewards, such as food and water (Ikemoto and Wise 2004), and is believed to be similar, if not identical, to drug rewards (Carelli 2002).

GCs exert their effects via binding to two types of receptors: mineralocorticoid receptors (MR) and glucocorticoid receptors (GR). MR has a high affinity for GCs and is nearly fully occupied, whereas GR has a lower affinity for GCs and so is occupied when GC concentrations are high, such as after stress. The interaction between GCs and dopamine is suggested to be GR-dependent as administration of GR antagonists induced a drop in dopamine levels, whereas MR antagonists had no effect (Marinelli et al. 1998). This interconnectivity between the dopamine and stress suggests an important role for GC-activated GR in dopamine-related emotional behavior.

Energy regulators leptin and insulin (which are associated with the HPA axis as earlier discussed) can also target the dopamine neuron system due to their broad expression of receptors in several brain regions. This includes the VTA, a key structure in the reward processing pathway (Figlewicz et al. 2003), serving to mediate the effects of these hormones on reward-seeking behavior. Intraventricular insulin and leptin in rats were shown to decrease sucrose self-administration and reverse place preference conditioned with high-fat diet, suggesting a role in modulating reward-related feeding (Figlewicz et al. 2004, 2006). Thus, insulin and leptin influence the brain reward pathway, decreasing the rewarding effect of food through decreased dopamine output.

However, studies in rats show obesity reduces sensitivity to insulin through decreased adipose signals or resistance at receptor level (Ikeda et al. 1986), and therefore this decrease in the hedonic value of food discussed above is impaired. Additionally, evidence also shows that consumption of hyperpalatable foods may negate chronic stress-induced inhibition of dopamine release. This shows that the

hedonic and emotional aspects of feeding can affect food behaviors as well as the caloric and nutritional value of food.

Hedonics and Addictive Properties of Food

Alongside motivation to eat, stress-generated reward system sensitization can lead to excessive intake of hyperpalatable food. Research into food intake has shown there is a significant overlap with substance addictions on the reward center, with both pathways also driven by negative reinforcement. Stress, particularly uncontrollable stress, is a potent reinforcement type that promotes acquisition of drugs of abuse (Sinha 2008).

In regard to eating behavior, the consumption of high-fat, high-sugar diets and activity of the HPA axis have been shown to be influential on each other. Animal studies provide evidence that stressed rats with ad libitum access to calorically dense lard and sucrose displayed reduced ACTH responses compared to those with access to normal diet only (Pecoraro et al. 2004). This is described as "self-medication" with food. Additionally, in this 2 × 2 study, the same rats also increased the proportion of hyperpalatable foods consumed compared to their non-stressed controls. Similar reduction in chronic stress responses was found when increased plasma corticosterone, hypothalamic CRH, and reduced hippocampal GR expression were normalized after consuming palatable high-fat diets (Maniam and Morris 2010). Hyperpalatable foods also have the ability to activate the reward pathway through both the fast sensory inputs and post-ingestion consequences such as raising glucose concentration in the blood and brain as well as adiposity (Volkow and Wise 2005).

Moreover, addiction-like neuroadaptive responses in reward pathways have been observed. For example, rats showed a decreased dopamine release in the NAcc after deprivation following a high sucrose diet, in comparison to those on an unrestricted diet (Avena et al. 2008). Such neuroadaptations can lead to increased compulsive eating behaviors and drive to eat, with accumulating evidence that hyperpalatable food has properties that promote dependence. Animal studies have provided evidence that rats fed hyperpalatable, high-sugar, and high-fat diets developed patterns of increased consumption as well as withdrawal symptoms when returned to normal diet (Johnson and Kenny 2010; Avena and Hoebel 2003; Lutter and Nestler 2009). These food-seeking behaviors are also seen in humans. After a monotonous diet, cues of favorite foods produced greater activation of the hippocampus, insula, and caudate, three areas reported to be involved in drug craving (Pelchat et al. 2004).

An explanation for the seemingly "addictive" property of palatable food comes from evidence that it can cause a repeated increase in dopamine, similar to that of substance misuse, and endogenous opioid dependence (Rada et al. 2005; Colantuoni et al. 2002). Endogenous opioids terminate the HPA axis stress response as a defensive mechanism against its detrimental effects (Kreek and Koob 1998). In terms of opioid's impact on eating behaviors, rats injected with opioids responded by overeating, and in contrast, when injected with an opioid antagonist, rats suppressed overeating of hyperpalatable food (Kelley et al. 2000; Apfelbaum and

Mandenoff 1981). Thus, opioids and palatable food engage in a bidirectional relationship such as that palatable foods can sustain opioid release and opioid release can increase palatable food intake. Overall, with food shown to provide reward, and hyperpalatable foods offering short-term pleasure and negative reinforcement, it may motivate stress-related eating as a way to regulate stress responses.

Stress and Eating Patterns

Indirectly stress can lead to behavioral changes, and these include eating too much or eating unhealthily, starting or increasing drinking and smoking (Gonzalez and Miranda-Massari 2014). It is widely accepted that stress can change eating behavior and trigger irregular eating patterns; however, these associations are mainly relying on cross-sectional studies, and underpinning mechanism has not been fully unraveled. Additionally, the relationship between stress and eating behavior is not simple and has been described as bidirectional. Eating pattern is considered healthy when people consume regular meals and snacks of varied dietary composition which enables them to maintain healthy body mass over time and prevent diet-related chronic disease. Eating patterns and food choices are influenced by a variety of factors which relate to socioeconomic status, culture and environment, gender and age demographics, health literacy, education attainment, overweight and underweight status, and psychological stress. The relationship between stress/negative mood and eating behavior has been studied in dietary studies looking into behavior outcomes such as snacking, choices of specific foods, overall energy consumption and diet patterns/quality, and psychological stress outcomes such as perceived stress and perceived negative affect/mood (Khaled et al. 2020a).

In terms of the impact of stress on food consumption, whether stressed people will eat more than usual amount of food intake or undereat seems to depend on the stressor severity (acute vs. chronic). There seems to be a tendency for eating less as the severity of stressor is increasing in humans (Torres and Nowson 2007). There is some evidence from longitudinal and cross-sectional studies that chronic life stress will lead people to choose hyperpalatable and comfort foods such as take-away food and sweet, high-fat, and savory snacks. Sometimes the consumption of these energy-dense foods occurs in the absence of true homeostatic hunger; this is when stress can be linked with hedonic overeating and weight gain in the long term (Wardle et al. 2011). When the effect of stress on food consumption and selection of food is examined in artificial laboratory environment, evidence is still scarce, and the stress induced in artificial lab-setting has produced equivocal effects on eating behavior change, all of which will be discussed in depth later in this chapter.

The Impact of Eating Patterns on Stress and Mood

The therapeutic role of high-quality diets and healthy nutrients in management of stress and stress-related mental illness is an emerging area in the field of nutritional

psychiatry. Different national and international organizations (Mental Health Foundation 2017; Jacka et al. 2014) advocate that healthy dietary patterns, such as the Mediterranean diet (MD), which includes foods of anti-inflammatory (omega 3 long-chain fatty acids in fish), antioxidant (polyphenols in fruits, legumes, olive oil), and healthy gut microbiota properties (dietary fiber, fermented dairy), can exert metabolic and brain neuroendocrine benefits to preserve mental health (Firth et al. 2020a). The International Society for Nutritional Psychiatry Research has published a consensus report which states that lifestyle factors such as diet should be modifiable targets for management of stress and related comorbidities (Sarris et al. 2015). Importantly, diet modification can be a noninvasive and cost-effective prevention and treatment strategy for mental ill-health.

Our recent meta-analysis of epidemiological studies found an association between poor diet quality (i.e., high in saturated fat, sugar, and salt and low in fiber, fruit, and vegetables) and stress in women of childbearing age (Khaled et al. 2020a). We have also corroborated further these findings with new evidence. Our previous work highlighted that the more childbearing women adhered to a high-quality diet, i.e., MD, the less stressed they felt. Conversely, consumption of a Western-style diet (highly processed food and refined grains), common in childbearing-aged women, was associated with higher stress (Khaled et al. 2020b, 2021).

Compelling evidence suggests that psychological stress and low mood can be somewhat preventable through "whole diet" improvements, though very little is known about how a high-quality whole-food diet can influence stress and consequently mood; the molecular mechanisms involved are not fully understood (Firth et al. 2020b). A recent meta-analysis on healthy dietary indices demonstrated that good adherence to healthy diet patterns and in particular to a MD pattern seems to decrease the risk of depression ($N = 36{,}556$, OR = 0.67, 95% CI: 0.55–0.82, I2 = 33.1%), with low heterogeneity between studies (Lassale et al. 2018). A large cross-sectional study ($n = 1634$, aged 18–65 years, 68% females, from the Netherlands) has investigated whether this association can be attributed to some MD food components or to all MD food groups. When looking into food groups in isolation, they found that non-refined grains, vegetables, and to some extent moderate alcohol intake appeared to be related to lower depression and anxiety. A low-quality diet as a whole was linked to higher depression symptoms (Gibson-Smith et al. 2020). The findings of this study can be possibly relatable to other north European populations with comparable food consumption patterns. For instance, fish intake in the Netherlands is only 53 g/week, and the majority (75%) is white fish (Gibson-Smith et al. 2020), and in the United Kingdom, mean consumption of oily fish was equivalent to 56 g/week in adults (NDNS 2019; Public Health England 2022). This is deemed well below the recommended one portion (140 g) of oily fish per week in all age groups. A recent meta-analysis of randomized controlled trials demonstrated the efficacy of dietary interventions in improving low mood in nonclinical depression. These dietary interventions overall had comparable aims, i.e., to replace the consumption of junk foods (refined, processed, and high in fat, sugar, and salt foods) with consumption of healthier options such as vegetables and pulses, thus increasing

dietary quality overall (Firth et al. 2019). Several RCTs have started to also highlight the benefits of MD on reducing depressive symptoms on those with clinically diagnosed depression (Jacka et al. 2017; Parletta et al. 2017; Francis et al. 2019). The proposed mechanism appears to be complex but tends to implicate the interactional effects of anti-inflammatory and antioxidant foods and nutrients of a classical anti-inflammatory dietary pattern such as the MD (Marx et al. 2021).

The relationship between chronic low-grade inflammation and stress is widely reported, and high circulating levels of pro-inflammatory cytokines have been found in people with elevated stress or depressive symptoms compared to healthy counterparts (Dowlati et al. 2010). Pro-inflammatory cytokines, such as interleukin (IL)-1β, IL-1 receptor antagonist (RA), IL-6, tumor necrosis factor (TNF)-α, and interferon (IFN)-γ, are part of the innate immune response. Both acute and chronic stress can cause an inflammatory response, but the exposure to chronic stress in particular will challenge endocrine and immune function and cause pathophysiological abnormalities such as chronic low-grade inflammation. If this inflammation is sustained in the long term, then it might contribute to the progression to depression. Indeed, pro-inflammatory dietary patterns such a Western diets are associated with a significantly higher prevalence of depressive symptoms, even among those without diagnosed mental disorders (Firth et al. 2019).

The MD is suggested to have an optimum nutrient profile that can offer protection from pro-inflammation and inflammation (Simopoulos 2008) and thus might prevent progression to stress and related mental disorders. Vegetables and fruits, non-refined grains, pulses, nuts, and olive oil are high-quality sources of minerals, fiber, alpha-linolenic acid (i.e., 18:3 *n*-3 polyunsaturated fatty acids (PUFA)), oils and vitamins, and antioxidants. Some vitamins (e.g., folic acid), minerals (e.g., zinc), essential fatty acids (such as long-chain *n*-3 PUFA), and polyphenols which are found in abundant amounts in plant-based foods could act in synergy to offer antioxidant and anti-inflammatory benefits. Antioxidants such as polyphenols can downregulate reactive oxygen species (free radicals) and thus reduce oxidative stress, which was found to be increased in people with chronic metabolic disease and mental illness (Jiang et al. 2021).

The anti-inflammatory profile of a MD is importantly attributed to the moderate consumption of oily fish and almost ideal ratio of omega-6 (*n*-6) to omega-3 fatty (*n*-3) acids of 2:1 of the diet. Current Western diets are characterized by a ratio of around 15:1, reflecting lack of *n*-3 fatty acids and surplus amount of *n*-6 fatty acids (Simopoulos 2008). The *n*-3 and *n*-6 PUFAs compete for the same enzymes in similar metabolic pathways; therefore, a balanced dietary intake is important for metabolic health. Increased intake of dietary *n*-6 fatty acids from refined plant oils (corn and sunflower) will be metabolized to arachidonic acid (AA) and AA-derived *n*-6 eicosanoids which increase production of circulating pro-inflammatory cytokines. On the other hand, *n*-3 PUFAs from diets high in fish, fish oil, and walnuts can reduce the production of AA metabolic, pro-inflammatory products (Kiecolt-Glaser 2010). Epidemiological studies show that people who consume a healthy diet which has higher levels of *n*-3 PUFAs as well as lower *n*-6/*n*-3 ratios have lower pro-inflammatory cytokine production and greater mood compared to counterparts

with at-risk mental health (Berger et al. 2017; Zhang et al. 2020). Additionally, marine *n*-3 PUFAs can downregulate pro-inflammatory cytokines (e.g., TNF-α) at molecular level and reduce postprandial inflammation typical after consumption of high-fat meals, thus blunting the pro-inflammatory potential of the Western diet (Calder 2015). Interestingly, olive oil consumption, the main source of fat and monounsaturated fatty acids (MUFAs) in the MD, has been found to associate with greater mood state and suppression of cortisol secretion which might indicate potential role of olive oils on reducing stress in the short term. This observation requires further corroboration with rigorous evidence (Mitsukura et al. 2021).

The low glycemic load (GL) of a MD pattern might also contribute to maintenance of low stress levels. A low GL diet supports a steady regulation of glucose homeostasis compared to frequent and rapid changes in blood glucose levels seen in unhealthy dietary patterns, such as the Western diet. A diet-induced hypoglycemia will trigger the autonomic nervous systemic to secrete compensatory stress-related hormones (cortisol, catecholamines, glucagon). Western diets with high content of refined grains and sugars will tend to stimulate repeatedly this metabolic and hormonal profile, therefore generating a chronic stress response.

The gut microbiome and its relationship to stress and mood present a cutting-edge research area. There is growing evidence that acute and chronic psychosocial stress might disrupt the microbial diversity and composition of the gut microbiota and consequently increase the pro-inflammatory response, influencing physical and mental health (Hantsoo and Zemel 2021). The gut microbiome is largely modified by diet composition. The MD pattern is known to promote a healthy gut microbiota because of its high content in fermented dairy foods and plant-based dietary fibers. All these foods are natural probiotics and prebiotics and can "feed" the gut microbiota with healthy bacteria and stimulate the production of beneficial by-products (e.g., short-chain fatty acids (SCFAs), neurotransmitters). Serotonin is a neurotransmitter produced in the gut and is known to mediate healthy mood via the gut-brain-axis system (Marx et al. 2021). More research is needed in humans to investigate the role of gut microbiome as a key moderator in the association between stress and inflammation.

The causal relationship between dietary patterns and risk of stress is not fully elucidated. Nevertheless, health promotion approaches can aim to raise the public's awareness and knowledge about the mental health benefits of healthy eating patterns and the detrimental impact of unhealthy meals. In this way, individuals can be empowered to adopt themselves a healthy lifestyle as a self-management approach to mitigate the risk of stress and low mood.

Individual Differences and Disordered Eating

There has been much research demonstrating the two-way relationship of stress on food intake, with some individuals increasing energy intake and others reducing their consumption in reaction to stress. Several studies have identified that almost equal proportions of individuals increase their food intake than decrease their food

intake. However, other studies suggest different levels of under- or overeating in reaction to stress. This issue of individual differences has attracted much research attention.

Stress and Undereating

Back in 1915, a book by Walter Cannon (1915), *Bodily Changes in Pain, Huger, Fear and Rage*, introduced the concept of reduced dietary intake in reaction to perceived stress. When conducting animal studies as a medical student, he discovered that when cats were frightened or alarmed, their digestion slowed or halted. In contrast, when the cats were comforted, their gastrointestinal activity returned to normal. He began to identify the physiological responses of stress in animals, focusing on the reactions of the SNS, such as increases in heart rate, rapid breathing, and the elevation of glucose in the blood stream. It is widely understood that in humans this "fight-or-flight" biological stress response was useful in evading predators. In response to threat, the body halts digestion and appetite signals, reallocating energy to focus on fighting or fleeing. However, our bodies still respond to stress in this manner, even when there is no serious threat.

Researchers have investigated the underpinning of undereating in humans in reaction to stress. However, different studies suggest varying rates of undereating in response to stress. For example, some studies suggest that equal number of normal eating individuals tended to decrease their energy intake than increase their energy intake in reaction to stress. A key study by Oliver and Wardle (1999) indicated that 42% of individuals self-reported that they ate less than usual in comparison to 38% who reported that they eat more than usual during periods of stress. However, other research reports much higher prevalence rates, suggesting that up to 70% of individuals may experience reduced appetite (Krumbacher and Meyer 1963) and up to 55% may eat less in response to emotional stress (Popper et al. 1989). This also indicates that there are two mechanisms that may be affected in reaction to stress, the reduced motivation to eat and the behavior of reduced dietary intake, and that reduced appetite may not necessarily correlate with reduced calorie intake.

When comparing underweight individuals to normal weight and overweight groups, it has been reported that those who were underweight ate less than their counterparts in times of stress. However, the underweight individuals tended to eat more during positive emotional states in comparison to the other groups, but this did not compensate for the calorie deficit during stressful periods. Geliebter and Aversa (2003) summarized that undereating during stressful states may contribute to the low body weight of the underweight individuals. More recently, a study conducted in the United States investigated eating habits and stress in reaction to the COVID-19 pandemic (Khubchandani et al. 2020). They found that one in ten participants engaged in unhealthy eating practices during the early stages of the pandemic in 2020. Of the individuals who changed their eating behavior, 51% reported undereating in reaction to stress: engaging in skipping meals, restricted eating, or fasting. The individuals who reported these unhealthy eating habits due to the stress

of the pandemic reported significantly higher perceived stress levels, indicating a cyclic pattern.

Stress and Overeating

As explained, there is ample evidence that a proportion of individuals tend to undereat in reaction to stress. However, systematic review evidence supports the notion that emotions, including stress, consistently elicit increased food intake (Devonport et al. 2019). Some studies have reported that twice as many participants increased than reduced their food intake (Kandiah et al. 2008). Alternatively, other research demonstrates that acute stress results in decreased calorie intake, whereas chronic, long-term stress results in increased consumption. However, it is not just overall calorie intake that can change in reaction to stress; in addition, it has been demonstrated that people tend to choose different kinds of food too. As previously discussed, hyperpalatable foods are thought to induce pleasure and reward, even triggering addiction or compulsion (de Macedo et al. 2016).

Studies have also demonstrated increased preference for energy-dense foods and a shift toward consuming more "snack-type foods" in times of stress (Torres and Nowson 2007). Specifically, individuals display a preference for sweet, salty, or high-fat snack food (Adam and Epel 2007), namely, chocolate, crisps, and ice cream (Costarelli and Patsai 2012). In turn, individuals also tend to report a decrease in their consumption of "meal-type" foods, such as meat, vegetables, and fruit (Wansink et al. 2003). However, the reasons underlying these choices are not confirmed. It is unclear the extent to which the biological reward pathway is responsible for the increased consumption of snack-type foods, meaning individuals are attempting to regulate their stress through the consumption of these foods. Or, alternatively, individuals may simply opt for snack-type foods due to time constraints and convenience during stressful periods. It is also unclear whether this equates to higher overall calorie intake and therefore the likelihood of weight gain. This evidence indicates that food choice needs to be considered in addition to energy intake to understand the stress-eating behavior relationship, especially due to the known role these hyperpalatable foods may play in the development of obesity.

On the other hand, research that focuses on emotional eating supports the notion that "emotional eaters" do seek these hyperpalatable foods to manage their negative emotions. Emotional eating is a term used to explain how individuals attempt to regulate their emotions by increasing food intake (Macht 2008). Emotional eaters might engage in increased eating as a pleasuring activity that helps to distract from the negative feelings associated with stress, but it is thought to be explained by high-cortisol reactions to stress in emotional eaters (Epel et al. 2001). In addition, emotional eaters are more likely to consume more sweet and high-fat foods in response to stress in comparison to nonemotional eaters (Oliver et al. 2000). Emotional eaters also tend to report more intense cravings and higher consumption (Macht and Mueller 2007). Emotion-related eating is of interest to researchers due to its confirmed association with weight gain and the development of obesity

(Torres and Nowson 2007). Coping with stress through eating has been highlighted as a significant barrier to healthy eating (Bennett et al. 2013) and maintaining a healthy weight.

This tendency to overeat in times of stress appears to be particularly evident in individuals who are restrained eaters. Research defines restrained eaters as those who continually limit their overall calorie intake by dieting chronically to manage or maintain their body weight. Paradoxically, these restrained eaters tend to be overweight or obese due to sporadic episodes of overeating triggered by stress (Herhaus and Petrowski 2021). Much cognitive attention and demand is involved in maintaining this constant state of dieting, exerting constant control over one's eating behavior. In research where brain region activity was studied, weaker cognitive control and conflict monitoring has been identified in unsuccessful restrained eaters (Zhang et al. 2021). It is understood that successful restrained eaters tend to display very high levels of self-awareness, constantly evaluating themselves in comparison to perceived standards and expectations, and are often highly concerned about how they are viewed by others.

According to restraint theory (Polivy and Herman 1985), these restrained eaters consistently exhibit this counter-regulation behavior, meaning that they consistently eat little and avoid the urge to eat, but when they have a temporary lapse in control, this will trigger overeating. In comparison, non-dieters maintain normal regulation in these situations. Herman and Polivy have conducted much research into the behavior of restrained or restrictive eaters, finding that when calm, these individuals maintain their low dietary intake. However, when a disinhibitor disrupts their usual restraint, they release their suppressed eating and tend to overeat. A disinhibitor could be alcohol, depression, or stress; these factors distract them from their usual chronic restraint, diminishing impulse control. However, this was not always the case. One such example is an experiment conducted by Heatherton et al. (1993), where restrained eaters were asked to complete a puzzle. One group of restrained eaters who failed the puzzle was asked to evaluate their performance by watching a videotape of themselves failing the task. This group of restrained eaters did not experience disinhibited eating after the task as other groups did. The researchers surmised that this was due to maintaining their high level of self-awareness while watching the video feedback; therefore, they remained restrained in their eating behavior.

The research consensus is that overeating or binging when experiencing stress can be a paradoxical consequence of restrained eaters' constant attempts at restricting their calorie intake. Further research showed that when restrained eaters are stressed, they tend to overeat the foods that they normally avoid to maintain their body weight, such as high calorie, high fat, or sugar snack-type foods. Kandiah et al. (2008) confirmed that highly restrained eaters tend to choose significantly more types of sweet foods and beverages in times of stress than low-restrained eaters. Restrained eaters are also reported to experience intense guilt when giving into food cravings (Macht and Mueller 2007) and are said to be more punishment sensitive, engaging in behaviors to punish themselves to avoid undesirable outcomes, such as weight gain (Jonker et al. 2021). This indicates the

potential negative psychological consequences of a restrained eater's lapses of self-control and how this can consequently feed into a cycle of self-punishment and continual restrained eating.

Coping Strategies

How one chooses to deal with stress can be a major determinant of health outcomes. Prolonged overconsumption of unhealthy or "comfort foods" in times of stress may contribute to the development of obesity, and studies have found that they do not provide comfort beyond that of other foods or no food at all. On the other hand, it is important to consider the physical and mental health problems that one could face due to chronically decreasing food intake in times of stress. Coping mechanisms can be employed to reduce these irregular stress-eating patterns. Coping refers to the behaviors in which individuals engage in to manage, tolerate, reduce, or rectify stressors including emotion-focused strategies, problem-focused strategies, or avoidance behaviors. Emotion-focused methods of coping tend to focus on managing or relieving the emotional reaction to the stressor, whereas problem-focused strategies attempt to tackle the problem, including seeking instrumental support, planning, or inputting boundaries and time management. Avoidance coping encompasses activities individuals engage in to avoid dealing with the stressful situation itself. It is important to note that emotion and avoidance coping is not always disadvantageous. Avoidance is considered maladaptive as it does not tackle the stressor in question; however, it can be useful to temporarily relieve the negative emotions.

Coping is fundamental to understanding how individuals deal with stress and the long-term consequences this can have on physical and mental health, specifically in disordered eating. Review evidence suggests a mediating factor between stress and subsequent unhealthy eating behavior (over- or undereating) may be the individual's learned coping strategies (Ball and Lee 2000). It is well understood that those with eating pathology have more difficulty in managing stress and display maladaptive coping techniques, such as avoidance and rumination (Rawal et al. 2010). Recent research supports the link between repetitive negative thinking (also known as rumination) and eating problems in both clinical and nonclinical samples. Therefore, coping skills are an important component in the treatment of eating pathology (Vanderlinden et al. 2007). It is well established that more adaptive, problem-focused techniques can be learned and improved when individuals are provided resources to promote more effective coping responses. Such methods that might be useful in breaking the link between stress and unhealthy eating behaviors include mindfulness practice (Hernando et al. 2019) or therapy based on tackling rumination (Kaplan et al. 2018).

Applications to Other Eating Disorders

Previous research has shown that individuals with EDs have difficulties in self-regulating and coping with stress. In this chapter, we discussed potential psychological interventions to strengthen ways of coping with stress and mitigate the tendency to engage in unhealthy eating patterns, including mindfulness practice or therapy based on tackling rumination or maladaptive repetitive thought. Mindfulness has been widely implemented within research into the treatment and prevention of EDs. Systematic review evidence from Beccia et al. (2018) recommends mindfulness as an evidence-based strategy to reduce ED risk factors and increase protective factors, such as self-esteem. Several EDs have been associated with high levels of ruminative thoughts and preoccupation with body shape and weight. Therapy that addresses rumination has been proven an effective non-pharmacological intervention in other psychiatric disorders. Further research in larger clinical samples of eating disorder sufferers is required to fully understand the potential benefits of this type of psychological intervention.

Mini-Dictionary of Terms

- **Adrenocorticotropic hormone:** a polypeptide tropic hormone of HPA axis, which regulates cortisol production.
- **Agouti-related peptide:** an energy balance peptide, increasing food intake when stimulated.
- **AMP-activated protein kinase:** enzyme in cellular energy homeostasis which regulates diverse metabolic pathways in multiple peripheral tissues.
- **Autonomic nervous system:** it comprises two parts, the sympathetic and para-sympathetic nervous system, and controls involuntary physiological processes.
- **Catecholamine:** hormones released in response to physical or emotional stress consisting of dopamine, adrenaline, and noradrenaline.
- **Corticotropin-releasing factor:** a peptide hormone with several actions. In the HPA axis, it stimulates ACTH release.
- **Cytokines:** small proteins released from activated cells of the immune system influencing the nervous system activity, mediating and regulating immunity, inflammation, and hematopoiesis.
- **Eicosanoids:** the compounds derived from arachidonic acid or other polyunsaturated fatty acids of 20-carbon length.
- **Endocrine system:** network of glands that make hormones.
- **Glucocorticoids:** corticosteroids involved in metabolism with anti-inflammatory and immunosuppressive effects.
- **Hypothalamic-pituitary-adrenal axis:** the interaction between the hypothalamus, pituitary gland, and adrenal glands.
- **Mesolimbic dopaminergic system:** connects the VTA in the midbrain to the ventral striatum of the basal ganglia in the forebrain, the reward pathway.
- **Neuropeptide Y:** stimulates increased appetite and food intake.

- **Oxidative stress:** imbalance between the reactive oxygen species (free radicals) and antioxidant defenses.
- **Transcription factor nuclear factor-κB:** regulates genes responsible for both the innate and adaptive inflammatory and immune responses.

Key Facts

- Stress prevalence statistics show nearly three quarters of adults report feeling stressed, with elevated levels in young adults.
- Stress has been found to be a key element in developing adverse health outcomes, mental health problems, and behavioral change such as altered eating patterns.
- The "flight-of-sight" stress response is characterized by increases in heart rate, rapid breathing, blood glucose levels, and decreased digestion and appetite signals.
- Food intake response is similarly noted when stressed; 42% self-reporting eating less and 38% self-reporting eating more than usual.
- The relationship between stress and eating behavior is complex and bidirectional, although the physiological changes and type of stress appear to be underling mechanisms.
- When stressed there is heighted preference for hyperpalatable, energy-dense foods, high in sugar and fat, which have properties that promote dependence and neuroadaptive responses much like drug addictions.
- Pro-inflammatory dietary patterns can exacerbate symptoms, while anti-inflammatory dietary pattern such as the Mediterranean diet reduces stress.

Summary Points

- High stress levels can damage health when they become chronic and are not resolved.
- Glucocorticoids (GCs) stimulate eating during stress recovery to replace energy used during a stressful condition.
- High levels of GCs have been linked to disordered eating behaviors.
- High circulating levels of pro-inflammatory cytokines are found in people with elevated stress or stress-related mental illness.
- Mediterranean dietary pattern can offer optimum nutrient profile to protect from pro-inflammation and inflammation.
- Psychological stress and low mood could be preventable through "whole diet" improvements.

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5 Gene Variants Involved in the Etiopathogenesis of Eating Disorders: Neuropeptides, Neurotransmitters, Hormones, and Their Receptors

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Contents

Introduction 77
Family Studies 77
Candidate Gene Association Studies 78
Genome-Wide Association Studies 79
Gene Variants 79
Serotonin Pathway 80
Brain-Derived Neurotrophic Factor Gene 81
Dopamine Receptor Family 81
Opioids and Their Receptors 83
Endocannabinoid Pathway 83
Appetite Regulatory System 84
Other Genes 86
Rare Genetic Variants 87
Conclusions 88
Summary Points 88
References 89

Abstract

Eating disorders have a deep social, mental, and physical impact and multifactorial origins, but the strong genetic component is universally corroborated. Genetic factors account for approximately 56–84% of liability to anorexia nervosa, 28–83% of liability to bulimia nervosa, and 41–57% to binge eating disorder.

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Twins studies have provided an irrefutable proof on the heritability of these disorders. Other types of genetic studies in human and in animal models followed, including single nucleotide polymorphisms association studies, genome-wide association studies, whole genome sequencing, and linkage analysis, which allowed to delineate the etiology of eating disorders and to identify the genes and their variants associated with the pathologies. In this scenario, Next Generation Sequencing technologies can be considered as an ideal diagnostic approach. This chapter summarizes the present knowledge on the molecular etiology and genetic determinants of eating disorders including serotonergic genes, dopaminergic genes, opioid genes, endocannabinoid genes, appetite regulation genes, and others. Furthermore, the growing scientific interest to identifying causal genes behind EDs leads to identify some rare genetic variants. Eating disorders have been considered "sociocultural creations," but probably the environments alone cannot explain the etiology. Genetic factors together with environmental triggers, mental status, and social pressure to thinness are interconnected and may influence epigenetic mechanisms and consequentially gene expressions.

Keywords

Eating disorders · Anorexia nervosa · Bulimia nervosa · Binge eating disorders · Genetic test · Polymorphisms · Serotonergic genes · Dopaminergic genes · Opioid genes · Endocannabinoid genes · Appetite regulation genes · Rare genetic variants · Genome-wide association studies · Whole-exome sequencing

Abbreviations

5-HT	5-Hydroxytryptamine
5-HTTLPR	5HT-transporter-linked polymorphic region
ACTH	Adrenocorticotropic hormone
AEA	Arachidonoylethanolamine
AGRP	Agouti-related protein
AN	Anorexia nervosa
ANGI	Anorexia Nervosa Genetics Initiative
ANKK1	Ankyrin repeat and kinase domain containing 1
BDNF	Brain-derived neurotrophic factor
BED	Binge eating disorders
BN	Bulimia nervosa
CART	Cocaine and amphetamine regulated transcript
CCK	Cholecystokinin
COMT	Catecholamine-O-methyltransferase
DA	Dopamine
DRD2	Dopamine receptor 2
DRD4	Dopamine receptor 4
DSM-V	*Diagnostic and Statistical Manual of Mental Disorders Fifth Edition*

EDs	Eating disorders
ESRRA	Estrogen-related receptor alpha
FAAH	Fatty acid amide hydrolase
GCAN	Genetic Consortium for Anorexia Nervosa
GLP-1	Glucagon-like peptide 1
GWAS	Genome-wide association studies
HDAC4	Histone deacetylase 4
OXM	Oxyntomodulin
PEA	Palmitoylethanolamide
POMC	Proopiomelanocortin
PP	Pancreatic polypeptide
PPARγ	Peroxisome proliferator-activated receptor gamma
PYY	Peptide YY
SNPs	Single nucleotide polymorphisms
WTCCC-3	Wellcome Trust Case Control Consortium-3

Introduction

Eating disorders (EDs) are divided in eight categories according to the *Diagnostic and Statistical Manual of Mental Disorders Fifth Edition* (DSM-V) (American Psychiatric A 2013) and represent serious psychiatric illnesses (Treasure et al. 2020; Martinussen et al. 2017) with a high mortality rate (Arcelus et al. 2011; Smink et al. 2012) and an important genetic component (Yilmaz et al. 2015), confirmed firstly by twin and family surveys (Bulik et al. 2000) and secondly by single nucleotide polymorphisms (SNPs) association studies (Rask-Andersen et al. 2010; Paolacci et al. 2020). Even if DMS-V describes different categories with specific feeding behaviors and psychiatric/mental comorbidities, this chapter will focus on the three most common EDs, anorexia nervosa (AN), bulimia nervosa (BN), and binge eating disorder (BED), due to a current lack of genetic and epidemiological research on other EDs groups.

Family Studies

Twin, family, and adoption studies have shown that EDs are heritable (Thornton et al. 2011). In detail thorough results are available for anorexia nervosa (AN) with 56–84% of hereditability (Strober et al. 2000; Bulik et al. 2000; Klump et al. 2001; Munn-Chernoff and Baker 2016), bulimia nervosa (BN) with an average of 47% (Strober et al. 2000; Munn-Chernoff and Baker 2016), and binge eating disorder (BED) with 41–57% (Javaras et al. 2008).

Different and independent research works demonstrated that the risk of developing AN is approximately 11-fold greater for a first-degree relative of individuals with AN or BN than for the general population (Bulik et al. 2000; Klump et al. 2001). The relative risk for BN is around 4 times greater for female relatives of affected

probands (Bulik et al. 2000). A recent study on full-sisters and maternal half-sisters shows that AN and BN overlap between phenotype and may share up to 60% of genetic effects (Himmerich et al. 2019; Yao et al. 2021).

Candidate Gene Association Studies

Candidate gene association approach for EDs is widely used to understand the etiology of these complex and multifactorial disorders (Rask-Andersen et al. 2010; Yilmaz et al. 2015), which are caused in part from a genetic predisposition, but also from the psychological factors together with environmental risks: vulnerability, life transition, sexuality, dieting, childhood abuse or traumatic events, media, sociocultural pressure, family values, and others triggers (Fig. 1). Accumulating pieces of evidence have suggested that different SNPs and also VNTRs are associated with abnormal feeding behavior; in particular these polymorphisms are placed on crucial genes related to I) *mental illness*, such as serotonin receptor family (*5-HT2AR, 5-HT3AR, 5-HT3BR, 5-HT1DR*), brain-derived neurotrophic factor (*BDNF*), and norepinephrine (*NE*); II) *feeding motivation and reward system*, among these dopamine receptor family (*DRD2, DRD3* and *DRD4*), ankyrin repeat and kinase domain containing 1 (*ANKK1*), opioids (*OPRD1*), cannabinoids (*CNR1*), and catecholamine-O-methyltransferase (*COMT*); III) *appetite regulatory system*, for example, leptin, ghrelin, agouti-related protein

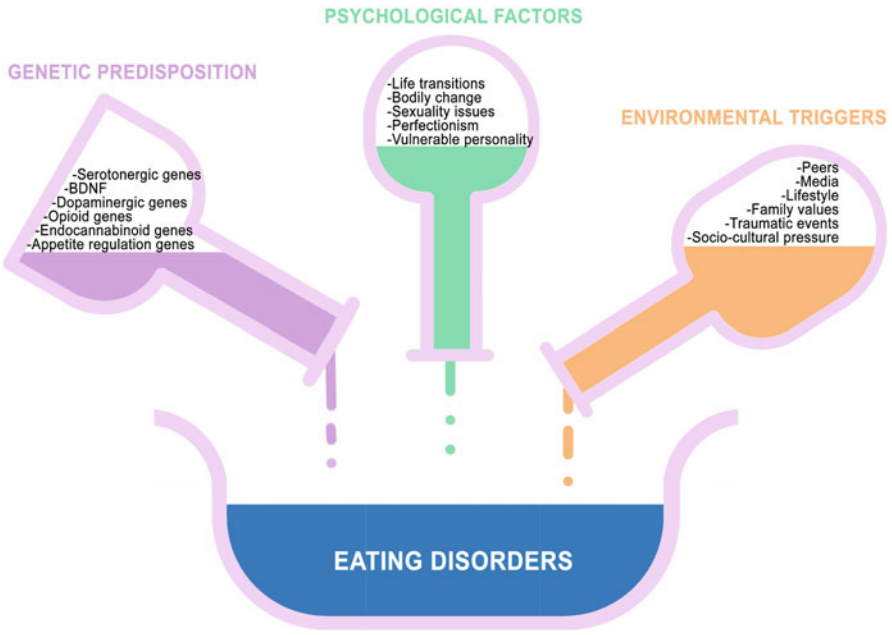


Fig. 1 Triggering causes underlying eating disorders

(*AGRP*), glucagon-like peptide (*GLP-1*), cholecystokinin (CCK), melanocortin 4 receptor (*MC4R*), neuropeptide Y (*NPY*), pancreatic polypeptide (*PPY*), and oxyntomodulin (*OXM*); IV) *neuroendocrine system and sex hormones*, estrogen receptor 2 (ESR2); V) *immune system and inflammatory response*, such as tumor necrosis factor-alpha (TNF alpha); and VI) other pathways under investigation or until now unexplored.

Genome-Wide Association Studies

Nowadays genomic-wide association studies (GWAS), thanks to high throughput genomic sequencing technology and with the collaboration of Psychiatric Genomic Consortium, have started to unlock the biological basis and genetic contributions of particular EDs as defined in DMS-V. Until now, five different GWAS have been conducted (Nakabayashi et al. 2009; Wang et al. 2011; Boraska et al. 2014; Duncan et al. 2017; Watson et al. 2019) with large cohort of patients from different ethnicities affected by particular EDs versus healthy controls (CTRs). AN, probably one of the most severe psychiatric diseases difficult to treat, reveals that several loci have been involved and 133 genes are implicated in the etiology of disease with an important hereditability, around 11–17% for common genetic variants. Unfortunately, this approach yielded results so far only for AN (Bulik et al. 2019), so a major effort is required to the scientific world for future discoveries. Together with an increase of GWAS sample size, other phenotypes beyond AN must be included, not only to improve genetic contribution knowledge, but also to open the way to novel and effective treatments for EDs patients, still now inadequate (Davis and Attia 2019).

Gene Variants

Several neuropeptides, neurotransmitters, hormones, and receptors are involved in EDs. Moreover, a lot of patients present comorbidity, such as anxiety, mood disorders, impulsive-compulsive disorders, and personality disorders, and for this reason understanding the etiology of EDs is extremely difficult.

Genetics research can improve knowledge about the heritability of EDs, but we should not forget the importance of environment factors, childhood abuses, family context, aesthetic canons in industrialized society, and media and websites messages of thinness, that contribute to development of EDs (Fig. 1). The complex network of involved neuropeptides, neurotransmitters, hormones, and their receptors requires a multimodal treatment approach.

In this chapter we decided to describe the growing scientific interest to identifying causal genes behind EDs, bringing back the most relevant scientific researches with strong evidences and associations, confirmed in independent works.

Serotonin Pathway

The serotonin or 5-hydroxytryptamine (5-HT) system, which comprises 14 or more receptor subtypes and the 5-HT transporter (5-HTT), is involved in mood, food intake, and body weight regulation (Yokokura et al. 2019) and for this reason is surely the most investigated pathway, together with dopamine system.

Due to the psychological profiles of patients, in particular affected by AN, which show an altered perception, personality, and mood, it has been hypothesized that 5-HT activity is altered in the acute illness state of AN. In fact, serotonin is involved in a broad range of functions and acts as anorexigenic factor that promotes satiety. As with AN, BN patients develop an egosyntonic personality, so it is a conceivable role of serotonergic system dysfunction in this particular eating disorder onset and progression (Kaye et al. 2005).

Most positron emission tomography studies of AN patients have targeted the 5-HT1A and 5-HT2A receptors and 5-HTT, also known as 5-HTTLPR, encoded by the *SLC6A4* gene (Boehm et al. 2020). Positive correlations have been found between re674386 SNPs in the 5-HT1A receptor and restrictive type of AN in independent works (Brown et al. 2007). Several laboratories and groups of research around the world have been found a strong association between -1438A/G polymorphism in *5-HT2A* receptor gene (re6311) and AN (Hinney et al. 1997; Enoch et al. 1998; Nishiguchi et al. 2001; Ricca et al. 2002; Ceccarini et al. 2020). Similar results were obtained for BN (Ricca et al. 2002), but not for BED (Ricca et al. 2002; Ceccarini et al. 2020).

A 43-basepair insertion/deletion in serotonin transporter gene *SLC6A4* (5-HTTLPR), generating a long (L) and short (S) genotypes respectively, was extensively studied in AN, BN, and BED with different and sometimes conflicting results (Hinney et al. 1997; Monteleone et al. 2006; Tasegian et al. 2016). Abnormalities in peripheral 5-HT uptake have been observed in BN patients (Steiger et al. 2011), but there are conflicting results (Polsinelli et al. 2012; Trace et al. 2013). Additionally, Monteleone and co-worker, who analyzed the 5-HTTLPR polymorphism in obese people, found L-allele overexpression in 77 BED patients (Monteleone et al. 2006). On the other hand in a group of obese women, the mean BMI was higher for the SS genotype than for combined LL and LS genotypes (Sikora et al. 2013).

Other polymorphisms, such as rs6318 (Cys23Ser) in 5-HT2C receptor, have been examined in EDs, but allele frequencies were unchanged in patients and healthy control group.

Anyway, it is unlikely that this pathway is the only one involved in the onset of EDs because it is associated with numerous psychiatric disorders and therefore cannot be considered a specific vulnerability factor for AN, BN, or BED (Paolacci et al. 2020; Trace et al. 2013).

Brain-Derived Neurotrophic Factor Gene

Brain-derived neurotrophic factor (*BDNF*) is a neurotrophic protein that supports the growth, survival, and differentiation of neurons. BDNF is ubiquitously expressed and in terms of eating behavior is involved in appetite suppression by downstream regulation of melanocortin signaling in the hypothalamus (Ribasés et al. 2004). The BDNF level in serum was deeply investigated in EDs patients, and the results demonstrated that it was significantly reduced in particular in AN and BN (Mercader et al. 2007; Saito et al. 2009) with a strong correlation with low body mass index (BMI). For this reason, BDNF plasma levels were suggested as a candidate biomarker. In terms of genetic variations, one of the most extensively researched SNPs in the coding region of *BDNF* gene is the rs6265, where the common G allele that encodes for valine in position 66 is replaced with A allele that codifies for methionine (commonly referred to as Val66Met). This SNP has been strongly associated with different sub-groups of EDs (AN, BN, and BED) in different ethnicities (Ribasés et al. 2004; Mercader et al. 2007; Rosas-Vargas et al. 2011; Ceccarini et al. 2020), suggesting that this neurotrophic protein may act in both appetite and satiety brain centers as orexigenic and anorexigenic signal through complex interactive network. A complete functional characterization of this SNP needs to be deeply studied in the near future.

Another SNP in the promoter region of the same gene is rs56164415 (commonly referred to as −270C/T) and is associated with EDs predisposition. Its role remains still controversial, especially due to the challenges associated with studying this low minor allele frequency SNP in small study samples (Mercader et al. 2007; Yilmaz et al. 2014).

Dopamine Receptor Family

Dopamine (DA) is a catecholamine neurotransmitter highly expressed in the central nervous system (CNS) and implicated in wide array of brain functions including feeding behavior, motor activity, and reward (Sobik et al. 2005). Based on these evidences, genes coding for enzymes, receptors, and transporters involved in DA pathways have been considered candidates for gene association studies in patients affected by EDs.

In particular different SNPs located in ankyrin repeat and kinase domain containing 1 (*ANKK1*), dopamine receptor 2, 3, and 4 (*DRD2*, *DRD3*, and *DRD4*) genes, have been found to be significantly associated with EDs in several studies (Ariza et al. 2012; Davis et al. 2012; Duncan et al. 2017).

A1-allele of rs1800497 SNP (also known as Taq1A allele or AA) in the *ANKK1* gene has been reported to reduce receptor activity with lower availability in striatal D2/D3 receptors (Eisenstein et al. 2016). Its frequency was significantly higher in obese group than in lean controls (Ariza et al. 2012), whereas BED patients that showed a higher proportion of homozygotes for the A2-allele (GG) (Davis et al.

2012). BED Italian patients homozygous for the G-allele of ANKK1-rs1800497 exhibited a significant association with binge eating episodes.

rs6277 SNP in the *DRD2* gene (commonly referred to as C957T) has been associated with changes in DRD2 expression and dopamine neurotransmission (Hirvonen et al. 2009), and T-allele homozygosity has been found highly correlated with BED risk (Davis et al. 2012).

In the same gene, rs1799732 SNP (-141C indel), previously shown to affect DRD2 transcription efficiency, has been showed to have a positive susceptibility in 191 AN patients, but no replication studies have been carried out (Bergen et al. 2005).

Recently, it has been proved that AN patients carrying the homozygous variant Gly9Gly genotype in the dopamine D3 receptor (*DRD3*) have a more severe symptomatology (Duncan et al. 2017).

Several studies have demonstrated a correlation between EDs and -521C/T SNP (rs1800955), located in the promoter region of *DRD4*; notably the T allele is associated with personality traits related to AN (Munafò et al. 2008).

Recently, for the first time, it was observed a strong association between another SNP (rs936461) situated in the promoter of DRD4 gene (A809G) and two specific EDs subgroups, BN and BED, which showed a strong prevalence of homozygous GG. This data needs to be confirmed.

Another interesting polymorphism is the 120-base pair (bp) tandem repeat (TR), located in the promoter region of DRD4. This polymorphism consists of a long (L) and a short (S) allele with opposite effects on the DRD4 expression level: L-allele is a negative modulator whereas S-allele induces higher transcriptional levels of the gene (D'Souza et al. 2004). Interestingly, the S-allele has been associated with AN bingeing/purging subtype but not with AN restrictive subtype, and interestingly, patients with AN carrying the S-allele displayed significantly higher weight and height than patients not having the S-variant (Gervasini et al. 2013). Recently it has been demonstrated a significant association between the 120 bp TR polymorphism and BN and BED susceptibility. Indeed, SS and SL genotypes have significantly more presence in the BN and BED groups in comparison with the healthy control. Moreover, it was found a higher BMI in BED patients carrying SS or SL genotypes compared to LL homozygotes.

Probably, the most widely studied is a variable number of tandem repeats, known as 48-bp VNTR, in the exon 3 of *DRD4*. The allele with 7 repeats has been shown to reduce the receptor expression and affinity for DA and was strongly associated with overeating, obesity (Gervasini et al. 2018), drug abuse, and related comorbidities (Botticelli et al. 2020). Women, carrying at least one copy of an allele with 7 or more repeats (>7R), have increased BMI, with the highest BMI values observed in 7R/7R homozygotes (Sikora et al. 2013). The same genotype (7R/7R) is also associated with a greater risk for AN (Gervasini et al. 2013). Probably this association is due to the reducing receptor expression that leads to a disturbing reward pathway and an abnormal food intake.

Opioids and Their Receptors

Opioid peptides play a key role in feeding behavior generating motivation and pleasure in food consumption, raising suspect that opioid genes also play a decisive role in EDs (Fuss et al. 2015).

Several SNPs in the opioid delta 1 receptor (*OPRD1*) located in chromosome 1, such as rs536706, rs760589, rs204081, rs569356, rs521809, and rs4654327, were associated with risk of AN by independent studies (Brown et al. 2007).

Some reward-related brain dysfunctions have been described also in rodent animal models of BN by affecting opioid levels (Avena et al. 2008). The BN treatment with naloxone that is an opioid receptor blocker is very effective (Valbrun and Zvonarev 2020).

The opioid antagonist treatments decrease intake of fat and sucrose diets and suppress palatable food intake (Naleid et al. 2007). Memantine, a drug commonly used to treat the symptoms of Alzheimer's disease, attenuated the expression of opioid physical dependence in humans, indicating that glutamatergic neurotransmission at the NMDA receptor site contributes to the maintenance of opioid dependence. Interestingly, in rat BED model, memantine treatment blocks the compulsivity associated with the intake of the highly palatable food (Popik et al. 2011).

Endocannabinoid Pathway

Endocannabinoid system plays a key modulatory role of energy balance by controlling food intake through central and peripheral mechanisms that orchestrate energy homeostasis. Endocannabinoids (eCBs) are lipid messengers that are involved in overall body weight control. In fact, the cannabinoid receptors, CB1 and CB2, are expressed in the hypothalamus and other brain regions that control food intake (González et al. 2021). Genetic variants in *CNR1* and *CNR2* genes coding for cannabinoid receptors CB1 and CB2 affect body weight and food intake and are associated with AN (Soria-Gòmez et al. 2007). Systemic and local administrations of both exogenous cannabinoids (i.e., THC) and endocannabinoids (i.e., AEA, 2-AG) increase food intake in animals. This hyperphagic action is mediated by CB1 receptors since they are blocked by specific CB1 receptor antagonists (Scopinho et al. 2011). Cannabidiol, a constituent of *Cannabis sativa*, can prevent the hyperphagic effect induced by the CB1 receptor agonist (McLaughlin et al. 2003). Instead, CB1 receptor antagonists are hypophagic and reduce body weight (Riedel et al. 2009). Also, the phyto-9 cannabinoid-tetrahydrocannabivarin, which behaves as a CB1 receptor antagonist, decreases food intake and body weight (Siegfried et al. 2004). Genetic variants in *CNR1* gene are thought to contribute to AN susceptibility. The involvement of *CNR1* trinucleotide repeats could mediate the non-Mendelian inheritance of AN, but functional studies are needed to prove the differential effect of the various (AAT)n repeats on the CB1 receptor (Fuss et al. 2015).

Monteleone et al. demonstrated that rs1049353 (also known as 1359 G/A) in the *CNR1* gene and rs324420 (cDNA 385C to A) in the endocannabinoid degrading enzymes fatty acid amide hydrolase (FAAH) are significantly associated with both AN and BN with a synergistic effect of the two SNPs in AN (Monteleone et al. 2009). An association of a *CNR2* polymorphism with BN has also been observed (Scherma et al. 2014).

The role of the cannabinoid receptors is also supported by studies performed on anandamide, also known as N-arachidonoylethanolamine (AEA), which plays a key role in feeding behavior generating pleasure in food consumption (Rueda et al. 2002). By binding to CB1R, anandamide inhibits neuronal differentiation and causes the retraction of neurites (Gaetani et al. 2008). Plasma levels of anandamide were down-regulated in AN patients.

Palmitoylethanolamide (PEA) is an endogenous fatty acid amide that binds the peroxisome proliferation-activated receptor α (PPARα) and the cannabinoid-like G-coupled receptors GPR55 and GPR119. The transcription factor PPARα in the small intestine controls the anorectic action of exogenous PEA (Clayton et al. 2021). PEA might function as a biosensor for dietary fat because intestinal concentration of PEA decreases in response to high-fat feeding in mouse (Monteleone et al. 2015). In AN patients, plasma PEA concentration increases after exposure to a non-favorite meal and in hedonic eating.

Appetite Regulatory System

The communication between gut and hypothalamus involves appetite hormones that include orexigenic and anorexigenic hormones, such as ghrelin, leptin, cholecystokinin (CCK), peptide YY (PYY), pancreatic polypeptide (PP), oxyntomodulin (OXM), and glucagon-like peptide (GLP)-1. This complex interaction between the central nervous system and the intestinal tract by humoral factors and neuronal pathways has been named brain-gut-axis.

After feeding, anorexigenic peptides are released while the levels of the orexigenic peptide ghrelin reduce. Ghrelin (also called the hunger hormone), the natural leptin antagonist, is an appetite stimulating hormone produced in the stomach and pancreatic cells. Its level is inversely associated with body mass index (BMI) in the general population, and it has effects on feeding behavior, reward mechanisms, reproduction, and growth (Perry and Wang 2012). AN patients have higher levels of ghrelin in the plasma, likely in response to prolonged starvation (Blauwhoff-Buskermolen et al. 2017). Leu72Met (rs696217) in ghrelin gene (GHRL) is one of the most studied SNPs and was associated with BED patients and with the risk to developing an ED (Monteleone et al. 2007). In a family trios study, Dardennes et al. found a prevalence of transmission of Leu72Met in AN patients, in particular the purging AN-subtype (Dardennes et al. 2007). Polymorphisms in ghrelin and its receptor *GHSR1a* are not associated with BN (Monteleone et al. 2006). Other SNPs in GHRL gene and its receptor *GHSR1a* were investigated, such as

rs4684677 (Gln90Leu) and rs34911341 (Arg51Gln), but conflicting results were obtained.

Leptin, on the other hand, is a hormone produced by adipocytes and enterocytes, involved in the food intake and regulation of energy balance both long and short term (Steiner and Romanovsky 2007). There are low levels of plasma circulating leptin in cerebrospinal fluid (hypoleptinemia) in AN patients (Föcker et al. 2011). Even if the serum level of leptin is significantly decreased in AN patients, it is only moderately increased in obese patients. Moreover, a positive correlation of plasma leptin levels and BMI in subjects with BN has been described. The plasma leptin levels are restored in remitted BN patients and are a relevant factor for remission (Homan et al. 2014). Because leptin is able to modulate reward-related behavior, leptin gene (LEP) and its receptor (LEPR) were investigated in a lot of candidate-gene association studies, but no evidences in AN and BN were yielded so far. Yilmaz and co-worker in 745 individuals with AN, 245 individuals with BN, and 321 controls found a negative association with two SNPs located in LEPR, rs1137100 (Lys109Arg) and rs1137101(Gln223Arg), previously associated with EDs in a small group of patients (Yilmaz et al. 2014). Although leptin modulates reward-related behavior that has a relationship with BN, currently conflicting results were obtained on the association of reward learning and plasma leptin levels in BN. However, a positive correlation of plasma leptin levels and BMI in subjects with BN has been described. The plasma leptin levels are restored in remitted BN patients and are a relevant factor for remission (Homan et al. 2014).

The brain homeostatic control of feeding involves not only neural circuits located in the hypothalamus (hunger signals, initiating feeding behavior), but also the brainstem (satiation signals) (Cuesto et al. 2017). Hypothalamic NPY/AGRP neurons produce neuropeptide Y, and agouti-related peptide produces an orexigenic signal by increasing the release of adrenocorticotropic hormone (ACTH), cortisol, and prolactin and is involved in appetite regulation. These neuropeptides are associated with high food intake by up-regulation in AN (Galusca et al. 2015). Orexins are orexigenic neuropeptides involved in endocrine system regulation, with an important function in insulin, glucagon, and leptin secretion in response to glucose (Park et al. 2015). An increased concentration of NPY, which mediates leptin receptors, is associated to body mass deficiency with high concentrations of leptin, suggesting defects in the regulatory axis. AGRP rs13338499, a SNP located in a putative transcription factor-binding site, upstream of *AGRP* gene with a possible regulatory role, was significantly associated with lowest BMI in AN patients (Yilmaz et al. 2014).

CCK, a peptidic hormone of the gastrointestinal system, secreted into the duodenum from cells of mucosal epithelium, is another actor that promotes satiety, but has been also associated with anxiety, panic, and hallucinations. CCK stimulates digestion of proteins and lipid in the small intestine. Its plasma levels in AN patients and control group are similar both prior to and after feeding, but more data are necessary because in some analysis, CKK plasma in AN patients showed a post-prandial increase in CKK plasma levels (Cuntz et al. 2013; Richard et al. 2014). Five SNPs in the 3′ untranslated (UTR) region of the *CCK* gene were analyzed by De

Krom et al. (2006), and a strong association was found only for one SNP, rs11129946; in particular the researchers demonstrated a higher number of AC carriers (heterozygous) in AN group (De Krom et al. 2006). BN patients, on the contrary, seem to have impaired secretion of CKK that is a satiety factor and PYY secretion inductor. Hence, depressed PYY levels may result from reduced CCK secretion. Moreover, there is a negative correlation between PYY increase and ghrelin decrease. For which a pathway involving peripheral hormonal signals, such as ghrelin and PYY, may be related to BN (Smitka et al. 2013). However, only one association study has been performed in Japanese population in AN and BN subjects with positive correlation (Miyasaka et al. 2006), but further investigation will be needed because the ethnicity is a fundamental and essential point to take into consideration when we talk about genetic association studies.

Another neuropeptide involved in EDs is proopiomelanocortin (POMC) synthesized mainly in the anterior pituitary and cleaved in a-MSH, ACTH, and the opioids beta-endorphin and Met-enkephalin. POMC is an anorexigenic peptide, is mainly expressed in the arcuate nucleus, and associated with appetite regulation, as well as the secretion of glucocorticoids. Moreover, cocaine- and amphetamine-regulated transcript (CART) is an anorectic peptide widely expressed in both the central and peripheral nervous system which as POMC is regulated by leptin and it has been related with addictive behaviors and stress responses (Bakhtazad et al. 2016). The most common SNP located in *POMC* gene is rs104257 because it is considered a putative transcriptional binding site. Until now negative results were obtained.

Other Genes

Other metabolic pathways together with a huge number of genes are under investigation, but *FTO* (fat mass and obesity-associated) gene located in the chromosome 16 deserves a particular attention. Several SNPs in the coding region of *FTO* gene (in particular in the first intron) are strongly associated with obesity in young and in adults. rs9939609 is for sure the most frequently described, and the A-allele is strongly associated with obesity and with type 2 diabetes mellitus. Even if *FTO* is indisputably correlated with obesity, uncertainty remains about the potential association of this gene with EDs such as AN and BN or BED. 6101 individuals from three European countries (Germany, Italy, and Spain) divided in AN, BN, and CTRs were recruited, and results highlight an important association of the A-allele at rs9939609 with both AN and BN groups (Müller et al. 2012). Besides, the same A-allele was associated with BED (Castellini et al. 2017); for this reason it is possible to hypothesize that this crucial SNP represents a potential additive risk factor for EDs persons, with bodily disorders to develop higher emotional eating and binge eating behaviors.

Rare Genetic Variants

With the recent advancements in high-throughput sequencing, it is now much easier to detect rare variants (minor allele frequency of less than 1%). The role of rare and structural variants in EDs was explored by studies of whole-exome and whole-genome analyses. The previous gene expression studies had offered insight into the genes and molecular mechanisms that influence EDs. However, such data are available so far mainly for AN patients but not for other sub-groups.

For example, a whole-exome analysis in two independent studies found pathogenic variants in the neuronatin (NNAT) gene. The first one to report this association between AN and NNAT gene was Lombardi et al. (2019). We independently confirmed this data in our Italian cohort (Ceccarini et al. 2021), and in particular found three variants in NNAT gene in four probands out of a total of 68 patients analyzed (6% of total samples). Two variants had been previously reported by Lombardi et al. (2019), one nonsense (p.Trp33*) and one rare variant in the 5′UTR, while one variant has never been associated with AN yet (Ceccarini et al. 2021).

Moreover, we found in our study potential deleterious variants in two other genes, PDE11A and SLC25A13, and we predicted deleterious variants in the following 12 genes, CD36, CACNA1C, DRD4, EPHX2, ESR1, GRIN2A, GRIN3B, LRP2, NPY4R, PTGS2, PTPN22, and SGPP2 (Ceccarini et al. 2021), but these data need to be confirmed in a large cohort of AN patients.

Novel non-synonymous and missense variants in the exons of SLC6A4 gene, using Sanger sequencing, were found in 86 Mexican patients with AN and BN (Hernández-Muñoz et al. 2020). Recently, a positive relationship between the SLC6A4 methylation levels (15 CpG sites in the gene promoter) and the resting-state functional connectivity between the dorsolateral prefrontal cortex and the salience network has been found in AN patients (Boraska et al. 2014; Boehm et al. 2020).

Bienvenu and co-worker have found seven de novo missense variants in four potential genes (CSMD1, CREB3, PTPRD, and GAB1) which belong to the same signaling pathway involving neuron differentiation and dopamine pathway in nine studied AN patients (Bienvenu et al. 2020).

A whole-exome sequencing analysis in AN patients identified genes carrying damaging variants belonged to three crucial pathways: (a) neuropeptide hormone signaling, (b) inflammatory pathway, and (c) cholinergic neurotransmission (Lutter et al. 2017). Another whole-exome sequencing study in EDs patients was carried out by Bergen et al. in 2019 and identified novel variants in seven genes: TTC22, MRPS9, DNAJC30, HEPACAM2, USP20, ESF1, and CDK5RAP1 (Bergen et al. 2019). It should be stated that the functional relevance of all these gene variations for the etiology of EDs remains to be demonstrated. They all could represent polymorphisms without biological effects.

A single genome-wide association study recognized a locus on chromosome 12 (lead rs4622308 SNP) related to AN in a region that regards also diabetes mellitus type 1 and autoimmune disorders. Successively the Anorexia Nervosa Genetics

Initiative (ANGI), the Genetic Consortium for Anorexia Nervosa (GCAN), and the Wellcome Trust Case Control Consortium-3 (WTCCC-3) along with UK Biobank have detected eight chromosomal regions, comprising 120 genes, significantly associated with AN. Analyses in silico and research by available large-scale in vitro data have revealed that four of the genes of these chromosome regions might be more likely to be associated to the AN etiology: *CADM*1, *MGMT*, *FOXP1*, and *PTBP2* (Watson et al. 2019; Paolacci et al. 2020; Yokokura et al. 2019).

In a large screening of 152 candidate genes by GWAS, rare variants associated to AN were identified in *EPHX2* that encode a protein involved in cholesterol metabolism. Moreover, variants in *ESR2*, encoding the estrogen receptor 2, can be associated with AN in female (Cui et al. 2013).

However, at the base of the limits of these studies in AN, there are several factors, such as the winner's curse, small sample size, moderator variables explaining, and lack of heterogeneity of the cohorts (Watson et al. 2019, 2021). Anyway, the results obtained in these studies support the view that AN is a highly polygenic and multifactorial disease.

Finally, by whole-genome sequencing and linkage analysis to analyze two families with recurrence of EDs were detected a missense variant co-segregating with the affected family members in Estrogen Related Receptor Alpha gene (*ESRRA)*, and a potentially damaging variant in histone deacetylase 4 (*HDAC4*) that plays a significant role in the estrogen system. Transcriptional studies revealed that expression of the *HDAC*4 deacetylase repressed the transcription of ESRRA-induced target genes, whereas *ESRRA* and *HDAC4* exhibited interaction in both in vivo and in vitro studies. For which variants in *ESRRA* and *HDAC4* cause a decrease in the activity of ESRRA and an increase in the likelihood of AN onset (Sild and Booij 2019).

Conclusions

To date, the genetic risk architecture underlying EDs remains largely unexplored; however, like most other psychiatric illnesses, the heritability of EDs appears to follow both a non-Mendelian pattern and in part a Mendelian pattern, suggesting that large numbers of genes spanning multiple regions of the genome are involved in susceptibility.

Summary Points

- EDs have a deep social, psychological, and physical impact and are associated with a high level of mortality.
- Several neuropeptides, neurotransmitters, and hormones are involved in EDs.
- Genetic determinants of EDs include serotonergic genes, dopaminergic genes, opioid genes, endocannabinoid genes, appetite regulation genes, and others.
- Genetic test can be considered as an ideal diagnostic approach, especially by use of NGS technologies.

- Genetic variants and environmental triggers could modify the epigenome that, in turn, influence the onset of EDs.

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Genes and Eating Disorders

6

A Focus on the Solute Carrier Family 6 (Neurotransmitter Transporter, Serotonin), Member 4 (*SLC6A4*) Gene

Beatriz Camarena and Sandra Hernández-Muñoz

Contents

Introduction 96
Role of Serotonin in Eating Disorders 97
Characteristics of the Serotonin Transporter (SERT) 98
SLC6A4 Serotonin Transporter Gene 98
Genetic Association Studies 99
Studies of Association of the SLC6A4 Gene and Psychopathological Traits in Eating Disorders 101
Gene x Environment Interaction Studies in Eating Disorder 101
Studies of Sequence of SLC6A4 102
Conclusions 102
Key Points 103
Key Facts of Genes and Eating Disorders: A Focus on the Solute Carrier Family 6 (Neurotransmitter Transporter, Serotonin), Member 4 (*SLC6A4*) Gene 104
Summary Points 104
Applications to Other Areas 104
Mini-Dictionary 105
References 106

Abstract

Eating disorders are complex and multifactorial disorders, in which social, familial, and genetic factors are involved. The serotonin transporter is a key molecule in modulating eating behaviors. The *SLC6A4* gene codes for the serotonin transporter protein, and it has been suggested as an important candidate in ED.

In this chapter, we described the findings of the association between *SLC6A4* gene variants and ED. Most genetic studies have focused on the analysis of a polymorphism located in the promoter region, the 5-HTTLPR, which has been

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reported to predict a change in the gene expression. Furthermore, the association between psychiatric comorbidities related with a dysfunction in serotonin pathways suggests an involvement in the susceptibility to ED.

In the future, it will be interesting to carry out the analysis of genetic variants in populations not studied to identify variants that to date have not been observed in Caucasian populations.

Keywords

Eating disorders · *SLC6A4* · Gene · Genetic variants · SERT · 5-HTTLPR · 5-HTT · Association study · Serotonin transporter · Interaction · Environment · Anxiety · Anorexia nervosa · Bulimia nervosa · Binge eating disorder

Abbreviations

5-HT	5-Hydroxitriptamine, serotonin
5-HTTLPR	Serotonin transporter-linked polymorphic region
AN	Anorexia nervosa
ANP	Anorexia nervosa purgative
ANR	Anorexia nervosa restrictive
BED	Binge eating disorder
BN	Bulimia nervosa
BNP	Bulimia nervosa purgative
CNS	Central nervous system
DSM-5	*Diagnostic and Statistical Manual Version 5*
ED	Eating disorders
ICD-11	International Classification of Diseases version 11
SERT	Serotonin transporter protein
SLC6	Solute carrier 6 transport family
SLC6A4	Solute carrier family 6 member 4 (*Homo sapiens*, human)
SRIs	Serotonin reuptake inhibitors
TM	Transmembrane protein
VNTR	Variable number of tandem repeats
WES	Whole-exome sequencing
WGS	Whole-genome sequencing

Introduction

Eating disorders (ED) are severe psychiatric disorders defined by abnormal food consumption patterns. The *Diagnostic and Statistical Manual Version 5* (DSM-5) (American Psychiatric Association, 2013) and the International Classification of Diseases version 11 (ICD-11) include anorexia nervosa (AN), bulimia nervosa (BN), and binge eating disorder (BED). Eating disorders are complex disorders that involve severe changes in attitudes and behaviors related to food intake in response to perceptual distortions about body dimensions, as well as the phobic

fear of gaining weight. The etiology of ED is unknown; however, it is suggested as a multifactorial disorder that results from a complex interaction of predisposing, precipitating, and perpetuating factors. Family and twin studies suggest that heritable components play an important role in the susceptibility to develop an ED (Strober et al. 2000).

The restriction of food intake normally reduces the levels of serotonin (5-HT, 5-hydroxitriptamine) in the central nervous system inducing hyperphagia and obesity; however, in AN patients, the low serotonin level does not decrease the food intake remaining a reduced body weight (Kaye et al. 1984). Thus, disturbances in the brain serotonin system have been related to ED, such as in psychopathology traits that contribute to the vulnerability to develop an ED. In addition, AN and BN patients respond to serotonin reuptake inhibitors (SRIs), which act by blocking the serotonin reuptake through the serotonin transporter protein.

The serotonin transporter (SERT) is a key protein responsible for terminating the synaptic action of serotonin after the neurotransmitter release modulating the serotonin function in the brain. The serotonin transporter is encoded by the *SLC6A4* gene, and there have been several genetic studies proposing this gene as an interesting candidate gene for eating disorders. Also, it has been implicated in anxiety, depression, impulsivity, and obsessiveness traits related to the risk to develop an ED.

One of the most studied polymorphisms of the *SLC6A4* gene is the 5-HTTLPR (serotonin-linked polymorphic region) located in the promoter region and characterized for conferring protein gain or loss of function. In this book chapter, we review the investigations about the genetic studies related to *SLC6A4* and eating disorders in several populations.

Role of Serotonin in Eating Disorders

The neurobiological studies have provided information on dysfunctions of neurotransmitter function in the modulation of appetitive behaviors and emotional states in the eating disorder etiology (Kaye et al. 2009, 2013). The interest in the role of serotonin in ED is supported for their important role in postprandial satiety. Steiger (2004) suggests that an increase in the 5-HT tone is related to a reduction in food consumption, whereas a low serotoninergic tone is related to an increase in food consumption and promotion of weight gain, characteristics observed in patients with AN and BN (Bailer et al. 2007; Yokokura et al. 2019).

Also, the disturbances observed in the 5-HT activity may be involved too in the vulnerability to develop risk psychopathological traits in AN and BN patients. Interestingly, patients with AN present several traits related to increased serotonin neurotransmission such as obsessiveness, perfectionism, anxiety, and harm avoidance; and BN patients showed traits related to a decrease in serotonin neurotransmission such as impulsivity, dysphoric mood, and emotional dysregulation. The co-occurence of some ED symptoms after the recovery may suggest premorbid traits contributing to pathogenesis of AN and BN.

Characteristics of the Serotonin Transporter (SERT)

The solute carrier family 6 (SLC6) transport family is a secondary active co-transporter formed for 12 hydrophobic membrane-spanning domains with cytoplasmic NH2 and COOH termini. The TM3 and TM4 are separated by a large hydrophilic loop that carries two canonical sites for glycosylation. SERT also contains potential phosphorylation sites for several kinases (Hoffman et al. 1991; Kristensen et al. 2011; Pramod et al. 2013).

The protein is preferentially located in the presynaptic space at the axonal terminals and is also found in cells specialized in the storage or systemic inactivation of 5-HT, including the specialized cells of the intestine, placenta, platelets, and blood lymphocytes (Faraj et al. 1994; Gordon and Barnes 2003; Tao-Cheng and Zhou 1999). The SERT is a protein responsible for introducing 5-HT into the cell into the synaptic space of the serotonergic neuron, consequently reducing the availability of 5-HT in the extracellular environment; it has become the key protein for maintaining serotonergic homeostasis in the paraventricular nucleus (Murphy et al. 2008; Murphy and Moya 2011; Schwartz et al. 2000).

Transporters have been associated with a series of complex diseases in humans that make this family a critical target for study, and several members of this family are directly involved as therapeutic targets in pharmacological treatments. Also, it has been proposed that genetic variants in the serotonin transporter gene can alter the functionality of SERT and compromise the serotonergic homeostasis in the brain (Hu et al. 2006; Prasad et al. 2009).

SLC6A4 Serotonin Transporter Gene

The SERT protein is encoded for *SLC6A4* gene in humans, and it is located on chromosome 17q11.2, composed of 15 exons. The sequence predicts a 630-amino acid protein with 12 transmembrane domains (Lesch et al. 1994; Ramamoorthy et al. 1993). Differential splicing in exons 1A, 1B, and 1C result in several mRNA species regulating tissue-specific expression in humans (Murphy et al. 2008).

Studies of genetic variation have identified several variants in the coding and non-coding regions of the gene. The high allelic heterogeneity observed in the *SLC6A4* gene may explain the controversial findings reported in the different populations analyzing eating disorder patients. In particular, a polymorphism in the promoter region is one of the most studied, denominated 5-HTTLPR (serotonin transporter-linked polymorphic region), and characterized for an insertion/deletion of 43 base pairs, defining a short (S allele) and a large allele (L allele) related with changes in the activity and expression of SERT (Heils et al. 1996). Nakamura et al. (2000) identified an A to G (rs25531) single-nucleotide polymorphism in the L allele defining a triallelic system with a functional expression of the L_G variant similar to the S allele compared with the L_A (Hu et al. 2006; Wendland et al. 2006).

Additional gene variants have been identified in the *SLC6A4*. A variable number of tandem repeat (VNTR) was identified in intron 2 showing enhancer-like

properties (MacKenzie and Quinn 1999). Also, non-synonymous SNPs have been identified in the *SLC6A4* gene such as Gly56Ala, Ile425Val, Leu362Met, Ser293Phe, and Thr4Ala showing differential 5-HT transport activity of SERT-coding variants in transfected HeLa cells compared with hSERT cDNA (Prasad et al. 2005).

In exon 3, it was reported a change of amino acid Leu255Met that at the extracellular level changes the loop, away from the glycosylation and phosphorylation sites in the protein. In exon 9, the Ile425Val localized in the TM8 transmembrane region confers gain of function and altered the affinities at substrate 5-HT and, also, modifies the secondary structure of the alpha helix by affecting SERT (Sutcliffe et al. 2005; Prasad et al. 2009). It is possible that the combination of common and rare variants of *SLC6A4* gene may confer risk to express differential expression of SERT in the susceptibility to develop several psychiatric and psychopathological conditions.

Genetic Association Studies

The important role of SERT in the brain and body process suggests that a dysfunction in the serotonin pathways may be involved in the etiology of ED; therefore, it has been analyzed in several genetic association studies proposing it as an interesting candidate gene (Hernández-Muñoz and Camarena-Medellin 2014).

Most genetic association studies of the *SLC6A4* gene have focused on the analysis of the 5-HTTLPR polymorphism. Family-based association studies reported a preferential transmission of the S allele in families with AN (Hinney et al. 1997; Urwin and Nunn 2005; Chen et al. 2015), and a case-control study observed the finding of an association between S allele and AN (Matsushita et al. 2004). Also, it was observed a significant association between the S variant and BN in the Caucasian population. In particular, patient carriers of two copies of the short allele showed a seven times higher risk of BN (Di Bella et al. 2000). Other findings reported an association between the L variant and BNP (Monteleone et al. 2006). Analysis of triallelic polymorphism 5-HTTLPR/rs25531 found an association between the S/L_G alleles and BN in the Mexican population (Camarena et al. 2018). Previous studies analyzing the triallelic polymorphism showed that the S allele was associated with AN; however, other findings did not find an association (Calati et al. 2011; Lee and Lin 2010; Solmi et al. 2016). Two meta-analysis studies showed an association between the low activity allele and anorexia nervosa (Lee and Lin 2010; Calati et al. 2011); however, a meta-analysis in the largest sample of ED patients analyzed did not find an effect of biallelic and triallelic polymorphisms on the risk to develop ED (Solmi et al. 2016). The analysis of this polymorphism in binge eating disorders did not show an association (Monteleone et al. 2006; Palmeira et al. 2019). Future studies in ED should explore the role of ethnicity in the variability of allele frequencies and the psychiatric comorbidity as a possible source of bias in the replicability of the findings to understand the role of the gene in ED (Tables 1 and 2).

Table 1 Family-based association studies of *SLC6A4* in eating disorders

Study	Polymorphism	Trio families	Findings
Urwin et al. (2003)	5-HTTLPR	AN = 106	No association
Urwin and Nunn (2005)	5-HTTLPR	AN = 114	Association with S allele
Camarena et al. (2012)	Gly56Ala	AN = 79	Major transmission of Ala56 allele
Chen et al. (2015)	5-HTTLPR	AN = 198	Major transmission of S allele

Table 2 Case-control association studies of *SLC6A4* in eating disorders

Study	Polymorphism	Sample	Findings
Hinney et al. (1997)	5-HTTLPR 5-HTTLPR	AN = 55 Ob = 385 Uw = 112	No association
Di Bella et al. (2000)		AN = 112 BN = 50 Controls = 120	Association with S allele in BN
Sundaramurthy et al. (2000)	5-HTTLPR	AN = 138 Controls = 90	Association of S allele
Fumeron et al. (2001)	5-HTTLPR	AN = 67 Controls = 148	Association with S allele
Lauzurica et al. (2003)	5-HTTLPR-VNTR Intron 2	BNP = 102 Controls = 107	No association
Matsushita et al. (2004)	5-HTTLPR	AN = 77 BN = 118 Controls = 290	High frequency of S allele in ANR and ANBP
Rybakowski et al. (2006)	5-HTTLPR	AN = 132 Controls = 93	There was no association
Steiger et al. (2009)	5-HTTLPR	AN = 17 BN = 108 EDNOS = 60	Association between L_A allele and ED and AN subtype inhibitory/compulsive
Steiger et al. (2011)	5-HTTLPR	AN = 244 BN = 442 EDNOS = 112	No association
Camarena et al. (2012)	Gly56Ala	AN = 72 BN = 189 Controls = 226	Association between rare variant 56Ala and AN
Camarena et al. (2018)	5-HTTLPR/ rs24531	BN = 189 AN = 72 Controls = 337	Association with S/L_G alleles and BN ($p = 0.0088$)

VNTR, variable number of tandem repeats; Ob, obese; Uw, underweight

The analysis of a VNTR polymorphism located in intron 2 did not show an association in BNP patients. Also, haplotype analysis of 5-HTTLPR and VNTR-2 intron did not find significant differences between cases and controls (Lauzurica et al. 2003).

Interestingly, the analysis of the Gly56Ala variant in a case-control study reported an association with ED. In particular, it was observed a high frequency of 56Ala rare

allele in ED patients compared with controls (Camarena et al. 2012). The analysis of additional variants located in the *SLC6A4* gene may support additional information about the region that in linkage disequilibrium may be related to the susceptibility to ED.

Studies of Association of the SLC6A4 Gene and Psychopathological Traits in Eating Disorders

The presence of psychopathology has been estimated in 53 to 93% of ED patients (Garner 1993; Barajas-Iglesias et al. 2017). Interestingly, the *SLC6A4* gene is related with the susceptibility to develop several psychopathological traits, which are associated with a heightened risk of eating disorder. Also, the comorbid psychopathological features are related to the symptomatic expression and maintenance of an eating disorder (Bruce and Steiger 2013; Cassin and von Ranson 2005; Hollander 2013). The ED are complex psychiatric disorders, and identified homogeneous subtypes maybe help to identify the risk genes to develop the disorder. Therefore, several genetic association studies support the view that candidate genes do not participate in the susceptibility to ED but predispose to develop risk traits related to the ED.

In particular, patients with BN carriers of S allele 5-HTTLPR polymorphism showed an increased harm avoidance, elevated affective instability, comorbid borderline personality disorder, and impulsivity (Monteleone et al. 2006; Steiger et al. 2005, 2007). Two studies reported an association between the S variant and increased severity of depressive and bulimic symptoms in adolescents with ED (Castellini et al. 2012; Mata and Gotlib 2011). A latent class analysis observed an association between L_A allele of the triallelic polymorphism 5-HTTLPR/rs25531 and inhibited/compulsive group compared with dissocial/impulsive and low psychopathology groups (Steiger et al. 2009).

Interestingly, GWAS (genome-wide association studies) have been performed in AN identifying some variants related to psychiatric and metabolic conditions; however, the studies did not identify variants in the gene most analyzed in ED, the *SLC6A4* gene. No GWAS in BN has been conducted, and BED has been analyzed in comorbidity with bipolar disorder (Bulik et al. 2021). To date, the Eating Disorders Working Group of the PGC (Psychiatric Genomics Consortium) is interested in the inclusion of participants of diverse populations that facilitate the identification of variants in AN, BN, and BED (Hübel et al. 2018).

Gene x Environment Interaction Studies in Eating Disorder

Twin studies support evidence about environmental factors related to the risk to develop an ED. In particular, it has been reported that stressful life events increased susceptibility to ED.

Gene-environment interaction studies, such as the one performed in AN, reported interaction between a non-shared environment (personal problems) and the S-HTTLPR variant (Karwautz et al. 2011); also, a study reported an interaction between the S variant and insecure attachment in BN patients with a history of physical abuse and sexual activity during childhood (Steiger et al. 2007). In another study, an interaction was reported in patients with ED between self-mutilation behaviors and suicide attempts and the L-5-HTTLPR variant (Steiger et al. 2011). Studies in adolescent participants showed an interaction between S/L_G alleles of the triallelic system, and higher levels of childhood trauma showing several eating behaviours (Stoltenberg et al. 2012), and interaction between S allele and the experience of sexual abuse is related with higher binge eating and drive for thinness scores (Akkermann et al. 2012). A meta-analysis study analyzing the role of 5-HTTLPR and environmental and psychological factor interactions in the risk to ED showed that the S allele interacted with sexual and physical abuse to predict increased risk of bulimia-spectrum eating pathology (Rozenblat et al. 2017).

Studies of Sequence of SLC6A4

Whole-genome sequencing (WGS) and whole-exome sequencing (WES) are useful tools to identify the genetic architecture of complex diseases. These methodologies are based on the hypothesis of identified rare variants in common diseases that may be etiologically relevant (Dickson et al. 2010; Raychaudhuri 2011). To date, the exome-wide association studies in ED did not identify variants in the *SLC6A4* gene (Cui et al. 2013; Scott-Van Zeeland et al. 2014; Lutter et al. 2017; Lombardi et al. 2019; Bienvenu et al. 2019).

Interestingly, sequencing studies of the *SLC6A4* gene reported a genetic variant located in exon 9, the rs28914832, associated with compulsive traits and AN (Ozaki et al. 2003). Sequence analysis of five candidate exons of the *SLC6A4* gene identified in AN restrictive two novel variants (g.130delA and c.1740G>A), three synonymous variants (rs57172732, rs55908624, rs74478645), and a missense variant (rs11803088111) considered as deleterious and damaging variant (Fig. 1). In BNP were identified two novel variants (g.295C>G and c.1725G>A) and a non-synonymous variant (rs28914832), reported as benign (Fig. 2). Also, it was observed the 425 V variant in three patients with BN variant reported in patients of obsessive-compulsive spectrum (Hernández-Muñoz et al. 2020).

Conclusions

The current evidence suggested that the relationship between the *SLC6A4* gene and ED could be the result of multifactorial factors. The genetic susceptibility of the *SLC6A4* gene to ED and the comorbidity observed in the patients may suggest that both conditions share common variants related to the etiology and the phenotypic characteristics; therefore, it may be important to identify homogeneous phenotypes

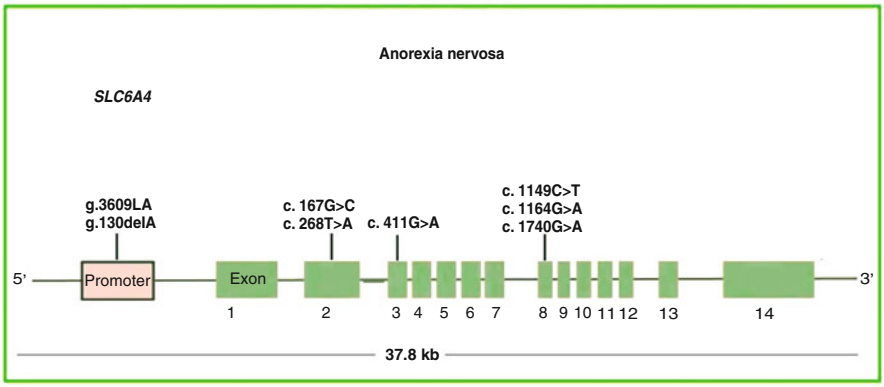


Fig. 1 Genetic variants identified in the gene in anorexia nervosa patients

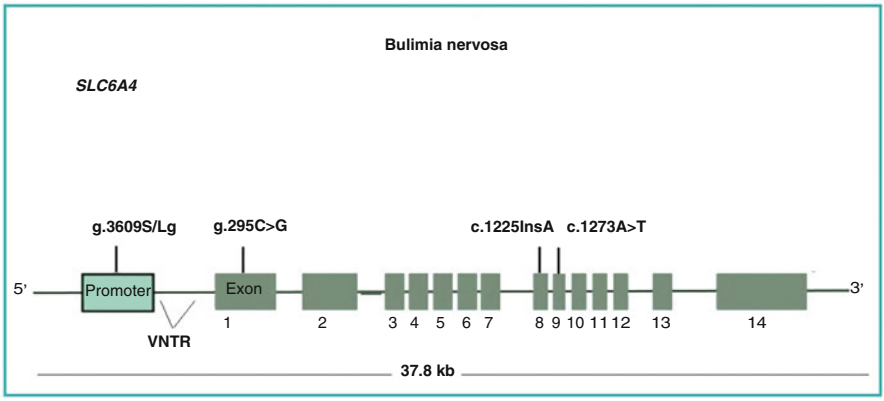


Fig. 2 Genetic variants identified in the gene in bulimia nervosa patients

that help us to detect the risk genes associated with the susceptibility to develop a particular phenotype.

Future studies in large sample sizes of patients with AN, BN, and BED are required to identify variants with a causal effect that helps us to understand the role of the *SLC6A4* gene in the susceptibility to develop an eating disorder.

Key Points

- 5-HTT key protein. Regulation of serotonin reuptake in the synapsis.
- Genetic variants. Modulate the gain of function of the protein.

Key Facts of Genes and Eating Disorders: A Focus on the Solute Carrier Family 6 (Neurotransmitter Transporter, Serotonin), Member 4 (*SLC6A4*) Gene

- Dysfunctions in the serotonin pathways are related to the etiology of eating disorders.
- Genetic variants of the *SLC6A4* gene are associated with anorexia nervosa and bulimia nervosa.
- The *SLC6A4* gene is associated with psychopathological risk traits in anorexia nervosa and bulimia nervosa.
- The biallelic and triallelic polymorphisms of the promoter region have been associated with eating disorders.
- Sequence analysis identified rare and low-frequency variants associated with anorexia and bulimia nervosa.

Summary Points

- The serotonin transporter is a key molecule that participates in the satiety signal in the brain participating in the susceptibility to eating disorders.
- Genetic studies suggest that the SLC6A4 gene is a candidate gene for eating disorders.
- The most studied polymorphism is the 5-HTTLPR located in the promoter region, which has been associated with susceptibility to eating disorders and psychopathological risk traits.
- Some studies support the evidence of Gene x environment interaction is related with the risk to develop an ED.
- The analysis of diverse populations may help to identify variants that confer genetic vulnerability to eating disorders.

Applications to Other Areas

The acknowledgment of the genes involved in the etiology of ED and with the clinical characteristics of a particular phenotype helps to develop new pharmacological treatments. In addition, the subjects at risk to develop an ED might receive genetic counseling to help to understand the risk of these diseases for the patient and their family.

The identification of the psychopathological traits related to the worsening of ED symptoms may help to find psychological therapies aimed to treat the severity of the disorder, for example, impulsivity in BN or perfectionism in AN.

An integrative treatment in ED patients that include psychologist, genetic counselors, psychiatrists, nutritionist, and physicians may be important to identify a personalized treatment and support for the patient and their family.

Identifying the medical comorbidities in the ED may help physicians in the treatment of medical complications and nutritional rehabilitation to develop personalized and integrative treatments.

Mini-Dictionary

Allele	It is one of two or more versions of DNA sequence at a given genomic location.
Chromosome	Threadlike structures made up of DNA that serve to carry the genomic information from cell to cell.
Exon	A polynucleotide sequence in a nucleic acid that codes information for protein synthesis.
Family study	Studies analyzing whether a disease or trait runs in a family
Gene	A specific sequence of nucleotides located in a chromosome and that is the functional unit of inheritance.
GWAS	Genome-Wide Association Study (GWAS) is an approach that involve scanning marker across the genomes of many people to identify genetic variants associated with risk of traits or diseases.
HeLa	It is an immortal cell line used in scientific research.
Interaction	It is the process by which two or more genes influence one another or with environmental factors in different ways affecting a phenotype.
Polymorphism	Two or more variant forms of a specific DNA sequence that can occur among different subjects or populations.
Promoter	A short DNA region where transcription of a gene begins.
Reuptake	Prime mode of inactivation of a neurotransmitter that is released from neurons.
Synapse	The site of transmission of electric nerve impulses between two nerve cells (neurons).
Transmembrane protein	A type of integral membrane protein that spans the entirety of the cell membrane.
Twin study	Studies conducted on identical or fraternal twins to analyze the contribution of genetic and environmental influences for traits or diseases.
Variant	A change in the DNA sequence.
VNTR	Variable number of tandem repeat (VNTR) is a location in the genome where a short nucleotide sequence is organized as a tandem repeat.
WGS	Whole genome sequencing (WGS) is a methodology to determine the entire DNA sequence of an organism at a single time.
WES	Whole exome sequencing (WES) is an approach that involves sequencing the protein-coding regions of the genome.

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Eating Disorders in Athletes

7

Melda Pelin Yargic and Faik Ozdengul

Contents

Introduction 112
Prevalence of EDs in Athletes 113
Risk Factors 113
Which Sports Disciplines Are at Higher Risk for EDs? 114
EDs in Male Athletes 115
Special Considerations on Anorexia Nervosa in Athletes 115
Special Considerations on Bulimia Nervosa and Binge Eating Disorder (BED) in Athletes ... 116
Special Considerations on Orthorexia Nervosa in Athletes 116
Relative Energy Deficiency in Sport (RED-S) 117
Tools for Screening EDs Specifically in Athletes 117
Application to Other EDs 119
Mini-Dictionary 119
Key Facts of EDs in Athletes 119
Summary Points 120
References 120

Abstract

Eating disorders (EDs) and disordered eating behaviors are common among athletes, more common in female athletes than males. Certain sports disciplines put athletes at more risk than others. Special attention should be given to the athletes of aesthetic sports, endurance sports, and weight category sports in terms of the risk of EDs. However, these risk factors should not result in creating a stereotype of "the athlete with ED" as such stereotyping may lead to an overlooked diagnosis of EDs in different athletes. In fact, male athletes have a higher rate of EDs than general population. Particular personality traits are common

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between EDs' patients and athletes. This intersection certainly creates a difficulty in identifying athletes that are especially at risk due to their personality characteristics, but this challenging situation also holds promising possibilities for treatment. Unhealthy weight management strategies are often observed among athletes. Comprehending the systemic effects of energy deficiency in sports is crucial for a multifaceted understanding of ED in athletes. Health-care professionals' awareness and knowledge on EDs in the athletic population and specific tools for screening may help in preventing irreversible consequences.

Keywords

Athlete · Sports · Lean sports · Energy availability · Eating disorder

Abbreviations

AN	Anorexia nervosa
BED	Binge eating disorder
BN	Bulimia nervosa
CHRIS-73	The College Health-Related Information Survey
ED	Eating disorder
FAST	The Female Athlete Screening Tool
LEAF-Q	The Low Energy Availability in Females Questionnaire
ON	Orthorexia nervosa
RED-S	Relative Energy Deficiency in Sport

Introduction

Engaging in regular exercise is beneficial to one's health in numerous aspects. It protects against cardiovascular diseases, diabetes, hypertension, obesity, stroke, several types of cancer, and so on (Ruegsegger and Booth 2018). It also has positive effects on mood states such as anxiety, stress, and depression (Mikkelsen et al. 2017). Besides all these substantial benefits, engaging in sports is associated with an increased risk of eating disorders (EDs) (Currie 2010). In fact, EDs are quite common among athletes (Bratland-Sanda and Sundgot-Borgen 2013).

Sports nutrition is a delicate subject. High energy and micronutrient demands of athletes can be met with rigorous planning and a painstaking application. And this needs to be maintained regularly for many years. Most athletes begin training at very early ages, and their preoccupation with food begins with it. As athletes reach adolescence, sensitive body image issues come to the stage. Unfortunately, the culture of specific sports almost promotes EDs during childhood and adolescence. Additionally, using/abusing sports supplements-drugs is common at all levels of sports (Ozkan et al. 2020; Yargic et al. 2021). Things get even more complicated if an athlete becomes famous. Being constantly under media attention, receiving frequent criticism from referees, fans, and sports commentators on their bodies put athletes, particularly ones with a perfectionist personality trait, at high risk for EDs

(Currie 2010). Such intersections are common in sports, as many athletes consider themselves to be perfectionists, many athletes are under performance pressure, and many have high media attention. Unfortunately, it is not always possible for athletes to get proper and high-quality counseling either, because health professionals also have very variable levels of knowledge and awareness about athlete nutrition and EDs in athletes (Curry et al. 2015; Özdengül and Yargic 2020). Understanding and hopefully preventing EDs in athletes is particularly important not only for their own health and well-being but also because they are role models to many children and adolescents.

In this chapter, we will try to review the risk factors, sports disciplines with high association with EDs, prevalence of EDs in athletes, ED in male athletes, special considerations for different types of EDs, and finally valid screening tools specifically developed for athletes.

Prevalence of EDs in Athletes

Prevalence studies on EDs consistently report more EDs in females than in males (Bratland-Sanda and Sundgot-Borgen 2013). This is also true when it comes to athletes; female athletes have a higher prevalence of EDs than male athletes. Schaal et al. reported that 4% of male vs. 6% of female athletes suffered from an ongoing ED, while 5.5% of male vs. 11.2% of female athletes suffered from a lifetime ED (Schaal et al. 2011). Nichols et al. reported 20.0% prevalence of disordered eating behavior among high-school female athletes (Nichols et al. 2007). In the study of Sundgot-Borgen and Torstveit, a prevalence rate of 20% was reported in female athletes vs. 8% in male athletes, while male controls' ED prevalence was 0.5% and female controls' was 9% (Sundgot-Borgen and Torstveit 2004). Byrne and McLean evaluated female and male elite athletes' and controls' eating behavior via structured diagnostic interviews and revealed that ED rates are as follows: female athletes 22%, male athletes 4%, female controls 5.5%, and male controls 0% (Byrne and McLean 2002). Although numbers vary, a consistent finding is that athletes are at higher risk than controls and females are higher than males.

Risk Factors

Some of the risk factors are common to the general population, while others are specific to athletes. Some of the general risk factors are female gender, body dissatisfaction, certain personality traits (such as perfectionism), low self-esteem, and history of abuse. Some of the risk factors specific to the athletic population are pressure from the coach, pressure to be successful, early onset of sport-specific training, and early onset of puberty (Sanford-Martens et al. 2007; Bratland-Sanda and Sundgot-Borgen 2013). Several situations were additionally identified as triggering factors for EDs in athletes. These include dieting for an extended length of

time, frequent weight swings, a rapid increase in training volume, and traumatic occurrences such as an injury or the loss of a coach (Sundgot-Borgen 1994).

Which Sports Disciplines Are at Higher Risk for EDs?

It is well known that prevalence of EDs is higher in athletes than in general population (Sundgot-Borgen and Torstveit 2004). However, the difference is much more prominent in certain sports disciplines.

In aesthetic sports, where athletes succeed according to the referee's opinion and aesthetic evaluation, physical appearance and leanness gain special importance. Gymnastics, rhythmic gymnastics, figure skating, roller skate figure skating, ballet, and dancing are examples of such sports. The frequency of EDs is found to be increased in the competitive athletes of these branches (Krentz and Warschburger 2011) (Fig. 1).

In endurance sports, a common belief is that being leaner would lead to faster paces because the athlete wouldn't have to carry the extra weight (Schotzko 2021),



Fig. 1 A young female gymnast. It should be a priority of sports-health professionals to keep those who are at high risk of ED safe. (Image: Freepik)

Table 1 Examples of sports disciplines with higher risk of EDs

"Lean" sports		
Aesthetic sports	Endurance sports	Weight category sports
Gymnastics, rhythmic gymnastics, figure skating, roller skate figure skating, ballet, dancing	Distance running, rowing, cycling	Judo, taekwondo

and in accordance with this belief, a high prevalence of EDs is observed in endurance runners and cyclists (Sundgot-Borgen and Torstveit 2004).

In many sports disciplines, such as wrestling, karate, and judo, athletes compete in narrow weight categories. Commonly, these athletes lose and gain weight rapidly, using unhealthy methods. These athletes are also at higher risk for EDs according to studies (Sundgot-Borgen and Torstveit 2004; Ackerman et al. 2011) (Table 1).

EDs in Male Athletes

EDs are predominantly studied in female athletes. This may be creating an erroneous representation of people who are at high risk for EDs in the eyes of physicians. Also, screening tools focus on female athletes with questions regarding menstrual health. However, research shows clearly that male athletes have higher rates of EDs than nonathlete males (8% vs. 0.5%) (Sundgot-Borgen and Torstveit 2004). EDs were found to be common among male rowers, cyclists, and even bodybuilders (Thiel et al. 1993; Goldfield et al. 2006; Riebl et al. 2007).

The image of a female gymnast that comes to mind first when it comes to "EDs and sports" is, of course, based on a scientific basis. However, stereotyping this example should not result in ignoring the EDs of many different athletes.

Special Considerations on Anorexia Nervosa in Athletes

In 1983, researchers reported that a subgroup of male runners' psychological traits were very similar to those of female anorexia nervosa patients. They called these male runners "obligatory runners." The common traits and behaviors were inhibition of anger, perfectionism, unrealistic high self-expectations, physical resilience, refusal to acknowledge possibly substantial debility, tendencies toward depression, weight preoccupation, rigid dieting, and running to compensate for overeating (Yates et al. 1983). Later, it was proposed that some characteristics of athletes which are often associated with anorexia nervosa are perhaps the reason behind these athletes' success (Thompson and Sherman 1999).

Many similarities between AN patients and athletes definitely complicate defining athletes who are at higher risk of EDs due to their personality traits, but it should be kept in mind that they may also assist in the treatment process.

Special Considerations on Bulimia Nervosa and Binge Eating Disorder (BED) in Athletes

Athletes need to maintain a certain body weight and composition for a long period of time (Yargic et al. 2020). For this purpose, many of them often utilize unhealthy weight management strategies. Such unhealthy behaviors include strict dieting, fasting, restricting fluids, spitting, excessive exercising, training in heated rooms, self-induced vomiting, and using laxatives/enemas/diuretics (Artioli et al. 2010; da Silva Santos et al. 2016). Such pathological weight management methods are sometimes accompanied by binge eating attacks as well. These combined make up for a substantial part of the diagnostic criteria of bulimia nervosa. One study with 218 female gymnasts revealed that more than one third of participants reported binge eating at least once a week, almost half of them (48.6%) exercised in order to burn calories for more than 2 hours a day, and one fifth did strict diets or fasting in the previous year. Indeed, in this study, 4% of participants have met the full criterion of bulimia nervosa (Petrie and Stoever 1993). Such behavior is not only common in female gymnasts but in a broader athlete population, including among male athletes that engage in power sports. For example, high prevalence rates of binge eating (48%), bulimia nervosa (30%), and preoccupation with body weight and body image (84.6%) were observed among competitive male body-builders (Goldfield et al. 2006). Although a wide range of athletes are at risk of bulimia nervosa and BED, special attention should be given to athletes who compete in weight categories, as they practice rapid weight loss methods more often.

Special Considerations on Orthorexia Nervosa in Athletes

Orthorexia nervosa, unlike other EDs, is shaped around an obsession with healthy eating, which has no relation to body weight or body perception. In this regard, the control of body weight is not in the focus. Instead, food sources, the way the food is prepared and packaged, naturalness, and healthiness are at the forefront. There is a moderate correlation between exercise addiction and orthorexic eating, but this correlation doesn't imply that all athletes are prone to orthorexia (Strahler et al. 2021). It's not infrequent that elite athletes develop unhealthy habits, such as substance, alcohol, or drug abuse (Reardon and Creado 2014; Martens 2017). Therefore, the inference that elite athletes adopt a healthy lifestyle and thus should be more inclined toward orthorexic behavior cannot be made so easily. Indeed, research examining ON tendencies of athletes shows a great deal of diversity in results. Some studies find that being an elite athlete, recreational athlete, or a sedentary person doesn't affect one's tendency toward ON, whereas others report ON to be a frequent ED among athletes (Segura-García et al. 2013; Özdengül et al. 2021).

Relative Energy Deficiency in Sport (RED-S)

A relative deficiency in energy refers to the mismatch between the energy that the athlete receives with the diet and the energy that she/he spends on exercise. Energy that will support the functions necessary to maintain the ideal health and performance of the body cannot be contained in the system. Available energy is calculated by subtracting the energy consumed by exercise (kcal) from the energy received by diet (kcal) and dividing the difference by lean body weight (kg). The ideal available energy level for the physiological function of women has been determined as 45 kcal/kg FFM/day (Loucks and Thuma 2003). On the other hand, the value of 30 kcal/kg FFM/day has been determined as a value where the functions of many systems are disrupted and energy availability is low (Williams et al. 2015) (Fig. 2).

A very important issue regarding the RED-S syndrome is that it is not always related to a disordered eating behavior. An athlete can simply be unaware of the negative energy balance. Additionally, many athletes suffer from asymptomatic vitamin deficiencies regardless of their eating habits (Dönmez et al. 2018). Mostly, this is due to being reckless of their dietary needs. Even so, understanding RED-S and its multisystemic effects is crucial in evaluating and treating athletes who are in energy deficit due to an ED (Fig. 3).

This syndrome was previously known as the female athlete triad, which had a narrower scope. The female athlete triad is a diagnosis limited to bone and reproductive health. On the other hand, the diagnosis of a relative lack of energy in sports also includes disorders associated with the endocrine system, immune system, cardiovascular system, gastrointestinal tract, hematological system, metabolic system, and growth and development (Mountjoy et al. 2018) (Table 2).

Tools for Screening EDs Specifically in Athletes

There are several validated tools to screen for disordered eating in athletes and some are in development. The College Health-Related Information Survey (CHRIS-73) is one of these available instruments. It is validated among college student athletes and consists of four factors (mental health, eating problems, risk behaviors, and

$$\text{Available Energy} = \frac{[\text{Calorie input (kcal)} - \text{Calorie expended by exercise (kcal)}]}{\text{Lean body mass (kg)}}$$

Fig. 2 Equation of available energy level



Fig. 3 Interpretation of available energy levels in females

Table 2 Effects of energy deficiency on systems

Endocrine	Disturbed hypothalamic-pituitary-gonadal axis Disturbed thyroid function Alterations in appetite regulatory hormones Decreased insulin and insulin-like growth factor 1 Increased growth hormone resistance Elevated cortisol levels Disrupted gonadotropin-releasing hormone pulsatility Alterations of LH and FSH release Decreased estradiol and progesterone levels	Nattiv et al. (2007), Misra (2014), Allaway et al. (2016), Gordon et al. (2017)
Bone	Decreased bone mineral density Impaired bone microarchitecture Higher risk for bone stress injuries Decreased bone formation and increased bone resorption	Hind et al. (2006), Ackerman et al. (2011), Papageorgiou et al. (2017)
Cardiovascular	Early atherosclerosis Endothelial dysfunction Disturbed lipid profile Valve pathologies Pericardial effusion Bradycardia Hypotension Arrhythmias	Rickenlund et al. (2005), O'Donnell et al. (2011), Spaulding-Barclay et al. (2016)
Immunological	Increased upper respiratory symptoms Lower immunoglobulin A secretion rates Increased risk of illness	Shimizu et al. (2012)

performance pressure) (Steiner et al. 2003). Another tool, which was developed for female athletes, is the ATHLETE questionnaire. The ATHLETE questionnaire has five factors (drive for thinness and performance, social pressure on eating, performance perfectionism, social pressure on body shape, and team trust). All of these factors are predictive of disordered eating in female athletes (Hinton and Kubas 2005). As EDs are more common in females, more tools are developed for identifying them in females. Another example of such questionnaires is the FAST (the Female Athlete Screening Tool). With high internal consistency and high discriminative validity, FAST is a valid tool for detection of disordered eating in female athletes (McNulty et al. 2001). The Low Energy Availability in Females Questionnaire (LEAF-Q) consists of 25 items. It doesn't only question disordered eating but

Table 3 Summary of the tools for screening EDs specifically in athletes

College Health Related Information Survey (CHRIS-73)	Steiner et al. (2003)
The ATHLETE questionnaire	Hinton and Kubas (2005)
The Female Athlete Screening Tool (FAST)	McNulty et al. (2001)
Low Energy Availability in Females Questionnaire (LEAF-Q)	Melin et al. (2014)

also injuries and gastrointestinal and reproductive function because the LEAF-Q was originally developed as a screening tool for the female athlete triad (Melin et al. 2014) (Table 3).

Application to Other EDs

Athletes are prone to almost all types of EDs. Athletes' shared personality traits with anorexia nervosa patients, unhealthy weight management strategies shared with bulimia nervosa patients, binge eating shared with binge ED patients, and frequent disordered eating habits shared with eating disorders not otherwise specified (EDNOS) patients paint a picture of the grift and complex situation. Understanding, evaluating, preventing, or treating EDs is challenging in the athletic population. Considering the high prevalence of EDs in athletes, screening should be done periodically for all types of EDs.

Mini-Dictionary

- **Lean sports:** Sports disciplines that put high emphasis on physical appearance and leanness.
- **Non-lean sports:** Sports disciplines such as ball sports or power sports with no special emphasis on having a lean appearance.
- **Relative energy deficiency in sport:** A multisystemic syndrome that results from low energy availability in athletes.
- **Energy availability:** The energy difference between dietary intake and exercise-related expenditure in proportion to lean body weight.
- **Prevalence:** The proportion of a specific population that has a certain condition/disease/disorder in a given time.

Key Facts of EDs in Athletes

- Certain sports are categorized as "lean sports." Athletes of these sports disciplines share the belief that leanness is associated with athletic success. These disciplines include aesthetic sports (such as gymnastics, dancing etc.), endurance sports (such as running, cycling, rowing, etc.), and weight category sports (such as judo).

Summary Points

- Athletes that perform lean sports are at higher risk for EDs.
- Female athletes are at higher risk for ED than male athletes, but disordered eating is common among male athletes as well.
- Certain personality traits of athletes are common with anorexia nervosa patients.
- Unhealthy weight management strategies are often utilized by athletes.
- There are tools for screening EDs specifically in athletes.

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8 Eating Disorders in Children and Adolescents with Attention Deficit Hyperactivity Disorder

Zahra Saif and Haitham Jahrami

Contents

Introduction 124
ADHD: A Prevalent Neurodevelopmental Disorder in Children and Adolescents 125
ADHD Diagnosis and Etiology 125
ADHD Comorbidities 126
Eating Patterns of Children with ADHD 127
Loss of Control (LOC) Eating/Binge Eating 128
Binge Eating Disorder (BED) 129
Bulimia Nervosa (BN) 130
Anorexia Nervosa (AN) and Avoidant/Restrictive Food Intake Disorder (ARFID) 130
Prevalence of ED in Children and Adolescents with ADHD 131
The Role of Gender in the Prevalence of ED Among Children and Adolescents with ADHD 132
Risk Factors for ED in Children and Adolescents with ADHD 133
Psychiatric Comorbidities and Emotional Regulation Difficulties (ERD) 133
Sleep Disturbances: The Overlooked Factor for Disordered Eating 134
Digital Media Use Influences on Body Satisfaction and Eating Behaviors 134
Possible Mechanisms Underlying the Association Between ADHD and ED 136
Clinical Implications/Clinical Management of ADHD and Eating Disorder 137
Applications to Other Eating Disorders 138
Mini-Dictionary of Terms 139
Key Facts of Eating Disorders in Children and Adolescents with ADHD 140
Key Facts of Reward Deficiency Syndrome (RDS) 140
Key Facts of Stimulant Drugs for ADHD 140
Summary Points 140
References 141

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Abstract

Eating disorders (ED) are prevalent comorbid conditions in children and adolescent with attention deficit hyperactivity disorder (ADHD). It is estimated that children with ADHD have up to threefold increased risk for eating disorders compared to healthy controls most predominately for binge eating disorder and bulimia nervosa. Psychiatric comorbidities like depression, anxiety, and substance use disorders are common in children and adolescents with both ADHD and ED that need to be addressed early for optimal management. The roles of psychopathology, emotional regulation difficulties, and impulsivity features of ADHD as mediators between ADHD and ED have been widely highlighted in the literature. The chapter goes on to investigate the association between ADHD and ED in pediatric population based on review of the literature. Besides, studying disordered eating behaviors, and risk factors and underlying mechanisms for ED in children and adolescents with ADHD, is needed to develop effective intervention modalities for ADHD and ED.

Keywords

ADHD · Adolescents · Anorexia nervosa · Attention deficit hyperactivity disorder · Binge eating · Bulimia nervosa · Children · Disordered eating behaviors · Eating disorders · Eating habits · Food addiction · Food restriction · Obesity · Teenagers

Abbreviations

ADHD	Attention deficit hyperactivity disorder
AN	Anorexia nervosa
ARFID	Avoidant/restrictive food intake disorder
BED	Binge eating disorder
BMI	Body mass index
BN	Bulimia nervosa
DSM-V	American Psychiatric Association's Diagnostic and Statistical Manual, fifth edition
EAT-26	Eat Attitudes Test-26
ED	Eating disorders
ERD	Emotional regulation difficulties
LOC	Loss of control
RDS	Reward deficiency syndrome

Introduction

Attention deficit hyperactivity disorder (ADHD) is the most common neurodevelopment disorder that affects children and adolescents less than 17 years old. Despite the variance in the prevalence rate of ADHD across countries, a meta-

analysis of over one million participants across the world found that ADHD prevalence estimate is around 7.2% (Thomas et al. 2015). ADHD is marked by its behavioral manifestation that can occur in childhood, but persists into adulthood. Individuals with ADHD can show persistent symptoms of either inattention, hyperactivity-impulsivity, or a combination of inattention and hyperactivity-impulsivity. These behavioral symptoms in school-aged children and adolescents are associated with developmental issues and impairments in social, academic, and occupational functioning resulting in dysfunctions in the individual and family life (Berger 2011).

ADHD coexists with some comorbid conditions, nonpsychiatric and psychiatric, that can complicate the path to recovery and make the management of such chronic illness more complex (Akmatov et al. 2021). Predominant ADHD comorbid conditions include conduct disorder, oppositional defiant disorder, behavioral problems such as substance use, learning difficulties, and anxiety and mood disorders (Rader et al. 2009; Bélanger et al. 2018). Eating disorders (ED) is one of these co-occurring diagnoses that has received high attention. There is compelling evidence suggesting that individuals with ADHD have three times increased risk for ED (Jahrami et al. 2021b).

Intensive investigation of ADHD comorbid conditions like eating disorders is vital for developing an optimal treatment approach since comorbidities can affect the clinical presentation and severity of illness, response to therapeutic intervention, and prognosis (Bélanger et al. 2018). This chapter aims to investigate the association between ED and ADHD in children and adolescents and highlight its implications for effective treatment management.

ADHD: A Prevalent Neurodevelopmental Disorder in Children and Adolescents

ADHD Diagnosis and Etiology

After depression and anxiety, ADHD is the third most prevalent mental health disorder worldwide, affecting more males than females in a 3:1 ratio (Polanczyk et al. 2015). ADHD is classified as a neurodevelopmental disorder by the American Psychiatric Association's Diagnostic and Statistical Manual of Mental Disorders, fifth edition (DSM-V), and is defined as "a persistent pattern of inattention and/or hyperactivity-impulsivity that interferes with functioning or development and negatively impacts social and academic/occupational activities" (2013). The presentation of ADHD is affected by gender; it has been discovered that males have a higher risk of developing ADHD, specifically the combined presentation hyperactivity/impulsivity, while inattention presentation is more common in females. To meet DSM-V diagnostic criteria for ADHD, the child must present with a 6-month history of inattention, distractibility, hyperactivity, fidgetiness, and/or impulsivity, and these symptoms should be present in multiple settings including home, school, and/or clinical settings. ADHD is mostly identified in school-aged children as child behaviors become noticeably inconsistent with their developmental age and cause distress,

poor academic performance, and functional and social impairments at home and school.

Although a definite causality of ADHD remains unknown, ADHD has multiple etiologies, including a mix of genetic, neurological, and environmental factors. Factors affecting brain development or linked to brain injuries, such as hypoxic-anoxic brain injuries, epilepsy disorders, and traumatic brain injury, are the most common neurological factors contributing to ADHD risk. Pregnancy and birth complications such as low birth weight and preterm birth and uterus exposure to excessive alcohol and tobacco are among environmental risk factors for ADHD (Banerjee et al. 2007). Besides, exposure to adverse life events, unhealthy family environment, psychopathology of parents, and poor parenting strategies/style are associated with ADHD symptoms (Huhdanpää et al. 2021). It can be proposed that the interaction between the genetic and environmental factors throughout illness account for the complexity of ADHD.

The management of ADHD is based on behavioral intervention, pharmacologic therapy, or combined. Nonetheless, behavioral interventions are the most common intervention. It consists of life skills and social skills training, behavioral modification, parenting skills training, and family support groups. The pharmacologic therapy is based on the use of psychostimulant medications, such as methylphenidate and mixed amphetamine salts, or non-psychostimulants, such as atomoxetine. The psychostimulant treatments are associated with a reduction in symptomatology and improvement in functional and academic performance. The adoption of combined pharmacologic and behavioral interventions has been highly recommended as behavioral interventions can aid in reducing the need for a high dosage of medications, thereby reducing some of its undesirable side effects (Rader et al. 2009).

ADHD Comorbidities

ADHD has multiple comorbidities that determine the course of illness and prognosis. The most predominant comorbid conditions are represented in the Fig. 1.

It is worth showing that these comorbid conditions share some commonality with ADHD in terms of symptom similarities and etiologies, many of which are listed as part of the 16 differential diagnoses for ADHD set by the DSM-IV, while the rest are conditions that are frequently misdiagnosed as ADHD (Bélanger et al. 2018). This makes the diagnostic process of ADHD challenging, especially with the variations in diagnostic methods and the absence of biological markers.

The prevalence of ADHD comorbid conditions in children is high. It has been estimated that more than one-third of children with ADHD had at least one or more comorbid conditions. Fifty percent of these children are likely to have ADHD symptoms in adulthood. The main predictors that account for symptom persistence include severe symptomatology, ADHD combined subtype (inattention/hyperactivity), and psychiatric comorbidity, namely, mood disorders, multiple comorbidities, and parental anxiety (Lara et al. 2009).



Fig. 1 Attention deficit hyperactivity disorder comorbid conditions. Common comorbid conditions associated with attention deficit hyperactivity disorder

Eating Patterns of Children with ADHD

The association between ADHD and obesity has been extensively researched since both conditions are major public health problems that impact people of all ages and are linked to high morbidity and mortality rates. Contrary to the presumption that ADHD can be associated with weight loss due to hyperactivity symptoms, it has been found that children and adults with ADHD have significantly higher rates of more than average body mass index (BMI) and/or obesity. Based on the findings of a recent meta-analysis of 42 studies involving a total of 728,136 individuals (48,161 ADHD subjects; 679,975 comparison subjects), 70% of adults with ADHD and 40% of children with ADHD had an increased risk for obesity compared to the general population (Cortese et al. 2016). It is worth noting that the obesity prevalence was significant in included studies after adjustment for age, gender, race/ethnicity, family status and structure, and parental

education. It has been found that both males and females with ADHD hyperactive-impulsive presentation had considerably higher BMI compared to those without ADHD, yet only females with ADHD inattentive presentation had significantly higher BMI. However, most of the published studies did not control for the effect of medication and psychiatric comorbidity, especially that besides ADHD, depression, and anxiety are associated with obesity among children and adolescents. Conversely, several research evidences pointed to the high prevalence of ADHD symptomatology in children seeking obesity treatment. Considering the mixed findings related to whether ADHD precedes obesity or obesity leads to ADHD symptoms, this bidirectional relationship between the two conditions is complex and unclear, requiring rigorous testing. Some argue that the interplay between genetic factors and shared unhealthy lifestyle factors, including diet, sleep, and physical activities by family members, may explain the correlation between obesity and ADHD in children (Cortese 2019).

The link between ED, obesity, commonly known weight-related problems, and ADHD is established, and eating patterns of children with ADHD have been widely investigated. This section will address key findings related to disordered eating patterns in children and adolescents with ADHD.

Loss of Control (LOC) Eating/Binge Eating

In pediatrics, LOC eating is a form of disinhibited or binge eating behaviors that is characterized by frequent consumption of large amounts of food and difficulties resisting the urge to eat. LOC eating also is predictive for excessive weight gain and negative psychological consequences. Recurrent LOC or binge eating is the hallmark behavior of ED diagnoses including bulimia nervosa (BN) and binge eating disorder (BED). It has been noted that only a few children and adolescents meet the criteria for BED; therefore, the adoption of LOC eating term over BED is more favorable for this population group (Tanofsky-Kraff et al. 2008).

It has been found that around two-thirds of adolescents with obesity experience LOC eating (Wentz et al. 2019). Besides, the odds of LOC eating are significantly higher in children with ADHD; it is estimated to be 12 times more in those with than without ADHD (Reinblatt et al. 2015b). There is a positive correlation between ADHD symptoms and overeating behaviors in the aspects of unhealthy diet intake, increased frequency of overeating episodes and diet speed, and emotional eating, in which the person tends to overeat in response to emotional distress, eating for pleasure, and eating in response to external cues such the deliciousness and appearance of food (Kaisari et al. 2017). Some of the prominent aspects of LOS eating in youths include eating in reaction to stimuli, eating alone or while watching TV, and having poor awareness of the amount of food consumed or what is going on in the moment (Tanofsky-Kraff et al. 2008). It has been suggested that those youths with LOC eating are at greater risk for developing a disordered eating attitude and depressive and anxiety symptoms in the long term (Tanofsky-Kraff et al. 2011).

A study evaluated response inhibition in youth with LOC eating, adopting performance-based measures as objective measure and parent rating scale as a subjective measure, found that the manifestation of impaired response inhibition is significantly higher among those with than without LOC eating. This can represent the role of impulse control deficits as a potential mediator between ADHD and LOC (Reinblatt et al. 2015b). Impaired impulse control and impaired executive function are hypothesized to be mechanisms contributing to disinhibited eating behaviors. There is growing evidence suggesting the role of childhood impulsive behaviors to be above inattention and hyperactivity effects in predicting pathological eating behaviors during adolescence. Moreover, conflictual parent and child relationships and high emotion expression are common in families having children with ADHD and are assumed to be a predictive factor for disordered eating in girls with ADHD. Nevertheless, it has been found that families with high emotional expressions characterized by high levels of criticisms and punitive parenting style can predict eating pathology only after controlling for ADHD. This may support the notion that internalized variables such as impulsivity, rather than externalized ones, have a role in pathological eating behaviors (Mikami et al. 2008).

Binge Eating Disorder (BED)

Recurrent episodes of binge eating/LOC eating have been found to have a clinically significant association with eating disorders. Numerous studies have demonstrated the association between ADHD and BED in adults. Only a few studies have affirmed this association in pediatric population. Data from a cross-sectional study based on clinical mental health settings has shown that children with ADHD had 16 times increased odds for developing BED, based on rigorous diagnostic criteria, compared to their counterparts without ADHD. It is estimated that 24% of children with ADHD had met the diagnostic criteria for BED (Reinblatt et al. 2015a). Besides, those children with BED and ADHD had higher rates of depressive symptoms and greater BMI and obesity rates, with those who were prescribed antidepressants having significantly higher BMI. It is worth noting here that the role of psychiatric comorbidity as a potential mediator between ADHD and BED has not been investigated in most published pediatrics studies. Interestingly, recent evidence on adults with ADHD pointed out that after adjusting for comorbid psychopathology, the association between BED and ADHD did not reach statistical significance (Ziobrowski et al. 2018). Such evidence may support the hypothesis that underlying psychopathology may affect the association between binge eating and ADHD; thus, taking psychopathology into account is pivotal to best understand this association between BED and even other ED and ADHD.

Bulimia Nervosa (BN)

During binge eating episodes, adolescents have greater tendencies to develop concerns such as overeating, weight, and shape (Hilbert and Czaja 2007). The development of bulimia nervosa (BN) in pediatrics with childhood ADHD is high (Cortese et al. 2007), and is likely to manifest during mid-adolescence (Mikami et al. 2010). Owing to body weight and shape dissatisfaction and potentially peer pressure, adolescents with ADHD have higher tendencies to engage in purging and other inappropriate compensatory behaviors to prevent weight gain following binge eating. Similarly, some suggest that obese youth with bulimic behaviors are likely to present with ADHD symptoms (Cortese et al. 2007). Both conditions share similar clinical features in terms of impaired impulse control. Some argue that childhood impulsivity is a strong predictor for BN symptoms during adolescence. Moreover, Schweickert et al. (1997) argued that disordered eating in adolescents with ADHD is a maladaptive compensatory mechanism to manage frustration associated with deficits of attention and organization skills. It is possible to argue that the inattention dimension of ADHD may contribute to disordered eating patterns. Still, the compulsive eating behaviors can interrupt one's activity, leading to worsening of inattention symptoms.

Anorexia Nervosa (AN) and Avoidant/Restrictive Food Intake Disorder (ARFID)

Eating and weight-related problems lead to the adoption of unhealthy weight control behaviors such as dieting and skipping meals, which were found to be a predictor for weight-related issues in adolescence (Neumark-Sztainer et al. 2007). The interplay between negative body image, weight control-related social pressure, and restraint eating can contribute to development of AN characterized by extreme self-starvation. AN is prevalent mostly in female but far less compared to BED. Attempts to establish a connection between AN and ADHD were weak, and the association between these concurrent conditions was not significant (Råstam et al. 2013).

The onset of restrictive food behaviors can start early in young children and lead to nutritional deficits. Avoidant/restrictive food intake disorder (ARFID) has proven to be common co-occurring eating disorder with ADHD. Unlike AN, food restricting behaviors in ARFID are not attributed to distorted body image or weight concerns. Rather, it can be related to decrease interest in food, repulsion of some food characteristics, or fear from eating. Similar to children and adolescents with ADHD, pediatrics with ARFID has higher vulnerability for anxiety disorders. It has been proposed that anxiety affects the reasoning behind restrictive food behaviors in ADHD, thereby serving as a trigger for ARFID (Nicely et al. 2014). Attention should be directed toward unfavorable side effects of some

stimulant therapy drugs for ADHD management, namely, loss of appetite especially for those with ARFID, which can aggravate food restraint behaviors (Pennell et al. 2016).

Children with ADHD are likely to have difficulty adhering to meals' time schedule with a higher frequency of irregular eating time and skipping meals. ADHD children's diet is characterized by lower nutritional value as they incline to consume less fruit and vegetables but high sweetened beverages. Also, children with ADHD have limited involvement in physical activities (Ptacek et al. 2014). It worth mentioning that patients with ADHD may present with normal weight, but still suffer from disruptive eating behaviors that require early detection and intervention. Even in the absence of disordered eating, higher ADHD symptomatology predicts high fat mass on later ages (Bowling et al. 2018) and increased risk for malnutrition (Güngör et al. 2016).

Prevalence of ED in Children and Adolescents with ADHD

Our research group has published a case-control study on the prevalence of ED in a sample of children and adolescents with ADHD conducted in the Child/Adolescents Psychiatry Unit – Kingdom of Bahrain. Seventy cases with ADHD aged between 8 and 19 years old were recruited and matched with 140 healthy controls. The Eating Attitudes Test-26 (EAT-26) was used as measure to estimate risk of ED. We found that children and adolescents with ADHD have a threefold higher risk for ED than healthy controls (Jahrami et al. 2021b). These findings are in line with Nazar et al. (2016) results that patients with ADHD have threefold increased risk for ED, while patients with ED have twofold risk for ADHD. Our data also revealed that increased BMI/body weight is a predicator for increased risk of ED. In addition, we found that female has slightly increased risk for ED than male though it did not reach statistical significance which is perhaps due to the small sample size (Jahrami et al. 2021b). The increased risk of ED among female cases is consistent with preliminary evidence from epidemiological studies in which ED is more common in females than males (Striegel-Moore et al. 2009).

The Table 1 represent the key findings.

The greater manifestation of ADHD symptomatology in patients with ED is associated with more severe eating pathology, though differences do exist between ED subtypes. The table below represents estimated prevalence rate of different ED in pediatrics with ADHD. BN is the most prevalent form of ED among people with ADHD (Nazar et al. 2016). Similarly, it has been found that patients with BN and BED, characterized by poor impulse control, are more likely to present with more ADHD symptoms compared to those with AN (Fernández-Aranda et al. 2013) (Table 2).

Table 1 Sociodemographic characteristics and risk of eating disorder: comparison between cases and controls

Characteristics	Cases/($N = 70$)	Controls (N-140)
ED status measured by EAT-26		
Normal At risk	68.57 31.43	87.86 12.14
Medication CNS stimulants methylphenidate	38.57	—
Categorical variables (%)		
Gender (male)	74.29	74.29
Gender (female)	25.71	25.71
Overweight	18.57	47.86
Obese	4.29	14.29
ADHD type		
Inattentive. Hyperactive-impulsive. Mixed type.	24.29 17.14 58.57	
Continuous variables (mean)		
Age	13.45	15.62
Body mass index (BMI)	19.02	25.57

Key findings of risk of eating disorders among children with attention deficit hyperactivity disorder compared to controls. From Jahrami, AlAnsari et al. (Jahrami et al. 2021b) with permission

Table 2 Prevalence rate of different eating disorders in pediatrics with attention deficit hyperactivity disorder

Eating disorder diagnoses	Prevalence in children and adolescents with ADHD (%)
Bulimia nervosa	9–34.9
Binge eating disorder	19.8
Anorexia nervosa	3–16.2

Estimated prevalence rate of different eating disorders in pediatrics with attention deficit hyperactivity disorder based on recent research evidence

The Role of Gender in the Prevalence of ED Among Children and Adolescents with ADHD

There is an interesting evidence suggesting the ADHD precedes the development of ED. In other words, ADHD is a risk factor for ED in youths and adult. There is consensus that both girls and boys with ADHD are at increased risk for ED. Nevertheless, the findings are mixed regarding the effects of gender on the ADHD and ED. It has been found that girls with ADHD and ED are more vulnerable to depressive and anxiety disorders and behavioral disturbances, including addictive behaviors, than those girls with ADHD only indicting heightened risk for morbidity and dysfunction (Biederman et al. 2007). Longitudinal study revealed that girls with ADHD have higher prevalence of anxiety and depressive symptoms but a lower prevalence of antisocial disorders compared to boys (Biederman et al. 2010). The

level of BN symptoms is higher in girls than boys with ADHD, while binge eating manifest more in boys. There are no significant gender differences in the age and body weight of patients with ED at presentation (Welch et al. 2015). The size of increased risk of ED diagnoses in pediatrics with ADHD is very similar to that of adults. Given that growing body of evidence has showed the association between ADHD and obesity, the risk association between ADHD and ED in both genders is around double that association with obesity (Nazar et al. 2016).

Risk Factors for ED in Children and Adolescents with ADHD

Psychiatric Comorbidities and Emotional Regulation Difficulties (ERD)

Depression, anxiety, and substance use disorders are common psychiatric comorbid conditions linked to ED, and, likewise, it has been linked to ADHD. It has been found that individuals with ADHD and ED are at greater risk of psychiatric comorbidity compared to those with ED or ADHD only. As stated earlier, it can be argued that psychiatric comorbidity may account partially for the association between the two diagnoses (Ziobrowski et al. 2018). Consequently, it can complicate the management of both disorders as those with high psychiatric comorbidities are likely to experience greater occupational and psychosocial dysfunction and poorer patient and family quality of life (Kandemir et al. 2014).

Emotional regulation difficulties (ERD) are facets of response inhibition problems and are identified as a core risk factor for both ADHD and ED (Christian et al. 2020). Emotional regulation constitutes five processes: situation selection, situation modification, attentional deployment, cognitive change, and response modulation (Sheppes et al. 2015). During negative emotional state, individual's perceptions and modulation of situations and ability to manage emotional regulation processes can be impaired, consequently increasing tendency to involve in inappropriate actions/maladaptive behaviors including pathological eating, which in turn can induce negative affectivity. The role of ERD in predicting persistence of ADHD symptoms overtime is established (El Archi et al. 2020). Greater ERD at baseline account for higher ADHD symptomatology at follow-up (Masi et al. 2020) leading to functional impairments and psychosocial dysfunction. It has been found that youth diagnosed with ADHD has lower tolerance for stress and frustration than those without ADHD (Barkley 2016) and is at greater risk for suicidal and self-harm behaviors, poor adherence to treatment, and greater stress level (Seymour et al. 2012). The inattention features of ADHD correlate with impaired situation identification, while hyperactivity-impulsivity features are related to poor emotional response inhibition. Robust evidence has revealed that relationship between ADHD and disordered eating (addictive-like eating) is mediated by emotional regulation as illustrated in Fig. 2. Similarly, ERD in adolescents with ADHD account for increased vulnerability for various addictive disorders such as games and food addictions (Evren et al. 2018) and substance use (Poon et al. 2016).

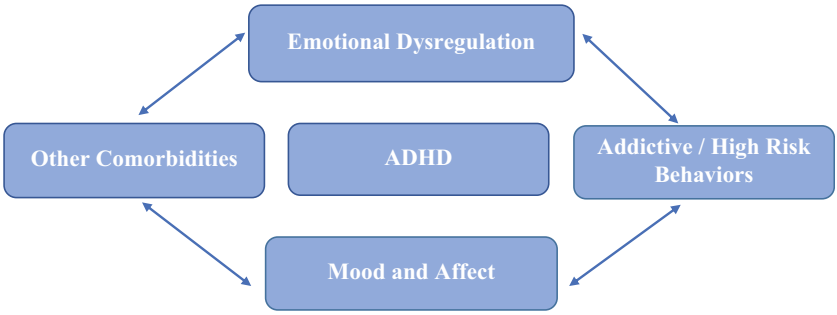


Fig. 2 The role of emotional regulation difficulties as a mediator between attention deficit hyperactivity disorder and disordered eating. The link between attention deficit hyperactivity disorder symptoms, emotional dysregulation, affect, and addictive/high-risk behaviors

Sleep Disturbances: The Overlooked Factor for Disordered Eating

The interrelationships between sleep disturbances and ADHD are complex and potentially multifactorial. Sleep disturbances are more prevalent among children and adolescents with ADHD compared to the general population. It is estimated that between 25% and 50% of children and adolescents would present with sleep problems including difficulty initiating and/or maintaining sleep along with daytime sleepiness (Cortese et al. 2009). Interestingly, excessive daytime sleepiness has been positively associated with symptoms of hyperactivity, inattention, and impulsivity in children. Nováková et al. (2011) argue that circadian system subtle differences between children with ADHD and those without are contributing factors that can affect sleep quality, attention, and activity level, thereby imposing greater consequences on daytime functioning. Moreover, individuals with ED have significantly higher risk for sleep problems, obesity, and daytime dysfunction.

Studies have pointed out that sleep deprivation can contribute to disruption of appetite-regulating hormones leading to weight gain and obesity and an increased risk for mood disorders (Allison et al. 2016). Indeed, sleep intervention for children and adolescents with ADHD is crucial to manage the disorder and its comorbidities. Authors emphasized the importance of sleep and other lifestyle factors as they are directly linked to the presentation, progression, and management of ADHD and its comorbidities. Sleep health intervention for children with ADHD is effective in promoting sleep quality and generating positive psychosocial functioning in terms of improving physical and mental well-being and social functioning (Keshavarzi et al. 2014).

Digital Media Use Influences on Body Satisfaction and Eating Behaviors

Numerous studies raised the concern about the negative influences of excessive use of digital media among children and adolescents. With the ongoing coronavirus

pandemic, a surge in the use of digital media among people of all ages has been reported as the transition to digital world has become inevitable. A recent evidence highlighted the connection between increased exposure to digital media, namely, gaming and social media, among children with ADHD and increased severity of ADHD core symptoms, executive function impairments, negative emotions, and other behavioral problems (Shuai et al. 2021). Social media use has been found to contribute to various psychiatric disorders including affective disorders and eating disorders. Digital media use, especially appearance-oriented social media, has been linked to increased body dissatisfaction, drive for thinness, and eating issues with adolescents especially more prone to these impacts due to their developmental characteristics (Rodgers and Melioli 2016). Popular youths' websites place great emphasis on physical appearance which is perceived by adolescents as the central component of online identity that has been normally targeted during cyberbullying (Berne et al. 2014). Besides, the importance of thinness is frequently reaffirmed in the content of the websites, many of which present eating disorders as a life-choice rather than a severe form of psychiatric disorder. Clearly, the influences of digital media use among children with ADHD are vast and are associated with worsening of health outcomes as illustrated in Fig. 3.



Fig. 3 Digital media use influences on children and adolescents with ADHD. The influences of excessive digital media use on the cyber-psychosocial behaviors of children and adolescents with ADHD

Besides, nomophobia (no mobile phone phobia) has become an emerging phenomenon affecting all people in our digital era but mostly youths, which is linked to an increased risk for psychopathology. Nomophobia has been found to be positively associated with anxiety symptoms in young individuals (Güneş and Özdemir 2021). A recent study examined the association between symptoms of nomophobia, food addiction, and insomnia found that the rate of moderate to severe nomophobia among young adults is approximately 93%, while the rate of food addiction is around 19% and rate of moderate to severe insomnia is 14%. Interestingly, in this study, nomophobia has been significantly associated with insomnia but not food addiction (Jahrami et al. 2021a). Considering that this study specifically targets young adults, future studies should examine the association between nomophobia, ADHD symptoms, and disordered eating in adolescents with ADHD.

Possible Mechanisms Underlying the Association Between ADHD and ED

The role of dopaminergic signaling system in explaining the linkage between ADHD and ED has been widely highlighted. Reward deficiency syndrome (RDS) is related to the reward circuitry of the brain, resulting in hypodopaminergic function. The abnormality of brain dopamine (DA) function has been reported in individuals with ADHD, SUD, and ED making them more susceptible to reward sensitivity including food-related rewards than the majority of people and tendencies for craving behaviors (Broft et al. 2012).

The effect of impulsivity, inattention, and hyperactivity on the severity of eating disorder symptoms has been widely investigated. Evidence has revealed that inattention and impulsivity (but not hyperactivity) combined predicted bulimic behavior 5 years following an ADHD diagnosis (Cortese et al. 2007). A possible link between impulsivity and BN has been discovered by various authors. Recent evidence has affirmed the positive relationship between impulsivity and bulimic symptoms, drive for thinness, as well as other disordered eating patterns (Christian et al. 2020). Childhood impulsivity is related to increased vulnerability for ED during adolescence. Nevertheless, direct causal relationship between impulsivity dimension of ADHD and ED is not established and is still questionable and can be only answered by longitudinal studies.

Ample evidence has demonstrated that obese ADHD patients at risk for eating disorders were primarily inattentive. It is possible that poor awareness to internal signals of hunger and satiety associated with the inattention dimension of ADHD contributed to pathological eating behaviors both binge and restrictive (Kaisari et al. 2018). Moreover, alterations in executive function including impairments in attention, decision-making, cognitive flexibility, and response inhibition do affect functional tasks including food-related tasks. To sum up, the possible mechanisms underlying the association between ADHD and ED are complex and not clear, and it can be described as a combination of biological, psychological, and social/environmental factors as illustrated in Figs. 3 and 4.

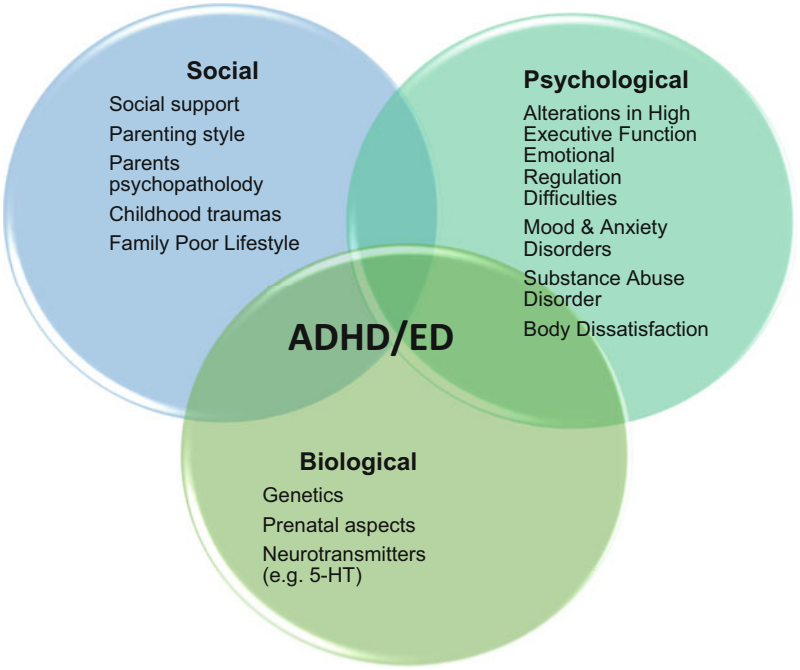


Fig. 4 Main factors associated with attention deficit hyperactivity disorder and eating disorder comorbidity. Key proposed factors underlying the association between attention deficit hyperactivity disorder and eating disorder

Clinical Implications/Clinical Management of ADHD and Eating Disorder

Essentially, a comprehensive assessment of children and adolescents with ADHD entails investigation of potential comorbidities, physical examination, and detailed history of child behaviors from multiple informants as some core symptoms of ADHD might not be observed in clinical settings. This can aid in narrowing ADHD differential diagnosis considerably. Besides, continuous follow-up of ADHD over time from childhood till adulthood is essential for capturing comorbidities and providing early multidimensional interventions that should firstly address conditions causing major distress and functional impairments. Central to this process is understanding the interplay between environmental and genetic factors and modifying environmental risk factors at early stages as part of prevention interventions. At the same time, children and adolescents with ED or obesity should be screened for ADHD symptoms pertaining to the increased prevalence of ADHD symptoms among obese children (Cortese et al. 2016).

A combination of pharmacologic interventions to manage ADHD and ED core symptoms and cognitive behavioral therapy to manage maladaptive behaviors,

ERD/negative affectivity, and control impulses is highly desirable. The psychostimulant treatment can bring about positive changes in high executive and organization skills and impulse control that account for normalization of eating patterns in the long term. Previous evidence revealed that the continuation of ADHD treatment for obese patients over 1 year generates favorable outcomes as it was associated with an average 15 kg weight loss compared to 3 kg weight gain among non-treated (Levy et al. 2009). It is worth noting that weight management issues need to be considered when prescribing medication for ADHD either for children or young adults. Moreover, the dietary pattern and physical fitness of children with ADHD should be addressed and monitored systematically by healthcare workers and lifestyle counseling should be offered to patients and families, even for those with normal body weight who may exhibit disordered eating patterns. Sleep interventions to regulate children sleeping schedule can improve daytime function and enhance emotional well-being and promote social behaviors (Keshavarzi et al. 2014). Supervision of digital media usage is recommended for the management of ADHD core symptoms (Shuai et al. 2021).

As implications for future studies, in order to develop better insight into the relationships between ADHD and ED, longitudinal studies should examine full range of eating patterns and behaviors including loss of control over eating and restraint eating and explore possible shared mechanisms between ADHD, impulse control and attention deficits, and emotional dysregulation. Additionally, in-depth examination of ADHD comorbidities during adulthood is equally important even when symptoms are less disabling especially that ADHD progression from childhood to adulthood is not linear (Weissenberger et al. 2017). Besides, pubertal stage and adjustment for comorbid disorders should be considered in prospective studies examining the association between ADHD and ED. Similarly, screening adolescents with obesity and/or eating problems for ADHD symptoms is worth considering. Targeting behavioral factors that promote excessive weight gain or other weight-related issues may be a potential point of intervention. Moreover, clarification of relevant behavioral factors is required before prevention efforts may be designed and implemented.

Applications to Other Eating Disorders

In this chapter, we review evidence on the prevalence of ED among children and adolescents with ADHD and the association between both disorders. The increased prevalence of ED in individuals with ADHD up to three times necessitate screening those with ADHD for ED symptoms (Jahrami et al. 2021b) and vice versa (Cortese 2019). In-depth screening for comorbidities like depression, anxiety, and addictive disorders, likely to lead to poor functional outcomes, from childhood to adulthood is of relevance. This has implications for other eating disorders since psychopathology plays a key role in mediating the correlation between ED and ADHD plus predicting

health outcomes (Ziobrowski et al. 2018). ED prevention and treatment should focus on managing ERD and negative affectivity in vulnerable population such as youths with neurodevelopmental disorders from early stages (Christian et al. 2020). Additionally, managing impulsive behaviors and alterations in executive function which may affect one's ability to process sensory information related to body's basic needs as hunger/satiety is imperative (Kaisari et al. 2018). Enhancing functional connectivity of brain reward through achieving DA homeostasis in the brain can decrease tendencies for multiple addictive, compulsive, and impulsive behaviors, thereby helping in not only managing food addictive behaviors but also lowering risk for SUD commonly seen in those with ED (Broft et al. 2012). To achieve this, a combination of both pharmacologic therapies specifically ADHD stimulants drugs and behavioral interventions are suggested. The combined intervention has been proven effective in regulating disordered eating patterns though further longitudinal studies are required (Rader et al. 2009). Central to behavioral interventions for an optimal management of ED is the provision of lifestyle interventions that do not only target dietary pattern but also tackle weight management issues, physical fitness, and sleep intervention. Modifying the lifestyle behaviors within the social environment in which patient with ED and family live is highly valuable. Since binge and bulimic eating are related to obesity and ED in children and adolescents, comprehensive assessment of eating attitude is deemed important as part of preventative measure for both obesity and other ED.

Mini-Dictionary of Terms

- Dopamine is a critical neurotransmitter in the brain that is normally released when the brain is expecting a reward; thus, it plays a role in how we feel pleasure.
- Emotional regulation difficulties (ERD) are defined as poor responsiveness to emotions due to dysfunctional understanding, reactivity, and management or response modulation (Mennin et al. 2007)
- Nomophobia is a form of situational phobia characterized by excessive fear or worries of not having own mobile phone or not being able to use it.
- Response inhibition is a cognitive process related to one's ability to suppress actions considered to be inappropriate in a given context, thereby helping in adopting more appropriate goal-driven behaviors.
- Reward deficiency syndrome (RDS) is a hereditary and epigenetic condition that causes damage to the reward circuitry of the brain, resulting in hypodopaminergic function. RDS is caused by the combination of several strong neurotransmitters, resulting in aberrant seeking behaviors.
- Stimulant is a type of medicine that speeds up the transmission of signals between the brain and the body by boosting the levels of certain brain chemicals, like dopamine and norepinephrine, making someone feel more aware, alert, or energetic.

Key Facts of Eating Disorders in Children and Adolescents with ADHD

Key Facts of Reward Deficiency Syndrome (RDS)

- Both ADHD and ED rely on the same dopaminergic signaling system.
- Patients with ED show abnormalities in brain dopamine (DA) function similar to those seen in people who abuse substances (Broft et al. 2012).
- Dopaminergic signaling is essential for motor activity and emotional responses and behavior, including learning, motivation, sleep, mood, and attention.
- Abnormalities in DA lead to poor reward response inhibition and addictive-like eating.
- The linkage between ADHD and dopaminergic system helps in explaining its association with ED and many other comorbidities.

Key Facts of Stimulant Drugs for ADHD

- Stimulants are the first line of drug treatment for children with ADHD. They include methylphenidate (Ritalin) and amphetamine (Adderall).
- Stimulants target receptors of the brain chemical DA as DA is related to many health disorders such as ADHD, SUD, schizophrenia, and obesity.
- Stimulants are considered effective in improving ADHD symptoms in about 70% to 80% of children.
- Some stimulants can cause loss of appetite, weight loss, and trouble sleeping.
- Stimulants are used either alone or in combination with behavioral therapy.

Summary Points

- There is significant positive association between ADHD and ED.
- Children and adolescents with ADHD have been found to have threefold increased risk for ED besides increased risk for obesity and increased BMI.
- ED as ADHD comorbidity is associated with increased prevalence of psychiatric comorbidities, namely, depression, anxiety, and addictive disorders leading to negative psychosocial consequences.
- The prevalence of BN and BED is high among children and adolescents with combined subtype compared to those with AN.
- Impulsivity is a common clinical feature for both ADHD and ED that may account for the association between both disorders.
- ERD are among risk factors for both ADHD and ED that are hypothesized to be a mediator between ADHD and disordered eating.
- The adoption of combined pharmacologic and behavioral interventions in the management of ADHD can contribute to symptom reduction, thereby aiding in

regulating disordered eating patterns and promoting academic and social functioning.
- Screening for comorbidities in children with ADHD is required for effective management
- Sleep problems are prevalent in both ADHD and ED and associated with daytime dysfunction. Sleep interventions have been found effective in managing ADHD and its comorbidities.
- Limiting high exposure to digital media is required to manage ADHD core symptoms and minimize its influences on body image and eating behaviors.

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Insomnia in Eating Disorders

9

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Contents

Insomnia in Eating Disorders 146
Defining Insomnia 147
Insomnia as Transdiagnostic Across Psychopathology 148
Insomnia Disorder and Symptoms in Eating Disorders 149
Hypotheses for Understanding the Underlying Mechanisms of Insomnia and Eating Disorders 151
Hypothesized Psychological Factors 151
Hypothesized Biological Factors 153
Hypothesized Social Factors 154
Treatment Implications 155
Conclusion 157
Applications to Other Eating Disorders 158
Mini-dictionary of Terms 158
Key Facts of Insomnia and Eating Disorders 158
Summary Points 158
References 159

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Abstract

Sleep and eating are both essential life functions. Dysregulation in either sleep or eating behaviors can result in significant problems with physical and mental health. Insomnia is a common sleep complaint, in which people report difficulty with initiating or maintaining sleep or waking up too early. When these symptoms are frequent, chronic, and associated with daytime dysfunction, then individuals may meet the criteria of insomnia disorder. Despite emerging evidence suggesting that insomnia symptoms and insomnia disorder are elevated in people with eating disorders, there remains much to be learned about the mechanisms underlying the association between insomnia and eating disorder pathology. In this chapter, we provide the reader with an overview of the nature of insomnia disorder in people with eating disorders, potential mechanisms for their co-occurrence, and current evidence-based psychological methods of treating insomnia symptoms. Future directions for research are offered to drive further study, which has implications for how both eating disorders and insomnia symptoms are treated.

Keywords

Sleep · Insomnia · Eating disorders · Anorexia nervosa · Bulimia nervosa · Binge eating disorder · Cognitive-behavioral therapy · Orexin · Ghrelin · Leptin · Treatment

Insomnia in Eating Disorders

Insomnia disorder is one of eleven sleep disorders described in the *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* (*DSM-5*), and by far the most common (American Psychiatric Association 2013). In addition to the significant psychosocial and occupational impairment caused by insomnia disorder, the economic burden is high; for example, in the United States, insomnia disorder is associated with $100 billion in yearly healthcare costs (Taddei-Allen 2020).

Considering the widespread effects of sleep on health and functioning, insomnia and its treatment is a promising area of study, most notably in the mental health literature where insomnia has recently been linked to the onset, course, and severity of various forms of psychopathology, including affective disorders and substance-use disorders (Hertenstein et al. 2019; Lancel et al. 2021). In fact, treating insomnia in adjunct to treating these other psychiatric conditions can produce treatment effects on both the psychiatric condition and insomnia symptoms (Taylor and Pruiksma 2014). Such results have ignited hope in the arena of eating disorders, where insomnia disorder is highly prevalent.

The nature of the association between insomnia disorder and eating disorders and options for treatment of co-occurring symptoms remains relatively understudied. Thus, the purpose of this chapter is to increase understanding within the community of eating disorder providers and researchers of the diagnostic criteria and theoretical

models of insomnia disorder, explore the co-occurrence of insomnia disorder and eating disorders, and explicate treatment options.

Defining Insomnia

Insomnia disorder is characterized by difficulty initiating or maintaining sleep, or waking up earlier than desired, with daytime impairment, despite adequate opportunity and circumstances to sleep for at least 3 nights per week for at least 3 months (Table 1). Typically, a threshold of 20 to 30 min is used to define the point at which sleep onset or failure for maintenance is non-normative (American Psychiatric Association 2013). Insomnia disorder is unique from many other sleep disorders because it requires sleep disturbance *and* subjective complaints of impairment. Specifically, individuals must report clinically significant daytime dysfunction, which can include problems like fatigue, difficulty concentrating, mood disturbances, irritability, or worrying about sleep that affect social, occupational, and academic functioning. Consequently, it is not recommended that certain objective sleep measurements, such as polysomnography, are exclusively used for diagnosis, as they may fail to distinguish between people with and without insomnia (Schutte-Rodin et al. 2008).

Insomnia symptoms fall into two categories: acute or persistent (also known as chronic insomnia or insomnia disorder). Acute insomnia is determined when symptoms are experienced for more than 1 month but less than 3 months and is reported by approximately 30–50% of the population each year (Ellis et al. 2012). Persistent insomnia occurs when symptoms are experienced for more than 3 months and is reported by approximately 10% of the population (Morin et al. 2015). Unless readers carefully examine the duration of symptoms assessed in different insomnia disorder measures, whether a study assessed acute or persistent insomnia disorder may not be explicitly known. A closer look at the literature suggests that, in general, studies

Table 1 DSM-5 criteria for insomnia disorder

Criteria	Detail
Dissatisfaction with sleep quantity or quality (one or more symptoms) despite adequate opportunity to sleep	Difficulty initiating sleep Difficulty maintaining sleep Awakening earlier than desired with an inability to go back to sleep
Symptom frequency	Minimum 3 nights per week
Symptom duration	Minimum 3 months
Clinically significant daytime dysfunction	Impairment or distress related to social, work, educational, or other domains of functioning
Rule-out diagnoses	Not attributable to the physiological effects of a substance Not better explained by or occur exclusively within the course of another sleep-wake disorder Not better explained by co-occurring mental disorders or medical conditions

investigate persistent insomnia, which we will refer to as insomnia disorder from hereon. Even with this general acknowledgment, prevalence and incidence differ across studies based on the criteria used to define the disorder (Bos and Macedo 2019). Notably, insomnia disorder prevalence is elevated in psychiatric populations, with one study using a mixed psychiatric sample of people with affective and psychotic disorders finding that 32% of patients met *DSM-5* criteria (Seow et al. 2018).

Insomnia symptoms and insomnia disorder are not meant to be interchangeable; rather they represent dimensional and categorical conceptualizations of a type of problematic sleep behavior. As a parallel, the difference between insomnia symptoms and insomnia disorder can be likened to the difference between "eating disorder symptoms" and "eating disorder" – specific criteria related to duration of symptoms and impairment must be met to receive a diagnosis. Nonetheless, many studies use insomnia disorder, insomnia symptoms, and sleep disturbance interchangeably and may not explicitly identify how insomnia disorder is operationalized or measured. Similarly, studies often use terms like "sleep disturbance," "poor sleep," "short sleep," or "sleep restriction" and measure these concepts with objective measures of sleep (i.e., sleep polygraph variables, slow wave sleep, EEG) and/or self-reported measures of sleep duration, fragmentation, or quality; however, shortened sleep duration or sleep disturbances are not necessarily indicative of insomnia. For example, shortened sleep duration may represent normal sleep patterns for some people and solely relying on the objective measure without measuring impairment could result in incorrectly classifying people as having insomnia. On the other hand, people may have insomnia with or without shortened sleep duration (Bathgate et al. 2016). Another challenge with interpreting the literature on insomnia is one of differential diagnosis. In some cases, sleep disturbances may be incorrectly classified as insomnia symptoms, rather than other sleep disorders that result in disrupted sleep patterns (e.g., obstructive sleep apnea, nightmare disorder, delayed sleep-wake phase disorder). Thus, careful examination of the frequency, duration, and impairment related to insomnia symptoms, as well as understanding the limitations of certain self-report or objective measures, is critical for interpretation.

Insomnia as Transdiagnostic Across Psychopathology

The study and interpretation of insomnia is complicated by the transdiagnostic nature of insomnia symptoms across mental disorders (Dolsen et al. 2014; Harvey 2008), which can make it difficult to determine whether insomnia exists independently or dependently of another psychological disorder. This can be especially challenging when insomnia symptoms are part of the diagnostic criteria of other common co-occurring psychiatric disorders, such as major depressive disorder or generalized anxiety disorder. However, insomnia disorder can be diagnosed *in addition* to another mental disorder when symptoms meet certain diagnostic thresholds (i.e., difficulty initiating or maintaining sleep for $\geq$3 nights/week $\geq$3 months, along with daytime dysfunction) and are associated with distress and impairment

independent of the "primary" condition. Although insomnia disorder may begin with the onset of a psychiatric disorder, it often develops its own unique maintaining factors that persist regardless of the presence or absence of the other condition (Spielman et al. 1987). Indeed, even when co-occurring psychological conditions such as depression or anxiety disorders are successfully treated, insomnia disorder frequently does not remit without specialized insomnia treatment (Carney et al. 2007, 2011; Cousineau et al. 2016; Mason and Harvey 2014), which further supports the distinction as an independent diagnosis. In sum, it is important for readers to understand that insomnia disorder is an independent psychiatric diagnosis which often co-occurs with other forms of psychopathology (Harvey 2001) and is associated with concurrent increased severity of psychopathology and poorer well-being (Lancel et al. 2021).

Understanding insomnia disorder as a co-occurring condition is valuable because insomnia disorder may influence the trajectory of psychological disorders. For example, elevated insomnia symptoms at discharge from successful treatment for depression, anxiety, and substance-use disorders are associated with increased risk of relapse for these conditions (e.g., Babson et al. 2013; Chen et al. 2017; Manber et al. 2008; Ohayon and Roth 2003; Short et al. 2017). Importantly, treating insomnia disorder can alter the risk of relapse for co-occurring disorders, as in one study which found a sustained reduction in depression symptoms for 1 year after treatment for insomnia disorder (Cheng et al. 2019). This may be particularly relevant for eating disorders because psychological disorders for which insomnia symptoms are a common feature, including major depressive disorder, post-traumatic stress disorder, and generalized anxiety disorder (Hertenstein et al. 2019; Li et al. 2016; Thun et al. 2019), are associated with increased severity and poorer treatment outcomes in eating disorders (Becker and Grilo 2015; Keshishian et al. 2021; Mitchell et al. 2021; Trottier 2020).

Based on the extant body of literature on insomnia as a risk factor for other forms of psychopathology, it is highly warranted to examine if insomnia symptoms, and more specifically, insomnia disorder, function as a similar risk factor for onset, severity, and treatment outcomes in eating disorders. Such knowledge would be critical in informing the use of interventions to treat co-occurring insomnia in people with eating disorders and potentially enhance treatment outcomes among eating disorder populations.

Insomnia Disorder and Symptoms in Eating Disorders

The comorbidity between eating pathology and sleep problems has been supported in the literature for decades (e.g., Crisp et al. 1971; Franklin et al. 1948; Latzer et al. 1999), but only recently has there been an increased focus on insomnia disorder and its symptoms, specifically. Currently, the investigation of insomnia symptoms and insomnia disorder in eating disorders is limited to populations with anorexia nervosa (AN), bulimia nervosa (BN), binge eating disorder (BED), and night eating

syndrome (NES). There is virtually no data on insomnia in feeding disorders such as pica, rumination disorder, or avoidant/restrictive food intake disorder (ARFID).

Of the existing research focused on insomnia in eating disorders, subjective measures of insomnia reveal relatively similar prevalence rates, degree and severity, and level of impairment among the eating disorder categories, such as AN, BN, and BED (Allison et al. 2016; Cinosi et al. 2011; Kim et al. 2010). There have also been attempts to use objective measures of sleep disturbance, which provide varying conclusions about the differences between types of eating disorders compared to self-report measures of insomnia disorder. For example, objective measures of sleep behaviors have found that AN is more likely to be associated with poor sleep quality and hypersomnia (i.e., increased duration of sleep), people with BN more commonly report problems with sleep latency (i.e., difficulty falling asleep), and people with BED and NES report more frequent awakenings (Cinosi et al. 2011; Lundgren et al. 2008). It is important to note, however, that because the diagnosis of insomnia disorder also requires subjective impairment, it is not surprising that objective measurements of sleep patterns do not always converge with self-report measures of insomnia.

Another, arguably more effective, way to understand insomnia in eating disorders is to focus on the similarities, rather than the differences, of insomnia symptoms across eating disorder diagnoses. Taking a shared-features approach like this aligns with the widely adopted transdiagnostic approach to psychological disorders, which is particularly relevant in the case of eating disorders where diagnostic migration between types of eating disorders is common (Ackard et al. 2011; Milos et al. 2005). When eating disorder populations are studied together, prevalence rates are as high as 50.4% (Kim et al. 2010), with the most common insomnia symptom being difficulty initiating and maintaining sleep (e.g., Asaad Abdou et al. 2018; Bos et al. 2013) and increased impairment of daytime functioning (e.g., Tromp et al. 2016).

Insomnia symptoms can also be examined based on the behaviors common across eating disorders, such as engagement in restriction, compensatory behaviors, or loss-of-control eating. With this approach, it is apparent that insomnia symptoms are especially prevalent among people presenting with binge-purge symptoms, both in non-clinical (e.g., Aspen et al. 2014; Bos et al. 2013; Goel et al. 2020; Kandeger et al. 2019; Lin et al. 2020; Lombardo et al. 2020; Natale et al. 2008; Serra et al. 2020; Soares et al. 2011; Tromp et al. 2016) and clinical populations (e.g., Allison et al. 2016; Asaad Abdou et al. 2018; Cooper et al. 2020; Della Marca et al. 2004; Lauer and Krieg 2004; Lombardo et al. 2015; Ralph-Nearman et al. 2021; Tanahashi et al. 2017). Finally, the severity of insomnia symptoms is often proportional to the severity of eating disorder symptomology at a single point in time as well as after eating treatment (Bos et al. 2013; Lombardo et al. 2015). These findings suggest that insomnia appears to be a clinical marker of current behavioral disturbances among eating disorders and may be of interest as a secondary parameter to eating disorder recovery.

Hypotheses for Understanding the Underlying Mechanisms of Insomnia and Eating Disorders

Part of unlocking the potential for treating insomnia in people with eating disorders is understanding the link between the two disorders. The mechanisms underpinning the association between eating disorders and insomnia are complex, and likely involve an interplay of psychological, biological, and social factors (e.g., Christensen and Short 2021). Key theories in both the insomnia and eating disorder domains can help us to understand what may differentiate those who go on to these conditions from those who do not. In the following sections, we outline potential shared areas of overlap that may explain the co-occurrence of insomnia disorder and eating disorders.

Hypothesized Psychological Factors

According to the Cognitive Model of Insomnia (Harvey 2002), insomnia symptoms are perpetuated by an interaction between maladaptive cognitive processes, behaviors, and emotional responses. In this model, maladaptive cognitive processes include misconceptions about normal sleep, excessive worry about the consequences of inadequate sleep, and other sleep impairing dysfunctional cognitions (e.g., cognitive inflexibility, rumination). One such example of a dysfunctional cognition includes commonly reported thoughts like "I will not be able to function tomorrow if I do not get 8 hours of sleep tonight." Behavioral mechanisms that perpetuate insomnia involve maladaptive sleep-incompatible behaviors (also known as "safety behaviors," e.g., daytime napping to compensate for a night of poor sleep) and sociocultural variables and trends (e.g., technology use) which reinforce sleep-incongruent cognitions (Bos and Macedo 2019). Therefore, according to this model, sleep problems are developed and maintained when worry about not obtaining adequate sleep (cognition) impedes the ability to fall asleep (behavior), which induces rumination about the implications of sleep disturbances (cognition), resulting in heightened negative affect (emotion), thereby perpetuating the inability to fall asleep (behavior).

According to the transdiagnostic Cognitive-Behavioral Model of Eating Disorders (Fairburn 2008; Fairburn et al. 2003), eating disorders are also developed and maintained through an interplay between cognitive processes, behaviors, and emotional responses. To provide one example, preoccupation with body shape and weight (cognition) may drive attempts at food restriction (behavior). When food is eventually and inevitably consumed (behavior), a negative self-evaluation (cognition) and negative emotionality (emotion) may ensue, which then perpetuates the preoccupation with body shape and weight (cognition), potentially driving increased engagement in restriction, purging, or excessive exercise (behavior).

We hypothesize that placing these psychological models together may offer insight into mechanisms driving the association between insomnia and eating disorders (Fig. 1). For instance, worry and unrealistic expectations about sleep

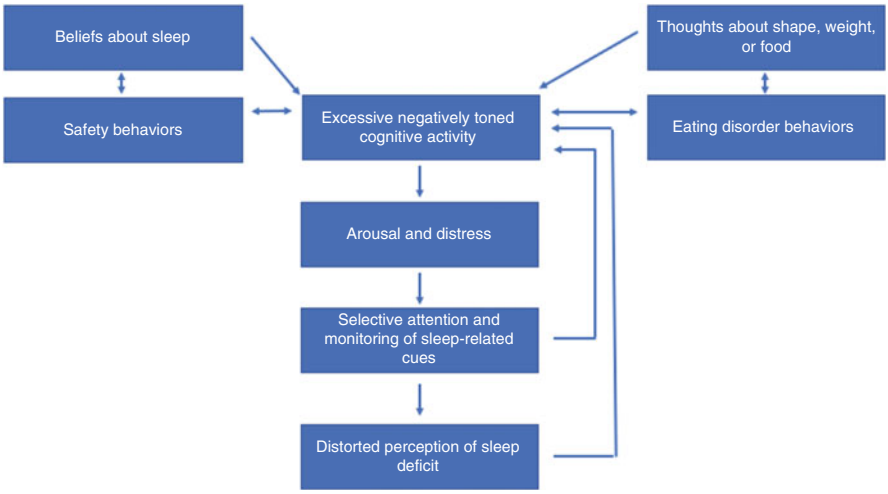


Fig. 1 Proposed integrated cognitive-behavioral model of insomnia and eating pathology extended from Harvey (2002) and Fairburn et al. (2003)

(cognition) and preoccupation with body weight and shape (cognition) could increase arousal and therefore interrupt the ability to fall asleep (behavior). In turn, this may increase vulnerability to negative affect (emotion), which could result in decreased ability to inhibit rumination about body weight and shape (cognition) and which may heighten arousal and interfere with sleep processes. Increased arousal due to distress about sleep or eating behaviors could then result in increased use of eating disorder behaviors to reduce negative affect (behavior), thereby perpetuating eating disorder symptoms. Thus, our proposed integrated cognitive-behavioral model of sleep and eating behaviors suggests a complex interaction between cognitions, affect, and behavior that heighten symptoms of both insomnia disorder and eating disorders.

Another hypothesis linking insomnia symptoms to eating disorders is that they share a common variance with depression and anxiety symptoms (e.g., Daga et al. 2011; Staner 2010; Xiao et al. 2021), and thus, there is a common diathesis for these disorders (Aspen et al. 2014). In other words, the relationship between insomnia and eating disorders is driven by these third variables related to internalizing psychopathology. On one hand, some studies show no difference in insomnia symptoms in the presence or absence of depression (Latzer et al. 1999) and that the link between insomnia symptoms and eating disorders remained after accounting for depression (Nagata et al. 2020). However, other studies show that depression and anxiety mediate the association between insomnia symptoms and eating disorder pathology in non-clinical (Goel et al. 2020; Lombardo et al. 2014) and clinical populations (Lombardo et al. 2015).

Hypothesized Biological Factors

Several hormones and neuropeptides have been implicated in both sleep and eating behaviors, and their interaction may underlie dysfunction present in both insomnia disorder and eating disorders. For example, insomnia symptoms are associated with dysregulated levels of leptin and ghrelin (e.g., Motivala et al. 2009; Spiegel et al. 2004; Taheri et al. 2004), which are appetite-regulating hormones that influence hunger, satiety, and consumptive behavior. Ghrelin and leptin interact with a neuropeptide called orexin, which influences sleep and arousal (Willie et al. 2001). One theory is that when people are not experiencing eating disorder symptoms, glucose and leptin suppress orexin, allowing for normal sleep-wake patterns; however, for people with eating disorders, glucose and leptin levels can become altered, thereby causing dysregulated orexin neuronal firing. Similarly, when people experience malnutrition, there may be alterations in the availability of orexin receptors. It is hypothesized that these changes in orexin levels and/or orexin receptor availability increase arousal, thereby impairing sleep processes (Willie et al. 2001); however, the literature on the association between plasma orexin levels and BMI has shown mixed findings (Bronsky et al. 2011; Janas-Kozik et al. 2011; Sauchelli et al. 2016; Steward et al. 2019).

Given that eating disorders and insomnia disorder occur more frequently in women compared to men, there may be sex-related biological factors that contribute to higher symptom co-occurrence. For example, reproductive hormones, such as estradiol, progesterone, and testosterone, are linked to eating disorder symptoms and eating behaviors (Baker et al. 2012; Ma et al. 2020; Mikhail et al. 2021), as well as to insomnia symptoms (Marver and McGlinchey 2020; Suh et al. 2018). Interestingly, both binge eating behaviors and insomnia symptoms are more prominent during the premenstrual week and during the first few days of menstruation than at other times (e.g., Baker and Driver 2004; Gladis and Walsh 1987).

Some studies have posited that insomnia symptoms may interact with body mass or nutritional status in people with eating disorders. First, some people with higher or lower body weights may experience physical discomfort due to their size, which can result in sleep difficulties (Lundgren et al. 2008). Second, neurobiological differences associated with low body weight may be associated with insomnia symptoms (Della Marca et al. 2004); however, it is also possible that these differences may be driven by malnutrition. It is important to note that malnutrition is not distinct to anorexia nervosa or low-weight eating disorders and that people with all eating disorder diagnoses can be malnourished. Disentangling the effects of weight versus nutritional status is an important next step for this line of inquiry. Finally, there is limited literature suggesting that weight gain in people being treated for AN was associated with improved subjective sleep (Ghoch et al. 2016; Pieters et al. 2004); however, it is unclear the extent to which this is driven by weight status itself versus malnutrition status or changes in other psychological variables (e.g., reduced anxiety). Interestingly, in one study, although the authors found that sleep latency became more normative after weight restoration, there was a persistence in increased wake

time after sleep onset, suggesting that weight changes were not sufficient to resolve insomnia symptoms (Ghoch et al. 2016).

Similarly, the possibility of weight driving insomnia in eating disorder populations is challenged by studies where the relationship between insomnia symptoms and eating disorder pathology persist even after controlling for body mass index (Schmidt and Randler 2010; Soares et al. 2011). These findings suggest that it may be behavioral and physiological characteristics of eating disorders such as weight fluctuations, binge eating, purging, exercise, and metabolic and endocrine changes that result in the significant sleep problems characteristic of insomnia (Lauer and Krieg 2004; Tromp et al. 2016). For some people, the act of bingeing and purging can be physically exhausting or results in temporary relief of fears of weight gain and therefore has a calming effect. In these cases, it is not uncommon for people to want to nap after a binge-purge episode (Benca and Schenck 2005). Daytime napping can throw off the sleep-wake cycle and lead to difficulty falling asleep later that day. Alternatively, some people may experience a surge of energy or adrenaline as a result of bingeing and purging, and if this is the case late at night, the person will have trouble falling asleep. Accordingly, intervening on eating disorder behaviors, especially bingeing and purging, has the potential to reduce insomnia symptoms.

Hypothesized Social Factors

Social timing and behaviors have the potential to influence sleep and eating pathology. Eating patterns are considered to be a zeitgeber (i.e., factor that influences circadian rhythms); as such, when dysregulated, they may also alter sleep processes (Stephan 2002). Furthermore, one can consider the instability in sleep and eating times resulting from social engagements or work demands that conflict with natural circadian rhythms. People may have differing sleep schedules across the week, such that they may stay up later and sleep in on weekends or non-work days when they have decreased obligations. These changes may lead to difficulty falling asleep at typical hours on the non-work days due to dysregulated biological rhythms and lack of opportunity to build sleep drive (Wolfson and Carskadon 1998). Over time, this could lead to the development of insomnia symptoms and insomnia disorder (Brandão et al. 2021; Foster et al. 2013; Henderson et al. 2019). Similarly, such fluctuating schedules may also alter the timing of meals and natural hunger drives. When individuals stay up late to socialize, they may consume food at later times, which can impact arousal and quality of sleep. For example, one study found that when food was consumed less than one hour prior to bedtime, there were increased reports of waking after sleep onset accompanied by increased sleep duration, which the authors hypothesize is an attempt to compensate for the inefficient sleep caused by frequent awakenings (Iao et al. 2021). More frequent or late-night eating behaviors due to increased time awake may also increase the drive for individuals to engage in compensatory behaviors to make up for perceived excessive calories consumed. Furthermore, sleeping in may also result in meal skipping, which could reinforce maladaptive eating patterns. The inconsistency resulting from these

fluctuating sleep cycles may make individuals with eating disorders experience dysregulated hunger and fullness cues, which could maintain eating disorder pathology.

There are also developmental considerations in terms of control over sleep and eating behaviors. Both are characterized by decreased personal control in childhood and adolescence (e.g., caregivers more likely to determine timing), with increased control gained as people age. In particular, emerging adulthood is characterized by changes in responsibility and identity development, which includes independence over health behaviors including sleeping and eating (Miller et al. 2002). For many, there is often an abrupt shift in sleep schedules, which can increase the risk of experiencing insomnia symptoms (Gellis et al. 2014; Maslowsky and Ozer 2014; Wolfson and Carskadon 1998). The unstable and unstructured nature of this developmental period is a time of increased vulnerability to the onset of mental health problems (Kessler et al. 2005), including eating disorders (e.g., Lipson and Sonneville 2017). Further developmental milestones, such as pregnancy and parenthood, can also have dramatic impacts on both sleep (Da Costa et al. 2021; Parfitt and Ayers 2014; Román-Gálvez et al. 2018; Sedov et al. 2021) and eating behaviors (Bye et al. 2021) and understanding how to support people as they navigate these times of increased stress is critical. Longitudinal studies are needed to better understand how insomnia and eating disorder symptoms may be associated with increased risk at developmental transition periods.

Treatment Implications

Despite the effect that insomnia symptoms can have on eating disorder symptoms and treatment trajectory (Allison et al. 2016; Aspen et al. 2014; Cinosi et al. 2011; Lauer and Krieg 2004; Lundgren et al. 2008; Tromp et al. 2016), there is little data on how to tailor sleep interventions to eating disorder populations and address insomnia symptoms as a means of improving treatment.

Insomnia symptoms and insomnia disorder may be treated using either non-pharmacological (i.e., behavioral sleep medicine) or pharmacological approaches (e.g., medications such as benzodiazepines or "z-drugs"). Currently, the American Academy of Sleep Medicine recommends that non-pharmacological interventions, such as cognitive-behavioral or behavioral therapy, be used as a first line treatment for insomnia disorder (Edinger et al. 2021). Cognitive-behavioral therapy for insomnia (CBT-I; Morin 1993) has demonstrated strong empirical support in reducing insomnia symptoms and dysfunctional beliefs about sleep at end-of-treatment, with effects maintained over a year-long follow-up period (Soh et al. 2020; Thakral et al. 2020; van der Zweerde et al. 2019). In CBT-I, factors that contribute to the maintenance of insomnia are addressed with techniques such as psychoeducation about sleep, stimulus control techniques (i.e., limiting activities in bed to sleep and sexual activity), sleep restriction and titration (limiting time in bed to consolidate fragmented sleep and/or reduce sleep latency), sleep hygiene, and cognitive restructuring of dysfunctional beliefs about sleep.

CBT-I is a highly flexible treatment program. It is typically conducted over a period of 4–8 weeks and can be delivered effectively in group or individual formats. Furthermore, telehealth-delivered CBT-I has demonstrated noninferiority to in-person interventions, meaning that the current evidence supports the use of either modality (Soh et al. 2020). Further, CBT-I is a robust treatment that remains efficacious even when comorbid mental or physical health disorders are present (Wu et al. 2015).

Unfortunately, there is a dearth of research into the best ways to apply CBT-I for treating insomnia symptoms or insomnia disorder in people with eating disorders. The extant evidence from the literature on insomnia disorder co-occurring with post-traumatic stress disorder, with depression, or with anxiety disorders suggest that integrating CBT-I into treatment for these disorders shows promise for improving insomnia symptom severity, as well as the reducing symptoms of the co-occurring diagnoses (e.g., Belleville et al. 2016; Colvonen et al. 2018; Manber et al. 2008; Talbot et al. 2014; Taylor et al. 2018). Furthermore, given the impacts of insomnia on factors such as emotion regulation, concentration, and memory, treating insomnia symptoms prior to engagement in treatment for eating disorders could be helpful for increasing the efficacy of eating disorder interventions. This rationale has been applied to post-traumatic stress disorder treatment, with one case study suggesting the use of CBT-I as a preparatory treatment for exposure therapy for post-traumatic disorder (Baddeley and Gros 2013). However, the literature on the most effective timing of insomnia treatment deployment is still developing, and more trials are needed to determine the most appropriate approach to treatment staging. Within the field of eating disorders, there has yet to be a comprehensive trial testing the efficacy of CBT-I in this population, much less trials on how to optimize timing of insomnia treatment delivery (i.e., whether treatment of insomnia should occur prior to or after treatment of the so-called primary disorder). However, researchers are beginning to study this question (e.g., Christensen et al. 2021). This is a notable gap in the clinical literature, particularly given the prevalence of clinically significant insomnia symptoms in eating disorder populations.

Another limitation for the delivery of insomnia interventions to people with eating disorders at this time is that there is a dearth of treatment providers who offer evidence-based behavioral sleep medicine interventions. Across the field of clinical psychology, training in behavioral sleep medicine is lacking; for example, a 2020 survey of clinical psychologists found that only 5% had received instruction in treating sleep disorders during their career, although many identified this as an important area of interest (Zhou et al. 2020). To address this need, a free web-based CBT-I training program called *CBTIweb* has been developed to offer comprehensive education in the assessment and treatment of insomnia (Taylor et al. 2021). Eating disorder treatment providers interested in becoming competent in CBT-I may consider this program, as well as resources offered by the Society for Behavioral Sleep Medicine, an international society dedicated to the scientific study of sleep, and the Board of Behavioral Sleep Medicine, a non-profit organization that credentials providers in behavioral sleep medicine (specifically, the Diplomate of Behavioral Sleep Medicine or DBSM).

Finally, another difficulty for eating disorder treatment providers who may wish to address insomnia symptoms in their practice is that few, if any, resources for CBT-I have been tailored to the treatment needs of this population. This is important because current recommendations found in CBT-I may or may not be appropriate for use with people with eating disorders and may fail to adequately address the ways that maladaptive eating behaviors maintain insomnia symptoms. For example, practitioners who use CBT-I may recommend moderate daytime exercise as a way of helping lower arousal for nighttime – in many people with eating disorders, such a recommendation may be contraindicated for their recovery or must be carefully monitored to ensure that it does not exacerbate their symptom profile. Similarly, as part of CBT-I, providers may identify and challenge negative thought processes, such as worry, which are posited to interfere with sleep onset. In the case of people with eating disorders, it is certainly possible that rumination or intrusive thoughts related to shape, weight, or control over eating may comprise these negative thought processes. In this case, tailoring aspects of CBT-I to specifically target eating-related concerns that maintain problematic sleep patterns may be critical. For example, the "worry time" recommended in CBT-I to reduce arousal in bed could be specifically designated for times to worry about body shape and weight concerns. Similarly, clinicians may wish to identify if eating behaviors (e.g., hunger or loss-of-control eating) are interfering with ability to fall and stay asleep. More research is needed on the best ways to address the specific needs of clients with eating disorders and how to translate this into effective insomnia disorder treatments.

Conclusion

Tremendous progress has been made over that past two decades, and investigating the role of insomnia in various forms of psychopathology has provided interesting insights on etiology and treatment that have great potential for the field of eating disorders. Overall, the literature supports the idea that insomnia symptoms are common and associated with increased eating disorder symptom severity. There remains much to be explored about the specific biopsychosocial mechanisms linking insomnia symptoms and eating disorder symptoms, and consequently the co-occurrence of insomnia disorder and eating disorders. In particular, it is necessary to move our direction of research from *if* the two conditions are linked to *how* and *why*, as well as research investigating the best ways to treat their co-occurrence (e.g., Christensen et al. 2021). Longitudinal studies that explore how these symptoms fluctuate over time relative to each other could offer insight into mechanisms. Similarly, researchers and clinicians may wish to consider incorporating measures of insomnia symptoms into treatment studies to better characterize the influence of insomnia symptoms on eating disorder treatment trajectory, which could provide important insights into how to approach treatment. Finally, overall greater education for eating disorder treatment providers in how to identify and treat insomnia is necessary so that clinicians can feel empowered to intervene on these often-debilitating symptoms. Overall, the study of sleep and eating disorders is rich with

opportunities across the translational spectrum, from mechanisms to implementation, and has great potential to improve quality of life for people with eating disorders.

Applications to Other Eating Disorders

In this review, we take a transdiagnostic approach to discussing the association between insomnia and eating disorders; thus we cover literature related to anorexia nervosa, bulimia nervosa, binge eating disorder, and other eating disorders.

Mini-dictionary of Terms

- **Cognitive-Behavioral Therapy for Insomnia**: An empirically supported, first-line treatment for insomnia disorder, which has shown to have strong effects on reducing insomnia symptoms and maintaining remission from insomnia disorder over time.
- **Ghrelin**: A hormone involved in the regulation and signaling of hunger.
- **Insomnia disorder**: Insomnia symptoms (difficulty falling asleep, staying asleep, or waking up too early) accompanied by daytime impairment that occurs at least three times per week for a minimum of three months.
- **Insomnia symptoms**: Sleep disturbances characterized by difficulties falling asleep, staying asleep, or waking up too early, despite having adequate opportunities for sleep.
- **Leptin**: A hormone involved in regulation and signaling of satiety.
- **Orexin**: A neuropeptide involved with sleep-wake processes and arousal.

Key Facts of Insomnia and Eating Disorders

- Insomnia symptoms and insomnia disorder can have serious impacts on physical and mental health.
- Insomnia disorder has been associated with increased risk for the onset, exacerbation, and relapse of internalizing disorders.
- Insomnia disorder often requires insomnia-focused treatment to fully remit.
- Insomnia symptoms and eating disorder symptoms share common psychological, biological, and social substrates that may increase the odds of co-occurrence.
- Insomnia and eating disorder symptoms are most likely linked through bidirectional associations.

Summary Points

- People with eating disorders report elevated insomnia symptoms.
- Insomnia disorder is an independent mental health condition that may co-occur with eating disorders and, thus, requires separate assessment and treatment.

- The co-occurrence between insomnia disorder and eating disorders likely occurs due to psychological, biological, and social factors.
- Cognitive and behavioral treatments show strong evidence for reducing symptoms of insomnia disorder.
- To date, there is limited information about the best way to treat insomnia symptoms and co-occurring insomnia disorder in people with eating disorders.

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Uric Acid Levels and Eating Disorders

10

Tanya Goltser Dubner, Ruth Giesser, Amit Shalev, Shikma Keller, Ronen Segman, and Esti Galili-Weisstub

Contents

Introduction 168
UA Physiological Roles and General Pathophysiological Aspects 169
UA Measurement in Body Fluids 170
Gender Effects on SUA 170
UA in the Central Nervous System (CNS) 171
UA in Neuropsychiatric Disorders 171
UA in Eating Disorders (ED) 172
Conclusion 174
Applications to Other Areas 175
Mini-Dictionary of Terms 175
Key Facts 176
Summary Points 176
References 176

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Abstract

Uric acid (UA), the end product of purine metabolism, is actively reabsorbed and may modulate behaviors relevant to eating disorders (ED) and play a role in its pathophysiology. Previous evidence suggests higher UA levels among anorexia nervosa–binge eating/purging (AN-BP) subtypes and tophaceous gout as a potential complication in long-standing severe cases. Several factors may affect UA levels including fructose and purine dietary intake, hydration status, reproductive hormonal levels, and renal function, with chronic laxative and diuretic use and repeated vomiting associated with renal dysfunction and hyperuricemia. High UA levels have been proposed in turn to exert a central effect augmenting foraging-like, impulsive–addictive behavioral tendencies and may thus contribute to AN-BP pathophysiology. Larger case–control studies prospectively documenting UA among ED patients stratified according to restrictive and binge eating/purging subtypes are important to validate UA abnormalities in ED and establish its potential utility as an aid in clinical assessment and follow-up. UA and purinergic neurotransmission may constitute novel thitherto unexplored targets for the treatment of behavioral manifestations among AN-BP patients.

Keywords

Uric acid · Salivary biomarkers · Eating disorders

Abbreviations

AN-BP	Anorexia nervosa–binge eating/purging subtype
AN-R	Anorexia nervosa restrictive subtype
ATP	Adenosine triphosphate
BED	Binge eating disorder
BMI	Body mass index
CNS	Central nervous system
CSF	Cerebrospinal fluid
ED	Eating disorders
HPRT	Hypoxanthine–guanine phosphoribosyltransferase
LNS	Lesch–Nyhan syndrome
MSU	Monosodium urate
SUA	Serum uric acid
UA	Uric acid
XOR	Xanthine oxidoreductase

Introduction

Levels of uric acid (UA), the waste product of purine metabolism, are higher in apes and humans due to an evolutionary loss of uricase activity and active renal reabsorption mechanisms, suggesting important physiological roles as an antioxidant and a neural modulator of behavior. Its proposed evolutionary advantage

increasing foraging behaviors under conditions of food shortage has been further suggested to exert potentially hazardous consequences under conditions of fructose- and purine-rich diets, contributing to obesity and metabolic disorders and potentially serving to augment impulsive addictive behavioral tendencies through its central actions. Preliminary evidence including case reports and initial studies points to potential alterations of UA levels among ED patients, with AN-BP patients demonstrating excessive UA levels. In the following chapter, we will briefly summarize relevant physiological and pathophysiological aspects of UA; survey previous data implicating a role for UA in neuropsychiatric disorders; concentrate on evidence linking it with the clinical course and pathophysiology of ED, highlighting potential factors affecting its levels among ED subtypes; and discuss potential implications for UA as a clinically useful biomarker and putative novel therapeutic target for addressing some of the behavioral tendencies gone awry among ED patients.

UA Physiological Roles and General Pathophysiological Aspects

UA is the end product of purine metabolism in all cells, produced through the oxidation of xanthine and hypoxanthine by xanthine oxidoreductase (XOR), allowing elimination of nitrogen waste products (Hille 2005). Produced by oxidative phosphorylation in mitochondria, adenosine triphosphate (ATP) constitutes the major energy transfer coenzyme in the body. It is first metabolized to adenosine, which is then metabolized to inosine via adenosine deaminase and finally to urate via XOR (Cipriani et al. 2010).

The normal serum uric acid (SUA) concentration, largely derived from hepatic degradation of purines, with a range of 3.0–6.8 mg/dL (178–400 μM) is affected by multiple factors including age, gender, and several disease processes. The pathophysiologic role of UA is not clearly understood despite decades of research. UA represents the most abundant antioxidant in human plasma, appearing as monosodium urate (MSU) under physiological PH (Mikami and Sorimachi 2017). Elevated plasma urate among humans and higher primates is the result of urate oxidase inactivation, preventing its degradation to allantoin, consequent to evolutionary mutations timed to the Miocene era that are believed to have perpetuated by conferring a selective advantage through elevating blood pressure and antioxidant capacity (Johnson et al. 2005). Under physiological conditions, UA accounts for 30–50% of the antioxidant capacity, scavenging free oxygen radicals and preventing lipid peroxidation (Crawley et al. 2022). Mechanisms for its active reabsorption by the kidney further point to an important physiological role for UA (Bobulescu and Moe 2012). Recent changes in the industrialized world, with increasing availability of purine-rich food sources such as meat and fructose, have led to increased UA plasma concentrations nearing the limits of its solubility, resulting in increased rates of urolithiasis and gout (Choi et al. 2004). UA concentrations beyond its plasma solubility can lead to chronic deposition of MSU crystals in human joints resulting in inflammatory manifestations as well as joint damage produced by tophi in gout arthritis (Shiozawa et al. 2017). As SUA oversaturation results in crystallization of

MSU and clinical gout, drugs have been developed to lower SUA, through inhibition of the XOR enzyme, increasing urinary UA excretion (uricosurics) or degrading soluble urate (uricases) (Terkeltaub 2010).

Reducing SUA to subsaturation levels allows dissolving of MSU crystals, preventing gout exacerbations, and clearing tophi Shiozawa et al. 2017). Increasing SUA concentrations have been associated with the current pandemic of metabolic syndrome, obesity, hypertension, insulin resistance, and ensuing cardiovascular and renal complications (Johnson et al. 2005; Sharaf El Din et al. 2017). While UA's antioxidant action may exert a beneficial role against oxidative cellular damage and aging, excessive SUA may become prooxidant contributing to metabolic syndrome, cardiovascular disease, chronic heart failure, and metabolic syndrome (Lippi et al. 2008). More recently, a U-shaped association of SUA with all-cause mortality has been suggested with SUA appearing to exert both systemic pro-inflammatory effects that contribute to disease as well as protective antioxidant properties, with XOR enzymatic activity, which catalyzes the last two steps of purine degradation, contributing to both reactive oxygen species and UA formation, both affecting vascular redox hemostasis (Crawley et al. 2022). Indeed, recent evidence suggests both elevated and low SUA may be risk factors for renal, cardiovascular, and pulmonary disorders (Crawley et al. 2022).

UA Measurement in Body Fluids

While serum UA levels constitute the current gold standard for the clinical detection of hyperuricemia and gout, several studies have reported the use of salivary UA concentrations as a disease biomarker. Salivary UA has a robust consistent linear correlation with serum UA ($r = 0.69$) (Riis et al. 2018) and has been suggested as a noninvasive alternative in various clinical settings, (Singh et al. 2019; Soukup et al. 2012; Puschl et al. 2020; Maciejczyk et al. 2020) and several methods for determination of saliva UA concentrations have been developed (Liu et al. 2021; Bukharinova et al. 2021). Of note however, saliva UA measurement may be biased by high abundance of proteins, bacteria, and cells in the oral cavity as well as gingival bleeding and food and drink residues (Liu et al. 2021) that need to be controlled for. Female UA values are generally somewhat lower than male values, (Adamopoulos et al. 1977) and large representative studies among healthy age- and gender-stratified populations are required to establish clinically accepted normative value ranges for salivary UA.

Gender Effects on SUA

Women of reproductive age generally manifest lower UA than men, in part related to both estrogen and progesterone increasing renal UA clearance (Adamopoulos et al. 1977). Consequently, gout afflicts men much more often and is infrequent among women before menopause (Jung et al. 2018). As luteinizing hormone reverts to

prepubertal secretion patterns among AN-R patients, lower estradiol levels result in hypothalamic oligo-amenorrhea (Misra and Klibanski 2016) and would be expected to lower renal clearance of UA, elevating SUA levels. Normal menstrual cycle fluctuations in estrogen and progesterone levels are dose dependently correlated with SUA levels during the menstrual cycle (Mumford et al. 2013). Among postmenopausal women receiving combined estrogen–progestogen treatment, though not with estrogen therapy alone, supplemental hormonal therapy has been shown to reduce UA levels (Jung et al. 2018) and the incidence of gout (Bruderer et al. 2015).

UA in the Central Nervous System (CNS)

Most of the peripheral circulating UA is generated by the liver and with SUA concentrations typically tenfold higher in the periphery than cerebrospinal fluid (CSF) levels (Parkinson Study Group S-PDI et al. 2014). There is evidence to suggest that UA may exert antioxidant and neuroprotective roles in the CNS (Cipriani et al. 2010), with a number of neurodegenerative disorders associated with lower plasma UA levels. Purinergic receptors and enzymes degrading ATP into adenosine and inosine are ubiquitous in multiple brain regions including the cerebral cortex, hypothalamus, basal ganglia, hippocampus, and other limbic areas (Burnstock 2008). Both adenosine and ATP stored in nerve terminals act as purinergic neurotransmitters and co-transmitters in both nerve and glial cells (Burnstock 2008). The actions of ATP are mediated via ionotropic P2X and metabotropic P2Y receptor subfamilies, whereas adenosine actions are mediated via P1 (A1 or A2) adenosine receptors (Krugel 2016).

UA in Neuropsychiatric Disorders

Lesch–Nyhan syndrome)LNS) is a rare inherited X-linked recessive disorder, caused by HPRT1 gene mutations encoding a dysfunctional hypoxanthine–guanine phosphoribosyltransferase (HPRT), resulting in enzymatic deficit and early developmental accumulation of extreme UA levels with renal and neurological complications and gout arthritis (Nyhan et al. 1993). Despite general cognitive disability among LNS that results in compromised discernment of specific behavioral symptoms, patients typically present with compulsive self-injurious behaviors that range from explicit physical self-mutilation, to coprolalia, spitting, and self-induced vomiting, to more subtle displays including refusing recompenses, engaging in self-defeating behaviors, and frustrating and infuriating caregivers when affection is desired (Gualtieri 2002). Enzymatic deficiency early in development interferes with neurodevelopment, and while treatment with the XOR inhibitor allopurinol reduces UA levels, it does not remedy the self-injurious behavioral manifestations (Bell et al. 2016). Furthermore, LNS variant phenotypes that possess over 1% enzymatic HPRT activity do not express self-injurious behaviors, and it is thus less

probable that such manifestations result from the central action of extreme UA levels (Bell et al. 2016).

UA and purinergic neurotransmitters including adenosine and ATP have been shown to contribute to the regulation of important CNS functions including convulsive threshold, memory, cognition, sleep, activity, appetite, mood, social interaction, drive, impulsivity, and intelligence (Alvarez-Lario and Macarron-Vicente 2010; Ortiz et al. 2015). Purinergic neurotransmission has been mechanistically implicated in multiple CNS pathological processes including traumatic brain injury, cerebral ischemia, neurodegenerative diseases, multiple sclerosis, and epilepsy, neuropathic pain, and migraine, as well as in several neuropsychiatric disorders including affective and anxiety disorders, schizophrenia, and alcohol and drug addiction (Burnstock 2008). Several neurodegenerative disorders including Parkinson's disease, (Chen et al. 2012) Alzheimer's disease, (Du et al. 2016) and amyotrophic lateral sclerosis (Abraham and Drory 2014) have been associated with lower SUA and thus suggested to support a neuroprotective role of UA in aging and neurodegeneration. Increased SUA has been reported among bipolar disorder patients (Bartoli et al. 2016), and lower SUA levels among major depression and anxiety disorder patients (Black et al. 2018) that normalize after treatment (Bartoli et al. 2018). Allopurinol has been demonstrated to exert a specific therapeutic effect in manic episodes, (Chen et al. 2018) and as altered XOR activity has been associated with free radical-mediated neurotoxicity, cell damage, and inflammation, XOR inhibitors have been suggested as having therapeutic potential worth exploring for various psychiatric disorders (Martorell et al. 2021).

UA in Eating Disorders (ED)

Several lines of evidence implicate a role for altered UA metabolism in ED. Ostojic and Maas (2018) summarize evidence based on the proposed role of evolutionary uricase loss as driving foraging behavior during food shortage epoch, a neurostimulant role for adenosine neurotransmission, SUA associations with different personality traits, and additional pathophysiological aspects (Simeunovic Ostojic and Maas 2018). Fructose, via its metabolic end products vasopressin lactate and UA, promotes energy storage in the form of fat and glycogen, decreasing mitochondrial ATP and increasing glycolysis, gluconeogenesis, insulin resistance, sodium retention, vasoconstriction, blood pressure elevation, innate immunity stimulation, and foraging behaviors with hyperosmolality-driven thirst and leptin resistance inducing hunger as a mechanism to increase weight (Johnson et al. 2020). The loss of uricase activity among early hominoids during the mid-Miocene era results in higher UA response to fructose, associated with higher stimulation of fat and glucose production. While converging to facilitate survival advantage under conditions of scarce nutrient resources, excessive fructose increases risk for obesity, metabolic diseases, dementia, and cancer (Johnson et al. 2020). Excess dietary fructose intake and high UA levels have been proposed to result in a hyperactive foraging response and contribute to behavioral disorders including attention-deficit hyperactivity

disorder, mania, and aggressive–impulsive behaviors including bulimia, substance use disorders, and risk taking (Johnson et al. 2021).

Several previous small observational studies have documented SUA levels in ED. Two small early studies reported a higher than expected percentage of ED patients presenting with abnormally high SUA levels. In one study, 11 of 27 chronic AN patients had excessive UA at presentation for treatment (Umeki 1988). Another small study reported 9% of a cohort of consecutive ED patients presented with elevated UA at presentation, proposing a potential link with excessive physical exercise-related ATP utilization or starvation-related decrease in renal clearance of UA (Gupta and Kavanaugh-Danelon 1989). A retrospective cohort study reported a threefold higher frequency of renal calculi among AN, with 16% having UA urolithiasis, compared with only 5% among female controls (Denburg et al. 2017). Whereas ammonium urate stones are infrequent in clinical practice, they are repeatedly reported in AN and associated with laxative abuse (Fukai et al. 2017; Dick et al. 1990). Several observations of excessive SUA with tophaceous gout as a possible complication of chronic AN have been reported and ascribed to chronic laxative use resulting in pseudo-Bartter syndrome secondary to laxative abuse, (Adam and Goebel 1987) chronic diuretic use (Hayem et al. 1996; Nakazawa et al. 2004 or chronic kidney impairment accompanying dehydration and low potassium levels with recurrent self-induced vomiting (Kishibe et al. 2010). We reported higher salivary UA levels among a cohort of adolescents with ED, mostly presenting with AN-R compared with age- and gender-matched healthy controls (Giesser et al. 2020). Patients were at the initial phases of illness, and none suffered gout, kidney stones, or renal failure upon medical examination. There was a trend for higher salivary UA levels among ED groups with purging behaviors ($n = 9$), suggesting these may contribute to elevate UA among the ED groups. However, salivary UA remained significantly higher among the larger AN-R groups ($n = 30$) compared with control values, suggesting additional factors underlie elevated UA among AN-R. None of the patients reported diuretic or laxative abuse, and all had normal renal function (Giesser et al. 2020). Only 6 of 83 subjects in our entire sample reported oral contraceptive use, while most AN patients had secondary amenorrhea, which may have contributed to elevated SUA. A larger study reported SUA levels sampled at admission and following hospitalization among 160 adult patients with severe AN or avoidant restrictive food intake disorder (Watters et al. 2022). Serum UA tended to be at the low normal range for a majority of AN-R patients at admission and attributed to malnutrition and low dietary intake of nutrients containing purine and fructose. However, elevated initial SUA, sometimes to abnormal values, were observed among AN-BP patients and correlated with higher urea and creatinine (Watters et al. 2022). Whereas a mean increase in SUA was observed following hospitalization and suggested to relate to improved nutritional status, AN-BP patients with high SUA at admission tended to decrease to normal levels following treatment and suggested to relate to improved hydration and renal function (Watters et al. 2022). Patients with low serum UA levels on admission took longer to gain weight, required more calories for effective refeeding, and had a longer hospitalization. Furthermore, patients presenting with SUA below the normal

range were more likely to suffer comorbid anxiety and depression (Watters et al. 2022). While SUA data in this study were derived from larger metabolic panels routinely drawn from hospitalized patients and lacked a matched control comparison group, resorting instead to population reference values, they point to a potential dynamic interplay of several factors that may be affecting SUA among ED and suggest a potential value for considering SUA in the clinical evaluation and follow-up of ED patients. Results also point to the importance of stratification of SUA levels between restrictive and binge eating–purging subtypes (Watters et al. 2022). Larger prospective studies accounting for menstrual phase and correlating UA with reproductive hormonal levels among AN during exacerbation and remission phases, as well as UA changes in response to oral contraceptives, are required to shed further light on such contribution. Differing dietary compositions have been associated with altered UA levels (Schmidt et al. 2013) and could potentially account for some of the UA differences observed. Thus, a high fructose/purine diet that would account for increased UA levels (Choi et al. 2004) could partly contribute to increased SUA among AN-BP patients. A positive correlation with SUA has been previously noted among high BMI subjects, which may represent part of a metabolic syndrome (Krzystek-Korpacka et al. 2011). In our adolescent sample (Giesser et al. 2020) as well as the larger adult sample, (Watters et al. 2022) BMI did not significantly correlate with UA levels. Elevated SUA was reported to accompany late-stage extreme starvation, resulting from protein degradation after fat stores have been depleted and serving to stimulate foraging behavior (Johnson et al. 2009). Such mechanism may take place among patients with severe AN-R suffering extreme cachexia, requiring further study.

Conclusion

UA levels may be altered in ED through several factors including nutrient intake, hydration status, and renal impairment resulting from dehydration related to chronic diuretic use, vomiting, or laxative use. UA may act as a neuro-stimulant, increasing foraging-related impulsive–addictive behaviors, and may thus be hypothesized to increase binge eating–purging-type behavioral manifestations, thus contributing to a vicious cycle. This is in line with previous case reports as well as preliminary studies by us (Giesser et al. 2020) and others (Watters et al. 2022) observing increased UA levels among purging AN patients. Peripherally produced UA has been reported to produce hypothalamic gliosis and alter leptin response, through triggering the expression of pro-inflammatory cytokines and activating the NF-κB pathway (Lu et al. 2015). Larger case–control prospective studies beginning at the premorbid phases among high-risk adolescents and extending to the exacerbation and remission phases are required to further elucidate on a putative role for UA as a state or trait prognostic marker, among stratified ED subtypes (restrictive vs. binge eating/purging subtypes), aided by the availability of noninvasive salivary measures, and are required to further explore the clinical utility of UA as a biomarker during the

assessment and follow-up phases of ED treatment protocols. Prospectively documented correlations with complicating clinical course measures and endocrine, metabolic, behavioral, and cognitive aspects, including structured quantitative measures encompassing personality traits and impulsivity and addictive indices, are required to further shed light on its putative role in ED pathophysiology. Intriguingly, just as allopurinol has been shown to have promise in the treatment of bipolar manic episodes, (Machado-Vieira et al. 2008) UA and purinergic neurotransmission may present an unexplored avenue for the treatment of binge eating/purging aspects of ED.

Applications to Other Areas

Increased SUA has been reported in bipolar disorder, and allopurinol has been shown to exert a beneficial effect in the treatment of mania, suggesting involvement of the purinergic system in regulating energy levels and impulse control. Importantly, the suggestion that UA may promote increased impulsive–addictive tendencies may cross diagnostic boundaries, as indirectly supported by above positive correlations of excessive SUA with the food craving and binge eating/purging subtype of AN. Such observations may be confounded however by dietary composition, renal impairment, dehydration due to recurrent vomiting, diuretic and laxative use, etc. A study comparing obese individuals with binge eating disorder (BED) to obese subjects without binge eating found the former to have higher SUA after controlling for BMI (Succurro et al. 2015). While such observations cannot differentiate a causal role for UA in promoting BED, given the mechanistic basis for UA's central behavioral modulatory effects cited above, applying Mendelian randomization strategies (Konig and Greco 2018) and directly examining a role for pharmacologically reducing SUA levels in alleviating such behavioral tendencies appear warranted. If proven viable, the potential implications of such interventions may extend beyond ED and other psychiatric diagnostic categories to the much broader problem of obesity in developed countries.

Mini-Dictionary of Terms

- Uric acid (UA): The end product of purine metabolism.
- Monosodium urate (MSU): UA crystals deposited in human joints resulting in inflammatory manifestations as well as the joint damage produced by tophi in gout arthritis.
- Lesch–Nyhan syndrome)LNS): A rare inherited X-linked recessive disorder, caused by HPRT1 gene mutations encoding a dysfunctional hypoxanthine–guanine phosphoribosyltransferase (HPRT), resulting in enzymatic deficit and early developmental accumulation of extreme UA levels with renal and neurological complications and gout arthritis.

Key Facts

- UA is the end product of purine metabolism.
- Humans have high UA levels due to lack of uricase activity and active renal reabsorption.
- UA plays important physiological roles and is a major antioxidant.
- Excessive UA levels can result in gout and are associated with metabolic disorders.
- Several factors may alter UA levels, making it a clinically relevant biomarker among ED patients.
- Salivary UA constitutes a noninvasive measure correlating with serum UA.
- UA may act as a behavioral modulator in the CNS promoting impulsive addictive eating patterns.

Summary Points

- UA, the final purine degradation nitrous waste product, is not further degraded and actively reabsorbed in humans, possessing significant antioxidant capacity, but may exert detrimental pro-inflammatory effects at very high and low concentrations.
- Salivary UA concentration possesses a consistent linear correlation with serum UA levels and suggested to constitute a noninvasive alternative in clinical settings.
- UA adenosine and ATP participate in purinergic neurotransmission, affecting key CNS functions; altered SUA levels have been associated with neurodegenerative processes and psychiatric disorders; and allopurinol has been demonstrated to exert a specific antimanic effect in bipolar disorder and may possess a potentially beneficial behavioral modulatory effect in AN-BP and BED.

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The Virtually Delivered Body Project (vBP): A Viable Option for Large-Scale Prevention of Eating Disorders

11

Ata Ghaderi

Contents

Introduction 182
Eating Disorders in Context 182
Prevention 183
The Main Prevention Strategies for EDs 184
Cognitive Dissonance Theory and Its Implication for Prevention 185
Dissonance-Based Intervention and Body Project 187
The Efficacy and Effectiveness of the Body Project 189
Influencing Public Health: Prevention on Broad Basis 189
The Promise of Internet and Digital Techniques 190
vBP 191
Applications to Other EDs 193
Mini-Dictionary of Terms 193
Key Facts of the Virtually Delivered Body Project (vBP) and EDs 194
Summary Points 194
References 194

Abstract

Eating disorders (EDs) are common conditions. No more than 25% of those afflicted seek professional help, and of the minority who receives evidence-based treatments, only about 50% recover completely. Consequently, prevention is an imperative. The currently most investigated and effective prevention strategy for EDs is the dissonance-based intervention, known as the Body Project. In order to make it more suitable for implementation of prevention on a large scale, we adapted the Body Project to be delivered virtually. This intervention exerts its effect most optimally if it is delivered in a group context. Virtual Body Project (vBP) provides more flexibility in terms of facilitating participation as the

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participants do not have to travel to meet in groups, recruitment on a large scale, strategies to decrease the stigma that might hinder participation in prevention efforts, and efficient ways of providing booster sessions. Our first evaluation of the efficacy of the vBP has shown promising outcomes. The vBP was compared to a credible placebo condition (expressive writing, EW) for a duration of 24 months and a waitlist control group for 6 months. The incidence of EDs in vBP (three cases: 2%) across 24-month follow-up was 77% less than among participants in the EW condition (13 cases: 8.8%), which denotes a significant difference (hazard ratio: exponential $B = 0.26$, 95% confidence interval [0.075, 0.92], $p = 0.037$). If the outcomes are replicated in future studies, the vBP might be a viable option for future evaluation of scalable prevention of EDs.

Keywords

Prevention · Dissonance-based intervention · Body project · Body dissatisfaction · Incidence · Implementation · Booster session · Expressive writing · Selective prevention · Outcome

Abbreviations

ED	Eating disorder
EDs	Eating disorders
vBP	Virtual Body Project

Introduction

Eating Disorders in Context

Eating disorders (EDs) are common conditions among adolescents and young adults. Between 1% and 3% of young adult females suffer from a full syndrome ED, and at least twice as many meet the criteria for subclinical diagnoses of EDs (Ghaderi and Scott 2001; Hudson et al. 2007). Adding the adolescents into the equation and given the early onset of EDs, the emerging picture suggests that 13% of females suffer from a full or subthreshold ED (Allen et al. 2013; Stice et al. 2013; Swanson et al. 2011). A large number of young females experience significant difficulties in relation to eating and their body image, with marked impact on their quality of life, everyday functioning, and behaviors that make them more vulnerable for the development of EDs (Ghaderi 2001; Ghaderi and Scott 1999, 2001). What is also worrying is the increased rate of extreme dieting and physical exercises as a probable consequence of excessive preoccupation with healthy eating and fitness due to influences exerted via various social media channels. Normative data for men are lacking, and available studies might provide a biased estimate of EDs among men. This might be due to several factors such as differences in clinical characteristics of males and females (Welch et al. 2015), lower likelihood of receiving a diagnosis of ED (Currin et al. 2007), and lower tendency to seek treatment among males (Striegel

et al. 2012), as well as a more pronounced stigma related to EDs for men as EDs are stereotypically viewed as a female disorder (Griffiths et al. 2014). Although lack of data makes it difficult to provide a clear picture of the prevalence, effect, and outcome of EDs for men, a substantial portion of those suffering from EDs are men, and future research needs to include them in the studies of EDs to a much higher extent. It is also important to consider other gender minority groups in this context as they generally seem to have a higher risk for psychopathology including EDs (Mensinger et al. 2020; Ngata et al. 2020). However, the scarcity of data on outcomes of interest from these groups makes it necessary to focus on females only, in this chapter.

EDs are characterized by emotional distress, functional impairment, relapse, and chronicity (Arcelus et al. 2011), as well as significantly increased mortality rate (Welch and Ghaderi 2014). Sadly, the majority (around 75%) of those with EDs do not seek professional help (Hudson et al. 2007; Keski-Rahkonen et al. 2009; Kessler et al. 2013). This might partly explain the high prevalence of EDs among middle-aged women. Micali et al. (2017) reported a 1-year prevalence of EDs of 3.6% among middle-aged females (Micali et al. 2017). Furthermore, not all the patients who seek help receive evidence-based treatment, many relapse and need additional treatment, and the cost of treatment is high. It has been shown that the age-adjusted costs for the treatment of anorexia nervosa and bulimia nervosa are comparable to the cost of treatment for schizophrenia (Striegel-Moore et al. 2000).

To summarize, EDs are prevalent, they tend to have a chronic course, and they have a profoundly negative impact of the quality of life and functioning of those afflicted. The majority of those with ED do not seek professional help, and a significant portion of those seeking help do not recover. Thus, a contextual perspective on EDs raises the imperative of prevention, as in many other severe mental disorders.

Prevention

Although we axiomatically believe that prevention is always a more optimal and efficient choice than treatment, it certainly is an empirical question in reality, given the conditions under which prevention is implemented. Issues such as the availability of prevention interventions with known efficacy, the acceptability of such programs, the infrastructure for providing the intervention and reaching the target population, the level of prevention (i.e., universal, selective, or indicative), the costs of providing the program, the sustainability of the intervention across time, and the need for cultural adaptions would determine whether a certain prevention intervention under specific conditions would be efficacious or not. Another important issue is the potential discrepancies between efficacy and effectiveness interventions and the need to implement prevention strategies on a large scale if we aim to make a difference on the public health level. Below, a summary of what we know about prevention of EDs will be presented to put the currently most investigated prevention method called the Body Project and its virtual version into a context.

The Main Prevention Strategies for EDs

The prevention strategies within the field of EDs might be divided into three categories: (1) first-generation, mainly didactic, psychoeducational strategies including programs presenting symptoms and outcomes of EDs; (2) strategies based on multicomponent programs focusing on factors such as critical thinking about media messages, improving self-esteem, and coping with stress, as well as programs based on the principles driven from cognitive behavior therapy; and (3) strategies based on cognitive dissonance theory, such as the Body Project that targets at-risk groups and focuses on amenable and crucial risk factor for EDs. These three main categories are illustrated in Fig. 1.

The first category reflects very early efforts to prevent EDs. These first-generation prevention programs were basically unsuccessful at reducing risk factors for EDs (Stice and Shaw 2004). As expected, concerns were raised at an early stage regarding potential iatrogenic effect of such programs (O'Dea and Abraham 2000; Russell and Ryder 2001), which according to Levine et al. (1999) was no cause of despair or defensiveness, given that these efforts presented initial steps in prevention of EDs compared to, for example, extensive theory and research on the prevention of substance abuse (Levine et al. 1999). These programs were later on developed further into multicomponent psychoeducational programs and in some cases incorporated skills-building, which represent the second category of prevention strategies. The second category constitutes several prevention programs. Those with more empirical evidence of efficacy are, for example, the Student Bodies (Taylor et al. 2006), the Girl Talk (McVey et al. 2003), and the Weigh to Eat (Neumark-Sztainer et al. 1995). The third category comprises dissonance-based prevention programs, commonly referred to as the Body Project. The last category has currently the most empirical support including efficacy trials, effectiveness studies, and comparative trials, all with independent replications (Stice et al. 2019a). vBP is one of the most

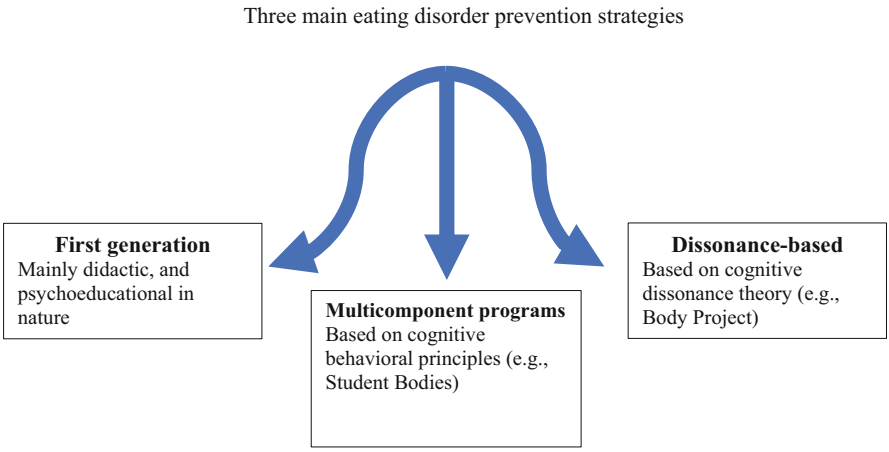


Fig. 1 The three main categories of prevention programs for EDs

recent extensions of the Body Project to approach the goal of building an efficacious prevention intervention that can be implemented on a broad basis to make a difference in public health.

Cognitive Dissonance Theory and Its Implication for Prevention

Dissonance-based interventions are built upon cognitive dissonance theory (Festinger 1957). According to Festinger (1957), we feel psychological discomfort when we have inconsistent cognitions, and the discomfort motivates us to alter our cognitions in order to reach a higher level of consistency in our cognitions (beliefs, assumptions, facts, images, etc.). To help people change the attitudes that are not serving them in the long run (e.g., "It's important to be thin and fit to be successful"), one possible strategy is to ask them act in a way that is inconsistent with that attitude (e.g., talk about the negative outcomes of such an attitude, write a letter or a brief manifesto to criticize the thin ideal, ask other people to consider these negative outcomes, act contrary to their practical habits related to being thin, etc.). Such acts seem to generate cognitive dissonance, as they represent counter-attitudinal stance. As we tend to avoid cognitive dissonance, we will be prone to change our original attitude to reduce the dissonance and experience consistency in our cognitions. Interestingly, we also tend to change our future behavior to reduce cognitive dissonance (Aronson 1980). The processes in a cognitive dissonance-based intervention are illustrated in Fig. 2.

As seen in Fig. 2, the new information that is acquired during the intervention leads to a state of cognitive dissonance due to the inconsistency that emerges as a consequence of taking a new stand, arguing for new ideas or behaviors that go against the previous perception, belief behavior, or attitude, and makes the individual prone to make changes in his or her attitudes to once again return to a state of balance and harmony.

As noted by Festinger (1957), an important precondition for emerging dissonance is the sense of voluntary inclusion and processing of a counter-attitudinal stance. If we take a counter-attitudinal stance (e.g., writing a letter) as a consequence of the circumstances (e.g., due to external demand, or for receiving monetary compensation for the time we devote on the task), then we attribute our act to such circumstances and do not feel any dissonance (e.g., "I did it because I had to," or "I needed that money"). Thus, we need to create a situation in which the participants engage in counter-attitudinal acts in a curious and open manner to feel they take possession of the new attitudes that underlie their stance. This is usually more easy to do in a group format, and taking a counter-attitudinal stance in a group context seems to produce more dissonance (Green et al. 2005). When we take a stance for something in a group context, compared to when we read and write about it on our own without sharing it with anybody else, we are perceived as a proponent for that idea, and in the same manner as our self-concept is a reflection of our understanding of how others perceive us, then we internalize the idea. This produces cognitive dissonance and lays the ground for change in the original attitude and corresponding behaviors.

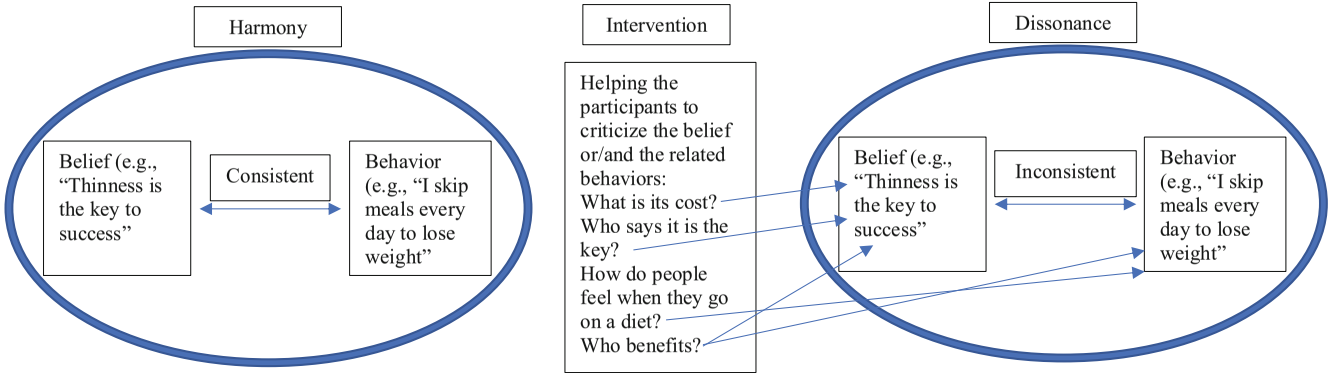


Fig. 2 Illustration of how an intervention based on cognitive dissonance theory may influence beliefs and/or behaviors. The upcoming dissonance due to emerging inconsistency (right side) motivates the individual to change his/her beliefs or behaviors in line with newly acquired information to return to a state of harmony

Dissonance-Based Intervention and Body Project

Based on the evidence on the efficacy of the dissonance-based intervention in many areas such as safe sexual practice (Stone et al. 1994), smoking onset (Killen 1985), and substance use (Barnett et al. 1996), Stice et al. (2000) developed a dissonance-based intervention for targeting thin-ideal internalization, which is one of the best established and malleable risk factors for EDs (Stice 2001). The choice of the thin-ideal internalization was also based on the dual pathway model of bulimia nervosa (Stice 1994) and its putative effects on negative affect, body dissatisfaction, dieting, and ED symptoms (Stice 2001). As noted by Stice et al. (2008), the dual pathway model has some similarities with the cognitive behavioral model of EDs (Fairburn et al. 2009), in which overevaluation of controlling eating, weight, and shape increases the likelihood of restraint and dieting that in turn increases the risk for ED symptoms.

The development of the dissonance-based intervention for EDs has been an iterative process (Stice et al. 2008). In its first version, it consisted of three 1-h group sessions that later on expanded to four sessions, and its efficacy and effectiveness has been investigated in a large number of studies with promising results. The intervention is now recognized as the Body Project since the publication of the first manual with the same name (Stice and Presnell 2007).

The four-session version is the one most extensively investigated. The main content of the vBP is summarized in Table 1.

In the first session, the participants receive a brief rationale for the intervention: Discussing the costs and consequences of the beauty ideal that is currently maintained through different mechanisms in our societies might help them feel more satisfied with their bodies. The intervention is not presented as a strategy to prevent EDs but as a way of improving body image. Voluntary commitment to try the approach is solicited basically each session. The group then tries to collectively define the origins of the thin ideal and how it is maintained. Other important questions that are discussed interactively are the impact of messages related to the beauty ideal from different persons and who (e.g., various corporates) actually benefits from internalization of this message. Finally, as a homework assignment, the participants are asked to write a letter to a young girl about costs of pursuing the thin ideal and to stand in front of a full-size mirror and note positive self-qualities in terms of behavioral, social, emotional, and physical features. The participants are asked to complete these exercises before the next session and to bring them to discuss in the group.

The second session starts with reviewing the homework exercises (i.e., reading their letters and discussing their positive qualities lists). Next, they engage in a role-play during which they dissuade the group facilitator out of pursuing the thin ideal. The homework assignments before the next session are to generate a top 10 list of things females of the same age can do to challenge the current thin or beauty ideal and to write a letter to someone who has pushed them to pursue the thin ideal, including how this affected them and how they would react to it now.

Table 1 Brief description of the main content of the vBP through sessions 1–4

Sessions	Homework assignments
Session 1 Declaring voluntary nature of participation in the group[a] Brief rationale for the intervention Origins of thin/beauty ideal Costs and consequences of the beauty ideal Who benefits from this ideal?	**Session 1 homework assignment** Write a letter to a girl of the same age about the costs of pursuing the thin ideal Mirror exercise: note positive self-qualities: social, emotional, behavioral, and physical
Session 2 Reading their letters and discussing Role-plays: to dissuade the group leader out or pursuing the thin ideal	**Session 2 homework assignment** Generate a top 10 list of things to challenge the current ideal of beauty Writing a letter to someone who pushed them to pursue this ideal
Session 3 Reviewing the homework exercise Diverting thin-ideal comments through role-plays Discussing personal body image concern	**Session 3 homework assignment** Challenge your body image concerns (behavioral experiment) Act on an item on the list of things to do to challenge the current thin ideal
Session 4 Reviewing the experience of behavioral challenge and body activism Resisting future pressure to be thin (role-play and discussion) The benefits of the group discussions	**Session 4 homework assignment** Self-affirmation exercises Writing a letter to a girl of same age who avoids body image concerns Engaging in future activism

[a] This is repeated at each session

The main content of the third session is to review the home exercises, to complete role-plays wherein they divert thin-ideal comments posed by the facilitator, and to discuss personal body image concerns. They are also asked to complete two homework assignments. One is to engage in behaviors that challenge their body image concerns using behavioral experiments (e.g., wearing clothes they have been avoiding due to their body dissatisfaction), and another one is to choose one of the items on their list of things that females of the same age can do to challenge the current ideal and to act on it, after sharing their list and discussing it with the group.

The last session consists of discussing the home exercises (i.e., their experience with the behavioral challenge and body activism); how to resist future pressure to be thin, and especially subtle messages conveying the thin ideal, by discussing and role-playing responses to such pressure; and how the group has been beneficial to them. As final homework assignments, they are asked to engage in some self-affirmation exercises (e.g., appreciating positive comments about their looks instead of invalidating them) and to write a letter to another young girl about avoiding body image concerns and to engage in further body activism.

The Efficacy and Effectiveness of the Body Project

The Body Project has been evaluated in a large number of studies. Several reviews are available, and the most recent meta-analytic review of the dissonance-based interventions (Stice et al. 2019a) has shown promising effect in terms of reduction of thin-ideal internalization, body dissatisfaction, dieting, negative affect, and ED symptoms, both when compared to a minimal intervention and a credible alternative intervention. A previous meta-analysis of all prevention trials for ED (Stice et al. 2007) showed larger effects for programs that were interactive, selective (i.e., focusing on participants with a risk for ED compared to universal prevention), and multisession and only focused on females. These characteristics are the defining structural features of the Body Project. In line with the theory and outcome from previous trials, the most recent meta-analysis (Stice et al. 2019a) of the dissonance-based intervention also found larger effects when more dissonance-inducing activities were included, groups were larger, participant was voluntary, and body dissatisfaction was required (selected prevention). Interestingly, effects were larger when intervention was delivered in person versus online (Stice et al. 2019a). However, the online intervention was not done in group but delivered as an individual intervention, and in addition to significant heterogeneity of the effects of online delivery of the method, the online versus group delivery of the intervention only moderated one of the five outcomes.

Until recently, a full online delivery of the Body Project, using the group format, and peer facilitators that were trained and supervised had not been evaluated. Such a format might have major implications for broad implementation of the Body Project, especially as the Body Project has currently the best evidence of efficacy for prevention of EDs.

Influencing Public Health: Prevention on Broad Basis

How useful is a prevention program if it cannot be implemented on a broad basis to make a difference on public health? Researchers have succeeded to develop a good number of efficacious prevention programs within different areas such as depression and anxiety in young people (Werner-Seidler et al. 2017), suicide prevention among youth (Wasserman et al. 2015), parent training to prevent conduct disorder among children (Kellam et al. 2011), and programs for prevention of substance use (Arango et al. 2018), prevention of transition to psychosis (Hutton and Taylor 2014), and EDs (Stice et al. 2019a). However, very few efficacious prevention programs are broadly implemented to improve mental health problems on a societal level, beyond randomized controlled trials, and effectiveness research. As have been argued in the case of prevention of depression, efforts to implement prevention programs might only succeed if they are structurally embedded at local, regional, and national level and target the strongest determinants of risk (Ormel et al. 2019). To facilitate structural embedding of prevention programs into existing institutions within the domains of health care, child care, and education, factors such as the intensity of the

programs, demands on resources, special education for delivery and time needed to implement an intervention, format of delivery, and flexibility and level of complexity are important to consider, in addition to political decision to implement such programs. We are currently in an era of digital revolution with smartphones and Internet that brings a fresh array of possibilities for broad implementation of prevention of mental disorders, including EDs.

The Promise of Internet and Digital Techniques

With increasing access to Internet and smartphones, most people are getting access to more education and opportunities than before. Efficacious prevention programs have largely remained in the shadows of the heavy burden on mental health professionals and low access to psychological treatment for those in need of such services. With the new technology, several obstacles can be overcome, and prevention can be more easily provided broadly. Interventions using mobile technology and Internet have been shown to be effective in the treatment of many types of psychiatric disorders (Andersson et al. 2019). This promise might be extended to prevention. We do not any longer need to think of prevention as an activity that has to be delivered to a group of people gathering at a specific location. The mobile and Internet technologies provide a great range of flexibilities and possibilities such as momentary monitoring, automatic or personalized feedback, digital meetings, and apps that can be accessed at any time to obtain information or to visualize and foster skills. In addition, the technology makes it possible to provide makeup sessions through recoding of meetings for participants who miss some sessions. Finally, this technology might also be helpful in combating the shame and stigma associated with mental health issues. It provides possibilities for a new way of interacting with both information and other people.

Given these opportunities, it was a logical next step to investigate the efficacy of the Body Project when delivered digitally. In addition, although previous efforts to provide the Body Project through Internet did produce some beneficial effects (Stice et al. 2012), the long-term outcome was not as favorable as the face-to-face trials of the Body Project (Shaw et al. 2016; Stice et al. 2014). The Internet version of the Body Project was previously delivered as an individual treatment. The group context of delivery was absent in this mode of delivery (Stice et al. 2012). It turned out that ED onset was significantly lower in the peer-led version of the Body Project compared to the Internet version (Stice et al. 2017). The lower efficacy of the individually delivered version of the Body Project through Internet was theoretically expected, as higher level of dissonance is produced in group format and higher dissonance is in turn related to better outcome. Consequently, we adapted the Body Project to be delivered virtually (thus virtual Body Project: vBP) with a group leader and no more than six participants per group.

vBP

In the vBP, we retained the content and principles basically identical to the original version (Stice et al. 2017) and made minor adjustment for smooth delivery through the Internet (Ghaderi et al. 2020). When the trial was running, the freely available videoconference technologies were not stable enough to allow more than five to eight participants. During the last years, and due to the pandemic, these technologies have advanced, and inclusion of larger group and more than one group leader is nowadays possible without subscription to very expensive online videoconferencing services. Smaller groups are easier to constitute, and fewer people will face difficulties in agreeing on a time point for the each of the 4 weeks of the intervention. Smaller groups might be a more efficient choice for future implementation of the vBP, but current technology allows test of the efficacy of larger groups too.

We recruited 431 female participants, aged 15–20 years, from across Sweden. The study was approved by the Regional Ethics Board in Stockholm (Dnr. 2015/841–31/2 and 2015/2051–32) and registered on ClinicalTrials.gov (NCT02567890). The main inclusion criteria were to report a subjective sense of body dissatisfaction, which is a known risk factor for the emergence of EDs (Ghaderi and Scott 2001). Exclusion criteria were symptoms of severe depression or anxiety in need of treatment, indications of suicidality, concurrent psychological treatments, meeting the DSM-5 diagnostic criteria (American Psychiatric Association 2013) for a full diagnosis of EDs or other specified EDs, or other serious conditions such as bipolar disorder that required psychiatric care.

Participants were randomized into three conditions: (1) vBP, which consisted of four interactive occasions, some homework assignments, and monitoring; (2) expressive writing (EW) (placebo/attention control); and (3) a waitlist control condition. Those in the waitlist condition received the vBP as soon as they completed the 6-month follow-up assessment. The EW condition was designed to match the frequency of the vBP. It consisted of brief written instructions sent to participants weekly over 4 weeks. They were asked to write about their thoughts, emotions, and images as well as any other content that comes to their mind in relation to their body. They were asked to write for 40 min each week. This was somewhat different compared to previous trials of the Body Project where the EW has been used as placebo condition. In previous trials, the participants were asked to write about emotionally significant topics and not specifically issues related to their body image or body dissatisfaction. Also, in contrast to previous versions of the Body Project, in the vBP, participants also received a written booster reminder at the 12-month follow-up. They were reminded of the issues raised during the intervention, and those in the EW conditions were asked to once again take some time to write about anything that comes to mind in relation to their body.

Direct and long-term effects of the interventions (6, 12, and 18 months post-intervention) were investigated by systematic measurements. ED diagnoses were assessed using the Eating Disorders Examination (Fairburn 2008; Fairburn and Beglin 1994), and risk factors and other outcomes were investigated using established self-report questionnaires. For details, please see Ghaderi et al. (2020).

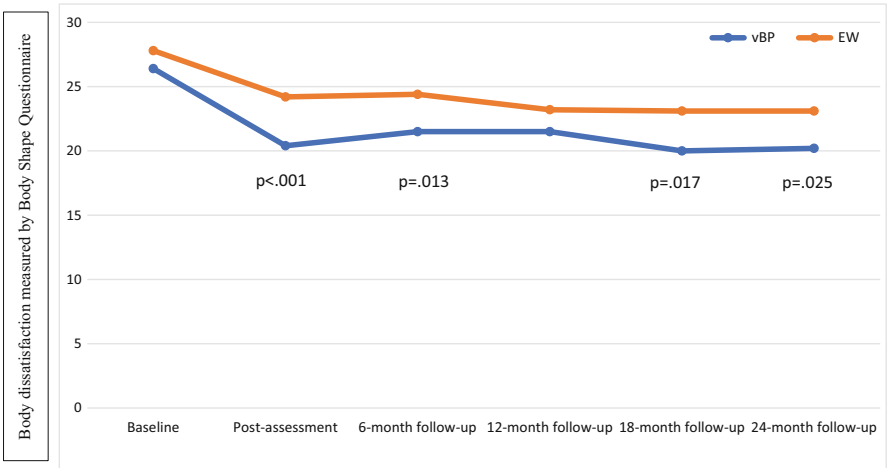


Fig. 3 The change in body dissatisfaction in the vBP versus the placebo condition (EW) across the 24-month follow-up. The difference between the conditions is significant (based on Sidak post hoc test) at posttreatment, as well as 6-, 18-, and 24-month follow-up

The incidence of ED onset over 24-month follow-up was 3 in vBP (2.0%) and 13 in EW (8.8%), which denotes a significant difference (hazard ratio: exponential $B = 0.26$, 95% confidence interval (CI) [0.075, 0.92], $p = 0.037$). Incidence of ED onset in vBP participants was 77% less than among participants in the EW condition.

Participants in the vBP condition reported significantly greater reduction in ED symptoms and clinical impairment, as well as internalization of thin ideal compared with the waitlist participants at postintervention and 6-month follow-up.

Body dissatisfaction is a major risk factor for ED. The intervention resulted in significantly larger reduction of body dissatisfaction in the vBP condition compared to the placebo condition. The pattern of change across the 24-month follow-up is illustrated in Fig. 3.

Compared to participants in the EW, which was perceived as a credible intervention, those in the vBP reported greater reduction in ED symptoms, restraint, body dissatisfaction, and internalization of thin ideal at the end of the intervention, as well as at 6-, 12-, 18-, or 24-month follow-up. Interestingly, participants in the EW condition reported significantly greater reduction in clinical impairment and body dissatisfaction at postintervention compared with the waitlist participants.

Although the intervention was delivered virtually, rather than in person, the reduction in the incidence of EDs was notable. If these outcomes are replicated in future trials of the vBP, it might be a viable option for future evaluation of scalable prevention of EDs. The vBP provides more flexibility and makes it easier to participate and to compensate for missed sessions by reviewing the recorded sessions ahead of the coming one whenever the participants miss a session. In addition, the virtual delivery allows the participants to participate in the intervention anonymously in the group if they wish, which probably decreases the stigma related to

EDs. The intervention can also be delivered by trained peers who do not have to be present at a specific location to run the groups. Although we allowed the participants to be fully anonymous, if they wished so, none chose to participate anonymously. Smartphone and computers are becoming more and more available globally, and especially smartphones are becoming more affordable even for people in poor countries, which brings a promise for increased possibility of preventive efforts for not only EDs but for mental health problems in general.

Applications to Other EDs

Most studies conducted on the Body Project target older teenagers and young adults, but they encompass the ages 11 to 64 years across trials (Stice et al. 2019a). The vBP did also target the same age group (15–20 years old). Although a few studies of the Body Project have been evaluating the outcome among a younger target group (Halliwell and Diedrichs 2014; Rohde et al. 2014), it seems that the results are stronger for those aged 15 and above (Stice et al. 2019b). This might be due to the fact that the peak risk period for the onset of EDs occurs between 16 and 19 years of age (Hudson et al. 2007) or that the intervention per se is more effective for older participants. This means that the intervention has not been evaluated in as many trials for younger children and adolescents, which is a significant issue, as a mentionable number of cases of anorexia nervosa have a fairly early onset. More trials of the efficacy and effectiveness of the vBP should be conducted on the younger age group.

Any advances in the prevention of EDs might have broader implications for the prevention of other mental health problems. The lessons learned from the vBP might be efficiently used in the prevention of other conditions and problems among children, adolescents, and adults.

Mini-Dictionary of Terms

- Body Project: A manualized intervention, based on cognitive dissonance theory to reduce the risk for onset of EDs.
- Virtual Body Project: Digitally delivered version of the Body Project, with one group facilitator and four to six participants.
- Risk factors: Variables such as thin-ideal internalization or body dissatisfaction that in prospective studies have been shown to predict onset of EDs.
- Universal prevention: Prevention efforts that target the entire subset of general population (e.g., all children attending schools in grades 5 to 8).
- Selective prevention: Prevention efforts that target those who are at risk of developing the condition that we want to prevent (e.g., young people with body dissatisfaction).

- Indicated prevention: Prevention that targets individuals who already exhibit some signs of the condition that we want to prevent (e.g., individuals with some early symptoms of EDs).

Key Facts of the Virtually Delivered Body Project (vBP) and EDs

- The incidence of EDs in the vBP was 77% less than in the placebo condition.
- The vBP provides a more flexible format for delivering the intervention than the face-to-face mode.
- The vBP seems to decrease the incidence of EDs through the same mechanisms (reducing the internalization of the thin ideal) as in the in-person version of the Body Project in general.
- The vBP seemed to be acceptable to the participants, and all the participants chose to participate without concealing their identity, although they all had the choice to participate anonymously.
- Booster sessions can more easily be delivered in the vBP compared to in-person delivery of the intervention.

Summary Points

- EDs are prevalent conditions and present a major source of suffering, morbidity, and mortality for adolescents and young adults.
- Dissonance-based intervention (mainly the Body Project) is currently the most researched and efficient prevention program for EDs.
- Efficacious prevention programs need to be delivered in a format that builds the ground for scalable implementation to make a difference in public health.
- vBP is a step forward, as it simplifies the delivery of the Body Project.
- Despite being implemented virtually, rather than in person, it resulted in notable reduction in incidence of EDs.
- vBP might be a viable option for future scalable prevention of EDs, if its outcomes and processes are replicated in independent studies.

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Time-Related Changes in Eating Disorders 12

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Contents

Introduction 200
Changes in the Concept and Diagnosis of EDs 201
Anorexia Nervosa (AN) 201
Bulimia Nervosa (BN) 202
Transition of Diagnostic Criteria for AN and BN 203
Time Trend of Incidence and Prevalence 206
Western Countries 207
Non-Western Countries 211
Changes in Clinical Picture 213
Middle-Aged Women 213
Men 214
Conclusion 215
Applications to Other Eating Disorders 216
Mini-dictionary of Terms 216
Key Facts of Time-Related Changes in Eating Disorders 217
Summary Points 217
References 217

Abstract

This chapter provides an overview of changes in the trends of anorexia nervosa (AN) and bulimia nervosa (BN) over time. The concepts of AN and BN have barely changed since they were incorporated into the operational diagnostic criteria in the 1980s. Epidemiological studies in Western countries have revealed increases in AN and BN since the 1930s and 1970s, respectively. Subsequently, AN has remained constant since around the 1970–1990s, although its incidence has increased among young women, whereas BN peaked around the 1990s and has since decreased. Further, compared to Western countries, reports from

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non-Western countries are insufficient in number and detail. Research participants with eating disorders (EDs) have expanded to include not only young women, but also men and middle-aged women. Further research is needed on EDs across global regions, cultures, genders, and ages.

Keywords

Eating disorders · Anorexia nervosa · Bulimia nervosa · Time trend · History · Incidence · Prevalence · Western countries · Non-western countries · Middle-aged women · Men · Eating behavior

Abbreviations

AN	Anorexia nervosa
AN-BP	Anorexia nervosa – binge/purging type
AN-R	Anorexia nervosa – restricting type
BED	Binge eating disorder
BMI	Body mass index
BN	Bulimia nervosa
BN-NP	Bulimia nervosa – non-purging type
BN-P	Bulimia nervosa – purging type
DSM	Diagnostic and Statistical Manual of Mental Disorders
ED	Eating disorder
ICD	International Classification of Diseases

Introduction

Cases of disordered eating behaviors were first reported in the England in 1680s, evolving into the current concept of eating disorders (EDs). As of 1980s, they were regarded as culture-bound syndromes existing only in Western cultures. It was assumed that the pathology of EDs stemmed from certain characteristics of Western culture (Prince 1985; Swartz 1985). When they began being reported in non-Western countries, it was speculated that the introduction of Western sociocultural factors in these regions influenced their occurrence (Keel and Klump 2003). The term "socio-cultural" includes not only a variety of perspectives that began in the West, such as industrialization, urbanization, modernization, and globalization, but also aspects of Western culture, such as ideal thinness and the Western diet (Weissman 2019). Furthermore, the concept of acculturation, defined as the process of psychosocial change that occurs when an individual or group encounters another culture, has received attention for its impact on EDs (Alvidrez et al. 1996; Weissman 2019; Melisse et al. 2020). Unique cultures of non-Western countries have also been shown to influence EDs (Pike and Borovoy 2004). Thus, EDs can be described as "culture-reactive" rather than "culture-bound" (Di Nicola 1990; Keel and Klump 2003; Alfalahi et al. 2021).

Although genetics plays a significant role in the development and maintenance of EDs (Bulik et al. 2016), sociocultural factors are consistently recognized as impacting their cause, progress, and outcome (Pike et al. 2014; Weissman 2019). However, it is difficult to directly prove the relationship between sociocultural factors and the development of EDs.

This study thus aims to understand how EDs have changed over time. First, we will attempt to describe how EDs have been viewed historically and how their conceptions have altered with time. We will then explain the epidemiological time trends regarding EDs in Western and non-Western countries. Finally, we will detail the shift in the population that suffers from EDs worldwide.

Changes in the Concept and Diagnosis of EDs

In this section, we will describe how disordered eating behavior was historically viewed and came to be conceptualized as anorexia nervosa (AN) and bulimia nervosa (BN), as well as the changes in diagnostic criteria for these conditions since their conceptualization as psychiatric disorders.

Anorexia Nervosa (AN)

In the ancient West, long before the conceptualization of EDs, the practice of "self-starvation" was a component of religious rituals. Its purpose was to practice asceticism, obtain forgiveness for sins, lose weight "so as to pass through the narrow gates of heaven," protect oneself from demons, purify oneself, and gain psychic powers. Ascetic fasting was practiced by early Christian monks (Bemporad 1997) and medieval Chinese Daoist priestesses (Lo et al. 2012), to seek the salvation of the soul by abstaining from all desires.

From the medieval to the early modern period, there seemed to be an increase in the number of saints who undertook intense fasts to approach God, believing that they could not obtain salvation unless they purified their own bodies. Their intense fasting sometimes led to death by starvation. An example was Caterina Benincasa of Italy, known as "Saint Catherine of Siena" and venerated as one of the patron saints of Europe. She began strict fasting at a young age, eating only bread, raw vegetables, and water by the age of 16, ultimately consuming almost nothing but the Eucharist by the age of 25. She refused to eat even when others attempted to force her and remained consistently active until her death at the age of 33: the same age as Christ (Bell 1985). Although it is unclear whether such "holy anorexics" desired thinness and feared becoming fat, they share similarities with present-day AN patients who exhibit extreme fasting beyond normal asceticism, social withdrawal, and stubborn refusal to eat.

EDs first appeared in medical literature in 1689. Morton (1694) described two cases in England of a teenage boy and girl, detailing restricted eating and severe weight loss, which may be similar to AN today. Gull (1873), also from England, first

used the term "anorexia nervosa" to describe a starvation condition caused by psychological problems. He described several treatment strategies, including living away from family and a nutritious diet. Simultaneously, Laségue (1997), from France, gave a detailed clinical report on the psychopathology of AN and the difficulties of its treatment. After this period, additional psychological features of AN, such as weight phobia, were also reported.

In 1914, German pathologist Simmonds reported Simmonds' disease, a disorder of the pituitary gland with symptoms including anorexia, atrophy of sexual features, absence of libido, hypotension, bradycardia, and hypoglycemia. This led to the continued misconception that AN was caused by pituitary disease. However, Berkman's (1930) study comprising 117 patients revealed that psychic disturbance is followed by anorexia; the resulting small intake of food leads to inanition, which is associated with a low rate of metabolism. Furthermore, Sheehan (1939) reported that emaciation due to Simmonds' disease was rare, resulting in the differentiation of AN from Simmonds' disease. The misconception that AN was caused by a pituitary disease was corrected, and the psychological cause theory was reapplied. Habermas (2015) claimed that, in Nazi Germany, political background contributed to the focus on the somatic aspects of AN, as the regime systematically murdered psychiatric patients, making it far safer for them to have their AN treated as a somatic rather than as a psychiatric condition. Regarding reaffirmation of the psychological causes of AN, Ryle (1936) described the understanding and treatment behind AN in detail, including its mental, physical, and psycho-behavioral characteristics, which can be considered the basis for the modern interpretation of AN. In the 1940s, the psychopathology of AN was interpreted based on psychoanalytic theory (Lucas 1981).

In the 1970s, psychological research on AN, developing into modern psychotherapy, began to be conducted. Bruch (1973) posited problems in body perception, emotional processing, and interpersonal relationships as the core aspects of AN, developing her theory of psychopathology through animal studies on attachment, noting that many psychological problems resulted from starvation. In 1972, Feighner et al. proposed a diagnosis of AN from the standpoint of operational diagnostic criteria for psychiatric disorders, based on descriptive symptoms, avoiding past theoretical and etiological perspectives. In these criteria, AN was defined not only as weight loss; a desire for thinness; lack of insight; and a distorted, implacable attitude toward food and weight; but also in terms of physical signs of binge eating; self-induced vomiting; and emaciation (e.g., amenorrhea, lanugo, and bradycardia). In addition, the age of onset was defined as less than 25 years, indicating that AN is considered an adolescent-onset disorder.

Bulimia Nervosa (BN)

Binge eating in individuals with AN was described by Gull in 1873, as follows: "Occasionally for a day or two, the appetite was voracious." However, binge eating and self-induced vomiting, without accompanying underweight, did not receive much attention for a long time. There is speculation that "nervous vomiting,"

which was medically described in the late nineteenth century, may have been BN (Van Deth and Vandereycken 1995). However, its psychological characteristics were not described.

Little attention was paid to BN until the 1970s. After binge eating was noticed in an AN group, individuals within the normal weight range suffering from binge eating, vomiting, and laxative abuse were identified. The term "bulimia nervosa" was coined in 1979 by Russell in England, who defined it as an irresistible urge to overeat, followed by self-induced vomiting or purging, and a morbid fear of becoming fat. Since most individuals with BN had a history of AN, he described BN as "an ominous variant of AN."

It is possible that the nature of EDs has contributed to the difficulty in describing their history. This is because, in general, individuals with EDs deny engaging in food restriction, excessive exercise, binge eating, and self-induced vomiting.

Transition of Diagnostic Criteria for AN and BN

Figure 1 shows the changes in diagnostic criteria for AN and BN.

The Diagnostic and Statistical Manual of Mental Disorders (DSM)-III was published by the American Psychiatric Association (1980). It proposed the diagnostic criteria for AN, largely following the Feighner criteria, and the new criteria for bulimia. While the Feighner criteria emphasized self-directed attitudes toward thinness, the DSM-III incorporated characteristics such as disturbance of body image and intense fear of becoming obese. Bulimia was considered a syndrome involving recurrent episodes of binge eating, with depressed mood and self-deprecation following the bingeing episodes. Its diagnostic criteria also included the presence of weight loss attempts (severely restrictive diets, self-induced vomiting, or use of cathartics or diuretics) and weight fluctuations, which were not an essential part of the criteria. Bulimia could be diagnosed simply by repeated episodes of binge eating that were difficult to control, without compensatory behavior. It was distinguished from AN by the fact that the weight loss was not as severe as in AN and bulimic episodes were not considered to be caused by AN. However, in "rare instances," AN and BN could be listed together if both the criteria were met.

DSM-III was revised to DSM-III-R (American Psychiatric Association 1987), and "bulimia" was changed to "bulimia nervosa." The diagnosis of BN is now based on the requirement that the patient regularly engages in behaviors that prevent weight gain (self-induced vomiting, use of laxatives or diuretics, strict dieting or fasting, or vigorous exercise). In DSM-III-R, as in DSM-III, both AN and BN diagnoses were given to individuals exhibiting all symptoms of being underweight, binge eating, and purging.

Subsequently, in DSM-IV (American Psychiatric Association 1994), the diagnostic criteria for AN included two subcategories: the restricting type (AN-R) and the binge eating/purging type (AN-BP). BN was clearly distinguished from AN for the first time by the addition of the item "The disturbance does not occur exclusively during episodes of Anorexia Nervosa." It was also divided into two subcategories:

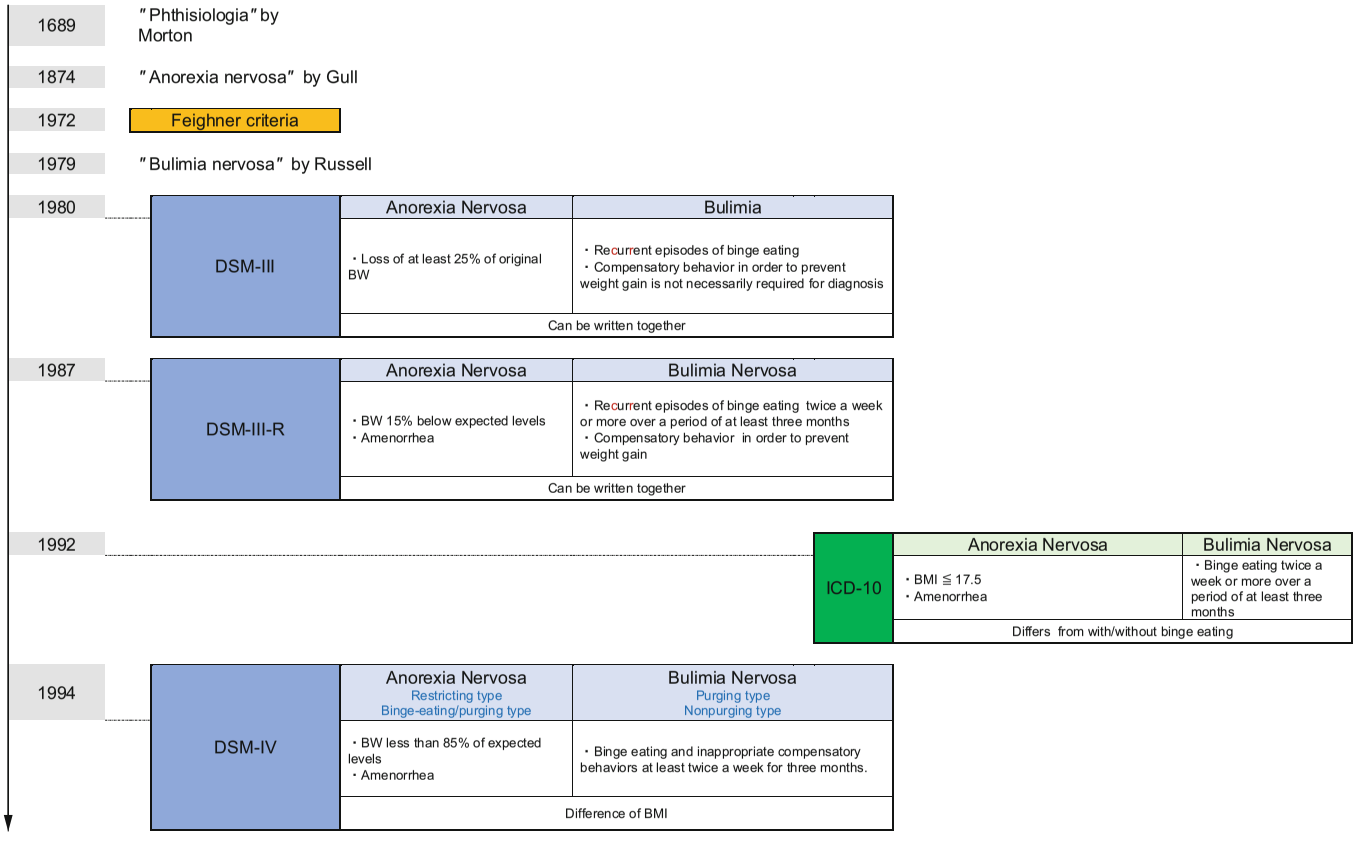


Fig. 1 Changes in diagnostic criteria for anorexia nervosa and bulimia nervosa. *BW*, body weight; *BMI*, body mass index

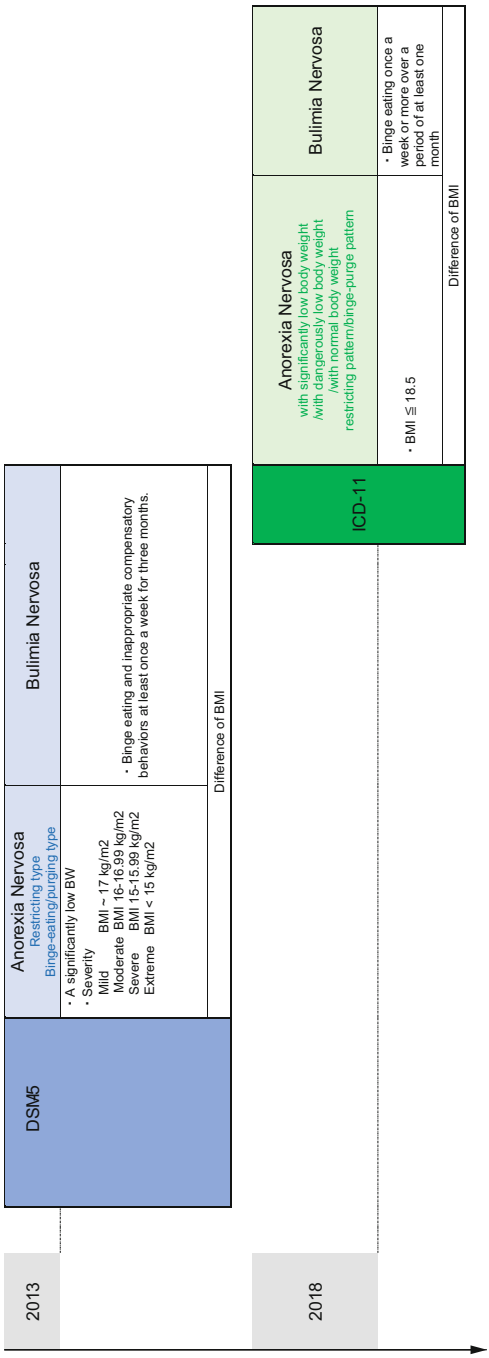


Fig. 1 (continued)

the purging type (BN-P), using self-induced vomiting or the misuse of laxatives, diuretics, or enemas as compensatory behaviors to prevent weight gain, and the non-purging type (BN-NP), involving fasting or excessive exercise.

In DSM-5 (American Psychiatric Association 2013), the diagnostic criteria for AN included the phrases "intense fear of gaining weight or of becoming fat, or persistent behaviors that interfere with weight gain." Although there were clear behaviors that prevented weight gain, AN could be diagnosed even if there was no obvious desire for thinness or fear of obesity. The BN subcategories of purging and non-purging were eliminated. In addition, a new diagnosis, binge eating disorder (BED) – primarily characterized by recurrent episodes of binge eating without repetitive inappropriate compensatory behaviors to prevent weight gain – was incorporated.

Contrarily, the World Health Organization (1992) published the International Classification of Diseases 10th Revision (ICD-10), listing AN and BN in the ED section. Since DSM-III and DSM-III-R defined the characteristics of AN and BN as being underweight and engaging in binge eating, respectively, individuals exhibiting both characteristics were diagnosed as having both AN and BN, leading to a complexity. To avoid this, ICD-10 simply separated AN and BN based on the presence or absence of binge eating, regardless of weight. In the subsequent DSM-IV and DSM-5, AN and BN were classified according to Body Mass Index (BMI). The ICD-11 (World Health Organization 2021) also classified AN and BN according to BMI, in a way similar to DSM-5. In ICD-11, AN can be coded according to BMI severity and further coded in terms of the causes of being underweight (restricting patterns and binge-purge patterns).

Thus, with regard to the diagnostic criteria for EDs, the following have been changed with each revision to the DSM and ICD: the definition of low BMI, frequency of binge eating and compensatory behaviors, duration of symptoms, and whether or not amenorrhea is included (Fig. 1). However, the basal concepts of AN and BN have remained largely consistent for over 40 years.

Time Trend of Incidence and Prevalence

This section describes the time trends in the incidence and prevalence of EDs in Western and non-Western countries. Methodological issues must be understood to interpret the incidence and prevalence of EDs, which are often excluded from epidemiological surveys for reasons of efficiency, because of their relatively low incidence and prevalence in the general population. Therefore, most epidemiological reports are based on primary care outpatient case registries, cases from mental health facilities, or those identified through inpatients, rather than among the general population. It is important to note that both incidence and prevalence can vary widely depending on the study population. They are lower in the general population, primary care facilities, and specialist hospitals, in that order (Martínez-González et al. 2020). This low trend is related to the access to health care and the choice of health care facilities according to the severity of the ED, stigma around mental

illness, and the ED pathology of denial. (Ali et al. 2017; Raisanen and Hunt 2014). In addition, the different diagnostic criteria used reflect varying rates of incidence and prevalence (Galmiche et al. 2019; Mustelin et al. 2016). If a syndrome is newly named as a disease, or if recognition of the disease by medical professionals and society in general increases, the detection and consultation rates of patients will increase (Weissman 2019).

Incidence reflects the number of new cases of a disease per year, being expressed as the number of cases per 100,000 person-years. Prevalence counts the cases of the disease at a particular time, regardless of its onset, thus including both existing and new cases. Keel and Forney (2015) explained the incidence and prevalence of EDs as follows: Incidence can be used to not only understand whether a disease is becoming more or less common in a population over time, but also explore etiology; prevalence is useful to not only understand the public health impact of a problem and the need for prevention and treatment, but also examine the differences in disease risk among various populations. Regarding EDs, incidence is more likely to be used when addressing the etiological theory that sociocultural changes contribute to their development (Keel and Forney 2015).

We attempted to use incidence information as much as possible to understand the temporal trends in the onset of EDs; however, limitations exist, especially for non-Western countries, where incidence rates are not well-reported. After describing the epidemiological changes in Western countries, where fluctuations in the incidence of EDs over time are better understood, the non-Western regions will be discussed.

Western Countries

Incidence studies in Western countries originated with the report by Willi and Grossmann (1983). Many reports indicate that the incidence of AN among young women has increased since the 1930s. Some researchers report that the overall incidence of AN had increased since the 1930s and has remained constant since the late twentieth century (Van Eeden et al. 2021), while others report that it continues to increase (Martínez-González et al. 2020). In contrast, it appears that the incidence of BN, on which epidemiological data has been collected since the 1970s, peaked in the 1990s and has since decreased in these countries.

Anorexia Nervosa

EDs, both AN and BN, tend to occur in adolescent girls and young adult women (Treasure et al. 2020). Most incidence and prevalence studies on AN have focused on these populations (Martínez-González et al. 2020). Table 1 shows the incidence of AN per 100,000 females in the following reports from three countries.

In the United States, studies on trends related to the incidence of AN in Rochester, Minnesota, for more than 50 years – 1935 to 1989 – reported an increase during the observation period. Population-based studies were feasible in Rochester, where health care was largely self-contained within the community, and Lucas et al. (1999)

Table 1 Incidence of anorexia nervosa per 100,000 females

Study	Subject	Country	Criteria	Ages	Period	Incidence	95%CI
Lucas et al. 1999	Outpatient	United States	DSM-III-R	All[a]	1935–1949	15[b]	9.3–20.6
					1950–1959	7.6[b]	3.9–11.4
					1960–1969	12.8[b]	8.5–17.2
					1970–1979	14.5[b]	10.66–19.7
					1980–1989	22.9[b]	17.3–28.6
				15–24	1935–1949	26.5	13.68–46.25
					1950–1959	30.8	15.38–55.13
					1960–1969	54.3	35.49–79.61
					1980–1989	75.5	54.87–101.37
Willi and Grossman 1983	Inpatient	Switzerland	Feighner/DSM-III	12–25	1956–1958	4	1.92–7.36
					1963–1965	6.8	3.96–10.89
					1973–1975	16.8	11.89–23.06
Milos et al. 2004			DSM-III-R		1983–1985	16.4	12.12–21.8
					1993–1995	19.7	14.15–26.75
van Son et al. 2006	Outpatient	The Netherlands	DSM-IV	5–64	1985–1989	13.4	9.92–17.63
					1995–1999	15	11.36–19.44
Smink et al. 2016					2005–2009	11.8	8.5–16
van Son et al. 2006				15–24	1985–1989	47.6	32.1–67.92
					1995–1999	65.8	45.31–92.44
Smink et al. 2016					2005–2009	66.1	43.53–96.11

This table is based on Table S3 and S4 by Martínez-González et al. (2020)
Feighner, Feighner criteria; *DSM*, Diagnostic and Statistical Manual of Mental Disorders
[a]Sex-adjusted per 100,000 inhabitants/year White population in Monroe country
[b]Incidence per 100,000 person-years directly age adjusted to 1970

counted the AN cases in the medical records of all local health care providers, including general practitioners and specialists. They found no increase in its incidence either in women aged over 25 or in men. However, the incidence among females aged 15–24 years underwent a long-term linear increase over the 50-year study period, from 26.5/100,000 (95% confidence interval (CI) 13.68–46.25) in 1935–1949 to 75.5/100,000 (95% CI 54.87–101.37) in 1980–1989. The increase in overall incidence of AN since 1950 was due to an increase in the number of young women.

In a study conducted in Switzerland, the incidence of severe AN was observed for 40 years, from 1956 to 1995, in a geographically defined region over five sampling periods. The same methodology was used across all periods, except that, after 1983, the DSM-III-R diagnostic criteria were used instead of the previous DSM-III criteria (Willi and Grossmann 1983; Willi et al. 1990; Milos et al. 2004). Data were obtained from the case records of almost all internal medicine, pediatric, and psychiatric clinics in the region, and medical records of all hospitals in the canton of Zurich were screened to identify the first hospitalization of each female patient with AN. The incidence among females aged 12–25 years was 4.0/100,000 (95% CI 1.92–7.36) in 1956–1958, 6.8/100,000 (95% CI 3.96–10.89) in 1963–1965, 16.8/100,000 (95% CI 11.89–23.06) in 1973–1975, 16.4/100,000 (95% CI 12.12–21.8) in 1983–1985, and 19.7/100,000 (95% CI 14.15–26.75) in 1993–1995. These data indicate that the incidence of AN among the at-risk population increased until the 1970s, after which it reached a plateau. In a review that included these studies and examined the period up to about the year 2000, Hoek (2006) noted that the incidence of AN increased steadily until 1970 and then stabilized.

Later, in the Netherlands, the incidence of AN was reported to have stabilized around the year 2000 (Smink et al. 2016). A study investigated changes in the incidence of EDs in a large representative sample of the Dutch population, using primary care data from 1985 to 2009 (Van Son et al. 2006; Smink et al. 2016). The overall incidence of AN among women was quite stable over the observation period: 13.4/100,000 (95% CI 9.92–17.63) in 1985–1989, 15.2/100,000 (95% CI 11.36–19.44) in 1995–1999, and 11.8/100,000 (95% CI 8.5–16) in 2005–2009. The incidence among women aged 15–24 years was 47.6/100,000 (95% CI 32.1–67.92) in 1985–1989, 69.5/100,000 (95% CI 45.31–92.44) in 1995–1999, and 66.1/100,000 (95% CI 43.53–96.11) in 2005–2009, suggesting that although the incidence among women in this age group increased during the 1980s and 1990s, it has remained stable since (Smink et al. 2016). Hoek (2016) provided a review of studies, including those of Van Son and Smink et al., again concluding – as in his previous review (2006) – that the incidence of AN has been stable since 1970.

Recently, a meta-analysis reported an increased incidence of AN among women of all ages and among younger women (10–30 years). Martinez-González et al. (2020) conducted a systematic review based on articles published from 1980 to 2019, mainly from Western countries, performing a meta-analysis of 31 studies divided into outpatient health care services and hospital admission, considering the fact that the incidence of AN varied widely among the study population depending upon the methodology. The results showed that the linear trend increased among women of all ages, both in studies with hospital admission records and in those based

on outpatient health care services. The incidence of AN was 8.8/100,000 (95% CI: 7.83–9.80) for studies with outpatient women and 5.0/100,000 (95% CI: 4.87–5.05) for studies with inpatient women. In young women, the incidence of AN was 63.7/100,000 (95% CI 61.21–66.12) among outpatients and 8.1/100,000 (95% CI 7.60–8.53) among inpatients. The incidence of AN among women, thus, varied widely, from 0.5–318.0/100,000. Cohort studies were also reviewed in this report (Martínez-González et al. 2020). A much higher incidence of 120.0 to 318.9/100,000 was observed in females compared to previous studies (Ghaderi and Scott 2001; Lahortiga-Ramos et al. 2005; Keski-Rahkonen et al. 2007). Martínez-González et al. (2020) concluded that the high values in their review were to be expected, given the use of adolescent and young female samples, and the screening strategies implemented to detect cases. Although the overall incidence was reported to be increasing in women, Van Eeden et al. (2021) stated in their review that the increased incidence of AN might be explained by greater public awareness, better detection, and the use of broader diagnostic criteria, and that the overall incidence rate of AN has remained considerably stable over the past decades.

The prevalence of AN was reported to be less than 1–4% in a review in Europe (Keski-Rahkonen and Mustelin 2016).

In conclusion, the incidence of AN among adolescent and young adult women has increased over the years since the first half of twentieth century. It is, however, unclear whether this reflects an increase in incidence or an earlier age of detection (Van Eeden et al. 2021). The incidence of AN among women peaked around the 1970–1990s. Since then, some reports have indicated that it has remained stable while others claim that it has been increasing. Time trends in incidence must be understood carefully, as they are constantly subject to methodological problems, and their interpretation may vary depending on the length of the study period.

Bulimia Nervosa

Since BN was recognized as a diagnosis (Russell 1979) approximately 100 years following AN, there is less information available on its incidence compared to that of AN. According to observations over time, the incidence of BN peaked around the 1990s and has been declining since.

Hall and Hay (1991) reported that the number of patients seen by community ED services in New Zealand increased from 6/100,000 to 44/100,000 between 1977 and 1986. In the Netherlands, a primary care survey showed an upward trend in the incidence of BN in the 1980s, increasing from 7.2/100,000 (95% CI 4.0–13.1) in 1985 to 15.2/100,000 (95% CI 10.0–23.1) in 1989 (Hoek et al. 1995). However, long-term studies have since shown that the incidence of BN was 8.6/100,000 (95% CI 6.7–11.0) in 1985–1989, 6.1/100,000 (95% CI 4.5–8.2) in 1995–1999, 3.2/100,000 (95% CI 2.0–4.9) in 2005–2009 (95% CI 4.5–8.2), and 3.2/100,000 (95% CI 2.0–4.9) in 2005–2009 (Smink et al. 2016). Therefore, it is estimated that BN has been on a downward trend since peaking around 1990.

In the United Kingdom, incidence studies of BN in primary care have shown a similar declining trend, peaking in the mid-1990s. In a 1988–1994 study, the incidence of BN among women aged 10–39 years more than tripled, from 14.6/

100,000 (95% CI 7.2–22.0) in 1988 to 51.7/100,000 (95% CI 45.6–57.9) in 1993 (Turnbull et al. 1996). However, continuous research has shown that the subsequent time trend of the incidence of BN among women aged 10–39 years peaked in 1996 and that incidence then declined to 30.7/100,000 (95% CI 24.3–40.0) in 2000.

A Danish study based on nationwide psychiatric register data detected an increasing incidence of BN between 1995 and 2010, ranging from 6.3/100,000 to 7.2/100,000 (Steinhausen and Jensen 2015). However, after adjusting for the rate of increase in the use of mental health services, the incidence of BN showed a declining trend, ranging from 6.3/100,000 to 4.2/100,000, and was the same among women in the 16–19 and 20–29 age groups, which had the highest incidence.

Another study conducted in Norway with data obtained from the National Patient Register (Reas and Rø 2018) confirmed a significant decrease in the overall incidence of BN in secondary care between 2010 and 2016, from 18.5/100,000 (95% CI 16.9–20.2) in 2010 to 16.1/100,000 (95% CI 14.6–17.2) in 2016, with a significant decrease in the average annual percentage point change(−4.2%). There was a significant decrease in incidence among all age groups, except for girls aged 10–14 years who showed an increasing trend, suggesting an earlier age of onset or detection. The peak incidence was reported among women aged 20–29 years.

The prevalence of BN was reported to be less than 1–2% in a review by Keski-Rahkonen and Mustelin et al. (2016) covering Europe as a whole.

Non-Western Countries

In this section, non-Western countries – including East Asia, West Asia, Latin America, and Africa – are discussed to explain the changing epidemiology of EDs. Research on non-Western EDs began much later in comparison to the West and is currently limited, especially in most African countries. Epidemiological data on mental disorders, in general, vary widely among regions of the world (Baxter et al. 2013), with scarce information on time trends of EDs in the non-Western world, outside some regions of East Asia.

East Asia

Japan was one of the first non-Western countries to report EDs. First, several case reports of AN were published in the 1960s (Ishikawa et al. 1960), followed by an increase in cases of AN and BN in the 1970s (Pike and Borovoy 2004). The first cross-sectional epidemiological survey was conducted in 1981 and showed that the incidence of AN in the 10–29 age group was 16.6/100,000 in 1981, 21.8/100,000 in 1992, and 76.4/100,000 in 1998. BN was first surveyed in 1992, with an incidence of 7.8/100,000 in 1992, 39.4/100,000 in 1998, and 38.4/100,000 in 2014 (Nakai et al. 2018). Thus, while the incidence of AN has been increasing, that of BN has not changed since the 1990s (Nakai et al. 2021). However, Nakai et al. (2021) claimed that the incidence of BN may have been underestimated, because the survey was conducted in a hospital rather than at a primary care setting, mainly dealing with individuals with BN. It should also be noted that the results are not strictly

comparable because the diagnostic criteria and participants included in the surveys differed from one time period to the other. However, the prevalence of EDs in Japan is said to have reached a high level, similar to that of Western countries, by the 1980s (Pike and Borovoy 2004; Hoek 2006) and has continued to increase after 1990 (Nakai et al. 2021). In addition, a Japanese clinical sample showed a decreasing trend in BMI and worsening psychopathology related to AN-R over a 30-year period from 1988 to 2018 (Harada et al. 2021). This suggests that while the incidence of AN among Japanese women is on the rise, BMI and ED-related psychopathology is also becoming more severe.

In Taiwan, an epidemiological time trend was reported using national health insurance claims data from 2002 to 2013 (Tseng et al. 2020). During that period, the incidence of AN did not change, although it increased slightly among the 10–14 and 30–39 age groups; however, the incidence of BN increased significantly in the years before 2009 and then decreased. The overall stable pattern of AN, increasing in younger age groups, and the increasing-then-decreasing pattern of BN are similar to those of Western countries. The incidence of AN and BN during the study period was 1.1/100,000 (95% CI 1.05–1.15) and 6.1/100,000 (95% CI 6.02–6.26), respectively. The incidence of AN was lower than that in other countries, while that of BN was within the range reported in Western countries. The low incidence of AN could be attributed to a lack of awareness and the low standard weight of Taiwanese, which makes it difficult to detect disease-related weight loss (Tseng et al. 2020). The most common age at which AN and BN were first detected was between 20 and 29 years, which was higher than that reported in Western Europe (Tseng et al. 2020).

West Asia

Due to the lack of valid data for this region, it is difficult to examine how incidence and prevalence have changed over the years (Melisse et al. 2020). In Arab countries, curvy bodies are considered to indicate fertility, and there is no traditional ideal of thinness. However, a review of studies conducted in Arab countries between 1986 and 2019 found that 13–55% of individuals were at a high risk for ED, and the prevalence of EDs was higher among females and adolescents than among males and older individuals, respectively, mirroring the trends in Western countries (Melisse et al. 2020). In addition, Alfalahi et al. (2021) identified studies from the United Arab Emirates, Israel, Iran, and Pakistan, all of which used semi-structured interviews to diagnose EDs and identify prevalence from 1990 to 2020. Point prevalence was found to be 1.59% (95% CI 0.77–11.17) for AN and 2.41% (95% CI 0.04–8.24) for BN (Kazim et al. 2017; Pasternak et al. 2012; Jahromi et al. 2013; Suhail and Zaib-u-Nisa 2002; Alfalahi et al. 2021). While the findings should be interpreted cautiously due to the different backgrounds of the study subjects, the prevalence is comparable to that in the Western countries (Alfalahi et al. 2021).

Latin America

There are few reports from Latin America. Kolar et al. (2016) performed a literature review on the prevalence of EDs in Latin America and conducted a meta-analysis of studies from Argentina, Brazil, Chile, Colombia, Mexico, and Venezuela on the

general population. The point prevalence was 0.1% (95% Cl 0.02–0.23) for AN and 1.16% (95% Cl 0.55–1.98) for BN. They noted that prevalence appeared to be lower in AN and the same or higher in BN compared to Western countries. However, the time trends for incidence and prevalence were not examined.

Africa

Data from Africa are considerably limited, and reports are available only from few specific regions. Van Hoeken et al. (2016) conducted a review of the epidemiology of EDs on the African continent based on articles published between 2014 and 2016, reporting that only four articles provided accurate diagnostic assessments of AN and BN. They were from Egypt (Nasser 1994), Ghana (Bennett et al. 2004), Tanzania (Eddy et al. 2007), and Kenya (Aillon et al. 2014). Among 1476 young women, point prevalence according to the DSM-IV criteria was 0% for AN and 0.87% for BN (95% CI 0.22–1.51) (Van Hoeken et al. 2016). Williams et al. (2020) reported changes in the number of AN and BN admissions over time (21 years) in a tertiary ED care unit in South Africa from 1993. The number of AN cases remained constant, while the number of BN cases decreased, but no significant statistical difference was evident due to the small number of cases. To the best of our knowledge, there are no other reports of incidence or prevalence based on correct diagnostic criteria or their time trends in Africa.

Changes in Clinical Picture

As mentioned earlier, young women constitute the main population of patients with EDs (Van Eeden et al. 2021). However, over time, research has highlighted the need to recognize that those who fall outside this group – primarily older women and men – can also develop EDs (Nagata et al. 2020; Samuels et al. 2019). It is necessary for health care professionals to understand and reflect, in their clinical practice, the fact that disordered eating behavior and eating-related distress can occur regardless of gender or age. Thus, in this section we will focus on middle-aged women and men with EDs.

Middle-Aged Women

EDs were formerly considered to occur rarely after the age of 30 (Javaras et al. 2015), leading to an exclusion of middle-aged women from study samples (Hoek 2006; Smink et al. 2013). However, studies have found that a considerable number of middle-aged adults also have EDs (Podfigurna-Stopa et al. 2015). A prospective population-based study of all patients aged 15 years and older in Spain from 2005 to 2009 unexpectedly observed newly diagnosed patients aged 45 and older (Larrañaga et al. 2012). In this study, the incidence of EDs among 15–24-year-olds was 4.4/100,000, while that among over 45-year-olds was as high as 1.1/100,000; moreover, most of these patients were females (Larrañaga et al. 2012), indicating that there may

be several non-negligible female patients with EDs of a wider age range than previously thought. Middle-aged patients with EDs have either young-onset prolonged or late-onset ED (Kodama et al. 2017). Prolonged cases are often clinically problematic, with repeated treatment failures and physical severity (Kotilahti et al. 2020). On the other hand, it has been argued that patients diagnosed after midlife may have prolonged adolescent-onset ED rather than late onset ED (Scholtz et al. 2010). Brown et al. (2020) conducted a prospective study in which 900 male and female college students, averaging 20 years of age, were followed up every 10 years for 30 years. By the end of the study, approximately 70% of both men and women were still being followed up. Although the prevalence of EDs decreased with age, some women were first diagnosed with an ED at the age of 50, suggesting that EDs could occur in middle age, with a point prevalence of 0.42 (Brown et al. 2020). In addition, a prevalence study of a longitudinal community-based sample found that although 15.3% of women had met the criteria for a lifetime of any ED by midlife, only few middle-aged or older women had access to health care services for ED (Micali et al. 2017). Moreover, there were a significant number of sub-threshold patients who did not fully meet the diagnostic criteria in middle age (Micali et al. 2017). However, even for EDs below a broadly defined threshold, middle-aged women have been reported to exhibit distress and disability comparable to women who fully satisfy the diagnostic criteria for EDs (Mangweth-Matzek et al. 2014a). Given all of this, we must determine the broad age range of EDs without underestimating middle-aged women.

Men

Although one of the earliest reports on EDs was the case of an adolescent male by Morton (1694), males have often been excluded from ED studies. In DSM-5 (American Psychiatric Association 2013), the amenorrhea criterion was removed. As a result, compared to DSM-IV, medical professionals can more easily diagnose male patients with AN. Recently, studies on male patients have received more attention (Raevuori et al. 2014; Murray et al. 2017).

In clinical samples, the male-to-female ratio of ED patients has been described as 1:10 (American Psychiatric Association 2013), based on several studies conducted at specialized hospitals in the 1990s (Andersen 1990). A lifetime prevalence study of AN and BN in the general population was conducted in the United States from 2001 to 2003; however, it reported a male-to-female ratio of 1:3 (AN 0.3%, 0.9%, BN 0.5%, 1.5%; Hudson et al. 2007). In addition, the 2008 Australian Epidemiological Survey ratio of adults reporting ED behaviors such as strict dieting/fasting or binge eating ranged from 1:3 to 2:3 (Mitchison et al. 2013). This underrepresentation of male patients in clinical practice may be attributed to stigma and a lack of awareness among the general public, which discourages men from seeking medical attention (Raisanen and Hunt 2014; Murray et al. 2017). In addition, males with EDs are understood to have maladaptive muscularity-oriented attitudes and behaviors, which are less likely to fit the pathology of the internalization of thinness ideals, which are

considered typical among females with AN (Murray et al. 2017). This may be reason why males may not be identified as having an ED using the existing diagnostic criteria and screening instrumentation (Murray et al. 2017; Mangweth-Matzek et al. 2016).

Early onset EDs in male children and adolescents have also been reported. An Australian study from 2002 to 2005 of children and early adolescents aged 5–13 years, who visited a specialist pediatric institution, revealed a boy-to-girl ratio of 1:3 (Madden et al. 2009). A 2005–2006 study of children and adolescents (<13 years old) from a specialized facility in the UK revealed that the male-to-female ratio was 1:4 (Nicholls et al. 2011). Mangweth-Matzek et al. (2014b) conducted an epidemiological review of EDs in middle-aged and older adults, reporting that the overall prevalence of EDs according to the DSM-5 criteria was 1–2% in middle-aged and older men, and approximately 3–4% in women. Furthermore, Brown et al. (2020) found that even among middle-aged women, the prevalence of ED diagnosis decreased with age, while it remained stable in men; thus, by age 50, there was no longer a significant difference in point prevalence between men and women. Apart from the adolescent-to-young-adult age group, which has been highlighted as the most common target for EDs – that is, children, middle-aged adults, and older adults – sex differences in prevalence may be small.

Conclusion

This chapter provided an overview of how EDs have changed, chronologically, over time.

A case discovered by Morton in 1689 is considered the first report leading to the current understanding of EDs. The concepts of AN and BN have barely changed since 1980, when they were incorporated into the operational diagnostic criteria of the DSM and the ICD.

Epidemiological studies that began in the late twentieth century in Western countries have reported an increase in AN and BN. AN in young women has continued to increase, while overall AN has remained constant or has increased since around the 1990s. In contrast, BN increased from the 1990s to the 2000s and then decreased. However, reports from non-Western countries are insufficient, making it difficult to draw a comparison with reports from Western countries. In non-Western countries, the adoption of Western culture, especially the idealization of thinness, has been reported to increase EDs, although Western culture is not the only factor that influences their development.

Furthermore, the population recognized as being affected by EDs has expanded over time to include not only young women, but also men and middle-aged women. However, the current diagnostic criteria do not adequately address all such non-typical cases of EDs.

The time-related changes in EDs indicate the need to perceive them as multifarious and multifaceted disorders. Further research is needed to understand not only

individuals with EDs across different cultures, genders, and ages, but also the differences among them.

Applications to Other Eating Disorders

In this chapter, we described how anorexia nervosa (AN) and bulimia nervosa (BN) have been viewed historically and how their conceptions have changed with time. We also explained the epidemiological time trends related to AN and BN in Western and non-Western countries. Finally, we covered details regarding shifts in the population that suffers from AN and BN worldwide and the understanding thereof. However, we have not discussed the history and epidemiological time trends for other new subtypes of EDs, such as avoidant restrictive food intake disorder (ARFID) and binge eating disorder (BED), due to the lack of research. The main diagnostic feature of ARFID is avoidance or restriction of food intake manifested by a clinically significant failure to meet nutritional requirements or insufficient energy intake through the oral intake of food. ARFID neither include the features of AN – such as the fear of gaining weight or of becoming fat – nor specific disturbances in relation to the perception and experience of one's own body weight and shape. Similarly, BED involves binge eating, but not the recurrent inappropriate compensatory behavior (e.g., purging, driven exercise) exhibited in BN.

EDs have been considered to include an aspect of culture-reactiveness. Further, individuals with AN and BN typically have a culture-reactive desire for a slim physical shape; in contrast, ARFID and BED do not seem to display such culture-reactive features. Historical and epidemiological research on ARFID and BED may allow us to confirm the extent to which culture affects these EDs, in comparison to AN and BN. This could contribute to prevention and treatment policies for EDs.

Mini-dictionary of Terms

- **Acculturation**. Acquisition or assimilation of a particular society's culture by an individual or group from another culture, or a psychological change associated with it.
- **Culture bound syndrome**. A combination of signs and symptoms that are confined to a limited cultural area by specific psychosocial characteristics.
- **Incidence**. The rate of new cases of a disease, occurring in a specific population over a particular period. It is used to determine whether a disease is becoming more common in a population over time.
- **Prevalence**. The rate of cases of a disease at a particular time, regardless of when the onset occurs, thus including both existing and new cases.
- **Westernization**. Adoption or the process of adopting Western culture by a given society, not only in areas such as diet and attitude of high concern toward body shape, but also more broadly, such as in industry, technology, science, education, politics, economics, law, religion, and philosophy.

Key Facts of Time-Related Changes in Eating Disorders

- Eating disorders (EDs) are serious mental illnesses characterized by disordered eating and related psychological distress.
- EDs such as anorexia nervosa and bulimia nervosa are more common in young women, while men and middle-aged and older women also suffer from eating behavior problems and associated distress.
- EDs were first conceptualized in Western countries, but they have also increased in non-Western regions where Western culture has been introduced.
- This chapter describes the history of EDs, epidemiological changes, and EDs worldwide, with the goal of understanding how EDs have changed over time.
- Understanding time-related changes in EDs worldwide teaches us that an ED is more than just a disease associated with the idealization of thinness.

Summary Points

- Diagnostic criteria for EDs in the DSM and the ICD have not changed significantly since the 1980s.
- There are methodological issues in assessing the epidemiological time trends of EDs.
- In Western countries, the overall incidence of AN increased until 1970–1990s and then stabilized, although its incidence among adolescent and young women has continued to increase. The incidence of BN peaked around the 1990s and has been declining since.
- More epidemiological studies on EDs conducted in non-Western countries are needed.
- A considerable number of middle-aged women and men also have eating behavior problems.

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The Connection Between Eating Disorders and Substance Use Disorders

13

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Contents

Introduction 225
Eating Disorders 226
Substance Use Disorders 227
Genetics 227
The Role of Serotonin 228
The Role of Dopamine 228
Genetics and ED-SUD 229
Neurobiology 230
Neurobiology of SUD 230
Neurobiology of ED 231
Neurobiology of ED-SUD 231
Neuroimaging Findings in SUD and ED 232
Temperament 233
Impulsivity in SUD and ED 234
Executive Function Deficits 234
Executive Function Deficits in SUD and ED 235
Emotion Regulation 235
Emotion Regulation in SUD and ED 236
Additional Shared Risk Factors for SUD and ED 236
Adverse Events, Trauma, and SUD 237
Adverse Events, Trauma, and ED 237
Adverse Events, Trauma, and ED-SUD 237
Clinical Implications 238
Conclusions 240
Mini-dictionary of Terms 241
Key Facts of Substance Use Disorders 242

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Summary Points 242
References 243

Abstract

Eating Disorders (ED) and Substance Use Disorders (SUD) commonly occur. In fact, approximately 50% of individuals with an ED report abusing alcohol or an illicit substance. Given the high rates of co-occurrence of ED and SUD, it is important to understand the connection between these disorders to guide prevention and treatment efforts. This chapter reviews shared etiological factors connecting ED and SUD. More specifically, neurobiological and candidate gene studies independently exploring SUD and ED suggest that similar genetic variants in both the dopamine and serotonin systems might influence ED-SUD comorbidity. Connections between ED and SUD are accounted for by shared characteristics related to reward sensitivity, impulsivity, executive function deficits, and emotion dysregulation. Additional shared risk factors include stress, environment, and trauma. These shared etiological factors highlight the importance of treating transdiagnostic mechanisms that contribute to both ED and SUD. Interventions that target the reward system, temperament, emotion regulation, and stressor-related symptoms are all essential to this work.

Keywords

Substance use disorders · Eating disorders · Emotion regulation · Impulsivity · Trauma · Reward sensitivity · Transdiagnostic · Neurobiology · Genetics · Executive function

Abbreviations

5-HIAA	Serotonin metabolite 5-hydroxyindoleacetic acid
5-HT	Serotonin
ACC	Anterior cingulate cortex
ACE	Adverse childhood event
ACT	Acceptance and commitment therapy
AN	Anorexia nervosa
AN-BP	Anorexia nervosa, binge/purge type
AN-R	Anorexia nervosa, restricting type
AUD	Alcohol use disorder
BED	Binge-eating disorder
BN	Bulimia nervosa
CBT	Cognitive behavioral therapy
CSF	Cerebrospinal fluid
DA	Dopamine
DBT	Dialectical behavior therapy
DSM-5	Diagnostic and Statistical Manual of Mental Disorders, 5th Edition
ED	Eating disorder
ED-SUD	Persons with comorbid ED and substance use disorder
ER	Emotion regulation

MBRP	Mindfulness-Based Relapse Prevention
OBE	Objective binge episode
OSFED	Other specified feeding or eating disorder
PTSD	Posttraumatic stress disorder
SUD	Substance use disorder
UFED	Unspecified feeding or eating disorder

Introduction

While much has been studied of the assessment, treatment, and etiology of substance use disorders (SUDs) and of eating disorders (EDs), the research is only now catching up to understanding the unique implications of co-occurring eating and substance use disorders (ED-SUDs). In fact, studies indicate that approximately 50% of individuals with EDs also misuse substances, which is five times the abuse rate seen in the general population (CASA 2003). As a result, these individuals experience lower rates of treatment response, higher relapse rates, more severe medical complications, and higher risk of early mortality (Harrop and Marlatt 2010; Lindblad et al. 2016).

Commonly abused substances found among the ED population include alcohol, cannabis, illicit drugs such as opiates and stimulants, over-the-counter medications such as laxatives and diuretics, as well as prescribed medications such as benzodiazepines. Misuse of nicotine and caffeine is also found to be highly correlated in this population due to the appetite-suppressant qualities of these substances. Women with Bulimia Nervosa (BN) and Anorexia Nervosa, Binge-Purge subtype (AN-BP) are at the highest risk of comorbid alcohol or illicit drug use (Bulik 1987).

This high-risk subset of the ED population is often limited in their access to appropriate treatment services because of the lack of assessment, intervention, and training of co-occurring disorders in such settings. Without specific knowledge or education in the area of ED-SUDs, many providers do not feel adequately equipped to manage the medical, physical, or behavioral symptoms that present within this patient population. As a result, treatment programs tend to provide either sequential treatment, whereby the most acute disorder is treated first, or concurrent treatment, whereby different providers offer specialized services apart from each other. Neither of which have proven to be effective long-term treatment approaches.

It is therefore no wonder that providers, clinicians, and carers may feel challenged in supporting ED-SUD patients in receiving the care and treatment that they need. Confounding factors such as neurobiology, temperament, and trauma play an integral role in the etiology and presentation of ED-SUDs. As such, locating comprehensive, integrated care models to address the unique needs of this population can be challenging at best.

This chapter aims to clarify the link between EDs and SUDs by outlining the unique considerations of these disorders. Given the high rates of co-occurrence of ED and SUD, it is important to understand the connection between these disorders, as well as how they present together. In this chapter, we provide an overview of the

genetic, neurobiological, personality, and temperament factors contributing to the development of ED and SUDs, and shared risk factors such as stress, environment, and trauma. Finally, we will highlight the clinical implications of treating this high-risk patient population. Our hope in exploring the connection between ED and SUD is to better guide prevention and treatment efforts for these commonly co-occurring disorders.

Eating Disorders

Eating disorders (EDs) are serious psychiatric illnesses that are associated with significant morbidity and mortality (Arcelus et al. 2011). The *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* (*DSM-5*; APA 2013) recognizes five EDs. Anorexia nervosa (AN) is characterized by a significantly low body weight given considerations such as age, sex, developmental trajectory, etc. Persons with AN exhibit a fear of gaining weight or becoming fat and/or engage in behaviors that interfere with weight gain (e.g., dietary restriction). They also report an undue influence of their body weight or shape on their self-evaluation and/or denial of the seriousness of their low body weight. AN has two subtypes: The binge/purge subtype (AN-BP) is characterized by objectively large binge-eating episodes (see Bulimia Nervosa below for further definition) and/or purging behaviors (e.g., self-induced vomiting, laxative misuse, thyroid medication manipulation, etc.). Either binge or purge behaviors must be present to diagnose AN-BP (both may occur but is not necessary to diagnose this subtype). Persons with the restricting subtype (AN-R) do not engage in binge/purge behaviors and typically exhibit significant dietary restriction. They may also engage in compensatory exercise to interfere with weight gain.

Bulimia nervosa (BN) features objective binge episodes (OBEs), which are characterized by intake of an objectively large amount of food (i.e., greater than what most people would eat in similar situations) over a discrete period (e.g., 2 h). The OBE must also feature a sense of loss of control over eating (e.g., feeling as though one cannot stop eating). BN also features inappropriate compensatory behaviors, such as self-induced vomiting or dietary restriction. Persons with BN display an overvaluation of body weight or shape on their self-evaluation. For example, someone with BN may use their body shape to determine whether they are a good or bad person. Additionally, persons with BN cannot be at a significantly low body weight. Binge-eating disorder (BED) also features OBEs; however, the OBEs occur in the absence of inappropriate compensatory behaviors. Persons with BED also display cognitive symptoms related to binge eating (e.g., eating alone because of embarrassment associated with binge eating). Additionally, persons with BED may not be at a significantly low body weight.

The other two EDs recognized in the *DSM-5* (APA 2013) are "Other specified feeding or ED" (OSFED), which is a residual diagnostic category for clinically significant ED symptoms that do not meet diagnostic criteria for AN, BN, or BED, and "Unspecified feeding or ED" (UFED), which is a diagnostic category meant to

denote clinically significant eating pathology with insufficient information to assign one of the ED. It is worth noting that OSFED and UFED are no less serious or impairing than the other EDs and that the most prevalent ED diagnostic category in epidemiological samples is OSFED (Mitchison et al. 2020).

Substance Use Disorders

Substance use disorders (SUDs) are a class of psychiatric illnesses associated with the maladaptive use of one or more substances (e.g., drugs, medications, etc.; APA 2013). There are ten classes of substances recognized in the *DSM-5* SUD classification system (alcohol, cannabis, anxiolytics/sedatives/hypnotics, caffeine, hallucinogens, stimulants, inhalants, opiates, tobacco, and "other"). Eleven SUD diagnostic criteria describe problems subsequent to substance use (e.g., interpersonal problems, medical complications) and at least two criteria must be endorsed to diagnose a SUD. The severity of the SUD is based on the number of symptoms reported concurrently (i.e., mild = 2–3 symptoms, moderate = 4–5 symptoms, severe $\geq$6 symptoms). Persons with SUDs tend to exhibit impulsivity and emotion-regulation deficits (see "Temperament" section below for further description).

As discussed in the chapter Introduction, there are several classes of substances that persons with EDs are more likely to abuse. Individuals with EDs who abuse alcohol or cannabis may do so in order to impact their eating behaviors. For example, lowered inhibitions that may accompany alcohol use may result in the person feeling as though they have "permission" to engage in binge-eating behaviors, which the person may otherwise refrain from engaging in when not under the influence. Similarly, persons with EDs may use cannabis to induce feelings of hunger, and/or to regulate negative emotions. In contrast, persons with EDs may abuse stimulants (e.g., cocaine, Adderall), caffeine, or nicotine for their appetite-suppressant effects and in order to facilitate weight loss. Other substances that can be relevant to persons with EDs include laxatives, diuretics, enemas, suppositories, thyroid hormone, insulin, anabolic steroids, and diet pills. Although many of these substances have medical usefulness (e.g., persons with Type I diabetes must take insulin), their use can be considered maladaptive if the recommended dosage is manipulated and/or they are used for purposes unintended by the manufacturer (e.g., laxative abuse for the purpose of weight loss). In summary, persons with EDs may abuse substances in order to directly impact their ED (e.g., stimulant abuse to suppress appetite), to cope with negative emotions (e.g., cannabis abuse to escape distress), or both.

Genetics

Extensive research demonstrates genetic contributions to the development of SUD and ED independently. Family studies exploring disorder risk among first-degree relatives consistently reveal that both SUD and ED aggregate within families (Strober et al. 2000; Wang et al. 2012). Twin studies further corroborate the familial

components of SUD and ED (Trace et al. 2013; Wang et al. 2012). Molecular genetic approaches also highlight the associations between specific genes that influence the emergence of SUD and ED. Below is a review of research implementing these study designs that highlight the genetic variations impacting serotonin and dopamine that might contribute to the association between SUD and ED.

The Role of Serotonin

A prominent molecular genetic approach includes candidate gene studies, which investigates the relation between a specific genetic variant and a disorder. Serotonin has been studied extensively using candidate gene studies in both SUD and ED independently. The data on SUD and the polymorphism of a serotonin transporter gene, 5-HTTLPR, are robust. Meta-analytic data reveal that the short allele of 5-HTTLPR is significantly associated with alcohol dependence (e.g., McHugh et al. 2010). Data are mixed regarding the association between 5-HTTLPR and nicotine or related phenotypes, with some studies indicating a relation with the short allele, some with the long allele, and others suggesting no relation exists (Herman and Balogh 2012). Research investigating the 1438G/A polymorphism in the HTR2A gene demonstrates the G allele is significantly associated with alcohol dependence (Nakamura et al. 1999). The A allele of the 1438G/A polymorphism in the HTR2A gene also emerges as significantly associated with tobacco smoking (Polina et al. 2009).

The majority of research exploring the serotonin system in ED has also concentrated on 5-HTTLPR. Meta-analytic data suggest that individuals with at least one copy of the short allele of this gene were more likely to have AN (e.g., Lee and Lin 2010). Evidence for the influence of this polymorphism in BN and BED is mixed, as some research supports the impact of 5-HTTLPR in patients with BN and BED and others lack data to suggest a significant association (Lee and Lin 2010). Meta-analytic data have also identified a significant association between the HTR2A promoter region polymorphism(−1438G/A, rs6311) and AN (Gorwood et al. 2003).

The Role of Dopamine

Candidate gene studies have also explored dopamine in both SUD and ED independently. Research on SUD and dopamine is extensive, given the role dopamine plays in reward and motivation. Meta-analytic work investigating the TaqIA polymorphism indicates the A1 allele is significantly associated with alcohol dependence (Tammimäki and Männistö 2010) and increased risk for nicotine dependence (e.g., Munafò et al. 2004). The A1 allele also emerges as significantly related to greater heroin consumption and an increased risk for a cannabis-related "high" at an earlier age (Conner et al. 2005). Studies exploring the Val158Met polymorphism suggest that the presence of the Val allele significantly increases the risk for smoking and

cannabis use. Notably, no relation has been identified between the Val158Met polymorphism and alcohol dependence (Tammimaki and Mannisto 2010). Further data suggest other genetic variants in the catechol-O-methyltransferase (COMT) gene and the dopamine system are associated with cocaine use or dependence (Haile and Kosten 2007).

Less research is available investigating the role of dopamine genes in ED. Population-based data highlight that the A1 allele in the TaqIA polymorphism (i.e., rs1800497) in the dopamine D2 receptor gene (DRD2/ANNK1) is associated with greater food craving and motivation for food (Epstein et al. 2007). Available research in ED specifically suggests that the A1 allele is associated with psychological characteristics of AN and BN (i.e., drive for thinness, feelings of inadequacy, and worthlessness) and sensation seeking among women with bulimia-spectrum disorders (e.g., Groleau et al. 2012). Alternatively, other data indicate that as the number of A2 alleles of the TaqIA polymorphism increases, the larger the association with AN-BP (Bergen et al. 2005). The Val allele of the Val158Met polymorphism emerges in some research as significantly associated with AN and BN (Mikołajczyk et al. 2006; Yilmaz et al. 2011); however, other data reveal that the Met allele is associated with AN or do not establish any association between ED and alleles in the COMT gene (Brandys et al. 2012).

Genetics and ED-SUD

Available research investigating ED-SUD comorbidity is limited to family and twin study designs. Data examining familial co-aggregation are rather sparse and, generally, results support independent transmission of ED and SUD. In contrast, twin studies offer data to suggest shared familial association. The first exploration of genetic similarities between alcoholism (alcohol dependence or problematic drinking) and BN indicated a small overlap (6%; Kendler et al. 1995). Further research investigated genetic overlap between BN symptom count and several SUD, estimating correlations with AUD at 0.53, any illicit drug use disorder at 0.37, and smoking 0.35 (Baker et al. 2010). More genetic correlations were observed between alcohol misuse and inappropriate compensatory behaviors, estimated at 0.61, and alcohol misuse and binge eating, estimated at 0.31 (Slane et al. 2012). An assessment of overlap between AUD and combined binge-eating and inappropriate compensatory behaviors identified a genetic correlation of 0.33 (Munn-Chernoff et al. 2013). Taken together, results from recent twin studies suggest that ED-SUD comorbidity might be more related to specific ED symptoms, rather than a specific diagnosis. Indeed, this might explain the higher frequency co-occurrence of SUD with binge-purge type ED (Munn-Chernoff and Baker 2015).

In sum, candidate gene studies independently exploring SUD and ED suggest that similar genetic variants in both the dopamine and serotonin systems might influence ED-SUD comorbidity (Munn-Chernoff and Baker 2015). Evidence from twin studies specifically examining this comorbidity suggest genetic overlap,

especially in regard to SUD and binge-purge symptomatology. Molecular genetic studies exploring cross-disorder association analyses are an important area for future research to further understand the genetics involved in ED-SUD comorbidity.

Neurobiology

Research exploring central neurotransmitter systems and brain circuitry in SUD and ED independently offer data to suggest similar patterns of dysfunction. Serotonin (5-HT) plays a major role in a number of behavior and psychological functions, such as behavioral inhibition, appetite regulation, and mood; therefore it has been extensively studied in patients with ED, and to a lesser extent with individuals with SUD. As dopamine (DA) is closely involved in the processing and response to rewarding and punishing stimuli, it also has been studied in samples of ED and SUD. More recent neuroimaging research exploring the brain reward system offers evidence to suggest that neural pathways related to DA might also be important in the connection between ED and SUD.

Neurobiology of SUD

Exploration of 5-HT in SUD at is relates to pathology is complicated, as acute consumption of substances, such as alcohol, stimulants, cocaine, and opioids, initially increases extracellular 5-HT but promptly suppresses 5-HT neurotransmission (Kirby et al. 2011). Further, 5-HT neuronal response seems to normalize with long-term exposures to substances; however, 5-HT neurotransmission appears to cease with withdrawal (Kirby et al. 2011). This observation likely contributes to dysphoric mood states and cravings, thereby triggering substance seeking and consumption to modulate negative mood (Kirby et al. 2011).

Cerebral spinal fluid (CSF) research examining serotonin metabolite 5-hydroxyindoleacetic acid (5-HIAA) levels presents mixed findings across various substances. Overall, some data indicate that individuals who abuse alcohol and ecstasy demonstrate significantly low 5-HIAA when compared to healthy controls; whereas other data have found no differences among those with alcohol dependence or cocaine abuse and controls (e.g., Agartz et al. 2003; Roy et al. 2002). Similarly, brain imaging research exploring the 5-HT transporter in substance abuse provides mixed findings, with support for increased, normal, or decreased 5-HT availability (e.g., Cosgrove 2009).The amount of literature on 5-HT in SUD is sparse and does not provide a uniform description; however, available data indicate that chronic substance use might be associated with lower CSF 5-HT metabolites, and alterations in 5-HT system activity might contribute to mood fluctuations and associated emotional difficulties.

Neurobiology of ED

For ED, CSF studies evaluating patients currently diagnosed with AN-R reveal significant reduction in 5-HIAA (e.g., Jimerson et al. 1990). Alternatively, recovered AN-R individuals exhibit increased concentrations of CSF 5-HIAA. A similar pattern exists in BN, with more severe patients currently diagnosed with BN displaying lower CSF 5-HIAA levels (Jimerson et al. 1992) and recovered BN individuals exhibiting elevated concentrations of the metabolite (Kaye and Weltzin 1991). It appears that increased 5-HT brain levels might precede the development of ED. Depletion of the dietary precursor of 5-HT, tryptophan, through restriction might impact affective states for individuals predisposed to ED that trigger and reinforce disordered eating behaviors. Specifically, acute tryptophan depletion in AN seems to reduce dysphoric mood states, reinforcing restriction, while it seems to exacerbate dysphoric mood states in BN, reinforcing binge eating.

Brain imaging research demonstrates elevated 5-HT_{1A} receptor binding across most brain regions in samples of individuals currently diagnosed with AN-R and AN-BP, as well as AN-BP after recovery. Alternatively, recovered AN-R individuals displayed normal 5-HT_{1A} receptor binding mesial temporal and subgenual cingulate regions, which has been associated with harm avoidance (Bailer et al. 2005). Individuals with symptomatic BN also exhibit increased 5-HT_{1A} receptor binding, specifically in the medial prefrontal cortex, posterior cingulate, and angular gyrus of the parietal cortex (Tiihonen et al. 2004); yet, data suggest BN individuals continue to display increased 5-HT_{1A} binding when recovered (Bailer et al. 2010). Further, both symptomatic and recovered AN individuals present with reduced 5-HT_{2A} receptor binding in the frontal, parietal, and occipital cortices (e.g., Audenaert et al. 2003). Recovered BN individuals also demonstrate reduced 5-HT_{2A} receptor binding in orbitofrontal cortex (Kaye et al. 2001), which research implicates is associated with inhibitory processes. This altered 5-HT receptor function likely impacts mood dysregulation in ED.

Neurobiology of ED-SUD

Available research suggests that both SUD and ED might share an important overlap in 5-HT that relates to inhibition, appetite, and affective challenges. Although more data in this area are needed, it appears the behavioral manifestation of low CSF 5-HT metabolites in SUD and BN display similarities, in that reduced levels are associated with dysphoric mood states that contribute to the consumption of substances and/or food.

In contrast to 5-HT, research examining DA in SUD is much more extensive, as it is involved in the rewarding effects of drugs. Brain imaging studies indicate that individuals currently addicted to substances, including cocaine, heroin, alcohol, methamphetamine, and nicotine, exhibit significant reductions in DA D2 receptor availability and DA release in the striatum, and this persists months after detoxification (e.g., Volkow et al. 2007). Consumption of substances is associated with large

and fast increases in extracellular DA in the striatum, mimicking those induced by physiological dopamine, therefore reinforcing substance use (Volkow et al. 2009). Indeed, lower DA D2 receptor availability in the ventral striatum is associated with greater alcohol craving (Heinz et al. 2004), higher consumption (Martinez et al. 2005), and larger risk for relapse (Guardia et al. 2000). Notably, low premorbid DA D2 receptor levels might increase vulnerability to developing SUD, as high levels of D2 DA receptor availability in the striatum appear protective against the reinforcement of substance use (e.g., Volkow et al. 2002).

Similar to substances, DA is also involved in the rewarding effects of weight and feeding behaviors. Research on individuals recovered from AN identified increased binding of DA D2/D3 receptors in the anterior ventral striatum (Frank et al. 2005). In contrast, patients currently with BN exhibit decreased DA D2/D3 receptor binding in the striatum, in addition to reduced DA release (Broft et al. 2012). Moreover, data suggest a significant negative association between the frequency of both binge eating and vomiting and the striatal DA response (Broft et al. 2012). Consumption of palatable food is also associated with DA release, therefore reinforcing overeating and purging. Notably, individuals recovered from BN and AN-BP demonstrate normal DA D2/D3 striatal binding, suggesting that frequent binge-eating and vomiting behavior leads to the downregulation of DA receptors in the striatum (Broft et al. 2012).

Taken together, it appears that BN and SUD might share DA D2 receptor-related vulnerabilities to the rewarding aspects of substances and highly palatable foods. Specifically, it seems that decreased DA D2 receptor binding availability and DA release in the striatum are markers of both disorders. The consumption of both food and drugs might be an attempt to alleviate the reduced reward and self-medicate a hypoactive dopaminergic system (Broft et al. 2012). On the other hand, contrasting DA D2 receptor patterns in AN might contribute to individuals with the disorder being "protected" from SUD (Kaye et al. 2013).

Neuroimaging Findings in SUD and ED

Neuroimaging studies examining the brain reward systems that are related to DA function highlight the neural circuity contribution to behavioral symptoms. Research in this area investigating SUD suggests disrupted function of the prefrontal cortex through its involvement in higher-order executive functioning and regulation of limbic brain regions. These deficits in the prefrontal cortex contribute to impaired response inhibition, related to dorsal anterior cingulate cortex hypoactivity, and increased activation in many prefrontal cortex regions (e.g., ventral striatum, anterior cingulate cortex [ACC], amygdala) in response to visual drug-related cues (e.g., Goldstein and Volkow 2011).

Functional magnetic resonance imaging studies investigating ED demonstrate altered activity within and/or between ventral limbic and dorsal cognitive circuits,

brain regions associated with inhibitory control, and reward-related behaviors. Individuals with ED demonstrate altered reward sensitivity associated with limbic circuitry, with increased behavioral inhibition related to exaggerate dorsolateral cognitive circuity in AN, and decreased inhibitory control related to impaired frontostriatal circuitry in BN (e.g., Wierenga et al. 2015). The deficits in circuity associated with self-regulatory control in individuals with BN likely contribute to binge eating, difficulty resisting urges to purge, and other impulsive behaviors. Further, individuals with AN exhibit reduced activation in the insula, lateral prefrontal cortex, and parietal lobe, and increased activation in the medial prefrontal cortex, when presented with visual food-related stimuli (e.g., Holsen et al. 2012). On the other hand, individuals with BN exhibit increased activation in the insula, ACC, and ventral striatum when exposed to visual food-related stimuli (e.g., García-García et al. 2013). The differences in circuity related to the anticipation of food rewards likely drives the contrasting drives to approach and avoid food observed between AN and BN.

The deficient activation of brain regions related to inhibitory control in BN mirrors similar patterns of activation identified in SUD (Goldstein and Volkow 2011). Further, the increased activation in response to visual food cues observed in BN parallels increased activation in these regions in SUD exposed to visual drug cues. Notably, patients with AN demonstrate contrasting patterns of neural activation in response to rewards, which likely relates to lower rates of SUD among these individuals. Overall, it appears that the same neural pathways that reinforce motivation to approach food are also activated in response to drugs of abuse.

Temperament

Individuals with temperamental traits of reward sensitivity and impulsivity may be at high risk of developing SUD and ED. As previously highlighted in the neurobiological section of this chapter, reward sensitivity appears to play a central role in the development of both EDs and SUDs.

Impulsivity is an important mechanism believed to underlie both disordered eating and substance use. Impulsivity is a multidimensional construct that incorporates components of lack of planning and rash behavior without careful deliberation or consideration of consequences (e.g., Moeller et al. 2001). As part of this multidimensional construct, researchers have focused on two emotional aspects of impulsivity that appear to contribute to both ED and SUDs. *Positive urgency*, the tendency to act rashly when experiencing a positive mood, and *negative urgency*, the tendency to act rashly when experiencing negative mood. Impulsivity, specifically the components of positive and negative urgency, may account for how individuals respond to stress and intense emotion. Therefore, someone who engages in disordered eating or substance use may impulsively turn to these behaviors when in distress or feeling intense emotions to relieve distress and alter mood in the short term.

Impulsivity in SUD and ED

To date, there is considerable research indicating that individuals with SUD typically display impulsive behaviors and are impaired at delaying gratification of rewards (Hester et al. 2010). Numerous studies show that individuals who misuse substances report higher levels of impulsivity and novelty seeking than nonclinical controls. Studies using behavioral measures show that when given a choice, substance users engage in rash and impulsive decision-making and show greater preference for small, immediate rewards over larger, delayed rewards (e.g., Petry 2002). Furthermore, longitudinal research with college students shows that positive urgency predicts engagement in illegal drug use, increased quantity of alcohol consumption, and problems associated with alcohol use (Cyders et al. 2009). Similarly, negative urgency is associated with increased alcohol consumption and negative outcomes (Cyders et al. 2009).

In EDs, impulsivity appears to contribute particularly to binge-eating behaviors. Research suggests that individuals who binge eat tend to make risky decisions and have difficulty focusing attention and delaying rewards (Manwaring et al. 2011). Similarly, individuals who binge and purge tend to be characterized more by impulsivity and score higher on measures of sensation seeking than AN-R or healthy controls (e.g., Cassin and von Ranson 2005). Furthermore, higher levels of self-reported negative urgency predicts binge-eating symptoms in BN and BED (e.g., Fischer et al. 2008). On the other hand, research indicates that individuals with AN tend to be higher in self-directedness and lower in novelty seeking than those who binge eat or do not have an ED (Cassin and von Ranson 2005). This further highlights the unique role of impulsivity to binge-eating behaviors, and may also account for the higher association of SUD to those with EDs with a binge-eating component.

Impulsivity may also explain why individuals with SUDs and EDs engage in behavior that is rewarding in the short term (e.g., substance use, binge eating), despite their negative consequences in the long term. Consistent with this theory, existing findings indicate that affective instability, impulsivity, and novelty seeking are common in patients with EDs who engage in substance abuse (Aldao et al. 2010). This heightened impulsivity underlying both ED and SUD may account for the range of impulsive behaviors often seen in the ED-SUD population, including suicidal behavior, self-injury, and shoplifting (e.g., Fichter et al. 1994). This connection may also explain poor treatment outcomes and high relapse rates for both ED and SUD (e.g., Nederkoorn et al. 2007).

Executive Function Deficits

Executive function deficits are common features of both ED and SUD that are closely linked to impulsivity. Executive functioning generally refers to a group of cognitive processes responsible for self-regulatory and goal-oriented behaviors. This includes cognitive functions such as decision-making, cognitive flexibility, and

inhibitory control. Inhibitory control refers to the ability to suppress, interrupt, or delay an overt behavior (behavioral inhibition) or cognitive process such as attention (cognitive inhibition).

Executive Function Deficits in SUD and ED

Research suggests that individuals with SUD show greater deficits in executive functions compared to healthy controls. For example, AUD has been associated with deficits related to inhibition and attention. Difficulties with executive control may serve as a risk factor for the development of SUD (Tarter et al. 2003). In support of the theory of executive function deficits in SUD, individuals who misuse alcohol and drugs tend to demonstrate poor performance on behavioral tasks reflecting impulse control, such as delay discounting and Go/No-Go tasks (e.g., Bickel et al. 2007). One confounding variable in exploring the connection between executive control and substance use is that chronic substance use may also lead to worsening executive control deficits throughout the course of the addiction (de Wit 2009).

For ED, deficits in behavioral control may play a particularly important role in the development of binge eating due to the loss of control over eating that is a key element of the experience of a binge-eating episode. In support of this theory, research highlights both cognitive and behavioral control deficits in BN (Wu et al. 2013). Meta-analyses show that patients who engage in binge eating, including AN-BP, BN, and BED have impaired control in general and particularly related to disease-specific stimuli (food/eating/weight) compared to healthy controls (Wu et al. 2013). Difficulties with behavioral control may also explain why rates of other impulsive behaviors are higher among individuals with BN, including elevated rates of substance use compared to AN (without binge-eating behaviors). In AN, on the other hand, theories posit that increased cognitive control may promote and maintain excessive control over food intake. Research support indicates that individuals with AN do not generally show difficulties with behavioral inhibition.

Limited empirical data exist examining the neuropsychological profile of ED-SUD. However, findings indicate that individuals with ED who also engage in substance abuse demonstrate greater problems with executive control compared to ED patients without substance abuse (e.g., Lozano-Madrid et al. 2020).

Emotion Regulation

Emotion regulation (ER) is an important mechanism identified in the development and maintenance of both SUD and ED (Baker et al. 2004). Emotion regulation is a multidimensional construct defined as a complex set of abilities including (a) awareness, understanding, and acceptance of emotions, (b) ability to control behavior when experiencing negative emotions, (c) ability to use situationally appropriate strategies to modulate emotions flexibly in order to meet individual goals and situational demands, and (d) willingness to experience negative emotions

(Gratz and Roemer 2004). When someone experiences emotion dysregulation, they exhibit difficulties in one or more of these dimensions of emotion regulation. Theoretically, an individual who has difficulty with emotion regulation may engage in maladaptive behaviors such as disordered eating and substance use in order to avoid or modulate emotional experiences.

Emotion Regulation in SUD and ED

Data suggest that ER difficulties are an important risk factor for the development of SUDs, and several theoretical models of SUDS point to emotion dysregulation as motivator for ongoing drug use and risk of relapse. Substances play an important role in mood regulation. They can act by increasing positive emotions as well as alleviating negative emotional states (e.g., anxiety reduction, relieving pain, reducing sadness). Thus, for individuals with ER deficits, substances serve as a compelling way to regulate emotional experience. Those with SUDS demonstrate poorer ER skills than healthy controls (e.g., Fox et al. 2008), and ER deficits and emotional suppression are associated with increased substance use (e.g., Berking et al. 2011). Furthermore, SUD patients show impairments in emotional awareness and clarity, as well as deficits in accepting and tolerating negative emotions (Fox et al. 2008).

Individuals with ED display a broad pattern of deficits in various dimensions of ER, and greater degree of ER difficulties is associated with more severe ED behaviors in both AN and BN (Lavender et al. 2015). Similar to the function of substances, ED behaviors such as binge eating, purging, and food restriction serve as an attempt to modulate mood, forming and maintaining maladaptive ER strategies. For example, a review of individuals with AN-R, AN-BP, and BN shows that across these diagnoses, individuals reported a limited repertoire of skills to regulate emotions and reported maladaptive strategies and reduced capacity for tolerating emotional distress (Lavender et al. 2015). Furthermore, there is evidence to suggest that individuals with binge-purge behaviors may experience greater ER difficulties than those with restricting-type behaviors.

In support of the connection between ER underlying both ED and SUDs, existing findings indicate that affective instability and negative urgency are common in individuals with EDs who also engage in substance abuse (e.g., Fisher et al. 2012). Research examining ER in adults presenting to ED treatment suggests that those with ED-SUD demonstrate greater ER difficulty, including engaging in goal-directed activity when distressed, higher impulsivity, and limited emotion regulation strategies when compared to individuals with ED alone (Claudat et al. 2020).

Additional Shared Risk Factors for SUD and ED

Research consistently points to the impact of exposure to severe adversity, especially in childhood, on health. Indeed, early life trauma is associated with later development of both substance-related problems and disordered eating (e.g., Leza et al.

2021). Theoretically, substances and/or food might both be employed to self-medicate and alleviate trauma-related distress among individuals struggling with emotion regulation.

Adverse Events, Trauma, and SUD

Studies exploring child maltreatment consistently reveal its association with an increased risk of SUD. A scoping review exploring the link between adverse childhood events (ACE) and SUD identified a higher prevalence of ACE in SUD than the general population. A positive association between ACE and the development and severity of SUD was also observed (Leza et al. 2021). Moreover, childhood adversity is associated with an increased risk of posttraumatic stress disorder (PTSD; Widom 1999). Research exploring samples of individuals seeking treatment for SUD indicate a significantly high prevalence of childhood adversity and PTSD, and in the majority of cases, PTSD preceded SUD (Dansky et al. 1994). The observed rates of childhood maltreatment in individuals with PTSD and SUD suggest a relation between childhood trauma and later development of these disorders.

Adverse Events, Trauma, and ED

Individuals with ED endorse a history of childhood adversity more frequently than the general population, and the experience of childhood abuse exacerbates the severity of ED symptoms (Guillaume et al. 2016). Traumatic events seem to be a significant causative risk factor for the development of binge-eating and purging behaviors, specifically, while results are mixed for restricting behaviors (Caslini et al. 2016).

An important mediator between a history of adversity and the development of ED is the presence of PTSD or related symptoms. Patients with comorbid BN and PTSD endorse larger increases in negative affect before purging, larger decreases in negative affect after purging, and larger increases in positive affect after purging when compared to patients with BN alone (Karr et al. 2013). Data suggest that childhood adversity is associated with later development of ED, and comorbid PTSD might worsen prognosis.

Adverse Events, Trauma, and ED-SUD

Data suggest that individuals with comorbid SUD and ED often endorse a history of adverse experiences. For example, significantly higher rates of prior sexual abuse emerge in patients with comorbid SUD and ED (Deep et al. 1999). In individuals with ED, childhood adversity is associated with a higher number of impulsive behaviors, including alcohol and illicit drug abuse (Corstorphine et al. 2007).

Further, patients with BN who endorse a history of sexual or physical abuse demonstrate higher rates of PTSD, substance dependence, and more severe ED pathology (Matsunaga et al. 1999). Data from the National Comorbidity Survey Replication observed the highest rates of PTSD and subthreshold PTSD in patients with comorbid SUD and ED (specifically, individuals with bulimic symptomatology) when compared to either disorder alone or no disorders (Brewerton and Mitchell 2012).

Notably, early traumatic experiences might prompt neurobiological changes that contribute to the pathophysiology of SUD and ED. Early stressors contribute to the dysregulation of the hypothalamic-pituitary-adrenal axis, which is involved in the pathophysiology of SUD and ED (e.g., Liu et al. 1997). Early stressors can also result in increased noradrenergic activity, which might increase the neurobiological vulnerability to the development of PTSD, SUD, and ED (e.g., Sanchez et al. 2001). Further, research reveals the impact of early trauma on the neurotransmitters involved in reward-related behaviors, indicating that childhood adversity might predispose individuals to develop SUD and ED by directly influencing the reinforcing effects of food and substances (e.g., Meaney et al. 2002).

As not all individuals with a history of trauma develop significant psychopathology, other factors, like genetics, might also impact the development of SUD and ED following traumatic experiences. Research demonstrates that individuals with the 5-HTTLPR S allele and a history of childhood trauma are more likely to experience comorbid BN-spectrum disorders and SUD (Richardson et al. 2008). Overall, data suggest that adverse experiences contribute to the later development of both SUD and ED, and individuals with the comorbid diagnoses experience more severe pathology.

Clinical Implications

To date, there are no evidence-based treatments or formal protocols for treating individuals that present with both ED and SUD. This results in very few treatment centers comprehensively targeting ED and SUD at the same time. As such, individuals experience fragmented treatment, with individuals presenting to SUD treatment targeting their substance use primarily, and individuals presenting to ED treatment primarily targeting their disordered eating. The challenge of this is that neither of the symptoms is being addressed in an integrated fashion, thus leading to vacillation of symptomatology over time. This phenomenon is often described by clinicians as the "Whack-a-mole" effect. Whereas, addressing one set of symptoms only results in an increase in the other addictive or problematic behaviours. Overall, this contributes to higher rates of relapse in this population (e.g., Dennis and Helfman 2010).

Given these limitations, experts have called for more integrated treatments to concurrently treat ED and SUD, implemented by a treatment team that is trained in evidence-based treatments for both disorders. As part of integrated treatment for ED-SUD, it is recommended providers utilize motivational interventions to engage individuals in treatment. As cognitive-behavioral therapy (CBT) has a strong

Table 1 DSM-5 substance use disorder diagnostic criteria (APA 2013)

DSM-5 substance use disorder diagnostic criteria		
A.	A problematic pattern of substance use leads to clinically significant impairment of distress, as manifested by at least two of the following, occurring within a 12-month period:	
	1.	The substance is often taken in larger amounts or over a longer period than was intended.
	2.	There is a persistent desire or unsuccessful efforts to cut down or control the substance use.
	3.	A great deal of time is spent in activities necessary to obtain the substance, use the substance, or recover from the effects of the substance.
	4.	Craving, or a strong urge to use the substance.
	5.	Recurrent substance use resulting in a failure to fulfill major role obligations at work, school, or home.
	6.	Continued substance use despite having persistent or recurrent social or interpersonal problems cause or exacerbated by the effects of the substance.
	7.	Important social, occupational, or recreational activities are given up or reduced because of substance use.
	8.	Recurrent substance use in situations in which it is physically hazardous.
	9.	Substance use is continued despite knowledge of having a persistent or recurrent physical or psychological problem that is likely to have been caused or exacerbated by the substance.
	10.	Tolerance, as defined by either of the following: (a) A need for markedly increased amount of the substance to achieve intoxication or desire effect. (b) A markedly diminished effect with continued use of the same amount of the substance.
	11.	Withdrawal, as manifested by either of the following: (a) The characteristic withdrawal syndrome for the substance. (b) The substance (or a closely related substance) is taken to relieve or avoid withdrawal symptoms.

evidence base for both ED and SUD, CBT interventions are typically utilized, such as self-monitoring, functional analysis, contingency management strategies, and education on coping skills . Another recommended component of treatment is assessing the adaptive function of eating disorder behaviours and substance use, to understand the underlying motivation behind engaging in these behaviors (e.g., reduce anxiety, avoid unpleasant emotions, control appetite, etc). Psychotropic medications are making their mark on the recovery landscape, as they are effective in stabilizing mood and comorbid psychiatric conditions that are often present in ED-SUD (Table 1). Additionally, medical monitoring is essential both for ED and SUD (Dennis et al. 2014).

More recently, treatment providers have begun adapting and implementing treatments that are more transdiagnostic in their approach, rather than focusing primarily on ED or SUD symptoms and behaviors. These transdiagnostic approaches typically incorporate components of mindfulness practice, with the aim of assisting individuals in reducing their dysfunctional behavior by increasing their ability to accept and allow their internal experiences and emotions. One potentially promising transdiagnostic

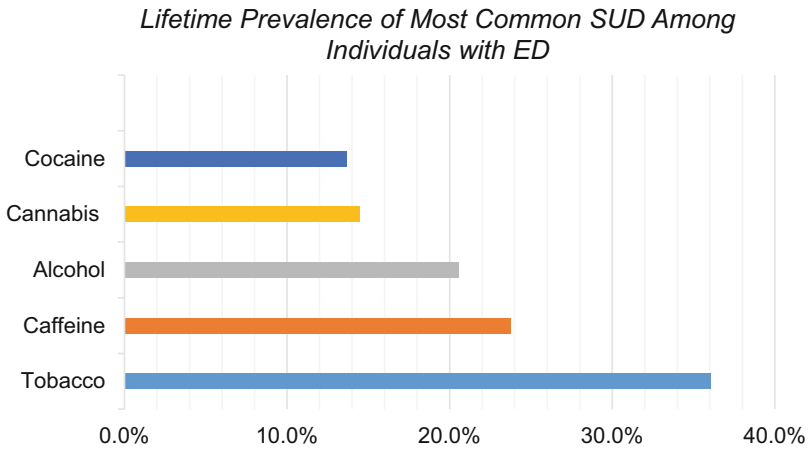


Fig. 1 Lifetime prevalence of most common SUD among individuals with ED (Bahji et al. 2019)

treatment approach is Dialectical Behavior Therapy (DBT; Linehan 1993). In DBT, individuals are encouraged to accept their emotional experiences, while also learning adaptive strategies to cope with their emotions. DBT is a well-established treatment for individuals with severe and multiple psychological disorders, and provides a framework to target multiple problem areas in an integrated manner. Although only one study has investigated the application of DBT for co-occurring EDs and substance use, findings from this study are promising, and indicate that integrated DBT for ED-SUD was associated with decreased substance use severity and frequency, as well as decreased emotional eating (Courbasson et al. 2012). More research is needed in this area; however, data are hopeful (Figs. 1 and 2).

Conclusions

The overlap of shared etiology for ED and SUD highlighted in this chapter has significant implications for the treatment of ED and SUD. We understand many features of EDs and many of SUD; however, linking the two has received considerably less research and clinical attention. As such, many professionals continue to struggle in the treatment of ED-SUD. Understanding the overlap of ED and SUD may help guide prevention and treatment efforts by highlighting the importance of treating the underlying, transdiagnostic mechanisms that contribute to both disorders. Interventions that target the reward system, temperament, and emotion regulation are all essential to this work. Furthermore, given the significant link between adverse events, trauma, and stressors to both eating disorders and substance use disorders, it is important that treatment approaches address trauma and other stressor-related symptoms to aid in the recovery process. Continued work on elucidating the connection between ED-SUD is essential in improving our prevention and intervention efforts for this high-risk population.

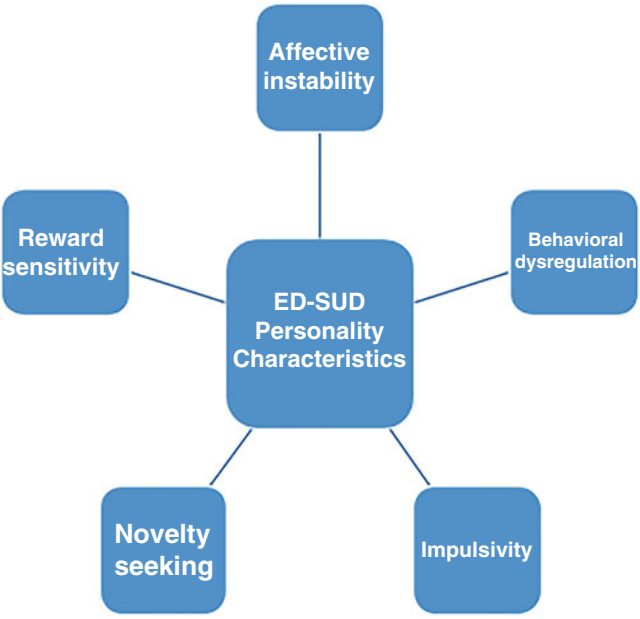


Fig. 2 Personality characteristics common among comorbid SUD and ED

Mini-dictionary of Terms

- **Adverse childhood event**. A traumatic experience occurring during childhood (e.g., child maltreatment)
- **Emotion regulation**. A complex set of abilities including (a) awareness, understanding, and acceptance of emotions, (b) ability to control behavior when experiencing negative emotions, (c) ability to use situationally appropriate strategies to modulate emotions flexibly in order to meet individual goals and situational demands, and (d) willingness to experience negative emotions
- **Executive functioning**. A group of cognitive processes responsible for self-regulatory and goal-oriented behaviors
- **Dopamine**. A neurotransmitter closely involved in the processing and response to rewarding and punishing stimuli
- **Negative urgency**. The tendency to act rashly when experiencing a negative mood
- **Positive urgency**. The tendency to act rashly when experiencing a positive mood
- **Serotonin**. A neurotransmitter involved in the regulation of mood, sleep, learning, memory, and physiological processes such as vomiting
- **Temperament**. Biologically based differences in individual behavior
- **Trauma**. An emotional response to a serious event that oftentimes involves threat of harm or death

- **"Whack-a-mole" effect**. Behavior change targeting one symptom/set of symptoms that leads to vacillation of symptomatology over time (e.g., addressing ED behaviors which leads to increased SUD behaviors)

Key Facts of Substance Use Disorders

Substance use disorders (SUDs), as defined in the DSM-5 (APA 2013), are a class of psychiatric illnesses associated with the maladaptive use of one or more substances (e.g., drugs, medications, etc.)

Symptoms of SUD fall into four categories including: impaired control, risky use, social problems, and physical dependence.

There are ten classes of substances recognized in the *DSM-5*: alcohol, cannabis, anxiolytics/sedatives/hypnotics, caffeine, hallucinogens, stimulants, inhalants, opiates, tobacco, and "other."

The severity of the SUD is based on the number of symptoms reported concurrently (i.e., mild = 2–3 symptoms, moderate = 4–5 symptoms, severe $\geq$6 symptoms).

The coexistence of both a mental health and a substance use disorder is referred to as co-occurring disorders.

Summary Points

- Substance use disorders and eating disorders commonly co-occur, and they share many etiological factors
- Candidate gene studies independently exploring SUD and ED suggest that similar genetic variants in both the dopamine and serotonin systems might influence ED-SUD comorbidity, as they impact reward and mood
- Affective instability, impulsivity, and novelty seeking are common in patients with EDs who engage in substance abuse
- Individuals with SUD, as well as individuals who engage in binge eating (including AN-BP, BN, and BED) show greater deficits in executive functions compared to healthy controls
- Early life trauma and adverse events are associated with later development of both substance-related problems and disordered eating
- There are currently no evidence-based treatments or formal protocols for treating individuals that present with both ED and SUD
- Research highlights the importance of targeting the underlying, transdiagnostic mechanisms that contribute to both ED and SUD, including the reward system, impulsivity, emotion regulation, and trauma and stressor-related symptoms

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Fluid Restriction in Eating Disorders

14

Elizabeth Hamlin

Contents

Introduction 250
Recognizing Intentional Fluid Restriction 251
How Much Fluid Does a Patient Need? 252
Who Restricts Fluids? 253
Why Do Patients Restrict Fluids? 254
Clinical Cases 255
Case 1: Adele 255
Case 2: Bianca 256
Case 3: Celia 257
Treatment of Fluid Restriction 259
Fluid Replacement 259
Behavioral Interventions 261
Psychological Interventions 262
Applicability to Other Eating Disorders 265
Mini-dictionary of Terms 266
Key Facts About Fluid Restriction 266
Summary Points About Fluid Restriction 267
References 267

Abstract

Although eating disorders are traditionally conceived of as disorders of food intake (American Psychiatric Association, Diagnostic and statistical manual of mental disorders, 5th edn. American Psychiatric Publishing, Arlington, 2013), patients with eating disorders can also experience dysregulated fluid intake, including intentional restriction of fluids. This clinical phenomenon has been observed and documented over the past two decades but remains under-recognized and poses a danger to patients and a source of frustration for treatment

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providers, who often struggle to successfully address this challenging behavior. This chapter examines the phenomenon of intentional fluid restriction even though little has been written about it, assessing its prevalence, its associated psychiatric diagnoses, and how to recognize fluid restriction in clinical work with patients with eating disorders. Motives underlying intentional fluid restriction are explored through detailed case presentations, and interventions focusing on behavioral and psychological change are discussed.

Keywords

Eating disorder · Restriction · Fluids · Borderline personality · Trauma · Anorexia nervosa · Bulimia nervosa · Atypical anorexia · Dehydration · Self-injury

Abbreviations

Kcal	kilocalories
mL	milliliters

Introduction

Eating disorders characterized by intentional restriction (anorexia nervosa, bulimia nervosa, and atypical anorexia) are traditionally conceived of as disorders of food intake (American Psychiatric Association 2013), in which patients become preoccupied with weight and shape and so alter their patterns of eating and/or digesting food. However, patients can also experience dysregulation in fluid intake (Hart et al. 2005), which can be manifested either by drinking fluids to excess (Marino et al. 2009) or intentionally restricting fluid intake (Lowinger et al. 1999; Hart et al. 2005, 2011; Abraham et al. 2006; Hamlin 2020). This chapter represents an attempt to examine the phenomenon of intentional fluid restriction in patients with eating disorders, with a focus on how this behavior manifests and alters the course of treatment in the psychiatric inpatient setting, with adult and young adult patients, since this is the setting in which all previous studies of this behavior have been conducted. As will be discussed in this chapter, it is nonetheless likely that at least some form of intentional restriction of fluids also occurs in outpatient and day treatment settings. Intentional fluid restriction does occur in the child and adolescent population as well, though this chapter focuses on older teenagers and adults.

In the inpatient setting, fluid restriction is often observed in patients who exhibit many other eating disorder behaviors, including restricting food, purging, and abuse of laxatives and diuretics (Hamlin 2020). Despite occurring in the context of a number of different eating disorder behaviors, intentional fluid restriction often comes to be "the star of the show" and the focus of clinical attention due to the significant attendant medical decompensation (orthostatic tachycardia, hypotension, dizziness, and falls) that occurs as a result of this behavior. At times, intentional fluid restriction becomes the chief issue prolonging the inpatient hospital stay (Hamlin 2020; Lowinger et al. 1999).

Although intentional fluid restriction may come to be the focus of inpatient treatment, patients rarely identify restriction of fluids as a reason for seeking treatment and may not even disclose this behavior as a concern during the admission process or in initial meetings with the treatment team. The treatment team (broadly including nursing staff, patient support staff, therapists, dietitians, and psychiatrists) may notice that a patient is not drinking very much but assume that this is unintentional. Unfortunately, even once recognized as intentional, fluid restriction remains difficult to treat, and patients continue to believe that this behavior is necessary for physical and emotional regulation (Hamlin 2020, 2022).

This chapter provides an overview of intentional fluid restriction in patients with eating disorders, beginning with how to recognize this behavior when it occurs. The chapter discusses how patients who restrict fluids understand this behavior and attempt to provide insights into what factors make this behavior so difficult to treat. In order to illuminate the complexities underlying intentional restriction of fluids in patients with eating disorders, this chapter provides three detailed case presentations. Treatment of intentional fluid restriction from biological, behavioral, and psychological standpoints will be discussed. Ultimately, this chapter argues that, by narrowly focusing on eating disorders as related to weight and shape, the DSM overlooks many of the psychological factors that lead to fluid restriction and to the perpetuation of eating disorder symptoms more generally, contributing to the lack of recognition of this phenomenon in the eating disorder treatment community and associated scientific literature.

Recognizing Intentional Fluid Restriction

Intentional fluid restriction is easiest to recognize in highly structured treatment approaches, such as inpatient or residential units, simply because these are the settings in which staff are present throughout the day and night who are trained to monitor how much a patient is drinking. Some treatment centers may even mandate that a patient drink a certain quantity of fluids with each meal or snack – in this case, it is evident when a patient is not doing so despite prompting. Additionally, most eating disorder treatment centers attempt to ensure that patients are not dumping out fluids (or food) in sinks or in the trash. Patient self-report of past or current behaviors surrounding fluid intake is often attempted during admissions screenings or in initial assessments on the unit, but the data may be unreliable (Zerbe 2008; Zerbe and Bradley 2018). A patient who is attempting to come into a hospital setting may work to convince the treatment team that she (female pronouns are used in this chapter for convenience, though men also experience eating disorders) is "sick enough"; conversely, a patient who is attempting to avoid a particular treatment intervention may tell her family and her treatment provider that she is hydrating appropriately.

In the outpatient setting, where it is more difficult to monitor fluid intake, much more is of necessity based on the patient's self-report, though many outpatient treatment programs incorporate some supervised meal situations. However, other factors may signal that a patient is dehydrated, and, if a patient is unable to correct

this dehydration with prompting and encouragement, this may be a sign of intentional fluid restriction.

One of the most common signs of dehydration, for example, is a change in pulse. Because of the decrease in circulating blood volume, the heart must beat faster in order to circulate the appropriate volume of blood around the body. Thus, dehydration may be signaled by an increase in pulse. Over 100 beats per minute meets the definition of tachycardia; in patients who restrict fluids, 120 or 130 beats per minute is not uncommon. An increase in pulse when the patient changes position (orthostatic tachycardia) is also often observed. With this change in pulse, there may also be a drop in blood pressure, a sign that the heart is not able to compensate completely for the decrease in circulating volume (Jequier 2010). A drop in blood pressure is not uncommon in patients who primarily restrict food. However, in these patients, who are restricting food but not fluids, a bradycardia is often observed, rather than the tachycardia of acute dehydration (Mehler and Andersen 2010). Laboratory findings consistent with dehydration include increased BUN and increased creatinine, especially with BUN:creatinine ratio of 20:1 or greater (Mehler and Andersen 2010).

In addition to the objective signs of dehydration, symptoms of dehydration that patients may report include dizziness, especially with position change, at times accompanied by vision change (vision briefly going black or spotty). Patients may report loss of consciousness or falls, especially with position changes. In patients who intentionally restrict fluids, the experience of dizziness is often a conflicted one (Hamlin 2020) – on the one hand, they do not like the sensation, on the other, they also rely on it to feel like they are suffering enough or are deserving of treatment. When patients stop feeling dizzy or show improvement in vital signs, they may report concerns about being "sick enough."

How Much Fluid Does a Patient Need?

In treatment settings in which a dietitian is available, it is optimal to rely on the dietitian's expertise in calculation of how much fluid is needed for a given patient. However, not all treatment settings may have ready access to dietitians. There are several different ways to calculate fluid needs. Two will be discussed here – the Holliday-Segar formula (Holliday and Segar 1957), which relies primarily on a patient's weight, and a simpler calculation that takes age and weight into account when determining fluid requirements.

The Holliday-Segar formula is based on a patient's weight in kilograms. It calculates energy expenditure in kcal based on weight and calculates fluid needs using a 1 kcal expenditure = 1 mL fluid equation. Although this formula was originally developed for children, it is also used to calculate an adult's fluid needs. It is important to bear in mind, however, that the calculation yielded by both this equation and the subsequent one reflect total fluid needs, not free fluid needs. Therefore, some of the patient's fluid needs will be met by food, which contain some amount of water, or milkshake-textured nutritional supplements.

An alternative calculation of fluid requirements estimates a need for fluids in adults over 30 of 30–35 mL/kg, in young adults of 35–40 mL/kg, and in adolescents of 40–60 mL/kg (Sucher and Nelms 2016). This calculation can be adjusted up or down depending on the patient's underlying medical conditions or medication use.

These two methods of calculating fluid requirements do yield different results. For a 45 kg adult patient, the Holliday-Segar formula yields daily fluid need of 2000 mL. The alternative calculation based on weight yields a fluid need between 1350 and 1575 mL. If the patient were a younger adult, this range would change to 1575 mL and 1800 mL.

Ultimately, although calculation of fluid requirements can be roughly estimated using either of these formulas, a dietitian's input is essential to consider the multitude of factors that make each patient unique, including underlying medical conditions, co-occurring use of medications, energy expenditure, and degree of dehydration.

Who Restricts Fluids?

It is difficult to estimate the prevalence of patients with eating disorders who restrict fluids, and, in fact, none of the existing literature addresses this issue. In part, this relates to the discussion above – unless the patient is in an inpatient setting where her fluid intake is closely monitored, it is difficult to determine when a patient is restricting fluids. Much is based on self-report (Hart et al. 2005), which can be exaggerated or minimized for various reasons (Zerbe 2008; Zerbe and Bradley 2018). Additionally, even when a patient in the inpatient or residential setting is observed to be restricting fluids, it is not always evident whether this behavior is intentional or an unintended consequence of restriction of food (Logue 2018; Engell 1988). To determine whether fluid restriction is intentional or unintentional, it is generally necessary to discuss this with the patient and to seek her perspective on her behaviors.

Even assessing basic demographic characteristics of which patients tend to intentionally restrict fluids is difficult, with different studies showing vastly different results. Patients either tend to be adolescents (Lowinger et al. 1999; Hart et al. 2005) or they are often well into adulthood (Hamlin 2020). Patients tend to have low weight (Lowinger et al. 1999; Hart et al. 2005), or their weight tends to be above their ideal body weight (Hamlin 2020). Intake of fluid occurs before improvement with food intake (Lowinger 1999) or occurs long after improvement with food and often becomes the primary factor prolonging inpatient hospitalization (Hamlin 2020). Hamlin (2020) examines co-occurring psychiatric diagnoses in patients who intentionally restrict fluids and finds that depressive disorders, anxiety disorders (especially generalized anxiety disorder), borderline personality disorder, and/or post-traumatic stress disorder occur in the vast majority of patients. Other studies do not discuss diagnostic comorbidities (Lowinger et al. 1999; Hart et al. 2005), and an attempted search for personality traits linked with fluid restriction did not discover any personality traits that correlated with different patterns of fluid intake (Abraham et al. 2006). The only demographic characteristic on which all published studies

agree is that patients who restrict fluids, similar to patients with anorexia nervosa and bulimia generally, are primarily female.

It is unclear why studies differ so greatly in terms of demographic findings. Notably, Hamlin's examination of fluid restriction occurs about 10 years after the other studies cited. In the intervening decade, it may be the case that hospitalized patients have simply become sicker and more complicated to manage; anecdotal data certainly supports this observation. Additionally, Hamlin's (2020, 2022) data comes from an inpatient eating disorder unit in the USA, whereas other groups cited work out of the UK (Abraham et al. 2006) and Australia (Lowinger et al. 1999).

Another possible explanation of differences may relate to the technological changes that have occurred even in the intervening 7 years since Hart's 2011 paper, and certainly in the 19 years since Lowinger et al. (1999) first commented on the phenomenon of fluid restriction. Over this decade, the Internet has become an increasingly common way for patients to learn both not only about recovery from eating disorders but also about perpetuation of these disorders in Internet fora devoted to "pro-ana" behaviors (Barth 2016; Wooldridge 2014). It is possible that various "pro-ana" sites also identify fluid restriction as a desirable behavior, and this may help to account for the increasing visibility of this phenomenon.

Why Do Patients Restrict Fluids?

Patients report varying reasons for why they restrict fluids. Often, they cite reasons similar to those offered for restriction of food – namely, "wanting to be in control" and "wanting to feel empty" (Hart 2011). Patients also cite concerns about fear of fullness and about "water weight" (Hamlin 2020, 2022). However, just as with restriction of food, patients often offer multiple reasons for their behaviors – after all, "wanting to be in control" or "to feel empty" can be accomplished through any number of different (maladaptive) behaviors, and it is the job of the treatment provider to determine what other reasons coexist with the automatic response of "water weight."

Hamlin (2020) summarizes some of the other reasons patients offer for restricting fluids. Some patients tentatively report a belief that their body simply does not require fluids or requires much less fluids. This belief at times approaches delusion. Patients speak longingly of a desire to exist without a body. They hate and fear the feeling of being bound to a fleshy, vulnerable, needy body, and they try to deny it through all possible means.

Other patients offer associations between intake of fluids and specific past traumas. Some of these traumas involve the ingestion of fluids – near-drownings or forced ingestions of alcohol – and others involve genital traumas, and patients' subsequent difficulty being aware of their genital region when they need to urinate.

Finally, though this list is not exclusive, some patients admit to the inpatient unit without any difficulty with fluid intake but develop intentional fluid restriction during their hospital admission, often when other patients are also displaying this behavior. Patients may formulate their new symptom of fluid restriction as a way to

convey their deep conflict about relinquishing eating disorder symptoms; they may also acknowledge that it serves as a communicative behavior, intended to elicit a specific response from the patient's treatment team or someone else who is important in the patient's life.

Ultimately, like most eating disorder behaviors and psychiatric symptoms more generally, intentional restriction of fluid often has multiple meanings. The best way to find out the meaning of the behavior for a specific patient is to ask her. While the patient may initially simply respond that she is concerned about weight or control, a more detailed inquiry into the behavior (Sullivan 1976) that remains curious and respectful will usually elicit other fantasies, fears, and beliefs. Patients readily give voice to their hatred of their bodies and subsequent desire to deprive and destroy them.

Clinical Cases

Identities of all patients have been disguised. In some cases, the description of a patient represents a composite of several similar patients.

Case 1: Adele

Adele was a married woman in her early fifties with a long history of an eating disorder that had endured despite multiple attempts at inpatient treatment. Adele restricted food and fluids, purged, and used laxatives. With a BMI of 36, Adele's eating disorder fell under the criteria of Other Specified Feeding or Eating Disorders, specifically the subheading of Atypical Anorexia (American Psychiatric Association 2013). Adele presented with multiple physical complications related to her eating disorder behaviors, including feeling chronically dizzy, struggling to think clearly, and falling frequently. Due to her orthostatic hypotension and tachycardia, dizziness, and refusal to drink fluids, a nasogastric tube was placed at time of admission.

Developmentally, Adele reported a history of severe and prolonged trauma, including ongoing sexual abuse by both her father and an uncle that had started in childhood and continued until she left home at age 14, following a pregnancy resulting in a miscarriage. Adele's mother had been aware of the abuse but had not interfered, viewing the abuse as the cost of maintaining her own marriage. While still a teenager, Adele married a man with significant mental health issues of his own. Around this time, Adele's eating disorder began; its subsequent severity resulted in repeated hospitalizations. In the 30 years prior to her admission, the longest Adele had stayed out of a structured hospital or day hospital setting was about 6 months.

Prior to Adele's admission, her husband had lost his job, forcing them to move back into the family home with Adele's mother. Adele's eating disorder symptoms had increased in intensity following this move, but Adele denied strong feelings about this, acknowledging only that she felt "annoyed." Notably, this was characteristic of Adele's emotional responses throughout the course of treatment. All affect

was split off into intense loathing of her body. Outside of this, she experienced few emotions in the rest of her life, even when thinking or talking about her trauma, which she did dispassionately.

After 2 weeks of inpatient treatment, Adele was able to resume eating food but continued to restrict fluids. A significant accomplishment for her was to be able to swallow medications with a few sips of water; her normal routine was to swallow them dry. Adele was ambivalent about the possibility of drinking more fluids. On the one hand, she liked not feeling as weak and dizzy as she had prior to admission, and she recognized that this related to being hydrated through the fluids in the nasogastric tube. On the other hand, however, she hated her body, which she felt had betrayed her so deeply, so intensely that perhaps she did deserve to feel dizzy and to fall, if it meant that her body suffered. Adele described a feeling of being at war. She did not want to die, yet she wanted to destroy her body completely.

In addition to this, Adele also described a more specific rationale for her intentional restriction of fluids: She did not wish to urinate. As a result of her childhood trauma, Adele tried strenuously to ignore her genitals. Any sensation in her genital area resulted in dissociation, often followed by superficial self-injury to ground herself. Since urination was viewed with fear and disgust, hydration equaled retraumatization, perpetuating Adele's desire to deny or destroy her body.

Ultimately, despite an extended course of treatment on the inpatient unit, Adele's need to punish her body prevailed at least partially: She was able to accept fluid delivered via nasogastric tube and the urination that resulted, but she was unable to hydrate orally. Adele used her body as a receptacle for her intense emotional pain, and she feared that any change would result in the unbearable emotional pain that she so assiduously split off. Adele discharged from inpatient treatment to her mother's home eating an oral meal plan but with nasogastric tube in place and a plan for continuous hydration at nights.

Case 2: Bianca

Bianca was slightly younger than Adele, a married woman in her early 40 s with a long history of difficulties with eating dating back to adolescence. She presented to treatment because her family physician had become concerned by Bianca's recurrent episodes of syncope and hypotension, which resulted from her severe restriction of food and fluids. In addition to these behaviors, Bianca used diet pills to control her appetite and give her energy. Despite these symptoms, which had resulted in her near-total inability to function in her daily life, she remained only slightly under ideal body weight. Diagnostically, she met criteria for Anorexia Nervosa, Restricting Type (American Psychiatric Association 2013). Like Adele, the severity of Bianca's restriction of food and fluids necessitated placement of a nasogastric tube shortly after admission.

Bianca had been raised in a family in which a woman's appearance mattered. She had been an attractive child. Her mother and grandmother were proud of her good looks and hoped that these would result in a marriage out of the family's

working-class background. They cautioned her, however, about a familial tendency to become overweight, and, from puberty onward, they encouraged her to carefully monitor her diet and exercise.

Her family's wishes paid off, and in her early 20s Bianca married a business executive. She had children and did not work outside the home. During her children's early years, Bianca was relatively content – she took care of the home and the children and scrupulously maintained her weight and appearance according to her husband's preferences. However, as her children aged, Bianca became less and less content with this arrangement, feeling neglected by her husband's frequent travels for business and leisure. The stressors precipitating Bianca's move to severe restricting appeared to be her son's increasing independence as well as a golf trip planned by her husband that coincided with their wedding anniversary.

Once on the unit, Bianca struggled to increase oral intake of food and fluids, citing both concern about weight and appearance as well as a fear that, if she were to resume eating and drinking, her life would revert to the way it had been previously, which Bianca increasingly felt to be unacceptable. Her pattern on the unit was to make some progress with eating and drinking, then to experience a conflict with her husband, who expressed frustration with her prolonged hospital stay, and then to regress with oral intake, at times needing to be sent out to the medical hospital for intravenous fluids due to her dizziness, hypotension, and falls.

Bianca's eating disorder behaviors did not arise solely in response to her conflicts with her husband and anxiety about her son's independence – concerns about weight and shape clearly dated back to her family of origin, with their preoccupation about Bianca's weight and need to impress a husband. Bianca, in her feelings of anger and abandonment, chose consciously to use what had always been prized – her thin body – as a weapon, attempting through her restriction of fluids to communicate her anger and to simultaneously punish her husband and to keep him close. Although she was able to make some consistent improvement with eating, she struggled to make progress with drinking fluids, since she believed that, if she improved, she would return home to an unchanged and intolerable situation, a belief confirmed by family sessions with Bianca and her husband. Ultimately, Bianca identified a social event occurring in her community that she was motivated to attend. This led to improvement in fluid intake – although she protested that this was occurring only because she was "forced" to do so – followed by discharge home.

Case 3: Celia

Celia (see Hamlin 2020 for a full discussion of this case), in her early 20s, was much younger than Adele or Bianca. She engaged in extreme restriction of food and fluids, limiting herself to under 500 calories a day, and drinking about a cup of fluids. She also abused laxatives, diuretics, and diet pills, and frequented "pro-ana" websites (Wooldridge 2014). Celia was very focused on her body image and hated her body shape and weight, which, despite her reported behaviors, had remained within normal range. Like Adele, she thus met diagnostic criteria for Other Specified

Feeding or Eating Disorder, specifically the subheading of Atypical Anorexia (American Psychiatric Association 2013). She was determined to lose weight and identified a goal weight that was so dramatically low as to be likely incompatible with life. She reported, without particular distress, that because of her eating disorder behaviors, she had been falling and "blacking out," and she was no longer able to work.

Celia was the younger of two children, raised primarily by her father after a messy divorce when she was five. (Celia's favored older brother, by contrast, was raised by their mother.) Celia's father struggled with chronic physical pain, depression, and substance addiction, and he and Celia moved in with her paternal grandparents when she was ten, who also struggled with chronic pain, sequelae of their many years of factory work. Celia's father and grandparents clearly cared for her but struggled to meet her needs as they battled their own illnesses. Celia attempted to live with her mother and brother briefly during her teenage years, but she was encouraged to return to her father – Celia's own depression and chronic pain were perceived to be too difficult to handle by her mother and stepfather. Shortly after returning to her father and grandparents, Celia's depressive symptoms increased significantly, resulting in frequent hospitalizations during her late adolescence.

On the inpatient eating disorder unit, Celia continued to refuse food and fluids, resulting in unstable vital signs and intense dizziness. Her physical concerns did not appear to cause her any emotional distress, and she often asked to know her blood pressure, wanting this value as low as possible. Nonetheless, she readily agreed to placement of nasogastric tube for supplemental nutrition and hydration. With this intervention, within 3 weeks of admission, Celia resumed normal eating behaviors, but she continued to refuse to drink fluids, insisting that she could not tolerate the feeling of fluid in her body and that she dreaded "water weight." Notably, however, she continued to receive fluids from the nasogastric tube without issue – it was only the thought of drinking independently that led to the concerns about "water weight."

Because of Celia's minimal progress with oral hydration and her long history of psychiatric hospitalizations, the treatment team began to wonder whether she had become dependent on the hospital setting and decided to try a different tack. Instead of having fluids run continuously and at a low rate through the nasogastric tube, which, staff worried, might prevent Celia from feeling any impetus to drink independently, the pump attached to the nasogastric tube would be stopped. Throughout the day, Celia would be encouraged to drink orally, and, if she did not, then a nurse would rapidly bolus the volume of fluids she was supposed to have consumed through the tube.

This intervention backfired spectacularly. Although intended to encourage Celia to be more independent in drinking fluids, its result was that Celia became even more reliant on staff. Celia valued being sought out by staff and encouraged to drink. She valued the brief physical contact that came with being bolused with fluids. Unlike her early life, in which her brother had been favored and in which she herself had been relegated to the background, here, it was Celia who was being selected for special attention and cared for. Unfortunately, there was no incentive here to move toward independence with fluids, and the treatment team decided to resume the

standard intervention of running supplemental fluids through the nasogastric tube at a constant low rate.

However, the experiment of bolusing fluids did demonstrate how much Celia longed for others to take care of her physically and emotionally, something that Celia was increasingly able to acknowledge verbally as treatment progressed. Slowly, Celia was able to discuss her feelings of having been abandoned by her mother, and of her desperate longing for her mother to care for her. Like Bianca, Celia used fluid restriction to communicate deep feelings that she struggled to articulate. Unlike Bianca, however, Celia's fluid restriction was not done consciously, and the target of her communication (her mother) was no longer available to receive Celia's message. As Celia became increasingly able to discuss her feelings of abandonment and despair, she was gradually able to make progress with fluid intake, and ultimately, she left the hospital to return to her father and grandparents.

Treatment of Fluid Restriction

Fluid Replacement

Patients who restrict fluids do require replacement of fluids. Especially when fluid restriction is accompanied by other maladaptive coping behaviors, or arising in context of borderline personality disorder, treatment providers may struggle with feeling angry or frustrated, and may even conclude, "She'll drink when she's thirsty." Unfortunately, this is not the case. As patients restrict food and fluids, their appetites and thirst ultimately decrease (Engell 1988; Logue 2018), and as in the cases discussed above, patients' motivations to restrict fluids are often stronger than any biological imperative to drink. Thus, patients may require supplemental fluids.

In medical hospitals, supplemental fluids are often provided intravenously (IV). The benefit of this approach is that fluids are delivered directly into the circulatory system, which can serve to stabilize blood pressure and pulse. When a patient is admitted into a medical hospital, she often receives IV fluids continuously, and, depending on her degree of dehydration and underlying physical condition, this approach may at least initially be required. A downside of this intervention, however, is that it places the patient in a relatively passive position, often lying in a hospital bed for days or weeks. An associated downside is that this intervention is generally possible only in a medical, rather than a psychiatric or outpatient, facility: Psychiatric facilities are generally not medically able to support IV treatments, and there may be concerns about suicide risk or infection in allowing a patient to ambulate freely around a psychiatric unit with an IV running. Similarly, continuous IV fluids are not usually possible in the outpatient setting.

Alternately, when a patient is in an inpatient psychiatric setting or outpatient, she might be sent to an emergency department (ER) or outpatient medical setting that can offer IV fluids. In this setting, one or two liters of IV fluids are administered over a period of a few hours. Following this administration, the patient is then able to

return to her previous environment. Of course, with this intervention, if the patient continues to restrict fluids, her body will again become dehydrated over a period of some days, requiring repeated administrations of IV fluids.

In inpatient psychiatric settings, the nasogastric (NG) tube is often used to administer supplemental fluids in addition to supplemental nutrition. (Tubes like NJ tubes, which extend into the jejunum rather than the stomach, are sometimes used; these require imaging when placed and so are more often used in environments that have access to radiology.) NG tubes can be programmed to administer fluids at a low rate over a several-hour period, or even continuously. Alternately, NG tubes can be used to bolus a larger quantity of fluids periodically throughout the day, often contingent upon the amount of fluid the patient is able to consume orally.

Whether fluids are administered via NG tube at a continuous low rate or as boluses often depends on the preferences of the patient and the treatment provider, as well as institutional regulations, which may mandate one option over the other. Each option does have benefits and drawbacks. Some patients and treatment providers advocate for the bolus method, arguing that, if the patient receives all her fluid needs via NG tube, she is disincentivized to drink orally, especially when she has a concern about "too much" fluids causing "water weight." Since the amount of fluid bolused often relates to how much the patient has drunk orally, she is then able to see her progress as she improves her own intake in requiring less fluid to be bolused. However, as is demonstrated in the case of Celia, some patients view the opportunities for closeness and staff attention inherent in bolusing fluids as a disincentive to drink orally. While NG tubes running continuously do also require staff attention for maintenance, the patient is not put in a position where she is being directly "fed" or nourished by staff, which many patients find appealing. (Some of the more unusual treatment approaches in real life and depicted on screen appear to be based on patients' underlying fantasies of dependency. These include the film "To the Bone" (2017) as well as the treatments provided by Peggy Claude-Pierre in the 1990s (Osgood 2018).)

In the outpatient setting, NG tubes are often impractical, though there have been cases in which outpatients have been able to successfully utilize these interventions, as in the case of Adele. It is often difficult logistically to set up this intervention, as it requires minimum a physician willing to order the supplies and some access to home health. For patients who are chronically unable to take fluids orally and have poor IV access, sometimes a port is placed. This is an exception rather than the rule, and it will not be discussed fully in this chapter.

Ultimately, in the outpatient setting, patients and providers must rely primarily on oral fluids. Some creativity is needed here in working with the patient to identify a fluid that feels tolerable. Many patients will report preference for caffeinated fluids, especially coffee or diet soda. These fluids are often used to provide energy, to induce a diuretic effect, or to alter metabolism and promote weight loss. When the patient is prompted to select a noncaffeinated fluid to drink, she will often state that she "does not like water" (Hamlin, unpublished data) or that she is frightened of calories in fluids. (One of the injunctions that comes from diet culture and often forms an early rule in the development of an eating disorder is "Don't drink your

calories.") Low-calorie lemonade or flavoring packets may be more tolerable to patients than water, although even the low number of calories per packet may feel excessive. Especially in patients who struggle with electrolyte abnormalities as may occur from purging or laxative use, drinks containing electrolytes, such as Gatorade or its lower-calorie alternatives, may feel tolerable to patients.

Behavioral Interventions

Once a suitable fluid replacement has been selected, the question remains of how a treatment provider can help a patient to be able to drink enough of it. There are a few behavioral interventions that are often attempted and that can be helpful.

One intervention that is often utilized in the outpatient setting is a variant of a food/fluid diary. The patient and treatment provider together set a daily goal for fluid intake, and the patient is encouraged to write down everything she drinks over the course of the day (Hart et al. 2005 use this approach in the inpatient setting also). The patient can record this on paper or electronically. There are several phone applications also designed for this purpose, including ones in which the information is sent daily to the outpatient treatment provider, often a dietitian, who can review in real time. If the patient feels it is helpful, a reward system can be instituted if the patient meets her fluid goals, which should be discussed in advance by the patient, her family (if applicable), and her treatment provider.

If this intervention is being used, it is important that the structure of treatment allows for frequent meetings between the treatment provider and patient, including the possibility of electronic meetings. (It is likely not feasible, for example, to have the patient attempt this approach for a month without checking in.) Additionally, it is important to engage in collaborative, rather than prescriptive, goal-setting, even if the initial goal that the patient identifies still does not meet her oral fluid needs. This is another reason why frequent visits become necessary, so that progress can be reviewed, and goals can be adjusted.

In the inpatient setting, a variant of this intervention is often attempted. The patient and treatment provider discuss the patient's fluid needs and collaboratively set a goal for fluid intake at each meal or snack. (Eating disorder programs in the USA are generally set up to provide three meals and three snacks daily.) At each meal or snack, the specified amount of fluid is present on the patient's tray, and she receives support and encouragement to drink that amount.

The next step after this is to help the patient internalize the ability to know when she needs to drink. This can be accomplished by having staff label a water bottle with various marks, indicating how far down the bottle the patient should drink by certain times of day. (There are water bottles available commercially for this purpose that come premarked.) The patient is encouraged to carry the water bottle with her throughout the day and to refer to it to remind herself what she should be doing.

These interventions, however, do not address directly the patient's anxiety about drinking or reluctance to do so. Rather, they capitalize on any existing motivation the patient may have as well as whatever therapeutic rapport exists in terms of setting

and working toward goals. An additional intervention that can be used in fluid restriction as well as in other settings that begins to blend the behavioral with the psychological is exposure and response prevention therapy (ERP) (Gallagher et al. 2018).

In ERP, the patient and treatment provider work together to develop a ranked list or hierarchy of situations that cause intense anxiety for the patient. These situations can include things the patient may do or even things that she may see or imagine. For patients who restrict fluids, some of these feared situations may include drinking a glass of water, imagining drinking a glass of water, or even seeing a picture of a glass of water. The hierarchy is organized from situations causing relatively little anxiety to those that would cause panic, and, systematically, the patient and treatment provider work together to progress through this hierarchy, using techniques of habituation to accustom the patient to a situation that would induce a relatively low level of anxiety before moving to those that would cause more intense anxiety. The intent of this technique is to help the patient to habituate progressively to lower levels of anxiety, thus enabling the patient to progress to more and more difficult exposures. When ERP is used, it needs to be applied frequently (ideally daily) and consistently. Additionally, because the patient is going to be intentionally entering into situations that provoke intense anxiety, she does need to have some ability to tolerate distress – treatment using this approach can be derailed if it is met by an intensification of self-harm or suicidal behaviors. Thus, it may be necessary to simultaneously do work with the patient on distress-tolerance and grounding techniques.

Because ERP is most effective when it is initially targeted toward a level of anxiety that a patient is able to manage, there is sometimes frustration for the treatment provider in that it may seem that little progress is being made. Again, patience and consistency are key here. While the patient is working on habituating to exposures to small amounts of fluid, she may continue to require supplemental fluids as discussed above.

Psychological Interventions

Although, in some cases, the behavioral interventions discussed above are sufficient to help the patient to improve her fluid intake, in other cases, these interventions fail to gain ground. These patients are likely the ones discussed initially by Lowinger et al. (1999) as the set of patients "where fluid restriction was a major behavioral problem" (p. 392). The cases of Adele, Bianca, and Celia discussed above also describe patients for whom behavioral approaches, including ERP, are insufficient to help the patient be able to drink on her own. In these patients, it is essential to consider the patients' understanding of their behaviors, what purpose it serves, and what the feared consequence is if fluid restriction is given up. These cases are discussed below to demonstrate how additional psychological interventions may be used in patients who restrict fluids. While potential interventions are discussed from a perspective that is generally psychoanalytic in orientation, reflecting the

author's training and background, the practitioner of CBT, DBT, schema therapy, or any number of therapies will likely be able to identify applicable interventions along these lines.

As discussed above, initially patients often link their fluid restriction to concerns about weight and caloric intake (Lowinger et al. 1999; Hart et al. 2011; Hamlin 2020). However, in many cases, a respectful detailed inquiry can result in additional explanations for their symptoms. Often, this additional material opens a way forward for psychological interventions to gain ground. As anyone who has worked with patients with eating disorders knows, attempting to argue with patients about calories, weight, and the need for hydration is doomed to failure (Hamlin 2022), since eating disorders are almost always about more than just weight (Bruch 1978).

Each of the cases discussed above demonstrates different determinants governing fluid restriction. The case of Adele demonstrates the intensely conflicted relationship that a survivor of sexual trauma may have with her body. Adele, like many traumatized patients with eating disorders (Zerbe 2008), experiences her body as a weak, untrustworthy *thing*, somehow separate from her and something that has fundamentally failed her. Her fluid restriction allows her to avoid experiencing body sensations linked with trauma while simultaneously expressing her contempt in a form of retaliation – since Adele's body has let her down so many times, she too will ignore its needs. Psychological interventions for Adele, although ultimately unsuccessful in the inpatient setting, would need to help Adele to identify the anger that is so noticeably absent when she discusses her traumatic past. Adele has created a vertical split (Goldberg 1975) such that she struggles to experience emotion other than a feeling of anger at her body (and even this feeling is often difficult for her to access, since her behaviors have become so automatic).

Initial interventions may focus on helping Adele to identify emotions as they arise during the course of the day. DBT work can be very helpful in this area, using emotion-identification wheels and frequent check-ins with the patient to help her monitor changes in affect as they occur. This can help the patient to feel more attuned to her own experience and ultimately to pay attention to and to be curious about her own emotional experiences, something that Adele clearly struggles with.

Ultimately, as Adele gained knowledge of her day-to-day emotions, she would be increasingly able to access anger. Initially, this anger would again arise in an everyday context, with the patient able genuinely to experience anger related to interpersonal frustrations, for example, something much less threatening than experiencing anger related to past traumas. Over time, she would be able to begin to acknowledge and bear her trauma-related anger, reclaiming this affect from the war waged on her body. Of course, during this entire course of treatment, Adele would still need extensive hands-on support with nutrition and hydration.

In contrast to Adele, Bianca was very aware of the anger that motivated her, yet her body remained the battleground on which she fought for the recognition from her husband that she craved. Like Adele, Bianca felt betrayed by her body, but for different reasons. Bianca's body had been formulated by her family and culture (referring here not to a specific ethnic or geographical culture, but rather to the unspoken set of rules governing the family and particular society in which Bianca

was raised) as a tool for getting what she wanted (Orbach 1986). An implicit bargain had been made – if she kept her body a certain way, she would be rewarded with love, admiration, and financial success. As she aged, it seemed that this bargain was no longer being upheld, and Bianca was furious. She turned to the tool she knew to rectify this situation and, by ruthlessly attacking her body, hoped desperately to convince her husband to return to the unstated terms of their agreement.

Psychological interventions for Bianca would need to introduce her to the idea that verbal processing of emotion was acceptable, an idea not supported by the reality in which she lived. The flip side to this encouragement to process emotion, however, was the need for Bianca to be aware that verbally expressing a wish or a need did not mean that this need would be fulfilled. Again, this is a dilemma that many therapeutic modalities address. Many patients with eating disorders value their disordered behaviors because they derive a sense of control from them, a control that is absent when attempting to interact verbally with another person with their own feelings and thoughts. Motivational interviewing techniques (Paris and Martino 2018) could be helpful for Bianca in persuading her to try a new way of relating; DBT interpersonal effectiveness skills (Linehan 1993) might help her communicate her anger in a way her husband and family would be more likely to hear. Ultimately, Bianca would need to relinquish her tried-and-true method of communicating with her body for the more uncertain, messier, but potentially more rewarding method of direct verbal communication. As with Adele, initial frustrations inherent in this new approach would likely lead to repeated assaults on her body, and she would likely need significant support with nutrition and hydration as she attempted to negotiate a new way of being.

Adele and Bianca's restriction of fluids were strongly related to anger, Adele's anger directed almost entirely at her body, and Bianca's directed outward but expressed using her body in order to communicate. Celia's restriction of fluids is again different. For Celia, some unacknowledged anger was present in her fluid restriction, anger at her mother who had so easily walked away. But much of what Celia worked to acknowledge in treatment was grief. Her restriction of fluids had been an attempt to communicate how much she needed someone to care for her, how ill-equipped she felt to care for herself, and the person whom she had wanted to receive that communication had been her mother, and specifically the mother who had rejected child-Celia.

As Celia was able to discuss her feelings of rejection and anger, she also could acknowledge both verbally and emotionally that the loss she had experienced was irreversible. There would be no chance to relive her childhood with the mother she had needed. If she were to go on in the world, it would always be as someone who had not gotten what she had needed. This deep grief that arises with acceptance of an unalterable loss is an important component of many different modalities of psychotherapy – mourning as described by Freud (1917), Klein's depressive position (1935), both of which are aspects of psychoanalytic theory, and radical acceptance as described in DBT (Linehan 1993). It is a version too of the serenity prayer commonly used in 12-step programs, "accepting the things that can't be changed."

The grief and feeling of helplessness that arises in this process is difficult for clinicians to bear as well; unfortunately, some clinicians are unable to tolerate it. This often results in attempts to repair or reparent the patient trying to fulfill her unmet needs in the past by gratifying those needs in the present. This is what the intervention of bolusing fluids represented for Celia. These interventions, although well-intended, are doomed to failure. No amount of gratification of wishes in the present can correct for what has been lost in the past. Psychotherapeutic work with Celia worked to help her mourn and to try to move forward in the world despite her losses.

Applicability to Other Eating Disorders

"An eating disorder needs to be considered a disorder of fluid intake, as much as a disorder of food intake" argues Hart et al. in 2011. Nonetheless, in the decade since that statement was made, intentional fluid restriction continues to be under-recognized in work with patients' eating disorders. What has led to the broader reluctance to acknowledge that disordered drinking behaviors, and specifically restriction of fluids, often play large parts in disordered eating?

One argument relates to the way the Diagnostical and Statistical Manuals (American Psychiatric Association 2013) conceives eating disorders. The DSM takes patients' concerns about weight, shape, and body size at face value and formulates eating disorders as fundamentally being about weight and shape. (Two of the three diagnostic criteria for anorexia nervosa are related to weight and body image; a criterion for bulimia nervosa also indicates that a patient's "self-evaluation [must be] unduly influenced by body shape and weight" (American Psychiatric Association 2013)). In fact, the concerns about weight and shape are the only psychological, rather than physical or behavioral criteria, offered by the DSM in its diagnostic formulation. Underlying issues that often contribute to eating disorders, including but not limited to control, concerns about maturity, displaced anger, and attempts to cope with trauma, which are widely recognized (Bruch 1978; Zerbe 2008, among others) by clinicians working with patients with eating disorders, are ignored.

Because eating disorders have been defined diagnostically by being primarily about weight and shape, behaviors that do not directly relate to weight and shape are easy to overlook. Clinicians new to the field of eating disorders are often surprised to find patients who restrict fluids, since water, at any rate, has no calories and does not cause weight gain. If the point of the illness is to lose weight, they wonder, then what is the reason for restricting a calorie-free substance? (Indeed, the phenomenon of hydroloading, alluded to in the beginning of this chapter, in which patients intentionally drink excessive amounts of water in order to feel full and suppress appetite, is also a behavior that sometimes occurs in eating disorders.) The DSM's narrow focus on weight as a motivation for eating disorders creates a blind spot when it comes to intentional fluid restriction. Unfortunately, this narrow focus also obscures underlying issues present in other forms of eating-disordered behavior.

This chapter introduces the phenomenon of intentional restriction of fluids in eating disorders, and, in doing so, attempts to demonstrate the heterogeneity of

eating disorders. Unlike the classic view of the eating disorder patient as an emaciated high-functioning adolescent (Bruch 1978), this chapter shows eating disorder behaviors occurring at patients across a range of body weights and shapes. Unlike some descriptions of patients with eating disorders as sullen, hostile, and unable to tell their own stories (Boris 1984), this chapter demonstrates patients' fundamental desire to communicate their experiences of themselves and their bodies. Intentional fluid restriction is a behavior that is often frustrating for the clinician and challenging to treat. It is often a sign of deep unverbalized emotion, especially of anger and grief, but, like all eating disorder behaviors, it serves as both a symbol and concrete action, since it is constantly being acted out upon the body, resulting in real physical consequences. As this chapter has shown, fluid restriction is a behavior that must be addressed on all levels. On the physical level, the patient requires hydration to maintain hemodynamic stability. Behaviorally, the patient needs to be able to make change in how she approaches drinking fluids so that she can function outside of the hospital setting and move toward a healthier and more fulfilling life. Yet it is also imperative to work toward a psychological understanding of fluid restriction as a behavior that can help to illuminate some of the underlying emotions perpetuating the eating disorder as a whole. Psychological understanding and the subsequent interventions it facilitates help to connect the eating disorder patient's preoccupations with her body with her deep emotional distress, linking up her split-off emotions. Although this process of change is discussed in this chapter only in relation to fluid restriction, understanding the patient's underlying emotions is important in the successful treatment of all eating disorder behaviors.

Mini-dictionary of Terms

- Affect – emotion, feeling
- DSM – the Diagnostic and Statistical Manual of Mental Disorders, 5th edition. A manual that provides diagnostic criteria for all recognized mental disorders
- Fluid restriction – intentionally not drinking fluids, or trying to limit the amount of fluids one drinks
- Hydroloading – intentionally drinking excessive amounts of fluids, usually water, to fill the stomach and suppress feelings of hunger. Sometimes patients will hydroload when they know that they are going to be weighed by a treatment provider in order to manipulate the number on the scale
- Water weight – belief often held by patients who intentionally restrict fluids that ingestion of fluids leads to weight gain

Key Facts About Fluid Restriction

Patients with eating disorders sometimes restrict fluids as well as food. This is often overlooked because fluids do not have calories and do not fit into a model of eating disorder that is only about weight. Patients do need to be hydrated even when they do

not feel able to drink – forms of hydration include intravenous fluids, fluids delivered through nasogastric tubes, and oral fluids. Patients may have many different reasons for intentional fluid restriction related to other issues, including trauma or interpersonal stressors. It is essential to work with the patient to understand these issues in order to help the patient change the behavior.

Summary Points About Fluid Restriction

- It is often under-recognized because it is often not looked for.
- Patients have many different reasons for restricting fluids. The best way to know why a patient is restricting fluids is to ask.
- Patients who restrict fluids often engage in many other kinds of eating disorder behaviors. Nonetheless, some remain at or above ideal body weight. This does not mean that their eating disorder is any less severe.
- Patients require simultaneously to be hydrated, to work behaviorally on improving their own hydration, and to work psychologically on associated issues.

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Features of Medical Consultations Before the Onset of Eating Disorders

15

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Contents

Introduction 270
Risk Factors and Prodromes as Predictors for Future Emergence of EDs 271
Features of Medical Consultations Before the Onset of EDs 272
Other Important Features of EDs 274
Prevention of EDs, Intervention Programs, and Impact 276
Applications to Other EDs 279
Mini-Dictionary of Terms 280
Key Facts of Features of Medical Consultations Before the Onset of EDs 280
Summary Points 280
References 281

Abstract

Despite the growing amount of evidence about the consequences of long-term eating disorders (EDs) as well as the importance of an early recognition and intervention in the prognosis, there is still a lack of awareness in the detection of

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prodromal or nonspecific symptoms before the onset of the disease. The duration of untreated illness has a great impact on the development of an ED; therefore, emerging programs to promote the prevention and an early detection should be considered. In this sense, primary care has an important role since they are generally the first stage of assessment and detection of these patients. For this reason, continued medical training is appropriate to take nonspecific or prodromal symptoms into account and promote early referrals to specific units.

Keywords

Eating disorders · Anorexia nervosa · Bulimia nervosa · Binge eating disorders · Prodromes · Risk factors · Nonspecific symptoms · Primary care · Early detection and intervention · Prevention

Introduction

Eating disorders (EDs) are serious mental disorders with a relatively high prevalence specially around young women and are associated with significant psychiatric and medical consequences. Mortality is increased in all EDs with anorexia nervosa (AN) having the highest mortality rate of any psychiatric illness (Arcelus et al. 2011). While the overall incidence rate remained stable over the past decades, there has been an increase in the high-risk group of 15–19-year-old girls. It is unclear whether this reflects earlier detection or an earlier age at onset (Smink et al. 2012). Nevertheless, within the recent past, it is relevant to take into account that the impact of the COVID-19 pandemic on ED has created a global context likely to increase risk factors and symptoms (Rodgers et al. 2020). Apart from that, regarding early intervention of ED, arguments are compelling, given the lasting impact of symptoms on brain, body, and behavior (Schmidt et al. 2016). As a matter of fact, not only in ED but, for example, in psychosis, intervening during early stage, when symptoms are likely to be more malleable, is seen as critical in promoting favorable long-term outcomes (Penttilä et al. 2014).

Further, a growing body of evidence suggests that the onset of the disease in adolescence could play an important role as a key factor when prefrontal brain areas, important in self-regulation, are developing (Keverne 2004). Therefore, since neuroprogression or neurobiological changes may alter the trajectory of illness, highlighting the importance of illness duration is particularly pertinent (Treasure et al. 2015).

The research to date has tended to focus on the etiology and treatment of ED rather than the duration of untreated ED (DUED) itself. However, it has long been known that in AN illness duration is a key predictor of outcome (Steinhausen 2002). Furthermore, although the etiology of ED still remains unknown, evidence suggests an interaction between genes and environment contributing to the risk (Culbert et al. 2015). It is well known that there are certain factors that may increase the risk of having an ED, and therefore it is very important for the mental health professionals

and general physicians to consider them to start an early treatment. Likewise, it is particularly relevant to encourage early referral from primary care in view of the fact that here the risk factors, symptoms, or even prodromes are assessed in a first stage (Brown et al. 2018).

Risk Factors and Prodromes as Predictors for Future Emergence of EDs

We use the term "prodrome" particularly in clinical practice to determine an early symptom or cluster of symptoms that appear prior to the development or onset of the full disorder. Therefore, prodromes and risk factors are essentially different from the ED-related symptoms which are a specific feature of the ED (Table 1). While prodromes are the previous step of the disease, risk factors show a vulnerability to developing the disorder and may remain out of view or latent for a long period of time, or what is more, the patients may never progress to clinically significant eating pathology. Nonetheless, both prodromes and risk factors precede the onset of the syndrome (Stice et al. 2010).

What we know about risk factors is largely based on cross-sectional and retrospective studies. Consequently, several factors such as parental factors and family

Table 1 Summary of key constructs

Term	Definition	Measurement
Prodrome	Symptom or symptoms that can indicate the future onset of a disorder that are also a feature of the disorder. For example, the elevated body dissatisfaction or self-reported dieting that initiates the onset of an ED would be considered prodromes	Diagnostic interview, such as the eating disorder diagnostic interview
Risk factor	Factors that increase the probability of developing the disorder	Depends on the risk factor (e.g., dieting and can be measured by self-report; thin-ideal internalization can be measured by self-report or a diagnostic interview)
Subthreshold eating disorder/ partial syndrome ED	Descriptive label for a cluster of symptoms that meets some of the criteria for an ED, but not enough symptoms are present for full diagnosis	Diagnostic interview
Eating disorder symptoms	Symptoms that are defining features of an eating disorder	Diagnostic interview or self-report
Eating pathology/ disordered eating	Abnormal eating behavior	Diagnostic interview or self-report (i.e., binge eating or dietary restriction)

and peer environment have been identified (Pike et al. 2008). Moreover, the known period of risk spans from the early prenatal period to adulthood.

To date, the most consistent risk factors are the following: perceived pressure to be thin, pursuit of the thin ideal, weight concerns and body dissatisfaction, self-reported dieting, negative affect, and substance use (Stice et al. 2010). However, as before mentioned, risk factors affect 30–70% of adolescent girls, whereas eating pathology affects fewer than 10% of adolescent girls (Barker and Bornstein 2010) and therefore does not always represent potential prodromes of an ED.

In order to highlight the importance of risk factors in terms of heritability, family studies have determined a well-established linkage between ED and genetics, which could play an important role in the development of the disorder (Hubertus Himmerich, Jessica Bentley 2019). Indeed, the first-degree relatives of individuals with AN have an approximately tenfold greater lifetime risk of falling ill with an ED than relatives of unaffected individuals (Lilenfeld et al. 1985). Further, research studies investigating genetic risk factors (e.g., genome-wide association studies, twin studies, or family studies) have recently identified specific loci for AN suggesting a polygenic nature with several genetic variants of small effect being involved particularly in AN (Wang et al. 2011; Duncan et al. 2017). However, genetic studies in other ED are relatively scarce.

On the other hand, less is known about prodromes in ED and specially how to identify them as they may present differently depending on diagnosis or culture. Several studies investigating prodromes have come to the conclusion that both weight concerns and dietary restraint may be prodromes indicating an onset of threshold or subthreshold pathology. Thus, a prodromal stage has been defined indicating features of a full disorder, a phase that is very well known across other psychiatric disorders such as psychosis (Barajas et al. 2017), where its delineation has demonstrated significant clinical and economic impact (Savill et al. 2019).

It is estimated that patients receive their first treatment after an average of two and a half years up to 6 years (Austin et al. 2020). In consequence, since, as mentioned above, the DUED is very important for the prognosis of the disease, a reasonable approach to tackle this issue would be to better understand ED prodromes and the features of medical consultations before the onset of the disorder and, thus, provide early intervention strategies.

Features of Medical Consultations Before the Onset of EDs

Medical consultations before the onset of the disorder specially in primary care are crucial for the development of effective prevention or early intervention due to the fact that are mostly the entry point to specialist care for ED patients. Only few studies have studied the features of medical consultations prior to the onset. Gomez del Barrio and colleges have recently retrospectively analyzed data from the year prior to the diagnosis observing that patients attended more consultations (primary care,

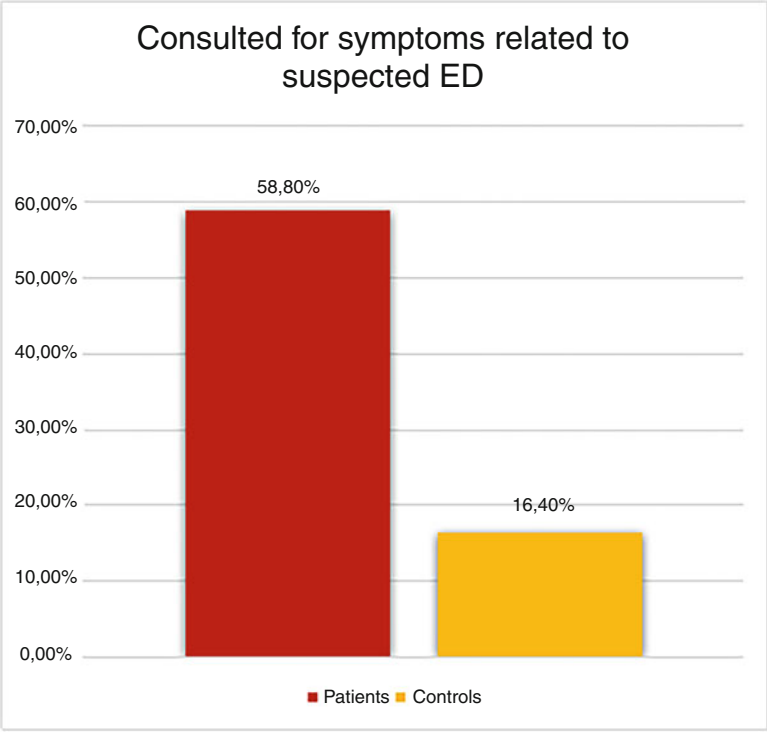


Fig. 1 Prodromal symptoms in medical consultations in primary care

specialized care, and emergency department) than controls. It is interesting that more than half of them were likely to be related with prodromes (Fig. 1) although the mean duration of untreated illness (DUI) was about 7 months, which means that they were not correctly identified. These results may indicate that not enough attention to prodromes is paid in primary care from where patients are mainly referred and there is strong rationale for early intervention in ED as it is not well established yet (Gómez Del Barrio et al. 2021).

This study draws our attention to the nonspecific ED symptoms that could play an important role in the diagnostic approach to these disorders in early stages or even before the onset. To some extent, they found several nonspecific symptoms that are likely to be prodromes hiding an incipient ED such as gynecological symptoms (e.g., amenorrhea or menstrual irregularities) and digestive symptoms such as abdominal pain, epigastralgia, constipation, or even lumbar pain. Besides, analytical changes such as anemia or electrolyte changes (hyponatremia from excess water intake; hypocalcemia from vomiting) should also be considered by clinicians as part of an initial stage of the disease. Malnutrition symptoms are also a relevant point in these disorders, and, therefore, medical consultations must also contemplate its consequences such as dizziness, syncope or fainting, and paleness in patients.

Other Important Features of EDs

Regarding the basic facts of ED according to the Academy for Eating Disorders, clinicians should know that they frequently affect teenagers and young people but also children and adults of all genders, ethnic backgrounds, cultures, and body weights, and, therefore, nonjudgmental management is critical. It is important to remember that they are not lifestyle choices but serious mental disorders that imply self-destructive behaviors that the patient cannot control.

In addition to the common symptoms that show these patients, they sometimes may present with other signs and/or nonspecific symptoms as a consequence of dieting, food and water restriction, nutritional deficiency, and binge eating and purging behaviors. For this reason, the Academy for Eating Disorders has recently reported a document to promote recognition and prevention describing critical points for a better understanding and clinical approach to these disorders. Table 2 illustrates the different signs and symptoms can occur in patients with an ED; however, it should be noticed that sometimes they are not so obvious (AED report 2021).

Taking the above into account, since patients may not easily recognize the seriousness of their illness and/or may not readily disclose their symptoms to healthcare providers, a comprehensive assessment by clinicians should be performed. Laboratory or basic diagnostic tests recommended for all patients with a suspected ED are shown in Table 3. However, referrals for evaluation and treatment by ED specialists are still far from being appropriate to make a great impact on the prognosis of the disease. Indeed, it is thought that young patients with a short DUI could be more worried about their symptoms (Gómez Del Barrio et al. 2021) and thus consult more often about prodromal or nonspecific symptoms, thereby representing a crucial opportunity for the recognition and referral for specialty intervention (McClelland et al. 2018).

Considering the importance of a short illness duration and a rapid early intervention and the necessity of a higher knowledge about ED among clinicians specially in primary care, practical support or continued training is required.

To solve this problem, an early intervention program named first episode rapid early intervention for eating disorders (FREED) was recently developed in England reducing waiting times of assessment and thus the DUED. It is based on easy access, encouraging early referral from primary care to deliver a rapid, person-centered, and effective service (Brown et al. 2018).

On the other hand, a recent systematic review performed by McClelland and colleagues identified a broad range of ED-specific symptoms (e.g., early eating difficulties, dietary restriction, fasting, body dissatisfaction, and weight/shape concerns) and other psychiatric disorder-related symptoms (e.g., depression and anxiety) prior to ED onset. Additionally, they discover that it may be possible to predict, to some extent, an ED phenotype following the symptom trajectories, for example, conflicts, struggles, and undereating in relation to AN and overeating in relation to bulimia nervosa (BN) (McClelland et al. 2020).

In addition, although binge eating disorders (BED) may not be as well known as AN or BN, they are the most prevalent of all ED. However, despite the high

Table 2 Different signs and symptoms that can occur in patients with an ED

General
Marked weight loss, gain, fluctuations, or unexplained change in growth curves or BMI percentiles in a child or adolescent who is still growing and developing
Cold intolerance, including hypothermia (low body temperature), general chilliness, or cool hands and feet which may or may not manifest a blue or purple color
Weakness
Fatigue and reduced energy
Presyncope (dizziness)
Syncope (fainting)
Greater focus on "healthy" or "clean" eating, rigid exercise patterns
Increased spending of money on binge foods
Using the bathroom after meals to purge
Evidence of purging found in the bathroom by other members of the household
Ear/nose/throat and eyes
Oral trauma, lacerations, petechiae on back of throat
Perimylolysis (dental erosion on lingual and occlusal tooth surfaces) and dental caries (cavities)
Parotid gland enlargement and pain
Cheilosis (cracked, sore skin at the corners of the mouth)
Dry eyes, blurred vision
Difficulty swallowing dry foods or liquids
Cardiorespiratory
Chest pain
Heart palpitations and cardiac arrhythmias
Bradycardia (low heart rate at rest)
Hypotension (low blood pressure)
Dyspnea (shortness of breath)
Edema (swelling)
Gastrointestinal and genitourinary
Epigastric discomfort
Abdominal bloating
Early satiety (fullness) and nausea
Gastroesophageal reflux (heartburn)
Hematemesis (blood in vomit)
Hemorrhoids and rectal prolapse
Constipation
Endocrine
Shakiness, weakness, sweating, chest pressure, confusion, or nausea, which may signal hypoglycemia (a significant cause of death in EDs); hypoglycemia may also be asymptomatic
Amenorrhea or oligomenorrhea (absent or irregular menses)
Low sex drive (related to suppressed sex hormone production of estrogen/testosterone)
Bone fractures, including stress fractures due to low bone mineral density/osteoporosis
Infertility
Neuropsychiatric
Depressive/anxious/obsessive/compulsive symptoms and/or behaviors

(continued)

Table 2 (continued)

Poor concentration or memory loss
Insomnia
Self-harm
Suicidal thoughts, plans, or attempts
Reduced flexibility, creativity, and spontaneity, with increasing rigidity around social engagements and mealtimes
Seizures
Substance use or abuse
Dermatologic
Lanugo hair growth
Hair loss
Carotenoderma (yellowish discoloration of skin)
Russell's sign (calluses or scars on the back of the hand associated with self-induced vomiting)
Poor wound healing
Dry, brittle hair and nails
Fragile, dry skin that bruises or tears easily
Sores or bruises over bony prominences

prevalence, it remains underrecognized and undertreated, suggesting that awareness and recognition should be improved by clinicians. Further, as previously mentioned, it is important to consider patient factors as many of them are even unaware of the disorder and often hide their eating behaviors (Kornstein 2017).

In addition to a thorough clinical assessment, clinicians should incorporate screening tools that may help to overcome communication barriers and contribute to a better recognition of the disease. A validated screening tool such as the SCOFF questionnaire (Table 4), which was designed for nonspecialists, may be useful in the recognition and identification of ED (Morgan et al. 1999).

There is, therefore, a definitive need for an early intervention through the recognition of specific and nonspecific symptoms as well as ED prodromes in a secondary prevention. In this respect, it is important especially for general practitioners and pediatricians to have competence regarding primary and tertiary prevention for EDs to facilitate and accelerate referral into specialist care (House et al. 2012). With regard to primary care, we talk about primary prevention and screening to identify people with emerging or early EDs ensuring access to early evidence-based treatment.

Prevention of EDs, Intervention Programs, and Impact

The past 20 years has seen the rapid development of prevention programs in multiple fields in medicine including preventive interventions in ED, given the significant public health burden and the consequences of the delay in the diagnosis and long-term effects (Grange and Loeb 2007). Treatment costs are high for AN and other EDs

Table 3 Laboratory studies recommended and potential findings

Basic diagnostic tests indicated for all patients with a suspected ED	**Potential abnormal findings in a patient with an ED**
Complete blood count	Leukopenia, anemia, or thrombocytopenia
Comprehensive metabolic panel to include electrolytes, renal function tests, and liver enzymes	Glucose: Low (poor nutrition) Sodium: Low (water loading or laxatives) potassium: Low (vomiting, laxatives, diuretics) Chloride: Low (vomiting, laxatives) Blood bicarbonate: High (vomiting), low (laxatives) Blood urea nitrogen: High (dehydration) Creatinine: High (dehydration, renal dysfunction), low (poor muscle mass) Calcium: Slightly low (poor nutrition at the expense of bone) Phosphate: Low (poor nutrition and early refeeding syndrome) Magnesium: Low (poor nutrition, laxative use) Total protein/albumin: High (in early malnutrition at the expense of muscle mass or milk of magnesia use), low (in later malnutrition) Aspartate aminotransaminase (AST), alanine aminotransaminase (ALT): High (starvation)
Electrocardiogram (ECG)	Bradycardia (low heart rate), prolonged QTc (>450 msec), other arrhythmias
Additional diagnostic tests to consider	**Potential abnormal findings in a patient with an ED**
Thyroid hormone testing	TSH: Low or normal T4: Low or normal (euthyroid sick syndrome) T3: Low if below metabolically healthy weight
Gonadotropins (LH and FSH) and sex steroids (estradiol and testosterone)	LH, FSH, estradiol (women), and testosterone (men) levels: Low or low normal
Erythrocyte sedimentation rate (ESR)	ESR: Low (starvation)
Prealbumin	Prealbumin: Low (in protein-calorie malnutrition) – But only reflective of the past 72 h pretest

Table 4 An example of a validated screening tool for EDs – the **SCOFF**

S – Do you make yourself *sick* because you feel uncomfortably full?
C – Do you worry you have lost *control* over how much you eat?
O – Have you recently lost more than *one* stone (6.35 kg or 14 lb.) in a 3-month period?
F – Do you believe yourself to be *fat* when others say you are too thin?
F – Would you say *food* dominates your life?

[a]Two or more positive responses on the SCOFF indicate a possible ED and should prompt referral for further evaluation

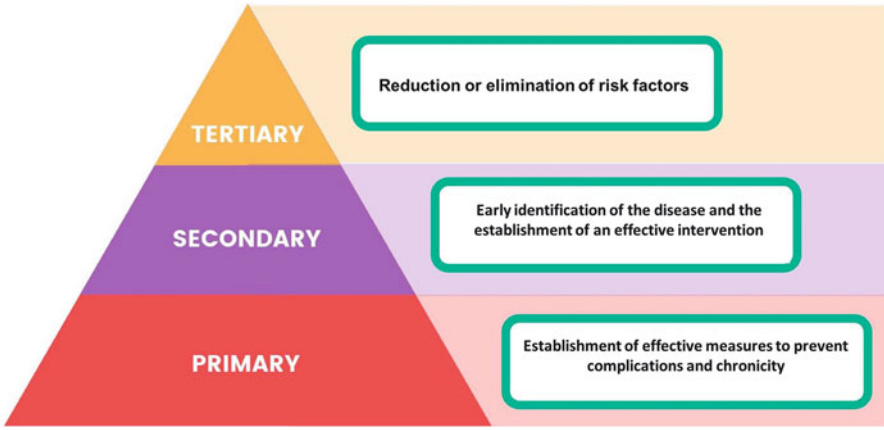


Fig. 2 Prevention stages in ED

that fail to respond to first-line therapies that, by some means, are not available to all (Ágh et al. 2016). However, it is important to consider that professionals with appropriate advanced training are probably insufficient and therefore it is necessary to focus on preventive programs of early intervention.

It is estimated that there is often a delay between presentation with clinically significant symptoms and referral or diagnosis (1 year for AN and around 4 years for BN). Therefore, early interventions even for mild cases or false positives are preferable (Allen et al. 2020).

Previous research findings into preventive interventions in ED show significant effects for risk factors and symptom reductions. A recent systematic review and meta-analysis of prevention in ED was reported by Le et al. (2017) concluding that several preventive strategies for ED could have potential benefits in reducing several risk factors targeting population with symptoms of the disorder (e.g., prodromes such as body dissatisfaction or weight concern) but not yet a diagnostic level.

Prevention has been traditionally classified into three different stages (Fig. 2). **Primary prevention** involves the reduction or elimination of risk factors that lead to the beginning of the disorder. **Secondary prevention** consists of early identification of the disease and the establishment of an effective intervention. **Tertiary prevention** implies the establishment of effective measures to prevent complications and chronicity (Caplan 1980).

It has been estimated that over half of the prevention programs have demonstrated effectiveness for reducing risk factors while 29% reduce actual and future eating behaviors (Shaw et al. 2009).

Generally, primary prevention is the standard or ideal strategy of prevention. ED prevention programs should be oriented toward the promotion of general health and the development of positive attitudes, incorporating basic aspects such as self-esteem improvement, basic training on nutrition, and fighting against social media pressure for thinness (Raich et al. 2007).

The role of general practitioners and pediatricians is to ensure health promotion, organize prevention activities in school or workplaces, work with the family, promote protecting factors among patients, and even improve levels of knowledge on the recognition of ED. On the other hand, tertiary prevention is also important to avoid chronicity and prevention of relapse, and it is therefore relevant to take into account that probably similar symptoms to the first-onset EDs emerge. For this reason, clinicians should keep an eye on medical consultations related to potential ED symptoms.

Interventions based on *cognitive behavioral therapy* (CBT) including interactive and Internet-based approaches have demonstrated to produce significant effects in reducing ED risk factors and onset risk in some high-risk populations. It is becoming increasingly difficult to ignore the importance of social media in these psychiatric disorders among young people in fact, growing evidence supports Internet-based programs for ED that appear to be substantially effective (Jacobi et al. 2012).

Cognitive dissonance (CD) interventions which are programs designed to reduce subscription to the thin ideal have produced a 60% statistically significant and clinically meaningful reduction (Stice et al. 2008).

Another intervention, promoting participant-driven improvements to dietary intake and physical activity, has also demonstrated a significant reduction of ED onset (Stice et al. 2013).

To sum up, health promotion paradigm is to date shown as the most effective method in the prevention of ED. Therefore, the main goal of a prevention program is to modify behaviors and attitudes and promote a higher knowledge of the disorder. This requires the utilization of implication techniques as well as an active participatory and experimental pedagogical methodology.

Applications to Other EDs

Those patients who do not meet the diagnostic criteria for any other ED such as other specified feeding eating disorder (OSFED) are characterized by less frequent symptoms, which could entail an obstacle in the recognition of the disorder. However, this category consistently represents the largest proportion of ED diagnoses although even much less research attention has been paid in the literature (Withnell et al. 2022). Other EDs, such as pica, rumination disorder, avoidant/restrictive food intake disorder (ARFID), and unspecified feeding or eating disorder (UFED), appear to be less frequent and subthreshold disorders. However, as a matter of fact, they are easier to be ignored by clinicians without specific training, and they remain largely underdiagnosed. In this sense, it is thought that these disorders are not well known and are difficult to identify by untrained clinicians as screening tools are made for threshold ED (i.e., AN, BN, and BED) and may not be useful for other EDs. Therefore, a better knowledge of this field or a proper communication between primary care and specific ED units is required to avoid both nutritional and psychopathological consequences of a delayed care.

Mini-Dictionary of Terms

- *Duration of untreated illness*: It is defined as the time between the onset of the disease and treatment initiation.
- *Prodromes*: They are early symptoms that indicate the impending onset of a psychiatric condition.
- *Risk factors*: They identify individuals who are at elevated risk for future emergence of the disorder.
- *Early intervention*: An intervention based on a "stage of illness" model that prioritizes young people who have recently (within 3 years) developed an ED.
- *Prevention programs*: They target at-risk but asymptomatic individuals or individuals with subsyndromal symptoms of a disorder.

Key Facts of Features of Medical Consultations Before the Onset of EDs

- Treatment is more likely to be successful when patients have suffered from an ED for a shorter period of time.
- A long DUI is a relevant outcome predictor associated with severe complications such as increased mortality.
- A higher knowledge of ED is required among clinicians to provide an early referral and intervention.
- Prodromes and nonspecific symptoms of ED are often overlooked in medical consultations.
- Prevention and early intervention programs have a great impact in the prevention, recognition, and prognosis of the ED.

Summary Points

All clinicians specially in primary care (general practitioners and pediatricians) play an important role in the assessment and recognition as well as follow-up of ED within a satisfactory communication and coordination with ED specialized units. In this respect, emerging technologies utilization may be suggested as a strong liason mechanism between primary care and specialized care by means of telehealth use or a specific coordination and supervision program. This highlights the importance of continued training in primary care to reduce illness duration and therefore medical and economic consequences of ED. Finally, investigation and clinical experience emphasize the importance of an early recognition based on adequate medical training among primary care clinicians to take nonspecific symptoms into consideration.

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The Role of Parents and Other Caregivers in the Early Detection of Eating Disorders

16

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Contents

Introduction 284
The Early Intervention Continuum 286
The Role of Parents in Early Detection 288
Earliest Detectable Symptoms 289
Barriers to Early Detection of Eating Disorders 292
Parent-Led Early Intervention Programs 295
Parent-Led Risk Factor Reduction 295
Parent-Led Treatments for the Prodromal Phase 298
Parent Support in the Early Eating Disorder Phase 300
Conclusion 302
Applications to Other Eating Disorders 305
Mini Dictionary of Terms 305
Key Facts of Parent-Led Early Detection 306
Summary Points 307
References 307

Abstract

Early detection of emerging eating disorder symptoms is critical to rapid intervention, which can reduce the negative impact of illness on individuals, families, and society. However, the evidence base to guide these efforts is quite limited. This chapter reviews existing research related to early detection (noticing the earliest symptoms) and early intervention (targeting symptoms at the earliest point possible) for child and adolescent eating disorders, emphasizing the role of parents and other primary caregivers. Early intervention can be redefined to encompass distinct phases of an emerging eating disorder including risk factors, prodromal symptoms, and initial disorder onset. Extant research suggests that specific behaviors like extreme diet changes are the most easily detected by

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others, although a variety of other behavioral and cognitive symptoms are present prior to eating disorder onset. Improving eating disorder education and support will be critical for parents and others in the early detection network (e.g., schools, healthcare providers). Once concerns are identified, parents have a role in carrying out early interventions to reverse the risk factors, early symptoms, or early disorder phase of illness. Interventions targeted to each phase will likely draw from eating disorders prevention science (particularly selective and indicated prevention approaches), treatment research, or both. Overall, research on early interventions is lacking, with most falling within child and adolescent anorexia nervosa. In general, research highlights the experiences of girls and young women from white Western European and North American backgrounds, leaving room for scientific advancement within early detection and early intervention for diverse individuals.

Keywords

Early detection · Early intervention · Parents · Primary caregivers · Eating disorders · Disordered eating · Children and adolescents

Abbreviations

FBT family-based treatment

Introduction

Eating disorders are serious and persistent mental illnesses that often begin in adolescence. The presence of an eating disorder can create psychological and physical consequences for the young person and distress for parents and other primary caregivers (e.g., Cottee-Lane et al. 2004). For example, eating disorders can change family dynamics to include more unhelpful communication styles and high negative emotions (e.g., McDermott et al. 2002; Woodside et al. 1995). Family involvement in treatment is the standard of care for the majority of child and adolescent eating disorders (Hilbert et al. 2017), such as family-based treatment (FBT) where parents take the lead in reversing the impact of the illness. Some of the negative changes in family dynamics resolve after FBT (Ciao et al. 2015), suggesting the essential role of parents in promoting recovery from an eating disorder and restoring family functioning.

Treatment of pediatric eating disorders through specialized care has a relatively high success rate (e.g., Lock et al. 2010; Le Grange et al. 2015), especially compared to lower recovery rates in adult eating disorder treatments. Studies of children and adolescents with eating disorders show that recovery is more likely with a shorter duration of illness and a quick uptake of treatment, while recovery is less likely the longer the patient is ill (e.g., le Grange et al. 2012; Steinhausen et al. 2003). Earlier

intervention puts recovery in closer reach, as illnesses can become more severe over time. Given this, there is consensus that identifying the earliest symptoms possible–and intervening rapidly–is key to reducing the burden of eating disorders. These efforts emphasize pediatric populations (individuals younger than age 18), since eating disorders frequently emerge during adolescence and early adulthood and initial symptoms and risk factors can develop much earlier. And yet, there is surprisingly little research on *how* to detect eating disorders as early as possible within young people and what tools can be used to confidently conduct early interventions. Moreover, it leaves an important question unanswered: *who* is best situated to identify eating disorders in young people at their earliest possible point?

While parents and other primary caregivers may be ideally situated to support the eating disorder recovery process, they report hesitation surrounding early detection of symptoms. In particular, parents are uncertain about whether eating disorder symptoms are severe enough to warrant intervention (e.g., Cottee-Lane et al. 2004; Ciao et al. 2020; Eichhorn 2008), and they report low confidence about the appropriate steps in finding help (Ciao et al. 2020). In fact, families can take a year or more to seek professional help for restrictive eating disorders in childhood or adolescence that involve weight loss (Lebow et al. 2015). It is crucial to address this hesitation and reduce the help-seeking delay. Parents have an important role within early detection, since placing the burden of identification on the young person is most likely unrealistic. A lack of insight into the illness and its symptoms is part of the psychopathology of anorexia nervosa (Ali et al. 2017), and many eating disorder symptoms can be easily hidden or dismissed within a diet-focused culture that normalizes extreme diet and exercise behavior as well as weight and shape preoccupation (e.g., Starzomska and Tadeusiewicz 2016).

Throughout this chapter, we review the evidence to support parents and other primary caregivers as the ideal agents of early eating disorder detection. We also present existing research on how to empower caregivers to seek help as rapidly as possible and support recovery through early intervention programs. Since the onset of the earliest risk factors and symptoms of eating disorders are most likely to occur before adulthood, this chapter will focus on early detection and early intervention for individuals under 18 years old. When possible, we summarize research across eating disorder experiences, although the majority of research falls within child and adolescent anorexia nervosa. This emphasis on anorexia nervosa within pediatric research is likely due to the younger age of onset relative to other eating disorders and the significant risk of death associated with the illness (e.g., Auger et al. 2021). In general, the existing research also highlights the experience of girls and young women from white Western European and North American backgrounds. We recognize these limitations and are hopeful that future research will be more inclusive of the eating disorder experiences of diverse individuals including boys and young men, those with gender expansive identities, people with marginalized racial and ethnic identities, and those with fat bodies.

The Early Intervention Continuum

One practical barrier to advancing knowledge on early detection and early intervention for eating disorders is an inconsistency in defining exactly what constitutes "early." Research on this topic is in its infancy relative to other fields like psychosis where definitions and early interventions are more established (e.g., McGorry et al. 2008). Across studies in eating disorders, the term "early intervention" describes treatments geared toward different populations, including:

1. Individuals at **high risk** for developing an eating disorder (with one or more risk factors associated with eating disorder onset in longitudinal research).
2. Those with specific **prodromal eating disorder symptoms** (with one or more clinical symptoms of an eating disorder without reaching the full diagnostic threshold).
3. Individuals who were recently diagnosed with an eating disorder for the first time (i.e., who are experiencing their **first episode of the illness**). In theory, the diagnosis occurs shortly after the disorder begins to capture the true early period of illness, but the definition is sometimes looser (e.g., it could include the first several years after diagnosis, regardless of actual onset or start of the illness).

In addition, there is variation in how individuals are classified into the categories above, such as the suggestion that the prodrome encompasses risk factors like body dissatisfaction (Stice et al. 2010), and disagreement about whether to classify subthreshold eating disorder symptoms among children and adolescents as prodromal or more similar to a full-threshold case (Le Grange and Loeb 2007). Altogether, these inconsistencies present the field with a challenge, as the goals of early intervention will differ based on the target eating disorder experiences. This topic also bridges prevention science and treatment research, creating additional discrepancies in how language is used and interventions are applied. Objectives of early interventions can range from:

1. Reducing risk and preventing the emergence of any eating disorder symptoms (if targeting high-risk individuals).
2. Reducing initial symptoms and preventing the onset of a diagnosable eating disorder (if targeting prodromal symptoms).
3. Decreasing the amount of time between illness onset and help-seeking (if targeting the first episode of illness).

In an effort to standardize our definitions and advance progress in the fields of prevention and treatment research, experiences of emerging illness could easily be mapped onto a continuum of eating disorder development (e.g., using the staging model of Treasure et al. 2015). In a model like this, separate phases of illness can divide the experience of eating disorders into:

1. **Pre-disorder:** A phase where risk factors are absent or intermittent.
2. **Risk factor phase:** The presence of one or more longitudinally identified risk factors like dietary restraint and body dissatisfaction, which can become more rigid and dominating over time.
3. **Prodromal phase:** Persistent risk factors convert to one or more initial eating disorder symptoms (e.g., restraint becomes severe dietary restriction that leads to weight loss; body dissatisfaction transitions to organizing self-worth around weight and shape).
4. **Early disorder phase:** Initial symptoms worsen, accompanied by additional eating disorder symptoms and potentially other psychiatric symptoms. These symptoms coalesce in the first episode of illness.
5. **Established disorder phase:** Without intervention, the disorder persists, worsens, and/or transitions to another eating disorder.
6. **Severe and enduring phase:** Disorder eventually becomes a severe and enduring illness that can be resistant to treatment.

The time-based parameters for each phase are uncertain, with 1–3 years suggested as the early illness phase (e.g., Treasure et al. 2015) and greater than 7 years for severe and enduring (e.g., Touyz et al. 2013). We suggest that the early disorder phase is defined as the first year after onset to capture a critical period for early intervention on newly developed illness. The years after include the established disorder phase followed by severe and enduring. Research should continue to explore time-based indicators for each phase. While an eating disorder can begin at any age, if we assume an average age of onset, the risk factor phase would emerge during middle childhood, intensify during early adolescence, and transition to early symptoms and disorder onset during adolescence or early adulthood (Fig. 1).

While this continuum assumes a linear progression, with experiences developing in severity over time, this will not be the case for all individuals. It also is important to recognize that there is attrition across phases, with individuals in each phase recovering rather than becoming more severe. In fact, the *majority* of individuals would likely not progress to the next phase (Stice et al. 2010). We instead present this

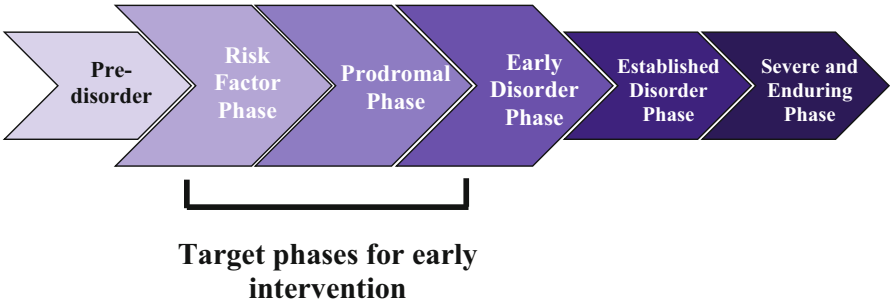


Fig. 1 The eating disorder continuum

model as a conceptual map for understanding how early detection can disrupt this developmental process, and when exactly early interventions might occur. **Early detection**–noticing the earliest symptoms that will become an eating disorder–would ideally occur in the late risk factor phase throughout the prodrome and continue into the initial early disorder phase. **Early interventions**–to relieve existing symptoms and stop them from progressing to the next phase–could occur across the risk factor, prodromal, and early disorder phases and be tailored in their intensity to match the phase (with more intensive interventions for later phases of illness). Early detection and early interventions targeting the eating disorder prodrome, when the first illness symptoms are emerging, are likely to have the greatest payoff in terms of identifying the individuals most likely to develop clinical eating disorders, but before symptoms become more severe and persistent.

Research evaluating early interventions for children and adolescents in these target phases is quite limited. Existing tools are drawn from eating disorder prevention research (selective prevention for the risk factor phase and indicated prevention for the prodromal phase), eating disorder treatment research (adapted for the prodromal phase and early disorder phase), or a blend of these approaches to address early and emerging eating disorder concerns. However, early intervention is defined, the task of detection–identifying symptoms when they first become concerning–still remains primary.

The Role of Parents in Early Detection

In theory, parents and other primary caregivers who are involved in their child's day-to-day life can observe eating and exercise habits and identify any concerning changes. And yet, there is poor understanding of the extent to which parents *do* notice emerging eating disorder symptoms. Across different mental illnesses, parents can miss or misidentify their child's psychological symptoms. Evidence for this includes discrepancies in parent-child reports of mental illness experiences. In general, parents and children are likely to agree on observable behaviors but disagree about the existence of internal symptoms (e.g., cognitions, mood; e.g., Salbach-Andrae et al. 2009). This highlights how internal experiences can easily remain private.

Eating disorders involve both observable behaviors (e.g., extreme diet or exercise changes, binge eating, compensatory behaviors) and internal symptoms (e.g., the cognitive experiences of body image disturbance), as well as physical changes such as weight loss or gain. Younger individuals may have significant denial of their illness and the psychological aspects of eating disorders (Le Grange and Loeb 2007), which makes parental reports especially important as complementary sources of information. However, research on the consistency of parent-child reports of an eating disorder (e.g., Mariano et al. 2013) suggests poor to moderate agreement about the presence of particular symptoms, with the lowest agreement for cognitive symptoms. Research in nonclinical samples also finds disagreement, where parents are less likely to identify bulimic symptoms compared to adolescents (e.g., Swanson et al. 2014; Bartholdy et al. 2017), but more likely to notice thinness and weight loss

(e.g., Swanson et al. 2014). Secrecy and shame can obstruct parental identification of bulimic symptoms. When these symptoms *are* noticed by parents, they may mark the severity of these behaviors, which makes swift intervention more urgent (Swanson et al. 2014).

Despite the challenges of identifying symptoms, studies of adolescents currently in eating disorder therapy show that parents *are* often the first to notice the symptoms and take action to find help (Ciao et al. 2020; Rosello et al. 2021a). The role of parents and other primary caregivers is particularly important when it comes to identifying anorexia nervosa (e.g., Laporta-Herrero and Latorre 2020), where patients may conceal or deny dietary restriction and weight loss and earlier help-seeking increases the chance of recovery. Taken together, this highlights the important role of parents and primary caregivers in noticing and intervening on eating disorder symptoms, particularly but not only for symptoms that may be under-recognized and/or underreported by the young person experiencing them. Efforts to improve early intervention should recognize the essential role of parents in detecting early symptoms and provide them with relevant support. It may be especially important to educate parents about the bulimic and cognitive symptoms of eating disorders that are harder to detect from the outside so they can increase their chance of recognizing them.

Another critical avenue for early detection is *not* relying solely on parents, but also educating other people who have regular contact with young people experiencing eating disorders (e.g., coaches, teachers) about the signs and symptoms of eating disorders and how to confront concerning symptoms (Ciao et al. 2020). In particular, school nurses and school counselors could be an ideal resource for those suffering from eating disorders, their caregivers, and the teachers and other school leaders who interact with them daily (e.g., Funari 2013). Primary care physicians also serve an important role in early detection efforts, as they have annual contact with young people and monitor growth in height and weight. They are often the first step for consultation about suspicions of an eating disorder, but research shows that primary health care providers feel under-equipped to adequately identify and refer cases of eating disorders (Johns et al. 2019).

Earliest Detectable Symptoms

Longitudinal research offers insight into modifiable factors that increase the risk of developing an eating disorder over time. These risk factors–primarily explored in female-identified individuals–include perceived pressure to be thin, internalization of thin body ideals, weight concerns, body dissatisfaction, dieting, negative affect, and substance use (Stice et al. 2010). However, these experiences are relatively common (e.g., they impact 30–70% of adolescent girls) while less than 10% of adolescent girls have symptoms of an eating disorder (Stice et al. 2010). Making broad risk factors a candidate for early detection means identifying many people who will never progress to an eating disorder. However, prevention interventions targeting the risk factor phase may have goals beyond reducing eating disorder onset,

for example reducing the distress of body dissatisfaction in and of itself to improve quality of life. And yet, more focused early detection–for example looking for persistent or rigid risk factors or symptoms within the eating disorder prodrome–may have greater payoff in terms of targeting individuals most likely to develop a full-blown illness. Even if prodromal symptoms do not progress, subthreshold eating disorders in adolescents are associated with distress and impairment similar to full-threshold cases (e.g., Stice et al. 2009), emphasizing the importance of detection and early interventions for this phase.

A recent systematic review suggests several candidates for early detection within the eating disorder prodrome. The authors evaluated longitudinal studies predicting eating disorder diagnoses in nonclinical samples of children and adolescents (McClelland et al. 2020). Although just over half of the 22 studies were rated as good quality, in general, a number of specific and general symptoms predated an eating disorder diagnosis. The earliest symptoms included problematic eating before age 10 (e.g., picky eating, conflicts around eating). Symptoms were more varied from ages 10–13, with both eating disorder symptoms (dieting, body dissatisfaction, and bulimic symptoms) and general psychiatric symptoms (anxiety and depression) associated with eventual eating disorder diagnoses. From age 15 onward, behavioral symptoms were most often related to later eating disorders, including binge eating, compensatory behaviors, and non-suicidal self-injury (McClelland et al. 2020). Conflicts around eating and distressing meal times have been suggested elsewhere to predate eating disorder onset in adolescence (Le Grange and Loeb 2007), making this a viable target for the earliest identification efforts, although these behaviors do not stand alone as prodromal symptoms (i.e., they are not clinical symptoms of an eating disorder). At later ages, a variety of specific–and mostly behavioral–eating disorder symptoms are candidates for early detection in the prodrome, such as dieting, body dissatisfaction, binge eating, and compensatory behaviors.

By asking young people and their caregivers to reflect on the time just prior to the start of an eating disorder (i.e., the potential prodrome), retrospective research can also inform early detection. In particular, the lived experience of parents provides unique insight into the symptoms of eating disorders that are the easiest to spot from the outside. Ciao et al. (2020) conducted qualitative interviews with 12 American caregivers of adolescents with an eating disorder diagnosis (1 biological father; 11 biological mothers; 93% white, 20% Hispanic) to solicit their experience identifying and responding to an eating disorder. The majority of parents who participated had a child with anorexia nervosa ($N = 8$), with the remainder diagnosed with other specified feeding or eating disorder ($N = 2$), bulimia nervosa ($N = 1$), or avoidant-restrictive food intake disorder ($N = 1$). Fifteen adolescent patients (ages 12–18; 100% female) shared their experiences separately. Weight loss and thinness were the earliest symptoms identified by parents, followed by extreme eating and exercise changes (e.g., severe dietary restriction, excessive exercise). While the early cognitive symptoms of eating disorders can be much harder to detect, adolescents in this study shared that body dissatisfaction *could* be observed by others (e.g., by looking for verbal comments of dissatisfaction with appearance). The majority of adolescents (60%) and parents (83%) reported that the parents–usually mothers–were the first

person to identify the disorder, but a variety of other individuals were also named as identifying the eating disorder early in its progression, including friends of the adolescent, teachers, coaches, and other adults (e.g., other family members and friends). This suggests both that parents can–and do–detect the early symptoms of eating disorders, and that other people notice these changes as well.

In a survey study with a similar aim, Rosello et al. (2021a) recruited the parents of 78 children and adolescents (ages 8–18; 94% female) with anorexia nervosa (64%), atypical anorexia nervosa (23%), or bulimia nervosa (13%). All patients were newly referred to a British child and adolescent eating disorder specialist service. This study mapped both symptom onset and length of time before seeking help. The earliest eating disorder symptoms observed by parents were changes in eating pattern (e.g., more rigidity or rules around eating; reported by 49 parents), followed by weight loss (reported by 27 parents). Other early symptoms included shape concerns (22 parents) and binge eating or compensatory behaviors (18 parents). Symptoms like weight concerns (2 parents), somatic symptoms (7 parents), and emotional changes (10 parents) were infrequently reported as first noticed. Strikingly, parents noticed weight and shape concerns an average of 1 year prior to the date the eating disorder diagnosis, with a large standard deviation (about 1 year). Changes in eating patterns were noticed an average of 10 months prior to diagnosis ($SD = 7.6$ months). Very few parents recalled symptoms more than 3 years prior to diagnosis (8%), suggesting that the year prior was an important period for the eating disorder's escalation. Of the parents in this study, a small proportion (6.4%) had consulted with a professional before seeking specialist intervention, hinting that changes are missed, normalized, or questioned for a long time.

In translating these study findings into actionable recommendations for parents and other primary caregivers, it is important to acknowledge the bias in parental recollections of concern, since the symptoms *did* eventually progress into a disorder. Increasing parental worry about specific symptoms (e.g., dieting) may result in overidentifying changes that could resolve without intervention. And yet for some, early detection could stall the progression to more serious illness. Across studies, the most consistent finding is that changes in eating patterns such as restrictive dieting commonly precede the onset of an eating disorder *and* are detectable by others for an extended period of time (Ciao et al. 2020; McClelland et al. 2020; Rosello et al. 2021a). Dieting changes between ages 10–13 could be particularly important to monitor closely (McClelland et al. 2020). Several studies hint that picky eating and conflicts around meals prior to age 10 might warrant additional screening (McClelland et al. 2020; Le Grange and Loeb 2007). Behavioral symptoms like binge eating and compensatory behaviors also predate an eating disorder diagnosis (McClelland et al. 2020), but these symptoms were mentioned less often by parents as the first to catch their attention (Ciao et al. 2020; Rosello et al. 2021a). This echoes the research that parents underreport bulimic symptoms relative to adolescents (Swanson et al. 2014; Bartholdy et al. 2017). However, given that behavioral symptoms are easier to detect from the outside than cognitive ones, raising awareness through education might result in increased detection.

There also was consistency across studies in identifying weight loss and thinness as a signal for concern (Ciao et al. 2020; Rosello et al. 2021a). However, it is important to note that weight changes are a downstream consequence of energy intake and expenditure changes. If observed too late, the diet and exercise changes may be routine and harder to disrupt. Furthermore, smaller body size is not a requirement for an eating disorder, and a screening approach that looks for excessive thinness alone would exclude restrictive eating disorders that occur within fat bodies. Although any significant or rapid weight change (e.g., a large shift in growth percentile) should be a sign of concern during childhood and adolescence, parents should also look for upstream behavior changes such as persistent eating and exercise habit changes, especially those tied to rigid cognitions (such as negative appraisals of body size or weight).

While these studies point to specific symptom targets for early detection, the execution of screening efforts is more difficult. The few studies addressing this topic suggest that parents should allow developmentally appropriate autonomy in eating and exercise domains while still being watchful of habit changes. For example, when reflecting on advice for earlier detection, both parents and adolescents suggested that being aware of the child's baseline behaviors would help to notice changes (Ciao et al. 2020). This included specific changes in eating habits (e.g., restriction, eating alone, negative relationships with food, eating "too healthy") and related behaviors like increased exercise and social withdrawal. Rosello et al. (2021a) suggest that parents look for persistent or excessive cognitions around weight, shape, size, or food control, and specific ties to behavior changes. Given that mood changes (e.g., anxiety, depression) can accompany eating-related changes and predate the eating disorder's onset (McClelland et al. 2020), parents can be on the lookout for constellations of symptoms and co-occurring changes across categories of behavior as a possible cause for concern. While early conversations about changes may seem unnecessary, more proactive steps to intervene as early as possible may keep symptoms from progressing. Parents and adolescents in the Ciao et al. study (2020) reflected that earlier intervention would have been helpful before symptoms became routine and incorporated into their daily lives (Table 1).

Barriers to Early Detection of Eating Disorders

A number of studies explore the challenges to identifying eating disorders within children and adolescents. Barriers exist across multiple contexts, including within the individual experiencing the disorder (e.g., hiding symptoms due to denial or shame; Laporta-Herrero and Latorre 2020; Swanson et al. 2014) and in the family context (e.g., parental hesitancy about the seriousness of symptoms when they emerge; Ciao et al. 2020; Cottee-Lane et al. 2004). Barriers also exist within the broader community of people who might detect concerning symptoms (e.g., lack of knowledge within primary healthcare providers; Johns et al. 2019). In addition, when symptoms or other aspects of the disorder (e.g., weight loss) progress slowly over time, it can be difficult to notice these changes. Since eating disorders often

Table 1 Early observable symptoms of child and adolescent eating disorders

Symptom	Observable examples	Source
Early problematic eating habits	Childhood picky eating Conflicts around mealtimes	Le Grange and Loeb 2007; McClelland et al. 2020
Extreme dieting or dietary restraint	Skipping meals Cutting or counting calories Rigidity or food rules (e.g., avoiding food groups) Avoiding social eating	Stice et al. 2010; McClelland et al. 2020; Ciao et al. 2020; Rosello et al. 2021a
Weight loss or thinness	Noticeable weight loss in short period of time (e.g., 3 months), regardless of starting weight	Ciao et al. 2020; Rosello et al. 2021a
Bulimic symptoms	Binge eating (losing control over type or amount of food eaten) Vomiting after meals Excessive exercise to compensate for food eaten	McClelland et al. 2020; Ciao et al. 2020; Rosello et al. 2021a
Body dissatisfaction	Comments about disliking appearance Efforts to conceal body (e.g., wearing baggy clothes) Negative remarks about shape or size Preoccupation with appearance	Stice et al. 2010; McClelland et al. 2020; Rosello et al. 2021a
Other social and emotional concerns	Anxiety Depression and other mood changes Non-suicidal self-injury Social withdrawal	McClelland et al. 2020; Stice et al. 2010; Ciao et al. 2020; Rosello et al. 2021a

begin during adolescence, symptom detection can be complicated by the normal developmental process of individuation, where children spend less time with their parents and are less likely to share their internal body image experiences with adults (Loeb et al. 2011).

Furthermore, the people who could potentially detect an eating disorder are embedded within a specific societal context, where normalization and praise of the early signs of eating disorders, such as eating "healthier" and increasing exercise, can make recognition challenging. Weight bias can lead to a failure to recognize problematic weight loss in individuals on the high end of the weight spectrum, even though emerging research shows the seriousness of anorexia nervosa across weight status (e.g., Garber et al. 2019). Stereotypes about who develops eating disorders–beliefs that they primarily impact young, affluent, white cisgender women–may impact the average person's understanding of these illnesses, who develops them, and whether treatment is warranted. Individuals whose identities and experiences depart from these eating disorder stereotypes (e.g., people of color, male-identifying and gender-expansive individuals, people with less financial affluence, people in fat bodies) experience barriers to identification and help-seeking (Sonneville and Lipson 2018).

Even when an eating disorder is correctly identified, the journey to finding appropriate treatment can be challenging. Parents may need additional information and support to intervene on emerging symptoms in their child. Research shows that family and friends seek out a variety of external resources to find help for an eating disorder, including self-help books, the Internet, and professional organizations and treatment centers (Ciao et al. 2020; Johns et al. 2019). Caregivers also seek out initial consultations within primary care (e.g., Cottee-Lane et al. 2004; Demmler et al. 2020; Johns et al. 2019; Laporta-Herrero and Latorre 2020), but report feeling like primary care physicians do not have adequate knowledge to intervene efficiently (Ciao et al. 2020). A systematic review identified multiple barriers to detecting eating disorders in healthcare contexts, including a lack of time and resources among providers and dismissing symptoms (Johns et al. 2019). Healthcare professionals themselves report challenges working with eating disorders, including their complexity, perceived low motivation for change, and a lack of training and resources (Johns et al. 2019). The lack of knowledge about eating disorders is a significant barrier to identification within primary care and referral to specialist care (e.g., Mitrofan et al. 2019; Johns et al. 2019). General practitioners need more support and training in screening for eating disorders (Reid et al. 2010), and utilizing appropriate referral channels for specialist services (Mitrofan et al. 2019).

Increased education on eating disorders is a proposed solution across studies that could address many of these barriers through improving mental health literacy (Ciao et al. 2020; Rosello et al. 2021a; Cottee-Lane et al. 2004). With increased access to educational and screening tools, parents, schools, and healthcare settings can serve as an important and interactive network for early detection of eating disorders. This includes understanding the central experiences within eating disorders (Bartholdy et al. 2017), including those symptoms that are more easily missed, hidden, or dismissed. It will be important to overlay this information with an awareness of typical and developmentally normal concerns around eating, weight, and bodies (Ciao et al. 2020). Education around eating disorder stereotypes can help to dispel myths and misunderstandings about who suffers from these illnesses and hopefully reduce stigma and shame surrounding help-seeking (Ali et al. 2017).

While primary caregivers are not solely responsible for detecting eating disorders, they are uniquely able to individualize educational information and adapt it to their family's culture and context. For example, parents should know that it is common for children and adolescents to have body dissatisfaction, particularly through puberty and if their bodies are different from dominant cultural appearance norms. Parents should also know when to be concerned, increase their monitoring, or start a conversation about these topics (Ciao et al. 2020). Close family members can know their child's typical habits and can be aware of the signs of an eating disorder that may match some changes they see – concerning changes that are not developmentally normal or normal for their individual child. However, parents need resources to serve as a first-line defense against emerging eating disorders, including adequate information *and* support. In a good example of this educational model, Loeb et al. (2011) outline the ways that anorexia nervosa can manifest during the developmental phase of middle childhood, with a focus on how parent-led

treatments can untangle the eating disorder from the developmental stage and promote recovery and a return to the previous trajectory.

Parent-Led Early Intervention Programs

Once emerging eating disorder symptoms are identified, parents and other primary caregivers have a unique role within early interventions. A limited number of parent-focused programs examine early intervention programs for children and adolescents across the risk factor, prodromal, and early disorder phases (Fig. 2).

Parent-Led Risk Factor Reduction

Many evidence-based risk factor reduction programs for children and younger adolescents are delivered within schools to universal audiences (Yager et al. 2013). In this context, everyone is included regardless of risk status (also called universal or primary prevention), placing programs just outside the scope of early intervention since they do not target high-risk individuals. Programs for older adolescents and young adults often screen for specific eating disorder risk factors (also called selective or secondary prevention), for example targeting adolescent girls with high body dissatisfaction through group dissonance interventions (e.g., Stice et al. 2010). While these programs can reduce eating disorder risk, decrease eating disorder symptoms, and even prevent the onset of eating disorders in girls and young women (Stice et al. 2019), they do not typically have a parental component. In fact, a 2014 review of parent-focused eating disorders prevention programs for children found that while 20 studies had at least a minimal parental component (e.g., providing parent materials to supplement a student-focused intervention), only two were high quality *and* significantly improved child eating disorder risk (Hart et al. 2015). This review included all types of prevention programs, regardless of the risk status of children.

Thus, to our knowledge just two programs investigate the potential for parent-led early intervention among high-risk individuals (parent-led selective prevention).

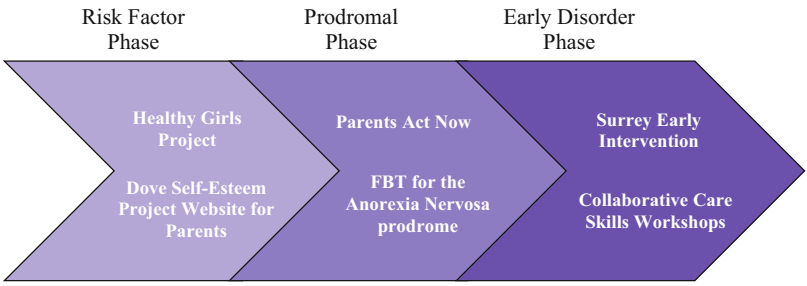


Fig. 2 Parent-focused early intervention programs

Table 2 Parent-focused programs for the risk factor phase

Program name	Program target	Key components
Healthy girls project	Mothers of girls ages 12–14 with body dissatisfaction	Four 90 min group workshops to address internalization of cultural beauty ideals Didactic content, behavioral activities, and discussion Homework to encourage conversations between mothers and daughters
Dove self-esteem project website for parents	Mother of girls ages 11–14 with body image concerns	Online platform with didactic materials, activities, and recommendations for body image behavior change Designed to promote body positivity in mothers and daughters

One of these programs was included in the parent-focused prevention review above (Hart et al. 2015) and one was published more recently; both programs target the mothers of adolescent girls with body image concerns (Corning et al. 2010; Diedrichs et al. 2016). Another parent-based program worth mentioning targets the early childhood years (ages 2–6; Hart et al. 2016). The *Confident Body, Confident Child* curriculum provides parents with strategies for building their child's healthy body image by addressing parenting factors known to increase the risk for childhood body dissatisfaction and subsequent disordered eating (e.g., parental criticism of weight). While this is an important program for broad-spectrum eating disorders prevention and promoting healthy body image, it currently falls outside of the early intervention framework because it does not target high-risk individuals or families (Table 2).

The ***Healthy Girls Project*** was designed for the mothers of American seventh and eighth grade girls (ages 12–14) with body dissatisfaction (Corning et al. 2010). A small randomized-controlled study recruited 31 mothers (ages 33–58; 83% European-American) to receive four weekly 90 min group workshops facilitated by a member of the research team or participate in assessments only. Workshop sessions addressed ways to reduce their daughters' internalization of cultural beauty ideals, a risk factor established to precede body dissatisfaction and dieting in a developmental model of eating disorder onset (Stice et al. 2000). Sessions included psychoeducation, behavioral activities, discussion, and homework. Mothers were provided with guidance on body image communication skills, and homework encouraged structured interactions around each topic (e.g., challenge your daughter to try an activity she has been avoiding due to body image concerns). Girls whose mothers participated in the workshop perceived less maternal pressure to be thin relative to the assessment-only control group through 3 month follow-up, suggesting that the *Healthy Girls Project* changed parent-child conversations surrounding body image. Girls also reported increases in body satisfaction after the intervention relative to the control group, but not through follow-up (Corning et al. 2010). While the benefits to the girls' own body image was limited, the impact on perceived

parental pressure highlights how a program like the *Healthy Girls Project* can be useful in raising awareness and changing familial conversations around appearance.

An intervention targeting a similar audience evaluated an online platform for mothers of daughters ages 11–14 with body image concerns (Diedrichs et al. 2016). The ***Dove Self-Esteem Project Website for Parents*** is an online platform designed to help mothers develop and maintain their daughters' positive body image, as well as their own. The *Dove Parents* website provides psychoeducational materials, activities, and recommendations for creating body image behavior change including critiquing media-based appearance ideals, changing negative conversations about appearance, discussing relational influences on body image, and engaging in body acceptance activities. In a randomized-controlled study, mother-daughter dyads in England ($N = 235$; mothers aged 28–54 and 93% white) either received a tailored version of the program (instructed to read specific articles), were given unstructured access to the web platform, or were allocated to assessment-only control. Exposure to the intervention was brief (30–60 min, on average). The tailored and unstructured interventions had some short-term impact on mother and daughter risk factors, but most changes were not maintained through 12 month follow-up. One important finding was that accessing the website increased the likelihood that mothers had conversations with their daughters about body image and sought additional help for their concerns (Diedrichs et al. 2016). This makes a resource like the *Dove Parents* website a viable candidate for promoting early detection of body image concerns and subsequent eating disorders.

Given the modest success of existing programs and the overall limited research in this area, it is still unclear exactly how to engage parents–and not just mothers–in eating disorders prevention for high-risk individuals. Importantly, existing research investigates only a portion of the individuals at highest risk for developing an eating disorder. For example, gender minority adolescents are uniquely high risk for developing eating disorders relative to their cisgender peers (Roberts et al. 2021), making gender-expansive youth important targets for future high risk programs. The current research on parent-led risk factor reduction is also limited to mostly white European and European-American participants. This neglects the racial and ethnic diversity within eating disorder experiences and the need to address the eating disorder vulnerability resulting from multiple marginalized identities (Burke et al. 2020). The lack of research on diverse experiences makes it difficult to draw conclusions about who may or may not benefit from parent-focused risk factor reduction. Diversity-focused body image programs exist for older, universal audiences (e.g., Ciao et al. 2021), and could be adapted to the parent-led context to support high-risk individuals within the early intervention spectrum.

It is interesting that the two existing parent-led programs for high-risk young people had a minimal long-term impact on young girls' body image. There are multiple explanations for this. It is possible that once eating disorder risk factors are present, intervening with parents alone is insufficient to create change. Parent-only interventions may also be a poor fit for this particular age range (both studies targeted early adolescence), or for cognitive symptoms like body dissatisfaction, or for programs that include only one parent or only mothers. However, both programs

had a positive impact on mother-daughter body image communication, and the *Dove Parents* program increased help-seeking for body image concerns (Diedrichs et al. 2016). These are important targets for the early detection of eating disorders. Given this, these types of parent-focused programs may be best used as adjuncts to individually focused programs such as dissonance-based interventions for girls and young women with body image concerns (Stice et al. 2019). They also could be shifted to include more education and support for parents surrounding screening and intervening on emerging eating disorder symptoms.

Parent-Led Treatments for the Prodromal Phase

Limited research has examined the role of parents once eating disorder risk transitions into clinical symptoms. This phase of early intervention bridges the gap between prevention and treatment. Indicated or tertiary prevention targets individuals experiencing initial symptoms of eating disorders; this also describes the prodromal phase of illness. To date, research on this topic is exclusive to children and adolescents with prodromal anorexia nervosa (Jones et al. 2012; Loeb et al. 2020) (Table 3).

An online program called ***Parents Act Now*** was developed for parents of girls ages 11–17 at high risk for developing anorexia nervosa (Jones et al. 2012; Jacobi et al. 2018). While the researchers describe the sample and program as targeting "high-risk" individuals, they include girls with an early anorexia symptom such as low weight or significant weight loss. In addition to the weight criterion, participants had either (1) high weight and shape concerns or high drive for thinness, or (2) at least one of four probable risk factors including high perfectionism, amenorrhea, excessive exercise, or a family history of an eating disorder. These inclusion factors situate the *Parents Act Now* intervention as a program for the prodromal phase of illness. The six session web-based program provides psychoeducation about eating

Table 3 Parent-focused programs for the prodromal eating disorder phase

Program Name	Program target	Key components
Parents Act Now	Parents of girls ages 11–17 with prodromal symptoms of anorexia nervosa	Six-session online program with FBT and eating disorder prevention techniques Eating disorder psychoeducation Encourages parents to intervene on concerning weight loss-related behaviors Parent discussion groups, weekly behavior monitoring and feedback
FBT for prodromal anorexia nervosa	Parents of children (any gender) ages 9–18 with prodromal symptoms of anorexia nervosa	14–50 min sessions over 6 months with FBT and eating disorder prevention techniques Family sessions following FBT phases and principles

disorders and encourages parents to intervene on any concerning weight loss-related behaviors using family-based treatment (FBT) and eating disorders prevention techniques. The program includes a moderated discussion group for parents and weekly monitoring of their child's weight, eating, and exercise behaviors with feedback provided by interventionists.

The feasibility, acceptability, and short-term benefits of the *Parents Act Now* program was established in an uncontrolled pilot study in Germany and the United States ($N = 46$; Jones et al. 2012), followed by a small randomized-controlled trial in Germany ($N = 66$; Jacobi et al. 2018). Unfortunately, there was low uptake of this program and high dropout among parents, with most parents failing to engage in a majority of the content (and 30% who never logged on at all). Among parents who participated, there was greater weight recovery among their children relative to a control group, with small to medium effect sizes (Jacobi et al. 2018). While the results of this study hint at the benefits of this early intervention, future research should attempt to understand parental barriers to accessing programs like these.

A more intensive program targeting young people with subthreshold anorexia nervosa examined the feasibility of an adapted version of **FBT for the anorexia nervosa prodrome** (Loeb et al. 2020). In a partially randomized design, young people in the United States ages 9–18 ($N = 59$; 85% female; 85% white) who had some but not all of the diagnostic features of anorexia nervosa were recruited to participate in either a 14-session manualized FBT intervention or 14 sessions of individual supportive therapy delivered by eating disorder therapists over a 6-month period. The adapted FBT treatment also drew from the eating disorders risk factor and prevention literature to ask parents to engage in new strategies such as modeling healthy, flexible eating for their child. The comparison supportive therapy intervention did not include a parental component. Results suggested the feasibility and potential benefit of both the family-based and individual interventions in improving symptoms of subthreshold anorexia nervosa (Loeb et al. 2020).

These two programs provide a limited view of how parent-focused interventions can help to reverse or improve the anorexia nervosa prodrome to prevent clinical cases of eating disorders. It is difficult to compare the interventions directly; although they shared a therapeutic approach (primarily FBT), they were delivered in very different doses (6 vs. 14 sessions) and through different modalities (online vs. in-person). Participants in both studies were predominantly female and from Western European and European-American backgrounds. Small sample sizes and a narrow focus on early anorexia nervosa highlight the need for additional research in this area and with broader eating disorder experiences. Programs that target the prodromal phase of illness to reduce initial symptoms and prevent clinical disorder onset are arguably one of the most important early intervention tools to expand in future research. When developing programs, researchers should involve parents in user-focused design of programming to ensure it meets their needs and to address any barriers to treatment uptake.

Parent Support in the Early Eating Disorder Phase

FBT has a relatively strong evidence base for treating children and adolescents with anorexia nervosa and modest empirical support for treating bulimia nervosa in this age range (Hilbert et al. 2017). FBT empowers parents to take charge of normalizing eating and exercise habits in their child to reverse the impact of the eating disorder. Although FBT is designed for children and adolescents at any stage of illness, research suggests that recovery is more likely when the duration of illness is shorter (e.g., le Grange et al. 2012). Therefore, several programs attempt to accelerate the uptake of evidence-based interventions and intervene during early stages of the illness. They also aim to increase parental support and success upon first beginning specialized clinical interventions like FBT (Table 4).

An adjunctive program called the ***Surrey Early Intervention*** for Child and Adolescent Eating Disorders offers parents additional information in a group format at the beginning of FBT (Nicholls and Yi 2012). Primary care referral systems in England recruit patients for the program, with an emphasis on early referral (shortly after a new eating disorder is diagnosed). The six-week program was designed to standardize the information typically provided to parents in the early stage of child and adolescent eating disorder treatment, with goals of increasing knowledge, skills, and parent confidence. Sessions are half didactic and half discussion, containing information on the impact of the disorder, identifying parental strengths, understanding stages of change, increasing communication, effective meal planning and refeeding, and managing disordered behaviors. A within-subjects design evaluated the parents of 64 children or adolescents (ages 8–18; 95% female) with a new diagnosis of anorexia nervosa or atypical anorexia nervosa. Parents attended the six 1.5 h therapist-led *Surrey Early Intervention* group meetings in addition to treatment as usual (Rosello et al. 2021b). Patients whose parents were in the program saw weight recovery success over time (through 6 months after the program) and improvement in eating disorder pathology (Rosello et al. 2021b). Although there

Table 4 Parent-focused programs for the early eating disorder phase

Program name	Program target	Key components
Surrey early intervention for child and adolescent eating disorders	Parents of children under age 18 (any gender) with anorexia-spectrum eating disorders	Six 1.5 h group sessions Adjunctive to FBT Didactic content to increase knowledge, improve communication, and promote FBT skills Group discussion
Collaborative care skills workshops	Caregivers of adolescent (15+) or adult patients (any gender) with an eating disorder	Six 2 h group workshops Adjunctive to outpatient therapy Didactic content to increase knowledge, support change, improve communication, and manage caregiving stress Exercises and practice

was no comparison group and it is difficult to separate the benefits of treatment itself from the adjunctive parent program, this suggests that parents may benefit from additional group support immediately after beginning family-based interventions for newly diagnosed anorexia spectrum eating disorders.

Other programs aim to provide support to caregivers during eating disorders treatment, but without the specific focus on the early eating disorder phase. One well-researched program is the ***Collaborative Care Skills Workshops***, which provide caregivers with skills to support their loved ones during outpatient eating disorders therapy (Treasure et al. 2007). Although the original workshops are not parent-specific and include all types of caregivers (e.g., spouses of adult patients), the program is available for patients as young as age 15. Across six 2 h sessions, caregivers are taught support skills based in communication strategies, motivational interviewing (meeting their loved ones where they are within the stages of change), and managing the stress of caregiving. Both the caregivers and the patients in the research on the *Collaborative Care Skills Workshops* are predominantly female identifying. Patients are between the ages of 15–33 and have a variety of eating disorders (most often anorexia nervosa). Initial studies among British caregivers found high program participation and positive improvements among caregivers, including increases in knowledge about caring for eating disorders and decreases in caregiving distress (e.g., Sepulveda et al. 2008). A small randomized-controlled study demonstrated similar benefits among Spanish caregivers participating in both skills-based and psychoeducation-based workshops (Sepúlveda et al. 2019).

Two adaptations of the *Collaborative Care Skills Workshops* target parents of adolescents specifically. *Experienced Carers Helping Others (ECHO)* was created for parents of adolescents under age 21 with anorexia nervosa (Hodsoll et al. 2017). Families were newly referred for specialist care within the National Health Service in the United Kingdom. The self-help program utilized books and DVDs, plus a study condition who received ten brief phone sessions (30–60 min). Unfortunately, program benefits were modest and uptake was relatively low (Hodsoll et al. 2017), warranting additional research before recommending this version of the workshops. A related Austrian intervention called *Supporting Carers of Children and Adolescents with Eating Disorders in Austria (SUCCEAT)* shows promise in supporting parents and other carers for adolescent anorexia nervosa as well as improving patient outcomes (Philipp et al. 2021; Truttmann et al. 2020). And yet, like the original *Collaborative Care Skills Workshop* programs, the *SUCCEAT* intervention does not focus on the early phase of illness in particular. However, adolescent-focused programs are likely to catch many individuals in the early phases of their disorder and are likely suitable for parent-led early intervention.

Two additional programs exist to reduce the gap between eating disorder onset and starting specialized treatment, which is an important target for early interventions aimed at the early disorder phase. These programs provide insight into system-wide strategies to encourage both early detection of eating disorders and rapid intervention uptake. The *First Episode Rapid Early Intervention for Eating Disorders (FREED)* is a transdiagnostic service model within England to encourage family involvement and evidence-based specialized eating disorder treatment for

emerging adults ages 16–25 (Schmidt et al. 2016; Brown et al. 2018). A primary aim of *FREED* is to reduce the duration of untreated illness by encouraging rapid specialist referral and reducing waiting time for specialty clinics, with the goal of beginning treatment within the first 3 years after eating disorder onset. Quasi-experimental pilot trials in England (e.g., Brown et al. 2018; McClelland et al. 2018) and a later multicenter implementation trial (Austin et al. 2021; Flynn et al. 2021) show success in these domains, as well as clinical improvement for patients in the service. *FREED* is a transdiagnostic service, targeting all eating disorders and is open to patients with all identities, although the majority of participants in research trials identify as female. Although it does not have the same early disorder focus, a similar health system model called *Psychnet* in Germany targets women of all ages with anorexia nervosa (Gumz et al. 2014, 2018). Health campaigns and systems management encourage early recognition of anorexia nervosa, reduce the duration of untreated illness, and encourage uptake of specialized evidence-based treatments.

This growing body of research suggests that caregivers and patients alike will benefit from additional information and caregiver support as they begin specialized eating disorders treatment. The changes to healthcare systems described within many of these research studies are impressive, with a focus on early detection of eating disorder cases, rapid referral to specialized care, and quick uptake of evidence-based interventions. In the child and adolescent age range, efforts focus on anorexia nervosa in the outpatient setting, and research takes place in Western Europe. Ongoing research should continue exploring these robust parent support programs delivered in other contexts and within different healthcare systems. In particular, parent-led programs targeting the early phase of illness will help to understand their role in supplementing FBT and other child and adolescent-focused eating disorder treatments.

Conclusion

Early detection and rapid intervention on emerging symptoms is essential to reducing the negative impact of eating disorders on individuals, families, and society. Redefining the period of early intervention to encompass multiple distinct phases of an emerging eating disorder will help to advance research and clinical interventions. We suggest that early detection can include high-risk behaviors and cognitions (e.g., dieting, body dissatisfaction), prodromal symptoms (e.g., severe dieting leading to weight changes, initial bulimic symptoms), and early illness (when symptoms pass the diagnostic threshold in the first episode of the eating disorder). Interventions targeted to each phase will draw from eating disorders prevention science (particularly from selective and indicated prevention approaches), treatment research, or both. An overall lack of research makes it difficult to highlight evidence-based parent-led programs for high-risk individuals, prodromal symptoms, or early phases of illness, but this leaves ample room for future research and intervention growth. Strengthening screening and early intervention efforts to target emerging symptoms and new eating disorder cases will be particularly important as cases of eating

disorders rise during and after the COVID-19 pandemic (e.g., Asch et al. 2021). Screening and early interventions for prodromal symptoms in particular may have the greatest payoff in terms of their potential to catch individuals most likely to convert to a full eating disorder that requires greater resources to treat.

Although research is still in its infancy, evidence suggests that parents and other primary caregivers can and should be part of the early detection system for emerging eating disorders. The behavioral symptoms of eating disorders (e.g., dietary changes) are an ideal candidate for parental early screening efforts, as these external symptoms are easier to spot relative to internal cognitive symptoms (e.g., body dissatisfaction). Other individuals in the daily lives of young people (e.g., teachers, coaches) are well placed to notice such changes, and primary healthcare providers are essential to early identification and referral systems. However, barriers to identification are present within each context, with a failure to identify concerning symptoms and refer to specialized treatment quickly. Some of these barriers can be addressed by increasing knowledge of eating disorders across contexts (particularly among parents, schools, and healthcare settings) and encouraging parents to situate this information within their own intimate knowledge of their child's habits. Parental support for early identification and early intervention efforts is essential, including programs and systemic changes to improve the entire early detection network.

Once symptoms are identified, early interventions should be tailored to the phase of illness. This includes prevention programs to diminish existing risk factors and to stop risk factors from progressing to clinical symptoms. However, the specific role of parents within this type of early intervention (also known as selective eating disorders prevention) remains uncertain. Two existing programs for mothers of early adolescent girls with body image concerns raise doubt about whether parent-only programs are sufficient to promote changes in high-risk individuals (Corning et al. 2010; Diedrichs et al. 2016). Ideally, parent-led prevention would promote body acceptance while reducing risk, and prevent the onset of eating disorder symptoms. While individually focused programs may have the greatest impact on these outcomes, more research is needed to explore the role of parents in reducing risk among diverse individuals. In the meantime, parent-focused programs for high-risk individuals might have a more important role in increasing education and awareness of eating disorders and catching emerging symptoms.

In fact, leveraging parents as the earliest detectors of eating disorders among children and adolescents may require involving them more heavily in prevention efforts for selective *and* universal audiences. Programs could draw on multiple bodies of literature:

1. Cross-sectional studies describing family factors that contribute to eating disorder risk such as weight-based criticism and weight loss encouragement (Gillison et al. 2016).
2. Cross-sectional and longitudinal research on family protective factors such as weight-neutral encouragement of healthy lifestyle and positive family communication (Gillison et al. 2016) and frequent family meals (Langdon-Daly and Serpell 2017).

3. Research on longitudinal individual risk factors in young people that strongly predict eating disorder onset such as body dissatisfaction and dieting (e.g., Neumark-Sztainer et al. 2011; Stice et al. 2010).

In addition to providing a more protective context for their child's body image development (e.g., by reducing weight-related comments), engaging parents in eating disorders prevention can increase their knowledge of and ability to screen for risk factors. Programs can provide tools for engaging with their child around identified weight, food, and body image concerns (e.g., teach skills for having conversations when concerns arise). Furthermore, programs should include specific information on eating disorders including seeking appropriate help for eating disorder symptoms. Importantly, programs should target the high-risk individuals and families who are underrepresented in current research, including those who are marginalized by dominant cultural appearance norms that overvalue white, cisgender, European features and bodies. One important caveat is that parents' own body image concerns, internalized weight bias, and disordered eating habits may interfere with their ability to provide the ideal supportive context to reduce their child's eating disorder risk. Programs could directly address these individual factors, as well as the structural barriers that influence them (e.g., diet culture, fat phobia).

There is a scarcity of research on parent-led early interventions for the prodromal phase of eating disorder illness. This is unfortunate, since the prodrome may be the optimal phase for early intervention to prevent disorder onset in highly vulnerable individuals. Two-parent programs based on principles of FBT show modest success for treating prodromal anorexia nervosa (Jones et al. 2012; Jacobi et al. 2018; Loeb et al. 2020), paving the way for future research to understand program tailoring and expansion to other eating disorders. This creates additional opportunities to draw from the fields of eating disorder prevention and treatment to create and evaluate brief interventions for varied prodromal symptoms.

Within the early eating disorder phase, parent-based early interventions draw from FBT and focus on supporting caregivers as they begin treatment for anorexia nervosa. For the early phase of other eating disorders, there is insufficient research to make evidence-based recommendations, but research addressing the early disorder experiences of bulimia nervosa, binge eating disorder, and other feeding and eating disorders will help to bridge this gap. Existing caregiver-focused programs are commendable for their transformative impact on healthcare systems, reducing the duration of untreated illness, and increasing access to evidence-based eating disorders care. However, as important as these programs are, they may not be serving the diverse range of individuals who suffer from eating disorders.

In general, research studies that inform the early detection and early intervention domains include a majority of presumed cisgender female participants with white Western European and European-American backgrounds. Future early intervention programs and research should address the diversity within eating disorders experiences, including racial and ethnic diversity, gender diversity, sexual diversity, ability, and more. Research shows that individuals with marginalized racial and ethnic identities are less likely to seek out initial eating disorder treatment compared to

those in racial majority groups (i.e., white individuals; Regan et al. 2017). A failure to include an intersectional focus within future studies will continue to limit access to individuals that already experience marginalization and contribute to exclusion, stigma within those communities, and exacerbation of illness. An understanding of unique risk and resilience surrounding body image, disordered eating, and eating disorders for those with intersecting identities will help to tailor early detection efforts and culturally adapt early interventions (Burke et al. 2020). Greater attention to systemic factors (e.g., white supremacy, capitalism, and diet culture) that contribute to body and appearance privilege and inequality will help to situate early eating disorder experiences within these broader forces.

The impact of the COVID-19 pandemic on eating disorder experiences is not fully understood, but some of the pandemic-influenced positive changes to the field (e.g., wide adoption of teletherapy) that have addressed treatment access barriers will hopefully persist for years to come. The eating disorder field can leverage these innovations to create and improve affordable and accessible digital health interventions that address early detection, prevention, and early interventions (Taylor et al. 2020). This includes online programs that parents can use more conveniently to increase their knowledge and skills needed to screen for and support eating disorder symptom recovery and similar programs for other important players in early detection such as schools and primary healthcare providers.

Applications to Other Eating Disorders

Research on the parental role in early detection and early intervention in children and adolescents is limited in its representation of different eating disorder experiences. The majority of research that informs early detection in this age group encompasses a variety of subclinical experiences, coming from general community samples to examine risk factors that predict eating disorder onset of all types (e.g., Stice et al. 2010) or disordered eating that encompasses varied experiences (e.g., McClelland et al. 2020). Once symptom severity worsens and early intervention programming begins, the research narrows. Parent-led risk factor reduction programs target body image disturbance specifically (Corning et al. 2010; Diedrichs et al. 2016). Research on parent interventions for prodromal symptoms of eating disorders in children and adolescents is limited to the anorexia nervosa spectrum (Jacobi et al. 2018; Loeb et al. 2020). Research on supporting parents in treating new eating disorder cases in this age range focuses on adolescent anorexia nervosa (Hodsoll et al. 2017; Philipp et al. 2021; Rosello et al. 2021b; Truttmann et al. 2020). Additional research is needed to explore parent-led interventions for other eating disorder experiences.

Mini Dictionary of Terms

- **Early detection:** Detecting the first possible symptoms of an emerging eating disorder (i.e., noticing changes shortly after they begin).

- **Early intervention:** Initiating interventions as quickly as possible after concerning symptoms emerge (e.g., intervening on persistent risk factors, prodromal symptoms, or new cases of eating disorders).
- **Family-based treatment (FBT):** Evidence-based intervention for child and adolescent eating disorders that utilizes parents and other primary caregivers to reverse eating disorder behaviors and promote the earliest stages of recovery.
- **Risk factor phase:** Period of time where an individual is experiencing one or more risk factors longitudinally associated with eating disorder onset.
- **Prodromal phase:** Period of time where an individual experiences one or several symptoms of a diagnosable eating disorder but does not reach the full clinical threshold.
- **Early disorder phase:** Period of time immediately after an individual crosses the threshold into an eating disorder, with a cluster of symptoms meeting the diagnostic threshold.

Key Facts of Parent-Led Early Detection

- Eating disorders are serious and persistent mental illnesses that often begin in adolescence and early adulthood.
- In children and adolescents, eating disorder recovery is more likely with a shorter duration of illness and a quick uptake of treatment, while recovery is less likely the longer the patient is ill.
- Identifying and intervening on the earliest symptoms of eating disorders will significantly reduce the burden of these illnesses, but there is limited research on early detection and intervention tools.
- Early detection refers to noticing the earliest symptoms of eating disorders, and early intervention targets symptoms at the earliest point possible.
- Early detection and early intervention efforts focus on the child and adolescent age range, when risk factors and initial symptoms are likely to develop.
- Given the challenges associated with self-identifying eating disorder symptoms, primary caregivers play an essential role in detecting the earliest symptoms among children and adolescents.
- Redefining the period of early intervention to encompass multiple distinct phases of an eating disorder will help to advance research and clinical interventions. Early detection and associated interventions can include high-risk behaviors and cognitions (e.g., dieting, body dissatisfaction), prodromal symptoms (e.g., severe dieting leading to weight changes, initial bulimic symptoms), and early illness (when symptoms pass the diagnostic threshold in the first episode of the eating disorder).
- Early detection and early interventions targeting the eating disorder prodrome, when the first illness symptoms are emerging, is likely to have the greatest payoff in terms of identifying the individuals most likely to develop clinical eating disorders, but before symptoms become more persistent.

Summary Points

- Across studies, the most consistent finding is that changes in eating patterns such as restrictive dieting commonly precede the onset of an eating disorder *and* are detectable by others for an extended period.
- Increasing education about both typical and concerning experiences surrounding eating, exercise, and body satisfaction is crucial for increasing the success of early detection efforts. This includes education for all in the possible early detection network, including parents, schools, and healthcare communities. Parents may benefit from education about the bulimic and cognitive symptoms of eating disorders in particular, as these can be hidden or more difficult to observe externally.
- Parent support for early identification and early intervention efforts is necessary, including programs and systemic changes to improve the entire early detection and referral network.
- Once concerns are identified, parents and other caregivers may have an important role in carrying out early interventions to reverse the risk factors, early symptoms, or early disorder phase of illness. Interventions targeted to each phase will draw from eating disorders prevention science (particularly from selective and indicated prevention approaches), treatment research, or both. However, the research is quite limited, particularly for parent-led risk factor reduction and interventions on the prodromal phase of illness.
- The majority of research on early intervention falls within child and adolescent anorexia nervosa, likely reflecting the prioritization of this illness due to its high risk of death. However, this leaves ample room for scientific advancement within other eating disorder experiences.
- In general, the existing research to inform early detection and early intervention efforts highlights the experience of girls and young women from white Western European and North American backgrounds.
- Future research should aim to be more inclusive of the eating disorder experiences of diverse individuals, including boys and young men, those with gender-expansive identities, people with marginalized racial and ethnic identities, and those with fat bodies.

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Alexithymia in Eating Disorders: A Narrative Review

17

Cecilia Serena Pace, Stefania Muzi, and Wanda Morganti

Contents

Introduction 314
Types of Alexithymia 315
Impact of Alexithymia Assessment on Research Findings 316
Structure and Rationale of the Current Review 317
Findings from Case-Control Studies 322
Findings in Cohort Studies with Community Samples Showing ED Symptoms 338
Findings from Clinical Samples: Alexithymia Differences According to AN and BN Diagnosis 339
Longitudinal Findings and the Impact of Alexithymia on ED Treatment Outcomes 340
The Longitudinal Variation of Alexithymia: Does It Have an Effect? 341
Therapeutic Implications and Applications 342
Limitations and Future Lines of Research 343
Conclusions 344
Mini-Dictionary of Terms 344
Key Facts of Alexithymia 345
Summary Points 346
References 346

Abstract

This chapter aimed to provide a narrative and critical review of the current knowledge of alexithymia in eating disorders. Results of previous reviews and meta-analyses on the topic have been reviewed and integrated with further studies retrieved through three searches in well-known databases (e.g., SCOPUS, EBSCO). Most of the research confirmed higher levels of alexithymia in all patients diagnosed with an eating disorder than in nonclinical individuals, with no clear differences according to the type of diagnosis (anorexia, bulimia, binge eating disorder, etc.), as well as in healthy individuals showing subthreshold

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eating disorder symptoms. Alexithymia tends to longitudinal stability, and the various influences on treatment outcomes and therapeutic implications are reviewed. In conclusion, alexithymia could be a crucial treatment target to achieve improvements in ED symptomatology, but more research is needed to understand how to develop alexithymia-oriented efficient treatments for ED patients. Limitations and future lines of research are also discussed.

Keywords

Review · Eating disorders · Alexithymia · Anorexia · Bulimia · Orthorexia · Intervention outcomes · Therapy · Case-control study · Longitudinal study · Community sample · Clinical sample · Children and adolescents · Adults

Abbreviations

AN	Anorexia nervosa
APA	American Psychiatric Association
BED	Binge eating disorder
BN	Bulimia nervosa
BVAQ	Bermond-Vorst Alexithymia Questionnaire
CREST	Cognitive Remediation and Emotion Skills Training
DDF	Difficulty describing feelings
DIF	Difficulty identifying feelings
DSM-5	*Diagnostic and Statistical Manual of Mental Disorders*, Fifth Edition
ED	Eating disorder
EDNOS	Eating disorder not otherwise specified
EOT	Externally oriented thinking
OAS	Observer Alexithymia Scale
TAS	Toronto Alexithymia Scale

Introduction

The profound and complex involvement of alexithymia in body-related disorders has been known since the first definition of the construct itself by the psychotherapist Sifneos (1973), who defined the core characteristics of the alexithymia observing similarities in numerous patients with psychosomatic disorders.

According to his observations, some scholars have developed a widespread definition of alexithymia (Taylor et al. 1997), which includes four core characteristics: difficulties in identifying feelings differentiated by bodily sensations, difficulties in finding the words to describe feelings, externally oriented style of thinking focused on material and pragmatic aspects of the experience rather than on the inner life, and a general lack of fantasy. While the centrality of this last aspect is debated despite that it has been recently reassigned (Bagby et al. 2006), decades of research have identified the compresence of the first three characteristics in numerous clinical and nonclinical populations (Muzi 2020; Salminen et al. 1999), including both

individuals diagnosed with eating disorders (EDs) and those showing subthreshold symptoms of ED (Nowakowski et al. 2013).

Nonetheless, before deepening the substantial investigation linking alexithymia to eating disorders, some clarifications on the multiple definitions of alexithymia and methods of assessment may help a reader to better evaluate the research findings here summarized.

Types of Alexithymia

Given conspicuous literature establishes the higher alexithymia as a factor of vulnerability for an individual's physical and mental health (Hemming et al. 2019; Lumley et al. 1996), professionals and researchers in different fields have worked to better specify its definition and increase clinical usefulness (Goerlich 2018).

For instance, it is now possible to distinguish alexithymia based on its supposed etiology (Messina et al. 2014), distinguishing organic, primary, and secondary alexithymia. Specifically, organic alexithymia is due to innate or congenital malformations or damages in the structures of the brain used to process emotions independent of the individual's life experience. Instead, primary alexithymia is deemed as a consequence of dysfunctional or traumatic early interpersonal relationships with primary caregivers, for which a child is hindered in the interpersonal acquisition of the rudiments of emotional awareness and regulation necessary for autonomous emotional management, which could manifest as alexithymia later in development (Taylor et al. 1997). Lastly, the secondary alexithymia would occur later in the development, as a consequence of brain damages due to accidents or medical surgery, so that the cause is organic but due to a life experience and not innate (Messina et al. 2014). This distinction has been proved to be useful in forecasting treatment outcomes, e.g., the longer but less complex intervention on organic alexithymia than on primary one (Messina et al. 2014), as well as in understanding which type of alexithymia could more negatively affect individuals' health and well-being.

Moreover, scholars debated whether alexithymia can be considered as a stable trait of personality or a state able to change during development (Martínez-Sánchez et al. 2003). In the first perspective, alexithymia is considered as a trait existing or not existing in individuals, allowing categorical classifications for which beyond a certain level one is considered alexithymic. Following this perspective, researchers have proposed a cutoff score defining clinically relevant levels of alexithymia at the self-rating scale Toronto Alexithymia Scale (TAS; Bagby et al., 1994) in its multiple versions, i.e., TAS-R, TAS-20, and TAS-26. On the other side, proponents of the second perspective suggest that alexithymia can vary throughout the life cycle, for example, changing from adolescence to adulthood, or in response to a specific condition – i.e., increasing during the lockdown (Pace et al. 2022, under review) or decreasing following a psychotherapeutic intervention – and its levels should be measured on a continuum (da Silva et al. 2018; Muzi 2020).

Impact of Alexithymia Assessment on Research Findings

Although the abovementioned two perspectives can coexist and can be seen as complementary, this debate continues to influence both the choice and the development of alexithymia assessment tools (for a comprehensive review, see Bermond et al. 2015). When alexithymia is considered a stable trait of personality, it is possible to categorize individuals as alexithymic or not based on cutoff scores (so far defined only for the TAS), and the evaluation of children and adolescents would be discouraged as their personality is still under construction and not stably defined. Conversely, considering the alexithymia a state, changing during the development and present in a continuum among individuals, the assessment would be performed also in minors but exclusively with tools providing a continuous score of alexithymia, which are the majority.

Briefly, tools to assess alexithymia pertain to three main methodological approaches: self-rating scales, observation scales, and projection scales (reviewed in Bermond et al. 2015). Self-rating scales include all questionnaires and scales where the individual is asked to self-evaluate his/her alexithymia by agreeing with a list of sentences describing dimensions of alexithymia. The level of agreement expressed for each sentence corresponds to a score (depending on the scoring system of the tool), of which the sum or the mean provides a total score of alexithymia. The most used tool to assess alexithymia, the questionnaire TAS, falls into this methodology. Its last version is the TAS-20, where the person is asked to agree to a set of 20 sentences aiming to cover 3 main dimensions of alexithymia, difficulty to identifying feelings (DIF), difficulty in describing feelings (DDF), and externally oriented thinking (EOT), each one with a dimension score. The sum of the scores in the three dimensions is the total score, which expresses the level of alexithymia self-evaluated by the person. Another pretty used self-rating questionnaire is the 40-item Bermond-Vorst Alexithymia Questionnaire (BVAQ; Vorst and Bermond 2001), which contains 40 sentences aiming to capture 2 dimensions of alexithymia, the cognitive factor and the affective factor, of which score results by the combination of factor analyses in 5 subdimensions (inability to differentiate between emotions, inability to verbalize emotions, inability to analyze emotions, inability to fantasize, and inability to experience emotions). The BVAQ does not provide a total score of alexithymia, and maybe it is less used than the TAS-20 because it is longer to administrate and the scoring system may be perceived as sophisticated.

Self-rating scales are quick and economic, but the goodness of the result is completely due to the ability of the items to describe the various facets of alexithymia and to their clear understanding by the self-evaluating individual. Moreover, some authors consider it paradoxical to self-evaluate one's ability to describe emotions to others (Bagby et al. 2006).

These authors claim that this problem can be overcome by using the second approach, the observer-rating scales. These scales can also contain a set of items or checklist that an external rater filled based on his/her knowledge of the evaluated person, retrieved with clinical observation or through interviews or observation procedures. An example of a tool within this approach is the Observation

Alexithymia Scale (OAS; Haviland et al. 2000), where an external observer (a parent, a clinician, a teacher) fills a questionnaire to rate the alexithymia of another person, rating five subdimensions (distant, somatizing, uninsightful, humorless, and rigid) summed in a total score of alexithymia. Another example is the Toronto Structured Interview for Alexithymia (TSIA; Bagby et al. 2006), a 45-min interview of 24 questions, administered and rated by trained professionals. Based on the TAS-20, the professionals ask questions covering the dimensions of DIF, DDF, EOT, and lack of fantasy, assigning a score of 0–2 based on their evaluation of the interviewer's responses. The interview provides scores for each dimension, grouped two by two in the macro-dimensions of affective awareness and operative thinking and summed in a total score. Observer-rating scales are deemed more accurate, but the results can be distorted by the rater judgment and preparation, and the tools in this approach are usually expensive with a longer procedure of scoring.

The limits due to biases and judgment of the rater could be overcome with the application of projection scales, where ambiguous stimuli (usual drawings) are shown to the person, who describe what he/she sees or answer questions. The Rorschach Alexithymia Scale (Porcelli and Mihura 2010) seems the unique tool to assess alexithymia, and it consists of a specific coding system applied on the Rorschach test. A limit of this approach is to require time and training for administration and scoring.

All these approaches can be combined or independently valid depending on the purposes of the assessment, but the majority of research employ self-rating scales, probably because they are faster and more used, facilitating the comparability of results of different studies and a fast screening in certain settings, e.g., medical. Specifically, the most used is the TAS-20, maybe because it is the only tool for which cutoff scores have been defined, allowing to classify the individuals based on the total score as not alexithymic (total score under 51), moderately alexithymic (between 51 and 60), or alexithymic (total score 61 or more), meanwhile providing scores global and in subdimensions.

Structure and Rationale of the Current Review

The current narrative review reports the main findings on alexithymia and eating disorders, summarizing findings of previous reviews on the topic (Gramaglia et al. 2020; Nowakowski et al. 2013; Pinna et al. 2015; Westwood et al. 2017, summarized in Table 1), and integrating their gaps in terms of time laps (2013–2021 in Nowakowski et al. 2013) or alexithymia measurement as, for the first time, not only studies with the TAS-20 or TAS-26 but also studies employing other measures have been reviewed (see filters in Fig. 1 for a panoramic of measures of alexithymia considered in the search strategy and all databases checked).

This review includes studies with individuals with diagnoses or symptoms for all eating disorders as defined in the DSM-5 (APA, 2013), especially those with AN and BN diagnosis/symptoms, considering the ongoing systematic reviews on similar topics recorded on PROSPERO (e.g., Koutoufa et al. 2019; Nelson 2019).

Table 1 Synthesis of the previous reviews and meta-analyses on alexithymia in eating disorders

Author	Year	Type	Title	# Studies	Main results
Nowakowski et al. (2013)	2013	Critical review	Alexithymia and eating disorders: a critical review of the literature	59	• ED patients are more categorized as alexithymic compared to the community sample • ED patients reported higher total alexithymia scores and higher scores in two factors of the TAS-20: DDF and DIF • In nonclinical samples, ED behaviors are associated with DIF and DDF higher scores • Mixed results were found for the hypothesis of a mediation role of general distress/ depression/anxiety over the relationship between alexithymia and ED • AN appeared to have higher alexithymia levels, especially in expressing emotions, than BN • BED patients, similarly to AN and BN, reported higher levels of alexithymia • Alexithymia and depression were influenced negatively by childhood maltreatment, and both could lead to an increased risk to develop an ED

(continued)

Table 1 (continued)

Author	Year	Type	Title	# Studies	Main results
					• After psychological treatment, alexithymia scores decreased. However, in ED sample the level remained clinically significant and different from the control
Pinna et al. (2015)	2015	Systematic review	Alexithymia in eating disorders: therapeutic implications	15	• The results from the longitudinal studies here analyzed are mixed. Some of them reported no association between TAS score and outcome variables or dropout, while others found a prediction role of alexithymic level over outcomes, especially for the DIF subscale, and a relation between dropout and TAS scores • Cross-sectional studies highlighted how ED patients had higher alexithymia scores than community samples • People with high levels of alexithymia tended to receive more treatments than non-alexithymic patients

(continued)

Table 1 (continued)

Author	Year	Type	Title	# Studies	Main results
					• Referring to the effect of ED treatment on alexithymia, the studies reviewed reported conflicting results: some highlighted improvement in alexithymic levels, some reported no change, and others showed a reduction in TAS score that remained clinically significant • Significant differences in TAS score with large effect sizes between ED and community sample, except for BED which reported medium effect sizes
Westwood et al. (2017)	2017	Systematic review and meta-analysis	Alexithymia in eating disorders: systematic review and meta-analyses of studies using the Toronto Alexithymia Scale	48 for the qualitative synthesis and 44 for the meta-analysis	• They found a publication bias in all the diagnostic groups • Age appeared to be positively associated with an effect size of clinical outcome in AN and BN • In AN studies, differences in BMI influenced the differences in alexithymia, enlarging effect sizes. Therefore, the BMI could be implied in the relationships between anorexia

(continued)

Table 1 (continued)

Author	Year	Type	Title	# Studies	Main results
					and alexithymia, but the effect of the latter on symptoms remains significant even if the BMI is controlled • Depression and anxiety in some studies were considered confounding variables and modified the relationship between TAS and ED • There is a paucity of studies involving BED patients • The agreement between TAS and other alexithymia measurements is still debated, as one study found differences in the results from TAS and TSIA
Gramaglia et al. (2020)	2020	Systematic review	Alexithymia and treatment outcome in anorexia nervosa: a scoping review of the literature	10	• The treatments presented in the review are CREST, group psycho-pedagogic method, group cognitive-behavioral therapy, a three-phase treatment program composed of various approaches, and group therapy that combined cognitive-behavioral and a dynamic approach

(continued)

Table 1 (continued)

Author	Year	Type	Title	# Studies	Main results
					• Alexithymia in the studies reviewed tended to remain high after treatment even if other outcomes improved (e.g., ED symptoms) • The improvement in TAS scores after treatment is still debated as CREST (only in individual format), a mixed approach including different types of treatment and a psycho-pedagogic intervention led to a decrease in TAS score, while other studies didn't arrive at the same conclusion

Table 2 details the studies included in the current review. First, results from case-control studies which compared alexithymia in ED clinical and nonclinical samples are presented. Then, studies on nonclinical populations are illustrated, to have a frame of connections in low-risk samples, useful for prevention purposes. Further, alexithymia is investigated in clinical samples, with a special focusing on the diagnoses of anorexia and bulimia. Lastly, findings from longitudinal studies and concerning alexithymia-related therapeutic outcomes and implications are reported, together with critical reflections about limits and gaps of the current knowledge.

Findings from Case-Control Studies

The comprehensive critical review by Nowakowski et al. (2013) concluded that individuals diagnosed with EDs of all types show significantly higher scores of alexithymia than nonclinical participants. More specifically, Nowakowski et al. (2013) suggested that ED patients scored higher than controls in DIF and DDF alexithymia dimensions, but not in EOT one.

Filter #1	eating disorders or anorexia or bulimia or disordered eating or orthorexia or purging or "night eating syndrome" or "Avoidant/Restrictive Food Intake Disorder" or "Unspecified Feeding disorder "or "Unspecified Eating Disorder" or "Other specified eating disorder" or "other specified feeding disorder" or "rumination disorder" or pica AND "PAQ" or "Questionnaire to Assess Alexithymia for Adolescents" or "Alexithymia Questionnaire for Children" or "Toronto Structured Interview for Alexithymia" or "TSIA" or "Rorschach Alexithymia Scale" or "Observer Alexithymia Scale" or "Bermond-Vorst Alexithymia Questionnaire" or "BVAQ" or "BIQ" or "Beth Israel Hospital Psychosomatic Questionnaire" or "DCPR-A"							
Database	PsycInfo	PsycArticles	Pubmed	WOS	Scopus	Proquest	Google Scholar	TOT
Results	16	0	328	15	317	384	23	1083
Selected	8	0	4	0	2	12	3	29
Filter #2	bulimia or disordered eating or orthorexia or purging or "night eating syndrome" or "Avoidant/Restrictive Food Intake Disorder" or "Unspecified Feeding disorder "or "Unspecified Eating Disorder" or "Other specified eating disorder" or "other specified feeding disorder" or "rumination disorder" or pica AND alexithymia or alexithymic or alexithym or alexitimia or "Toronto Alexithymia Scale" or "PAQ" or "Questionnaire to Assess Alexithymia for Adolescents" or "Alexithymia Questionnaire for Children" or "Toronto Structured Interview for Alexithymia" or "TSIA" or "TAS-20" or "Rorschach Alexithymia Scale" or "Observer Alexithymia Scale" or "Bermond-Vorst Alexithymia Questionnaire" or "BVAQ" or "BIQ" or "Beth Israel Hospital Psychosomatic Questionnaire" or "DCPR-A" AND treatment outcomes or efficacy or effectiveness or treatment or intervention or therapy or management or rehabilitation OR therapeutic implications							
Database	PsycInfo	PsycArticles	Pubmed	WOS	Scopus	Proquest	Google Scholar	TOT
Results	113	3	5924	239	>10000	1344	N.A.	>10000
Selected	13	0	11	13	0	9	0	46
Filter #3	anorexia nervosa or anorexia or anorexic or restrictive eating AND alexithymia or alexithymic or alexithym or alexitimia or "Toronto Alexithymia Scale" or "PAQ" or "Questionnaire to Assess Alexithymia for Adolescents" or "Alexithymia Questionnaire for Children" or "Toronto Structured Interview for Alexithymia" or "TSIA" or "TAS-20" or "Rorschach Alexithymia Scale" or "Observer Alexithymia Scale" or "Bermond-Vorst Alexithymia Questionnaire" or "BVAQ" or "BIQ" or "Beth Israel Hospital Psychosomatic Questionnaire" or "DCPR-A" AND treatment outcomes or efficacy or effectiveness or treatment or intervention or therapy or management or rehabilitation OR therapeutic implications							
Database	PsycInfo	PsycArticles	Pubmed	WOS	Scopus	Proquest	Google Scholar	TOT
Results	9	0	56	30	26	N.A.	>10000	>10000
Selected	1	0	2	2	2	0	2	9
Total documents included after screening and duplicates removal: 45								

Fig. 1 Filter and records retrieved for the research on alexithymia in eating disorders. *WOS* Web of Science, *N.A.* not applicable, when the search cannot be performed in the database for technical reasons due to the database. Filter#1 searched studies on alexithymia and ED from 2013 to 2021, also with different tools than the Toronto Alexithymia Scale. Filter#2 searched studies on alexithymia-related treatment outcomes in ED different than anorexia, and Filter#3 updated the alexithymia-related treatment outcomes in anorexia

Westwood et al. (2017) confirmed this conclusion, providing meta-analytic data on 44 high-quality studies with the TAS-20 and TAS-26, that added information about case-control differences based on ED diagnosis, in terms of anorexia nervosa (AN, general and specified as binge-purge and restricting type separately), bulimia nervosa (BN), and binge eating disorder (BED) (Westwood et al. 2017). The mean difference in total higher alexithymia scores with healthy controls showed large

Table 2 Studies included in the current review on alexithymia in eating disorders

Author, year	Sample (size, type)	% Males	Measure of assessment		Main results
			Alexithymia	Eating disorder	
Case-control studies					
Espina (2003)	145, mixed: 73 couples of parents of women with ED (20 AN-R, 23 AN-B, 30 BN), 72 couples of parents of women from the community	0	TAS-20	Diagnosis	• No differences in TAS-20 both total score and subscales among the three ED groups • In fathers: significantly differences between ED and HC in TAS-DIF ($p = 0.014$), in TAS-EOT ($p = 0.001$), and in TAS-total score ($p = 0.002$) • In mothers: significantly differences between ED and HC in TAS-DIF ($p = 0.009$), in TAS-DDF ($p = 0.010$), in TAS-EOT ($p = 0.000$), and in TAS-total score ($p = 0.000$) • The two groups of mothers (ED and HC) differed significantly in alexithymia rates ($p = 0.001$) • Comparing the four groups (ANR, ANB, BN, and HC), there were significant differences in TAS scores both in fathers ($p = 0.041$) and mothers ($p = 0.001$)
Gramaglia et al. (2016)	87, mixed: 39 AN and 48 community	0	TAS-20	Diagnosis	• AN > HC in TAS-DIF ($p < 0.001$), TAS-DDF ($p < 0.001$), and TAS-total score ($p < 0.001$)

Guiducci et al. (2018)	142, mixed: 25 AN, 25 BN, 50 community, 20 parents of EDs (8 fathers), 22 parents of community (10 fathers)	0	TAS-20; OAS	Diagnosis of ED made by a public health service and SCID-I	• TAS-20 total score: EDs > HC ($p < 0.002$) • TAS-20-DIF: EDs > HC ($p < 0.002$) • TAS-20-DDF: EDs > HC ($p < 0.002$) • TAS-20-EOT: EDs > HC ($p < 0.05$) • No significant differences in alexithymia between the two parents' groups using TAS-20 • OAS-total score: EDs > HC ($p < 0.002$; large effect size) • OAS-distant: EDs > HC ($p < 0.002$; large effect size) • OAS-uninsightful: EDs > HC ($p < 0.002$; large effect size) • OAS-somatizing: EDs > HC ($p < 0.002$) (the only one with a medium effect size of 0.58) • OAS-humorless: EDs > HC ($p < 0.002$; large effect size) • OAS-rigid: EDs > HC ($p < 0.002$; large effect size) • Daughters' evaluations of mother: OAS-total score: EDs > HC ($p < 0.05$) • Daughters' evaluations of mother: OAS-distant: EDs > HC ($p < 0.002$)

(continued)

Table 2 (continued)

Author, year	Sample (size, type)	% Males	Measure of assessment		Main results
			Alexithymia	Eating disorder	
					• Daughters' evaluations of mother: OAS-humorless: EDs > HC ($p < 0.002$) • Daughters' evaluations of father: OAS-uninsightful: EDs > HC ($p < 0.05$)
Kerr-Gaffney et al. (2020)	147, mixed: 51 AN, 50 recovered AN, 46 community	7.9 in AN, 2 in recovered AN, 6.5 in community	TAS-20	EDE-Q	• TAS-20-total score: ANs > recovered ANs > HC
Marchiol et al. (2020)	121, mixed: 93 ED (34 AN, 30 BN, and 29 BED) and 28 community	0	TAS-20	EDI-2	• TAS-DIF scores were significantly different among every clinical group and the HC group (AN $p = 0.0001$, BN $p = 0.001$, BED $p = 0.01$) • TAS-DDF scores were significantly different only between AN and HC ($p = 0.05$) • TAS-EOT scores presented no differences among groups • TAS-total scores were significantly different among every clinical group and the HC group (AN $p = 0.01$, BN $p = 0.01$, BED $p = 0.05$)
Nalbant et al. (2019)	64, mixed: 32 AN and 32 community	0	TAS-20	EAT-40	• TAS-20 total score: ANs > HCs ($p < 0.005$) • TAS-20-DIF: ANs > HCs ($p < 0.005$)

					• TAS-20-DDF: ANs > HCs ($p < 0.005$) • TAS-20-EOT: n.s.
Pace et al. (2015)	93, mixed: 45 mothers of ED patients (23 AN and 22 BN) and 48 mothers of women without clinical symptoms	0	TAS-20; OAS	SCID-I	• No differences between the two mothers' groups in both the TAS-total score and the subscales • Daughters' reports of alexithymic levels in mothers showed some significant differences in OAS-total score (ED > non-ED, $p = 0.01$), distant (ED > non-ED, $p = 0.00$), humorless (ED > non-ED, $p = 0.01$)
Pace et al. (2021)	44, mixed: 22 BED and 22 community	0	TAS-20	BES	• No differences in alexithymia levels between the clinical and the control group
Redondo and Luyten (2020)	361, mixed: 38 AN and 323 community	0	TAS-20	EAT-26	• Alexithymia was positively associated with ED symptoms • TAS-20-DIF fully mediated the relationship between attachment insecurity and all the ED subscales
Rozenstein et al. (2018)	60 dyads, mixed: 27 dyads (mothers and daughters with normal-weight binge-purge eating disorder or EDNOS binge-purge type) and 33 dyads from community	0	TAS-20	Diagnosis made to be hospitalized in the eating disorder department in the Sheba Medical Center	• TAS-total score: daughters with diagnosis > control ($p < 0.01$) • TAS-DIF: daughters with diagnosis > control ($p < 0.01$) • TAS-DDF: daughters with diagnosis > control ($p < 0.01$) • TAS-total score and subscales, no differences between the two mothers' groups

(continued)

Table 2 (continued)

Author, year	Sample (size, type)	% Males	Measure of assessment		Main results
			Alexithymia	Eating disorder	
Sfärlea et al. (2019)	86, mixed: 26 AN, 25 MD, 35 community	0	TAS	Diagnosis based on ICD-10	• The two clinical groups didn't differ in alexithymic level, but they differed from the HC group ($p < 0.001$)
Cohort/community studies					
Benau et al. (2020)	279	36.6	TAS-20	EDI-3	• Alexithymia seems to not distinguish between men and women although DIF appeared to be more concerning men and DDF to women
Biolcati et al. (2021)	394	20.8	TAS-20	EAT-26	• Age and alexithymia are not significant predictors of EDs • Among the samples, those who exceed the cutoff score for EDs have significantly higher alexithymia
Boscoe et al. (2021)	544 General population divided in ED and non-ED based on the EAT-26 score	12.3 male and 2.6 other	TAS-20	EAT-26	• The TAS-20 score didn't differ significantly between the ED group and the non-ED group
Casagrande et al. (2020)	111 General population, divided into normal weight and overweight	40.5	TAS-20	EDI-2	• TAS-20 total score: overweight > normal weight ($p = 0.003$) • TAS-20-DIF: overweight > normal weight ($p = 0.004$)

					• TAS-20-EOT: overweight > normal weight ($p = 0.009$)
Doba et al. (2018)	451	0	BVAQ	EDI	• Alexithymia strongly mediates the relationship between a low level of self-differentiation and ED symptoms
Giles et al. (2020)	401	0	TAS-20	EDE-Q	• TAS-20-DIF predicted ED's symptomatology ($\beta = 0.163$; $p = 0.01$)
Goetz et al. (2020)	151	26	TAS-20	EDE-Q	• Alexithymia appeared to play a role in increasing difficulties in modulating emotional and behavioral responses under stress conditions that could lead to ED symptoms
Obeid et al. (2021)	787	32.4	TAS-20	ORTO-R and EAT-26	• A higher level of orthorexia nervosa appeared to correspond higher level of alexithymia ($p < 0.05$) • Alexithymia did not seem a feature of orthorexia per se; other dimensions such as emotion dysregulation have an impact on the disease
Perry and Hayaki (2014)	201	40	TAS-20	BULIT-R	• In both samples, BN symptoms were positively associated with alexithymia (for males $p < 0.001$ and females $p < 0.05$)

(continued)

Table 2 (continued)

Author, year	Sample (size, type)	% Males	Measure of assessment		Main results
			Alexithymia	Eating disorder	
Strodl and Wylie (2020)	332	7.2 and other gender 5.7	TAS-20	TFEQ-R21	• There were no indirect effects between childhood trauma and disordered behaviors through TAS-DIF and TAS-DDF • All eating behaviors displayed significant bivariate correlations with DIF and DDF
Vander Wal et al. (2020)	79	0	TAS-20	EAT-26	• The women who showed higher EAT scores reported higher TAS-20 total score ($p < 0.001$), TAS-DIF ($p < 0.001$), and TAS-DDF ($p < 0.001$) compared to the ones with lower EAT score • Controlling for depression (DASS-21-D), the differences between the two groups remained statistically significant only for the TAS-total score ($p = 0.038$) and the TAS-DIF ($p = 0.004$)
Vuillier et al. (2020)	121	16.5	TAS-20	EAT-26	• Alexithymia had a full mediation effect in the relationship between autistic traits and eating psychopathology, accounting for the 18% of the effect of autistic traits on eating psychopathology
Wheeler et al. (2005)		0	TAS-20; APRQ	EHC	• Binge eating was significantly correlated with TAS-DIF ($p < 0.001$) and TAS-DDF

					($p < 0.01$) • The two alexithymia measures were weakly correlated
Clinical studies					
Abbate-Daga et al. (2013)	108: 76 AN-R and 32 AN-BP	0	Structured interview for DPCR	EDI-2	• Alexithymia was present in 54.6% of the total sample and was overrepresented in the AN-BP sample even if the difference between the two subtypes didn't appear to be significant ($p = 0.52$) • The sample was divided into three subgroups based on the severity of psychosomatic symptoms; in this case, alexithymic levels were statistically different ($p = 0.001$) with the "severe psychosomatic group" reporting the higher scores
Balottin et al. (2014)	46: 16 AN adolescents and 30 parents	0	TAS-20 and TSIA	Diagnosis of AN via DSM-IV-TR	• Parents: TSIA scores > TAS-20 scores in total and all the components of alexithymia • Daughters: TSIA total score > TAS-20 total score and TSIA EOT > TAS EOT
Brown et al. (2018)	114: 54 AN-R and 60 BN	6.1	TAS-20	Diagnosis	• No significant differences between the two subgroups in TAS-total score and all TAS subscales
Carrot et al. (2019)	150 patients and their parents	0	BVAQ-B	Short-CIDI, GOAS, EDI-2, EDDS	• BVAQ-B improved from baseline to months 12 and 18 both in the patients and parents in both single and multifamily therapy

(continued)

Table 2 (continued)

Author, year	Sample (size, type)	% Males	Measure of assessment		Main results
			Alexithymia	Eating disorder	
					• EDI-2 and EDDS scores improved from baseline to months 12 and 18 in patients in both single and multifamily therapy
Di Monte et al. (2020)	54	NI	TAS-20; TSIA	Obesity diagnosis with BMI >30	• For the TSIA: both total and all scores except DDF were significantly and positively associated with weight (total $p < 0.001$; DIF $p < 0.001$; EOT $p < 0.5$; IMP $p < 0.05$) • TAS-20 mean scores in the sample were lower than those reported in the general population ($p < 0.01$) • TSIA mean scores in the sample were higher than those reported in the general population ($p < 0.01$)
Guillén et al. (2014)	103: 58 AN, 27 BN, 18 EDNOS	7.8	TAS-20	SCID-P	• No significant differences between AN, BN, and EDNOS in alexithymia prevalence ($p > 0.94$) and TAS-20 mean scores ($p > 0.82$)
Hobson et al. (2020)	96	0	TAS-20	Diagnosis	• The continuous TAS-20 score didn't predict meeting autism criteria, while being above the TAS-20 threshold for alexithymia was predictive of meeting the criteria ($p = .04$)

					• TAS-20 score correlated significantly with the ADOS-SA ($p = 0.031$) • TAS-20 scores predicted scores on social insight measured by ADOS ($p = 0.01$), even when controlling for depression
Keating et al. (2013)	300: 109 AN, 130 BN, and 61 EDNOS	0	TAS-20	Diagnosis	• Alexithymia accounts for the relationship between attachment avoidance and body esteem
Torres et al. (2019)	125	0	TAS-20	IDED-IV	• TAS-DIF and TAS-DDF were strongly correlated ($r = 0.72$) but were two different dimensions • TAS-EOT is a salient component too
Longitudinal studies					
Caslini et al. (2015)	8: 3 AN-R, 2 BN, 3 EDNOS	0	TAS-20	EDI-2	• At the 1-year follow-up evaluation, there was no significant difference between the pre- and post-psychotherapeutic treatment
Castro et al. (2021)	48, mixed: 24 AN and 24 community	0	TAS-20	IDED-IV	• TAS-20 total score: AN > recovered AN ($p < 0.001$) • TAS-20 total score: recovered AN and HC n.s. • TAS-20-DIF: AN > recovered AN ($p < 0.001$); recovered AN > HC ($p < 0.05$) • TAS-20-DDF: AN > recovered AN ($p < 0.001$) • TAS-20-EOT: AN > recovered AN ($p < 0.01$)

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Table 2 (continued)

Author, year	Sample (size, type)	% Males	Measure of assessment		Main results
			Alexithymia	Eating disorder	
					• n.s. differences between recovered AN and HC in TAS-DDF and TAS-EOT
Courty et al. (2015)	60: 52 AN-R and 8 AN-BP	0	TAS-20	EDI	• Higher levels of symptoms remained associated with higher alexithymia over 18 months, even if the strength of the association decreased across time • Higher alexithymia predicted more symptoms during treatment • After 18 months, the mean score on the TAS-20 was still higher than the control populations from the literature • The TAS-20-EOT scores were relatively stable from baseline to 18 months
Glisenti et al. (2018)	6 BED	0	TAS-20	SCID-I; BES; EDEQ	• After emotion-focused therapy, the median posttreatment score ranks were not statistically lower than pretreatment neither for the TAS-20 total score nor for the subscales
Harrison et al. (2020)	12: 3 AN-BP and 9 AN-R	8.33	TAS-20	EDE-Q	• Individual Cognitive Remediation and Emotion Skills Training for Adolescents: TAS-20 total score: before treatment > after treatment ($p = 0.01$; $d = 0.62$)

					• Group Cognitive Remediation and Emotion Skills Training for Adolescents: TAS-20 total score: before treatment > after treatment ($p = 0.01$; $d = 0.65$) • EDE-Q didn't decrease both in individual and group format after treatment
Larsson et al. (2020)	29: 4 AN, 9 BN, 9 atypical AN, 3 atypical BN, and 4 unspecified ED	0	TAS-20	EDE-Q	• After treatment, TAS-20 total score was reduced ($p < 0.001$; $d = 0.75$) • After treatment, EDE-Q total score improved ($p = 0.009$; $d = 0.33$)
Meneguzzo et al. (2021)	100: 53 AN, 36 BN, and 11 BED	0	TAS-20	EDE-Q	• The three groups show different levels of TAS-20 total scores ($p = 0.02$) • Of the 67 patients who completed the treatment, 48 were above the cutoff score for the TAS-20, and 19 were below • The high alexithymic group showed an improvement posttreatment ($p < 0.001$). However in this group, the scores remain clinically significant
Milos et al. (2021)	50: 42 AN-R and 8 AN-BP	N.A.	TAS-20	EDEQ	• Comparing AN with non-restored weight and AN weight-restored, the first group reported a smaller volume in the crus I of the right cerebellum

(continued)

Table 2 (continued)

Author, year	Sample (size, type)	% Males	Measure of assessment		Main results
			Alexithymia	Eating disorder	
					• It appeared that to lower volume in this region, corresponded higher alexithymia scores
Savidaki et al. (2020)	14: 7 to dance movement therapy and 7 in the control group	0	TAS-20	Diagnosis	• The sample who underwent dance movement therapy reported a slight tendency of decrease in TAS-total score and subscales (n.s.). The control group showed a tendency to increase TAS scores (n.s.)
Shank et al. (2019)	200	46	Alexithymia Questionnaire for Children	EDE interview	• Alexithymia was associated with loss of control eating ($p = 0.01$) and with eating-related psychopathology ($p = 0.01$)
Torres et al. (2020)	7	0	TAS-20	IDED-IV and DEBQ	• The major changes after an emotion-focused CBT occurred in the TAS-DIF
Vrieze (2018)	53: 29 AN and 24 BN	0	TAS-20	EDI-3	• TAS-total score: BN > AN ($p = 0.014$) • ANs with the high level of alexithymia and AN with the low level of alexithymia reported differences in posttreatment ED pathology (high alex > low alex; high, M = 44, SD = 8.93; low, M = 30, SD = 2.52) • BNs reported no differences in posttreatment pathology across levels of alexithymia ($p = 0.07$)

NI no information, *AN* anorexia nervosa, *BN* bulimia nervosa, *HC* healthy controls, *TAS-20* Toronto Alexithymia Scale, *OAS* Observer Alexithymia Scale, *SCID-I* Structured Clinical Interview for DSM-IV Axis I Disorders, *EAT-40* Eating Attitudes Test-40, *EDE-Q* Eating Disorder Examination Questionnaire, *EDI-2* Eating Disorder Inventory-2, *BVAQ* Bermond-Vorst Alexithymia Questionnaire, *EDNOS* eating disorders not otherwise specified, *TAS-20-DIF* difficulty identifying feelings, *TAS-20-DDF* difficulty describing feelings, *TAS-20-EOT* externally oriented thinking, *n.s.* not significative, *AN-R* AN restricting subtype, *BITE* Bulimic Investigatory Test, Edinburgh, *AN-BP* AN binge-purge type, *CBT* cognitive-behavioral therapy, *BED* binge eating disorder, *EAT* Eating Attitudes Test, *IDED-IV* Interview for the Diagnosis of Eating Disorders-IV, *DEBQ* Dutch Eating Behavior Questionnaire, *TSIA* Toronto Structured Interview for Alexithymia, *DSM-IV-TR Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition, Text Revision, *Short-CIDI* Composite International Diagnostic Interview-short form, *GOAS* Morgan-Russell Global Assessment Outcome Schedule, *EDDS* Eating Disorder Diagnostic Scale, *PAQ* Perth Alexithymia Questionnaire, *BES* Binge Eating Scale, *DPCR* Diagnostic Criteria for Psychosomatic Research, *IMP* imaginal processes, *ADOS-SA* Social Affect of the Autism Diagnostic Observation Schedule, *EAT-26* Eating Attitudes Test-26, *SCID-P* Structured Clinical Interview for DSM-IV, Patient Edition, *TFEQ-R21* Three-Factor Eating Questionnaire, *EDI-SC* Eating Disorder Inventory-Symptom Checklist, *DSED* Diagnostic Survey for Eating Disorders, *AN-B* anorexia nervosa bulimic subtype, *CGI* Clinical Global Impression, *PSRS* Psychiatric Status Rating Scale, *DASS-21-D* Depression and Anxiety Stress Scale, depression subscale, *MD* major depression, *BULIT-R* Bulimia Test Revised, *APRQ* Alexithymia Provoked Response Questionnaire, *EHC* Eating Habits Checklist, *MINI* Mini-International Neuropsychiatric Interview, *AN-P* anorexia nervosa purging

effect sizes for participants diagnosed with AN (of both types almost equally), $d = 1.44$, or BN, $d = 1.26$. Instead, the comparison including individuals diagnosed with BED revealed a medium effect, $d = 0.76$. Moreover, the mean difference between anorexic participants and controls showed large effect sizes in DIF and DDF dimensions, $d = 1.57$ and $d = 1.11$, and small effect size in the EOT dimension, $d = 0.48$. However, this small difference in EOT scores disappeared in the AN-restrictive-type group, suggesting that it would be present between only in AN purging-type patients and controls, but the paucity of studies reporting dimension scores in this last type of AN patients prevented Westwood et al. (2017) to make the analysis necessary to confirm this hypothesis. Concerning differences between BN patients and controls, large effect sizes for both DIF ($d = 1.58$) and DDF ($d = 0.89$) were found, and no difference on EOT, in line with Nowakowski et al. (2013). Regarding BED patients, only two studies (Aloi et al. 2017; Pinaquy et al. 2003) provide information on differences in subdimensions, so Westwood et al. (2017) were not able to analyze mean differences.

The current search revealed that after Nowakowski et al. (2013), from 2013 to 2021, six case-control studies were published on this topic.

All the studies employing the TAS-20 confirmed the conclusions of the previous reviews, reporting statistically significant higher levels of total alexithymia, DIF, and DDF in ED patients than in nonclinical controls (e.g., Nalbant et al. 2019; Kerr-Gaffney et al. 2020). This case-control difference was also significant when the clinical sample was composed by participants diagnosed with BED and eating disorder not otherwise specified (EDNOS) (Rozenstein et al. 2018) and remained significant even when the ED symptoms and alexithymia of the patients decreased after treatment (Castro et al. 2021). Only one study (Guiducci et al. 2018) used the OAS (Haviland et al. 2000) – fulfilled by ED patients' parents – together with the TAS-20, confirming that girls with ED showed higher levels of alexithymia, DIF, and DDF than nonclinical ones in the TAS-20, as well as in the total score and several subdimension of the OAS.

Findings in Cohort Studies with Community Samples Showing ED Symptoms

Nowakowski et al. (2013) synthesized those nonclinical adolescents and adults showed more eating disorder symptoms (e.g., binge eating attitudes, excessive dietary restriction, or compensative behaviors such as purging or exercise) along with more alexithymia. Specifically, higher scores in DIF and DDF were related to more ED symptoms, while the factor EOT was not, in line with results in case-control studies. The unique exception was for orthorexic behaviors, related to all alexithymia dimensions including the EOT (Obeid et al. 2021).

Findings of further research retrieved for this review mainly confirmed these associations (see Table 1). For example, Benau et al. (2020) found high levels of

alexithymia in athletes showing eating-disordered behaviors and also reported gender differences in terms of more relations with the factor DIF in men and with DDF in women. Biolcati et al. (2021) found higher alexithymia levels in a subgroup of nonclinical adults who surpassed the cutoff score for a clinical risk of EDs, compared to those not at risk.

Moreover, in a study by Casagrande et al. (2020), overweight individuals without ED diagnoses showed higher scores of alexithymia, DIF, and EOT than normal-weight ones.

As exceptions, two studies did not find differences in alexithymia between groups of community adolescents with or without binge eating attitudes (Pace et al. 2021) and adults (Boscoe et al. 2021) at risk for EDs and not at risk, after a cutoff-based screening.

In addition, some studies investigated the predictive role of alexithymia in increasing ED symptoms. Specifically, Giles et al. (2020) found that higher levels of DIF alone predicted 16% more ED symptoms, while other studies found that alexithymia moderated the impact of other conditions, by increasing the vulnerability to ED symptoms in the case of autistic traits (Vuillier et al. 2020), or of women with a history of childhood abuse or neglect (Mazzeo and Espelage 2002), and adolescents showing low self-differentiation (Doba et al. 2018).

Findings from Clinical Samples: Alexithymia Differences According to AN and BN Diagnosis

Nowakowski et al. (2013) concluded that individuals diagnosed with anorexia seemed to show higher alexithymia than those diagnosed with bulimia, and also Westwood et al. (2017) results seem to suggest a difference in alexithymia between AN and BN patients. Indeed, this meta-analysis found case-control differences in all alexithymia subdimensions in anorexic patients compared to nonclinical participants, while bulimic patients did not differ from healthy controls in EOT, although a meta-analytic comparison concerning alexithymia levels between AN and BN patients was not performed up to now.

Moreover, further research here reviewed on this topic report contrasting results. Opposite to Nowakowski et al. (2013)'s hypothesis, Vrieze (2018) reports more alexithymia in bulimic than in anorexic patients and a different impact of alexithymia on treatment outcomes (significant in anorexic patients but not in bulimic ones; see below). Brown et al. (2018) did not find any difference in alexithymia total and subdimensions scores between AN-R and BN patients, and Guillén et al. (2014) also did not find significant differences in prevalence and scores of alexithymia of patients diagnosed for AN, BN, or eating disorders not otherwise specified.

Longitudinal Findings and the Impact of Alexithymia on ED Treatment Outcomes

The findings on the impact of alexithymia on ED treatment outcomes are controversial. On the one side, Nowakowski et al. (2013) reported that different emotion-oriented treatments reduced alexithymia levels of ED patients with different diagnoses, but it was unclear whether the reduction of alexithymia has beneficial effects in reducing ED symptoms. On the other side, a specific systematic review on therapeutic implications of alexithymia in eating disorders (Pinna et al. 2015) concluded that higher alexithymia was related to higher dropout and poorer treatment outcomes in ED patients benefiting from different types of intervention (e.g., group or individual psychotherapy); therefore it could be a crucial treatment target. More in detail, findings from longitudinal studies revealed that higher alexithymia at baseline predicted worse treatment outcomes in patients diagnosed for AN (Speranza et al. 2011), BN, BED, and EDNOS (Balestrieri et al. 2013; Leweke et al. 2009), especially in case of higher scores of DIF and DDF. In particular, in the study covering the longer period (i.e., 3 years), Speranza et al. (2011) found that more alexithymic AN and BN patients were more likely to receive more treatment, antidepressants, and be rehospitalized, regardless of the type of diagnosis. In other studies (Becker-Stoll and Gerlinghoff 2004; de Groot et al. 1995; Schmidt et al. 1993), the alexithymia level at baseline was not influential, but the level of alexithymia during the period of the treatment influenced the outcomes, as less alexithymic patients showed more improvements concerning ED symptoms, that persisted longer posttreatment even if the length and the type of the treatments in these studies were different (multimodal, cognitive-behavioral, psychodynamic, etc.). Moreover, in the studies documenting variation of alexithymia levels during the treatment, the persistence of high levels of alexithymia after treatment negatively influenced the improvements in terms of reduction of ED symptoms, both in adults (Schmidt et al. 1993; Becker-Stoll and Gerlinghoff 2004; Iancu et al. 2006) and in adolescents (Ohmann et al. 2013), the latter also showing higher dropout tendency.

The few studies retrieved in the current review, not included in previously cited reviews, did not seem to solve these controversies.

First, Vrieze (2018) reported countercurrent results, founding more positive posttreatment outcomes in AN patients who showed more alexithymia at baseline, and no differences associated with alexithymia levels in BN patients. Second, examining the efficacy of emotion-focused treatments, contrasting results suggested different associations according to patients' age group. Indeed, Harrison et al. (2020) suggested that the reduction of ED symptoms was independent of alexithymia variations in adolescents, as alexithymia but not ED symptoms decreased after both individual-based and group-based CREST interventions in AN teenagers. Differently, Larsson et al. (2020) found a reduction in both alexithymia and ED symptoms in adult females with different ED diagnoses, treated with a mixed intervention based on Emotion Regulation Group Therapy, Unified Protocol, Dialectical Behavior Therapy, and Acceptance and Commitment Therapy. Similarly, Castro et al. (2020) and Torres et al. (2020) observed a decrease of both ED

symptoms and alexithymia during a treatment. Lastly, Goetz et al. (2020) highlighted an indirect role of alexithymia, which could lead to ED by increasing the difficulties in modulating emotions and behavioral responses under stress conditions, directly related to ED symptoms.

The Longitudinal Variation of Alexithymia: Does It Have an Effect?

From the above, readers can note that several authors have tried to link the results of the treatment for ED to observed longitudinal variations of alexithymia, without reaching consensus. Both in previous reviews and the current research, few studies documenting longitudinal variations of alexithymia were studies on ED treatment outcomes, and none of them aimed to investigate the variation of alexithymia per se.

Specifically, Westwood et al. (2017) detected only one longitudinal study responding to their inclusion criteria (Speranza et al. 2011), which documented a decrease in alexithymia levels of anorexic patients over 3 years. Including all diagnoses of ED, Pinna et al. (2015)'s review found other 11 longitudinal studies (Balestrieri et al. 2013; Becker-Stoll and Gerlinghoff 2004; Ciano et al. 2002; Clyne et al. 2010; de Groot et al. 1995; Iancu et al. 2006; Leweke et al. 2009; Ohmann et al. 2013; Schmidt et al. 1993; Shiina et al. 2005; Storch et al. 2011), for a total of 12 studies up to 2015, all employing the TAS-20. Later, Gramaglia et al. (2020) performed another review on treatment outcomes in AN, including other six studies not included elsewhere (Adamson et al. 2018; Elzakkers et al. 2017; Giombini et al. 2019; Leppanen et al. 2018; Lundbad et al. 2014; Tchanturia et al. 2015).

Despite not being focused on alexithymia variation, the findings of these longitudinal studies led all authors of the cited reviews (Nowakowski et al. 2013; Pinna et al. 2015; Gramaglia et al. 2020) to note that alexithymia levels can decrease after psychological treatment, even if the target of the treatment is ED symptoms. Indeed, with rare exceptions (Ohmann et al. 2013; Schmidt et al. 1993; Shiina et al. 2005), most of these studies found a decrease of alexithymia levels after 9.6 to 40-week intervention of different types, such as individual or group psychotherapy (e.g., CREST), or psychoeducational, or multimodal (e.g., combining cognitive-behavioral and psychodynamic therapeutic approaches with hospitalization).

This alexithymia's decrease has been observed also by three studies retrieved for the current review, both in AN and BED adults (Castro et al. 2021; Torres et al. 2020) and in ED adolescents (Harrison et al. 2020). Torres et al. (2020) also observed a particular reduction in DIF levels among BED patients. However, the other two studies retrieved for the current review suggest the stability of alexithymia in ED patients (Courty et al. 2015; Meneguzzo et al. 2021). Moreover, employing the BVAQ, Courty et al. (2015) report still significantly after-treatment higher levels of alexithymia in AN patients compared to controls, which aligns with a common observation by the authors of the cited reviews that the levels of alexithymia tend to remain high in ED patients, even after a posttreatment reduction (Nowakowski et al. 2013; Pinna et al. 2015; Gramaglia et al. 2020).

Altogether, literature results suggest that alexithymia is not a completely stable personality trait, but is nonetheless highly resistant to change in adult ED populations. This calls for specific and well-directed efforts to reduce alexithymia in ED patients, considering the additional obstacle posed by the heterogeneity of treatments leading to an alexithymia reduction, which makes it difficult to isolate the more efficient for this goal.

Therapeutic Implications and Applications

Speranza et al. (2011) explored the role of alexithymia in predicting AN and BN patients treatment options, documenting that when alexithymia is high at baseline, the patient is more likely to receive more and constant treatment of all types (psychological, pharmacological, hospitalization), while patients showing alexithymia only posttreatment are more likely to be hospitalized, recurring to psychotherapy irregularly. This suggests that considering the alexithymia profile of ED patients can help to forecast what and how frequently they will require treatment. For this purpose, a mixed-method approach or at least observed-rating measures like the OAS or the TSIA (Bagby et al. 2006) would be preferable to self-rating scales such as TAS when alexithymia is assessed in ED patients, in agreement with Westwood et al. (2017) comments. Indeed, these methods would allow controlling effects of social desirability and comorbid conditions of depression and anxiety, which are suggested as influential in some studies (Eizaguirre et al. 2004; Gilboa-Schechtman et al. 2006; Giles et al. 2020).

Moreover, a proper suggestion for professionals working in the eating disorders field would be focusing on evaluation and intervention on the dimensions of difficulty in identifying feelings (distinguishing them from bodily sensations) and describing them verbally more than on the dimension of externally oriented thinking, which does not appear crucial in ED patients (Müller et al. 2003). Besides, particularly in AN patients, these two crucial dimensions DIF and DDF may show different mechanisms of action (Torres et al. 2019), suggesting their separate evaluation in case of anorexia.

Further, Gramaglia et al. (2020) found individual rather than group conditions as beneficial, whereas a professional would employ the CREST treatment. Besides, regardless of the individual or group condition, Harrison et al.'s (2020) results may suggest considering also the patient's age group when an alexithymia-oriented intervention would be designed. When the ED patient is an adolescent, the intervention of the patient's alexithymia alone may not be enough, and the family should be involved as well. Indeed, different studies documented higher levels of alexithymia in parents of anorexic girls (Balottin et al. 2014; Guiducci et al. 2018; Pace et al. 2015), with Carrot et al. (2019) documenting significant reductions of alexithymia in both parents and anorexic daughters in case of family therapy, and Duclos et al. (2014) report beneficial effects of the involvement of parents (particularly of the father) in intervention on anorexic daughter's symptoms reduction.

Limitations and Future Lines of Research

The meta-analysis by Westwood et al. (2017) has highlighted that differences in alexithymia scores between AN patients and controls are more marked in acute stages of the anorexic disorder course and at older ages when patients are deemed to have suffered from anorexia for longer or would have more likely shown comorbidities (e.g., of depression, obesity). Given later studies confirmed these observations (Castro et al. 2021; Torres et al. 2019, 2020), this calls for future research to understand if an alexithymia treatment may be more or less beneficial in these specific conditions, especially because certain types of treatment accounted for heterogeneity in alexithymia among ED patients across studies in Westwood et al. (2017). Further, the effects of alexithymia in EDs can be moderated by other factors, such as depression, anxiety, attachment (Pace et al. 2021), perfectionism (Ruggiero et al. 2011), as well as certain parental characteristics, firstly the parental levels of alexithymia, and attachment states of mind (Balottin et al. 2014; Pace et al. 2015).

Another point deserving more investigation concerns the consequences of treatment of alexithymia on ED symptomatology. Most interventions tested (e.g., Becker-Stoll and Gerlinghoff 2004) showed efficacy in decreasing the levels of alexithymia, but the consequences of such decrease on EDs are not clearly defined, and they should be tested in the future follow-up or other longitudinal studies. Moreover, Beadle et al. (2013) report that alexithymia of AN patients decreased as weight increased during the treatment, suggesting that there is not a single direction in which alexithymia affects ED symptoms, but also the opposite, and this should be further investigated in its implications. In this regard, more research on specific alexithymia-oriented interventions should be tested on ED patients or in the case of subclinical symptoms, maybe considering also family dimensions or intervention, e.g., on parental alexithymia (Pace et al. 2015), as well as setting-related variables such as the therapeutic alliance (Sarracino et al. 2013).

Moreover, not surprisingly clinical studies involved almost exclusively females, with rare exceptions (e.g., Harrison et al. 2020; Leweke et al. 2009; Shiina et al. 2005), but especially research on nonclinical samples would improve efforts to involve males, as useful to underline mechanisms of risk and onset and eventual gender features that protect males from both EDs and alexithymia impact on them. This would be particularly preventive from an intergenerational point of view, given the father's role in anorexic daughter's symptoms (Duclos et al. 2014).

Another critical consideration regards the almost exclusive use of the TAS among studies. Despite that this instrument well operationalized the current shared definition of the multidimensional construct of alexithymia, many authors raised doubts on its content and discriminant validity (e.g., with anxiety and depression; Honkalampi et al. 2010; Deno et al. 2011) and its efficiency regardless of the level of psychological distress (Marchesi et al. 2014; Preece et al. 2020). Even beyond the methodological limits, if the research is done entirely with the same tool, the possibility of finding discordant ones is reduced, on which much of scientific progress is based. Many questions raised by this and other reviews could be enriched by future research

employing a broader range of assessment methods for alexithymia, such as the mentioned OAS, B-VAQ, and TSIA or the Perth Alexithymia Questionnaire (Preece et al., 2018) and the Alexithymia Questionnaire for Children (Rieffe et al. 2006; Di Trani et al. 2009) for children and adolescents. Also, Balottin et al. (2014) found discordant results in AN adolescents and parents employing the TAS-20 and the TSIA, suggesting a mixed-method approach as fruitful to achieve nuanced and fruitful results.

Lastly, as a common practice, only documents in English have been screened in the current and cited reviews, neglecting studies written in other languages, which may have included suggestions to dispel remaining doubts.

Conclusions

Although many fruitful efforts have been made to prove the high alexithymia in ED patients or at-risk non-diagnosed, this review has revealed that there are still many points to be clarified. Specifically, eventual differences in alexithymia according to ED diagnoses and the direct or indirect impact of alexithymia on treatment outcomes are still unclear, so that it is it seems premature to confirm that an alexithymia-oriented intervention may be beneficial for reducing ED symptoms, despite some promising results. Lastly, further efforts are needed to clarify the influence of gender, age, and other moderators on the relationship between alexithymia and eating-disordered behaviors.

Mini-Dictionary of Terms

- **Primary alexithymia**. Type of alexithymia that occurs during the development, due to adverse experiences and failures in the primary relationships with caregivers. For a child, the bodily sensations (e.g., hunger) and the different emotions are undifferentiated, and they are all potentially fearful because he/she does not understand or differentiate them. In the beginning, the caregiver discriminates and names the different physiological and emotional states for the child, reducing the child's fear associated with them during daily dyadic interactions. If this interpersonal process works, the child will later be able to do it on his/her own. If this process fails, bodily and emotional states remain undifferentiated and a source of fear for the child, who is more likely to show more alexithymia later.
- **Organic alexithymia**. Type of alexithymia due to organic causes, such as damages in brain areas involving in emotional processing (i.e., anterior cingulate cortex, corpus callosum, basal ganglia, and right hemisphere).
- **Secondary alexithymia.** Type of alexithymia consequence of an illness, or surgery, or medical conditions (e.g., decreased oxygen tension) which have effects on brain functioning and emotional processing.

- **Narrative review.** Type of literature review including a critical, objective, and comprehensive analysis of the existing knowledge on a topic. It is particularly helpful to identify current trends, gaps, or incongruences in the literature through an objective critic of limitations and possible future directions of research.
- **Systematic review.** Rigorous type of literature review, aiming to examine all the existing literature around a clearly defined research question. It aims to synthesize the current knowledge highlighting commonalities among studies. The process of literature search, screening, exclusion, and analysis are rigorously documented.
- **Meta-analysis.** An optional part of a systematic review is a secondary research tool aiming to statistically summarize data from different studies on the same topic.
- **Case-control study.** An observational study that compares on a defined outcome two groups differing on a supposed causal attribution (e.g., clinical versus healthy individuals).
- **Longitudinal study.** A study where one or more variables is/are observed over an extended period in the same group of participants.
- **Cohort study.** A form of longitudinal study where it sampled a group of people sharing a certain characteristic, i.e., a cohort, to collect data on them at different time intervals.

Key Facts of Alexithymia

- At least 10% of nonclinical adults show high levels of alexithymia and more than 20% of adolescents. This percentage grows in clinical and at-risk samples (e.g., it ranges the 38 and the 85% in institutionalized adolescents).
- There are gender differences in alexithymia, and usually, females appear more alexithymic, showing more difficulty in identifying and describing feelings. Males usually show more externally oriented thinking.
- The alexithymic dimensions of difficulty in identifying feelings and difficulty in describing feelings seem to be higher in teenagers. As teenagers get older, these dimensions tend to decrease, becoming more stable around the 30 years of age.
- Alexithymia appeared to be a transdiagnostic risk factor for a conspicuous number of health problems, such as diabetes, somatoform diseases, depression, suicidality, and anxiety.
- Alexithymia could be considered as a trait, being developmental and emerging during childhood or early adult years (primary alexithymia), or as a state, emerging at any time in life after a stressful situation or trauma (secondary alexithymia).
- Although many types of psychotherapy could help an individual to improve emotional awareness, decreasing alexithymia, specifically alexithymia-oriented treatments are still lacking.

Summary Points

- Patients diagnosed with an eating disorder (of all types) show higher levels of alexithymia compared to healthy controls without a diagnosis.
- The existence of differences in alexithymia between ED patients with different diagnoses is still not clear.
- Longitudinal studies found a decrease of alexithymia after psychological treatment, without identifying one more efficient than others for this scope.
- Findings on the impact of alexithymia on outcomes of treatments to reduce eating disorder symptoms are controversial. Few studies investigate the predictive role of alexithymia on ED treatment outcomes, with contrasting findings.
- The investigation of the connections between alexithymia and eating disorder should be implemented, particularly involving males from the community population for preventive utility.

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Eating Disorder and Quality of Life

18

Jelena Milic, Dunja Stankic, and Dona Stefanovic

Contents

Introduction 354
General Characteristics of EDs 356
Comorbidities of ED 358
Relationship Between QoL and ED 358
Relationship Between System of Organs and EDs 359
Dynamics of ED and QoL 360
Considerations for Targeted Interventions for QoL in the Treatment of Patients with EDs ... 361
Conclusion 363
Mini Dictionary of Terms 363
Key Facts of Eating Disorders and Quality of Life 363
Summary Points 364
References 364

Abstract

Previously published evidence assess the Quality of Life (QoL) in people with eating disorders (EDs). In past decade with increasing interest in healthy aging, vegan and vegetarian food diets, as well as increased awareness of autoimmune protocol in eating, this has been subject to considerable research interest. The World Health Organization defines QoL as "an individual's perception of their

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position in life in the context of the culture and value system in which they live and in relation to their goals, expectations, standards and concerns." It is a multidisciplinary construct that includes perceptions about various aspects of life, including physical, psychological, social, and emotional domains.

QoL measures are beginning to be recognized as a key patient-oriented measure of outcome. As previously observed, studies in EDs have indicated significantly reduced QoL in this patient group, to a degree that is comparable with QoL findings in various other serious illnesses and disorders, such as angina and anxiety disorders. What is highly noticeable from the published evidence is that mental health of the individuals with EDs seems to be particularly impaired.

It remains unclear how specific symptoms and behaviors associated with EDs impact on QoL and further discussions are needed.

Keywords

Eating disorders · Quality of life · Health-related quality of life · Anorexia nervosa · Bulimia nervosa · Psychiatric illness · Mental health · Malnutrition · Hormonal disbalance

Abbreviations

AN	anorexia nervosa
ARFID	avoidant/restrictive food intake disorder
BED	binge eating disorder
BM	bulimia nervosa
ED	eating disorder
OSFED	other specified feeding and eating disorders
QoL	quality of life
UFED	unspecified feeding or eating disorder

Introduction

Eating disorders (EDs) present a type of serious mental health conditions that are divided into several categories. These categories include anorexia nervosa (AN) (Fig. 1), bulimia nervosa (BN) (Fig. 2), binge eating disorder (BED) (Fig. 3), and other specified feeding and eating disorders (OSFED) (Fig. 4). To the previously mentioned four EDs, two more should be added, which are attracting particular attention nowadays – avoidant/restrictive food intake disorder (ARFID) and unspecified feeding or eating disorder (UFED). This category of disorders is known by its serious and persistent problems in eating accompanied by disturbing thoughts and emotions. Early signs of an ED can also be behavioral, physical, or psychological. People who suffer from some form of ED usually eat restrictively, avoid certain foods, overeat, purify themselves by vomiting, abuse laxatives, or exercise compulsively. It is important to underline that there are very frequent variations in body weight, fatigue, and poor concentration, as well as the lack of

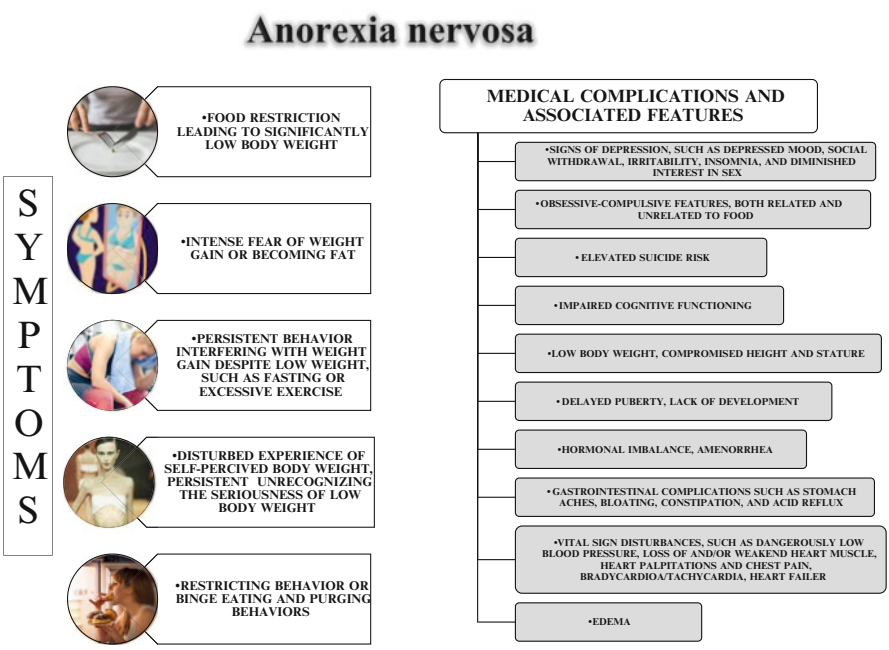


Fig. 1 Anorexia Nervosa: Symptoms and medical complications and associated features

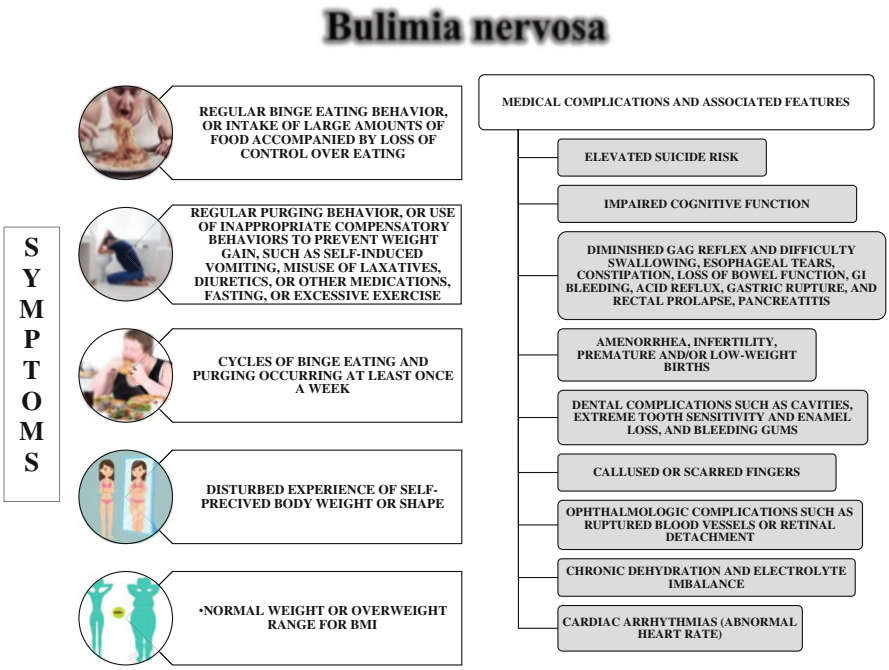


Fig. 2 Bulimia Nervosa: Symptoms and medical complications and associated features

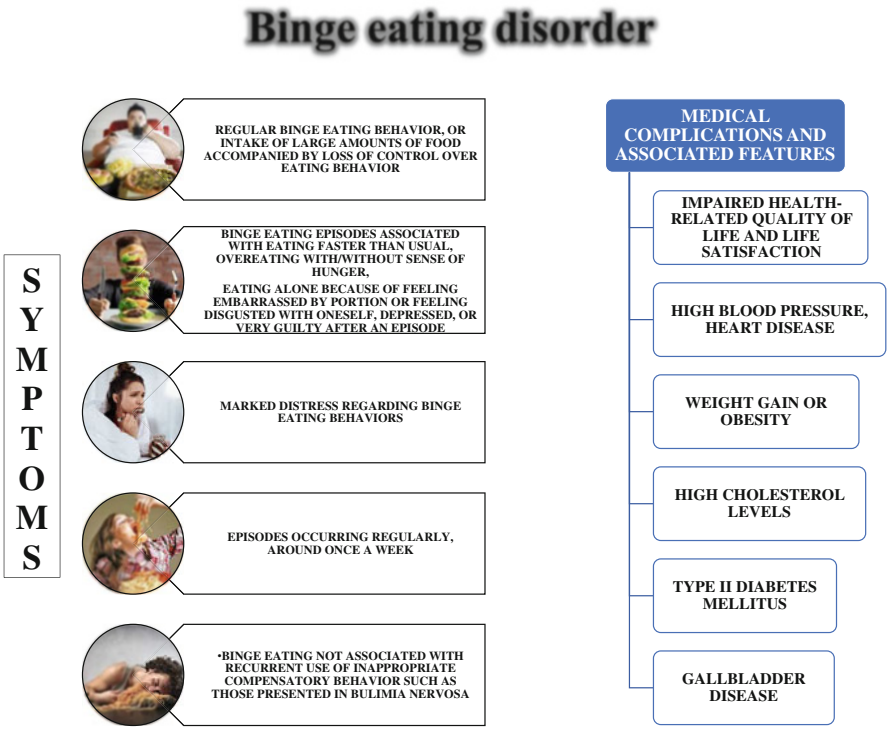


Fig. 3 Binge eating disorder: Symptoms and medical complications and associated features

energy to perform normal daily duties. The mentioned behaviors are manifested and repeated on a daily basis and that is why it even belongs to some kind of addiction (Walsh et al. 2020).

General Characteristics of EDs

It is often overlooked that EDs are actually very serious and potentially fatal diseases. When a person is preoccupied with food, their own weight, appearance, and body shape, it should arouse our suspicion that this may be the very beginning of this disorder (Treasure et al. 2010).

Globally, 5% of the population is affected by some form of ED. At first glance, it seems like a small number, but it is mostly harming young people, more precisely teenagers and adolescents who are already vulnerable due to increased maturing process. The estimations indicate that about several million people suffer from an ED at any given time. EDs can occur at any time of life and affect both men and women. However, they occur with a higher frequency in the female population between the ages of 12 and 35. In fact, it is anticipated that the number of people with ED is growing day by day for several reasons. EDs are a response to stress most often, so it

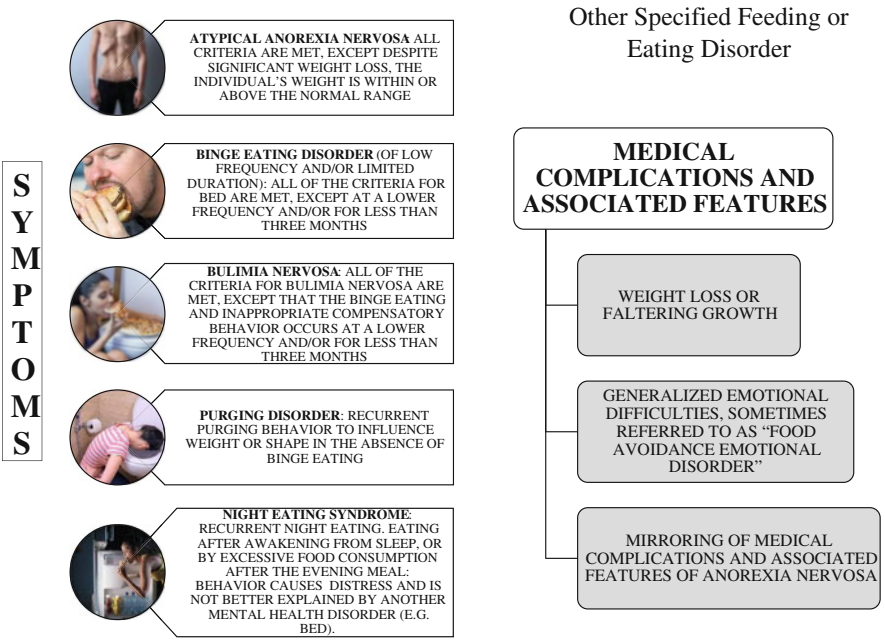


Fig. 4 Other specified feeding or eating disorder: Symptoms and medical complications and associated features

is not unexpected an increase in the number of the patients during the pandemic. Physicians are lately becoming more aware of the whole spectrum of the diseases that are under the category of EDs. On the good side, young people are more informed and seek help (Waller et al. 2014).

However, the causes of eating disorders are not fully understood, and perhaps additional understanding and research would help further understand the relationship between EDs and the QoL they lead. So far, the researchers have established that there is not just one cause but a whole range of aspects that are recognized so far: biological, social, psychological, and interpersonal causes. Equally important are the causes that lead to persistence of eating problems, given that EDs develop over a longer period of time, often several years (Currin et al. 2005).

For a better understanding of all EDs, it is very important to know the causes, clinical manifestation, therapeutic approach, and also the QoL they perceive. Each of the mentioned aspects equally contributes to that overall picture of how an ED affects an individual. Numerous analyses and studies have been done to show that people with an ED, of all subtypes according to the classification, lead a lower QoL than the control group, in this case people who do not have any subtype of eating disorder. Also, the same conclusions were reached when comparing with other psychiatric diseases. Poor QoL extends throughout the ED group regardless of the subtype the person suffers from, but it has been observed that people with BED report the worst QoL (Engel et al. 2009; De LA Rie et al. 2005; Jenkins et al. 2011).

Comorbidities of ED

It is very rare to see a person who has an isolated ED. Most often, in addition to ED, a person also has a mood disorder, anxiety disorder, or some other psychiatric illness.

Mental impairment of AN and BN patients varies. Comorbidity with affective disorders is found in AN patients. Comorbid affective disorders, anxiety disorders, substance-use disorders, and cluster B personality disorders are found in BN patients. As already mentioned previously in the text, complaints of patients with EDs includes preoccupation with food, shape, and weight and low self-esteem, but they also include body dissatisfaction, depression, and (social) anxiety.

In addition to psychological comorbidities, individuals can have a number of physical complications, may be exposed to emotional stress, poor social relationships, social isolation, and may have a poor QoL globally. The data show that in the group of psychiatric diseases, in the group of people with an ED, there is the highest risk of early death. On one side, this is precisely because of physical complications such as malnutrition, and on the other psychiatric disorders such as suicide (Weigel et al. 2016).

Relationship Between QoL and ED

Like many others serious psychiatric illnesses, ED directly affects the QoL and drastically impairs it. They can leave a deep negative impact on the life of an individual. The problem is not only based on the severity of these disorders but also on their duration. It should be emphasized that sometimes it takes a long time until the sick person gains insight into their condition and seeks for help. In the past, physicians also had difficulties to recognize the disorder in time and start with adequate therapy, but today a slight shift has been noticed in that aspect as well (Hay and Mond 2005; Padierna et al. 2000).

When it comes to predictive factors, studies have shown that organic or psychiatric comorbidities can have a much greater impact on the QoL on people diagnosed with EDs than age, BMI, psychiatric therapy, suicide attempt, or the number of emergency hospital visits.

An increasing number of studies have shown a need for specific measures of QoL, as well as that future research should measure comorbid anxiety and mood disorders as part of the assessment of the QoL of people with some of the EDs (DeJong et al. 2013; van Furth et al. 2016). Also, the question arises as to what are the factors that affect the length of the recovery itself and whether there are certain factors that indicate that a complete recovery will occur. The focus of further research could be to determine predictive factors for physical and mental aspects of QoL within AN, BN, and other eating disorders.

Taking into account the spectrum of damage that EDs bring with them, it is difficult to separate and especially underline which aspect is most affected. When we talk about physical impairments or medical complications that almost always accompany EDs, they are usually the result of disorders in eating and abnormal

compensatory behaviors such as self-induced vomiting or laxative abuse. People who have AN are malnourished, light body weight and, as a rule, have reduced bone density. Such bones are weak, brittle, and easily breakable with minimal trauma. Malnutrition directly affects the growth and development of children, the growth slows down. People are tired, listless, with a tendency to withdraw, a lack of energy for daily life obligations. They are very often ill and so they often miss school, everyday social activities, and in the end they feel alone, isolated, and excluded from social stories and currents. All this is reflected in professional life, changed interpersonal relationships, as well as family relationships.

Relationship Between System of Organs and EDs

Beside the mind and mental functions of the organism, the cardiovascular system, reproductive system, and urinary system, especially the kidneys, are also affected. People suffering from AN are at increased risk of developing arrhythmias and premature and sudden death. Anorexia nervosa is considered by many to be the most deadly psychiatric disorder. It is often underestimated that fat deposits have their physiological function, they are not necessarily something bad. Fat cells play a role in the production of hormones, both in women and men. A few fat cells will not be able to produce enough estrogen in women, or testosterone in men, which directly affects their reproductive function. Not everything is in hormonal disbalance, but also in the lack of vitamins, minerals, and proteins, together with the lack of hydration, which all together affect the reproductive system as well as all other organs and organ systems (Treasure and Schmidt 2005).

Special attention should be paid to reproductive health in both people with AN and people with BN. Studies have shown that EDs have a negative impact on the ability to stay pregnant. Also, it has been shown that this negative impact extends for years after the disease is in remission, which means that the negative impact is not exclusively related to the active and current form of the disease. Also, there is a higher chance that a person who suffers or had suffered from an ED will develop problem with the fertility. Considering the fertility and the possibility of conception, many medical professionals tend to only consider the potentials and health of females, while it is often forgotten that men who suffer from some form of ED are not spared. Irregular menstruation or even complete absence of the menstrual cycle for several months usually occurs in girls. With irregular menstruation comes ovulation disorder and therefore it is much harder for a woman to get pregnant. Studies have shown that women with low BMI, women who consume calories restrictively, or exercise excessively have some of the menstrual cycle disorders (Westmoreland et al. 2016) (Fig. 6).

Physical damage can also be expected in people with BN, if we know that the basis of this ED is overeating and then vomiting. That is why the most common changes are at the level of the upper parts of the digestive tract. The esophagus and stomach are most often affected, and sometimes problems with teeth also occur (Forney et al. 2016).

We can expect problems with digestion; due to provoked vomiting, the esophageal sphincter can be weakened, which can lead to gastroesophageal reflux disease, the acid returns from the stomach back to the esophagus. Stomach acid can also return to the laryngopharynx when coughing, hoarseness, sore throat, and dysphagia occur. Constant abdominal pain, bloating, and sometimes diarrhea or constipation may occur. A large number of stools on a daily basis can lead to damage to the anal blood vessels and the appearance of hemorrhoids, as well as to prolapse of the rectum. If a person uses certain medications and means for emptying, it can go to an addiction, emptying will no longer be possible or will be difficult without the use of additional means (Sansone and Sansone 2019). In practice, the abuse of diuretics can be seen, after which there are reduced values of potassium and dehydration. Such a condition additionally damages the kidneys; if such a condition of the organism lasts for a long time, their function may fail. We must not forget that low potassium levels can lead to arrhythmia, and cases of congestive heart failure and death have been reported (Brown and Mehler 2013).

Dynamics of ED and QoL

A special problem arises with the chronicity, all the previously mentioned impairments and difficulties that people face have a great impact on the further course of their lives. It has the enormous importance of assessing the quality of their lives. Also, changes in the diet, that is, a positive change in behavior in the diet itself will directly have a positive impact on QoL. We are talking about a vicious circle because the more severe the ED is, the worse the QoL, and such way of life is not stimulating for a person who suffers from any psychiatric illness. Described way of life directly stimulates a person to keep the previous eating patterns that are bad for their health (De LA Rie et al. 2005; Bijl and Ravelli 2000).

In patients with ED as well as in former patients with ED, self-esteem contributed the most to the QoL. Improving self-esteem seems to be important for a better QoL for both groups. Self-esteem and self-acceptance can be viewed as risk factors, but also as protective, preventive factors when we talk about EDs. Everything indicates that the QoL should be assessed in order to treat and assess the outcome itself, and not only in the assessment of the symptoms that the disorder gives. Today, QoL has become widely used in medical care as a measure of disease outcome, but its use as a measure of protection in mental health is less common. When the outcome criteria for recovery from an ED include an improved QoL for patients, then the focus of treatment should be both on reducing symptoms and improving QoL. By resolving the basic psychopathological mechanisms, low self-esteem and self-acceptance can reduce the bad consequences for other life domains of people with some form of ED. Consequently, treatments and therapies are more patient-centered rather than disease-oriented. This can help improve patient-centered care and can increase patient satisfaction with care, and thus we can expect a better therapeutic response (Fairburn et al. 2003) (Fig. 5).

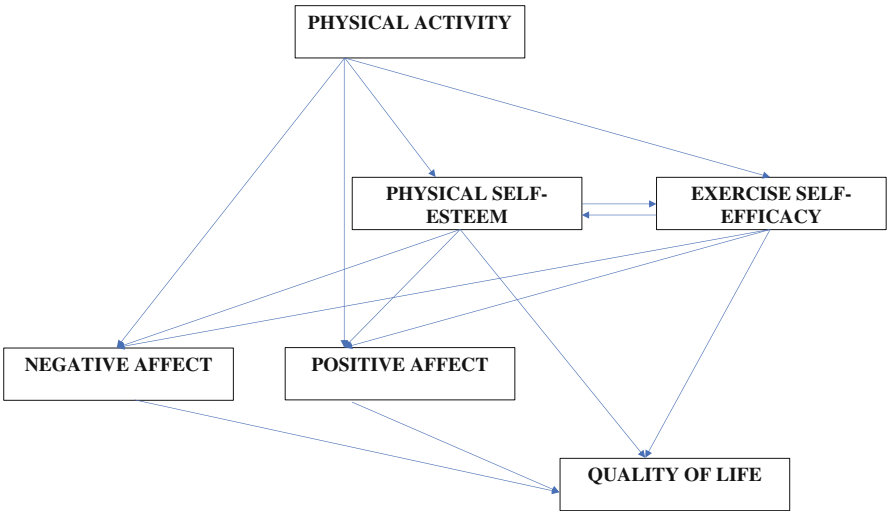


Fig. 5 Affect on quality of life

Considerations for Targeted Interventions for QoL in the Treatment of Patients with EDs

Targeted interventions that address QoL in the treatment of patients with EDs would be beneficial because improving QoL can contribute to resolution or improving symptoms. It should also be borne in mind that simply eliminating the symptoms of the disorder will not always and in every person completely solve the poor QoL reported by patients. QoL assessment is needed and should be the basis in treatment research, with a particular focus on a construct called quality of life related to health (HRQoL), which overlaps with QoL in the dimensions of physical, social, and mental health. Studies have shown that HRQoL improves after appropriate therapeutic approaches, but compared to patients with some other psychiatric illnesses (such as major depression), they were still dysfunctional. HRQoL is a multidimensional construct that reflects the degree to which an individual is healthy, comfortable, and able to enjoy life events, and should be studied with specialized psychometric tools in a particular disorder. It is significantly compromised in patients with EDs, due to the serious impact of the disorder on everyday life, and is associated with the cognitive and behavioral routines of the respondents, as well as interpersonal relationships (Meneguzzo et al. 2020). The use of general health quality of life helps to provide insight into the QoL of patient groups compared to other patient groups or the normal reference group. Whether current generic measures accurately quantify patients' QoL is a matter of debate (Carr 2001a, b; Muldoon et al. 1998) (Fig. 6).

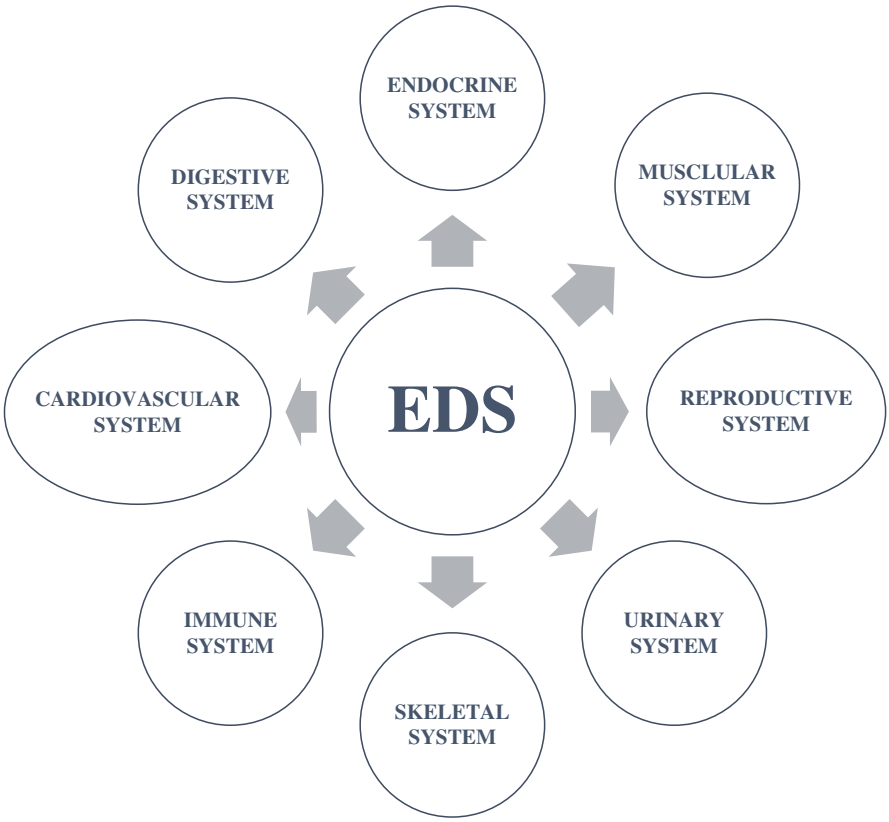


Fig. 6 Relationship between system of organs and EDs

In the large community study, they found that the QoL of ED patients was significantly worse than the QoL of the normal reference group and even worse than the QoL of patients with mood disorders, which is a great economic burden for a society. Former patients with ED continued to report poorer QoL than the normal reference group. The findings emphasize the impact of ED on physical, mental, and social well-being, even after symptom recovery. The impact of ED on QoL was even more serious than the impact of mood disorders. Self-esteem has shown the greatest association with QoL in both ED patients and former ED patients. In line with Padierna's findings, they found that severe pathology of EDs was associated with poorer QoL. One might hypothesize that although there has been a recovery in symptoms, the residual effects of the disorder may still have been manifest (Padierna et al. 2002). Beale and Ravelli found that people—with different types of psychiatric disorders—whose last psychiatric episode was more than 12 months earlier still show reduced functioning in the assessment (Bijl and Ravelli 2000).

Conclusion

QoL measures are beginning to be recognized as a key patient-oriented measure of outcome. As previously observed, studies in EDs have indicated significantly reduced QoL in this patient group, to a degree that is comparable with QoL findings in various other serious illnesses and disorders, such as angina and anxiety disorders. What is highly noticeable from the published evidence is that mental health of the individuals with EDs seems to be particularly impaired.

It remains unclear how specific symptoms and behaviors associated with EDs impact on QoL and further discussions are needed.

Mini Dictionary of Terms

- Bloating – Bloating is when your belly feels swollen after eating; it is usually caused by excess gas production or disturbances in the movement of the muscles of the digestive system.
- Chronicity – Continuing or occurring again and again for a long time.
- Constipation – Generally described as having fewer than three bowel movements a week.
- Diarrhea – Loose, watery, and possibly more frequent bowel movements.
- Fat cells – Also called adipocytes, they are connective tissue cells that have differentiated and become specialized in the synthesis (manufacture) and storage of fat.
- Hormones – Regulatory substances produced in an organism and transported in tissue fluids such as blood or to stimulate specific cells or tissues into action.
- Malnutrition – Includes undernutrition (wasting, stunting, underweight), inadequate vitamins or minerals, overweight, obesity, and resulting diet-related noncommunicable diseases.
- Menstrual cycle – During a normal menstrual cycle, the lining of a woman's uterus sheds; this cycle is part of a woman's reproductive system and prepares the body for a possible pregnancy.
- Reproductive health – Reproductive health is a state of complete physical, mental, and social well-being and not merely the absence of disease or infirmity, in all matters relating to the reproductive system and to its functions and processes.

Key Facts of Eating Disorders and Quality of Life

- Additional understanding of the causes of eating disorders will help us to better understand the relationship between EDs and the QoL, and for earlier recognition of the disorders.
- EDs have both physical and psychological consequences on the person.
- HRQoL reflects the degree to which an individual is healthy, comfortable, and able to enjoy life events, and it is significantly compromised in patients with EDs.

- QoL measures are patient-oriented measures of outcome.
- Comparing QoL in other serious illnesses and disorders, and in EDs we found out poor QoL in both groups.
- In the future, it should be resolved how specific symptoms and behaviors associated with EDs impact on QoL.

Summary Points

- EDs are actually very serious and potentially fatal diseases that most often affect younger population, generally women.
- EDs are multifactorial diseases, and some factors are recognized. Those factors are biological, social, psychological, and interpersonal.
- QoL is reportedly poor, and it does not depend on the ED subtype the person suffers, but the worst reported QoL is in the group of people with BED.
- Mood disorder, anxiety disorder, or some other psychiatric illness most often correspond with EDS.
- One of the main problems of the EDs are not only based on the severity of these disorders but also on their duration; sometimes it takes a long time to recognize ED both from a sick person and physicians.
- EDS affect and damage all organs and organ systems.
- Only eliminating the symptoms of the disorder will not always and in every person completely solve the poor QoL.
- Relationship between EDs and QoL can be presented as a vicious circle: the more severe the ED is, the worse the QoL, but positive change in behavior in the eating habits will directly have a positive impact on QoL.

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The Role of Denial in Eating Disorder Development, Assessment, and Treatment

19

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Contents

Introduction 368
Defining Denial of Disordered Eating 368
Etiology of the Denial of Disordered Eating 369
Consequences of Denial of Disordered Eating 370
Assessment 373
Treatment 375
Future Directions 377
Summary 378
Applications to Other Eating Disorders 378
Mini-Dictionary of Terms 379
Key Facts of Denial of Disordered Eating 379
Summary Points 379
References 380

Abstract

Denial of disordered eating (i.e., the tendency to conceal behaviors which reflect symptoms of an eating disorder) can be conscious or unconscious, ranging from lack of insight to deliberate refusal to disclose. Accordingly, denial of disordered eating may stem from various motivations such as a defense of self, shame and stigmatization, and/or fear of intervention. Denial of disordered eating is important to study and understand because it is associated with a variety of maladaptive consequences, including interpersonal conflict, suicidality, and further disordered eating. Denial of disordered eating also poses unique challenges to the assessment

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and treatment of eating disorders, which will be discussed within this chapter along with directions for future research.

Keywords

Denial · Lying · Concealment · Insight · Underreporting · Disordered eating · Eating disorders · Assessment · Diagnosis · Treatment · Help-seeking

Abbreviations

ACT	Acceptance and commitment therapy
CBT	Cognitive behavior therapy
DBT	Dialectical behavior therapy
DDEBS	Deliberate Denial of Disordered Eating Behaviors Scale
EAT	Eating Attitudes Test
EDI	Eating Disorder Inventory
FBT	Family-based therapy
NSSI	Non-suicidal self-injury
SAI	Schedule for the Assessment of Insight
SDBS	Self-Disclosure about Body Satisfaction scale
SDRE	Self-Disclosure about Restrained Eating scale
UDEBS	Underreporting of Disordered Eating Behaviors Scale

Introduction

The tendency to hide and conceal eating behaviors is common in individuals with eating disorders. In fact, most eating disorder patients deny that anything is wrong in the beginning months of their eating disorder, making denial of disordered eating a relevant construct in the field of eating disorder research, diagnosis, and treatment (Schoen et al. 2012). In this chapter, we will begin by defining denial of disordered eating, discuss the causes and consequences of denial and how to assess and treat individuals who engage in denial of illness, and discuss directions for future research.

Defining Denial of Disordered Eating

Denial of disordered eating can be considered a dimensional construct that exists along a spectrum, with lack of insight on one end and deliberate refusal of self-disclosure on the other (Konstantakopoulos et al. 2011). Lack of insight into the maladaptive thoughts and behaviors one has regarding one's body, eating, and related behaviors occurs unconsciously and refers to a lack of self-awareness and the inability to recognize that one has a mental illness (Konstantakopoulos et al. 2011). Lack of insight is often associated with a variety of mental health concerns, including psychosis, substance use, and mood, but is also a common feature of

eating disorders, one which contains clinical significance given that higher levels of insight are associated with better long-term outcomes (e.g., Greenfeld et al. 1991). To our knowledge, there is only one assessment instrument available to identify lack of insight pertaining to disordered eating (Konstantakopoulos et al. 2011), possibly because it takes awareness of a behavior or cognition to report on it, making assessment challenging. Conscious, or deliberate, denial of disordered eating may be easier to operationalize but poses its own challenges given that assessments of this kind ask participants to report on behaviors that they typically deliberately deny (Howard et al. 2020). In 1991, Vitousek and colleagues defined denial as any consciously or unconsciously motivated omission, concealment, or misrepresentation of behavior or internal experience. Recent research has adapted this definition to operationalize deliberate denial of disordered eating behaviors as any conscious omission, concealment, or misrepresentation of behavior related to disordered eating (Howard et al. 2020).

Etiology of the Denial of Disordered Eating

Individuals who experience disordered eating (i.e., behaviors which reflect symptoms of an eating disorder) may lie and conceal symptomatology for different reasons. An important distinction is made in the literature between denial in individuals who restrict food (i.e., limit the amount of food they eat) and denial in individuals who binge eat (i.e., lose control over their eating). People who restrict food may lie about disordered eating behaviors because they do not want someone to intervene on their behaviors, especially within a society that values thinness (Vandereycken 2006). For some individuals who engage in dietary restriction, their behaviors can become a part of their identity: a phenomenon known as egosyntonicity (Vandereycken 2006; Starzomska 2010). Therefore, a tendency to "fake good" and deny dietary restriction is in defense of their sense of self. This is particularly common in adolescence where we see a heightened egosyntonicity associated with identity development and decreased psychological flexibility (Fisher et al. 2001; Masuda et al. 2011). Other individuals who restrict food may deny eating disorder symptoms because their disordered eating behaviors give them a sense of self-efficacy or achievement, and they hide their behaviors from others so they will not lose this sense of control and success (Vitousek et al. 1991).

Individuals who binge eat differ from individuals who restrict their food intake in that they will more often conceal symptoms out of shame and fear of negative evaluation (Pettersen et al. 2008; Vitousek et al. 1991). Individuals who binge eat report feeling that others will view them as lacking will power and self-control (Pettersen et al. 2008). Although there may be differences in why denial is manifested in individuals who engage in different types of disordered eating behaviors, there are also some similarities, and it should be noted that eating disorders are often heterogeneous and many individuals who engage in restrictive dieting also engage in compulsive overeating. It is likely that, to some extent, individuals conceal eating disorder symptomatology regardless of specific disordered eating behavior,

because they do not want to be labeled or diagnosed with a mental illness and face stigmatization (Vandereycken 2006).

Understanding the etiology of denial may be important for identifying individualized treatment plans. For example, an individual whose symptomatology has become a part of their sense of self might engage in parts work (i.e., addressing conflicts between different parts of oneself; Schwartz and Sweezy 2020), whereas an individual who denies out of fear and shame might work on utilizing cognitive-behavioral strategies to challenge cognitive distortions (Beck 2011). Although attempts to deny disordered eating may arise from various motivations and thus have specific implications for treatment, they likely have similar deleterious impacts on relationships and eating behaviors.

Consequences of Denial of Disordered Eating

Social Consequences. One way in which the consequences of denial of disordered eating manifest is through the interpersonal impacts it has on the person and those around them. According to an interpersonal formulation of disordered eating, engaging in disordered eating behaviors can increase interpersonal problems, for example, individuals who engage in disordered eating may socially isolate to avoid intervention from others. Then, in turn, these interpersonal problems are believed to intensify disordered eating behaviors, for example, social isolation can lead to higher levels of depression and further engagement in disordered eating to regulate the higher levels of negative affect (Rieger et al. 2010). This interpersonal conceptualization of eating disorder development and maintenance emphasizes the link between disturbances of the self and the individual's perception of their social world, such that, as disordered eating behaviors increase, the way an individual views their social world becomes distorted (Wilfley et al. 2003). To date, interpersonal formulations postulate that disordered eating behaviors are ineffective strategies for regulating actual or perceived negative social evaluations (Rieger et al. 2010). For instance, the individual might attempt to escape from aversive affective states through engagement in disordered eating (Heatherton and Baumeister 1991). However, over time, disordered eating might act as a de facto social agent (one typically achieved through successful interpersonal interactions; Rieger et al. 2010), such that individuals attempt to regulate their mood through disordered eating as opposed to social engagement, ultimately leading to social isolation.

Lethal Consequences. Engagement in disordered eating, generally, is associated with an elevated risk of suicidality (Smith et al. 2018), with individuals with anorexia being anywhere from 18 to 31 times more likely to die by suicide than the general population (Preti et al. 2011). Given that denial of disordered eating behaviors may lead to social isolation, this puts an individual at increased risk for non-suicidal self-injury (NSSI) and suicidality (Howard et al. 2020; Rieger et al. 2010; Van Orden et al. 2010). Joiner's (2005) interpersonal theory of suicide suggests that the capability for suicide emerges because of high degrees of three states: acquired capability (i.e., exposing oneself to painful experiences), perceived

burdensomeness (i.e., the belief that one is a burden to others), and thwarted belongingness (i.e., decreased social connectedness; Van Orden et al. 2010). Denial of disordered eating behaviors may contribute to increased NSSI and suicidality because of the conflict and distancing it causes in relationships, contributing to a decreased sense of belonging. In fact, Howard and colleagues (2019) found that, among college women, deliberate denial of disordered eating behaviors accounted for significant variance in NSSI and suicidality above and beyond engagement in disordered eating alone, and individuals who engaged in denial of disordered eating were more likely to have engaged in lifetime NSSI and fall into an elevated suicide risk category compared to those who engaged in disordered eating but did not try to conceal it. These findings are important because they suggest that there are greater consequences for individuals who deny their disordered eating behaviors compared to those who engage in disordered eating without denial. The tendency to isolate oneself from others also poses a barrier to individuals receiving a formal eating disorder diagnosis given that these individuals tend to distance themselves from people who may intervene on their behaviors.

Help-Seeking Consequences. In clinical settings, it is widely understood that individuals who engage in disordered eating behaviors often conceal these behaviors (Vandereycken and Van Humbeek 2008), creating challenges for seeking treatment and frustration for providers. One of the most frequently cited barriers to seeking clinical help for disordered eating is individuals' denial of their illness and its overall severity (Ali et al. 2020). Despite the critical need for treatment of those with disordered eating symptoms, only a minority believe they need support for their condition (Webb and Schmidt 2021). Clinicians working with students at colleges and universities often report that it is difficult to get them the help they need given frequent denial of disordered eating and/or its severity (Webb and Schmidt 2021). This denial consequently results in delay of treatment for extended periods of time. This is an especially prominent concern for adolescents with anorexia nervosa, where denial is seen as a common feature of the disorder (Couturier and Lock 2006). Couturier and Lock (2006) studied symptoms of denial among 86 adolescents with anorexia nervosa and found that 42% of their sample either denied or minimized their symptoms. Denial was measured by a discrepancy between parent report of disordered eating symptoms and adolescent scores on the restraint subscale of the Eating Disorders Examination (EDE; Fairburn and Beglin 1994). Individuals who suffer from eating disorders notoriously pose issues to clinicians when it comes to accurate assessment, resulting in concerns of validity for diagnosis (Starzomska and Tadeusiewicz 2016). In fact, research suggests that the Eating Disorder Inventory (EDI; Garner et al. 1983) and Eating Attitudes Test (EAT; Garner et al. 1982) may not accurately reflect psychological components inherent in an eating disorder diagnosis due to denial of illness (Starzomska and Tadeusiewicz 2016).

Diagnostic Consequences. In the most recent version of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5; American Psychiatric Association 2013), a diagnosis of anorexia or bulimia warrants the presence of psychological symptoms, such as intense fear of gaining weight, refusal to maintain normal body weight, and self-evaluation unduly influenced by shape and weight. Assessment of

psychological symptoms already poses challenges for clinicians, given increased subjectivity associated with psychological symptom assessment compared to behavioral symptom assessment, which creates ambiguity in diagnosis; however, this dilemma becomes especially difficult when a client does not recognize or endorse their symptoms due to lack of insight or intentional denial. Inaccurate assessment of these psychological symptoms often leads to missed or mistaken diagnoses (Becker et al. 2009). Luck and colleagues (2002) illustrated this issue when validating the SCOFF questionnaire as a screening tool for clinical use. The study sought to validate the SCOFF questionnaire by seeing whether it could detect individuals previously identified as having an eating disorder through clinical interview. Although the SCOFF questionnaire identified most individuals with an eating disorder (11 out of 13), it failed to detect two cases due to denial and nondisclosure, illustrating the reality of clinical challenges pertaining to diagnosis.

Failure to detect eating disorders due to denial plays out in nonclinical arenas as well. For example, among college athletes, who are at heightened risk for developing an eating disorder due to an increased emphasis on shape and weight, denial is a pervasive concern (Plateau et al. 2014). In fact, eating disorders often go unrecognized by the coaches of collegiate athletes, who have one of the most important roles in recognizing disordered eating patterns in their athletes before the onset of a diagnosable eating disorder (Plateau et al. 2014). However, in this qualitative study, one in five coaches reported that they have never identified disordered eating behaviors in athletes, and they struggle to do so because of lack of confidence in having conversations about shape and weight and the common occurrence of denial in those afflicted with disordered eating. In this study, male coaches reported difficulty talking about disordered eating and related constructs, such as the absence of a menstrual cycle, with their female athletes, which could further encourage denial of disordered eating among female athletes. In general, coaches reported that it is common for athletes to hide or conceal disordered eating behaviors, subsequently serving to deteriorate the relationship between coach and athlete (Plateau et al. 2014).

Comorbid Diagnostic Consequences. Denial serves as a barrier to diagnosis but also as a barrier to detect problems that frequently co-occur with disordered eating, such as comorbid mood and personality symptoms. For example, adolescents with eating disorders report lower levels of internalizing problems (e.g., depression, anxiety) on self-report questionnaires compared to their parents' reports of their adolescents' internalizing behaviors (Salbach-Andrae et al. 2008), which contrasts with studies conducted with participants without eating disorders that have found less differences between adolescent and parent reports of internalizing problems (e.g., Crystal et al. 2001). Salbach-Andrae and colleagues (2008) posited that their findings of discrepant reporting among adolescents with eating disorders may be due, at least in part, to denial and minimization of their symptoms. Similarly, Vitousek and Stumpf (2005) suggest that denial and distortion in self-report make it difficult to assess comorbid personality functioning among individuals with eating disorders. Comorbid problems, such as internalizing and personality disorders, are important to understand given the implications they have for treatment outcomes and

accurate diagnosis and assessment. Individuals who meet criteria for more than one mental illness should receive treatment that takes their full symptomatology into account. Taken together, the consequences associated with denial of disordered eating makes the ability to assess denial itself important albeit challenging.

Assessment

Assessing denial of disordered eating is inherently challenging given that these assessments may be asking people to report on behaviors that they typically deny or that they may not be consciously aware of. The first issue with assessing denial of disordered eating pertains to whether an instrument is aimed at measuring unconscious lack of insight or deliberate denial of disordered eating.

Underreporting. Several studies have inferred denial of disordered eating (both conscious and unconscious) from low scores on self-report symptom questionnaires by participants who previously met diagnostic criteria for an eating disorder (Couturier and Lock 2006; Newton et al. 1988; Pryor et al. 1995; Viglione et al. 2006). For instance, in one of the earliest assessments of denial of disordered eating, Newton and colleagues (1988) found that of 66 women referred for eating disorder assessment, the individuals who were more likely to be diagnosed with an eating disorder were also more likely to report lower scores on the EAT (Garner et al. 1982). Similarly, other research on denial in eating disorders focused on denial in terms of refusal to endorse disordered eating in self-reports (Couturier and Lock 2006; Pryor et al. 1995; Viglione et al. 2006). These studies measured denial in clinical populations by having patients with known eating disorder diagnoses fill out self-report measures of disordered eating, such as the EDI (Garner et al. 1983) or the EAT (Garner et al. 1982); they interpreted lower scores as suggesting denial (i.e., if an individual with a known eating disorder does not self-report disordered eating, they are denying the problem).

Self-Report. Beyond assessments of denial by measurements of underreporting, previous self-report measures of denial of disordered eating behaviors are Basile's (2004) Self-Disclosure about Body Satisfaction scale (SDBS) and the Self-Disclosure about Restrained Eating scale (SDRE). The SDBS and SDRE measure disclosure regarding body image and dieting with questions such as: "Do you tell others when you think you are too thin?" "Do you tell others when you are on a diet?" However, scoring low on either scale does not necessarily measure denial because not telling someone how you feel about your body, or your dieting behavior, is not the same as lying or lacking awareness. Furthermore, questions regarding disclosure of eating disorder symptomatology in Basile's scales are limited to "dieting behaviors," whereas disordered eating behaviors span beyond dieting (e.g., self-induced vomiting, over-exercising, binge eating), and many individuals with an eating disorder do not think of their eating disorder as a "diet."

One study has attempted to measure eating disorder-specific insight directly by modifying the Schedule for the Assessment of Insight (SAI; Kemp and David 1997) to be eating disorder-specific (Konstantakopoulos et al. 2011). The SAI is a

semi-structured interview that assesses the ability to recognize that one has a mental illness, compliance with treatment, awareness of psychological changes, awareness of the need for treatment, awareness of psychosocial consequences of the illness, and the capacity to label aberrant psychological events as pathological (Kemp and David 1997). In the modified version, items pertaining to compliance with treatment were removed, and items related to the need for physical and psychological treatment specific to eating disorders were added (Konstantakopoulos et al. 2011). In this study, 40 participants with anorexia or bulimia and 35 healthy controls completed the questionnaire. Only six participants with anorexia demonstrated severe impairment of insight, and more participants with eating disorders endorsed deliberate denial of illness compared to a lack of awareness of the illness (Konstantakopoulos et al. 2011).

There has also been one recent attempt to measure deliberate denial of disordered eating using self-report. This measure is known as the Deliberate Denial of Disordered Eating Behaviors Scale (DDEBS; Howard et al. 2020). The DDEBS is a 12-item self-report questionnaire that assesses conscious omission, concealment, or misrepresentation of behavior related to disordered eating and contains items such as: "How often have you been dishonest about how much you ate?" "How often have you told people you felt sick to avoid eating?" Items for the scale were developed by adapting items from Vandereycken and Van Humbeek's (2008) retrospective survey data (see below), using Vitousek and colleague's (1991) definition of denial, holding focus groups, polling an expert panel, and empirically through factor analysis. The scale demonstrated initial evidence of reliability and validity (Howard et al. 2020). However, it should be noted that a concern arose in the development of the DDEBS about the ability of participants to honestly report on behaviors that they typically lie about. Therefore, an Underreporting of Disordered Eating Behaviors Scale (UDEBS) modeled after the Minnesota Multiphasic Personality Inventory (MMPI) Lie (L) scales (Hathaway and McKinley 1943; Butcher et al. 1989; Ben-Porath and Tellegen 2011) was developed to be used in conjunction with the DDEBS to assess validity of responses (Howard et al. 2022).

Retrospective. There has also been one attempt to measure concealment of disordered eating behaviors retrospectively. This untitled retrospective questionnaire surveyed former eating disorder patients at various stages of recovery and asked them questions regarding their most frequently used concealing behaviors at the beginning phase of their eating disorder (Vandereycken and Van Humbeek 2008). The questionnaire asks participants to report on concealing behaviors such as avoidance of eating ("to avoid eating with others, I most often said. . .") and false impression of eating ("to give the impression I had eaten. . ."). One problem with any retrospective survey is that retrospection can be influenced by the current state of an individual. Unsurprisingly, in this study, the longer the retrospection duration period, the less likely individuals were to report concealing behaviors (Vandereycken and Van Humbeek 2008). Nonetheless, this retrospective questionnaire provides useful information on the rates at which individuals that engaged in disordered eating endorsed using specific concealing behaviors. For example, among the 401 individuals polled, to avoid eating with others, 39.4% of individuals stated that they most

often said, "I have eaten already," and to give the impression that they were eating when they were not, 25.7% of individuals stated that they would most often attempt to eat slowly. Continued research and recent advances in the development of psychometrically valid assessment tools may assist in accurate assessment of denial of disordered eating behaviors that could inform treatment.

Treatment

As discussed throughout this chapter, denial of disordered eating poses unique challenges for both researchers and clinicians in the diagnosis and assessment of eating disorders. Denial can also make treatment particularly challenging. In fact, anorexia nervosa is often seen as treatment resistant. A systematic review conducted in 2013 identified four main themes in treatment-resistant eating disorder research: denial of illness, motivation to change, maintaining factors, and the therapeutic relationship (Abbate-Daga et al. 2013). Poor insight can even assume delusional features, making it even more challenging to treat these patients (Konstantakopoulos et al. 2012; Steinglass et al. 2007). However, most treatment-resistant patients show a deliberate denial of illness as opposed to a lack of insight (Konstantakopoulos et al. 2012), which some researchers attribute to immature defense mechanisms (Steinglass et al. 2007).

Empirically Supported Treatment. Despite the challenges that may accompany treatment given frequency of denial, some treatments may be particularly well suited to address denial within the context of therapy. One such empirically supported treatment is acceptance and commitment therapy (ACT; Hayes et al. 2006). Denial of disordered eating may result from individuals who engage in disordered eating not being able to tolerate negative thoughts and feelings, leading them to not only engage in disordered eating but conceal their behavior from others to avoid this discomfort. This intolerance is characteristic of diminished psychological flexibility (i.e., an inability to be in contact with the present moment and respond to the context functionally; Hayes et al. 2006). An inverse relationship between concealment and psychological flexibility has been demonstrated empirically in a cross-sectional study using male and female undergraduates (Masuda et al. 2011). Given that the overarching goal of ACT is to increase psychological flexibility, this treatment may be particularly well suited to treat patients who deny disordered eating behaviors. Family-based treatment (FBT) for children and adolescents with eating disorders may also be fitting given that it directly targets and resolves family-level variables, including secrecy (Loeb et al. 2019). FBT proposes that a child's eating disorder often becomes the "elephant in the room," with the child protecting the symptoms through secrecy and the parents or caregivers unsure how to broach the subject. FBT works to reverse secrecy by discussing progress and strategies for treating the eating disorder as a cohesive family unit (Loeb et al. 2019). Lastly, motivational interviewing (MI) may be indicated as a brief pretreatment intervention or as a stand-alone therapy for individuals who deny disordered eating symptoms (Weiss et al. 2013). In the early stages of MI, feelings of ambivalence (common to the stage

of contemplation) and the experience of denial (frequently experienced in pre-contemplation) are discussed. In later sessions, self-monitoring and Socratic questioning are introduced to assist patients in raising their consciousness about their disordered eating behaviors.

Other empirically supported treatment protocols could be modified to address denial. Dialectical-behavioral therapy (DBT) focuses on helping clients do what is effective in the long term (Linehan 2015), and many clients develop long-term goals pertaining to creating or strengthening healthy relationships. Although denial of disordered eating might assist a client in getting what they want in the short term (e.g., not having to eat in front of others), it is likely to harm them in the long term (e.g., developing and maintaining healthy relationships; Linehan 2015). DBT for eating disorders (Safer et al. 2009) could develop specific interpersonal effectiveness skills pertaining to honesty, and interpersonal effectiveness scripts from DBT could be modified for this purpose as well (Linehan 2015). For example, a client might be encouraged to describe, express, assert, and reinforce (DEAR) their needs to a loved one (e.g., "I have difficulty being honest around my eating habits. I feel concerned about judgment from others. Would you be able to help hold me accountable? I would really appreciate your help.").

Treatment Approach. In addition to the specific treatment being utilized, the approach to therapy and/or assessment is important in addressing denial. Michel (2002) argues that a therapeutic approach to assessment is a critical first step in overcoming difficulties posed by denial, minimization, and lack of insight in eating disorders. Therapeutic assessment differs from the traditional information gathering model because the assessor works to develop an empathic relationship with the client, collaboratively establish goals for the evaluation, and allow the client to explore results in conjunction with the assessor and on their own. Michel (2002) reported that, from their own experience, therapeutic assessment allows the examinee to retain some control over the process, especially in hospital settings, which allows for higher degrees of self-disclosure. Similarly, Starzomska and Tadeusiewicz (2016) emphasize the importance of building an honest and trusting relationship within the context of therapy to bypass pitfalls associated with the influence of denial. Qualitative research conducted with 14 women with eating disorders explored ways in which these women were able to move from denial to awareness (Schoen et al. 2012). The process of increasing awareness was reported to be influenced by interpersonal feedback. Verbal feedback that was described as showing concern, was goal-directed, and came from a trusted source was most likely to move women from denial to awareness (Schoen et al. 2012).

Treatment Modality. A final consideration is modality of treatment. Web-based and self-help programs can reduce barriers associated with denial, such as shame and stigmatization (ter Huurne et al. 2013; Yim and Schmidt 2019), but this consideration should be balanced with increased rates of secrecy attributed to ease of hiding symptoms when using telehealth (Hunter and Gibson 2021). For those hesitant to seek treatment, web-based and self-help treatment are better than no treatment at all. An online self-help cognitive-behavioral treatment (CBT) for bulimia has been found to be an acceptable treatment option for those with bulimic-type symptoms,

despite some difficulties with motivation and implementation (McClay et al. 2013). Another widely successful web-based program is *Student Bodies*, which targets disordered eating behaviors in young college women (Dev et al. 1999). Research suggests that this 8-week program reduces weight and shape concerns in college women at high risk for developing an eating disorder (Kass et al. 2014). These well-validated web-based and self-help programs might be more acceptable to people unwilling or unable to seek more traditional therapies.

Future Directions

Although great strides have been made in understanding the causes, consequences, and treatment of denial of disordered eating, future research is warranted. For example, future research might utilize longitudinal designs to investigate over what timeframe engagement in denial of disordered eating behaviors precedes increases in disordered eating, interpersonal difficulties, treatment avoidance, and other clinical correlates. Most of the research that has investigated denial of disordered eating has utilized cross-sectional designs, which does not tell us anything about the temporal sequencing of events or cause and effect. Therefore, it should also be investigated experimentally whether interventions that encourage honesty can lead to positive outcomes (e.g., decreases in disordered eating, body dissatisfaction, and suicide/self-harm tendencies and increases in help-seeking behaviors).

To date, most of the research on denial has largely utilized White female samples (e.g., Newton et al. 1988; Plateau et al. 2014; Schoen et al. 2012). While denial is likely relevant to men, denial may present itself differently in this population. For example, denial related to dietary restriction may not be as applicable to men, while there may be other areas of denial associated with attaining muscle mass (e.g., steroid use) that have been understudied. It is also important to study denial in particular cultures, or subcultures, where mental illnesses, including eating disorders, see higher rates of stigmatization and possibly higher rates of denial, such as Black and Latinx communities (Ward et al. 2013). Black and Latinx women may be less likely than young White women to seek help for or acknowledge disordered eating due to a lack of trust in health-care providers (Becker et al. 2009), especially given past abuses by health-care systems (Chou et al. 2012). Black women may also face pressure to reflect historical body-positive ideals and thus deny potential concerns (Lovejoy 2001). Although Black women may have developed a healthy resistance to negative societal images of themselves, including a rejection of mainstream body ideals, this resultant pressure to project resiliency may also result in a tendency to deny vulnerabilities related to body image concerns and disordered eating behaviors (Hooks 1993). Lovejoy (2001) suggests that self-reports of positive body image and denial of disordered eating among Black women in social science surveys should "be more closely examined if we are not to collude in the silencing of Black women's health problems" (256).

In addition, future research should continue to investigate the impacts of denial using both clinical and nonclinical samples. Those more familiar with eating

disorders may be better at hiding symptoms in a manner that avoids detection in assessments of denial; therefore, the validation of lie scales, such as the UDEBS (Howard et al. 2022), with clinical samples is warranted. There are also certain clinical samples that may be particularly motivated to conceal disordered eating (e.g., individuals with eating disorders who are on civil commitment), and understanding how to assess and treat these individuals has implications for our legal system, such as determining when and if someone gets off a civil commitment. Understanding the causes and consequences of denial and, subsequently, the most efficacious treatments for those who deny disordered eating is important if we are to successfully prevent and treat eating disorders.

Summary

Denial of disordered eating (i.e., the tendency to conceal behaviors which reflect symptoms of an eating disorder) can be conscious or unconscious, ranging from lack of insight to deliberate refusal to disclose. Accordingly, individuals may conceal eating disorder symptomatology for various reasons, including fear of intervention and a defense of self, but also because they do not want to be labeled or diagnosed with a mental illness and face stigmatization. The tendency for individuals who engage in disordered eating to deny their problems can lead to interpersonal conflict, suicidality, further disordered eating, avoidance of treatment, and difficulties with accurate diagnosis. Assessing denial of disordered eating is particularly challenging given that these assessments may be asking people to report on behaviors that they typically deny or that they may not be consciously aware of. However, recent advances in the development of psychometrically valid assessment tools, such as the DDEBS, may assist in accurate assessment of denial of disordered eating behaviors, which could ultimately lead to more effective treatment. Certain treatments may already be particularly well suited to address denial within the context of therapy, such as ACT, FBT, and MI. Beyond the specific treatment, the approach and modality to treatment may be just as important when working with individuals who deny eating disorder symptomatology. However, more research is needed, and understanding denial of disordered eating is still in its infancy.

Applications to Other Eating Disorders

In this chapter, we have defined denial of disordered eating, discussed the causes and consequences of denial and how to assess and treat individuals who engage in denial of illness, and discussed directions for future research. We have discussed denial of disordered eating broadly such that it applies to all eating disorders; however, it is most seen in anorexia. We have also discussed how etiology of denial of disordered eating might differ based on the type of eating disorder. Future research should continue to investigate various causes and consequences of denial and how to assess and treat individuals who deny based on specific eating disorder types

(e.g., anorexia, bulimia, binge eating disorder). For example, researchers could develop assessment instruments that inquire about denial of specific disordered eating behaviors, such as binge eating or compensatory behaviors. These scales could include items such as: "How often have you made up excuses so you can be alone to binge eat?" that would be applicable to those with bulimia or binge eating disorder. However, assessments of this kind will need to be careful to distinguish between people who report they have not *denied* engaging in specific behaviors and those who have not *engaged* in a specific disordered eating behavior.

Mini-Dictionary of Terms

- **Deliberate denial:** Conscious omission, concealment, or misrepresentation of behavior or internal experience.
- **Denial of disordered eating:** The tendency for individuals who engage in disordered eating to lie about or conceal their behavior.
- **Disordered eating:** Unhealthy eating patterns that reflect symptoms of an eating disorder but may not meet full criteria for an eating disorder.
- **Insight:** Self-awareness.
- **Interpersonal formulation of disordered eating:** Engaging in disordered eating behaviors can increase interpersonal problems; in turn, these interpersonal problems are believed to intensify disordered eating behaviors.
- **Underreporting of disordered eating:** Reporting fewer disordered eating symptoms than one engages in, which may occur consciously or unconsciously.

Key Facts of Denial of Disordered Eating

- Of eating disorder patients, 75% deny that anything is wrong in the beginning months of their eating disorder
- The most frequently mentioned barrier to help-seeking for an eating disorder is shame and stigmatization (85%) followed closely by denial of and/or failure to perceive the severity of the disordered eating (69%)
- Anosognosia, or lack of insight, is a defining feature of anorexia
- Denial of disordered eating stems from various motivations, which can include a defense of self, shame and stigmatization, and/or fear of intervention
- Denial of disordered eating can lead to interpersonal conflict, suicidality, further disordered eating, and delays in help-seeking

Summary Points

- Denial of disordered eating (i.e., the tendency to conceal behaviors which reflect symptoms of an eating disorder) can be conscious or unconscious, ranging from lack of insight to deliberate refusal to disclose

- Individuals conceal eating disorder symptomatology for various reasons, including fear of intervention and a defense of self, but also because they do not want to be labeled or diagnosed with a mental illness and face stigmatization
- Denial of disordered eating can lead to interpersonal conflict, suicidality, further disordered eating, avoidance of treatment, and difficulties with accurate diagnosis
- Assessing denial of disordered eating is challenging given that these assessments may be asking people to report on behaviors that they typically deny or that they may not be consciously aware of
- Recent advances in the development of psychometrically valid assessment tools, such as the DDEBS, may assist in accurate assessment of denial of disordered eating behaviors
- Some treatments may be particularly well suited to address denial within the context of therapy, such as ACT, family-based therapy (FBT), and MI
- The approach and modality to treatment may be just as important as the therapeutic intervention when working with individuals who deny eating disorder symptomatology
- Future research on denial of disordered eating should utilize longitudinal and experimental designs, samples other than White females, and both clinical and nonclinical populations

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The Role of the Dietitian

20

Treatment of Anorexia Nervosa, Bulimia Nervosa, and Binge Eating Disorder

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Contents

Overview of Dietetic Treatment for Eating Disorders 387
Nutrition Assessment 388
Nutrition Intervention, Monitoring, and Evaluation 390
Outpatient Dietetic Treatment for Eating Disorders 392
Calcium Foods 393
Protein 393
Carbohydrates 396
Fruits and Vegetables 396
Fluids 396
Nuts, Oils, and Fats 396
Diet Foods and Fillers 397

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Inpatient Dietetic Treatment for Eating Disorders, Including Considerations for Individuals with Anorexia Nervosa 397
Refeeding Syndrome 398
Nutrition Support for Inpatients 398
Considerations for Individuals with Bulimia Nervosa 399
Treatment Considerations for Individuals with Bulimia Nervosa 400
Considerations for Individuals with Binge Eating Disorder 401
Considerations for Individuals with Co-occurring Binge Eating Disorder and Obesity ... 401
Application to Other Eating Disorders 404
Mini-Dictionary of Terms 404
Key Facts 405
Key Facts Regarding the Role of Dietitians in Eating Disorder Treatment 405
Summary Points 405
References 406

Abstract

Current clinical practice guidelines support a multidisciplinary treatment approach to ensure individuals with eating disorders have access to medical, dietetic, and psychological interventions to maximize their chances of recovery. Dietitians play a key role in the treatment of eating disorders by assessing the severity of malnutrition, disordered eating patterns, and knowledge and skill deficits that prevent achievement and maintenance of optimum nutrition. Moreover, dietitians collaboratively develop individually tailored nutrition care plans which (1) address nutritional deficiencies and promote optimal nutritional status, (2) emphasize the role of adequate nutrition in addressing patients' individual and mental well-being, and (3) provide nutrition education to challenge inaccurate beliefs about food and eating. This chapter provides an overview of nutrition assessment and intervention for individuals with eating disorders broadly, as well as specific dietetic treatment considerations for individuals with anorexia nervosa, bulimia nervosa, and binge eating disorder.

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Keywords

Nutrition · Dietetics · Nutrition assessment · Malnutrition · Nutritional status · Refeeding syndrome · Nutrition support · Nutrition education · Energy intake · Nutritional rehabilitation

Abbreviations

AN	Anorexia nervosa
BED	Binge eating disorder
BMI	Body mass index
BN	Bulimia nervosa
CBT	Cognitive behavioral therapy
ED	Eating disorder
NG	Nasogastric
REE	Resting energy expenditure

Overview of Dietetic Treatment for Eating Disorders

Dietitians play a pivotal role in helping individuals with eating disorders (EDs) and their families understand the interaction between food, nutrition, and well-being, as well as supporting eating behaviors that align with treatment and recovery goals (Heruc et al. 2020). Specifically, the role of a dietitian is to identify and assess the severity of malnutrition, disordered eating patterns and knowledge, and skill deficits that prevent achievement and maintenance of optimal nutrition status (Setnick 2016). Dietitians help people with EDs and their families to develop individualized plans and encourage active learning opportunities to support new behaviors and acceptance of food-related tasks such as cooking and shopping (Setnick 2016). They also assess other comorbid conditions, such as refeeding syndrome, diabetes mellitus, food allergies, food intolerances, gastrointestinal conditions, and osteoporosis (Jeffrey and Heruc 2020), and ensure effective communication of nutrition care plans with other members of an individual's treatment team as well as families and carers.

Dietitians are responsible for managing the Nutrition Care Process defined by a comprehensive nutritional assessment, a nutritional diagnosis, implementation of a nutritional intervention, and monitoring progress toward treatment goals through an ongoing evaluation process (Jeffrey and Heruc 2020). This process should result in individually tailored nutrition care plans that correct nutritional deficiencies and promote optimal nutritional status, address the role of eating and adequate nutrition in physical and mental well-being, and provide education to challenge inaccurate beliefs about food (Setnick 2016; Hart et al. 2011b).

Practice standards for dietitians working with individuals with EDs have been published by the Australia New Zealand Academy for EDs (Heruc et al. 2020) and the Academy of Nutrition and Dietetics (Hackert et al. 2020). Dietitians should

consult these standards for detailed advice on the Nutrition Care Process to guide clinical practice and ensure effective, safe, and timely care in addition to consistent treatment approaches (Heruc et al. 2020).

Nutrition Assessment

Dietitians are likely to encounter individuals with EDs or disordered eating behaviors in their clinical work, even if EDs are not their specific area of practice. People with EDs may present to dietitians for seemingly unrelated nutritional issues that may include planning a vegetarian or vegan diet, support for food allergies or intolerances, or because they want to improve athletic performance. The general dietitian may encounter individuals with physical symptoms of an ED, electrolyte disturbance, or failure to gain weight despite apparent adequate intake that could be attributed to malnutrition or purging behavior. Other people at increased risk of an ED who may present to a dietitian include individuals with polycystic ovary syndrome (Lee et al. 2017), with type 1 diabetes mellitus (Young et al. 2013), seeking weight loss treatment or bariatric surgery with a history or diagnosis of other psychiatric illness (e.g., depression, alcohol misuse) (Mitchell et al. 2015), and with diagnoses requiring monitoring of dietary intake such as celiac disease (Satherley et al. 2016), inflammatory bowel disease (Abraham and Kellow 2011), or food allergies (Jafri et al. 2021).

As a result, all dietitians can be considered as "first responders" and have an important role in the identification of EDs, contributing to early intervention and access to treatment. Therefore, it is important that dietitians are aware of the clinical signs of an ED or individual at risk of an ED.

Nutritional Issues in Individuals with Eating Disorders

People with EDs engage in eating behaviors and dietary patterns with the aim of energy restriction for weight loss (Forbush and Hunt 2014). Underpinning these behaviors are disordered cognitions and beliefs relating to food and eating (Alvarenga et al. 2014). Nutritional issues and disordered dietary patterns commonly seen include:

- Avoidance of specific foods, including fat intake and other foods high in energy (Schebendach et al. 2011; Hart et al. 2018)
- Eating a limited and inflexible range of foods (Schebendach et al. 2011, 2012)
- Inadequate energy (calorie) intake (Chiurazzi et al. 2017)
- Nutritional deficiencies including calcium, fat-soluble vitamins, essential fatty acids, selenium, zinc, and B vitamins (Chiurazzi et al. 2017; Hanachi et al. 2019; Mehler 2017; Allen et al. 2013)
- Overconsuming low-energy foods; artificially sweetened products; "diet" foods, e.g., low-fat, low-carbohydrate, or low-sugar products (Hart et al. 2018); and excessive quantities of fruits and vegetables (Hart et al. 2018; Schebendach et al. 2017)

- Using fluids such as water, diet soft drinks, or coffee to suppress appetite and reduce the urge to binge eat (Forbush and Hunt 2014; Hart et al. 2018)
- A tendency to overestimate portion sizes (Dörsam et al. 2020)
- Counting calories (Levinson et al. 2017) or reading nutrition information panels on food packaging (Hart et al. 2008)
- Choosing foods with a "health halo" where a health benefit is attributed to the food making it more desirable (Schuldt et al. 2012)
- Over-involvement or avoidance of food preparation (Biddiscombe et al. 2018; Lock et al. 2012)
- Secretiveness including hiding or disposing of food and/or eating alone (Hackert et al. 2020)
- Disordered ways of eating such as inappropriate food utensils, excessive cutting of food, separating foods, and eating slowly (Hart et al. 2011b)
- Difficulty eating in social situations (Biddiscombe et al. 2018; Hart et al. 2018)
- Deficits in food literacy skills (i.e., the ability to plan and manage, select, prepare, and eat meals (Vidgen and Gallegos 2014)) including meal planning, preparation, and shopping
- Increased consumption of food-related content such as cookbooks and recipes (Grave et al. 2011) as well as social media content relating to fitness and dieting (Carrotte et al. 2015)

Nutritional issues which may be observed in individuals with binge eating disorder (BED) are listed below; however, current literature needs to be interpreted with caution as findings appear to vary depending on the methodology of dietary assessment used (Mourilhe et al. 2021):

- Foods high in sugar and fat, such as chocolate, cookies, and chips, are highly craved (Weingarten and Elston 1991; Reents and Pedersen 2021) and involved in typical binge eating episodes, compared to fruits and vegetables (Rosen et al. 1986).
- Energy intake is higher in females with obesity and BED on binge days compared to those with obesity without BED, as well as greater energy from fat compared to carbohydrate consumed by those with BED on binge days than those without (Raymond et al. 2012).
- Greater energy intakes (Raymond et al. 2012) and snacking (Harvey et al. 2011) reported at night.
- Breakfast is the least commonly consumed meal and the evening meal the most consumed meal (Harvey et al. 2011).

Nutrition Assessment for Eating Disorders

1. Food and nutrient intake
   - Premorbid and current dietary intake, with 24-h recall including fluid intake and macro- and micronutrient adequacy
   - Assessment of the risk of refeeding syndrome

2. Food and nutrient administration
   - How food is purchased and prepared, including planning, flexibility, timing of meals, and routines around food
   - Eating environment, considering location and with whom meals are eaten
3. Medication and complementary medicine use especially medications which affect appetite, resting metabolic rate, fluid excretion or metabolism, or misuse of medications such as insulin
4. ED-specific beliefs and behaviors
   - Knowledge, beliefs, and dietary rules about eating and reasons for these including the length of time and frequency of dietary restriction
   - The type, frequency, duration, and triggers of ED behaviors (e.g., binge eating, self-induced vomiting, hiding food, chewing and spitting, laxative, diuretic or other substance use)
5. Factors affecting access to food
   - Food insecurity
   - Confidence/ability to grocery shop, find appropriate recipes, and cook/prepare food
   - Access to appropriate kitchen and cooking equipment
6. Premorbid and current physical activity levels, including frequency, duration, type, and motivation
7. Nutrition-related person-centered measures
   - Goals of nutrition intervention and previous experiences with dietitians

Energy, fluid, and macronutrient requirements should be estimated, as well as recording of the following key anthropometric parameters:

- Current weight, height, and body mass index (BMI)
- Recent weight change and usual body weight
- Highest and lowest body weights and under what circumstances
- The impact of the ED on growth and development (e.g., in children, adolescents, and pregnant women)
- The individual's desired weight

It is important for the dietitian to liaise with a medical practitioner regarding specific medical complications associated with an ED. This will include monitoring of electrolytes, physical observations, and body weight. The most acutely concerning electrolyte abnormalities resulting from purging can be hypokalemia, hypochloremic alkalosis, hypomagnesemia, and/or hypophosphatemia. This may require emergency care and cannot be treated with dietary intervention alone (Setnick 2010).

Nutrition Intervention, Monitoring, and Evaluation

Key principles of nutrition intervention for the treatment of EDs include (Heruc et al. 2020; Hackert et al. 2020):

- Consideration of both psychiatric and medical risk factors and comorbidities
- Encouragement of a wide variety of foods from all food groups
- An emphasis on improving flexibility of food choice, eating socially with others and eating for enjoyment rather than to influence weight or shape
- The level of support available from carers/support people
- Monitoring and evaluation of chosen key nutrition indicators relevant to ED pathology as identified in the assessment

Eating adequately and regularly are core principles of treatment across all ED diagnoses and provide the basis of nutritional rehabilitation, to facilitate weight restoration (when required), and recovery from an ED. People with EDs should be prescribed an appropriate dietary regimen which meets nutritional requirements via three adequate main meals with two to three snacks. Eating regularly provides opportunities throughout the day to eat enough to meet energy requirements and prevent long gaps between eating, which can help in binge eating prevention. Additionally, blood glucose levels can be more stable, and there is opportunity to reconnect with body signals that support the intuitive eating process and regulate appetite. It is important to use an approach that does not focus on calorie counting, weighing or measuring foods. High-energy supplements and enteral feeding may also be considered. Nutrition intervention should also consider micronutrient requirements especially iron, calcium, and vitamin D which may require supplementation if adequate intake cannot be achieved orally, as well as ensuring fluids are not over- or under-consumed.

Nutrition Education and Counselling

Provision of nutrition education is a key aspect of nutrition intervention for EDs. Core nutrition education topics are provided in Fig. 1. It may also be appropriate for nutrition education to be provided to carers or support people of adults with an ED if consent is given. For children and adolescents, education is usually provided to the patient's parents/carers to facilitate their role in assisting their child normalize their eating. Nutrition counselling strategies which may be used by dietitians as part of nutrition intervention in EDs include motivational interviewing, goal setting, self-monitoring, and relapse prevention, as well as some components of cognitive behavioral therapy (CBT) such as graded exposure and behavioral experiments if the dietitian has received appropriate training and supervision.

It is essential to work with the treating team within the treatment model being implemented. For example, if a CBT intervention is being provided, dietitians can assist by providing education about metabolism, maintenance of body weight, and normal nutritional intake, which may promote engagement with CBT. In a family-based treatment approach, dietitians often consult with the family therapist around empowering the family to make appropriate choices around meal planning, adequate nutrition for age and physical activity level, and ensuring adequate food availability.

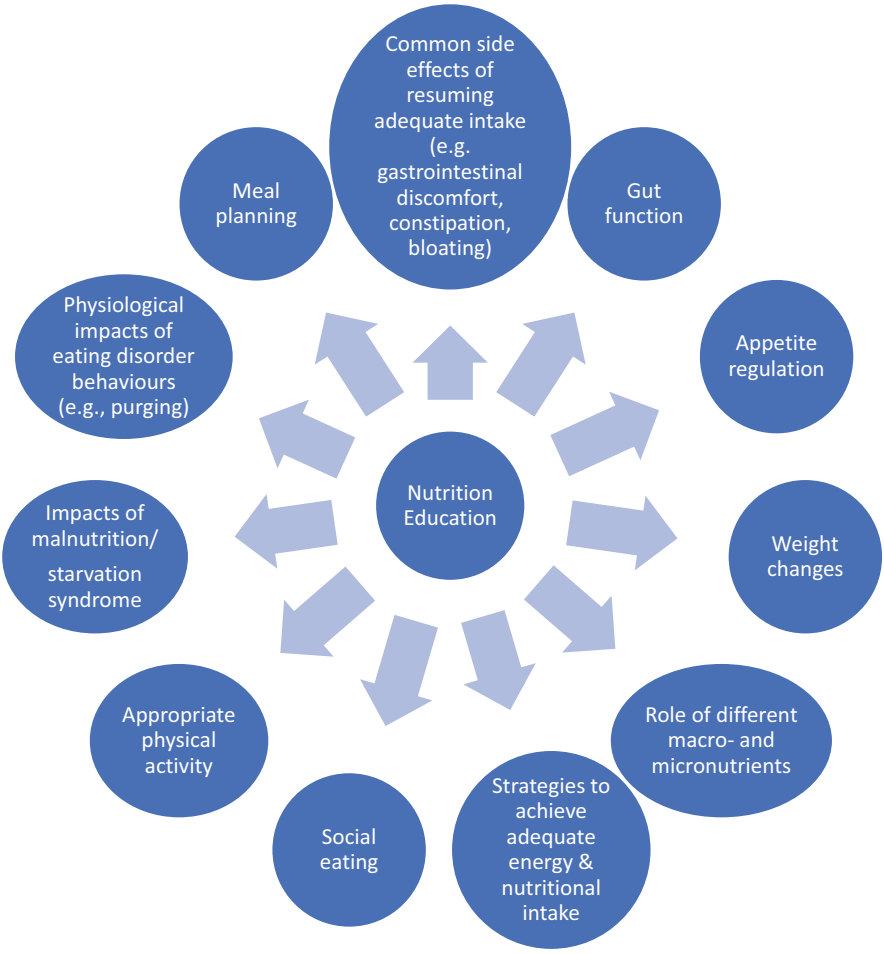


Fig. 1 Core nutrition education topics in nutrition intervention for eating disorders

Outpatient Dietetic Treatment for Eating Disorders

Goals of outpatient nutrition intervention for EDs include:

- Achieve a safe rate of weight restoration or weight maintenance.
- Reinstate or learn "normal" and healthy eating behavior, and provide nutrition education on the maintenance of long-term healthy eating essential for recovery.
- Increase intake from a variety of foods.
- Inclusion of "feared" foods.
- Increase intake of fats and oils to prevent essential fatty acid deficiencies if necessary.

- High intake of calcium-rich foods to improve bone density and prevent the early onset of osteoporosis if required.
- Minimize intake of low-energy foods/fat-reduced foods and "diet foods" where appropriate.
- Increase flexibility of food choices, eating out socially, and eating for enjoyment rather than for weight control.

There are a number of nutrition frameworks available that can be used to deliver nutrition intervention for EDs, including RAVES (Jeffrey 2021), the rule of threes (Herrin 2013), Plate-by-Plate Approach (Sterling et al. 2019), and The REAL Food Guide (Hart et al. 2018). All of these frameworks are practical tools to deliver an intervention to assist in meal planning and improving nutritional intake and are based on core nutrition and dietetic principles and the extensive clinical expertise of the authors as ED specialists. The latter framework, the REAL Food Guide, uses core principles of nutrition, with consideration of the belief systems that are frequently endorsed by individuals with an ED (Fig. 2).

Calcium Foods

Calcium foods are foods that are rich sources of calcium such as dairy products and calcium-enriched soy products. Fat-modified products, such as low-fat milk or diet yoghurt, are not recommended during nutritional rehabilitation. Because of restrictive eating behaviors, people with EDs severely compromise their chance of achieving peak bone mass and, as a result, often experience early onset of osteoporosis (Mehler 2017). Therefore, obtaining an adequate amount of dietary calcium is a key message and nutritional target for people with EDs. Avoiding or removing calcium-rich foods from the diet also means compromising adequate intake of many nutrients such as protein, vitamins (A, E, B12, and riboflavin), and other minerals (phosphorus, magnesium, potassium, and zinc). For those who choose not to have dairy products, calcium-*fortified* soy milk is the best option. It is essential that dietitians assess the brand, serving size, and frequency of calcium-rich foods as there is considerable variability in both the energy and calcium content of dairy alternatives.

Protein

A variety of animal and vegetarian protein foods are recommended daily. A simple method for achieving balanced meals at lunch and at dinner is to use the "thirds rule" (Fig. 3). This means that on an average-size dinner plate, one third of the plate should be filled by carbohydrate foods, one third by protein foods, and one third by vegetables. Many people with EDs choose a vegetarian diet because they believe it is a "healthier" way of eating (Zuromski et al. 2015). While it is possible to meet their nutritional needs with a vegetarian diet, it is important that alternative sources of iron and zinc are emphasized as part of their meal plan. It is also recommended

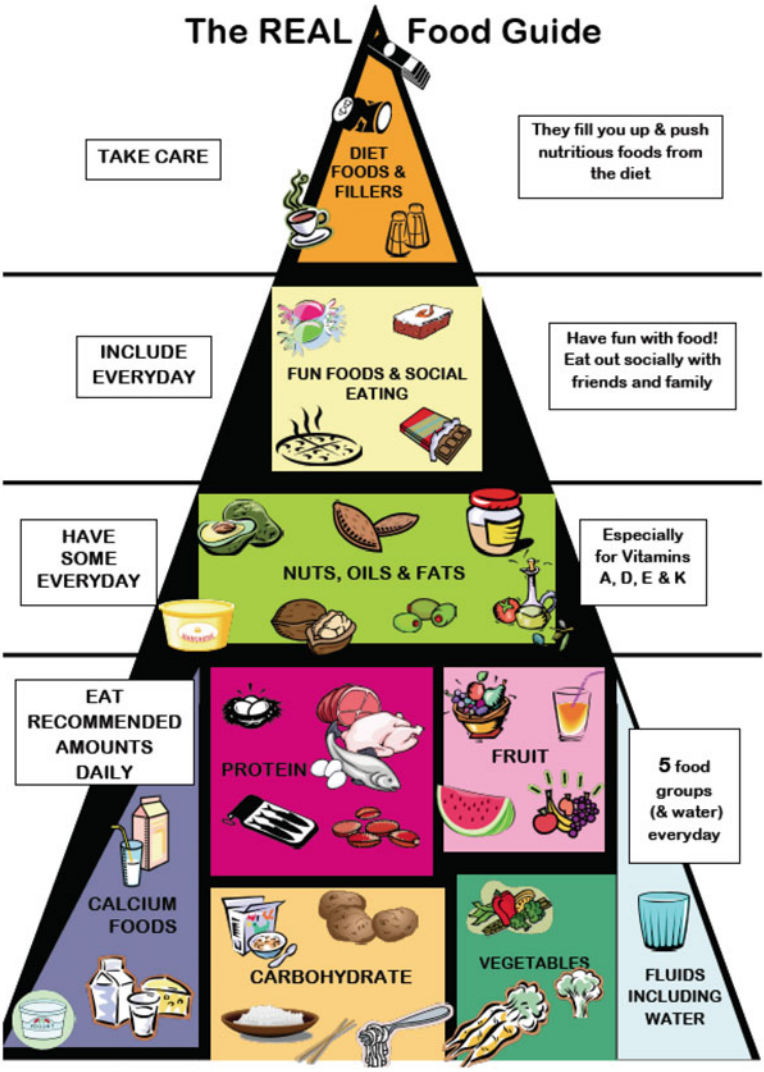


Fig. 2 The REAL Food Guide pyramid

that education is provided on factors that enhance and inhibit iron absorption, particularly as people with EDs may consume excessive volumes of tea and coffee with meals (Ahmad Fuzi et al. 2017), or as an alternative to eating adequately (Hart et al. 2018).

Current research indicates that adoption of a vegan diet before the onset of an ED might not necessarily be related to weight and shape motives or play a role in the development of an ED (Bardone-Cone et al. 2012; Heiss et al. 2017; Timko et al. 2012). However, individuals that adopt a vegan diet for weight and shape reasons are

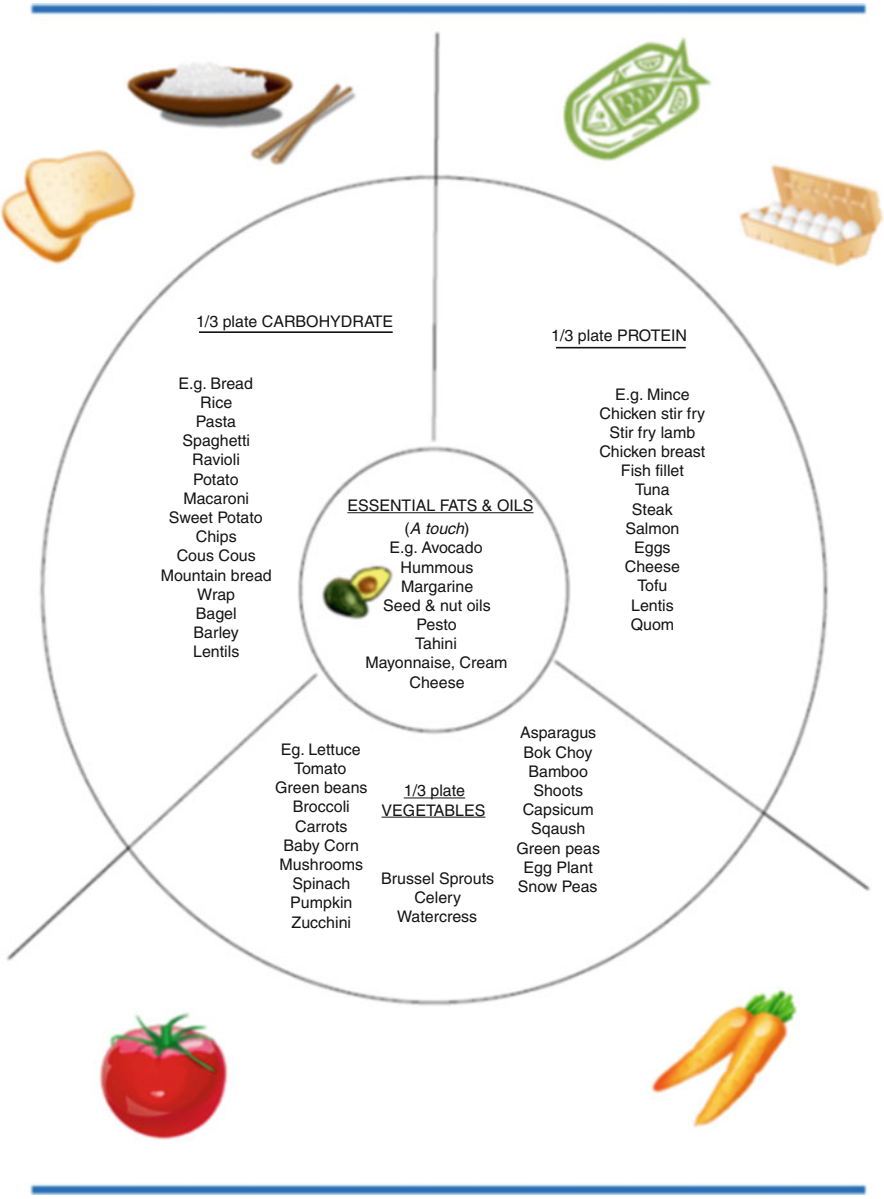


Fig. 3 Thirds rule for main meals

likely to be more at risk of an ED; and those who adopt meat avoidance and veganism after onset of the ED are more likely to be motivated to maintain their ED by the dietary adherence (Bardone-Cone et al. 2012). The dietitian should obtain a thorough history of the timing and motives of the onset of this dietary adherence in

order to provide the best advice to the individual. Nutrients that are at risk include iron, calcium, selenium, vitamin B12, and vitamin D, and supplementation may be required depending on the individual's intake of fortified foods. While there may be genuine ethical reasons for choosing a vegan diet, it is not recommended as a standard treatment for ED, and continued endorsement of such a diet involves restricted food choices, dichotomous thinking about food, hyper-vigilance about ingredient lists on food labels, and limitations on social eating such as avoiding restaurants or food prepared by others because of uncertainty about the ingredients used.

Carbohydrates

It is recommended that carbohydrate is included at breakfast, lunch, and dinner, as well as a snack option at least once per day. The amount of carbohydrate that is required is proportional to the amount of physical activity undertaken and if weight gain is required.

Fruits and Vegetables

A variety of different fruits and vegetables of different color are recommended daily. It is important fruits and vegetables are not eaten in excessive quantities as they are filling and push other nutritious food groups such as carbohydrate, fats, and protein foods from the diet.

Fluids

Water is included as a core food group of the REAL Food Guide to emphasize that adequate hydration is an important component of daily nutritional requirements and should be incorporated into meal plans. Disordered fluid intake is often observed in the majority of people with EDs, and fluid choices are often related to ED beliefs (e.g., as a weight control method by suppressing appetite or to aid vomiting (Hart et al. 2011a)). Some people with EDs will restrict fluid intake and put themselves at risk of dehydration, while others drink large quantities of fluid to manage feelings of hunger.

Nuts, Oils, and Fats

A balanced diet includes adequate amounts of dietary fats and oils and foods that contain them each day as low intake of fat-soluble vitamins and deficiencies of essential fatty acids have been documented in EDs (Misra et al. 2006; Allen et al. 2013; Swenne and Rosling 2012).

Fun foods and social eating are recommended to assist with meeting energy requirements and to challenge beliefs that these foods should be avoided or removed from the diet for good health (Hart et al. 2018). It is also clinically important from a dietary and psychological perspective to include higher-energy foods. Eating out and in social situations is recommended so that people with EDs practice skills that enable them to spend time with family and friends and participate in social activities that involve food, eating in a manner similar to others at a social event, and expanding eating experiences.

Diet Foods and Fillers

Low-energy foods are commonly used by people with EDs as a method of suppressing appetite and restricting energy for weight loss. From a nutrition standpoint, these foods become problematic when they make up a significant proportion of a daily intake as they replace or push out more nutritious foods from the diet. They may also keep individuals focused on dietary rules and restricting food, and the inclusion of diet foods and fillers is also counterproductive for weight restoration in those who need to regain weight. The recommendation is not necessarily to eliminate these foods but to "be careful" in regard to how they might affect overall dietary intake.

Inpatient Dietetic Treatment for Eating Disorders, Including Considerations for Individuals with Anorexia Nervosa

The majority of individuals with an ED can be managed in the community as an outpatient, but some individuals may require hospitalization. Reasons for an inpatient admission may include when thresholds for medical instability are triggered, when there is high frequency of compensatory behaviors, or there is minimal progress with outpatient intervention. Individuals who are well below an appropriate weight, such as those with a diagnosis of AN, may benefit from a greater level of structure or support provided in an inpatient setting. Goals of inpatient nutrition intervention for EDs include:

- Stabilize body weight and increase weight to a safer level through initiation of nutritional rehabilitation.
- Treat medical complications and restore medical stability.
- Reduce purging (i.e., vomiting/laxative use) or other disorder behaviors sufficient to restore medical stability.
- Initiate multidisciplinary care.
- Support development of appropriate eating behavior, allowing for continued medical stability in the community.
- Connect people with the next step of care for ED treatment on discharge.

Refeeding Syndrome

Refeeding syndrome describes a potentially fatal condition comprising metabolic and biochemical complications that can arise when malnourished individuals begin consuming an increased energy intake (Matthews 2019). These complications are considered to be a direct consequence of nutrient overload, particularly carbohydrate, fluid, and/or sodium, as the malnourished persons' weakened cardiopulmonary and gastrointestinal systems attempt to process larger quantities of oral, enteral, and/or parenteral nutrition (Matthews 2019; Skipper 2012). Refeeding syndrome's hallmark biochemical feature is hypophosphatemia, though a number of signs and symptoms may present during its development, ranging from hypokalemia to thiamine deficiency (Matthews 2019; Mehanna et al. 2008). Rebound hypoglycemia can also be an issue due to an influx of insulin in response to bolus carbohydrate. People with AN are typically considered to be at high risk of developing refeeding syndrome; however any person with an ED should be considered high risk, particularly if purging is a component of their presentation.

Refeeding syndrome is said to occur between days 2 and 5 of nutritional rehabilitation; however in a recent study with adult inpatients with EDs, electrolyte decreases were more common in the initial 24 h (Matthews et al. 2018). Prevention of refeeding syndrome is key. Nutritional rehabilitation should be commenced with care, combined with an awareness of risk factors. Prophylactic thiamine and multivitamin supplementation should be provided with consideration of phosphate supplementation. Regularly checking serum electrolyte levels (daily for at least the first 7–10 days), clinical monitoring (i.e., heart rate, blood pressure), and fluid status monitoring should also be provided in the early stages of nutritional rehabilitation.

Nutrition Support for Inpatients

While oral nutrition is most beneficial for people with EDs (Hart et al. 2013), continuous nasogastric (NG) feeds have benefits for medically compromised inpatients. This includes (1) energy and carbohydrate provision being easier to control (potentially reducing risk of refeeding syndrome), (2) fewer instances of hypoglycemic events (Matthews et al. 2018; Matthews-Rensch et al. 2021), (3) reducing physical discomfort for the person, (4) medicalizing the treatment (possibly reducing the power struggle between the person with an ED and treating team), and (5) transferring the responsibility of weight gain to the treating team (Hart et al. 2013).

Based on a nutritional assessment and particularly if there is no standardized protocol to guide clinical practice, it may be necessary for the dietitian to advise the treating team about the benefit of NG versus oral feeding. The greater the medical risk, the greater the importance of NG feeding to medically stabilize the inpatient. A time frame may be established in order to determine if the individual can eat adequately before NG feeding is started. Implementing close one-to-one nursing supervision if resources are available and use of food and fluid charts to document intake can be useful tools to inform the dietitian and the treating team. Meal support

therapy is also a useful strategy for inpatient staff to support oral intake of meals and snacks.

Feeding can be commenced once prophylactic vitamin supplementation has been commenced and serum electrolyte levels have been checked, with any abnormalities being corrected before and during feeding. A low-fiber, energy-dense enteral feed is recommended, with ≤50% of energy from carbohydrates. Traditionally, a "start low, go slow" method of feeding was recommended to prevent the development of refeeding syndrome (typically commencing at ~4000 kJ/day). However, research is now demonstrating that these methods have been too conservative and potentially placed inpatients at risk of the "underfeeding syndrome," longer lengths of stay, and further medical deterioration. Underfeeding syndrome refers to the weight loss and physical deterioration occurring in an inpatient because of failure to provide adequate nutrition support to reverse signs and symptoms of malnutrition. Adolescent inpatients with EDs have been safely commenced on feeds starting at 8000 kJ/day (Whitelaw et al. 2010; Garber et al. 2013; Parker et al. 2016; Golden et al. 2013), whereas adult inpatients have been safely commenced at 6000 kJ/day (Matthews et al. 2018).

Equations for estimating energy requirements are often inaccurate when calculated for individuals with AN (El Ghoch et al. 2012). Most overestimate requirements prior to nutrition repletion, when in a hypometabolic starved state (Cuerda et al. 2007). Energy requirements then increase disproportionately during the course of refeeding, and patients may become hypermetabolic (Wakefield and Williams 2009). Energy intake must be modified due to changes in resting energy expenditure (REE) during the course of refeeding in AN, which will impact the rate of weight gain (Mehler et al. 2010; Marzola et al. 2013). The increase in REE is multifactorial and thought to be due to an increase in lean body mass as the individual restores weight (El Ghoch et al. 2017), as well as the thermal effect of food (Moukaddem et al. 1997) (i.e., the increase in energy required to process, digest, and absorb nutrients), and psychological factors such as anxiety and fear of weight gain, which can also result in increased fidgeting and pacing (Marzola et al. 2013).

The optimal time to transition the individual from continuous NG feeds to oral nutrition has not been thoroughly investigated. Consideration should be given to the setting in which treatment is being provided, the individual's baseline weight, physical status, residual ED behaviors, and cognitive state, as the individual experiencing starvation syndrome is less likely to engage appropriately with an oral meal plan. Nasogastric feeding is a short-term strategy, and it is ideal to transition to the use of meal plans and meal support therapy to facilitate improved oral intake.

Considerations for Individuals with Bulimia Nervosa

Recurrent binge eating and compensatory behaviors (purging, dietary restriction, or excessive exercise) raise important nutritional issues for people with bulimia nervosa (BN).

Dietary restriction may be an important factor in binge eating behavior in BN (Latner and Wilson 2004; Masheb et al. 2011). This may place people at risk of semi-starvation, despite engaging in binge eating behavior (De Zwaan et al. 2002). Nutritional abnormalities occur and are dependent on the amount of dietary restriction during non-binge episodes and the extent of purging behavior (Henry and Ozier 2006). A recent study has also shown dietary restriction, even when arising from food insecurity, may increase or maintain BN by inhibiting regular eating patterns (Lydecker and Grilo 2019). It is important to be aware, however, that triggers for binge eating are complex and involve both internal (negative emotions and physical urges to eat foods) and external (dietary restriction) triggers (Chami et al. 2021). However, a recent study has found that skipping meals and dietary restriction were not associated with binge eating (Chami et al. 2021). It has also been highlighted that overeating behaviors may become habitual over time and can occur in the absence of internal cues (Treasure et al. 2018). This highlights the importance of targeting interventions to modify cognitive dietary restraint and as well as active dietary restriction.

Binge eating behavior can have significant physical and psychosocial impacts on people with BN. Physical impacts can include significant gastrointestinal symptoms, weight fluctuations, altered lipid profiles, and in some instances gastric dilatation or perforation (Gyurkovics et al. 2006). Increased risk of polycystic ovaries has also been reported (Waterhous and Jacob 2011). Self-induced vomiting and inappropriate use of substances for weight control (laxative agents or diuretics) are largely ineffective for weight loss and can raise significant nutritional risk (Hart 2016; Pomeranz et al. 2013). Dehydration and electrolyte abnormalities (particularly sodium and potassium) associated with purging are common in people with BN, and impairment of gastrointestinal and cardiovascular systems, hemorrhage, hepatic and renal complications, and chronic constipation or diarrhea can occur (Pomeranz et al. 2013).

Treatment Considerations for Individuals with Bulimia Nervosa

Cognitions and skills around food, eating, and body weight or shape, alongside dietary restriction, binge eating, and purging, are key areas for intervention. Nutrition interventions for people with BN aim to restore normal nutritional status and facilitate normal, regular eating behavior without the use of binge eating or compensatory behaviors. Strategies may include psychoeducation especially regarding the consequences of purging, assistance with meal and food planning, behavioral experiments, and self-monitoring. Medical guidance around stimulant laxative withdrawal and management, strategies to manage acid reflux symptoms, and encouraging adequate dental hygiene practices may be discussed. Dietary strategies to assist with bowel function include introducing adequate dietary fiber and fluid intake.

Regular patterns of nutritionally adequate dietary intake may assist in normalizing nutritional status, reduce urges to binge eat or purge, reduce preoccupation with food, improve feelings of hunger and satiety, and improve mood (AED 2020).

Frequent breakfast consumption has been found to correlate with more frequent meal consumption, reduced binge eating, and lower BMI (Masheb et al. 2011). Intuitive eating (where eating is guided by internal body cues) may also be associated with lower binge eating patterns (Linardon et al. 2020).

Particular consideration needs to be given to food shopping, food storage (impacting on accessibility of both "safe" foods and "trigger" foods), and the financial impact of purchasing increased quantities of food for an individual with BN. The macronutrient composition of the diet also appears to be important. One study found incorporating adequate protein in the diet of people with BN may reduce binge eating frequency (Latner and Wilson 2004). "Trigger" foods are incorporated gradually, alongside distraction and emotion regulation strategies. Targeted experiments with "trigger" foods are recommended by trained clinicians, for example, planning to introduce a small amount of the "trigger" food when there is limited opportunity to binge eat or purge. Self-monitoring of eating behaviors through food records, including factors that precede binge eating or compensatory behaviors, can raise self-awareness, assist in regulating eating, and identify food or nonfood triggers for binge eating and compensatory behaviors.

Considerations for Individuals with Binge Eating Disorder

Considerations for Individuals with Co-occurring Binge Eating Disorder and Obesity

Stunkard (1959), a well-known obesity clinician and researcher, was the first to report the episodic overeating behavior of a minority of his patients with obesity and to formalize this as binge eating or eating without satiation. Since then, it has been widely recognized as an important contributor to both the EDs and weight management areas. Although it is thought that 2% of community samples may have BED, up to 30% of people seeking treatment for obesity are likely to meet criteria (De Zwaan 2001). Binge eating disorder has been linked to chronic nutrition-related physical conditions such as weight gain and obesity, type 2 diabetes, metabolic syndrome, hypertension, dyslipidemias, and sleep disorders (Olguin et al. 2017). Comorbidity with other mental health conditions such as depression and anxiety is also well established (Sheehan and Herman 2015; Keski-Rahkonen 2021).

Research has shown that binge eating behaviors are growing more rapidly than any other disordered eating behavior (Hay et al. 2008). Binge eating disorder presents a unique paradigm that overlaps between EDs and weight management, meaning that these individuals may present to a range of clinical settings (Bertoli et al. 2016), including dietetic services. This highlights the importance of dietitians being equipped to manage people affected by BED. Treating people who are living with both obesity and BED is challenging for both the clinician and individual. In the weight management setting, binge eating may not be identified unless asked directly and even then may not be admitted to. Additionally, weight management dietitians may not ask about binge eating due to a lack of confidence in their ability to deal with

an ED. In clinical practice, it is often noticed that even when binges are reduced and food is in greater control, weight loss is unlikely to meet expectations, leading individuals (and potentially clinicians) to be disappointed.

Clinical trial data such as the US Look AHEAD study have reported that participants with obesity who consistently reported binge eating lost half as much weight by year 4 of the study as those whose binge eating remitted early or those who didn't binge eat at any time (Chao et al. 2017). Similarly, veterans with overweight or obesity in the ASPIRE low-intensity weight management trial differed in success according to their binge eating. Those with binge eating lost half the weight (1.4% of body weight) compared with those without binge eating (2.7%) (Masheb et al. 2015). The small minority with high-frequency binge eating gained 1.4% body weight over the 12-month trial. In addition, binge eating affects the longevity of weight loss. In a weight loss maintenance trial, those with binge eating regained weight at 1.5 times the rate of those without binge eating (Masheb et al. 2015).

In people with high BMIs, very low-energy diets or severely energy-restricted diets that use meal replacement therapy have been shown to be a highly effective treatment (Maston et al. 2019). These treatments are often criticized due to their restrictive nature and potential to be a major contributor to binge eating and lead to the development of EDs. However, some studies that involved highly restricted diets such as very low-energy diets have shown that binge eating generally is stable or improved post intervention (Raymond et al. 2002; Svendsen et al. 2008; Wadden et al. 1994; Pekkarinen et al. 1996). One small study showed that 57% of those with diagnosed BED at baseline had improvements in their BED with 30% no longer meeting criteria for BED or subclinical BED 1 year post intervention (Raymond et al. 2002). However, it should be noted that 10% who did not meet criteria for BED or subclinical BED at baseline developed BED and 14% developed subclinical BED by 1 year. Other studies have shown that it is not dietary restriction or restraint that impacts on the disordered eating but the individual's level of disinhibition (Svendsen et al. 2008; Fogelholm et al. 1999; Yanovski and Sebring 1994).

Despite BED and high BMIs commonly coexisting, treatment for individuals with BED living with obesity is problematic because the approaches used for weight loss generally do not focus on the presence of binge eating and its related psychological symptoms. Additionally, psychological treatments for EDs are generally ineffective in promoting weight loss (Palavras et al. 2021). Traditionally it has been recommended that BED be treated first as dieting or restricting intake may trigger more binge eating events, thus perpetuating the ED and making weight loss harder. Despite this recommendation, people living with concurrent BED and obesity are more likely to seek weight loss treatment than treatment for their ED (Star et al. 2015).

Cognitive behavioral therapy has the strongest evidence for treatment of adults with BED, while evidence for adolescents is more limited (Hay et al. 2014). Behavioral weight loss has also been shown to be effective in the short term (Hay et al. 2009), but not in the longer term (Wilson et al. 2010). Dietitian-delivered guided self-help has also been shown to be effective for individuals with binge eating

(Traviss-Turner et al. 2018). In a review that compared CBT and weight loss behavioral therapy on binge eating pathology and weight loss in those with coexisting BED and high BMI, found CBT was favored for short-term binge eating reduction, but this was not sustained at 12 months. Furthermore, there was insufficient evidence to suggest that one type of intervention was superior to the other for weight loss, binge eating remission, or reduction of binge eating frequency (Palavras et al. 2017). Recently there has been research that has focused on treating the two together, e.g., HAPIFED trial (Palavras et al. 2021; Da Luz et al. 2017). The program has been found to be equally effective as CBT-E in reducing ED symptoms but superior in inducing weight loss. However, more research is required.

Encouraging people living with both BED and obesity to seek psychological support if not offered as part of the weight loss intervention is recommended. Providing a nonjudgmental, non-stigmatizing approach may help the individual confide in the clinician. Acknowledging their desire and reasons for weight loss is important; however, addressing how this could be perpetuating the binge eating should also be acknowledged. There are many strategies that cross both weight management and ED interventions which may offer some hope, although it should be stated upfront that weight loss is not the aim of the initial treatment, and without understanding the drivers that maintain the binge eating, long-term solutions are unlikely.

Strategies that cross both treatment areas include:

- Monitoring intake, behavior, and reasons for eating/restriction.
- Ensuring a balanced diet with regular meals that is nutritionally complete and enjoyable, including a meal plan, discussing food groups, portion sizes, food swaps, and flexibility around food choice.
- Reducing grazing.
- Making the environment suit the way the individual wants to eat.
- Acknowledging body image and stigmatization and its role in thoughts and actions.
- Managing and identifying physical hunger and internal and external cues to eating.
- Ensuring weighing no more than once per week and discussing a nonjudgmental attitude to the number on the scales.
- Removing food labels (e.g., good vs bad foods and dieting rules) and avoiding calorie counting.
- Using cognitive behavioral techniques to change thoughts or emotions and subsequently actions including stimulus control, problem-solving, and distraction techniques. Other behavior techniques include goal setting, urge surfing, and mindfulness.
- Planning for the future and acknowledging that relapses are likely.
- Ongoing collaboration with a mental health clinician.

In addition to the components above, specific additional information gathered as part of the treatment of BED should include family weight history, dieting attempts

and reasons for weight gain, feelings and perceptions of their weight triggers to eating if known, and feelings of loss of control. More research is required to understand how best to treat the people living concurrently with BED and obesity as well as better collaboration between weight management and ED dietitians to improve clinical outcomes.

Application to Other Eating Disorders

This chapter has provided an overview of the principles of dietetic treatment for individuals with EDs with diagnoses of AN, BN, and BED as well as specific considerations for dietetic intervention in an outpatient or inpatient setting. Most nutritional issues and approaches discussed are also relevant to other ED diagnosis including other specified feeding and eating disorders (OSFED) such as atypical anorexia nervosa and avoidant/restrictive food intake disorder (ARFID). Individuals with ARFID, however, tend to restrict the amount of type of particular foods or good groups based on factors such as the appearance, texture, smell, or temperature of a food or due to past negative experiences such as trauma associated with a food experience such as choking. Current research recommends a CBT approach which involves gradually exposing the individual to feared foods, relaxation training, and support to change eating behaviors. Similar to treatment recommendations provided in this chapter, treatment for ARFID should be multidisciplinary involving psychological, nutritional, and medical input.

Mini-Dictionary of Terms

Food insecurity: The disruption of food intake or eating patterns because of lack of money and other resources.

Food literacy: The ability to plan and manage, select, prepare, and eat meals.

Nutrition assessment: A systematic approach to collect, classify, and synthesize important and relevant nutritional data from patients.

Nutrition Care Process: A systematic method that nutrition and dietetics practitioners use to provide nutrition care.

Nutrition intervention: A planned intervention aimed at changing a nutrition-related behavior, risk factor, environmental condition, or aspect of health status.

Nutrition counselling: A two-way interaction between a patient and dietitian to discuss results of a nutrition assessment; identify nutritional issues, needs, and goals; discuss and plan appropriate nutrition intervention; and determine frequency of nutrition monitoring and evaluation.

Refeeding syndrome: A potentially fatal condition comprising metabolic and biochemical complications that can arise when malnourished individuals begin consuming an increased energy intake.

Key Facts

Key Facts Regarding the Role of Dietitians in Eating Disorder Treatment

- Dietitians are highly educated at university in human physiology, biochemistry, nutritional science, and eating behavior.
- Dietitians play a crucial role in helping individuals with EDs understand the interaction between food, nutrition, and well-being and supporting them to achieve nutrition-related treatment and recovery goals.
- Dietitians encourage active learning opportunities to help teach new behaviors and acceptance of food-related tasks, e.g., activities such as cooking, shopping, or modeling normal eating behavior in a meal supervision format or as part of practical eating activities.
- Practice standards for dietitians working in EDs have recently been published to ensure effective, safe, and timely care for individuals with an ED in addition to consistent treatment approaches.
- Consistent and standardized dietetic practice may not only enhance the legitimacy and credibility of dietitians as part of the multidisciplinary team, but may also lead to improvements in clinical care for individuals with EDs.
- It is important that dietitians advocate for people with EDs to have access to relevant, accurate, and evidence-based nutrition information that contributes to their recovery.

Summary Points

- Dietitians are responsible for managing the Nutrition Care Process defined by a comprehensive nutritional assessment, a nutritional diagnosis, implementation of a nutritional intervention, and monitoring progress toward treatment goals.
- Dietitians are likely to encounter individuals with EDs or disordered eating behaviors in their clinical work, even if it is not their specific area of practice. As a result, all dietitians can be considered as "first responders" and have an important role in the identification of EDs, contributing to early intervention and access to treatment.
- People with EDs engage in eating behaviors and dietary patterns with the aim of energy restriction for weight loss. Underpinning these behaviors are disordered cognitions and beliefs relating to food and eating.
- Eating adequately and regularly are core principles of treatment across all eating disorder diagnoses, and provide the basis of nutritional rehabilitation, to facilitate weight restoration and recovery from an eating disorder.
- There are a number of nutrition frameworks available that can be used to deliver nutrition intervention for EDs, including RAVES, the rule of threes, plate-by-plate approach, and the REAL Food Guide.

- Refeeding syndrome describes a potentially fatal condition comprising metabolic and biochemical complications that can arise when malnourished individuals begin consuming an increased energy intake.
- While oral nutrition is most beneficial for people with EDs, continuous nasogastric feeds have key benefits for medically compromised inpatients.
- It is important for the dietitian to liaise with a medical practitioner regarding specific medical complications associated with an ED.

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Part II

Anorexia Nervosa

A Research Approach to Self-Report and Objective Measurements of Physical Activity in Eating Disorders

21

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Contents

Introduction 415
Assessment Tools for Measuring Objective and Psychological Components of PA in EDs 416
Self-Report Measurement of PA in EDs 416
Ecological Momentary Assessment of PA in EDs 421
Semi-structured Interviews of PA in EDs 424
Assessment Tools for Measuring Objective Components of PA in EDs 426
Objective Measurement: Types of Sensor Technology 426
Objective Measurement Outcome Variables 428
Strengths and Weaknesses of Objective PA Measurement 429
Future Directions of Assessment of Psychological and Objective Components of PA in EDs 430
Mini-Dictionary of Terms 431
Key Facts 432
Summary Points 432
References 432

Abstract

Physical activity (PA) is complex and difficult to characterize within eating disorder (ED) populations, due to the presence of both adaptive and maladaptive PA. To better understand PA in ED populations, it's important to consider both the psychological and objective factors of PA in EDs. Within ED research, PA has been most commonly measured using self-report, ecological momentary

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assessment, and clinician assessment of PA. While these forms of measurement capture many psychological factors of PA like exercise motivation, these measures are subjective methods prone to biases and are reliant on an individual's recall. In addition to self-report measurement, emerging research has begun to utilize objective measurement tools, such as wearable sensors, to assess the objective components of PA in EDs. Sensor technologies are automatic and continuous methods of measuring PA that do not rely on subjective reporting and instead offer real-time data collection. The following chapter reviews the current measurement tools available to assess both the psychological and objective components of PA in ED populations and proposes future use of a multimodal method of investigating PA in ED populations.

Keywords

Eating disorders · Physical activity · Maladaptive physical activity · Adaptive physical activity · Sensor technology · Wearable sensors · Ecological momentary assessment · Compulsive exercise · Excessive exercise · Driven exercise · Compensatory exercise · Self-report measures · Semi-structured interviews · Assessment tools · Objective measurement

Abbreviations

ACSM	American College of Sports Medicine
BMI	Body mass index
CDC	Center for Disease Control
CES	Commitment to Exercise Scale
CET	Compulsive Exercise Test
DSED	Diagnostic Survey for Eating Disorders
EAI	Exercise Addiction Inventory
ED(s)	Eating disorder(s)
EDE	Eating Disorders Examination Interview
EDE-Q	Eating Disorders Examination Questionnaire
EDI-SC	Eating Disorders Inventory-Symptom Checklist
EMA	Ecological Momentary Assessments
EMI-2	Exercise Motivations Inventory-2
GLTEQ	Godin Leisure-Time Exercise Questionnaire
IPAQ	International Physical Activity Questionnaire
METs	Metabolic equivalents
MVPA	Moderate-to-vigorous physical activity
OEQ	Obligatory Exercise Questionnaire
ORQ	Modified Obligatory Running Questionnaire
PA	Physical activity
PAR	Seven-Day Physical Activity Recall
PATX	Physical Activity Trend eXtraction
PPAQ	Paffenbarger Physical Activity Questionnaire
REI	Reasons for Exercise Inventory

Introduction

Physical activity (PA) is traditionally characterized as a healthy, adaptive behavior due to its physical and mental health benefits (Penedo and Dahn 2005; Catalan-Matamoros et al. 2016); however, among those with eating disorders (EDs), PA is commonly utilized as a maladaptive strategy to control an individual's shape and weight. Research classifies maladaptive PA as (1) PA intended to compensate for calories consumed during binge eating episodes and (2) PA that is driven (i.e., having a compulsive quality) and motivated by shape and weight concerns (Holland et al. 2014; Cook and Hausenblas 2008). Maladaptive PA is acknowledged in the field as a prominent factor in the etiology, development, and maintenance of symptoms across ED diagnoses (Meyer et al. 2011), and it is associated with several negative physical and psychological consequences (Lichtenstein et al. 2017). For example, individuals who engage in maladaptive PA may engage in PA to the point of injury, follow a rigid PA structure that interferes with other commitments (i.e., work, social events), or experience intense guilt or anxiety when unable to engage in PA. Maladaptive PA has also been associated with lower body mass index (BMI), higher levels of anxiety, and perfectionistic qualities (Shroff et al. 2006). Given the profound impact maladaptive PA has on individuals with EDs, it has increasingly become a focus of research as the field aims to gain further insight on how to prevent and treat maladaptive PA in the context of EDs.

While extant literature highlights the prevalence and importance of understanding maladaptive PA among ED populations, a growing body of research indicates that not all PA occurring among individuals with an ED is maladaptive. Rather, some individuals may engage in adaptive PA, which is characterized as PA that is non-compensatory, not solely intended to control shape or weight, and is non-driven. For instance, preliminary research using ecological momentary data revealed that 43% of individuals with binge-spectrum eating report both maladaptive and adaptive PA episodes (Lampe et al. 2021). Further, many individuals with EDs across diagnoses report engaging in only adaptive PA episodes (Wons et al. 2021; Lampe et al. 2021; Kerrigan et al. 2019). As the field continues exploring PA among ED populations, both maladaptive and adaptive PA should be considered when studying PA in EDs, as understanding both types of PA may enhance our understanding of the etiology, development, and maintenance of ED symptomology.

When studying PA in EDs, it is important to consider both (1) objective components of PA (e.g., frequency, duration, and intensity of PA) and (2) psychological components of PA (e.g., motivation to exercise, function of the exercise). To capture the objective and psychological components of PA in EDs, researchers must consider using rather complex multimodal assessment paradigms to fully capture both the objective and psychological components of PA in EDs.

Given the complex nature of assessing the psychological and objective components of PA in EDs, the following chapter aims to provide guidance around best practices for measuring the psychological and objective components of PA. The following sections will review (1) current assessment tools available to assess the psychological and objective components of PA in EDs and their purpose

and (2) the strengths and weaknesses of current assessment tools that assess psychological and objective components of PA in EDs. The chapter will end by providing guidance on multimodal assessment and future directions in the measurement of psychological and objective components of PA in EDs.

Assessment Tools for Measuring Objective and Psychological Components of PA in EDs

The main aim of the following subsections is to review current assessment tools, what psychological components of PA in EDs they assess, and the strengths and weaknesses of self-report measurements, EMA, and semi-structured interviews.

Self-Report Measurement of PA in EDs

Self-report tools are a common way to measure the psychological and objective components of PA among individuals with EDs. To date, self-reported PA has been primarily measured via surveys that assess the overall amount of PA engagement, including maladaptive qualities such as its driven or compensatory nature. Extant measures of self-reported psychological components of PA used in ED populations typically fall into one of three categories: (1) measures of general PA motivations (e.g., health improvement, enjoyment), (2) the compensatory nature of PA, and (3) the driven nature of PA engagement. See Table 1 for a complete list of self-report measures of PA in EDs.

Self-Report Measures of Objective Components of PA

Seven-Day Physical Activity Recall (PAR). The PAR (Blair et al. 1985) asks participants to recall morning, afternoon, and evening activities for the previous day until a full 7 days of information on minutes spent engaged in vigorous-intensity and moderate-intensity activities and sleep has been obtained. Cues are used to prompt classifications of activity into their respective intensities (i.e., light, moderate, and vigorous). While the PAR has not been validated in an ED population, it has demonstrated good validity in adult and young adult populations (Washburn et al. 2003; Lamb and Brodie 1990).

International Physical Activity Questionnaire (IPAQ). There are two versions of the IPAQ (Craig et al. 2003) that both assess PA engagement over the last 7 days. The short version (9 items) collects information from participants on the time spent walking, in vigorous- and moderate-intensity activity, and sedentary activity. The long version (31 items) collects detailed information within the domains of household and yard work activities, occupational activity, self-powered transport, and leisure-time physical activity, as well as sedentary activity. An additional question asks about the pace of walking and cycling. While the IPAQ has not been validated in ED samples, it has demonstrated adequate reliability across diverse populations (Craig et al. 2003; Lee et al. 2011; Bauman et al. 2009).

Table 1 Overview of measures of self-reported PA in EDs

Category	Measure name	Main construct assessed	Assessment period	Reliability in ED samples
Objective PA components	Seven-Day Physical Activity Recall (PAR)	Amount of time spent in "moderate," "hard," and "very hard" activity	Last 7 days	$r = 0.87$ with 7-day PA diary
	International Physical Activity Questionnaire (IPAQ)	Amount of time spent being active, sitting, walking, and engaging in moderate and in vigorous activity	"A typical week"	–
	Godin Leisure-Time Exercise Questionnaire (GLTEQ)	Frequency of engaging in bouts of at least 15 min of mild (e.g., "yoga, easy walking"), moderate (e.g., "fast walking, easy bicycling"), and strenuous (e.g., "jogging, vigorous swimming") activity during a typical week	"A typical week"	–
	Paffenbarger Physical Activity Questionnaire (PPAQ)	Number of flights of stairs climbed (i.e., 10 stairs per flight) and city blocks walked in a typical day and duration of weekly sports and recreational activities	"A typical day/week"	–
General PA motives	Reasons for Exercise Inventory (REI)	Exercise for: weight control, fitness, health, improving body tone, improving physical attractiveness, improving mood, and for enjoyment	In general	$\alpha =$ 0.67–0.81 across subscales
	Exercise Motivations Inventory-2 (EMI-2)	Exercise for: stress management, revitalization, enjoyment, challenge, social recognition, affiliation, competition, health pressures, ill-health avoidance, positive health, weight management, appearance, strength and endurance, and nimbleness	In general	$\alpha =$ 0.75–0.96 across subscales
Maladaptive PA	Eating Disorders Examination Questionnaire (EDE-Q)	Frequency of "hard exercise for weight/shape control"	Past 28 days	–
	Diagnostic Survey for Eating Disorders (DSED)	Frequency and duration of exercise for weight control	In general	–

(continued)

Table 1 (continued)

Category	Measure name	Main construct assessed	Assessment period	Reliability in ED samples
	Eating Disorders Inventory-Symptom Checklist (EDI-SC)	Percentage of exercise that is aimed at controlling weight	In general	$\alpha =$ 0.90–0.97
	Commitment to Exercise Scale (CES)	Obligatory aspects of exercising (e.g., feelings of guilt when an exercise session is missed and the feeling that general well-being is dependent on not missing an exercise session, the need to continue to exercise in the face of illness or injury)	In general	$\alpha = 0.96$
	Compulsive Exercise Test (CET)	Avoidance and rule-driven exercise; weight control exercise; exercise for mood improvement; lack of exercise enjoyment; and exercise rigidity	In general	$\alpha =$ 0.85–0.94 across studies
	[Modified] Obligatory Running Questionnaire (ORQ)	*Exercise behaviors*: Frequency and duration of exercise, solitary/secret exercise, the association between eating and exercise and hyperactivity *Exercise cognitions*: Motives for exercise, perceived adequacy and importance of exercise, feelings after exercise or failure to exercise	In general	–
	Obligatory Exercise Questionnaire (OEQ)	Emotional element of exercise; exercise frequency and intensity; and exercise preoccupation	In general	$r =$ 0.01–0.26 with EDI subscales
	Exercise Addiction Inventory (EAI)	Exercise salience, exercise for mood modification, conflict around exercise, exercise tolerance, withdrawal from exercise, exercise relapse	In general	$\alpha = 0.84$

Godin Leisure-Time Exercise Questionnaire (GLTEQ). The GLTEQ (Amireault and Godin 2015) assesses engagement in various types of PA over an average seven-day period. The questionnaire asks participants about the number of times they do

each activity for more than 15 min during their free time. Activities assessed are strenuous exercise (e.g., running, swimming), moderate exercise (e.g., fast walking, volleyball), and mild exercise (e.g., yoga, easy walking). The GLTEQ also asks participants how often they engage in any regular activity "long enough to work up a sweat" during a seven-day period. Participants can respond "often," "sometimes," or "never/rarely." While the GLTEQ has not been validated in ED samples, it has demonstrated adequate reliability in both adults and adolescents (Amireault and Godin 2015; Zelener and Schneider 2016; Godin et al. 1986; Jacobs Jr et al. 1993).

Paffenbarger Physical Activity Questionnaire (PPAQ). The PPAQ (Simpson 2011) asks respondents to report the number of city blocks they walk and the number of flights of stairs they climb on a typical day, as well as the frequency and type of any sports or recreational activities they participated in over the past year. Using subject responses to these questions, researchers can estimate energy expenditure by calculating a physical activity index (Paffenbarger Jr et al. 1978). Several additional questions assess the frequency and intensity of PA the respondent participates in. While the PPAQ has not been validated in ED samples, it has demonstrated adequate reliability among adults (Simpson 2011; Simpson et al. 2015).

Self-Report Measures of General PA Motivations

Reasons for Exercise Inventory (REI). The REI (Silberstein et al. 1988) assesses PA for the reasons of weight control, physical fitness, health improvement, improving body tone, improving physical attractiveness, improving mood, and enjoyment. The REI asks individuals to indicate whether each PA motive statement is an important reason that they have for exercising. Responses on the REI are made on a 7-point Likert scale ranging from "not at all important" to "extremely important." Additionally, the REI has demonstrated adequate validity in healthy adults (Courneya and McAuley 1995) and adults with anorexia nervosa (AN) (Young et al. 2017) across subscales.

Exercise Motivations Inventory-2 (EMI-2). While the EMI-2 (Markland and Ingledew 1997) also assesses PA for the reasons of enjoyment, health improvement, weight management, appearance, and physical fitness, it also assesses PA engagement for stress management, revitalization, challenge, social recognition, affiliation, competition, health pressures, ill-health avoidance, and nimbleness. The EMI-2 asks individuals to indicate whether each statement of PA motive was true for them personally or would be true for them if they did PA. Responses on the EMI-2 are made on a 6-point Likert scale ranging from "not at all true for me" to "very true for me." Additionally, the EMI-2 has demonstrated adequate validity among healthy adults (Markland and Ingledew 1997), though this instrument has not been validated in ED populations.

Self-Report Measures of Maladaptive PA

Diagnostic Survey for Eating Disorders (DSED). The DSED (Johnson 1987) assesses PA intended to "work off" calories consumed throughout the day. Specifically, the DSED assesses the general frequency and duration of PA for the purposes

of burning calories. DSED assessment of compensatory PA has not been independently validated.

Eating Disorders Examination Questionnaire (EDE-Q). The EDE-Q (Fairburn and Beglin 1994) focuses on the assessment of strenuous PA intended to control one's weight or shape. The EDE-Q assesses the number of times individuals "exercised hard as a means of controlling their shape or weight" over the past 28 days. EDE-Q assessment of PA has shown good reliability among adults with AN, though it has not been independently validated in other ED populations (Young et al. 2017).

Eating Disorders Inventory-Symptom Checklist (EDI-SC). Similar to the EDE-Q, the EDI-SC (Garner and Olmsted 1986) assesses the proportion of individuals' PA that is aimed at controlling their weight or shape. EDI-SC assessment of driven PA has not been independently validated.

Commitment to Exercise Scale (CES). The CES (Davis et al. 1993) measures obligatory or rigid aspects of PA (e.g., feelings of guilt when a PA session is missed and the feeling that general well-being is dependent on not missing a PA session, the need to continue PA in the face of illness or injury). The CES asks individuals to rate the extent to which each statement is generally true for them on a visual analog scale from "never" to "always." The CES has demonstrated good validity within ED populations (Davis et al. 1995; Young et al. 2017).

Compulsive Exercise Test (CET). The CET (Taranis et al. 2011) also measures obligatory or rigid aspects of PA. The CET asks individuals to rate the extent to which each statement is generally true for them on a 6-point Likert scale from "never true" to "always true." The CET has demonstrated good validity within adults with AN, though it has not been validated in other ED populations (Young et al. 2017).

Obligatory Exercise Questionnaire (OEQ). This measure assesses PA frequency and intensity, as well as preoccupation with PA and the emotional element of PA (Steffen and Brehm 1999). The OEQ has shown god validity in healthy adult populations (Duncan et al. 2012), and one study found small-to-moderate correlations between the OEQ and the EDI ($r = 0.01–0.26$ across EDI subscales; Steffen and Brehm 1999).

Exercise Addiction Inventory (EAI). Similar to the OEQ, the EAI (Griffiths et al. 2005) has also been utilized to assess driven PA in EDs. The EAI assesses PA salience, PA for mood modification, conflict around PA, PA tolerance, withdrawal from PA, and PA relapse. The EAI has demonstrated adequate reliability among a general adult population (Griffiths et al. 2005); however, it has not been validated among individuals with EDs.

Modified Obligatory Running Questionnaire (ORQ). A modified version of the ORQ for EDs has also been used to assess the obligatory nature of PA in ED populations (i.e., PA including, but not limited to, running; Blumenthal et al. 1984). This modified ORQ assesses both PA behavior (i.e., PA frequency, duration, secret PA, associations of PA with eating) and PA cognitions (i.e., motives for PA, perceived adequacy and importance of PA, feelings after PA, or failure to engage in PA). Validity information for the modified version of the ORQ is not available.

Strengths and Weaknesses of Self-Report Measures of PA

One benefit of self-report measures of PA in EDs (compared to objective measures of PA) is their ability to capture the compensatory or driven nature of PA, which is subjective and cannot be easily measured via objective measurement tools. Additionally, self-report measures can assess a broader range of constructs such as motivations for PA, compared to objective measures of PA. However, self-report measures of PA in EDs are also subject to several weaknesses. First, self-report measures rely on retrospective recall, which is subject to several biases as well as inaccurate reporting, and recent research has suggested that self-reported frequency of PA engagement is highly inaccurate (Mâsse and Judith 2012). Specifically, Mâsse and colleagues concluded that it is difficult to obtain valid estimates of objective PA components from self-report, as the minutes of PA obtained with self-report measures are biased (e.g., overestimating or underestimating PA). Additionally, we might expect that individuals with EDs would be at a higher risk for under-/overreporting PA engagement due to their increased concern with shape and weight (Dalle Grave et al. 2020). Second, many self-report measures of PA used in ED populations measure PA behavior and/or cognitions "on average" rather than on a specific timescale (e.g., within the last month), which makes reporting inaccuracies more likely. Only the Seven-Day PAR and EDE-Q assess recent objective components of PA engagement (ranging from the last 7 to 28 days). Finally, many measures of PA used in ED populations are not validated in those subpopulations. While many of the measures may apply to both general populations and ED populations, there may be differences in the presentation of PA behaviors among individuals with EDs that necessitate the revalidation of these measures in this group.

Ecological Momentary Assessment of PA in EDs

Several studies have used daily diary or EMA to measure both objective and psychological components of PA in ED samples. While EMA is still based on self-report, it offers the advantage to researchers of being able to capture PA behavior in real-time and in real-world settings through repeated administrations of surveys delivered to participants' smartphones or other handheld devices. See Table 2 for further details on EMA questions assessing PA in EDs.

EMA of Objective Components of PA

EMA of objective components of PA has broadly used a yes/no answer format to assess for engagement in PA over the preceding hours (Lampe et al. 2021; Pirke et al. 1991; Lavender et al. 2013, 2016; Ma and Kelly 2020; Davis et al. 1995). EMA questions have asked about the type of activity that participants engaged in (e.g., swimming, running) and the duration of PA engagement. No studies to date have independently assessed the intensity of PA using EMA. EMA assessment of PA frequency has demonstrated adequate validity among individuals with

Table 2 EMA measures of exercise used in ED samples

Category	Main construct assessed	Item wording (if available)	Reliability
Objective PA components	Exercise engagement (yes/no scale)	*Have you exercised since the last survey*?	–
	Activity type (e.g., running, swimming)	–	–
	Duration of exercise engagement	–	–
General PA motives	Exercise for: health improvement, emotion regulation, routine, enjoyment, shape/weight control, obligation or guilt	*Did you exercise for any of the following reasons?* ☐ *Because it was part of my routine* ☐ *Because I would feel guilty if I didn't* ☐ *To cope with a difficult emotion* ☐ *So that I could eat more later* ☐ *To improve my health* ☐ *Because I enjoy the activity* ☐ *To control my shape or weight* ☐ *Other (specify)*	$\alpha = 0.91$
Maladaptive PA	Frequency of thoughts about exercising to control weight and/or shape or burn calories	*Have you thought about exercising as a means of controlling your weight, altering your shape or amount of fat, or burning off calories*?	–
	Frequency of exercising to control one's weight and/or shape or burn calories	*Did you actually exercise to influence your shape or weight since the last time you were signaled*?	–
	Extent of exercising to control one's weight and/or shape or burn calories at each episode (assessed via 5-point Likert scale from "Not at all" to "Extremely")	*To what extent did you exercise to compensate for eating?*	$\alpha = 0.79$
	Frequency of urges to "over-exercise"	–	–
	Frequency of engagement in "excessive exercise" (measured via Likert scale from 1 "Not at all" to 6 "Extremely" or "A lot")	–	–
	Intensity of feeling driven or compelled to exercise during each episode (measured via Likert scale from 1 "Not at all" to 5 "Extremely")	*To what extent did you feel driven or compelled to exercise*?	$\alpha = 0.79$

binge-spectrum EDs (Lampe et al. 2021); however, it has not been validated in other populations.

EMA of General PA Motivations

One study has used EMA to assess general PA motivations. This study included assessment of PA for health improvement, mood improvement, as part of one's routine, enjoyment, weight control, and due to obligation or guilt (Lampe et al. 2021). Of note, these EMA items were based on the REI and EMI-2 questions and are thus very similar in nature. Additionally, EMA items assessing PA motives demonstrated a high reliability among individuals with binge-spectrum EDs (Lampe et al. 2021).

EMA Maladaptive PA

EMA has also been used to assess PA for the purpose of "working off" calories consumed throughout the day (Lampe et al. 2021; Fitzsimmons-Craft 2017; Stein and Corte 2003). One study used EMA to measure the frequency of thoughts about engaging in compensatory PA (Fitzsimmons-Craft 2017). EMA questions have also assessed both the frequency (Fitzsimmons-Craft 2017; Stein and Corte 2003) and extent (Lampe et al. 2021) to which each bout of PA was designed to compensate for eating. Questions asking about the extent of the compensatory nature of PA have used a 5-point Likert scale ranging from "not at all" to "extremely." One study by Stein and colleagues reported that PA items were derived from commonly used ED behavior questionnaires including the Eating Disorders Examination (Fairburn et al. 1993) and the Questionnaire on Eating and Weight Patterns-Revised (Yanovski et al. 2015). In one study, EMA assessment of compensatory PA demonstrated adequate reliability among individuals with binge-spectrum EDs (Lampe et al. 2021); however, it has not been validated in other populations.

Only one study to date has assessed the driven nature of PA via EMA (Lampe et al. 2021). This study used a question designed to capture the extent to which the individual pushed themselves, or felt compelled to exercise, during each bout of PA using a 5-point Likert scale ranging from "not at all" to "extremely." EMA questions assessing driven PA in EDs have demonstrated adequate reliability among individuals with binge-spectrum EDs (Lampe et al. 2021).

To date, three studies have used EMA to measure excessive PA engagement among individuals with EDs (Levinson et al. 2018; Sala et al. 2019; Vanzhula et al. 2020). One study measured the frequency of urges to "over-exercise" (Levinson et al. 2018), while two studies measured the frequency of actual engagement in self-reported "excessive exercise" (Sala et al. 2019; Vanzhula et al. 2020). No studies provided an operational definition of "excessive" nor reported reliability statistics within their sample. Additionally, EMA measurement of excessive exercise has not been validated.

Strengths and Weaknesses of EMA Measures of PA

EMA offers several notable methodological advantages over traditional self-report for the measurement of PA in EDs. First, information is collected in real time, which

minimizes the risk of recall bias. Second, information is collected within a real-world context, maximizing researchers' ability to observe behaviors outside the lab in an ecologically valid way. Finally, because EMA involves repeated administrations of short surveys, it is possible to establish temporal sequencing of events. This allows researchers to examine precipitants and consequences of PA engagement and associated psychological components.

However, EMA of PA in EDs has several weaknesses. First, EMA is a self-report measure and is thus subject to several biases such as social desirability bias. Further, to date, no study has validated reporting of objective components of PA engagement in ED populations, which may be affected by social desirability bias. Second, many studies using EMA to assess PA in this population do not include information on their definition of PA. For example, several studies reported that "ED behaviors were assessed, including exercise" (Lavender et al. 2013, 2016). In addition, one study reportedly measured "exercise episodes" in anorexia nervosa, using EMA, but the authors did not describe how they assessed PA (Ma and Kelly 2020), and several studies failed to define "excessive exercise" for readers or participants (Levinson et al. 2018; Vanzhula et al. 2020; Sala et al. 2019). Only two studies report training participants on how to recognize maladaptive forms of PA (Lampe et al. 2021; Fitzsimmons-Craft et al. 2016), which is important as ambiguity in this area could result in biased participant responses to EMA questions. Finally, only two studies reported that their items were derived from validated self-report measures of PA and ED behaviors (Stein and Corte 2003; Lampe et al. 2021).

Semi-structured Interviews of PA in EDs

Semi-structured interview tools are another common way to measure psychological and objective components of PA among individuals with EDs. To date, semi-structured interviews of PA are clinician-assessed and reliant on participant's recall. While the entire assessment may be lengthy, the questions regarding PA in a clinician assessment tool are often one to two questions with potential follow-up questions. Extant semi-structured interviews of PA focus on only maladaptive forms of exercise (i.e., driven exercise).

Semi-structured Interviews of Maladaptive PA

Eating Disorders Examination Interview (EDE). The EDE is a semi-structured interview that focuses on assessing driven PA that is intended to control one's shape and weight (Cooper and Fairburn 1987). The EDE assesses the number of days an individual has "felt driven or compelled to exercise" and "exercised as a means of controlling weight, altering shape or amount of fat, or burning off calories" over the past 3 months (Fairburn et al. 1993). Research supports that the EDE is reliable for use across EDs (Grilo et al. 2004; Rizvi et al. 2000). To date, no study has assessed the inter-rater reliability of the EDE exercise items (Berg et al. 2012). The current version of the EDE does not assess compensatory PA or adaptive PA;

Table 3 Semi-structured interview measures of exercise used in ED samples

Category	Main construct assessed	Item wording (if available)	Reliability
Maladaptive PA components	Driven exercise engagement (yes/no scale)	Required questions: 1. Over the past four weeks, have you exercised as a means of controlling your weight, altering your shape or amount of fat, or burning off calories? 2. Have you felt driven or compelled to exercise? Follow-up questions: 1. Typically, what form of exercise have you taken? How hard have you exercised? Have you pushed yourself? 2. Have you exercised even when it might interfere with other commitments or do you harm? 3. Have there been times when you have been unable to exercise for any reason? How has this made you feel?	–
	Frequency of driven exercise engagement	–	–
	Average duration of driven exercise engagement	–	–

however, some researchers have added items assessing compensatory and adaptive PA (Wons et al. 2021), but these items have not been independently validated. See Table 3 for further details on EMA questions assessing PA in EDs.

Strengths and Weaknesses of Semi-structured Interviews of PA

Semi-structured interviews allow the opportunity for probing and follow-up questions, which can lead to opportunities for more thoughtful and descriptive responses. In addition, clinicians are trained to assess different forms of PA, which may allow for a more accurate appraisal of maladaptive and adaptive PA than what a patient may report via self-report of EMA. However, semi-structured interviews of PA in EDs also demonstrate several weaknesses. First, like self-report measures, semi-structured interviews rely on the individual's retrospective recall, which can potentially result in inaccurate reporting and bias. Despite the EDE being reliable, studies have challenged the validity of the measure, given that responses rely on participant recall and self-report (Grilo et al. 2004). Second, the EDE does not capture the compensatory nature of exercise, adaptive exercise, or overall PA engagement. Given that semi-structured interviews are heavily reliant on participant recall, many of the weaknesses reviewed for self-report measures of PA apply to semi-structured interviews of PA.

Assessment Tools for Measuring Objective Components of PA in EDs

Despite self-report measures of PA being the most common way to measure PA in EDs, self-report measures have several weaknesses, including their inability to measure objective components of PA in EDs. This weakness has raised concerns around the accuracy of PA reported across ED samples (Bezzina et al. 2019; Mathisen et al. 2018) and in the general adult population (Prince et al. 2008). Such concerns within the ED field have led researchers to explore PA measurement through alternative techniques, including objective measurements of PA. Many objective measurements of PA used in EDs involve using different types of wearable sensor technology such as wearable portable motion sensors (e.g., accelerometers and pedometers) or wearable physiological sensors (e.g., heart rate sensors, carbon dioxide sensors) (Arnardottir et al. 2012; Chen et al. 2012; Maramis et al. 2014). The use of wearable sensors allows for objective, real-time measurements of PA that are not dependent on memory recall.

The term sensor is used to describe devices that translate physical measurement (e.g., heart rate) into a signal that can be interpreted by an apparatus or an observer (e.g., minutes of PA) (Chen et al. 2012). The sensor technologies most regularly used to objectively measure PA include the following wearable sensors: accelerometers, pedometers, heart rate sensors, and combination devices (Chen et al. 2012; Bratland-Sanda et al. 2011; Warren et al. 2010; Silfee et al. 2018).

Objective Measurement: Types of Sensor Technology

See Table 4 for a brief review of the types of sensor technology and the main PA constructs they assess.

Accelerometers. To date, accelerometers are the most widely used sensors for measuring objective components of PA in free-living settings, clinical settings, and within the ED field (Chen et al. 2012; Bratland-Sanda et al. 2011; Warren et al. 2010). Accelerometers are noninvasive and can be worn in various forms including as an armband, a wrist-worn device, and a hip-worn device. Accelerometers sense vibrations to obtain measurements of body movements and use an algorithm to process and differentiate between a locomotive and non-locomotive movement (Choi et al. 2011; Kozey et al. 2010; Nagayoshi et al. 2019). Further, as research

Table 4 Types of sensors and the main constructs assessed to measure objective components of PA

Type of sensor	Main constructs assessed
Accelerometers	Intensity, duration, frequency, and type of PA
Pedometers	Step count
Heart rate sensors	Intensity, duration, and frequency of PA
Combination devices	Step count, distance, sleep, and intensity, duration, frequency, and type of PA

has advanced, accelerometers can detect specific characteristics of PA such as the intensity, duration, frequency, and type of PA (i.e., playing basketball versus running) (Choi et al. 2011). For example, most accelerometers capture metabolic equivalents (METs), which can be coded through the sensor, or by hand, into minutes of light, moderate, and vigorous PA (Wons et al. 2021; Kozey et al. 2010). The standard MET cutoff points for determining the intensity of PA are the following: <3 METs light PA, 3–5.99 METs moderate PA, and ≥6 METs vigorous PA (Kozey et al. 2010). Accelerometers often export data that contains a MET reading per minute, which can be converted into minutes of light, moderate, or vigorous PA. Some accelerometers also have advanced multi-sensor technology that allows them to collect step count and heart rate data (Silfee et al. 2018), which is beneficial as it reduces the number of sensors a participant would need to wear to capture comprehensive and objective PA data.

Pedometers. Separate from accelerometer sensors are pedometer sensors, which solely measure step count. Since pedometers are specific to measuring step count, they aim to measure overall PA routine because they cannot detect specific types of PA (i.e., playing basketball versus running) (Palavras et al. 2015; McNamara et al. 2010). Although pedometers are not widely used within ED research, accelerometers with step-counting features are often used in ED research to determine overall how physically active an individual is on a daily, weekly, or more long-term basis (Silfee et al. 2018). Step count can provide information on overall PA levels for an individual and whether an individual's step count is compliant with recommended step counts (e.g., Centers for Disease Control (CDC) recommendations, treatment recommendations, weight loss recommendations).

Heart rate sensors. In addition to accelerometers and pedometers, heart rate sensors are also used to objectively measure PA in EDs. Using heart rate data is becoming a popular way to measure PA in EDs because similar to using METs, researchers can convert minute-by-minute heart rate data into minutes of light, moderate, and vigorous PA (Faust et al. 2019). Further, minutes of moderate-to-vigorous physical activity (MVPA) tend to be most often used when reporting objective components of PA because they indicate whether an individual is meeting the PA guidelines promoted by the American Heart Association's PA recommendation of at least 150 min of moderate PA weekly or 75 min of vigorous PA (Alharbi et al. 2016). Further, extant research demonstrates the use of developed frameworks to extract minutes of PA data from minute-by-minute heart rate data. For example, the Physical Activity Trend eXtraction (PATX) framework is commonly used, and it extracts minutes of MVPA data while considering an individual's age and heart rate zones, which are calculated and based on the CDC and American College of Sports Medicine (ACSM) heart rate zone recommendations (Faust et al. 2019). Calculations for determining heart rate zones are outlined in Table 5. Overall, using heart rate data is valuable for understanding the objective components of PA in EDs as it provides researchers with a better understanding of the duration, frequency, and intensity of PA in individuals with EDs.

Combination devices. Although accelerometers, pedometers, and heart rate monitors have utility in objectively measuring PA in EDs on their own, wearable fitness

Table 5 Target heart rate zone calculations as developed by PATX, CDC, and ACSM

Steps	Calculations
Step 1	Calculate age-predicted maximal heart rate (APMHR) APHMR = 220-age
Step 2	Calculate *moderate*-intensity physical activity target heart rate for the 64% and 76% maximal heart rate level 64% level = APMHR × 0.64 76% level = APMHR × 0.76
Step 3	Calculate *vigorous*-intensity physical activity target heart rate for the 77% and 95% maximal heart rate level 77% level = APMHR × 0.77 95% level = APMHR × 0.95

Note: *APHMR* age-predicted maximal heart rate

trackers that include some combination of these objective measurements are becoming more common. Current wearable fitness trackers in objective PA research include products like Apple, Garmin, Fitbit, Mi Band, Samsung, Jawbone watches, and more (Kaewkannate and Kim 2016; Liang et al. 2018). Wearable fitness trackers with multiple-sensor technology reduce the need for an individual to wear multiple sensors to capture all forms of objectively measured PA. Across the wearable fitness trackers listed, all include accelerometer sensor technology and include features like step count, an activity timer, distance recording functions, and sleep tracking (Liang et al. 2018). Apple, Samsung, Jawbone, Mi Band, and Fitbit wearable fitness tracker devices also include heart rate monitoring (Liang et al. 2018; Paradiso et al. 2020). The noninvasive nature and all-inclusivity of objective technology make combination devices sought after for measuring objective components of PA in EDs.

Objective Measurement Outcome Variables

To date, most extant research using objective measurements to capture the objective components of PA in EDs report on step count or minutes of PA and MVPA. As objective measurement techniques have become increasingly popular in the ED field, debate has arisen around whether step count or minutes of PA and MVPA is a better objective measurement of PA in EDs. While step count captures the overall movement and PA of an individual, it does not directly translate into an interpretable value that indicates the duration or intensity of an individual's PA. Work by Faust et al. (2019) suggests that minutes of MVPA is the best indicator for accurate PA levels and that heart rate is superior to step count in measuring MVPA because they found that greater time spent in MVPA based on target heart rate zone resulted in greater steps on average, but steps did not always result in greater MVPA. Further, heart rate is also often preferred over step count to measure minutes of MVPA because many factors can influence steps over time (i.e., dynamic environments where daily routines are subject to change), and step count cannot guarantee an individual is meeting the intensity or bout length guidelines necessary to for

Table 6 Objective measure outcome variables

Outcome variables	Main constructs assessed	Measurement route
Step count	Overall levels of PA	Pedometers, combination devices
Overall minutes of PA	Duration of overall PA	Accelerometers, heart rate sensors, combination devices
Minutes of MVPA	Duration of moderate-to-vigorous-intensity PA	Accelerometers, heart rate sensors, combination devices
Number of PA episodes	Frequency of PA engagement	Accelerometers, heart rate sensors, combination devices

classification as MVPA (Faust et al. 2019). Overall, step count is reliable for measuring how physically active an individual is overall, but minutes of MVPA should be used to determine the duration and intensity of PA in individuals with EDs.

Of note, it is important to take into consideration how to report step count and minutes of MVPA. A majority of work to date report step counts as a daily average. Many researchers collect step count data over 1 to 7 days to determine an individual's daily step count average (Del Giudice et al. 2021; Mathisen et al. 2018; Norris et al. 2017; O'Brien et al. 2018; Yao et al. 2021). For minutes of MVPA, many researchers report on total minutes of MVPA over the course of 1 week. When measuring MVPA it is important to keep in mind that historically, MVPA was counted if it occurred in a bout of at least 10 min. However, recent work suggests that minutes of MVPA that are not at least 10 min in duration are associated with a variety of positive health outcomes and should be counted when measuring total minutes of MVPA (Jakicic et al. 2019). See Table 6 for a brief review of the objective outcome variables from objective measurement of PA.

Strengths and Weaknesses of Objective PA Measurement

Objectively measuring PA in those with EDs allows researchers to assess PA in real time and does not depend on factors like an individual's recall, the accuracy of the reporting, and social desirability biases. As a result, objective measurement removes concern around the accuracy of patients reporting their overall PA. Preliminary research in the ED field demonstrates that objective techniques, such as using wearable fitness trackers to measure step count and minutes of MPVA, more accurately measure the amount of PA and increase the credibility and validity of the findings (Mathisen et al. 2018; Grosser et al. 2020). Further, unlike most self-report measures, objective measurements can accurately assess multiple dimensions of PA (e.g., frequency, intensity, duration, type), as well as increase our understanding of free-living, everyday activity (Silfee et al. 2018).

Although there are several strengths to using objective measures of PA in EDs, there are also weaknesses to consider. Some researchers have raised concerns about wearable fitness trackers potentially having a negative impact on the development and maintenance of ED symptoms (Simpson and Mazzeo 2017). More specifically,

there is concern that wearable fitness trackers with watch faces may display PA measurements and influence ED symptoms and behaviors. For example, an individual may look at their watch, perceive their step count for the day as low, become worried about gaining weight because they haven't been very active, and then engage in driven exercise to increase activity level and their step count. Additionally, objective measures of PA cannot separately measure maladaptive PA from overall PA, and they cannot measure psychopathology associated with the PA (i.e., maladaptive motivations for PA). Lastly, it can be costly to objectively measure PA in EDs as sensors and wearable fitness trackers vary greatly in price, costing up to $200 per device.

Future Directions of Assessment of Psychological and Objective Components of PA in EDs

Collectively, there are a variety of assessment tools that measure the psychological and objective components of PA in EDS. As a field, objective measurements tend to be underused. This is often because maladaptive PA is prevalent across EDs, and many of the psychological components associated with maladaptive PA are cognitive in nature (e.g., a sense of being compelled or driven to continue exercising) and thus cannot be assessed via wearable fitness trackers. However, by not using objective measures of PA as often as self-report, EMA, and semi-structured interviews to measure PA, the ED field is missing out on the valuable and reliable objective PA data that can come from objective measurement. Accordingly, more research using a multimodal approach, including self-report, EMA, semi-structured interviews, and objective measurements, is needed to assess the psychological and objective components of PA behavior in individuals with an ED, as it is not currently possible to dismantle adaptive from maladaptive PA based solely on the amount of overall PA alone, PA motivators, or intensity of PA. Understanding the psychological and objective components of PA in EDs continues to be complex, and ultimately, it will not fully be understood PA within the ED field until more studies use multimodal assessment to explore both the psychological and objective components of PA in EDs. To expand on this area of research, multimodal assessment is necessary across experimental and treatment studies that measure psychological and objective components of PA in individuals with EDs. Additionally, given that wearable sensors are still relatively new to measuring objective components of PA in EDs, exploratory research on the impact that wearable fitness trackers have on ED symptomatology and PA is necessary. Overall, using a multimodal approach to assess the psychological and objective components of PA in EDs will address the weaknesses of self-report, EMA, semi-structured interviews, and objective measurement tools as well as advance the ED field in our understanding of the role of PA in the etiology, development, maintenance, and treatment of EDs.

Mini-Dictionary of Terms

- **Adaptive physical activity**: Exercise that is not compensatory or driven in nature and is motivated by non-pathological physical benefits and mental health improvements.
- **Binge-spectrum eating disorders**: Eating disorders where participants experience binge eating episodes (e.g., binge eating disorder, bulimia nervosa).
- **Compensatory physical activity**: Exercise that is done in response to a binge eating episode to compensate for the calories consumed, with the ultimate goal of impacting one's shape or weight.
- **Driven physical activity**: Exercise that is compulsive and prioritized by an individual above all else, often within a rigid routine and leading to negative consequences, guilt, or anxiety.
- **Ecological momentary assessment**: A method of data collection that involves repeated measurement of behaviors, symptoms, thoughts, or emotions in real time within a participant's naturalistic environment.
- **Excessive exercise**: Exercise that is characterized as high in frequency, intensity, and duration, which may lead to injury.
- **Maladaptive physical activity**: Exercise that is intended to compensate for calories consumed, is driven and excessive in nature, and is motivated by shape and weight concern.
- **Metabolic equivalents**: A commonly used method for expressing the energy cost of physical activities as a multiple of the individual's resting metabolic rate.
- **Moderate to vigorous physical activity**: Physical activity that is characterized by significant increases in breath or heart rate (i.e., brisk walking, jogging, dancing, or cycling).
- **Objective measures**: A quantifiable and impartial method of data collection that is measured consistently (e.g., wearable sensor technology).
- **Physical Activity Trend eXtraction framework**: A specific procedure for preprocessing wearable fitness sensor data to impute missing data, personalize target zones, and extract physical activity trends.
- **Recall bias**: A cognitive error that may occur when an individual misremembers a previous event, which may result in the omission of details and inaccurate reporting when completing self-report measures.
- **Self-report measures**: A method of data collection that relies on an individual's report of their behaviors, symptoms, thoughts, or emotions.
- **Sensors**: Any objective piece of technology (often automatic, passive, and wearable) that uses sensors to measure a feature continuously, in real time, and translates this data into a readable signal.
- **Shape and weight concern**: An individual's concern related to the number on the scale and their physical appearance (i.e., size of their body, their figure).

Key Facts

- Physical activity in eating disorder populations can be both maladaptive and adaptive in nature.
- Maladaptive exercise is exercise that is intended to compensate for calories consumed, is driven and excessive in nature, and is motivated by shape and weight concern.
- Maladaptive PA is acknowledged in the field as a prominent factor in the etiology, development, and maintenance of symptoms across ED diagnoses.
- Adaptive exercise is exercise that is not compensatory or driven in nature and is motivated by non-pathological physical benefits and mental health improvements.
- Multimodal assessment is necessary to capture both the psychological and objective components of adaptive and maladaptive PA in EDs.

Summary Points

- Physical activity is complex and difficult to characterize within eating disorder population because physical activity can be both adaptive and maladaptive.
- Both psychological and objective components of PA need to be taken into account when measuring PA overall or adaptive and maladaptive PA in ED research.
- Physical activity among eating disorder populations can be measured using self-report questionnaires, semi-structured interviews, and objective measurement tools.
- While self-report and semi-structured interview measures can capture an individual's motivations for physical activity, they are subjective methods which are prone to biases or inaccurate reporting.
- Ecological momentary assessments allow for physical activity measurements to be collected in a naturalistic environment in real time, though this data is self-reported and may be subject to social desirability biases.
- Sensor technologies are objective, automatic, and continuous methods of measuring physical activity that do not rely on subjective reporting and instead offer real-time data collection.
- The authors propose a multimodal method of investigating physical activity in eating disorder populations that uses clinician-assessed, self-report, and objective measurements to fully capture both objective and psychological features.

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Body Mass Index and Body Fat in Anorexia Nervosa

22

Marwan El Ghoch

Contents

Introduction 440
Definitions of BMI and BF 441
BMI 441
BF 441
Methods of Assessment in AN Clinical Settings 441
Weight, Height, and Standard for BMI Determination 441
BF Estimation and Measurement 443
Changes in BMI and BF Before and After Weight Gain and Normalization 445
Relationship Between BMI, BF, and Clinical Outcomes 446
Remission, Recovery, and Risk of Relapse 446
Resumption of Menses and Reproductive Functions 446
Osteoporosis and Restoration of BMD 447
Summary 447
References 448

Abstract

Anthropometry is considered one of the main methods of nutritional assessment in individuals with anorexia nervosa (AN). In this chapter, we will focus on body mass index (BMI) and total body fat (BF). We introduce the reliable and validated techniques for their assessment during underweight, weight gain and after complete weight restoration, and their changes during the course of the disease. The chapter also discusses the association/relationship between BMI and BF and the most important treatment clinical outcomes in this population: (i) relapse, remission, and/or recovery; (ii) reduction and normalization in bone mineral density (BMD); and (iii) amenorrhea, resumption of menstrual cycle, and reproductive function.

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Keywords

Anorexia nervosa · Body mass index · BMI · Body fat · BF · Underweight · Weight restoration · Weight normalization · Weight · Osteopenia · Osteoporosis · Bone mineral density · BMD · Amenorrhea · Menses · Fertility · Pregnancy

Abbreviations

AN	Anorexia nervosa
BD	Body density
BF	Body fat
BIA	Bioelectrical impedance analysis
BMD	Bone mineral density
BMI	Body mass index
CT	Computed tomography
DXA	Dual-energy X-ray absorptiometry
MRI	Magnetic resonance imaging
ST	Skinfold thickness

Introduction

Nutritional assessment in any population is represented by an evaluation of objective and subjective data to determine the individual's nutritional status or growth patterns (Reber et al. 2019). Accurate assessment is vital and essential in different settings (i.e., in the general population and in the clinical setting). Its aim is to identify persons at risk of malnutrition, determine the nature of nutritional intervention, and monitor the effects of the intervention (Reber et al. 2019). Assessment has four main components, the anthropometric, biochemical, clinical, and dietary components (de Almeida et al. 1999).

Anthropometry is the measurement of the physical dimensions and macro-composition of the body (Gorstein and Akre 1988). It is the most used method in clinical settings for the assessment of nutritional status, especially when using approaches that do not rely on sophisticated instruments and are less expensive. Of these approaches, body mass index (BMI) and body fat (BF) are particularly noteworthy. In this chapter, we will first discuss the importance of the assessment of BMI and BF in patients with anorexia nervosa (AN) during underweight to establish the disease gravity and severity and also its use after treatment for eating disorders. Second, we will identify the best instrument for this aim in the clinical setting. Finally, we will discuss the association/relationship between BMI and BF as good predictors of the main three clinical outcomes (relapse and remission, amenorrhea and resumption of menses, and osteoporosis and bone mineral density [BMD] restoration).

Definitions of BMI and BF

BMI

The concept of BMI was first developed by the Belgian mathematician and statistician Adolphe Quetelet in 1832 (Eknoyan 2008). In his studies on the anthropometric data of human growth, he concluded that weight grows with the square of height and introduced the Quetelet index to describe the relationship between the two variables (Eknoyan 2008). Over a century later, the Quetelet index was used in obesity studies, and the term BMI was then introduced by physiologist Ancel Keys in 1972 (Keys et al. 1984). During that period and based on the data from the Seven Countries Study, researchers noticed that BMI appeared to be a good proxy for adiposity and overweight-related comorbidities (Keys et al. 1984).

BMI is defined as an individual's weight expressed in kilograms divided by the square of height in meters (Kg/m^2). It is very easy to measure and calculate and is therefore the most commonly used index to correlate risk of health problems with weight at a population level. However, as with many other measurements, BMI has certain limitations. Since it only relies on height and weight, it does not take into consideration different levels of adiposity based on age, physical activity levels, and gender. Therefore, it is expected that it over- or underestimates adiposity. The cutoff points of BMI in the general population, according to the World Health Organization (WHO) and Asian classification, as well as the DSM-5 severity specifiers based on thinness for adults with AN, are shown in Table 1.

BF

BF in humans is defined as the mass of fat in the total body mass usually expressed in kilograms. It includes both essential and storage BF. The former is necessary to maintain life and reproductive functions, and for this reason it is greater in females than males, because of the demands of childbearing and other hormonal functions. The latter consists of fat accumulation in adipose tissue, part of which protects internal organs. Age- and gender-specific cutoff percentage points were suggested by Gallagher and colleagues for underweight, normal weight, overweight, and obesity in African American, Asian, and White populations (Table 2) (Gallagher et al. 2000).

Methods of Assessment in AN Clinical Settings

Weight, Height, and Standard for BMI Determination

The determination of BMI in patients with AN is a usual procedure, following the standard formula of body weight in kilograms divided by the square of the height in meters. An individual is usually weighed in a barefoot position and wearing light

Table 1 *Nutrition status based on BMI* according to WHO and Asian classification; DSM-5 severity specifiers based on thinness for adults with AN

Population	BMI status
Adolescents	Underweight: BMI < 5th percentile Normal weight: BMI = 5th–85th percentile Overweight: BMI = 85th–95th percentile Obesity: BMI > 95th percentile
Adults (WHO) Adults (Asian)	Underweight: BMI < 18.5 Kg/m^2 Normal weight: BMI = 18.5–24.9 Kg/m^2 Overweight: BMI = 25.0–29.9 Kg/m^2 Obesity: BMI ≥ 30 Kg/m^2 Underweight: BMI < 18.5 Kg/m^2 Normal weight: BMI = 18.5–22.9 Kg/m^2 Overweight: BMI = 23.0–24.9 Kg/m^2 Obesity: BMI ≥ 25 Kg/m^2
DSM-5 severity specifiers based on thinness for adults with AN	Mild underweight: 17.0–18.5 Kg/m^2 Moderate underweight: 16.0–16.99 Kg/m^2 Severe underweight: 15.0–15.99 Kg/m^2 Extreme underweight: <15.0 Kg/m^2

Table 2 *BF* estimation for BMI status (underweight, normal weight, overweight, and obesity) in males and females in three suggested populations (African American, Asian, and White), as reported by Gallagher and colleagues (Gallagher et al. 2000)

Females				Males		
Age and BMI	African American	Asian	White	African American	Asian	White
20–39 years						
BMI < 18.5 Kg/m^2	20	25	21	8	13	8
BMI ≥ 25 Kg/m^2	32	35	33	20	23	21
BMI ≥ 30 Kg/m^2	38	40	40	26	28	26
40–59 years						
BMI < 18.5 Kg/m^2	21	25	23	9	13	11
BMI ≥ 25 Kg/m^2	34	36	35	22	24	23
BMI ≥ 30 Kg/m^2	39	41	41	27	29	29
60–79 years						
BMI < 18.5 Kg/m^2	23	26	25	11	14	13
BMI ≥ 25 Kg/m^2	35	36	38	23	24	25
BMI ≥ 30 Kg/m^2	41	41	43	29	29	31

indoor clothing to the nearest 0.1 Kg using an electronic weighing scale or 0.5 Kg with analogical scale. Height is measured to the nearest 0.5 cm using a stadiometer.

BF Estimation and Measurement

Several methods are available for determining BF, such as measurement with calipers or through the use of bioelectrical impedance analysis (BIA), dual-energy X-ray absorptiometry (DXA), hydrostatic underwater weighing, computed tomography (CT) scan, and magnetic resonance imaging (MRI) (Duren et al. 2008). In this section, we will describe the most common methods available in clinical settings for patients with AN.

Skinfold Thickness (ST)

ST is considered to be a simple and cheap anthropometric measurement to predict BF in relation to body density (BD). The most widely used method is that of (Durnin and Womersley 1974), which uses the log sum of four ST measurements to develop regression equations for males and females of different age groups.

ST is usually measured in triplicate to the nearest 0.2 mm by means of a plicometer at the biceps, triceps, subscapular, and supra-iliac sites. These measurements are used to estimate the BD using the age- and sex-specific predictive equations of Durnin and Womersley (Durnin and Womersley 1974). Consequently, BF% is then calculated by using determined equations. Table 3 shows the equations most commonly used in clinical setting studies to predict BF via ST in patients with AN (El Ghoch et al. 2012), as well as some examples of formulae used to calculate BD in different age ranges.

Body composition (i.e., BF) in patients with AN has been evaluated in numerous studies and using different approaches, but the few available studies comparing validated methods (e.g., DXA) with the ST method have produced inconsistent findings (El Ghoch et al. 2012). Some studies found that DXA gives a mean lower BF% than ST measurement in underweight patients with AN, while another study found the opposite result. After weight restoration, some studies found the ST measurement method led to a BF over- or underestimation (El Ghoch et al. 2012). The reasons for these discrepancies have not yet been clarified, but one possible

Table 3 *BF* estimation for BD as reported by (Durnin and Womersley 1974)

Examples of formulae to calculate BD in different age ranges in females:	
BD	16–19 years BD = 1.1549–0.0678 × log (biceps + triceps + subscapular + supra-iliac) 20–29 years BD = 1.1599–0.0717 × log (biceps + triceps + subscapular + supra-iliac) 30–39 years BD = 1.1423–0.0632 × log (biceps + triceps + subscapular + supra-iliac) 40–49 years BD = 1.1333–0.0612 × log (biceps + triceps + subscapular + supra-iliac)
Equations for the estimation of BF from BD:	
BF %	Siri equation = (495/BD) – 450 Brozek equation = (457/BD) – 414 Heyward equation = (526/BD) – 483

explanation is the use of inappropriate predictive formulae for patients with AN (El Ghoch et al. 2012). Therefore, the use of ST measurements does not appear to be an alternative to valid methods in estimating BF% before and after weight gain in patients with AN. Results derived from this method should be interpreted with caution (El Ghoch et al. 2012).

BIA

BIA is a noninvasive method based on the electrical current conductance properties of tissues. It is a commonly used technique for estimating body composition, based on a two-component body composition model (BF and fat-free mass [FFM]). BIA determines the resistance (impedance) to small electrical currents as they pass through the body's water pool. It measures changes in electrical conductivity via electrodes placed on the extremities. The lowest resistance values are used to estimate total body water (TBW), from which total body FFM is calculated.

Single-frequency BIA (SF-BIA) is the most commonly used, although this technique is limited in its ability to distinguish between intracellular and extracellular water and may be affected by hydration status or electrolyte imbalances. These two conditions are known to occur in patients with AN, i.e., in severely underweight patients (dehydration), caused by binge purging behaviors (electrolyte imbalances), and during refeeding (overhydration and electrolyte imbalances). A recent consensus paper by the Society on Sarcopenia, Cachexia and Wasting Disorders has discouraged the use of SF-BIA for the assessment of sarcopenia. Specifically, in AN patients with a BMI <16 Kg/m^2, BIA results are affected by variable tissue hydration and should be interpreted with caution during early refeeding. Despite ease and low cost in access to and operation of BIA, its suitability of BIA in the context of AN remains questionable, and its validity is influenced by sex, age, and disease state (Abbaspour et al. 2021).

DXA

The DXA method is rapid and cheap and only relies on a low amount of ionizing radiation. Moreover, it enables the assessment of regional composition measurements, which provides a distinct advantage compared with other approaches such as BIA or hydrodensitometry (Bredella et al. 2010). In addition, no special preparation is required, with the exception that subject needs to wear underwear and not wear any metal accessories. DXA uses a source that generates X-rays, a detector, and an interface with a computer system for imaging the scanned areas of interest. The effective radiation doses involved are small, making the technique widely applicable (Bredella et al. 2010).

The concept of DXA technology is that photon attenuation in vivo is a function of tissue composition. Rectilinear scanning of the supine body divides the body into a series of pixels, and, within each, the photon attenuation is measured at two different energies. The DXA body composition approach assumes that the body consists of three components distinguishable by their X-ray attenuation properties: fat mass

(FM), FFM, and bone mineral. DXA poses a problem if repeated frequently in young females, because of an accumulation of radiation exposure (Bredella et al. 2010).

Several studies have provided evidence that DXA shows high accuracy in estimating body composition with respect to the four-component model in young adults. Moreover, DXA measurements are highly reproducible, and the validity of DXA for measurement of BF in different samples has been previously proved. DXA is still debated as a gold standard technique for BF measurement, but it exhibits a high level of precision in adolescents and adults with AN. There is a strong correlation between DXA and CT independent from level of hydration; therefore, DXA can be used to assess body composition in patients with AN in clinical settings (Bredella et al. 2010).

Changes in BMI and BF Before and After Weight Gain and Normalization

A significant reduction in BMI and BF during AN is seen in adolescents and adults of both genders; however, there is a difference in how patients lose BF based on age. For instance, adolescent females with AN seem to lose more central (trunk, visceral) than peripheral (subcutaneous, extremity) BF (El Ghoch et al. 2015). On the other hand, young adult females and adolescent and young adult males with AN seem to display a preferential loss of BF from the extremities rather than the trunk (El Ghoch et al. 2017). The reasons for these discrepancies are unclear. However, short-term weight restoration treatments (i.e., 20 weeks) can determine a complete weight normalization of BMI ($\geq$19 Kg/m^2 in females and $\geq$20 Kg/m^2 in males) and a complete total restoration of BF in all patients with AN (adolescents and adults of both genders) (El Ghoch et al. 2015, 2017) with preferential accumulation of fat in the trunk (El Ghoch et al. 2015, 2017). The underlying mechanism behind this central adipose deposition (i.e., hormonal weight gain, rate and velocity, etc.) has not yet been clarified.

Despite this, it appears that the central fat deposition achieved immediately after weight restoration does not have any adverse effect on general and eating disorder psychopathology, either by causing any psychological distress or leading to higher rate of relapse (El Ghoch et al. 2014, 2016b). However, the cardio-metabolic effects of this abnormal BF distribution have not been tested in patient with AN after a complete weight restoration; only one study conducted in young adult females has reported that minimum short-term weight restoration showed a preferential redistribution of BF in the trunk region with respect to controls and that such a distribution was associated with insulin resistance status (Prioletta et al. 2011).

Further underlining this result, two studies conducted in young adult females with AN found that the abnormal BF distribution in central regions exhibited after short-term complete weight restoration tends to normalize within a 1- to 2-year period of normal weight maintenance (Dellava et al. 2011; Mayer et al. 2009).

Relationship Between BMI, BF, and Clinical Outcomes

Remission, Recovery, and Risk of Relapse

One of the most important clinical outcomes during the treatment of AN is relapse prevention with successful long-term normal weight maintenance (i.e., BMI $\geq$ 18.5 Kg/m^2 $>$ 1-year follow-up). The identification of factors in the early period after weight restoration that can predict relapse in longer follow-up is vital. The most consistent and robust early data have been provided by a multisite relapse prevention trial (Walsh et al. 2006) which reported that the only factors associated with long-term relapse were BMI at the end of treatment and the rate of weight loss in the first 4 weeks following hospitalization. However, more recently, two further studies in adults with AN reported a relationship between poor long-term outcome (i.e., relapse) and lower BF% in weight-restored inpatients (Mayer et al. 2007; Bodell and Mayer 2011), but recent studies have failed to replicate this finding in both adolescent and young adult females (Aguera et al. 2015; El Ghoch et al. 2016a, b). Future work should pay attention to this issue more closely.

Resumption of Menses and Reproductive Functions

There is a clear positive relationship between a higher BF% achieved after weight normalization and the resumption of menses in adolescent and young adult females with AN. A recent systematic review and meta-analysis published in 2019 showed that patients with AN who resume their menstrual cycle had a significantly higher mean BF% than those who did not (Traboulsi et al. 2019). Moreover, BF% was found to be an independent predictor of menstrual cycle resumption in this population; an increase of only one unit of BF% can increase the odds of menstruation by ≈15–20% (Traboulsi et al. 2019). There is a cutoff point of BF% ≈21 which is suggested as the minimum needed for resumption of the menstrual cycle (Traboulsi et al. 2019).

In the same direction, another recent systematic review published in 2020 only included only studies of completely weight-restored females who had recovered from AN over a follow-up period of between 6 and 18 years. This review revealed that appropriate treatment of AN leads to the normalization of reproductive functions, especially in terms of fertility, pregnancy, and childbirth rates. The meta-analysis confirmed this finding, where the pooled odds of childbirth rates between the AN group and the general population were not statistically significant (Chaer et al. 2020). The authors concluded that if patients with AN undergo appropriate eating disorder treatment and weight restoration, it appears to be unlikely that their reproductive health is affected (Chaer et al. 2020). However, since this finding is derived from only a few studies, it requires replication and confirmation.

Osteoporosis and Restoration of BMD

Reduced BMD (osteopenia or osteoporosis) is one of the most frequent medical complications of AN across adolescent and adult males and females and increases the risk of spontaneous fractures with respect to healthy controls (Tannir et al. 2020). Several factors have been identified to play a role in BMD reduction in AN. These include the underweight status, however expressed (i.e., BMI < 18.5 Kg/m^2 or $<$ 10th centile), associated with depleted BF (Tannir et al. 2020).

A recent systematic review regarding the effect of body weight and fat restoration and BMD in adolescent and young adults resulted in a number of findings (El Ghoch et al. 2016c). First, weight normalization is associated with the stabilization of BMD during the first year of follow-up in adolescent and young adult patients with AN (El Ghoch et al. 2016c). Second, weight restoration begins to determine an increase in BMD after approximately 16 months. This indicates that BMD gain is a slow process in adolescent and young adults with AN and that longer durations of weight maintenance are required to detect improvements in bone status (El Ghoch et al. 2016c). To reinforce these findings, one study found that in female adolescents with AN, normalization of total body and lumbar spine BMD occurs within nearly 30 months of complete weight restoration. Therefore, weight restoration should be considered the most effective strategy to determine improvement or restoration in BMD in adolescent and young adult patients with AN (El Ghoch et al. 2016c). However, this process seems to be slow and requires a certain period of time.

Summary

- BMI and BF are two important anthropometric indices of nutritional status in humans, and their assessment is crucial, especially in clinical settings
- During AN, significant reduction in BMI and BF is observed. BMI can be calculated through the standard formula. The DXA scan is usually available and widely used in clinical practice and has been extensively validated in comparison to gold standards in the precise measurement of total and regional BF in AN
- Adolescent females with AN lose more central (trunk, visceral) than peripheral (subcutaneous, extremity) BF. Adolescent males and adults of both genders with AN seem to have a preferential loss of BF from the extremities rather than the trunk
- BF is completely restored in all patients with AN after short-term weight normalization (BMI $\geq$ 19–20 Kg/m^2); with the occurrence of a central adiposity phenotype, it seems to normalize after 1 to 2 years of normal weight maintenance
- This central adiposity phenotype seems not to negatively influence treatment outcomes (i.e., relapse, eating disorder psychopathology, or psychological distress)

- Strong evidence indicates that the BMI (not the BF) achieved after short-term weight restoration predicted 1-year normal weight maintenance in females with AN
- The BF% is an independent predictor of the return of menses in patients with AN. Higher total BF% (at least 21%) is associated with the resumption of menses
- Appropriate eating disorder treatment for AN, which determines body weight and BF restoration, appears to lead to the normalization of reproductive functions, especially in terms of fertility, pregnancy, and childbirth rates
- During AN, underweight and BF depletion are important factors that lead to an impairment of bone metabolism and a significant reduction in BMD in adolescents and adults of both genders
- Weight restoration (BMI $\geq$ 18.5–19 Kg/m^2 or BMI $\geq$ 10th centile) in patients with AN is the most effective strategy that leads to the stabilization, improvement, and normalization of BMD after approximately 12,16, and 30 months, respectively

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Modeling Anorexia Nervosa

23

Brain Inflammatory Eicosanoids

Maria Scherma, Roberto Collu, Simona Dedoni, Walter Fratta, and Paola Fadda

Contents

Introduction 453
AA-Derived eiCs Pathways 455
eiCs Receptors 456
eiCs and Neuroinflammation 457
Animal Models of AN 459
Neuroinflammation in Animal Models of AN 460
eiCs in the ABA Model 460
Conclusion 463
Applications to Other Eating Disorders 463
Mini-Dictionary of Terms 464
Key Facts of Anorexia Nervosa 464
Summary Points 465
References 465

Abstract

Although the pathophysiology underlying anorexia nervosa (AN) has not been fully elucidated, inflammation appears to be a critical component of its course and progression. Eicosanoids (eiCs) are bioactive signaling lipids primarily derived from arachidonic acid which have gained considerable biological relevance for their involvement in central and peripheral inflammatory processes. They were first described as pro-inflammatory mediators, and only afterward their anti-inflammatory and pro-resolution activities were also highlighted. Recent findings suggest that alterations in eiCs signaling could contribute to the dysregulated

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inflammatory status observed in AN. In this chapter we will first overview the most important immunological functions of the eiCs, including the regulation of neuroinflammatory processes, and then we will summarize the current knowledge on their possible implication in the pathophysiology of AN, with a focus on animal models.

Keywords

Anorexia nervosa · Activity-based anorexia · Inflammation · Neuroinflammation · Polyunsaturated fatty acid · Arachidonic acid · Eicosanoids · Prostaglandins · Thromboxanes · Leukotrienes · Cyclooxygenases · Lipoxygenases · Cytochrome P450 epoxygenases

Abbreviations

2-AG	2-arachidonoylglycerol
5(S)-HETE	5(S)-hydroxyeicosatetraenoic acid
8(S)-HETE	8(S)-hydroxyeicosatetraenoic acid
12(S)-HETE	12(S)-hydroxyeicosatetraenoic acid
15(S)-HETE	15(S)-hydroxyeicosatetraenoic acid
20-HETE	20-hydroxyeicosatetraenoic acid
AA	arachidonic acid
ABA	activity-based anorexia
AEA	anandamide
ALA	α-linolenic acid
AN	anorexia nervosa
CB1R	cannabinoid type 1 receptor
CNS	central nervous system
COX	cyclooxygenase
CYP	cytochrome P450 monooxygenase
CysLT	cysteinyl-leukotriene receptors
DGLA	di-homo-γ-linolenic acid
DP	prostaglandin D receptor
EET	epoxyeicosatrienoic acid
eiCs	eicosanoids
EP	E-prostanoid receptor
FAAH	fatty acid amide hydrolase
FP	PGF2α receptor
GPCRs	G protein-coupled receptors
HETE	hydroxyeicosatetraenoic acid
HPETE	hydroperoxyeicosatetraenoic acids
IL	interleukin
IP	prostacyclin receptor
LOX	lipoxygenase
LTs	leukotrienes
LXs	lipoxins

MAGL	monoacylglycerol lipase
NSAIDs	nonsteroidal anti-inflammatory drugs
OEA	oleoylethanolamide
PBMC	peripheral blood mononuclear cell
PEA	palmitoylethanolamide
PGD2	prostaglandin D2
PGE2	prostaglandin E2
PGF2α	prostaglandin F2α
PGG2	prostaglandin G2
PGH2	prostaglandin H2
PGI2	prostacyclin I2
PGs	prostaglandins
PLA2	phospholipase A2
PPARs	peroxisome proliferator-activated receptors
PUFA	polyunsaturated fatty acid
TNFα	tumor necrosis factor-alpha
TP	thromboxane receptor
Tx	thromboxane

Introduction

Although the pathogenesis of anorexia nervosa (AN) has not yet been elucidated, it is widely acknowledged that biological factors contribute to its course and progression. For instance, alterations in neuroendocrine functions, including hypothalamic-pituitary axis dysregulation as well as changes in the levels of several appetite-regulating hormones (e.g., leptin, ghrelin), have been observed in anorexic patients (Schorr and Miller 2017). Also, altered neuronal bases of reward processes were suggested to contribute to the behavioral pathology of AN (Berner et al. 2019). Moreover, expanding evidence demonstrated that AN could be also related to a dysregulated inflammatory status that drives toward a pro-inflammatory profile (Butler et al. 2021). In this regard, increased serum levels of several pro-inflammatory cytokines, such as interleukin (IL)-1 beta (IL-1β), IL-1, and IL-6 and tumor necrosis factor-alpha (TNF-α), were found in anorexic patients (Solmi et al. 2015; Dalton et al. 2018). In addition, a recent proteomic study investigating a wide group of inflammatory-related proteins, including IL-6 and TNF-related proteins, shows that the pro-inflammatory profile appears to be associated with the acute stage of the disease (Nilsson et al. 2020). In agreement, two different studies showed an increased spontaneous release of pro-inflammatory cytokines from peripheral blood mononuclear cells (PBMCs) isolated from patients with AN that normalized upon refeeding (Vaisman and Hahn, 1991; Allende et al. 1998). Eicosanoids (eiCs) are bioactive signaling lipids derived primarily from omega-6 arachidonic acid (AA), one of the most abundant long-chain polyunsaturated fatty acids (PUFAs) in the brain (Bazinet and Layé 2014). Other eiCs precursors include omega-3 eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) (Fig. 1). In recent

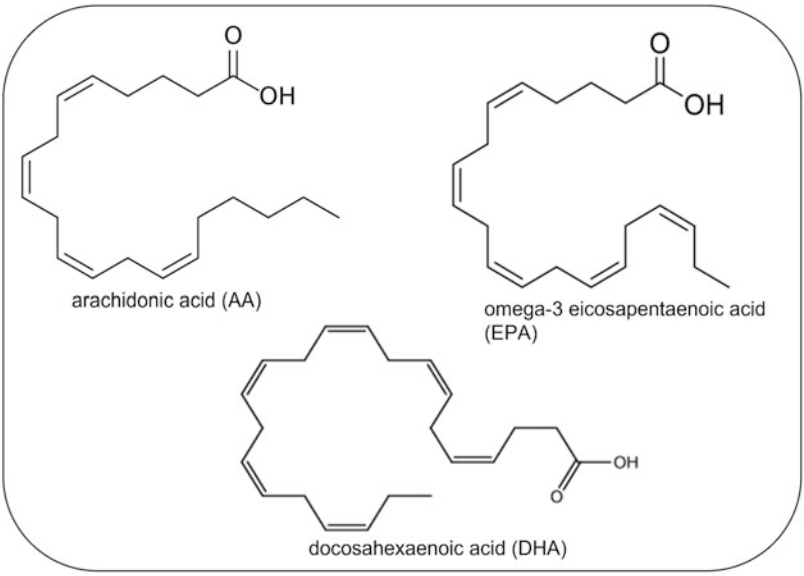


Fig. 1 Precursors of eicosanoids. Polyunsaturated fatty acids (PUFAs) omega-6 arachidonic acid (AA), omega-3 eicosapentaenoic acid (EPA), and docosahexaenoic acid (DHA)

years, eiCs have gained considerable biological relevance in relation to their involvement in a huge spectrum of physiological and pathological processes in the brain and throughout the rest of the body, including the regulation of important aspects of immunity and inflammatory responses (Leuti et al. 2020). Indeed, several eiCs and their associated receptors were shown to participate in the initiation, coordination, and resolution of inflammation (Tilley et al. 2001; Serhan et al. 2014). Recent findings suggest that alterations in the AA metabolic pathways, both in the periphery and in the brain, lead to an imbalanced production of eiCs that may contribute to the dysregulated inflammatory status observed in AN (Shih 2019; Collu et al. 2020; Caso et al. 2020). For example, protein expression of COX-2 was found increased in PBMCs of female adolescent patients with AN (Caso et al. 2020). Moreover, eiCs seem to be implicated in not only the risk of AN, but also in its comorbid psychopathology (Shih et al. 2016). On the other hand, several studies reported abnormal plasma levels of PUFAs in individuals with eating disorders, including AN (Langan and Farrell 1985; Satogami et al. 2019; Ayton 2004). Finally, the clinical importance of resolution of inflammation by PUFA treatments for weight and appetite restoration in AN, key clinical goals for patients, was also highlighted (Yehuda and Rabinovitz 2016; Shih et al. 2017). In this chapter, we will describe the most important immunological functions of the eiCs, including the regulation of neuroinflammatory processes, and we will overview the current knowledge on their possible implication in the pathophysiology of AN, with a focus on animal models.

AA-Derived eiCs Pathways

The major source of eiCs derives from the oxidation of AA which is released from the phospholipid pool in cellular membranes by enzymes of the phospholipase A2 (PLA2) superfamily in response to various physiological and pathological stimuli including inflammation (Harizi et al. 2008). An alternative source of AA involves the degradation of endogenous cannabinoids such as N-arachidonoylethanolamine, also known as anandamide (AEA), and 2-arachidonoylglycerol (2-AG), which are a group of lipid mediators playing a key role in critical pathophysiological functions that over the last decades have received growing amount of attention in regard to their involvement in inflammatory processes (Cabral and Griffin-thomas 2009). More specifically, the fatty acid amide hydrolase (FAAH) enzyme catalyzes the metabolism of AEA to AA and ethanolamine, whereas the monoacylglycerol lipase (MAGL) enzyme converts 2-AG to AA and glycerol (Ahn et al. 2008; Nomura et al. 2011) (Fig. 2). Once available, free AA can be metabolized by three different enzyme systems, namely, cyclooxygenases (COXs), lipoxygenases (LOXs), and cytochrome P450 monooxygenases (CYP). Activation of the COX pathway gives rise to the production of prostanoids, which represent the most abundant group of eiCs, and even though they are often synthesized and released during inflammation, acting as both pro- and anti-inflammatory mediators, they are also involved in the maintenance of physiological cell homeostasis. COXs catalyze the first step of prostanoids formation, in which AA is converted to prostaglandin (PG)-H2 via PGG2 reduction. PGH2 represents the common substrate for the enzymatic synthesis

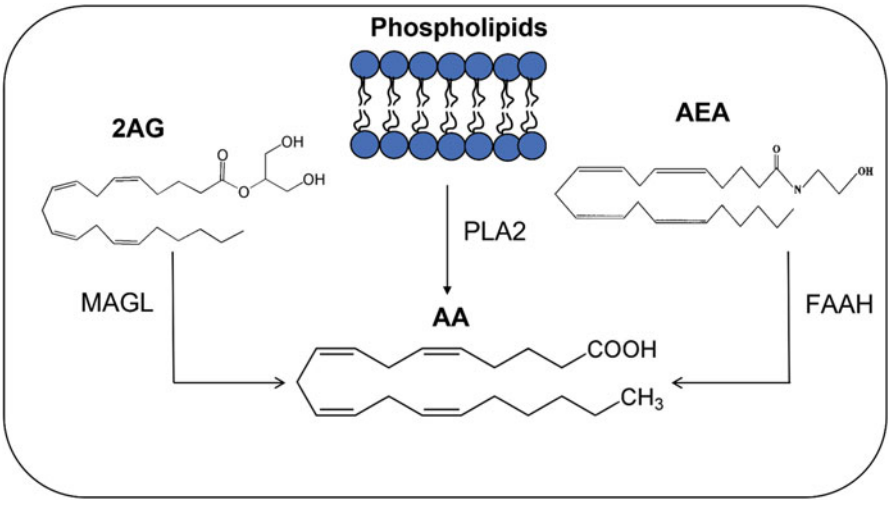


Fig. 2 Production of free arachidonic acid (AA). Free arachidonic acid (AA) derives from various intracellular sources: AA present in phospholipids membrane is released by phospholipase A2 (PLA2) in response to various stimuli; anandamide (AEA) is primarily hydrolyzed by FAAH to ethanolamine and AA; 2-arachidonoylglycerol (2-AG) is primarily hydrolyzed by MAGL to glycerol and AA

of PGD2, PGE2, PGF2α, prostacyclin (PGI2), and thromboxane A2 (TXA2). COXs exist in two distinct isoforms: the COX-1, which is constitutively expressed in several tissues and mainly involved in homeostatic functions, and the COX-2, which is typically induced in response to inflammatory stimuli (e.g., pro-inflammatory cytokine production, growth factors, hormones) and plays a major part in inflammatory processes (Harizi et al. 2008). LOXs are a family of lipid-peroxidizing enzymes (e.g., 5-LOX, 12-LOX, and 15-LOX) that metabolize AA into several hydroperoxyeicosatetraenoic acids (HPETEs, e.g., 5-HPETE, 12-HPETE, 15-HPETE), which are then reduced to hydroxyeicosatetraenoic acids (HETEs, e.g., 5-HETE, 12-HETE, 15-HETE), leukotriene A4 (LTA4), lipoxins A4 and B4 (LXA4 and LXB4). Moreover, LTA4 is rapidly metabolized to LTB4 or to cysteinyl leukotrienes (e.g., LTC4, LTD4, and LTE4) which are potent pro-inflammatory mediators. LTA4 could be also degraded to LXA4 and LXB4. In contrast to LTs and PGs, LXA4 and LXB4 are anti-inflammatory molecules (Wang et al. 2021). Finally, under the control of hormones, growth and transcription factors, AA can also be metabolized by many CYP including ω-hydroxylases, which generate HETEs (e.g., 6-HETE, 17-HETE, 18-HETE, 19-HETE, and 20-HETE) and epoxygenases whose activity results in the production of epoxyeicosatrienoic acids (EETs, e.g., 5,6-EET, 8,9-EET, 11,12-EET, and 14,15-EET) studied in conjunction with their involvement in inflammatory responses. All the pathways forming AA-derived eiCs are identified as the "arachidonate cascade" (Fig. 3).

eiCs Receptors

Upon release from the cell, eiCs affect cell function by binding to different G protein-coupled receptors (GPCRs), although some are also ligands for peroxisome proliferator-activated receptors (PPARs) (Murakami et al. 1999; Bishop-Bailey and Wray 2003). To date, nine membrane receptors for prostanoids have been identified and include four subtypes of the PGE receptor (EP1, EP2, EP3, and EP4), the PGD receptor (DP1 and DP2), the PGF receptor (FP), the PGI receptor (IP), and the TXA receptor (TP) (Narumiya et al. 1999). LTs receptors fall into two groups: BLT receptors (BLT1 and BLT2) and cysteinyl-leukotriene receptors (CysLT1 and CysLT2) (Yokomizo et al. 2018). Finally, the ALX receptors are related to the biological activity of LXs (Chiang et al. 2006). After receptor binding and activation, eiCs can modulate the generation rate of cytosolic second messengers (e.g., cAMP or Ca^{2+}), induce alterations in membrane potential, or activate specific protein kinases (Harizi et al. 2008) (Table 1). eiCs receptors are expressed in many cell types in the central nervous system (CNS) and are involved in various neural processes and pathways including neuroinflammation (Herbst-Robinson et al. 2015). Accordingly, eiCs production is remarkably increased during this pathological condition, and they cooperate with other inflammatory mediators (e.g., cytokines and chemokines) to mediate or debilitate this response (Phillis et al. 2006; Tassoni et al. 2008). Indeed, eiCs exert both pro-inflammatory (e.g., PGD2, PGE2, PGF2α, LTB4, TxA2, and TxB2) and anti-inflammatory (e.g., PGD2, PGE2, PGI2, LxA4, LxB4) effects

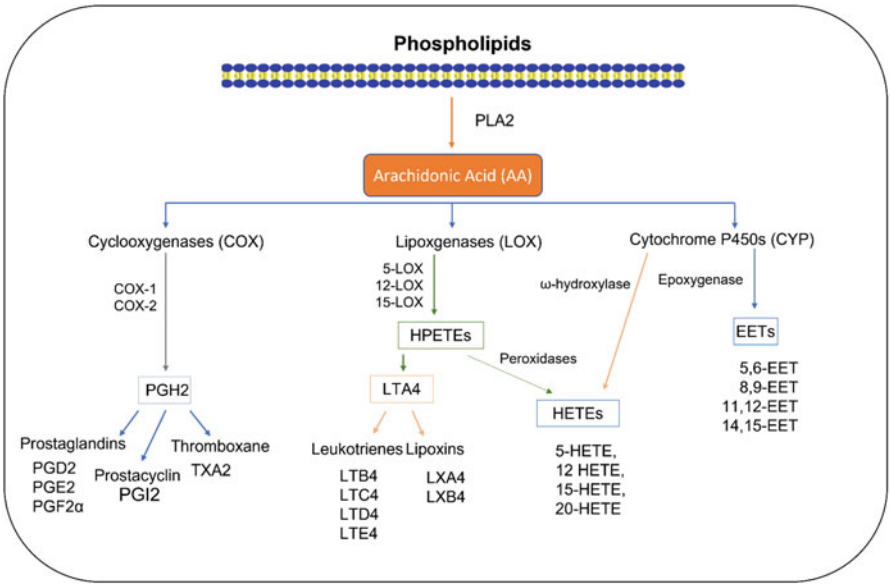


Fig. 3 Pathways of eicosanoids biosynthesis. Free arachidonic acid (AA) can be metabolized by three different enzyme systems: cyclooxygenases (COXs), lipoxygenases (LOXs), and cytochrome P450 monooxygenase (CYP). COX pathways produce prostaglandins (PGD2, PGE2, and PGF2α), prostacyclin (PGI2), and thromboxane A2 (TXA2). LOXs pathways produce leukotrienes (LTB4, LTC4, LTD4, and LTE4), lipoxins (LXA4 and LXB4), and hydroxyeicosatetraenoic acids (HETEs). CYP pathways produce HETEs and epoxyeicosatrienoic acids (EETs)

depending on the cellular context, the specific receptor expression profile, and the signal transduction pathways activated (Serhan et al. 2008).

eiCs and Neuroinflammation

Neuroinflammation is a protective mechanism against injury and disease that aims at preserving brain homeostasis by protecting the neural tissue integrity and function (Shabab et al. 2017). It involves the activation of several molecular and cellular events that take place to initially potentiate and then to regulate the inflammatory response. Neuroinflammation is triggered and sustained by the activation of different cells of the CNS including neurons, astrocytes, microglia, and oligodendrocytes. Among all these, microglial cells are responsible for initiating the inflammatory response (Gomez-Nicola and Perry 2015). Once activated, these resident immune cells induce the release of various inflammatory mediators, including cytokines and chemokines, which in turn stimulate the induction of inflammatory-related enzymes and receptors. Therefore, increased levels of these compounds play a significant role in the recruitment of immune cells in the brain. Indeed, cytokines and chemokines are able to stimulate the activity of PLA2 and, consequently, the release of free AA

Table 1 Eicosanoids receptors and their signaling pathways. Eicosanoids (eiCs) affect cell function by binding to different G protein-coupled receptors (GPCRs). Upon binding and receptor activation, eiCs can modulate the rate of cytosolic second messenger generation (cAMP or Ca^{2+}); ↑ increase, ↓ decrease

Receptor	Ligand	G protein	Transduction
EP_1	PGE_2 (PGI_2)	G_q/G_{11}	↑ Ca^{2+} mobilization
EP_2	PGE_2	G_s	↑ intracellular cAMP
EP_3	PGE_2	G_i/G_o - G_s - G_q	↑↓ intracellular cAMP ↑ Ca^{2+} mobilization
EP_4	PGE_2	G_s	↑ intracellular cAMP
DP1	PGD2	Gs	↑ intracellular cAMP
DP2/CHRT2	PGD2 (15d-PGJ2)	Gi/Go	↑ Ca^{2+} mobilization
$FP_{A,\ B}$	$PGF_{2\alpha}$	G_q	↑ Ca^{2+} mobilization
IP	PGI_2 (PGE_2)	G_s	↑ intracellular cAMP
$TP_{\alpha,\ \beta}$	TxA_2	G_q - G_i - $G_{12/13}$ - G_{16}	↑↓ intracellular cAMP ↑ Ca^{2+} mobilization
BLT_1	LTB_4	G_{16} - G_i/G_o - G_q/G_{11}	↓ intracellular cAMP ↑ Ca^{2+} mobilization
BLT_2	LTB_4 [12(S)-HETE 12(R)-HETE]	Simil- G_q - G_i - G_z	↓ intracellular cAMP ↑ Ca^{2+} mobilization
$CysLT_1$	LTD_4, LTC_2, LTE_4	G_q	↑ Ca^{2+} mobilization
$CysLT_2$	LTC_4, LTD_4, LTE_4	G_q	↑ Ca^{2+} mobilization

from neural membrane phospholipids (Lin et al. 2004; Farooqui et al. 2007). They also induce the expression of COX and LOX enzymes so that the released AA can be metabolized to give rise to the production of pro-inflammatory PGs (PGE2 and PGD2) and LTs, thus amplifying the initial inflammatory response (Mark et al. 2001; Phillis et al. 2006). In the brain, unlike other tissues, both COX-1 and COX-2 are expressed under physiological conditions (Bosetti 2007; López and Ballaz 2020). More specifically, both isoforms are constitutively expressed in neurons contributing to physiological brain functions, and COX-1 is also expressed in microglial cells (Maihofner et al. 2003). However, the expression of COX-2 can be rapidly induced in microglial cells under pathophysiological conditions including neuroinflammation (Akundi et al. 2005). Recent evidence suggests that COX-1 can also be upregulated in reactive microglia and may play a prominent role in the brain during neuroinflammation (Ghazanfari et al. 2021), and its activity appears to be necessary for COX-2 induction (Dargahi et al. 2011). Thus, it is important to point out that both isoforms may contribute to the release of pro-inflammatory PGs. Although PGE2 and PGD2 are potent pro-inflammatory molecules, they also have anti-inflammatory activity, and, as mentioned before, this depends on the type of cell and on the receptors that are activated. For instance, several studies have reported that PGE2 can significantly increase neurotoxicity by activating EP2 receptors, whereas PGE2-induced neuroprotection is mediated by the activation of both EP2 and EP4 receptors (Pooler et al. 2004; Echeverria et al. 2005). Similar to COXs,

5-LOX is expressed in neuronal and glial cells, and LTs signaling contributes to microglial and astroglial cells activation (Ciccarelli et al. 2004; Yu et al. 2014). Both COX and LOX enzymatic pathways are involved in the production of LXs that possesses anti-inflammatory and pro-resolution properties mediated by different mechanism including the inhibition of pro-inflammatory cytokine production (McMahon and Godson 2004).

Animal Models of AN

Various pathophysiological factors are involved in the onset and development of AN, and animal models greatly facilitated the progress of preclinical studies and the investigation of the mechanisms underlying the pathogenesis of the disease. The activity-based anorexia (ABA) model is so far the most used paradigm to mimic AN in rodents (Scharner and Stengel 2021). The combination of a scheduled time-restricted access to food (usually few hours per day) with the free access to a running wheel rapidly leads to a series of behavioral, neuroendocrine, and mood alterations that best represent the human pathological condition in rodents. A phenotype characterized by dramatic weight loss (up to 25% of initial body weight) and physical hyperactivity (increased running wheel activity) clearly distinguishes ABA animals from those exposed to exercise and food restriction only, and it's centrally associated with alterations of key neurotransmitter systems (e.g., endocannabinoid, dopaminergic, serotoninergic systems) and appetite-regulating hormones (e.g., leptin, ghrelin, corticosterone) involved in the modulation of both homeostatic and hedonic feeding processes (Collu et al. 2019) and in neuroinflammation (Collu et al. 2020). Other environmental models of AN have been developed and are based on the modification of the feeding patterns (dietary restriction models) or on the effect of stressful events (stress models) that are able to induce the development of key anorectic-like traits (Scherma et al. 2019). Among the genetic models, the anx/anx represents the most commonly used model for AN in mice (Nilsson 2019). This model is based on the spontaneous anx/anx mutation and was first identified by Maltais and collaborators in 1984. Mice carrying this mutation are characterized by poor appetite, reduced stomach size, inability to regulate food intake, lower body weight, and an emaciated appearance (Maltais et al. 1984). Interestingly, mutant anx/anx mice display alterations in different hypothalamic neurotransmitters and neuropeptidergic signals involved in the regulation of feeding and energy expenditure. However, the main limitation of using these mice as model of AN is the high rate of premature death due to critical health conditions (Nilsson 2019). Other genetic models consist of gene knockout approaches aiming at studying the specific contribution of candidate genes implicated in eating behavior or energy regulation. Some of these include the knockout models for genes encoding for the brain-derived neurotrophic factor, serotoninergic receptors, corticotropin-releasing factor, tyrosine hydroxylase, and muscarinic receptors (Kim 2012). Collectively, these models represent useful tools to investigate pharmacological, environmental, and genetic determinants that contribute to the development and

maintenance of the disease, as well as for the identification of new therapeutic targets for the pharmacological management of AN.

Neuroinflammation in Animal Models of AN

In agreement with the results obtained in clinical studies, preclinical evidence also support the notion of an impaired inflammatory status in AN. For example, ABA induction in mice resulted in increased mRNA levels of TNF-α and IL-1β in colonic mucosa as well as of IL-1β and interleukin-1 receptor type 1 in the hypothalamus suggesting intestinal and hypothalamic inflammation in these animals (Belmonte et al. 2016). Moreover, the expression of the anti-inflammatory cytokine IL-10 in colonic mucosa was also significantly increased during initial weight loss. The same study also showed an increased expression of the Toll-like receptor 4 in colonic epithelial cells and macrophages in ABA mice, and it is known that these receptors play a key role in the innate immune response by activating inflammatory processes that leads to the secretion of pro-inflammatory mediators (Barton and Medzhitov 2002). Also, the dehydration-induced model of AN increases microglial cells density and the expression of TNF-α, IL-6, and IL-1β in the hippocampus of young female rats, further supporting the hypothesis that AN may result in hippocampal neuroinflammation (Ragu-Varman et al. 2019). On the other hand, Barbarich-Marsteller and collaborators (2013) reported reduced hippocampal cell proliferation following ABA induction (Barbarich-Marsteller et al. 2013). Accordingly, evidence showed that caloric restriction alters both hippocampal neurogenesis and hippocampus-dependent forms of learning (Cardoso et al. 2016). Neuroinflammation has also been observed in the anorectic anx/anx mouse model of AN. In this animal model, microglial cells are selectively activated in the hypothalamus, and overexpression of genes involved in inflammatory process also occurred in this brain region (Nilsson 2019; Lachuer et al. 2005). Of importance, it has been suggested that inflammatory mediators can have profound effects on the brain function relevant to feeding behavior (Wong and Pinkney 2004). For example, pro-inflammatory cytokines (e.g., IL-1β and TNF-α) or stimulants of the release of cytokines such as lipopolysaccharide have been found to reduce food intake in animals (Gautron and Layé 2010).

eiCs in the ABA Model

The neuroinflammatory processes mediated by AA-derived eiCs in the ABA model were also investigated. Central administration of AA was found to affect feeding behavior by increasing the activity of the COX enzymatic pathway as well as the levels of TNF-α, IL-1β, and IL-6 raising an inflammatory response in the hypothalamus (Cheng et al. 2015). Increasing studies suggest that eiCs may also act downstream of cytokines during cachexia (Ross and Fearon 2002). Moreover, central administration of PGE2 was shown to induce neural activation in brain areas

involved in feeding and energy metabolism (e.g., hypothalamus) (Scammell et al. 1996; Lacroix et al. 1996). Recent findings revealed that under the ABA condition an array of eiC-mediated responses is observed in the brain of ABA rats. In particular, induction of and recovery from ABA were correlated with impairments of the COX, LOX, and CYP pathways with altered inflammatory eiCs profile and dysregulated expression of key metabolic enzymes in specific brain areas implicated in the development of the typical anorexic-like phenotype, e.g., in the prefrontal cortex, cerebral cortex, nucleus accumbens, caudate putamen, amygdala, hippocampus, and hypothalamus (Collu et al. 2020). Specifically, significantly altered levels of the main eiCs precursor AA, and of COX-derived prostaglandins (e.g., PGE2, PGD2, PGF2α) and thromboxane (e.g., TxB2), as well as of LOX- and CYP-derived hydroxyeicosatetraenoic acids (e.g., 5(S)-, 8(S)-, 12(S)-, 15(S)-HETE and 20-HETE) were detected in the brain of ABA rats. Of importance, the complex inflammatory response mediated by distinct routes of eiC signaling seems to suggest a selective influence of food restriction and exercise, the two key variables combined in the ABA paradigm. Interestingly, brain inflammation in ABA rats was shown to persist even after recovery, suggesting a long-term inflammatory effect that may serve as a substrate for relapse conditions (Collu et al. 2020). Of note, impaired levels of the two major endocannabinoids, AEA and 2-AG, and of the endocannabinoid-related acylethanolamides, oleoylethanolamide (OEA) and palmitoylethanolamide (PEA), were also observed in ABA rats (Collu et al. 2019). More specifically, at the end of the ABA induction phase, 2-AG was significantly decreased in different brain areas including the prefrontal cortex, cerebral cortex, nucleus accumbens, amygdala, hippocampus, and hypothalamus. In contrast, no changes were detected in AEA levels in any region, whereas the levels of OEA and PEA were decreased in the hippocampus and hypothalamus. Furthermore, cannabinoid type 1 receptor (CB1R) density was decreased in the dentate gyrus of the hippocampus and in the lateral hypothalamus. Both 2-AG levels and CB1R density were partially reverted toward control levels after recovery from ABA condition, whereas AEA levels became markedly reduced. Moreover, the pharmacological modulation of the endocannabinoid system was shown to effectively improve the anorexic-like ABA phenotype in rats by reducing body weight loss and running wheel activity and by normalizing levels of appetite-regulating hormones such as leptin and corticosterone (Scherma et al. 2017). The endocannabinoid system, including the aforementioned endocannabinoids AEA and 2-AG, together with the cannabinoid receptors (e.g., CB1R, CB2R) and their metabolic/biosynthetic enzymes, was shown to modulate neuroinflammation (Walter and Stella 2004). More specifically, endocannabinoids were shown to mediate anti-inflammatory responses by modulating immune cell functions. On the other hand, rat microglia primary cultures express CB1 and CB2 receptors (Walter and Stella 2004), and both 2-AG and AEA prevented the release of TNF-α when cells were activated by LPS (Facchinetti et al. 2003). Moreover, as mentioned before, the degradation of AEA and 2-AG by FAAH and MAGL enzymes can serve as an additional source of AA which can in turn be metabolized to eiCs (Ahn et al. 2008; Nomura et al. 2011). Of note, AEA and 2-AG can also be metabolized by COX-2, several LOXs, and CYP

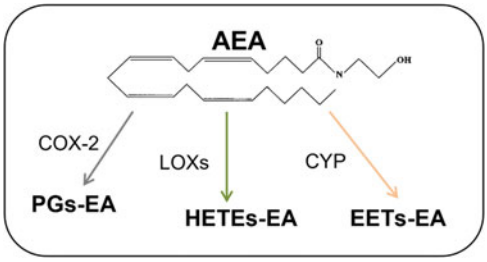


Fig. 4 Metabolism of anandamide (AEA) by eicosanoid biosynthetic enzymes. AEA can be subjected to oxygenation by COX-2, LOX, and CYP to form PGs-EA, HETEs-EA, and EETs-EA

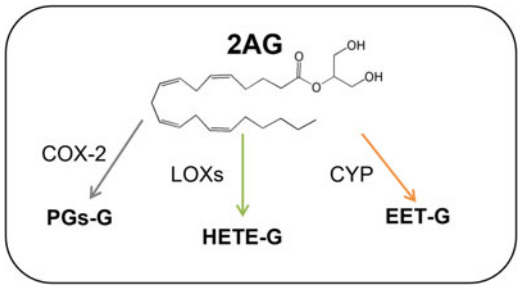


Fig. 5 Metabolism of 2-arachidonoylglycerol (2-AG) by eicosanoid biosynthetic enzymes. 2-AG can be subjected to oxygenation by COX-2, LOX, and CYP to form PGs-G, HETEs-G, and EETs-G

generating a plethora of bioactive lipids like prostaglandin-ethanolamides (PGs-EA) (e.g., PGG2-EA, PGH2-EA, PGD2-EA, PGE2-EA, PGF2a-EA, PGI2-EA) and prostaglandin-glycerols (PGs-G) (e.g., PGG2-, PGH2-, PGD2-, PGE2-, PGF2a-, PGI2-G), hydroxyeicosatetraenoyl-ethanolamides (HETEs-EA) (e.g., 11- and 15-HETE-EA) and hydroxyeicosatetraenoyl-glycerols (HETEs-G) (e.g., 15-HETE-G), and epoxyeicosatrienoyl-ethanolamides (EETs-EA) (e.g., 5,6-, 8,9-, 11,12-, and 14,15-EET-EA) and epoxyeicosatrienoyl-glycerols (EETs-G) (e.g., 11,12- and 14,15-EET-G) (Turcotte et al. 2015) (Figs. 4 and 5). Accordingly, specific genetic deletion of MAGL in astrocytes increases brain 2-AG levels and reduces the availability of AA for PGs synthesis and thereby attenuates LPS-induced neuroinflammation (Grabner et al. 2016). In agreement, brain levels of AA and several downstream AA-derived eiCs, including PGE2, PGD2, PGF2, and TXB2, were decreased in mice lacking the gene that encodes for MAGL (Nomura et al. 2011). Altogether these findings suggest that endocannabinoids degradation generates brain eiCs (e.g., PGs, HETEs) that promote neuro-inflammation. All these endocannabinoid-derived metabolites appear to be involved in the regulation of inflammatory processes by acting on specific receptors (Turcotte et al. 2015).

Conclusion

In light of the multiple functions exerted and based on the extent of neuroinflammatory processes mediated by AA-derived eiCs, this class of inflammatory lipids represents a key signaling system within the brain circuits involved in the regulation of neurobehavioral responses in AN. Therefore, further understanding on potential therapeutic approaches targeting different AA metabolic pathways or eiCs receptors is of particular interest. So far, studies have primarily focused on the pathways activated by lipids produced by the COX enzymes. In particular, the COX pathway is the target for nonsteroidal anti-inflammatory drugs (NSAIDs), which represent the most popular drugs for the treatment of inflammation, pain, and fever. Clearly, additional work is needed to deeply investigate the potential application within the scenario of AN condition and comorbidities pharmacological management. Overall, the evidence presented here highlight the important role that different eiCs pathways might have for future understanding of the neurobiology as well as for studying new pharmacological targets and approaches for the treatment of inflammatory-related processes in AN.

Applications to Other Eating Disorders

In this chapter we have reviewed the emerging role of a class of bioactive lipids derived from AA, the eiCs, in a broad range of pro- and anti-inflammatory processes related to physiopathological conditions. In particular, we have focused our attention on the potential involvement of the eiCs in brain neuroinflammatory processes in AN, a dramatic eating disorder with unclear etiology. In this regard, we have described how eiCs activity and their interaction with other well-known mediators of inflammation, such as cytokines and chemokines, influence a wide range of processes. Indeed, the complex signaling network of different inflammatory mediators, like eiCs and cytokines, was also described in the pathogenesis of obesity, further supporting neuroinflammation as a key factor in the onset and progression of eating disorders. As we all know, obesity is a growing worldwide health issue and together with high-fat feeding is associated with a systemic inflammatory status that leads to neuroinflammation, thus affecting not only the physiological activity of satiety signals but also influencing the development of central comorbidities such as depression and cognitive decline (Miller and Spencer 2014). In light of the repercussions for some cerebral functions, obesity-derived neuroinflammation represents a keen area of research to investigate the neurobiology of altered feeding disorders. A link between obesity and the eiCs-derived neuroinflammation has been observed in mice where increased microglia activation and altered eiCs profile were found and related to disrupted blood-brain barrier and impaired cognitive functions (Valcarcel-Ares et al. 2019). Considering the variegate roles of these mediators of inflammation in appetite, mood, and cognitive functions, these may serve as trait or biomarkers for AN and other eating disorders, as well as candidate targets for therapeutic approaches.

Mini-Dictionary of Terms

- **Anorexia nervosa**. Complex psychiatric disorder characterized by dramatic fear and control over body weight and altered image perception, extreme diet restriction, and intense physical activity.
- **Activity-based anorexia**. Rodent model of anorexia nervosa based on the combination of scheduled food restriction with access to physical exercise.
- **Neuroinflammation**. Activation of molecular and cellular processes of the brain's innate immune system as a protection against detrimental inflammatory response to physical or functional changes of the neural tissue.
- **PUFA**. Polyunsaturated fatty acids are cell components and precursors of various regulators of inflammation and immunity. Docosahexaenoic acid (C22:6 ω-3) and arachidonic acid (C20:4 ω-6) are the main PUFAs in the mammalian brain.
- **Arachidonic acid**. Represents around 20% of the total amount of the neuronal fatty acids and is mainly esterified in membrane phospholipids. Free arachidonic acid is released by phospholipases A2 and enzymatically converted into different eicosanoids.
- **Arachidonate cascade**. Includes all the pathways leading to the production and action of a wide range of inflammatory arachidonic acid-derived lipids called eicosanoids. Cyclooxygenases, lipoxygenases, and cytochrome P450 epoxygenases are the main enzymes of the arachidonic acid metabolism.
- **Eicosanoids**. Bioactive lipids derived by the metabolism of arachidonic acid and involved in the initiation, intensity, and resolution of inflammatory response.
- **Cytokines**. Small, secreted proteins with pro- and anti-inflammatory activity released by cells and involved in the initiation and persistence of the inflammatory response.
- **Microglia**. The primary immune cells of the central nervous system comprising up to 20% of the glial cell population. They are critically involved in the innate and adaptive immune responses.

Key Facts of Anorexia Nervosa

- Anorexia nervosa is the eating disorder with the highest mortality rate among all psychiatric disorders.
- It is characterized by food deprivation, dramatic body weight loss, and fear of gaining weight.
- Extreme physical exercise is often used as a strategy to control body weight.
- Anorexia typically emerges during adolescence and tends to have a chronic progression with frequent relapses.
- Mood and cognitive dysfunctions are typical co-occurrences in the disease.

Summary Points

- Eicosanoids are bioactive lipids derived from the metabolism of arachidonic acid by COX, LOX, and CYP enzymatic pathways.
- Eicosanoids act as both pro- and anti-inflammatory mediators of inflammation.
- Neuroinflammation plays a key role in the pathophysiology of anorexia nervosa.
- Rodents exposed to the activity-based model of anorexia nervosa (ABA) display significantly impaired brain inflammatory eicosanoids levels.
- Expression levels of PLA2, ALOX-5, and ALOX-15 enzymes of the eicosanoids biosynthesis pathways are altered in the brain of ABA rats.
- Diet restriction plays a key role in the neuroinflammation displayed by ABA rats.

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Anorexia Nervosa and Impact After Three Decades

24

Mortality and Beyond

Elisabet Wentz

Contents

Introduction 470
Sten Theander's Study in the Southern Part of Sweden 470
The Gothenburg Anorexia Nervosa Study 471
Background and Methods 471
Results 475
Comparisons Between Theander's Study and the Gothenburg AN Study 478
Discussion 478
Conclusions 482
Key Facts 483
Summary Points 483
References 483

Abstract

There are currently only two outcome studies of anorexia nervosa (AN) with a follow-up period of 30 years or more. Both of them have been carried out in Sweden, but apart from that there are few similarities. One of the studies was published in the mid-1980s and the other one 35 years later. The former reported high mortality rates, and the latter had not experienced any deaths during the 30-year follow-up. Can the development of specialized eating disorder services during the last decades of the twentieth century explain the difference regarding a fatal or nonfatal outcome between the studies? The truth is probably much more complex. The two studies will be described, and similarities and differences will be discussed in this chapter.

Keywords

Anorexia nervosa · Eating disorders · Outcome · 30 years · Mortality · Recovery

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Introduction

Follow-up studies of anorexia nervosa (AN) have been conducted since the 1950s. The outcome studies that were performed during the second half of the twentieth century have been reviewed by Steinhausen and included 119 patient series and approximately 5600 AN cases (Steinhausen 2002, 2009). Steinhausen's review concluded that half of all individuals with AN had recovered, one third had improved, one fifth were considered as chronic AN cases, and the mortality rate was 5%. The studies included in the review were heterogeneous in many respects. They were therefore divided into subgroups based on the duration of the follow-up periods: less than 4 years, between 4 and 10 years, and more than 10 years. Another categorization was based on whether the sample with AN had the onset of AN only in adolescence or whether the sample had a variable onset of AN, including onset in adulthood. In general, the outcome was better in the studies with only adolescent-onset AN cases. The highest mortality rates were seen in studies with variable AN onset and a follow-up period of more than 10 years. The two AN samples that will be introduced in the present chapter were included in the review by Steinhausen. A study by Theander (see below) (Theander 1985) excelled in terms of the unique follow-up period of 33 years and a mortality rate of 18%. The Gothenburg AN study (see below), which at the time had published 10-year follow-up data (Nilsson et al. 1999), represented a sample with only adolescent-onset cases of AN. The outcome in terms of mortality was encouraging, as no individuals had died. The Gothenburg AN study has continued to follow the AN sample including a matched control group, and a 30-year follow-up was published in 2020 (Dobrescu et al. 2020). Theander's study and the Gothenburg AN study are the only two AN outcome studies with a follow-up period of 30 years or more. In this chapter, the two studies will be presented and compared with each other, and similarities and differences between the two will be discussed.

Sten Theander's Study in the Southern Part of Sweden

Sten Theander, a psychiatrist and researcher at Lund University, Sweden, published his thesis, "Anorexia nervosa: a psychiatric investigation of 94 female patients," in 1970 (Theander 1970). He had aimed at conducting a retrospective study by tracing all female inpatients with AN in a defined area of southern Sweden. His search included medical records from departments of internal medicine, gynecology, pediatrics, child psychiatry, and psychiatry in the defined part of Sweden. The women had been admitted to hospital between 1931 and 1960. The mean observation time was 15 years. At the time of the first study, which took place in 1966, 94 women had been found in the records. Seventy-nine of the former AN patients underwent a personal interview with the researcher. The remaining 15 women had either died ($n = 10$), lived too far away to take part in the study ($n = 3$), or refused to participate ($n = 2$). The causes of death were either suicide ($n = 3$) or AN/undernutrition

($n = 7$). In the majority of the women ($n = 59$), the AN onset occurred before the age of 19 and included five women with an early onset, at age 11 and 12.

The women were divided into three groups depending on in which decade they had been hospitalized for the first time, 1931–1940, 1941–1950, and 1951–1960. The majority of the participants had been hospitalized during the last two decades. The women were also classified into three degrees based on the severity of the AN at first admission. The degrees were based on "the general state of health," and the most severe group was termed "cachectic," with grave undernutrition indicating "a vital risk." The cachectic condition was characterized by one or more symptoms including bradycardia, edema, and/or hypothermia (low body temperature). The cachectic group included 37 of the 94 women. Nine of the 11 women who had been admitted to hospital for AN between 1931 and 1940 were classified as cachectic. During the following two decades, the proportion of cachectic patients was less dominant, with 32% and 34%, respectively. All women who had died of undernutrition belonged to the cachectic group. Theander suggested that the decreased proportion of inpatients classified as cachectic over time was due to the fact that only the most severe cases were admitted to hospital in the 1930s, and most of these women had had a longer history of AN before being hospitalized.

In his thesis, Theander considered 63% to be recovered and defined the outcome as "completely free from anorectic symptoms," including having normal weight and normal menstruations and no weight phobia or bulimic symptoms (Theander 1985, 1970).

A second follow-up was conducted between 1982 and 1984 (Theander 1985, 1983) with a mean observation time of 33 years from the time of the original admission to hospital. The observation period showed great variation and varied from 24 to more than 50 years. Only one third of the former AN inpatients had ever been admitted to a psychiatric ward. Another seven women had died since the first study was conducted; two of them had committed suicide. In three cases, death was caused by AN, and another two had died from cancer. The subgroup with a fatal outcome corresponded to a mortality rate of 18%. A more encouraging finding in the 33-year follow-up was that 71 former AN patients (76%) were considered recovered and did not fulfill the criteria for AN or bulimia nervosa anymore. Only 6% were classified as having a poor outcome, i.e., the individual still suffered from AN or had had a "crossover" and now fulfilled the criteria for bulimia nervosa. Theander found that recovery rarely occurred after 12 years had elapsed since the onset of AN (Theander 1985).

The Gothenburg Anorexia Nervosa Study

Background and Methods

This prospective study originally aimed at performing an epidemiological study of adolescent-onset AN in Gothenburg by inviting all students born in 1970 ($n = 4291$), attending eighth grade, and living in Gothenburg in 1985. School health nurses in all

junior high schools were informed to weigh and measure the students. The adolescents completed a short self-report questionnaire pertaining to eating disorder-related symptoms. Maria Råstam, one of the initiators of the study, scrutinized all the students' grow charts in order to discover growth deviances (Rastam et al. 1989). The researchers found 25 individuals with AN. One of them, a girl, refused an in-depth examination, leaving 24 adolescents, 22 girls and two boys, all born in 1970, to form a population-based group. The school health nurses involved in the study also reported other adolescent cases with AN. These individuals were not born in 1970 but in adjacent years, in most cases between 1971 and 1974. This group, consisting of 27 young people, was compared with the population-based group regarding a considerable number of background variables, and almost total agreement between the groups was observed. The population-based group had, however, received treatment to a lesser extent. Based on the similar structure of the two groups, the researchers decided to pool them together to form the "AN group," which consisted of 51 individuals, 48 girls and three boys.

As a part of the study, the school health nurses were also asked to select comparison cases who matched the AN cases regarding age, sex, and schooling. This group was labeled the "COMP group" and also included 51 individuals, 48 girls and three boys. The young people in the COMP group had no history of AN or any other eating disorder.

The epidemiological study showed that the prevalence of AN before age 18 was 1.08% in females and 0.09% in males (Rastam et al. 1989).

The 51 AN and 51 COMP cases all agreed to an in-depth assessment including a physical examination and personal interview at the time of the original study. The mothers were interviewed regarding the child's early development, physical and psychiatric symptoms, and personality. Medical records including pregnancy, delivery, and the perinatal period were scrutinized by the researchers.

In total, the AN and COMP groups have been examined on five occasions. Table 1 shows the mean ages of the participants at the time of the five examinations (AN study 1, AN study 2, AN study 3, AN study 4, and AN study 5), beginning at age 16, the original study, until the 30-year follow-up. In the first four studies, there were no dropouts, i.e., all the 51 individuals in the AN and COMP group, respectively, agreed to participate. The project is characterized by studying a community-based (partly population-based) sample using a prospective case-control design.

At the 30-year follow-up, the participants were in their mid-40s (Table 1). All the individuals in the AN and COMP group had been traced. All the 51 COMP cases and 47 of the 51 AN cases agreed to participate. The reasons why four individuals in the AN group abstained were either due to living abroad and having a busy schedule at work ($n = 1$), being very disabled due to psychiatric morbidity ($n = 1$), or not feeling comfortable taking part in the study ($n = 2$) (Rydberg Dobrescu et al. 2020). The majority, 36 AN and 42 COMP cases, were interviewed face-to-face, and the rest were interviewed via online video conferences or telephone.

Table 2 shows all the assessments that were used in the 30-year follow-up. One of the outcome measures, the Morgan-Russell assessment schedule (Morgan and Russell 1975; Morgan and Hayward 1988), which has been used in all four follow-up studies,

Table 1 The Gothenburg anorexia nervosa study. Mean ages at examinations

	AN onset	AN study 1; original study	AN study 2; 6-year follow-up	AN study 3; 10-year follow-up	AN study 4; 18-year follow-up	AN study 5; 30-year follow-up
AN group	14.3	16.1 ($n = 51$)	21.0 ($n = 51$)	24.5 ($n = 51$)	32.4 ($n = 51$[a])	44.4 ($n = 47$[b])
COMP group	NA	16.0 ($n = 51$)	20.8 ($n = 51$)	24.2 ($n = 51$)	32.4 ($n = 51$)	44.2 ($n = 51$)

AN anorexia nervosa, *COMP* comparison, *NA* not applicable
[a]The mother of one participant was interviewed instead of the proband, since the proband considered herself too ill to take part
[b]All 51 individuals were traced and were alive, but four of them declined to participate in the study

deserves to be mentioned in more detail. The instrument supplies information, based on the individuals' BMI and menstrual status, on whether the outcome should be classified as good (normal weight + normal menstruations), intermediate (either normal weight or normal menstruations but not both), or poor (low weight, i.e., <18.5 kg/m^2, and no or scanty menstruations). A modified categorization suggests that all individuals with an ongoing eating disorder, irrespective of whether BMI and menstruations have normalized, should belong to the poor outcome category (Ratnasuriya et al. 1991). In addition, the Morgan-Russell assessment schedule includes five scales covering different areas that may be affected in individuals with a current or previous diagnosis of AN. The domains encompass food intake, menstrual pattern, and psychiatric, psychosexual, and socioeconomic status. A composite score, the Morgan-Russell averaged scale score, is calculated based on the five scales.

Two other outcome measures were used in the 30-year follow-up: the Global Assessment of Functioning Scale (GAF) (APA 1994), which measures both the degree of psychiatric symptoms and social/occupational functioning, and the 36-item Short Form Health Survey (SF-36) (Sullivan et al. 2002). The former scale has a span from 0 (severely impaired) to 100 (no impairment/very high functioning). The SF-36 (Sullivan et al. 2002) is a well-established and widely used instrument to measure health-related quality of life. It is the most frequently used health-related quality of life instrument in the field of eating disorder research (Treasure et al. 2015). It is a self-report questionnaire divided into four physical and four mental subscales. A composite score can be calculated for the physical (physical composite score, PCS) and the mental (mental composite sore, MCS) subscales.

Neurofilament Light Chain Protein in Serum

Blood samples were collected to investigate serum levels of biomarkers for neuronal injury seen in dementia and other neurodegenerative disorders. Neurofilament light chain protein (NfL) is a biomarker that can detect increased rates of axonal degeneration (Teunissen et al. 2005), including Alzheimer's disease (Mattsson et al. 2017) and traumatic brain injury (Rubin et al. 2019). An in-house single-molecule array (Simoa) assay (Quanterix®, Billerica, MA) was applied to measure serum NfL concentrations in the 30-year follow-up. The method delivers an approximately

Table 2 Assessments at the 30-year follow-up in the Gothenburg anorexia nervosa study

Assessment	Purpose
Weight and height	Assess outcome regarding anthropometric data
MINI International Neuropsychiatric Interview (MINI 6.0)	Assign psychiatric disorders
Structured Clinical Interview for DSM-IV (SCID-I) eating disorder module	Assign eating disorders
DSM-5 checklist for feeding and eating disorders	Assign eating disorders according to the DSM-5
The Short Form Health Survey (SF-36)	Assess outcome regarding health-related quality of life
Global Assessment of Functioning Scale (GAF)	Assess outcome regarding psychosocial functioning
The Morgan-Russell scales	Assess outcome regarding eating disorder symptoms, mental health, and psychosexual and socioeconomic state
Serum neurofilament light chain protein	Detect neuronal injury
Facial emotion recognition task	Assess capacity of facial emotion recognition
Instruments pertaining to physical and psychiatric status in offspring[a]	Detect symptoms of somatic and psychiatric disorders (including eating disorders) in offspring
Register search[a]	Attain information on offspring from the Medical Birth Registry to identify all births including delivery and perinatal status
Register search[a]	Attain information on inpatient hospitalizations and outpatient specialist consultation for psychiatric and somatic settings, pharmacological consumption, social assistance, disability pension, and sick leave to conduct health economic analyses

[a]Data not yet published

1000-fold increase in sensitivity (Rohrer et al. 2016). The correlation between cerebrospinal NfL and serum NfL has been shown to be robust (Lewczuk et al. 2018). The participants were asked whether they or any of their first-degree relatives suffered from dementia. The Swedish National Patient Register for in- and outpatient treatment was scrutinized regarding potential diagnoses of dementia, according to the ICD-9 and the ICD-10, among the participants. The data presented are limited to female participants, since male cerebrospinal NfL concentrations tend to be higher than female concentrations (Goossens et al. 2018). Blood samples were collected from 34 women in the AN and 38 women in the COMP group.

Facial Emotion Recognition Task

Twenty-six women who had recovered from eating disorders in the AN group and 31 women in the COMP group completed a facial emotion recognition task using the Tobii Studio 3.03 software. The participants were shown photos of faces expressing the emotions anger, fear, and happiness. The facial expressions varied between 0% (neutral), 40%, 60%, 80%, and 100% of the expression. A photo with the morphed

emotion (0%, 40%, 60%, or 80% of the full emotion) was presented to the left on a screen, and four faces expressing 100% of the different emotions (neutral, anger, fear, and happiness) were shown to the right on the same screen. The participant had to match the photo with the morphed expression to the left with one of the photos to the right showing the correct full expression. The task, which is entirely nonverbal, consists of 104 pictures, starting with 24 images as a training set. The number of correct answers, reaction time, and visual scanning behavior were registered and analyzed. Six of the participants in the AN group had shown diagnostic stability in previous studies regarding autism spectrum disorder (ASD), i.e., they had been assigned an ASD diagnosis in at least three of the four previous examinations by a blinded rater (Anckarsater et al. 2012). In the facial emotion recognition study, these six participants constituted a subgroup (recovered AN with ASD), and their data were compared with the remaining individuals in the AN group. It was considered important to analyze the subgroup with ASD separately, since individuals with ASD are known, in general, to pay less attention to eyes compared with typically developed individuals (Klin et al. 2002). In addition, facial emotion recognition is usually more challenging for individuals with ASD (Baron-Cohen et al. 2001). For further details regarding the methods, see Dinkler et al. (2019).

Definition of Full Eating Disorder Recovery

All follow-up studies based on the Gothenburg AN study have used the same definition for full eating disorder recovery. The criteria for recovery were fulfilled if the individual had not met any criterion for an eating disorder, exhibited BMI within the normal range, had had normal menstruations, and reported no dieting or preoccupation with body weight and shape during the last 6 months. The definition is in accordance with the proposal by Strober and colleagues (Strober et al. 1997); however, Strober's group only claimed a 2-month duration of recovery, compared with 6 months in the Gothenburg AN study.

The present chapter will focus on data from the three papers from the 30-year follow-up that have been published so far. The findings include general outcome, psychiatric morbidity including eating disorders, facial emotion recognition, and serum concentrations of neurofilament light chain protein signaling neural injury (Rydberg Dobrescu et al. 2020; Dinkler et al. 2019; Wentz et al. 2021).

Results

General Outcome

No participants had died, neither in the AN group nor in the COMP group, in the 30-year follow-up or in previous follow-up studies. Based on the modified Morgan-Russell outcome categorization, 72.3% ($n = 34$) had a good outcome, 8.5% ($n = 4$) had an intermediate outcome, and 19.1% ($n = 9$) had a poor outcome in the AN group. All individuals in the intermediate group had a low BMI, and all in the poor outcome group had a current eating disorder.

The AN group scored significantly lower on the GAF scale compared with the COMP group (AN: 60.72 (SD: 17.23); COMP: 80.20 (SD: 14.78); $p < 0.0001$). Regarding the health-related quality of life outcome, the AN group scored significantly lower on the mental composite score (MCS) of the SF-36, and on the mental subscale, "mental health," than the COMP group. In the AN group, those with a current eating disorder did not score lower than those without a current eating disorder on the SF-36.

Eating Disorder Outcome

Nine (19%) of the 47 individuals in the AN group had an eating disorder at the 30-year follow-up. Three of them had current AN, of whom two were "in partial remission." The most common eating disorder diagnosis was "other specified feeding and eating disorders" (OSFED), which affected five individuals. This diagnosis is assigned when the individual has "atypical AN" (weight loss criterion for AN not fully met) or almost fulfills the criteria for bulimia nervosa (low frequency of bingeing or purging and/or limited duration) or binge-eating disorder (low frequency of bingeing and/or limited duration). There are two additional OSFED subtypes: purging disorder and night-eating syndrome. In the AN group, two of the individuals with OSFED were categorized as atypical AN, and one each was classified as bulimia nervosa, binge-eating disorder, and the purging type. One individual in the AN group had binge-eating disorder. One woman in the COMP group had the OSFED-type night-eating syndrome. No further eating disorders were diagnosed in that group.

Over the 30 years, the mean duration of AN, if all AN episodes were included, was 4.9 years (SD 5.1), and the mean duration of all eating disorder episodes, including AN, was 10.2 years (SD 8.1). During the past 12 years, since the previous follow-up, 18 years after the onset of AN, 32% ($n = 15$) had at some time experienced an eating disorder including AN. Seventeen percent ($n = 8$) reported that they had suffered from AN at some point between the two latest follow-ups. Figure 1 illustrates the number and type of eating disorders that occurred in AN study 4 and AN study 5 and during the 12-year period between the two follow-up studies.

Psychiatric Morbidity

At the 30-year follow-up, 29% in the AN group suffered from anxiety disorders (COMP: 10%; $p < 0.05$), which constituted the most common psychiatric cluster at the time. Eighteen percent in the AN group had a current affective disorder, and 38% had at least one psychiatric disorder, excluding ongoing eating disorders (COMP: 12%; $p < 0.01$).

Neurodegenerative Findings

No individuals in the AN or COMP group had been assigned a diagnosis of dementia according to the Swedish National Patient Register. Figure 2 illustrates serum NfL concentrations in the women in the AN and COMP groups. The AN group exhibited significantly higher serum NfL concentrations than the COMP group (AN:

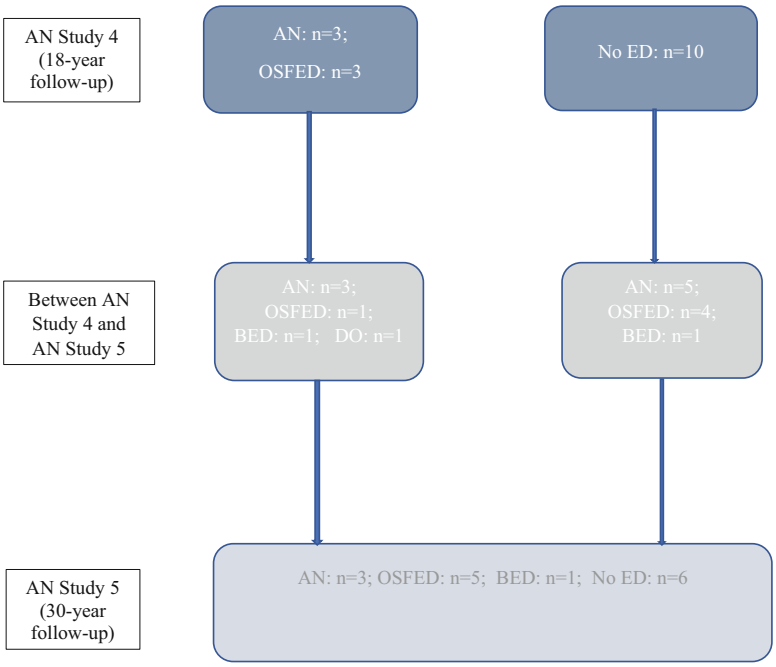


Fig. 1 Eating disorders in AN study 4 and AN study 5 and between the two follow-up studies**.** In AN study 4, six individuals had an eating disorder (ED). Ten individuals without an ED in AN study 4 had an ED relapse between AN study 4 and AN study 5. Altogether, 15 individuals (32%) had an ED between the two follow-up studies. In AN study 5, there were nine (17%) individuals with an ED. Six individuals with an ED between the two follow-up studies no longer met the criteria for an ED in AN study 5. AN, anorexia nervosa; BED, binge-eating disorder; OSFED, other specified feeding and eating disorders; No ED, no eating disorder; DO, dropout

27.7 pg/ml; SD: 22.0; COMP: 19.0 pg/ml; SD: 12.1; $p = 0.041$). Among the women in the AN group who no longer suffered from an eating disorder (28 of the 34 women who agreed to the collection of blood samples), an increased, albeit statistically nonsignificant ($p = 0.054$), serum NfL concentration was seen in relation to the serum NfL concentration in the COMP group. There was a statistically significant negative correlation between the serum NfL concentration and the current BMI in the AN group ($r = -0.44$), i.e., the lower the BMI, the higher the serum NfL concentration. This correlation appeared exclusively in the AN group. No significant correlation was seen between the total duration of AN during the 30 years and the serum NfL concentration in the AN group ($r = 0.15$).

Facial Emotion Recognition Task

The recovered AN women without ASD ($n = 20$) performed similarly to the women in the COMP group regarding accuracy, reaction time, and visual scanning behavior. The recovered AN women with ASD ($n = 6$) showed significantly higher accuracy than the recovered AN women without ASD regarding low expression intensity

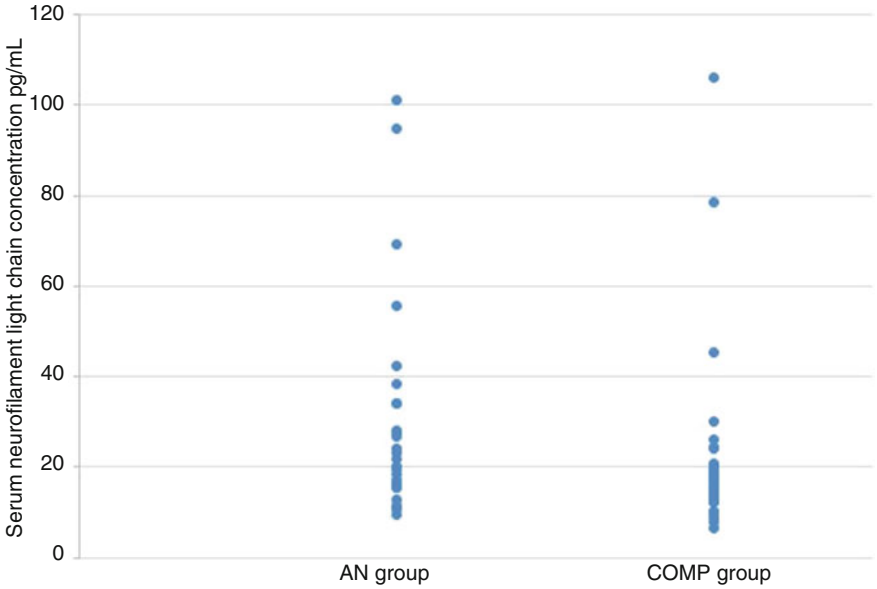


Fig. 2 The distribution of serum neurofilament light chain protein in women in the AN and the COMP group**.** AN, anorexia nervosa; COMP, comparison group

(40% of the facial expression) but not regarding the facial expressions with higher intensity (60% and 80%).

Comparisons Between Theander's Study and the Gothenburg AN Study

Table 3 compares the study designs, samples, and outcome of the two Swedish studies with a follow-up period of 30 years or more. Theander's study reported high mortality rates, while the Gothenburg AN study reported no deaths. On the other hand, Theander found that as much as 76% of his sample had recovered, and only 6% had an eating disorder 33 years after first admission to hospital. The corresponding data in the Gothenburg AN study showed poorer results: 64% had recovered, and 19% had a current eating disorder.

Discussion

The two studies presented in this chapter are very different in many respects, which makes it difficult to compare the outcomes. One study represents females admitted to hospital due to AN, mainly during the first half of the twentieth century, and the other study is based on a sample of individuals with adolescent-onset AN born in the

Table 3 Characteristics and outcome of the two studies with a follow-up period of at least 30 years

	Theander's study	The Gothenburg AN study
Characteristics		
Sample characteristics	Hospitalized AN patients	Adolescents recruited from the community including a total birth cohort
Study design	Initially retrospective; second assessment prospective	Prospective, case-control
Location	Southern Sweden	Gothenburg, Sweden (southwest Sweden)
Females/males	94/0	48/3
Control group	No	Yes; 51 individuals (48 females/3 males) matched for age, sex, and school and without a history of eating disorders
Observational time (years)	33 (on average 15 years between admission to inpatient treatment and first assessment; second assessment 18 years later)	30 (mean age at onset of AN: 14.3 years; fifth assessment after 30 years, at mean age 44)
Number of examinations	2 (1 retrospective, 1 follow-up study)	5 (1 baseline, 4 follow-up studies)
Outcome		
Recovered; n (%)	71 (76%)	30 (64%)[a]
Number of individuals with an eating disorder; n (%)	6 (6%)	9 (19%)[a]
Type of eating disorders	4 AN, 2 BN	3 AN, 1 BED, 5 OSFED
Deaths; n (%)	17 (18%)	0
Death caused by suicide; n (%)	5 (5%)	0

N number, *AN* anorexia nervosa, *BN* bulimia nervosa, *BED* binge-eating disorder, *OSFED* other specified feeding and eating disorders

[a]47 of the 51 in the AN group agreed to participate at the 30-year follow-up

second half of the same century and recruited from the community. Both studies originate in Sweden but were performed during different time periods, which probably had implications for the outcome.

Mortality only occurred in the study by Theander. How can that be explained? The most obvious explanation is the different selection of participants in the two studies. Theander's study included inpatients only, and the Gothenburg AN study was community-based. Half of the participants in the Gothenburg AN study constituted a total age cohort (born in 1970), and the majority of individuals in this population-based group had not received treatment for AN at the time of the original study (Gillberg et al. 1994). It can therefore be assumed that individuals who have a history of inpatient care due to AN belong to a more severe group than a community-

based sample. In his thesis, Theander classified the participants based on the severity of AN during the inpatient treatment. The most severe cases were labeled the cachectic group, and, in the thesis, all participants who had died due to undernutrition belonged to that category. The Gothenburg AN study did not include data regarding the number of participants who had received inpatient treatment for AN over the 30-year follow-up period. However, a study based on the 6-year follow-up, at mean age 21 years, reported that 13 of the 51 individuals (25%) had been treated in intensive care or in specialized AN inpatient units (Gillberg et al. 1994). At the 30-year follow-up, 23% stated that they had never received any treatment for AN or any other eating disorder (Rydberg Dobrescu et al. 2020). Another notable discrepancy between the studies that may have influenced mortality rates is the different time periods when the two studies took place: Theander's study, in which all individuals were born (and usually treated for AN) during the first half of the twentieth century, and the Gothenburg AN study, where the participants were born in the 1970s and had an onset of AN in the 1980s. Specialized eating disorder services had not yet been developed in Sweden in the 1980s, but health care in general had made huge progress compared with the first half of the 1900s. The more homogeneous sample in the Gothenburg AN study, consisting solely of cases with adolescent-onset AN, may also have contributed to the zero mortality, since the outcome is known to be better when the onset of AN happens in adolescence than later (Steinhausen 2009). Late onset of AN has been observed as a risk factor for premature death (Fichter and Quadflieg 2016). A meta-analysis of mortality in eating disorders published in 2011 found a standardized mortality rate (SMR) of 6 for AN, i.e., a sixfold increase in the risk of premature death among individuals with previous or current AN (Arcelus et al. 2011). The SMR was not calculated in Theander's study, but a mortality rate of 18% is remarkably high compared with a systematic review, based on outcome studies of AN during the second half of the nineteenth century, with a mortality rate of 5% (Steinhausen 2009). On the other hand, the Gothenburg AN study had an unforeseen low mortality rate, reporting no deaths. The FinnTwin study, a population-based project studying individuals with AN, reported zero mortality at 10-year follow-up (Mustelin et al. 2015), a result that is in line with that in the Gothenburg AN study.

In Theander's study, the eating disorder recovery rate is higher than in the Gothenburg AN study. The definition of recovery by Theander was not as detailed and strict as the one in the Gothenburg AN study. Theander did not specify the time frame of having been "completely free from anorectic symptoms," while the Gothenburg AN study required a duration of at least 6 months. Further, Theander did not require the absence of dieting, a criterion that was included in the full recovery definition in the Gothenburg AN study. In summary, the different definitions across studies may imply that the proportion of recovered women has been overestimated in the study by Theander compared with the Gothenburg AN study. There is, however, still no consensus regarding the characteristics of full recovery from an eating disorder (Khalsa et al. 2017).

The eating disorder prevalence was relatively low, 6%, in the 33-year follow-up by Theander and lower than the prevalence in the Gothenburg AN study where 19%

had an eating disorder at the 30-year follow-up. This is a "surprising" finding considering that the cases in Theander's original study in general exhibited a more severe variant of AN, including several patients who had been cachectic. The diagnostic criteria for eating disorders have changed considerably since Theander's work in the beginning of the 1980s. According to the criteria for AN in the DSM-III, published in 1980 (APA 1980), refusal to maintain weight over a minimal normal weight for age/height, and a weight loss of 25%, had to be met. In the DSM-III-R (APA 1987), published in 1987, the weight criterion had been modified and was now specified as "body weight 15% below that expected," and the weight loss criterion had been removed. According to the DSM-5 (APA 2013), amenorrhea, a criterion that was included in the DSM-III, the DSM-III-R, and the DSM-IV (APA 1994), is no longer a symptom that has to be present, and the weight criterion is fulfilled if BMI is below 18.5 kg/m^2 in adult cases with AN. To sum up, assigning an eating disorder diagnosis in the 1980s required a more severe condition than in 2013 when the DSM-5 was published. More eating disorder diagnoses have been established since the 1980s, including binge-eating disorder in the DSM-5. At the 33-year follow-up, Theander reported that two of the six women with an eating disorder had bulimia nervosa and the rest had AN. No one in the Gothenburg AN study, neither at the 18-year nor at the 30-year follow-up, met the criteria for bulimia nervosa. Based on the findings in the Gothenburg AN study, one could assume that individuals with a history of AN rarely cling to a diagnosis of bulimia nervosa two to three decades after the onset of AN. However, Theander's study implies another outcome; bulimia nervosa can still appear 33 years after the first hospitalization due to AN.

Theander stated that recovery was rare beyond 12 years after the onset of AN. The Gothenburg AN study could not completely corroborate Theander's findings. In the 18-year follow-up, there were six cases with eating disorders, including three with AN. The individuals with AN were all free from an eating disorder in the 30-year follow-up, i.e., they had recovered from AN more than 18 years after the onset of AN. In the 18-year follow-up study, two of the three individuals with another eating disorder did, however, not recover; one exhibited a crossover to AN, and one continued having another eating disorder. For that individual with another eating disorder in the 18-year follow-up study dropped out in AN study 5, why no information could be collected regarding the eating disorder outcome. Eddy and co-workers performed a 22-year follow-up study of patients with AN and bulimia nervosa who had been admitted to an eating disorder service (Eddy et al. 2017). The research group had previously conducted a 9-year follow-up and reported that 31.4% of the patients with AN were recovered after 9 years, and 62.8% were recovered 22 years after admission. There were, however, four of the original 121 AN patients who had been classified as recovered at the 9-year follow-up but later had a relapse and fulfilled the criteria for AN at the time of the 22-year follow-up. The findings are in accordance with the results in the 30-year follow-up study, namely, that an AN relapse may appear decades after the individuals had been classified as having recovered from AN.

In addition to the findings regarding full recovery rate, the proportion of individuals with a remaining eating disorder, and survival data, some other major findings in the 30-year follow-up also require attention. Psychiatric morbidity, excluding eating disorders, was surprisingly common; about a third of the individuals in the AN group had a psychiatric disorder, of which anxiety and affective disorders were the most frequent. Both anxiety and depression are almost ubiquitous in individuals with current AN. Depressed mood is usually secondary to starvation in individuals with AN. However, the overrepresentation of anxiety and affective disorders 30 years after the onset of AN implies that the individuals may have a susceptibility for these psychiatric disorders in addition to an eating disorder. An extensive genetic study using GWAS and involving almost 17,000 AN cases showed a relationship between AN and anxiety and affective disorders (Watson et al. 2019), a finding that corroborates the data in the 30-year follow-up study.

Another major finding in the 30-year follow-up was the elevated serum concentration of the brain injury marker NfL in the AN group. There was no significant difference between the serum NfL concentration among those with a current eating disorder and those without an eating disorder. The results may imply that brain tissue is more likely to show signs of damage in individuals with a history of AN compared with matched individuals without a history of an eating disorder. Interestingly, the duration of AN was not related to a higher serum NfL concentration.

The facial emotion recognition study is the first of its kind assessing women recovered from AN and investigating whether coexistent ASD has an impact on the results. Recovered women and women in the COMP group showed similar results regarding accuracy, reaction time, and visual scanning behavior. These findings indicate that no facial emotion recognition deficits should be expected in women recovered from AN. In the AN group, the subgroup of women with coexistent ASD performed better than the women without ASD regarding interpretation of facial expressions with low intensity. This result demonstrates an ability to detect glimpses of a facial appearance among the women with coexistent ASD. The discovery could be a symptom of "attention to detail," a finding which is usually present in individuals with ASD (Baron-Cohen et al. 2001).

Conclusions

Two Swedish outcome studies of AN with a follow-up period of 30 years or more were published in the 1980s and in the 2020s, respectively. The study published in the 1980s consisted of a sample with a more severe form of AN. All the patients had originally been hospitalized due to AN, while the other outcome study consisted of a community-based sample with adolescent-onset AN cases. The mortality rates were surprisingly high in the former study, while zero deaths had occurred in the latter study. The two studies reported better recovery rates from eating disorders than the recovery rate of 47% found in an extensive review of AN outcome studies published by Steinhausen in 2002 (Steinhausen 2002). The study from the 1980s found a lower prevalence of eating disorders after 33 years than the more recent outcome study

where as many as one in five still suffered from an eating disorder 30 years after the onset of AN. A comparison between the two studies implies that mortality due to AN seems to have decreased over the years, and the development of a better health-care system may have contributed to this finding. However, when comparing the two studies with regard to full eating disorder recovery rates and the prevalence of persisting eating disorders, there is no indication of a better outcome in the study published in 2020.

Key Facts

- AN has one of the highest mortality rates among psychiatric disorders
- Mortality rates in AN seem to have decreased compared with data based on studies from the twentieth century
- Recovery from AN after 12 years is rare but does occur
- Individuals who are admitted to inpatient treatment due to AN have a poorer prognosis regarding premature death

Summary Points

- A 33-year follow-up study of female inpatients with AN was performed in the 1980s. The study reported a mortality rate of 18%
- Of the women, 76% had recovered at the 33-year follow-up
- After 33 years, 6% still had an eating disorder, in most cases chronic AN
- A 30-year follow-up study of AN with adolescent onset was conducted during the second decade of the twenty-first century. No deaths had occurred in the study
- Sixty-four percent were considered fully recovered from AN at the 30-year follow-up
- Nineteen percent still had an eating disorder 30 years after the onset of AN
- Psychiatric disorders other than eating disorders were still common among the participants in the 30-year follow-up of AN
- The mean duration of AN (including all episodes) was 5 years in the 30-year follow-up

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Linking Anorexia Nervosa with the Gut Microbiota

25

A New Narrative

Radka Roubalova, Petra Prochazkova, and Hana Papezova

Contents

Introduction 489
The Microbiota-Gut-Brain Axis 490
Gut Microbiota Link to AN 492
Intestinal Microbial Metabolites in AN 498
Gut Microbiota Adaptation to Diet 500
Manipulating the Gut Microbiota 501
  Antibiotics 501
  Probiotics, Prebiotics, and Psychobiotics 502
  Fermented Food 502
  Fecal Microbiota Transplantation 503
Immunity Involvement 503
Potential Mechanisms in AN Development 504
Applications to Other Eating Disorders 505
Mini-dictionary of Terms 506
Key Facts of Human Microbiota 507
Key Facts of Microbiota in Patients with AN 507
Key Facts of Gut Microbiota Modifications 508
Summary Points 508
References 508

Abstract

In the present chapter, we provide a comprehensive review of the potential role of gut microbiota in the pathogenesis of anorexia nervosa (AN) and discuss the

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potential of modifying the gut microbiota as an adjunct to standard nutritional treatment protocols for AN patients. Recently, the gut microbiota has been increasingly recognized as an important factor contributing to various diseases, including psychiatric disorders. Gut microbiota communicates with the central nervous system on the gut-brain axis and potentially affects mental health. In patients with AN, the microbial composition and related microbial products differ from healthy individuals. The microbiota in the gastrointestinal tract is a very important antigenic source for the host immune system. Evidence is now emerging for an association between specific psychiatric disorders and altered immune reactions, some of which have been described in patients with AN. Some immune components have the potential to regulate brain functions and may underlie the pathology of anorexia nervosa.

Keywords

Microbiota · Microbiome · Anorexia nervosa · Microbiota-gut-brain axis · Dysbiosis · SCFA · Neurotransmitter · Fecal microbiota transplantation · Probiotics · Prebiotics · Autoimmunity

Abbreviations

ABA	Activity-based anorexia
AN	Anorexia nervosa
ATB	Antibiotic
BCAA	Branched-chain amino acid
BED	Binge eating disorder
BMI	Body mass index
BN	Bulimia nervosa
ClpB	Caseinolytic protease B
CNS	Central nervous system
DNA	Deoxyribonucleic acid
FMT	Fecal microbiota transplantation
fT4	Free thyroxine
GABA	Gamma-aminobutyric acid
GF	Germ-free
HPA axis	Hypothalamic-pituitary-adrenal axis
IBD	Inflammatory bowel disease
IBS	Irritable bowel syndrome
IgG	Immunoglobulin G
IL-17	Interleukin 17
IL-6	Interleukin 6
MC	Melanocortin
NPY/AGRP	Neuropeptide Y/agouti-related peptide
OTU	Operational taxonomic unit

PANDAS	Pediatric autoimmune neuropsychiatric disorder associated with streptococcal infections
POMC/CART	Pro-opiomelanocortin/cocaine- and amphetamine-regulated transcript
SAM	*S*-Adenosyl-L-methionine
SCFA	Short-chain fatty acid
TNF-α	Tumor necrosis factor alpha
TSH	Thyroid-stimulating hormone
α-MSH	Alpha-melanocyte-stimulating hormone

Introduction

The human gut is home to an enormous community of resident microorganisms called the microbiota, including bacteria, viruses, fungi, archaea, and protozoa. Among these, bacteria represent the best-studied group, with the estimated number in the adult "reference man" being approximately 3.8×10^{13} (Sender et al. 2016). The frequently used term microbiome refers to the collective genomes of the microorganisms in a particular environment. The gut microbiota composition varies throughout life. It is very dynamic in childhood and relatively stable during adulthood, but it declines and changes in the elderly. The human gut harbors from 200 to more than 1000 bacterial species. Everyone has a personalized gut microbiota containing a unique taxonomic composition, with only a small number of species being found in all humans, which is known as the core gut microbiota (Turnbaugh et al. 2009). Approximately a third of resident intestinal microbes are common to all individuals; the remaining part is unique for each host. The variable part is affected by various factors, like age, disease, diet, lifestyle, host genotype, medications, hygiene, geographical location, etc. It has been shown that some bacteria occur mainly in healthy people and have beneficial effects, while other commensal microbes may be pathogenic under certain conditions (the so-called pathobionts). However, it appears that a core "healthy" microbiota common to all individuals does not exist.

Moreover, it is sometimes difficult to distinguish whether a particular commensal microbe is harmful or beneficial, depending on the specific strain or location in the body. A compositional and functional alteration in the microbiota is called "dysbiosis" and is associated with many diseases, including neurological and psychiatric disorders (Liang et al. 2018). Microbiota dysbiosis is characterized by an increase in pathobionts, a decrease in commensals, or a decrease in microbial diversity, or it may be a combination of all three (Levy et al. 2017). The gut microbiota depends on ingested nutrients, which means that both short- and long-term dietary changes can affect the composition of microorganisms inhabiting the intestines (David et al. 2014). This chapter will discuss the importance of the gut microbiota relative to human behavior and describe how the gut microbiota is linked to anorexia nervosa.

The Microbiota-Gut-Brain Axis

The bidirectional neural communication between the brain and gut is well established. However, much of the earlier work regarding gut-brain communication concentrated on digestive functions and satiety. Neural signaling is supported by sophisticated interactions with the endocrine and immune systems. More and more evidence indicates that gut microbiota plays an essential role in this communication process. Microbial products can act either directly on enterocytes, gut-resident immune cells, and enteric nerve cells or indirectly on the central nervous system (CNS) via neuroendocrine and metabolic pathways. Therefore, we often use the "microbiota-gut-brain axis" to describe these interactions (Fig. 1).

Animal models are frequently used to understand the microbiota-host relationship. Perhaps the most important models use germ-free (GF) animals that have never been exposed to microorganisms. These animals can be colonized, for example, by the fecal microbiota of patients, and the effect of this transfer can be observed. Conventional animal models can be used to evaluate antibiotic or probiotic treatments relative to the microbiota. Many of these studies have consistently shown that the microbiota influences behavior (Table 1).

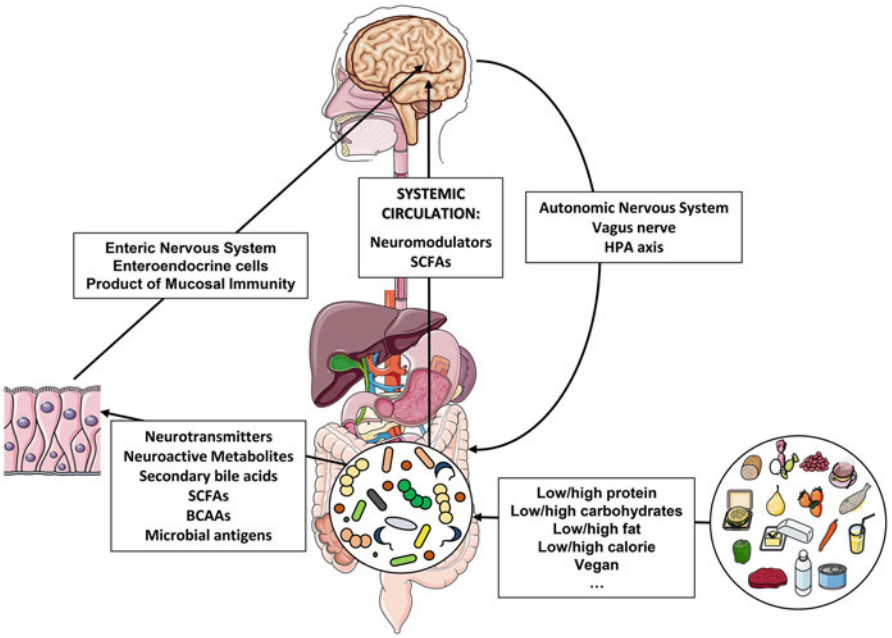


Fig. 1 Bidirectional communication between the gut microbiota and the brain. Diet affects the microbiota composition and, in turn, affects the whole cascade of molecules that may affect the central nervous system and human behavior. *SCFAs*, short-chain fatty acids; *BCAAs*, branched-chain amino acids; *HPA axis*, hypothalamic-pituitary-adrenal axis

Table 1 Examples of gut microbiota manipulations in animal models

References	Condition	Animal model	Type of microbiota manipulation	Significant results
Burokas et al. (2017)	Chronic stress	Male C57BL/6J mice	Prebiotic administration (FOS, GOS; 10 weeks)	FOS+GOS treatment exhibited both antidepressant and anxiolytic effects
Zhu et al. (2020)	Schizophrenia	Male C57BL/6J mice	FMT from schizophrenia patients	Induction of behavioral abnormalities (psychomotor hyperactivity, impaired learning and memory)
Savignac et al. (2016)	Anxiety	Male CD1 mice	Administration of GOS mix (3 weeks) prior to LPS injection	Anxiolytic effect of GOS; modulation of cortical IL-1β and 5-HT2A receptor expression
Guilherme et al. (2021)	Alzheimer's disease	5xFAD model mice	Probiotics and antibiotics administration (2 weeks)	The beneficial effect of antibiotics is based on their anti-diabetic potential
Murray et al. (2019)	Anxiety, depression	Male and female CD1 mice	Probiotics administration	Probiotics reduced LPS-induced sickness behavior and reduced cytokine production
Chevalier et al. (2020)	Depression	Adult male C57BL/6J mice	FMT from UCMS donors	Cellular and behavioral alterations, a decrease in endocannabinoid signaling

FOS, Fructooligosaccharide; *GOS*, Galactooligosaccharide; *LPS*, Lipopolysaccharide; *5-HT2A*, 5-hydroxytryptamine 2A; *FMT*, Fecal microbiota transplantation; *UCMS*, Unpredictable chronic mild stress

Various bacterial species produce metabolites able to influence host appetite and eating behavior by directly affecting nutrient sensing and appetite as well as affecting appetite- and satiety-regulating systems (van de Wouw et al. 2017). Altered gut microbiota has been described in patients with anorexia nervosa (Morita et al. 2015; Borgo et al. 2017; Prochazkova et al. 2021), in certain forms of malnutrition (Genton et al. 2015), and also in obese individuals (Crovesy et al. 2020).

The gut microbiota also affects the permeability of the gastrointestinal barrier. Excessive intestinal permeability, referred to as "leaky gut," results in increased translocation of microbial products across the gut wall and the development of low-grade inflammation. Increased intestinal permeability has been described in obese patients (Teixeira et al. 2012) and patients suffering from various psychiatric disorders (Safadi et al. 2021). One study in AN patients showed a decrease in intestinal permeability related to lactulose/mannitol absorption (Monteleone et al. 2004). In contrast, increased gut permeability was observed in the activity-based anorexia (ABA) mice model (Jesus et al. 2014). Some evidence suggests that anorexia nervosa and other eating disorders are associated with inflammatory

bowel disease, with AN being mostly associated with Crohn's disease (Ilzarbe et al. 2017). We can hypothesize that an increase in gut permeability, with subsequent translocation of microbial products, results in an inflammatory reaction that causes changes in the anatomy and physiology of intestinal tissue; this would explain both reduced gut permeability in later stages of AN and a higher risk of Crohn's disease.

As mentioned above, the intestinal microbiota modulates the CNS through neuroimmune and neuroendocrine mechanisms. Microorganisms produce and secrete hormones (serotonin, dopamine, norepinephrine, and gamma-aminobutyric acid (GABA)), respond to host hormones, and regulate the expression of host hormones (Neuman et al. 2015). Serotonin is linked to most of the behavioral characteristics seen in patients with AN. Tryptophan, the precursor of serotonin, is an essential amino acid, which is only available from the diet. Diet restrictions can result in a reduction in serotonin synthesis, thereby reducing the role of serotonin in neurotransmission at postsynaptic sites. This reduction can lead to depression, anxiety, hyperactivity, and behavioral impulsivity (Haleem 2012). Some evidence suggests that elevated dopamine levels initially trigger the reward system during food restriction and exercise. However, AN patients can become dependent on the reward, not unlike drug addiction (Sodersten et al. 2016). In addition, altered GABA levels play a role in various neuropsychiatry disorders such as anxiety and depression (Cryan and Kaupmann 2005). Prochazkova et al. found significantly reduced levels of dopamine and GABA and slightly reduced serotonin levels in the stool samples from patients with AN compared to healthy controls. A significant increase in the abundance of *Alistipes finegoldii* and *A. onderdonkii* was found in the gut microbiome of patients with AN. The *Alistipes* genus can hydrolyze tryptophan to indole and thus decreases serotonin availability and thus affects the microbiome-gut-brain axis (Prochazkova et al. 2021). However, the effect of altered intestinal neurotransmitter levels on the CNS is not well understood, and we can only speculate on the significance of these changes in patients with AN.

Gut Microbiota Link to AN

Diet and feeding behaviors are the most influential external factors for gut microbiota composition, and since AN is accompanied by starvation, it is evident that AN can induce changes in gut microbiota. Food and habitual diet shape the composition of the gut microbiota; the microbiota then provides nutrient signals to the host. The food composition and diversity determine which intestinal microbes will colonize, proliferate, persist, or vanish (Shanahan et al. 2017).

Interestingly, disturbances during microbiota development in infancy can contribute to the risk of immune and metabolic disease in later life. Additionally, the loss of microbes and their diversity in the elderly due to monotonous diets is associated with unhealthy aging and weakness. Moreover, loss of microbiota diversity is associated with a risk of inflammation and infections (Claesson et al. 2012). However, the effect of a dietary intervention varies extensively among individuals,

whereas factors determining an individual's responsiveness to dietary interventions are not known.

Currently, there are several studies on the gut microbiota in patients with AN, all performed on stool samples (summarized in Table 2). The outcomes of these studies are varied and inconsistent in terms of abundance, diversity, and microbial composition. Reduced alpha diversity (i.e., richness, abundance, and frequencies of species in a microbial ecosystem) in one analyzed index, which reflects the microbial variance within a particular sample compared to controls, was reported in three studies (Kleiman et al. 2015; Morkl et al. 2017; Hanachi et al. 2019), while in four other studies, no difference in alpha diversity was found (Mack et al. 2016; Borgo et al. 2017; Prochazkova et al. 2021; Schulz et al. 2021). Since the results vary between studies, it is difficult to unequivocally interpret the changes in alpha diversity in AN.

However, all studies found significant differences between microbiota composition of patients with AN and healthy controls. There are some indications that AN is associated with a distinct microbiota signature. One potentially important species is the archaeon *Methanobrevibacter smithii*, which showed increased abundance in several AN studies (Armougom et al. 2009; Million et al. 2013; Borgo et al. 2017). These archaea feed on waste products of polysaccharide decomposition and increase the transformation of nutrients into calories. Another possible signature of the AN microbiota is the decreased abundance of butyrate-producing bacteria, e.g., *Roseburia*, *Clostridium*, *Anaerostipes*, and *Faecalibacterium*, which was confirmed by almost all existing AN studies (Kleiman et al. 2015; Morita et al. 2015; Mack et al. 2016; Borgo et al. 2017; Hanachi et al. 2019; Prochazkova et al. 2021).

Similar to the altered microbiota in patients with AN (Prochazkova et al. 2021), overexpressed *Alistipes* and decreased *Faecalibacterium* numbers were found in patients with depression, which is a common AN comorbidity (Jiang et al. 2015). *Faecalibacterium* levels are reduced in many human diseases and disorders, and it is suggested that its greater abundance is associated with a healthier state and has been proposed as a potential therapeutic.

Another potential AN signature is the overrepresentation of the heritable *Christensenellaceae* family. Such an overrepresentation was found in the microbiome of AN patients as well as in those with lower body mass indexes (BMI) (Goodrich et al. 2014; Prochazkova et al. 2021).

Patients with AN exhibited increased interindividual variation in gut bacteriome composition compared to healthy individuals, manifesting as core microbiota depletion (Prochazkova et al. 2021). Greater interindividual variation of patients with AN can be elucidated by the so-called Anna Karenina principle, explaining that dysbiotic individuals vary more in microbial community composition than healthy individuals due to a stochastic microbiota response to disequilibrium states induced by stressors. Such effects on the microbiome are a common and vital response of animal microbiomes to stressors, and they are often associated with host health impairment (Zaneveld et al. 2017). It was shown that approximately half of microbiome-associated diseases follow this Anna Karenina principle and are caused mainly by highly dominant microbial species (Fig. 2; Ma 2020).

Table 2 Gut microbiota studies in patients with AN

Author, references	Population	Study design	Methods	Total changes	Bacterial differences in AN compared to healthy controls	Changes after the renourishment
Armougom et al. (2009)	AN = 9 C = 20	Cross-sectional study	qPCR	N/A	↑ *Methanobrevibacter smithii* ↔ *Bacteroidetes* ↔ *Firmicutes* ↔ *Lactobacillus* spp.	N/A
Million et al. (2013)	AN = 15 C = 76	Cross-sectional study	qPCR	N/A	↑ *Methanobrevibacter smithii* ↑ *Escherichia coli* ↓ *Lactobacillus reuteri*	N/A
Pfleiderer et al. (2013)	AN = 1	Case study	Culturomics Mass spectrometry Sanger sequencing	* Identification of 133 bacterial species (11 new species)	N/A	N/A
Morita et al. (2015)	AN = 25 C = 21	Cross-sectional study	16S or 23S rRNA-targeted qPCR	↓ Total bacteria	↓ *Streptococcus* ↓ *Clostridium coccoides* ↓ *Clostridium leptum* ↓ *Lactobacillus plantarum* ↓ *Bacteroides fragilis*	N/A
Kleiman et al. (2015)	AN1 = 16 AN2 = 10 C = 12	Longitudinal study	Pyrosequencing	↓ Alpha diversity * Significant differences in beta diversity between C and AN1	↑ *Parabacteroides* ↑ *Coriobacteriales* ↓ *Blautia* spp. ↓ *Anaerostipes* spp. ↓ *Faecalibacterium* spp.	*Alpha diversity remained significantly lower in patients with AN vs. C * Trend toward a

					↓ *Lachnospira* spp. ↓ *Ruminococcus* spp.	healthier state during treatment
Mack et al. (2016)	AN1 = 55 AN2 = 44 C = 55	Longitudinal study	16S rRNA gene sequencing	↔ Alpha diversity * Significant differences in beta diversity between C and AN1	↑ *Verrucomicrobia* ↑ *Bifidobacterium* ↑ *Anaerotruncus* ↑ *Clostridium clusters I, XI, and XVIII* ↓ *Roseburia* spp. ↓ *Gemminger* spp.	↑ Alpha diversity * Differences in beta diversity between C and AN2 did not normalized
Morkl et al. (2017)	AN = 18 C = 26	Cross-sectional study	16S rRNA gene sequencing	↓ Alpha diversity	↑ Coriobacteriaceae	N/A
Borgo et al. (2017)	AN = 15 C = 15	Cross-sectional study	16S rRNA gene sequencing qPCR	↔ Alpha diversity ↔ Beta diversity	↑ *Enterobacteriaceae* ↑ *Methanobrevibacter smithii* ↓ *Roseburia* spp. ↓ *Ruminococcus* spp. ↓ *Clostridium* spp.	N/A
Kleiman et al. (2017)	AN1 = 3 AN2 = 3	Weight restoration study	16S rRNA gene sequencing	N/A	N/A	* Patient-specific changes in composition and diversity over time
Hanachi et al. (2019)	AN = 33 C = 22	Cross-sectional study	16S rRNA gene sequencing	* Alpha diversity: ↓ Chao1 index, ↔ Shannon index * Significant differences in beta diversity between C and AN1	↑ *Turicibacter* spp. ↑ *Anaerotruncus* spp. ↑ *Salmonella* spp. ↑ *Klebsiella* spp. ↓ *Eubacterium* spp. ↓ *Roseburia* spp. ↓ *Anaerostipes* spp. ↓ *Peptostreptococcaceae*	N/A

(continued)

Table 2 (continued)

Author, references	Population	Study design	Methods	Total changes	Bacterial differences in AN compared to healthy controls	Changes after the renourishment
Prochazkova et al. (2019)	AN = 1	Case study	16S rRNA gene sequencing qPCR	* Increased alpha diversity and changes in composition over time after the FMT	N/A	N/A
Schulz et al. (2021)	AN1 = 19 AN2 = 19 C = 20	Longitudinal study	16S rRNA gene sequencing	↔ Alpha diversity * Significant differences in beta diversity between C and AN1	↑ *Anaerostipes* spp. ↓ *Enterobacteriaceae* ↓ *Romboutsia* spp.	∧ *Lachnospiraceae* ∧ Alpha diversity * Differences in beta diversity between C and AN2 did not normalized
Prochazkova et al. (2021)	AN1 = 59 AN2 = 52 C = 67	Longitudinal study	16S rRNA gene sequencing	↔ Alpha diversity * Core microbiota depletion and greater interindividual variation in the gut bacteriome and metagenome in patients with AN * Significant differences in beta diversity between C and AN1	↑ *Alistipes* spp. ↑ *Clostridiales* ↑ *Christensenellaceae* ↑ *Ruminococcaceae* ↓ *Faecalibacterium* spp. ↓ *Agathobacter* spp. ↓ *Bacteroides* spp. ↓ *Blautia* spp. ↓ *Lachnospira*	∨ *Megasphaera* spp. * Differences in beta diversity between C and AN2 did not normalized

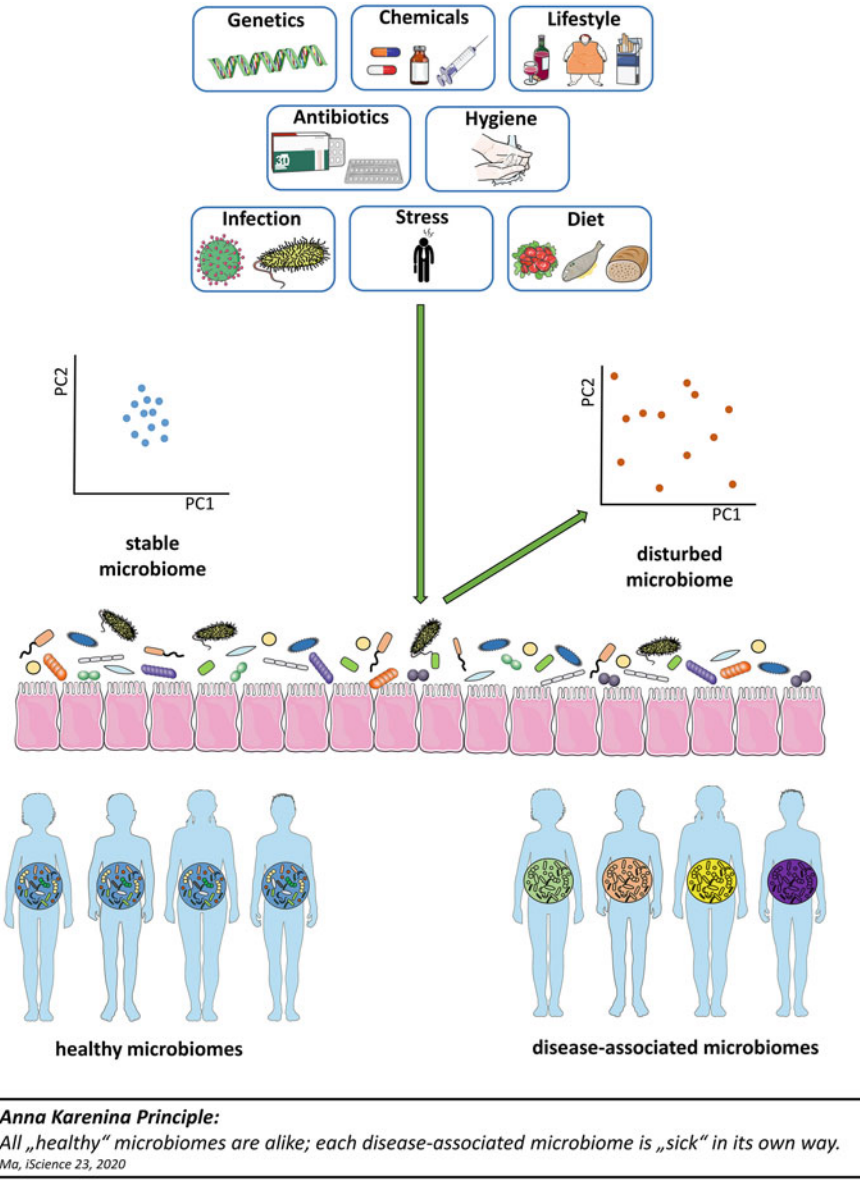


Fig. 2 Anna Karenina principle in human microbiomes associated with diseases. Many external factors influence the human gut microbiome. These can alter the microbiome by disrupting its stability and producing more dispersed microbiomes (right plot). Stable ("healthy") microbiomes form tight clusters on the ordination graph (left plot). Microbiome stability is an important sign of healthy host physiology. Dysbiotic (unstable) microbiomes are often associated with various diseases and are more heterogeneous. The Anna Karenina principle suggests that some stressors have stochastic rather than deterministic effects on community composition. Consequently, "healthy microbiomes are similar, but each dysbiotic microbiome is dysbiotic in its own way"

Four longitudinal studies compared fecal microbiota before and after weight restoration. A study with a small number of patients described a trend toward a healthier microbiota during treatment (Kleiman et al. 2015). The other three studies have consistently shown that patient renourishment led to only minor bacterial composition changes, and the bacteriome of patients after weight gain was still more similar to the bacteriome of patients at hospital admission than to the bacterial composition of healthy controls (Mack et al. 2016; Prochazkova et al. 2021; Schulz et al. 2021), which could be potentially linked to only partial weight recovery. These data suggest that alterations in the gut microbiome may be connected to AN causality rather than a consequence of low body weight or starvation.

Except for composition changes, variations in predicted metabolic pathways associated with AN were described by Prochazkova et al. (2021). For instance, an underrepresented *S*-adenosyl-L-methionine (SAM) cycle I pathway was detected in samples of patients with AN. Cellular L-methionine is converted to SAM, which is the principal methyl donor. Deficiency in SAM production and subsequent DNA methylation, an important epigenetic mechanism, is associated with severe neuropsychiatric diseases (Gao et al. 2018). Additionally, SAM is also essential for synthesizing various neurotransmitters, such as serotonin, dopamine, and norepinephrine. Interestingly, SAM was used as a dietary treatment leading to modulation of patient methionine metabolism via altered nutrient availability; the treatment showed promising results in depression disorders (De Berardis et al. 2016).

The composition of the microbiota does not answer the question of which bacterial species contribute to the pathophysiology of AN. Different strains of bacteria can have unique physiological roles associated with different diseases and disorders. In addition, bacteria of the same genus and even from the same species can have substantially divergent metabolic capabilities. Also, various bacterial species can duplicate the same metabolic functions and can deputize each other.

Intestinal Microbial Metabolites in AN

Some of the leading roles of the intestinal microbiota are associated with the breakdown of indigestible polysaccharides (human lacks the relevant enzymes), production of short-chain fatty acids (SCFA), production of specific vitamins, activation of genes regulating the absorption of nutritional components, epithelial differentiation, formation of the mucosal barrier, and immunological defense.

SCFAs are produced mainly by bacterial fermentation of dietary non-digestible carbohydrates. The three most abundant SCFAs, each with a different role in the human body, are acetate, butyrate, and propionate. The most abundant SCFA, acetate, is an essential metabolite for bacterial growth in the colon and is utilized in cholesterol metabolism and lipogenesis in peripheral tissues. Moreover, acetate crosses the blood-brain barrier and induces an anorectic signal via increased POMC/CART neurotransmission at glutamatergic neurons and via decreased NPY/AGRP neurotransmission at GABAergic neurons in the hypothalamic arcuate nucleus (De Vadder et al. 2014; Frost et al. 2014; Chambers et al. 2015). Butyrate is the

Table 3 Reported differences in bacterial SCFA abundance in feces of patients with AN compared to healthy controls

	Population	Acetate	Butyrate	Propionate
Morita et al. (2015)	AN = 25 C = 21	↓	↔	↓
Mack et al. (2016)	AN = 55 C = 55	↔	↓	↔
Borgo et al. (2017)	AN = 15 C = 15	↔	↓	↓
Speranza et al. (2018)	AN = 10 C = 8	↔	↓	↓
Prochazkova et al. (2021)	AN = 59 C = 67	↓	↓	↔

AN, anorexia nervosa; *C*, healthy persons
↓ lower than in healthy persons, ↔ not different from healthy persons

most important SCFA for human health since it is the main energy source for human colonocytes. It can induce apoptosis of colon cancer cells and activate intestinal gluconeogenesis. Moreover, butyrate has a well-characterized anti-inflammatory effect, both on intestinal epithelial and immune cells (Couto et al. 2020). Propionate is an energy source for epithelial cells. The liver regulates gluconeogenesis and satiety signaling through its interaction with the gut fatty acid receptors.

Acetate is produced by various bacterial species, whereas pathways for propionate and butyrate are more conserved and substrate-specific. The main butyrate-producing bacteria are anaerobes, and the low oxygen concentrations in the colon provide them with a favorable environment. The main butyrate-producing bacteria in the human gut are *Faecalibacterium prausnitzii* and *Clostridium leptum* from the family *Ruminococcaceae* and *Eubacterium rectale* and *Roseburia* spp. of the family *Lachnospiraceae*. Other bacteria, like *Eubacterium hallii* and *Anaerostipes* spp. can produce butyrate from lactate and acetate (Louis and Flint 2017).

An abundance of SCFA is inconsistently reported in AN studies (Table 3). While one study showed reduced acetate and propionate concentrations (Morita et al. 2015), another found decreased butyrate and propionate (Borgo et al. 2017). Longitudinal studies by Mack et al. (2016) observed slightly decreased butyrate levels, and Prochazkova et al. (2021) observed slightly decreased butyrate and acetate levels in patients with AN, but without change after weight gain. Although therapeutic renourishment in both studies led to increased BMI and improved psychometric parameters, SCFA did not change substantially during the hospitalization period, which could be associated with only a partial weight recovery.

Non-targeted metabolomic studies revealed metabolic changes in patients with AN, implying severe system disruptions, such as the development of inflammation and oxidative stress, altered free thyroxine (fT4) and thyroid-stimulating hormone (TSH) levels, vitamin deficits, muscle mass breakdown, and a decrease in ketone bodies (which are essential sources of energy for the brain and heart). Renourishment led to very slight improvements in the abundance of these

metabolites (Tomasova et al. 2021). Different metabolomic profiles were described between restricting and binge-purging AN, which are caused by the different eating and purging behaviors of these two types of patients with AN (Monteleone et al. 2021).

Gut Microbiota Adaptation to Diet

Gut microbiota is known to reflect the diet of the host. Data show that various dietary patterns, e.g., Western, Mediterranean, vegetarian, vegan, or keto diets, are associated with specific microbial communities (Singh et al. 2017). Each bacterial species uses a wide variety of strategies to adapt to the gut environment, mainly through the acquisition of available nutrients. Consistent findings show a greater *Firmicutes/Bacteroidetes* ratio in obese individuals compared to normal-weight people (Crovesy et al. 2020). Moreover, a growing body of evidence shows that obese individuals have more efficient energy extraction from a diet compared to lean people due to alterations in gut microbiota (Lee et al. 2020). Germ-free mice transplanted with "obese microbiota" had an increased capacity to harvest energy from the diet, which was reflected by the significantly greater increase in total body fat compared to mice colonized with "lean microbiota" (Turnbaugh et al. 2006).

On the other hand, recent studies have found a link between gut microbiota and severe acute malnutrition; there is a depletion in oxygen-sensitive prokaryotes and an increase in some potentially pathogenic bacterial species (Tidjani Alou et al. 2017). Mortality linked to severe acute malnutrition was related to diarrhea, low fecal butyrate and propionate concentrations, and high systemic inflammation. These conditions were not linked to specific pathogens, which suggests the absence of gut protective factors (Attia et al. 2016), such as a healthy mature gut microbiota. Fecal microbiota transplantation from undernourished children to germ-free mice-fed donor-like diets provided clinical evidence for a causal role of gut microbiota in disease pathogenesis (Blanton et al. 2016).

In patients with AN, an increased abundance of methane-producing archaeon *Methanobrevibacter smithii* was detected in studies by Armougom et al. (2009), Mack et al. (2016), and Borgo et al. (2017). Moreover, its abundance negatively correlates with body mass index (Million et al. 2013). This archaeon removes the end product H_2 from bacterial fermentation of polysaccharides, metabolizes it to methane, and thus increases energy extraction from the diet. Its increased abundance may result in the optimization of food transformation from very-low-calorie diets. It can be considered an adaptive response in energy-depleted organisms. An abundance of *M. smithii* could also be related to constipation (Ghoshal et al. 2016), a frequent gastrointestinal complaint of patients with AN, which discourages food intake by slowing down colonic transit.

Starvation-induced changes in the gut microbiome were detected in acute and chronic starvation using the activity-based anorexia (ABA) rodent model that mimics the key symptoms of anorexia nervosa, such as food restriction, weight loss, and hyperactivity. This model was established to better understand AN's

underlying pathophysiology. After a 20% loss of weight, decreased thickness of the colon layer and increased colon permeability were detected in these mice (Jesus et al. 2014). The gut microbiota that has adapted to a low-energy gut environment can play an important role in sustaining anorexia nervosa, possibly by directly affecting weight loss and behavior; this is supported by evidence from experiments with ABA mice after fecal microbiota transplantation (see below).

Manipulating the Gut Microbiota

Human gut microbiota manipulation as a disease treatment has become a very hot topic. There are several ways to manipulate the microbiota, e.g., the use of antibiotics (ATB); consumption of fermented food; use of probiotics, prebiotics, or even synbiotics; or fecal microbiota transplantation (FMT). These approaches are mainly used to treat gastrointestinal disorders, such as inflammatory bowel disease (IBD) or irritable bowel syndrome (IBS). Many of these treatments have also been tested with a variety of neuropsychiatric and mental health disorders. In anorexia nervosa, most of these modifications have been tested on mice, with few studies on patients with AN. An abundance of *Lactobacillus* and *Bifidobacterium* species, which is associated with deregulation of the appetite-regulating hormones leptin and ghrelin, has been consistently described in patients with AN (Queipo-Ortuno et al. 2013). It seems likely that targeting the gut microbiota could be an effective adjuvant to standard AN therapies.

Antibiotics

Antibiotics are considered very beneficial drugs for treating bacterial diseases. On the other hand, these drugs are potentially harmful. Their abuse is linked with microbiota impairment and disorders such as *Clostridium difficile* infection. Additionally, antibiotics are often used to assess the role of gut microbiota in various disorders.

No relevant studies have been conducted with AN patients, and few studies have described the effect of ATB treatment on the ABA rodent model. In ABA mice, an increased abundance of *Clostridium cocleatum* and several *Lactobacillus* species and a decreased abundance of *Burkholderiales* were found compared to control mice. Most of the observed alterations were caused by food restriction and were not affected by physical activity (Breton et al. 2021). Loss of body weight was less pronounced in antibiotic-treated ABA male and female mice than untreated mice, although food intake was similar. Similarly, increased fat mass and decreased lean mass were observed in ATB-treated mice. Furthermore, physical activity was reduced after antibiotic administration in male but not female ABA mice. ATB-treated male ABA mice showed altered anxiety-like behavior at the end of the experiment, which was associated with changes in the hypothalamic corticotropin-releasing hormone, hippocampal dopamine, and serotonin receptor

expression (Tirelle et al. 2021). Similarly, many studies have found that gut microbiota plays a role in the pathogenesis of anxiety and depression based on ATB treatment (Lurie et al. 2015).

Probiotics, Prebiotics, and Psychobiotics

A growing body of evidence shows that probiotics can modulate cognitive and emotional processes via the gut-brain axis in animal models (Valcarce et al. 2020; Yang et al. 2020). To our knowledge, no studies have described the effect of probiotics on anorexia nervosa in humans or ABA rodents; however, many studies have focused on their use in anxiety and depressive disorders, both of which are frequent concomitant psychological illnesses of patients with AN. Besides, probiotics (live microorganisms that, when administered in adequate amounts, confer a health benefit to the host), prebiotics (a substrate that is selectively utilized by host microorganisms conferring a health benefit), and synbiotics (contain both components) have been described to exert beneficial effects in both anxiety and depression (Liu et al. 2019; Haghighat et al. 2021). Recently, the term "psychobiotics" was coined targeting microbiota interventions that support good mental health. One promising psychobiotics is butyrate-producing *Faecalibacterium prausnitzii*, which can induce an anxiolytic and antidepressant-like phenotype in rats, probably via increased SCFA in the cecum and shifting the immune response in an anti-inflammatory direction (Hao et al. 2019). Reduced *Faecalibacterium* abundance was correlated with increased severity of depressive symptoms in patients with major depressive disorder (Jiang et al. 2015). In AN patients, *Faecalibacterium* levels were observed to be significantly decreased compared to healthy individuals (Prochazkova et al. 2021), while increased *Faecalibacterium* levels were associated with improved mental health, reduced depressive symptoms, and better sleep in patients suffering from bipolar disorder (Evans et al. 2017).

Fermented Food

Fermented foods contain three primary functional components – probiotics, prebiotics, and bioactive components, biogenics. These components influence the gut microbiota composition and function. Besides affecting macronutrient breakdown and absorption, they can change intestinal permeability and shift the immune response in the gut in an anti-inflammatory direction (Aslam et al. 2020). Moreover, fermented foods have been described to have beneficial effects on mental health parameters (Mohammadi et al. 2016). The functional properties of these foods may affect psychiatric disorders through the synthesis of neuroactive substances and modulation of the hypothalamic-pituitary-adrenal axis and the stress response (Aslam et al. 2020).

Based on all the evidence showing the impact of fermented foods on neuronal mechanisms, they can be considered a potential preventative or treatment for some

psychiatric disorders. Because anorexia nervosa is highly comorbid with mood, gastrointestinal, and immune disturbances, fermented foods could be added to standard nutritional treatment protocols as energy- and nutrient-rich components with very beneficial effects on the physical and mental health of patients with AN (Rocks et al. 2021).

Fecal Microbiota Transplantation

A recent case study of a patient with AN who underwent fecal microbiota transplantation showed a 13.8% weight gain over 36 weeks. The fecal microbiota donor was an unrelated healthy female with a BMI of 25. The gut bacterial composition of the patient's stools showed an increase in weighted phylogenic diversity at 6 and 12 weeks after FMT, especially in the phylum *Verrucomicrobia*. After treatment, the gut microbiota gradually reverted to its initial state. Additionally, FMT led to a significant increase in the fecal SCFAs, acetate and butyrate (de Clercq et al. 2019). In another FMT case study, a patient with severe chronic AN suffering from small intestinal bacterial overgrowth syndrome had increased richness and evenness of bacterial species and decreased fungal diversity after FMT. As with a previous study, total SCFA levels gradually increased after FMT. The metabolomic analysis detected various neurotransmitters and a downward trend in serotonin levels post-FMT. However, despite the improvement in gut microbiota composition, the patient did not show any signs of clinical improvement (Prochazkova et al. 2019). It seems apparent that choosing a suitable donor is a key parameter for a successful therapeutic transfer of gut microbiota. In anorexia nervosa, disease duration and severity are also important factors that must be considered during all types of therapy.

In various studies, gut microbiota transfer from lean or obese mice to GF or ATB-treated mice resulted in an altered capacity for energy harvest (Turnbaugh et al. 2006; Ellekilde et al. 2014). Similarly, the lean or obese phenotype was transferred with the human gut microbiota to GF mice (Ridaura et al. 2013). These findings show the close interconnection between intestinal microbiota and host energy balance.

Immunity Involvement

Extensive research into the composition and function of the microbiota is caused by the rapid development of culture-independent "omics" techniques, such as next-generation sequencing, shotgun metagenomics, metaproteomics, metabolomics, and metatranscriptomics. This research has revealed that the microbiota can affect multiple host functions, including immunity, metabolism, endocrine and nervous system, and nutritional responses (Gilbert et al. 2018). Perturbations in the gut microbiota composition can contribute to the activation of the immune system and the production of various neuroactive compounds, which can affect the development of anorexia nervosa (Roubalova et al. 2020). Various stressful situations can affect

bidirectional communication between the immune system and brain, contributing to psychopathologies, such as major depressive disorder, bipolar disorder, and schizophrenia (Muller 2017). The CNS communicates with the immune system via direct nerve connections with both primary and secondary lymphoid tissues.

Furthermore, cytokines produced by immune cells can cross the blood-brain barrier and affect the function of the CNS. The so-called sickness behavior is an example of such a behavioral alteration. Pro-inflammatory cytokines released in response to infectious agents result in loss of appetite, reduction of activity and social interactions, depressed mood, and loss of libido (Maier and Watkins 1998). It is a physiological process resulting in energy conservation, which is essential for the organism to fight the infection. Increased levels of pro-inflammatory cytokines, such as TNF-α, IL-17, and IL-6, have been detected in patients with AN (Roubalova et al. 2021). These cytokines can cause appetite reduction and thus participate in the development of this disease. Also, elevated levels of pro-inflammatory cytokines may be caused by greater permeability of a gut as described above. However, studies of "leaky gut" syndrome are quite contradictory, and more evidence is needed for such conclusions (see section "The Microbiota-Gut-Brain Axis").

The gut microbiota represents an antigenic source recognized by the mucosal immune system. Some of these molecules can structurally mimic host neuropeptides and neurohormones and thus trigger the production of antibodies that can cross-react with host compounds (Roubalova et al. 2020; Smitka et al. 2021; more in section "Potential Mechanisms in AN Development").

Malnutrition often causes immunodeficiency, comprising both cell-mediated and humoral immunities. In the case of anorexia nervosa, the immune impairments are usually less severe, probably because in malnutrition there is a lack of vitamins and proteins, while patients with AN predominantly suffer from a lack of carbohydrates and fats (Marcos et al. 2003). Another frequent immune-mediated disorder associated with anorexia nervosa is inflammatory bowel disease, specifically Crohn's disease. These disorders are widely studied for their interconnection with gut microbiota dysbiosis (Ni et al. 2017). We can assume that the altered microbiota in patients suffering from both IBD and AN is partly responsible for the development of both pathological conditions.

Potential Mechanisms in AN Development

The etiology of anorexia nervosa is believed to be multifactorial. The participation of the gut microbiota and related immune reactions may contribute to the development of the disease. Clinical and research evidence also suggests an association between pediatric autoimmune neuropsychiatric disorders linked to streptococcal infections (PANDAS) and anorexia nervosa. Conventional AN treatment in combination with antibiotics was effective in four children with acute onset of AN symptoms soon after an infectious disease (Sokol 2000).

The gastrointestinal tract, CNS, and gut microbiota produce many neuroactive compounds with orexigenic (appetite-stimulating) and anorexigenic (appetite-

suppressing) effects (Smitka et al. 2021). The balance between these factors regulates healthy food intake. Patients with AN cannot adapt their eating behavior to their energy requirements, which can be caused by dysregulation of appetite-regulating hormones (Estour et al. 2010). One of these neuroactive peptides, which has been consistently described to be reduced in patients with anorexia nervosa, is anorexigenic/anxiogenic alpha-melanocyte-stimulating hormone (α-MSH) which is produced by the anterior pituitary (Galusca et al. 2015; Roubalova et al. 2021). Interestingly, most patients with AN produce antibodies against this molecule (Fetissov et al. 2002; Roubalova et al. 2021). Caseinolytic protease B (ClpB), a bacterial heat shock chaperone protein produced by some *Enterobacteriaceae* family representatives, induces the production of antibodies that cross-react with α-MSH (Tennoune et al. 2014). Anti-α-MSH IgG antibodies can form immunocomplexes with this peptide and chronically activate the melanocortin (MC) system, which helps regulate feeding behaviors (Fetissov et al. 2008). α-MSH signals via the MC type 4 receptor, which is a key molecular pathway regulating appetite (Lucas et al. 2019). This interaction represents a potential pathophysiological trigger for the development of AN. Furthermore, some evidence suggests that increased diversity among gut bacterial species may result in a decreased abundance of species expressing ClpB with the α-MSH-like motif, which triggers the production of α-MSH cross-reactive IgA antibodies in the gut (Roubalova et al. 2021). Recently, one study showed the presence of IgA-secreting plasma cells educated in the gut positioned adjacent to the dural venous sinuses in human and mouse brains. These cells were almost undetectable in germ-free mice and substantially reduced in mouse brains after 6 weeks of antibiotic treatment (Fitzpatrick et al. 2020). These data suggest that the presence of meningeal IgA-secreting cells is dependent on the gut microbiome. We can assume that such antibodies directed against microbial structures and cross-reacting with appetite-regulating peptides could be important players in anorexia nervosa development.

An analysis of gut microbiota showed a shift toward increased mucin-degrading *Firmicutes* and *Verrucomicrobia* (mainly *Akkermansia muciniphila*) and away from carbohydrate-degrading species such as *Bacteroidetes* in patients with AN (Kleiman et al. 2015; Mack et al. 2016). This shift could increase digestion of protective intestinal wall mucus and further weaken the intestinal wall barrier in the colon, allowing greater translocation of bacterial products and components (Jesus et al. 2014; Mack et al. 2016), which could trigger immune and inflammatory responses and promote the development or increase the severity of anorexia nervosa.

Applications to Other Eating Disorders

In this chapter, we have reviewed studies dealing with the role of microbiota in the pathophysiology of AN. It has been shown that fecal metabolomic and microbiome profiles can distinguish between the restricting and binge-purging types of acute patients with AN (Monteleone et al. 2021). There have been no microbiome studies on how changes in gut microbiota affect eating disorders other than AN. However,

microbiota changes were proposed to modulate appetite regulation mechanisms in bulimia nervosa (BN). ClpB mimicking α-MSH was elevated in patients with BN, which triggered an autoimmune response (Fetissov and Hokfelt 2019). Similar to AN, autoantibodies against α-MSH that formed immunocomplexes with this peptide were also found in patients suffering from BN, but they differ in their affinity (Lucas et al. 2019). Increased levels of high-affinity anti-α-MSH or anti-ClpB autoantibodies can induce bulimia binge eating. In contrast, increased levels of low-affinity anti-α-MSH autoantibodies can induce anorexia (satiety effect) due to an epitope switch of the IgG forming immunocomplexes (Fetissov and Hokfelt 2019).

There are no microbiome studies on binge eating disorder (BED). However, BED is often accompanied by obesity, which is well-described in relation to the gut microbiota. The microbiota of obese individuals differs mainly with regard to nutritional behaviors, i.e., consumption of a high-calorie food leads to an increased abundance of carbohydrate-fermenting bacteria, which leads to elevated SCFA levels that provide an additional source of energy for the host that can be stored as lipids or glycogen. FMT studies showed the transferability of the obese phenotype together with the "obese" microbiota (Turnbaugh et al. 2006).

Considering the relationship between diet, microbiota, and eating disorders, more effort should be made to elucidate the effects of gut microbiota on the pathogenesis of these diseases. Specific signs of gut microbiota alterations could serve as biomarkers and improve the identification, prevention, and treatment of a range of eating disorders.

Mini-dictionary of Terms

- **Activity-based anorexia model**. A rodent model that reproduces the AN symptoms of body weight loss, hyperactivity, and self-starving by opting to run during limited food access.
- **Alpha diversity**. Microbiome diversity within each sample.
- **Anna Karenina principle**. A hypothesis applied to microbiome studies explaining the rise of heterogeneity/stochasticity in animal microbiomes associated with dysbiosis.
- **Beta diversity**. A measure of similarity or dissimilarity between two or more communities.
- **Dysbiosis**. Disrupted functional and compositional microbiota homeostasis.
- **Fecal microbiota transplantation**. Transfer of stool from a healthy donor into the gastrointestinal tract of patients.
- **Leaky gut**. Intestinal hyperpermeability, which allows bacteria and toxins to pass from the gut into the bloodstream.
- **Microbiome**. Collective genomes of microbiota in a particular environment.
- **Microbiota**. A community of microorganisms in a particular environment, i.e., bacteria, viruses, fungi, archaea, and protozoa.

- **Microbiota-gut-brain axis**. Bidirectional communication between the gut-brain axis (the central and enteric nervous system) and microbiota through neural, endocrine, immune, and humoral pathways.
- **Probiotics**. Live microorganisms that, when administered in adequate amounts, confer a health benefit to the host.
- **Prebiotics**. A substrate that is selectively utilized by host microorganisms conferring a health benefit.
- **Psychobiotics**. Probiotics that, when ingested, confer mental health benefits through interactions with commensal gut bacteria.

Key Facts of Human Microbiota

- A complex system of microorganisms populates all the epithelial surfaces of the human body.
- The gut microbiota is the largest microbial community in the body.
- The human gut microbiota ecosystem harbors approximately 3.8×10^{13} resident bacteria.
- Human-associated microbial communities vary predominantly during the postnatal and early stage of life.
- A healthy human gut microbiota is dominated by bacteria from two phyla, *Firmicutes* and *Bacteroidetes*.
- Gut microbiota communicates with the central nervous system via the microbiota-gut-brain axis.
- The gut microbiota is diverse, dynamic, and responsive to external influences, enhancing its potential as a target for therapeutic intervention.
- Microbial dysbiosis has been observed in a variety of diseases, including AN.

Key Facts of Microbiota in Patients with AN

- There are significant differences between the composition of the gut microbiota in patients with AN and healthy individuals.
- Increased abundance of *Methanobrevibacter smithii* and decreased abundance of butyrate-producing bacteria have been reported in patients with AN.
- Patients with AN exert core microbiota depletion signs and exhibit greater interindividual variation in the gut bacteriome, as well as in metagenome content compared to controls, suggesting altered bacteriome functions.
- The amount of short-chain fatty acids is reduced in the gut of patients with AN compared to healthy individuals.
- In patients with AN, reduced dopamine, GABA, and serotonin levels have been detected compared to healthy individuals.
- In patients with AN, antibodies are produced against bacterial structures that can cross-react with appetite-regulating hormones.

- In patients with AN, the permeability of the gastrointestinal tract appears impaired, enabling increased translocation of microbial compounds across the mucosal barrier.

Key Facts of Gut Microbiota Modifications

- The gut microbiota can be modulated using ATB, probiotics, prebiotics, fermented food, and FMT.
- Germ-free animals are an ideal model for the observation of gut microbiota function.
- Few studies have dealt with gut microbiota modifications in patients with anorexia nervosa.
- The lean vs. obese phenotype can be transferred via the gut microbiota.
- Microbiota modifications can affect anxiety and depressive disorders.
- Microbiota manipulation is a potential therapeutic strategy for the prevention and treatment of various neuropsychiatric diseases.
- Consumption of fermented food may help to restore a healthy gut microbiota in patients with AN.

Summary Points

- The gut microbiota is an important player in mental health, affecting the central nervous system via the gut-brain axis.
- Patients with AN have a significantly different gut microbiota compared to healthy individuals.
- Altered gut microbiota is accompanied by changes in microbial metabolic activity, such as reduction of certain SCFA and neuroactive compounds in patients with AN.
- Dysbiosis of the gut microbiota can trigger the production of antibodies that cross-react with certain appetite-regulating hormones.
- The gut microbiota plays a role in the development and severity of anorexia nervosa.
- Modifying the gut microbiota through the consumption of fermented foods could be a valuable adjunct to standard nutritional treatment protocols for patients with AN.

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Gender Aspects of Anorexia Nervosa: the Male

26

The Male

Hiral Kotadia

Contents

Introduction 514
Prevalence 514
Risk Factors, Symptom Onset, and Age of Presentation 515
Symptoms and Comorbidities 517
Medical Complications 522
Course and Prognosis 524
Treatment 525
Role of the Dietitian 525
Future Directions and Need for Awareness 531
Application to Other Eating Disorders 532
Mini-dictionary of Terms 532
Key Facts 533
Key Facts of DSM (Diagnostic and Statistical Manual of Mental Disorders) 533
Key Facts of BMI 533
Summary Points 533
References 534

Abstract

Anorexia nervosa (AN) is considered to be a disorder of females. However, the prevalence (proportion of population having disorder) of AN in males is rising. One of the contributing factors for this could be a better understanding of AN in males and its early recognition. AN varies in males and females in parameters of the age of onset, types of symptoms, ideal body image concerns, age of presentation, and treatment. This chapter focuses on the above aspects of AN in males. The goal of the chapter is to sensitize the readers (current and future clinicians,

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nutritionists, dieticians, or any other professionals dealing with AN along with other eating disorders) regarding the prevalence and presentation of AN in male population. This may help them to be vigilant and recognize AN in males in the early phase so that early and appropriate intervention could be offered.

Keywords

Anorexia nervosa · Eating disorder · Male · Gender · Body image · Weight · Body mass index · DSM-5 · Body fat

Abbreviations

AN	Anorexia nervosa
BMI	Body mass index
BMR	Basal metabolic rate
CBT	Cognitive behavioural treatment
DSM-5	Diagnostic and Statistical Manual version 5
DSM-IV	Diagnostic and Statistical Manual version 4
EDE-Q	Eating Disorder Examination Questionnaire
FBT	Family-based treatment
Kcal	Kilocalories
Kg	Kilogram

Introduction

According to the Diagnostic and Statistical Manual version 5 (DSM-5), anorexia nervosa (AN) can be characterized through three essential features: (1) persistent energy intake restriction leading to significantly low body weight; (2) intense fear of gaining weight or of becoming fat, or persistent behaviour that interferes with weight gain; and (3) a disturbance in self-perceived weight or shape (American Psychiatric Association 2013).

Prevalence

The lifetime prevalence (proportion of a population who, at some point in life, has ever had the illness) of AN in males ranges from 0.16% to 0.3%, while the incidence (number of individuals who develop an illness or during a particular time period such as a month or a year) is 15.7 per 100,000 people per year (Raevuori et al. 2009). The belief that AN occurs predominantly in females may lead to underestimation of the prevalence of AN in males, and the true prevalence rates could be much higher (Smink et al. 2014). The prevalence of AN in males is

increasing over a period of time. The male-to-female ratio of prevalence of AN is 1:10 (Swanson et al. 2011).

Risk Factors, Symptom Onset, and Age of Presentation

The following are risk factors for the development of AN in males:

(A) *Genetic factors*:
1. The role of genetic factors in males who develop AN is more as compared to females who develop AN. Multiple genes play a role in the etiology of AN (Nakabayashi et al. 2009).
2. Various genes that play a role in the functioning of various neurotransmitters (chemical molecules used by the nervous system to transmit messages between nerve cells) like serotoninergic, opioid, dopaminergic, and cholinergic system may lead to the causation of AN in males (Scherag et al. 2010).
3. Male individuals having first-degree relatives with eating disorders are more susceptible to developing AN in late adolescence to adulthood (Raevuori et al. 2008).
4. Males with female twins have a higher risk of developing AN as compared to males with a male twin (Procopio and Marriott 2007).

(B) *Hormonal factors*:
1. Estrogen (female sex hormone) is a causative factor for developing AN, while testosterone (male sex hormone) acts as a protective factor against the development of AN. This might be the reason that the prevalence of AN in males is much lower than in females (Klump and Culbert 2007; Ostlund et al. 2003).
2. The genetic risk for developing AN in males remains the same prepuberty as well as after the onset of puberty (puberty is the period during which adolescents reach sexual maturity and become capable of reproduction). But in females the genetic risk for developing AN increases from 0% to 50% after the onset of puberty. This also highlights the role of estrogen in causing or developing AN (Culbert et al. 2013; Klump et al. 2006).

(C) *Environmental (societal and cultural) risk factors*:
1. Premorbid (prior to illness) weight is also a significant factor in males contributing to AN in the future. Bullying and critical comments about the weight and body shape by peers may lead to overexercising and dietary restrictions. There is also some hormonal contribution in the development of AN in premorbid overweight/obese males (Raevuori et al. 2009).
2. Sexual orientation is also a contributory factor in the development of AN in males as compared to females. The standards and expectations regarding body shape and weight in homosexual males set by peer groups along with

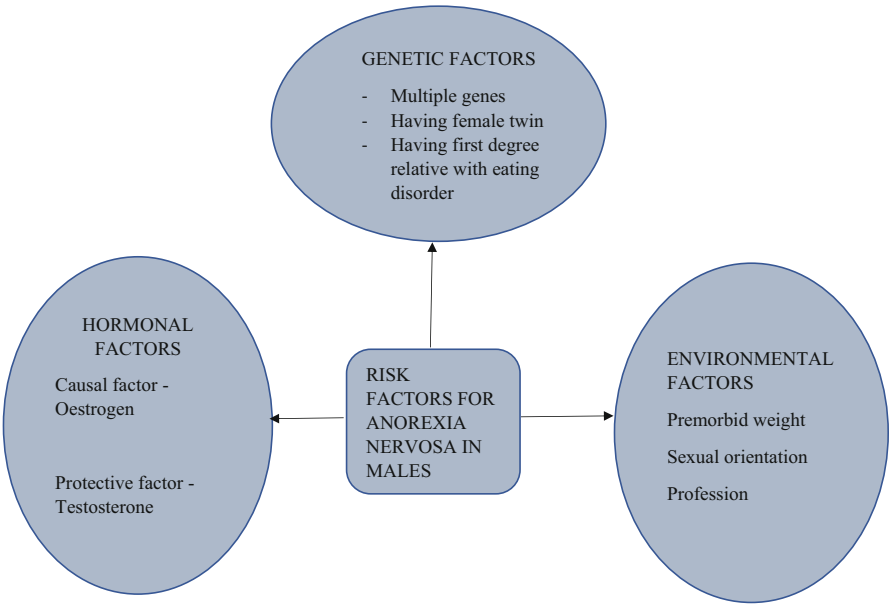


Fig. 1 Risk factors for the development of AN in males

the increased pressure to maintain a certain body type to attract a male partner play a significant role in the development of AN in later stages (Ming et al. 2013).

3. Professions like sports, athletics, and modeling also play a role in the causation of AN in males. The demands of the professional environment may directly or indirectly lead the male to indulge in dietary restrictions and more importantly in exercise regime which leads to an increase in muscularity. This may reinforce the body image concerns, and thus the symptoms of AN may persist for a long period of time (Nagata et al. 2019; Gorrell et al. 2021) (Fig. 1).

The onset of AN in males is generally in late adolescence (17–19 years of age) or early adulthood (the early 20s) as compared to females who generally have onset in early adolescent years (12–14 years of age) (Gueguen et al. 2012; Nagata et al. 2019). This data about the age of onset may not actually represent true information as males having AN are identified in later age and present to a hospital setting for treatment later as compared to females (Dalgliesh and Nutt 2013).

The common age of consultation seeking for symptoms of AN in males is late teenage years to early 20s. The delayed treatment-seeking in males could be due to the belief that AN occurs exclusively or predominantly in females, stigma, and poor awareness about eating disorders in males (Grillot and Keel 2018). The assessment interviewing technique and various structured scales currently used for assessing the

presence of AN is more female-centric, because of which AN in males could be commonly missed (Grillot and Keel 2018).

Symptoms and Comorbidities

Males having AN have a significant body image distortion and a consequent drive for thinness, similar to females. However, there are certain differences in terms of ideal body shape, methods used to reduce the body weight, premorbid (prior to illness) body weight, symptom presentation at first contact, medical complications, and psychiatric comorbidities.

Males with AN are more concerned about being lean and muscular rather than just being thinner. They are more inclined toward having a "six-pack" rather than a flat stomach. The body shape (muscularity) is more important to them rather than the body weight. Males with AN have to focus on the shape of their shoulders and the size of their chest in addition to their belly and thighs. This is different from females with AN who have a desire for thinness and low body weight (Darcy and Lin 2012; Murray et al. 2017a, b).

The methods used by males to achieve this ideal body shape are also different from the methods used by females to achieve a thin body. Males focus more on exercise to get this shape rather than restriction of dietary intake or use of laxatives which is more commonly used by females to achieve a thin body and low body weight. Males may tend to exercise more often due to cultural and social expectations (men need to be muscular and women are expected to be lean) (Holliday et al. 2005).

As mentioned earlier, premorbid weight is a risk factor in developing AN in males in late adolescence to early 20s. The more the premorbid weight, the more are chances of having AN later (Gueguen et al. 2012; Nunez-Navarro et al. 2012). As per the diagnostic criteria (DSM-5), the severity of AN is measured in terms of body mass index (BMI) which is an indicator of whether the person is overweight, underweight, or having normal weight. BMI is defined as the weight of the person (in kilograms) divided by the square of the height of the person (in centimeters).

Males who have higher premorbid weight have much higher BMI so, when they lose weight, they may still have normal or low normal BMI despite having AN. Clinically if we consider BMI as the only criteria to diagnose AN, many males having AN might remain undiagnosed and thus not receive the needed medical care and treatment. Hence, in males, the premorbid weight and the amount of weight loss over a period should be considered as an important factor to diagnose AN rather than only BMI at the time of presentation.

The symptom presentation of males with AN on first contact with a physician is slightly different from females in the following parameters:

1. Age of presentation – it is late as compared to females mainly due to two reasons. Firstly, the age of onset of AN is late in males, and, secondly, the time duration

between onset and visit to a physician is more in males with AN (it is on an average 1 year). The belief of the society that eating disorders including AN are present only in females and the stigma associated with it play a major role in poor awareness, identification, and acceptance of AN in males (Griffiths et al. 2015; Welch et al. 2015; Forman-Hoffman et al. 2008).

2. Weight and BMI at the presentation – as mentioned earlier, males with AN may present with normal weight and normal BMI despite the severity of AN. The reasons for this are high premorbid weight and an increase in muscle mass (mainly composed of protein) due to exercise and weight training but at a cost of significant loss in fat deposition which is harmful to the body.
3. The DSM-IV (American Psychiatric Association 1994) criteria used to diagnose AN were more female-centric (included amenorrhea which is an absence of menstrual periods which may be temporary or permanent and low BMI at presentation as a cutoff to diagnose AN). The DSM-5 criteria (implemented since 2013) on the other hand have tried to address the above aspects. However, the structured assessment tools for AN currently used are still female-centric leading to underdiagnosis and late diagnosis of AN in males.
4. Presentation with medical complications – males with AN present with more severe medical complications as compared to females with AN. The longer duration between the age of onset of symptoms and age at presentation to the physician in males as compared to females with AN is a significant factor contributing to the presence of severe medical complications at the time of presentation (Strother et al. 2012).

Males with AN have more psychiatric comorbidities (presence of other diseases) as compared to females with AN. The various psychiatric comorbidities in males with AN predominantly include mood disorders and substance use disorders. The most common associated psychiatric comorbidity is major depressive disorder (Manzato et al. 2017). The presence of comorbidities leads to an increase in the severity of AN, poor course of illness, increased need for treatment, and poor compliance to treatment. That is why it is necessary to evaluate the presence of psychiatric comorbidities in AN as addressing them may lead to significant and early improvement.

The following table (Table 1) lists the differences in males and females having AN in terms of the above parameters.

Images: Photographs of a 12-year-old male with AN

The images have been printed after taking consent from parents and assent of the patient

Images 1–4:	**At time of presentation**
	Weight – 20.3 kgs
	BMI – 10.36 kg/m^2

Table 1 Differences between males with AN and females with AN in terms of age of onset, age at presentation, ideal body shape, methods used, medical complications, and comorbidities

Various parameters in AN	Males with AN	Females with AN
Age of onset (years)	*Late teenage years (17–19 years)*	Early teenage years (12–14 years)
Age of treatment-seeking (years)	*Late teenage years to early 20s*	The mid- to late 20s
Ideal body image	*Muscular*	Thin and lean
Methods used to achieve an ideal body shape	*Excessive exercise and calorie control*	Dietary restriction and use of purgatives and laxatives
Medical complications	More and severe during the presentation	Less and mild at presentation
Psychiatric comorbidities	More frequent	Less frequent

Abbreviations: *AN* anorexia nervosa



Notice the loss of buccal fat.



Notice the loss of gluteal fat.





The loss of fat on the upper chest.
Notice that ribs are visible.

Medical Complications

Out of all the eating disorders, AN is the most severe due to significant malnutrition and higher chances of medical complications. These complications potentially affect all organs and systems. The severity of medical complications depends on the type of methods used to achieve weight loss (the restrictive methods have severe complications), the duration of illness, the rapidity of weight loss, weight at the time of presentation, and degree of malnutrition.

The loss of weight and malnutrition lead to compensatory mechanisms by reducing the energy expenditure which leads to various complications of the cardiovascular system, gastrointestinal system, and bone growth (Mehler and Brown 2015).

Carbohydrate is the main source of energy in the body. In AN, as the oral intake or purging is more, there is a significant decrease in carbohydrate intake and storage. Fat is the next source of energy. At the end of puberty, fat mass (that portion of the human body which is composed strictly of fat as opposed to fat-free mass) is around

12% in males as compared to 25% in females. In AN, there is significant fat loss. As the baseline fat mass in males is low, the loss of fat in AN is significant in males. Due to significant fat loss, there is an increase in ketones (a breakdown product of fat) leading to a pathological condition called ketosis which may lead to low blood pressure, kidney stones, constipation, nutrient deficiencies, and an increased risk of heart disease (Raevuori et al. 2009; Mehler and Brown 2015).

Pubertal development is longer in males. So, the growth spurt in males is late as compared to females. Their bones have greater linear growth and a greater bone mass compared with females. So, if males are affected in the early to mid-teens, the bone growth is significantly impaired which may lead to growth reduction and a final low stature. This may also lead to osteopenia (a medical condition in which the protein and mineral content of bone tissue is reduced) or osteoporosis (a medical condition in which the bones become brittle and fragile from loss of tissue) (Misra 2008; Misra et al. 2008; Modan-Moses et al. 2003).

Due to reduced energy expenditure, the cardiac activity for pumping blood decreases. Also due to loss of fluid in the body, hypotension (systolic blood pressure <90 mm Hg and diastolic pressure <60 mm Hg) may occur which may cause dizziness, blurring of vision, fainting, and fatigue. The reduced cardiac pumping activity leads to a decrease in heart rate known as bradycardia (heart rate <60/min). It may also lead to irregular heart rate and conduction abnormalities (a conduction disorder is a problem with the electrical system of the heart which controls the rate and rhythm of heart rate) known as arrhythmias which are life-threatening in nature (Misra et al. 2004; Niemeijer et al. 2015). An important cardiac structural change like reduction in cardiac muscular mass may be seen in restricting-type AN. Cardiovascular complications are important to evaluate as they are a cause of death in patients with AN in more than 50% of cases.

Complications of AN also include endocrinological complications (hormonal changes). There is a lowering of thyroid hormone levels in the body (Vo et al. 2016). One of the main functions of thyroid hormone is to maintain basal metabolic rate (BMR – a measurement of the number of calories needed to perform body's most basic (basal) functions, like breathing, circulation, and cell production). Because of the decrease in thyroid hormone levels, there is a decrease in energy expenditure needed for maintaining basic functions. The lowering of thyroid also causes a reduction in heart rate (Manzato et al. 2017).

The reduced food intake leads to a delay in gastric emptying which causes post meal fullness, bloating, and pain which further perpetuate the patient's desire to avoid food. At times it may lead to rupture of the esophagus or stomach which is a surgical emergency (Benini et al. 2004; Olausson et al. 2014).

The reduction in food intake or purging associated with AN leads to significant disturbances in serum electrolytes (various ions like sodium, potassium, or chloride which regulate the electric charge and flow of water molecules across the cell membrane and are essential for metabolism, for proper nerve and muscle functioning, and for maintenance of proper water balance and proper blood pH (acid-base balance)). This may lead to conditions like seizures, loss of consciousness, and arrhythmias (Berend et al. 2014).

Table 2 Various medical complications of AN in males

Medical complications (systems affected)	Signs and symptoms
Body fat loss	Ketosis (nutrient deficiency, low blood pressure, kidney stone, increased risk for cardiac disease)
Bone growth	Growth reduction, osteopenia, osteoporosis
Cardiovascular complications	Bradycardia, hypotension, arrhythmias, decrease mass of cardiac muscle
Endocrine complications	Hypothyroidism (decrease in BMR, low heart rate)
Gastrointestinal complications	Reduced gastric motility, bloating, esophageal rupture
Life-threatening complications	Cardiac arrhythmias, esophageal rupture, electrolyte disturbances

Abbreviations: *BMR* basal metabolic rate

The following Table 2 lists the various body systems affected due to AN in males.

Course and Prognosis

AN is generally a long-standing illness in both females and males. However, the chronicity in males is more due to delayed diagnosis and delay in treatment-seeking. The course of AN is almost the same in males and females if both are diagnosed and treated in the initial part of the illness and have a 60–70% chance of improvement and remission in AN if identified and treated early. Though males with AN seek treatment at a later stage, the duration of their admission stay and time taken to remission is much shorter as compared to females with AN. Also, they show better improvement as compared to females in parameters of weight and BMI in follow-up. However, due to delays in treatment-seeking in males, the course is more deteriorating as compared to females. Also due to the chronicity of illness, males have significant medical complications at the time of presentation. Of male patients with AN, 20–25% have a poor prognosis and suffer from the chronicity of the illness (Strobel et al. 2019; Quadflieg et al. 2019; Bardone-Cone et al. 2019).

The following are poor prognostic factors in males with AN (Hoang et al. 2014; Kask et al. 2017; Crisp et al. 2006):

1. Later age of presentation for seeking treatment
2. Lower BMI at presentation (<15 kg/m^2)
3. AN restrictive subtype

(AN is of two subtypes – restrictive subtype and binge eating/purging subtype. In the restrictive subtype, the weight loss is primarily achieved by fasting, dieting, and/or excessive exercise. There are minimal or no episodes of binge eating or purging, i.e., self-induced vomiting or the misuse of laxatives, diuretics, or enemas. However, in binge eating/purging subtypes, there are frequent episodes of binge eating and/or

purging. Because of no or minimal binge eating and significant dietary restriction, the restrictive subtype has more chances of BMI to be significantly low and hence leads to more complications and poor prognosis.)

4. Later age of onset of illness
5. Longer duration of AN
6. Higher percentage of weight loss
7. Lack of interest in exercise during illness
8. More psychiatric comorbidities
9. Previous treatment, disturbed childhood family relationships
10. An absence of premorbid sexual activity, masturbation habits, or sexual fantasies

Treatment

Apart from the societal belief that AN is a disorder of females and the reluctance of males in acceptance regarding the disorder, the other factor playing a role in delayed diagnosis and treatment setting is the lack of understanding in clinicians about the disorder, its occurrence in males, and the difference in presenting symptoms as compared to females. This delay in treatment-seeking leads to more medical complications and a poorer prognosis of the illness. The goals of treatment aims are (Hay et al. 2014):

1. Restoring a healthy weight (falling in the range of normal BMI percentile, normal sexual drive)
2. Addressing medical complications and psychiatric comorbidities
3. Educating the patient and family regarding illness and motivating the patient to increase oral intake and participate in treatment
4. Addressing patient's belief regarding the body image and societal concerns using medicinal treatment or psychological intervention
5. Working on prevention of recurrence of the illness

The following chart provides the treatment algorithm for treatment of AN (Fig. 2) (Table 3).

Role of the Dietitian

Dietitian plays a significant role in the treatment of AN specifically in the early phase for the purpose of nutritional refeeding. This includes the calculation of calories and enlisting the available food items for meeting this calorie intake. The dietitian should also involve the patient in making and implementing of diet chart. The role of a dietitian is equally important in inpatient and outpatient treatment of males with AN.

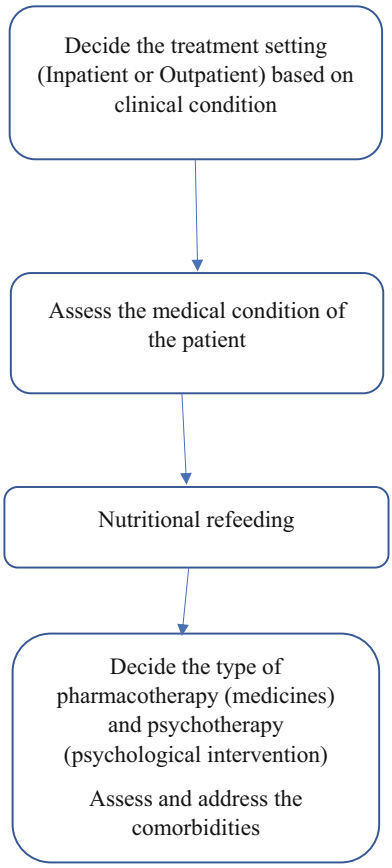


Fig. 2 Treatment algorithm for AN. The type of therapy may vary in individuals

Table 3 Guidelines for treatment of AN

Treatment of AN	General guidelines	Salient features for treatment in males having AN
Assessment	Interview, examination, and structured questionnaires like the Eating Disorder Examination Questionnaire (EDE-Q) to be used (Thomas et al. 2014)	The difference in ideal body image (more muscularity), high BMI at presentation, and BMI percentile (for males) is to be considered
Indications for inpatient treatment	BMI <15 kg/m^2 Rapid or continuing weight loss (>20% over 6 months) Weight <85%; acute weight decline with food refusal even if not <85% Of healthy body weight High physical risk Severe comorbid conditions Heart rate <50/min Blood pressure <80/50 mm Hg Severe electrolyte disturbances	The BMI in males at presentation can be high. So even BMI >15 kg/m^2 can be considered for admission based on other factors Separate settings for males are required as treatment in the same setting with females leads to more reluctance and feminization of disorder (Dearden and Mulgrew 2013; Räisänen and Hunt 2014)
Target weight	Restoring normal activity (resumption of menstrual cycles in females)	Measuring restoration of normal activity is difficult as there is no evident measure as compared to the resumption of menstrual cycles in females Return to normal sex drive is considered as a return to normal activity, but the definition of normal sex drive is very subjective (varies from patient to patient)
Nutritional refeeding	Start with 20–30 kcal/kg (1000–1500 kcal/day) and gradually increase or begin with 200–300 calories above the patient's usual caloric intake Recommended weight gain – 0.5 to 1 kg/week Prevent and treat refeeding complications (low potassium, low phosphorous, low calcium, refeeding edema – swelling caused by excess fluid trapped in body's tissues, cardiac arrhythmias)	Males may require higher initial calorie refeeding (3000–3500 kcal/day) as they have higher lean body mass and lower fat mass compared with female patients (Hay et al. 2014)
Pharmacotherapy	Fluoxetine – selective serotonin reuptake inhibitor (helps to deal with distressing thoughts regarding body image) Olanzapine, mirtazapine – helps in increasing appetite and thus gaining weight	Might require higher doses of medicines (Murray et al. 2017a, b)

(continued)

Table 3 (continued)

Treatment of AN	General guidelines	Salient features for treatment in males having AN
Psychological intervention (psychotherapy)	Family-based treatment (FBT) – involvement of family in initiating refeeding and restoration of weight in the patient (younger age of onset – family can be more involved as the patient is of younger age) Cognitive behavioural treatment (CBT) The core features of AN (food restriction and avoidance) are based on a schema (beliefs and ideas people have about themselves) which helps to form and maintain self-esteem; over a period of time, acting on schema becomes a habit CBT deals in restructuring this schema by structured methods and thus reducing patients' distress	An appropriate and comfortable environment is to be provided (men support group and male therapists) Males have late-onset and late presentation of illness with family involvement and family control. This might lead to FBT being less effective in males In males, individual therapy may be more helpful (Peterson et al. 2016) CBT in males has to focus more on schema regarding ideal male muscular image rather than focusing on drive for being lean and thin (Dalgliesh and Nutt 2013)

Abbreviations: *BMI* body mass index, *Kcal* kilocalories, *Kg* kilogram

Images 5–7:	**After treatment period of 5 months**
	Weight – 33.5 kg
	BMI – 17.1 kg/m^2


MACHO





Notice the improvement in fat deposition on the upper chest and the buccal fat.

Future Directions and Need for Awareness

There seems to be a common belief in physicians that eating disorders like AN are exclusively seen in females which leads to a dismissive attitude of physicians toward the male patients. This further contributes to the already existing stigma regarding eating disorders in males which leads to worsening of illness and delay in treatment-seeking and intervention. It is thus imperative to bring to attention the prevalence, symptom presentation, and management of male patients suffering from AN. There is also a need of sensitizing the physicians regarding the need of being vigilant about the symptoms of AN in males and psychoeducate the patient and family regarding the illness and need for treatment. The existing instruments (scales and questionnaires) are more female-centric and are insensitive toward muscularity-oriented

disordered eating. These need to be modified accordingly. This chapter tries to address these issues by sensitizing the readers.

Application to Other Eating Disorders

This chapter highlights the gender bias in the community and clinicians regarding the prevalence and diagnosis of AN. It focuses on creating awareness about symptom presentation, course, complications, and treatment of AN in males as compared to females. Similarly, the gender differences in the above aspects need to be considered in other eating disorders. Further studies are required to focus on various eating disorders in males to differentiate them from females. Male-centric assessment tools are required to evaluate for other eating disorders. The attitude toward the female centricity of eating disorders needs rectification to bring gender neutrality. Understanding the cognitive and behavioural aspects of other eating disorders in males may help in designing male-specific interventions like different models of cognitive and behaviour therapies. The DSM-5 has tried to make the diagnostic criteria of AN to be more gender-neutral by removing the criteria of the presence of amenorrhea and substituting the criteria of self-reporting of fear to gain weight with either reporting or observable behaviour about fear of gaining weight. This chapter suggests the need for consideration of a change in diagnostic criteria of other eating disorders and an inclination toward more gender neutrality.

Mini-dictionary of Terms

Acid-base balance: It is the balance between input (intake and production) and output (elimination) of hydrogen ion. This decides the level of alkalinity and acidity in your body. A balance between these is required to maintain regular functioning of the body.

Diagnostic and Statistical Manual version 5 (DSM-5): It is a classificatory system for mental health (psychiatry disorders) with diagnostic criteria to maintain uniformity in diagnosis. It includes eating disorders.

Eating Disorder Examination Questionnaire (EDE-Q): It is a self-reported questionnaire used to assess various parameters of eating disorders.

Estrogen: The main sexual hormone in females that is required for the development and regulation of sexual secondary characteristics such as pubic hair and breast along with the female reproductive system.

Psychotherapy: Various psychological interventions that help a person change thoughts and behaviors to deal with various stressors.

Sexual orientation: Who you are attracted to (male, female, both) and want to have a relation with. Same-sex orientation is homosexuality. The opposite sex orientation is heterosexuality. Orientation toward both sexes is bisexuality.

Testosterone: The main sexual hormone in males that is required for the development and regulation of sexual secondary characteristics such as body hair as well as the development of muscle mass and bone growth.

Key Facts

Key Facts of DSM (Diagnostic and Statistical Manual of Mental Disorders)

- First edition of DSM was published in 1844 (by American Psychiatric Association) for institutionalized patients with mental illness.
- The purpose was to develop a universal classification of mental health disorders to improve communication regarding the needs for proper care of the patients.
- Since then, four other editions of DSM have been released, the recent one being DSM-5 released in 2013.
- *DSM* contains descriptions, symptoms, and other criteria for diagnosing mental disorders to establish consistent and reliable diagnoses that can be used in the research as well as clinical management of mental disorders.

Key Facts of BMI

- BMI is defined as a person's weight in kilograms divided by the square of the person's height in meters (kg/m^2).
- It is a measure of nutritional status.
- The ranges of BMI are based on the effect that body fat has on the physical condition of the body.
- It is also a risk indicator of disease.
- The BMI ranges are based on the level of body fat.
- The more obese the person, the more the BMI.
- This increases the risk of various conditions like cardiovascular diseases, high blood pressure, osteoarthritis, some cancers, and diabetes.

Summary Points

- There is a common belief that AN is a disorder of females. However, this is not true and even males are vulnerable to this disorder.
- The lifetime prevalence of AN in males ranges from 0.16% to 0.3%, while the incidence is 15.7 per 100,000 people per year. The prevalence of AN in males is increasing over a period of time.
- The ratio of male to the female prevalence of AN is 1:10.
- The age of onset in males is around late teenage years to early 20s.

- The average time between symptom onset and consultation with a physician is much higher as compared to females.
- The symptom presentation in males is different from females – high premorbid weight, high BMI at presentation, and need for a muscular body as compared to the thin body in females.
- Exercise is a common mode used by males with AN to reduce weight and get a muscular body.
- The course of illness in males is similar to females if diagnosed and treated early.
- AN may lead to severe medical complications if not treated early and adequately.
- Psychotherapy along with pharmacotherapy is the mainstay for the treatment.

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The Biology of Anorexia Nervosa

27

A New Narrative Overview

Kamil Skowron, Magdalena Kurnik-Łucka, and Krzysztof Gil

Contents

Introduction 538
Clinical Presentation of Anorexia Nervosa 539
Neurohormonal Regulation of Appetite and Metabolism 542
Brain Centers of Energy Homeostasis 543
Hypoleptinemia in Anorexia Nervosa: A Chicken or an Egg? 544
Interaction of Metabolic State and Gonadal Function 546
Conclusions 547
Applications to Other Eating Disorders 548
Mini-Dictionary of Terms 548
Key Facts of Anorexia Nervosa 549
Summary Points 549
References 549

Abstract

Anorexia nervosa, one of the most deadly mental disorders, is a pathophysiologically complex mosaic of numerous extensively investigated pathways, and the current state of knowledge cannot provide us with one definite answer regarding its etiopathogenesis. Although classified as a psychiatric disorder, traditionally viewed as a consequence of the psychological features, the model explaining the onset and development of anorexia is multifactorial with growing interest in its metabolic origin. The clinical presentation varies in severity, but ultimately every organ in the diseased body is affected. There are many biological alterations that simply act in accordance with severe malnutrition and weight loss; nevertheless, there is an evident dysfunction in the course of adaptive pathways that induce or at least potentiate those changes. Based on human and animal studies, the most relevant streams in AN pathophysiology seem to point toward a relatively adequate peripheral response that fails to properly stimulate

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feeding-related neurohormonal brain circuits. This metabolic origin of AN is supported by molecular identifications of specific genetic polymorphisms. Endocrine adaptations involve among others hyperghrelinemia, hypoleptinemia, hypogonadotropic hypogonadism, and CRH hypersecretion. Those hormonal shifts interact not only with appetite-regulating brain regions but also affect energy expenditure, physical activity, behavior, cognition, as well as rewarding/motivational drive. This narrative review aims to present emerging biological concepts underlying anorexia nervosa.

Keywords

Anorexia nervosa · Malnutrition · Activity-based anorexia · Neurobiology · Hypoleptinemia · Ghrelin · Kisspeptin · Phoenixin · Hypothalamus · Appetite

Abbreviations

AgRP	Agouti-related peptide
AN	Anorexia nervosa
ARC	Arcuate nucleus
BMI	Body mass index
CART	Cocaine- and amphetamine-regulated transcript
CRH	Corticotropin-releasing hormone
GnRH	Gonadotropin-releasing hormone
HPG	Hypothalamic-pituitary-gonadal
KISS1	Kisspeptin
KISS1r	Kisspeptin receptor
LEP	Leptin gene
LHA	Lateral hypothalamic area
MRI	Magnetic resonance imaging
NPY	Neuropeptide Y
POMC	Proopiomelanocortin
sObR	Soluble leptin receptor
T3	Triiodothyronine
T4	Thyroxine

Introduction

Anorexia nervosa (AN), according to DSM-V criteria, is classified as a feeding or eating disorder characterized by restriction of energy intake leading to dramatically low body weight, intense fear of gaining weight or behavior preventing weight gain as well as a disturbance of body image, and/or lack of understanding of the danger of low body weight. The severity of weight loss is based on body mass index (BMI) derived from the World Health Organization categories for thinness in adults or corresponding percentiles in children and adolescents: BMI greater than or equal to 17 kg/m^2 (mild), BMI 16–16.99 kg/m^2 (moderate), BMI 15–15.99 kg/m^2 (severe),

and BMI less than 15 kg/m^2 (extreme) (American Psychiatric Association 2013). AN presents with various short- and long-term complications, depending on the severity of the disease, placing it at the top of the statistics when it comes to the all-cause mortality rate and suicide risk among all psychiatric disorders (Chesney et al. 2014). The recovery rate fluctuates from 0 to 92% (Steinhausen 2002; Auger et al. 2021). The lifetime prevalence of AN ranges from 0.3% to 1.5% and 0.1% to 0.5% for females and males, respectively, based on international data (Keski-Rahkonen et al. 2018), yet the risk of mortality in male patients was estimated to be more than twice that of female patients (Edakubo and Fushimi 2020). The average age of onset of AN is 16–17 years and has been considerably decreasing (Keski-Rahkonen et al. 2018).

Food restriction and subsequent malnutrition in AN may lead to severe multi-organ complications, such as cardiovascular, dermatologic, endocrine, gastrointestinal, hematologic, musculoskeletal, neurologic, ophthalmic, and pulmonary (Mehler and Brown 2015). Most of them are usually controllable after renourishment, symptomatic treatment, and psychotherapy (Westmoreland et al. 2016). Those complications resemble simple starvation (semistarvation) from the pathobiological point of view, but complete AN etiopathogenesis remains far from being understood (Skowron et al. 2020b). AN is primarily a psychiatric disease; still, there is only minimal to moderate evidence that available psychiatric medications are effective (Westmoreland et al. 2016; Flament et al. 2012; Kaye 2008; Claudino et al. 2006), which further supports the need for the in-depth understanding of biological factors relevant for AN.

Clinical Presentation of Anorexia Nervosa

A reduction of food intake and/or loss of appetite and hyperactivity with increasing anxiety are the core features of AN. Thus, as a direct consequence of malnutrition, AN patients present with a range of systemic symptoms (Table 1), from mild to life-threatening depending on the nutrition status and severity of weight loss (Mehler and Brown 2015; Rome and Ammerman 2015). The body's total energy expenditure relies on the resting energy expenditure (energy required for the essential physiological functions), the energy expended for muscular work (known as the thermic effect of exercise), and the thermic effect of food (metabolic costs of processing a meal). And on the cellular level, mitochondrial proton leak, Na+/K+ ATPase activity, and protein turnover are responsible for up to 75% of resting energy expenditure. Thus, weight loss achieved by food restriction is less than that calculated from the caloric deficit, and furthermore, weight loss declines with time due to continuous changes in the body's composition, its maintenance energy requirements, and hormonal mechanisms decreasing the metabolic activity at the cellular level (Abdel-Hamid 2002; Kinney 1995). Starvation-induced protein and fat catabolism accounts for the loss of cellular volume and function and ultimately atrophy of the liver, lymphoid tissue, gastrointestinal tract, muscles, kidneys, heart, and brain (Mehler and Brown 2015). Under physiological conditions, exercising contributes

Table 1 Clinical manifestations of anorexia nervosa together with their possible pathogenesis

Symptoms	Possible pathogenesis/ pathomechanisms	Symptoms	Possible pathogenesis/ pathomechanisms
Cardiovascular		**Hematologic**	
Arrhythmia	Malnutrition and weight loss, predominance of the parasympathetic nervous system	Pancytopenia	Malnutrition and weight loss
Bradycardia		↑INR	Liver damage and impaired synthesis of coagulation factors
Hypotension		**Musculoskeletal**	
Dermatologic		Fat and muscle tissue loss	Malnutrition and weight loss, endocrine alterations
Alopecia	Malnutrition and weight loss, hypothermia	Osteopenia or osteoporosis	Malnutrition and weight loss, ↓estradiol, ↑cortisol, entero-endocrine dysregulation (↓leptin), dysfunctional GH/IGF axis
Dry skin		**Neurologic**	
Lanugo hair		Cerebral atrophy	Malnutrition and weight loss
Pruritus		**Opthalmic**	
Acrocyanosis		Lagophthalmos	Malnutrition and weight loss, orbital fat atrophy
Endocrine and metabolic		**Psychiatric**	
Arrested growth	Dietary restriction, malnutrition and weight loss, ↑GH and resistance to GH, ↓IGF	Anxiety	Genetic predisposition, alterations in hypothalamic and mesocorticolimbic circuits, entero-endocrine dysregulation (↓leptin), dysfunctional GH/IGF axis
Amenorrhea	Malnutrition and weight loss, ↓GnRH, ↓FSH, ↓LH, ↓estradiol, ↓testosterone, ↓leptin	Depression	
Infertility		Physical hyperactivity	
Central diabetes insipidus	↓Antidiuretic hormone	Reluctance to eat	
Hypoleptinemia	Genetic predisposition, dietary restriction and weight loss, ↑CRH	**Pulmonary**	
Hypercortisolemia	Dietary restriction and weight loss, decreased metabolic clearance	Pneumonia	Malnutrition
Hypoglycemia	Dietary restriction and weight loss	Pneumothorax	
Hypothermia	Dietary restriction and weight loss, predominance of the parasympathetic nervous system	Respiratory failure	

(continued)

Table 1 (continued)

Symptoms	Possible pathogenesis/ pathomechanisms	Symptoms	Possible pathogenesis/ pathomechanisms
Thyroid abnormalities (↓T3, T4, TSH within normal range)	Dietary restriction and weight loss		
Gastrointestinal			
Bradygastria and delayed gastric emptying	Dysregulated microbiome-gut-brain axis, motor and sensory gastroduodenal dysfunction, impaired mucosal integrity, local low-grade immune activation, autonomic nervous system dysfunction, visceral hypersensitivity, altered regional brain activation		
Constipation			
Dysphagia			
Hepatitis			
Hausea, vomiting			

Abbreviations: *CRH* corticotropin-releasing hormon, *FSH* follicle-stimulating hormone, *GH* growth hormone, *GnRH* gonadotropin-releasing hormone, *IGF* insulin-like growth factor, *LH* luteinizing hormone, *T3* triiodothyronine, *T4* thyroxine

to the total energy expenditure through the cost of the exercise itself and the compensation of a diet-induced depression in metabolic energy (Abdel-Hamid 2002). Protein synthesis (and muscle size) should increase during exercise, thus protecting against the loss of fat-free mass (McArdle et al. 1996). Starvation-induced protein breakdown, which may be further potentiated by increased physical activity in case of AN, possesses a serious threat to life's maintenance. However, in contrast to marasmus, severe hypoproteinemia and hypovitaminosis rarely occur in AN patients, whose hypocaloric diets are relatively rich in protein and vitamins (Hebebrand et al. 1997). Yet, only around half of the women with AN recover after therapy, around 30% recover incompletely, and the rest either experience recurrent periods of remission and relapse or suffer from chronic disease even after re-nutrition and weight restoration (Schorr and Miller 2017).

AN may manifest with a range of gastrointestinal symptoms, which can be the very first physical signs of the disease. Frequently, detailed attention is paid to diet, body weight, and food-related gastrointestinal symptoms that may further result in a chronic dietary restriction (Sato and Fukudo 2015). However, cardiac complications are thought to be the most common cause of death in AN (Sachs et al. 2016; Olivares et al. 2005). Yet, foremostly, AN is characterized by broad endocrine manifestations due to hypothalamic-pituitary axis dysfunction and alterations in appetite-regulating hormonal pathways (Schorr and Miller 2017). These endocrine disturbances are not only an adaptation to the low energy state, but they can also exert detrimental effects on the host as they may maintain and intensify the disease with enduring

consequences (Støving 2019). Currently, their etiologic role cannot be excluded based on the available data. Those complex metabolic adaptations enable AN patients to survive with a BMI of around 10 kg/m^2, with only a few cases described with BMI below 9 kg/m^2 (Frolich et al. 2016). Weight loss is accompanied by an adaptive decline in serum concentrations of triiodothyronine (T3), thyroxine (T4), and thyroid-binding globulin to downgrade the metabolic rate and resting energy expenditure. Reverse T3 is elevated from increased peripheral deiodination of T4. The thyroid gland is atrophic even at normal levels of TSH in AN. Hypercortisolemia, which is also a consequence of the stress of chronic nutritional deprivation (together with hyperactivity), maintains euglycemia but also exerts a noxious effect on muscle mass and inhibits the hypothalamic-pituitary-gonadal axis. Corticotropin-releasing hormone hypersecretion directly contributes to weight loss and might be stimulated by increased ghrelin levels or be compensatory for cortisol resistance. The degree of hypercortisolemia correlates inversely with BMI, fat mass, and bone mineral density as well as directly with the severity of depression, anxiety, and hippocampal atrophy (Støving 2019; Schorr and Miller 2017). It should be also stressed that hypothalamic-pituitary-adrenal axis dysregulation was reported to persist after weight gain; however, its etiologic role cannot be fully confirmed (Schmalbach et al. 2020). The low energy availability in female patients may also result in hypothalamic amenorrhea. In addition to low estrogen levels, hypothalamic amenorrhea results in low androgen levels in AN (Schorr and Miller 2017). Increased ghrelin and cortisol levels during starvation also suppress gonadotropin secretion (Støving 2019). The recent DSM-V diagnostic criteria excluded amenorrhea as a criterion. Yet only a minority of females with AN continue to menstruate despite extreme weight loss and malnutrition, and thus the resumption of menses is an important indicator of recovery (Dempfle et al. 2013). Menstrual resumption in weight-recovered patients may be further restricted due to anxiety or physical hyperactivity (Jacoangeli et al. 2006). Also, adolescent boys with AN present with lower fat and lean body mass, lower testosterone and estradiol concentrations, as well as reduced bone mineral density compared to normal-weight controls (Schorr and Miller 2017; Misra et al. 2008). However, existing literature concerning endocrinopathies in male patients is limited. Still, estrogen and testosterone have well-established roles in maintaining muscle, mucous membrane, and bone mass (Misra et al. 2016) and pose a risk for permanent adverse effects in both sexes. It is also possible that deficiency in sex hormones aggravates anxiety and depression in AN independent of body weight (Miller et al. 2007).

Neurohormonal Regulation of Appetite and Metabolism

Over the past two decades, the health crisis of obesity and the multifaceted damage it causes have been a particularly important stimulus for scientists to expand research into the complex systems of regulating human metabolism. The acquired knowledge has enriched the set of tools that we can use to explain the basis of diseases characterized by disturbed energy homeostasis. Since AN is associated with the

lack of appetite as a complex interaction of hormonal and neuronal signals, it is understandable to search for its biological basis. A potential fundamental role of those appetite-driving biological mechanisms in AN has gained interest with the incorporation of advanced molecular and neuroimaging techniques into the investigation of AN etiopathogenesis. The analysis of genetic factors in the family context, including twin and adopted siblings, showed an estimated genetic contribution at the level of 50–60% (Bulik et al. 2015). The genetic variants determining low BMI were shown to be associated with AN through a two-way correlation (Watson et al. 2019).

On this basis, a neurobiological concept of susceptibility to AN began to emerge. The neurochemical basis of those concepts includes two major theoretical currents that revolve around dysfunction in the reward system and/or appetite-regulating neuropeptides. These pathways appear to integrate with the hypothalamus, the center of the body's metabolic balance. In patients suffering from AN, hypothalamic reactivity is blunted, and connectivity with brain regions involved in reward processing is decreased compared to healthy people (Simon et al. 2020).

Brain Centers of Energy Homeostasis

At the central level, regulation integrates signals from peripheral tissues and reacts to information from reward/motivation centers, creating a synthetic response of the body in the form of hunger or satiety that physiologically would reflect its metabolic demand. Although its clinical presentation resembles a set of adaptive physiological changes to the state of fasting, AN exhibits many neurobiological characteristics that significantly distinguish those two states. The hypothalamic control of appetite starts within the arcuate nucleus (ARC) where two distinct populations of neurons basically either stimulate (neuropeptide Y and Agouti-related protein) or inhibit (cocaine- and amphetamine-related transcript and proopiomelanocortin) food intake. Functional MRI of AN patients revealed that the number of neuronal fibers in the ARC is reduced, while the connectivity of the lateral hypothalamic area (LHA) increases (Florent et al. 2020). At the neurotransmitter level, glutamatergic signaling in ARC appears to behave oppositely to that in healthy control, as reflected in higher fasting concentrations and a paradoxical decline after feeding. ARC orexigenic neurons are stimulated by ghrelin, when the body is food-deprived, resulting in the release of neuropeptide Y (NPY) and Agouti-related protein (AgRP). Despite the physiologically increased secretion of ghrelin in AN, numerous reports indicated a lack of the expected accompanying upregulation in the NPY expression (Galusca et al. 2015). In this context, the impact of anorexigenic peripheral hormones on the functioning of the hypothalamus also seems to be important, taking into account that leptin inhibits AgRP/NPY neurons. However, the concentration of leptin in AN is significantly reduced. On the other hand, proopiomelanocortin (POMC) mRNA expression seems to adequately correspond with the nutritional status of AN patients, and so far no epigenetic changes typical of AN have been demonstrated (Candler et al. 2019).

The ARC neurons send multiple projections that form neuronal pathways between hypothalamic nuclei and with extrahypothalamic regions. Genes associated with AN were identified by their marked expression in two brainstem regions, the lateral parabrachial nucleus and the ventral tegmental area (VTA) (Howard et al. 2020). VTA, the center of the mesocorticolimbic dopamine system, projects into the ventral striatum, which in turn potentially could overcome hypothalamic hunger due to inverted effective connectivity between those areas. However, VTA of AN patients was shown to be hypoactive in reaction to food odors (Jiang et al. 2019). Physiologically, the hypothalamus, by activating LHA-derived GABAergic projections into the VTA, is believed to induce feeding behavior (Barbano et al. 2016). Moreover, LHA receives inputs from the ARC and expresses the orexigenic neuropeptides (orexins and melanin-concentrating hormone) which may evoke an excitatory effect on VTA dopaminergic neurons (Teegala et al. 2020). Activation of orexin receptors in the VTA was shown to increase food intake, while experimental LHA damage drastically reduced the amount of food consumption (Terrill et al. 2016).

Hypoleptinemia in Anorexia Nervosa: A Chicken or an Egg?

Energy expenditure can be further modulated by adipokines, with leptin being undoubtedly the most studied one in various contexts, including eating disorders. Leptin (from Greek λεπτός leptos, "thin") is a 167-amino acid peptide secreted in a pulsatile manner in proportion to the amount of body fat and exerts its action through binding to specific receptors located throughout the central nervous system (Park and Ahima 2015) as well as peripherally (Muoio and Lynis Dohm 2002). Higher leptin levels in women compared to men have been explained by the fact that subcutaneous fat produces more leptin than visceral adipose tissue and by a direct influence of sex hormones on leptin secretion (Hebebrand et al. 2007; Montague et al. 1997). Leptin affects the arcuate nucleus of the hypothalamus by binding to specific receptors, thereby inhibiting NPY/AgRP-expressing neurons and activating POMC and cocaine- and amphetamine-regulated transcript (CART) neurons. Leptin also directly reaches the nucleus of the solitary tract to amplify the short-term satiety signals from the gastrointestinal tract that are processed there (Morton et al. 2006). Key factors stimulating circulating leptin levels are excess energy, overfeeding, glucose, insulin, estrogen, and pro-inflammatory cytokines, while low energy states and fasting (as, e.g., in AN), as well as physical activity, cold exposure, thyroid hormones, and testosterone, decrease those levels. Leptin, displaying a circadian rhythm with the lowest levels at mid-afternoon and the highest levels at midnight, on the one hand, stimulates glucose uptake and fatty acid oxidation in the skeletal muscle, and on the other hand, it inhibits glucose production in the liver as well as glucagon and insulin secretion in the pancreas (Park and Ahima 2015).

The fundamental role of leptin in the regulation of metabolism and appetite is indisputable, with reduced levels in AN (Støving et al. 1998). Leptin levels in the cerebrospinal fluid were also decreased, although the cerebrospinal fluid to plasma

leptin ratio was higher in AN patients than in controls (Mantzoros et al. 1997). Successful re-feeding and weight recovery in AN are associated with an increase in free and bound plasma leptin levels (Ruscica et al. 2016). However, studies with more frequent measurements of leptin levels in adolescents with AN revealed that during weight gain, peak levels higher than the reference range were reached (Ballauff et al. 1999; Hebebrand et al. 1997). Thus, two questions should be asked – what factors particularly associated with AN might influence leptin levels (possibly bidirectionally?) and foremostly if there is any causal relationship between AN development and hypoleptinemia?

Firstly, it should be clarified that alterations in circulating leptin levels are dependent on splicing of leptin receptor mRNA, hypothalamic leptin receptors (long/signaling form of the leptin receptor, ObRb), and soluble leptin receptors (sObR or ObRe) binding most of the circulating leptin. The soluble receptor is upregulated in patients with acute AN, and consequently, the levels of free leptin are further reduced, while weight gain reduces the number of sObR receptors (Hebebrand et al. 2007). Recently, Mendelian randomization analysis of data sets from genome-wide and exome-wide association studies indeed demonstrated a causal effect of lower leptin levels on a higher risk of AN development, yet in females only (due to insufficient data from the male population) (Peters et al. 2021). Previously conducted genome-wide association studies of AN reported significant genetic correlations with both psychiatric phenotypes and metabolic traits, independent of the effects of common variants associated with BMI (Watson et al. 2019; Duncan et al. 2017). Genetic variation (rs12706832) in the leptin gene (LEP) was related to dissimilar dopamine release from the mesolimbic system in response to pain stress challenges. A positive relationship between plasma leptin levels and dopamine release was also observed (Burghardt et al. 2012), and leptin signaling pathways act as key modulators of post-absorptive signals on central dopamine release (de Araujo et al. 2012).

In mice, leptin signaling directly influenced gastrointestinal microbial composition, independently of food intake and body weight, and regulated antimicrobial peptide-encoding genes in the gut epithelium. The gut microbiome of intestinal epithelial leptin receptor knockouts demonstrated a significantly increased ratio of *Firmicutes* to *Bacteroidetes*, analogous to ad libitum-fed obese leptin-deficient mice (Rajala et al. 2014). Still, in AN patients, inconsistent results were observed between studies regarding the *Firmicutes*/*Bacteroidetes* ratio or the identity of altered levels of bacterial taxa (Skowron et al. 2020b). Most importantly, gastrointestinal microbiota may serve as a source of molecules of similar sequence and conformational homology with appetite-regulating peptides, including leptin or biogenic amines, for example, that can, directly and indirectly, modulate gut-brain axis (Clarke et al. 2014). The sequence homology with those peptides was identified among commensal and pathogenic microorganisms including *Lactobacillus*, *Bacteroides*, *Helicobacter pylori*, *Escherichia coli*, and *Candida* species. At the same time, IgG and IgA autoantibodies directed against leptin and other appetite-regulating peptides were present in human sera, which could further alter appetite regulation (Fetissov and Hökfelt 2019; Fetissov et al. 2008). Fetissov et al. reported that levels and

affinities of autoantibodies against those peptides correlated with psychopathological traits in AN patients (Fetissov et al. 2005). What is more, the levels of total short-chain fatty acids (acetate, propionate, and butyrate), resulting from non-digestible carbohydrate fermentation and supplying up to 10% of the host's daily caloric intake, have been changeably reported in AN studies, while branched-chain fatty acids (especially valerate and isobutyrate), resulting from protein fermentation, were increased in AN patients at the time of hospital admission (Skowron et al. 2020b). In mice, the activation of SCFA receptors localized in adipose tissue, namely, FFA2, FFA3, and HCA1, was found to increase the secretion of leptin (Zaibi et al. 2010). In humans, propionic acid stimulated leptin mRNA expression and secretion by omental and subcutaneous adipose tissue (Al-Lahham et al. 2010).

Furthermore, leptin influences emotions, cognition, and motivational drives related to hunger and may be bidirectionally influenced by stress (Appelhans 2010; Burghardt et al. 2012; Peters et al. 2021). Leptin receptors are found in brain areas that are involved in emotion recognition (Adolphs 2002), and leptin appears to enhance cognitive functioning and neuroplasticity (Paz-Filho et al. 2010). Human adipocytes express CRH-Rs, and CRH downregulates leptin production by mature adipocytes (Gioldasi et al. 2019). Interestingly, the relationship between leptin and vulnerability for depression in AN might depend on symptom severity and weight loss. During inpatient treatment and renourishment, higher leptin levels were associated with either greater feelings of depression, anxiety, and stress in patients with very low BMI and higher chronicity or lower psychological symptoms in patients with less severe symptoms (Stroe-Kunold et al. 2016).

Interaction of Metabolic State and Gonadal Function

To conserve the energy necessary for survival, the malnourished organism promotes the retention of energy-consuming reproductive functions. Thus, another key issue in AN is the extreme effect the central signaling that regulates food consumption imposes on the proper functioning of the hypothalamic-pituitary-gonadal (HPG) axis. It is worth noting that these interactions may steer in the opposite direction, which is reflected by the influence of the reproductive hormones on the energy balance such as an anorectic effect of estradiol (Eckel 2011). The HPG hormonal cascade is initiated with the activation of GnRH neurons potently stimulated by a neuropeptide called kisspeptin (KISS1) in response to metabolic signals. Hypothalamic kisspeptin-containing neurons are located mainly in the ARC and the rostral periventricular area of the third ventricle (RP3V) being responsible for pulsatile release of GnRH as well as preovulatory surge, respectively. KISS1 exerts its effects through a G-protein-coupled receptor 54 (GPR54 or KISS1r), the antagonism of which leads to the development of hypogonadotropic hypogonadism similar to the state of malnutrition (de Roux et al. 2003). The central regulation of KISS1 neuronal output is under the control of insulin, leptin, and ghrelin; however, circulating nutrients like glucose or amino acids through a set of protein kinases in kisspeptin neurons also directly modulate their activity. Fasting has been shown to reduce

kisspeptin expression in the hypothalamus as a potential result of hypoleptinemia (Castellano et al. 2005). The KISS1 serum concentration in AN appears to vary to a similar range as in healthy controls but is positively correlated with BMI and negatively with physical activity (Hofmann et al. 2017). In addition, subcutaneous administration of KISS1 has been shown to increase food intake and partially restore hypothalamus signaling in an animal model of anorexia (Skowron et al. 2020a).

Analysis of the HPG axis in anorexia took another big step with the discovery of a hypothalamic neuropeptide called phoenixin (PNX). It was found that through the GPR173 receptor, it increases the secretion of GnRH and LH in rats and thus impacts the reproductive cycle. In subsequent experiments, it was established that the infusion of PNX into the lateral ventricles of the rat brain increases food consumption, probably due to the opposite effect to co-expressed nesfatin-1 involved in the regulation of food intake, energy expenditure, and glucose homeostasis. Despite the sparse data on direct regulators, it has been suggested that PNX neurons sense and react to nutritional signals (McIlwraith et al. 2018). Malnourished patients with AN present a significantly decreased concentration of PNX.

Conclusions

The pathogenesis of AN is undoubtedly a multifactorial integration of interacting psychological and biological changes, and thus the disease is no longer considered as a psychiatric entity only. Peripheral and central dysregulation in the pathways directly and indirectly associated with appetite-regulating hormones seems to be critical for the disease initiation and perpetuation (Skowron et al. 2020b). There is much evidence gathered by molecular and neuroimaging studies that point out the underestimated relevance of AN organic origin, but it is still difficult to determine the extent of the changes that precede the clinical development of the disease. In fact, an ample amount of evidence regarding AN etiopathogenesis comes from animal studies. An activity-based rodent model of anorexia (ABA) is not only highly similar to AN, but it is also considered the best animal model of any psychiatric disorder. A reduction of food intake and/or loss of appetite and hyperactivity together with increasing anxiety as observed in human AN are at the same time the core features of the ABA model (Skowron et al. 2018, 2020b, 2021; Kurnik-Łucka et al. 2020). Although many of the symptoms are simply the consequences of severe malnutrition and weight loss, there is an evident dysfunction in the course of adaptive pathways that gradually complement the complex causes of AN. Thus, ABA, supplemented with human studies, provides us with an in-depth picture of AN that allows the introduction of targeted therapeutic interventions into clinical studies. All in all, based on the heterogeneity of the disease, its complex clinical presentation, and increasing prevalence in adolescents of both sexes, anorexia nervosa should be of interest to all clinical specialties.

Applications to Other Eating Disorders

In this chapter, we review studies that relate to the pathobiology of AN. A complex interaction of hormonal and neuronal signals results in the lack of appetite and quite often physical hyperactivity (Mehler and Brown 2015; Rome and Ammerman 2015). Hypothalamic reactivity is blunted, and connectivity with brain regions involved in reward processing is decreased in AN compared to healthy people (Simon et al. 2020). Interestingly, while hypoleptinemia, among other hormonal disturbances, is characteristic for anorexia nervosa (Støving et al. 1998), not hyperleptinemia but predominantly leptin resistance (together with physical inactivity) defines obesity (Considine et al. 1996; Brownson et al. 2005; Myers et al. 2008). What is more, the cerebrospinal fluid/blood leptin ratio was higher in AN (Mantzoros et al. 1997) and lower in obese humans (Caro et al. 1996; Schwartz et al. 1996) in comparison to control subjects. Physiologically, leptin serum levels were reported to be significantly and positively correlated with body weight, body mass index, abdominal circumference, and insulin and significantly and negatively correlated with peak oxygen uptake in both sexes. Peak oxygen uptake in men and physical activity in women were reported to be determinant factors for circulating leptin levels after adjusting for confounding factors (Miyatake et al. 2014). Foremostly, leptin maintains overall energy homeostasis (Izquierdo et al. 2019). Leptin also influences emotions and motivational drives related to hunger (Appelhans 2010; Burghardt et al. 2012; Peters et al. 2021) and may enhance cognitive function and neuroplasticity (Paz-Filho et al. 2010). However, recombinant human leptin (metreleptin) has little effect in patients with multifactorial obesity. Yet, it has been successfully used for the treatment of rare congenital leptin deficiency presenting with obesity and starvation-like symptoms including hypothalamic amenorrhea in females. Recently, metreleptin was also approved for the treatment of extremely hyperactive patients with AN off-label (Hebebrand et al. 2019).

Mini-Dictionary of Terms

- **The arcuate nucleus (ARC or ARH or infundibular nucleus).** An aggregation of neurons in the mediobasal hypothalamus that includes diverse populations of neurons maintaining several neuroendocrine and physiological functions, such as food intake, metabolism, and fertility
- **NPY/AgRP neurons.** Medial neurons in the arcuate nucleus involved in the neuroendocrine regulation of feeding and appetite stimulation
- **POMC/CART neurons.** Lateral neurons in the arcuate nucleus centrally involved in the neuroendocrine regulation of feeding and appetite suppression
- **Kisspeptin.** A protein hormone that, through its G-protein-coupled receptor (GPR54), is able to directly activate hypothalamic GnRH neurons, which is essential for successful reproduction

- **Phoenixin.** A ligand of the G-protein-coupled receptor 173 (GPR173) which is present in numerous hypothalamic neurons
- **Leptin.** A peptide secreted in a pulsatile manner proportional to the amount of body fat that exerts its effects by binding to specific receptors (ObR) located throughout the central nervous system

Key Facts of Anorexia Nervosa

AN represents a disorder with the highest mortality rate among all psychiatric diseases.

The average age of onset of AN is decreasing.

Detailed attention paid to diet and body weight may further result in a chronic dietary restriction typical for AN.

AN may manifest with a range of gastrointestinal symptoms, which can be the very first physical signs of the disease.

Food restriction and subsequent malnutrition in AN may lead to severe multi-organ complications.

A minority of females with AN continue to menstruate despite extreme weight loss and malnutrition, and thus the resumption of menses is an important indicator of recovery.

Renourishment and psychotherapy remain the cornerstones of treatment for most AN patients.

Summary Points

- Genetic studies demonstrated a causal effect of lower leptin levels on a higher risk of AN development
- Successful re-feeding and weight recovery in AN are associated with an increase in free and bound plasma leptin levels
- The relationship between leptin and vulnerability for depression in AN might depend on symptom severity and weight loss
- Kisspeptin signaling acts as a potential link between nutritional status and reproductive function of the organism
- Hypothalamic expression of kisspeptin is downregulated in AN
- Hypothalamic response to increased levels of ghrelin is blunted
- Susceptibility to developing AN may be associated with genetic alterations in the ventral tegmental area responsible for reward processing

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The Hippocampus in Anorexia Nervosa

28

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Contents

Introduction 556
Hippocampus in Animal Model of AN 558
Structural Studies 559
Functional Studies 561
Hippocampus in Other Eating Disorders 563
Applications to Other Areas 564
Mini-Dictionary of Terms 564
Key Facts of Hippocampus in Anorexia Nervosa 564
Summary Points 565
References 565

Abstract

The hippocampus is an anatomically complex structure that is peculiarly involved in the neurobiology of different brain disorders. At present, different studies evidence a role for this structure in the neurobiology of anorexia nervosa, but findings are rather inconsistent and heterogeneous both from a functional and structural point of view.

Activity-based anorexia models provided important insights into the possible functional, structural, and molecular involvement of the hippocampus in disordered eating behaviors and in excessive physical activity. Moreover, neuroimaging studies pointed out both structural and functional hippocampal alterations in the acute phases of the disorder.

The aim of this chapter is to summarize the main findings concerning hippocampal structure and function in anorexia nervosa.

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Eating disorders · Anorexia nervosa · Neuroimaging · Hippocampus · Animal models

Introduction

Several studies to date have evidenced the presence of both structural and functional brain alterations in patients with anorexia nervosa (AN). These alterations were observed both at the whole-brain level and at the level of some specific cortical and subcortical areas. However, the results of these studies are quite conflicting and inconclusive, due to methodological differences and some heterogeneity in sample selection (Collantoni et al. 2022; Meneguzzo et al. 2019).

A brain region that has attracted an important interest in the field of neurological and psychiatric disorders, including eating disorders, is the hippocampus.

From an anatomical point of view, the hippocampal formation is a complex structure located in the medial surface of the temporal lobe, inside the inferior temporal horn of the lateral ventricle, and it is composed of three distinct zones: the dentate gyrus, the hippocampus proper, and the subiculum (Anand and Dhikav 2012).

From a functional point of view, ever since the case report of patient H.M., who lost the ability to form new declarative memories after bilateral medial temporal lobectomy (Scoville and Milner 1957), the hippocampus has been associated with memory formation, consolidation, and retrieval. A few years later, the discovery of "place cells" in the rodent hippocampus revealed its involvement also in spatial representation and navigation, a result that has been later confirmed in human studies (Ekstrom et al. 2003; O'Keefe and Nadel 1978). However, in more recent years, several studies showed that the hippocampus subserves many cognitive functions other than memory consolidation and spatial navigation. A role of the hippocampal formation has been, indeed, demonstrated in decision-making, food intake regulation, reward, stress resilience, emotion regulation, and other cognitive functions (Kanoski and Grill 2017; Palombo et al. 2015).

The involvement of the hippocampus in such a variety of functions is supported by its high level of connections with both cortical and subcortical structures, making this structure an important hub for connective pathways (Maller et al. 2019). Moreover, according to the most recent literature, the hippocampus is functionally divided into two distinct regions: a "cold" dorsal one that primarily serves cognitive functions and a "hot" ventral one that is mostly related to mood, stress, emotion regulation, and social behaviors.

An important aspect of the hippocampus is that it is the only brain region, together with the subventricular zone in the lateral ventricles, in which neurogenesis persists throughout life. Neurogenesis, which primarily occurs in the subrganular zone of the dentate gyrus, is thought to play a crucial role in hippocampal functioning, in particular for memory consolidation, learning, and mood regulation

(Christian et al. 2014). The degree of neurogenesis, however, differs between individuals and seems to be influenced by several environmental factors. While some factors, like physical activity and intense navigation, tend to promote neurogenesis, other factors are usually associated with a decrease in neurogenesis (Van Praag et al. 2005). It has been shown, for example, that both acute and chronic stress suppress hippocampal neurogenesis in rodents by increasing the level of circulating adrenal steroids (Gould and Tanapat 1999). Another factor that seems to negatively affect neurogenesis, independently from stress and adrenal hormones, is sleep deprivation (Meerlo et al. 2009). Particularly interesting for the research on eating disorders is the evidence that the degree of neurogenesis is also influenced by an individual's diet and nutritional status. Reductions in neurogenesis have been mainly observed as a consequence of unhealthy and high-fat diets; however, evidence shows that a deficiency in some specific nutrients can also lead to a reduction in cell proliferation (Stangl and Thuret 2009).

The role of the hippocampus in the neurobiology of different psychiatric disorders has been extensively investigated.

Reduced hippocampal volume has been observed in several psychiatric disorders and is one of the most replicated findings in the study of major depressive disorder (MDD), with patients with prolonged illness duration presenting smaller hippocampi than patients at the first episode (McKinnon et al. 2009).

MDD seems also to be associated with reduced hippocampal neurogenesis, while an increase in hippocampal cell proliferation has been observed following pharmacological antidepressant treatments (Dranovsky and Hen 2006). A deficit in hippocampal neurogenesis during adulthood has been proposed to characterize the neurobiology of many other psychiatric disorders, including anxiety disorders, posttraumatic stress disorders, addictions, and schizophrenia. However, it is not yet fully clarified whether dysfunctional neurogenesis occurs as part of the disorder's pathophysiology or, alternatively, as an adaptive response that compensates for pathological conditions caused by environmental stressors.

Some studies, adopting both task-related and resting-state fMRI paradigms, also evidenced functional alterations of the hippocampus in different psychiatric disorders.

Patients with chronic MDD, for example, showed reduced activation of the right hippocampus, compared to healthy controls, when performing a recollection memory task, while they showed increased hippocampal activation when processing negative information (Jaworska et al. 2015; Milne et al. 2012). Task-related functional alterations have also been observed in patients with schizophrenia, who presented reduced hippocampal activation in tasks of emotional processing, navigation, and memory (Gur et al. 2002; Ledoux et al. 2013).

As regards resting-state studies, a meta-analysis conducted on 567 patients with schizophrenia and 470 patients with MDD reported decreased activation of the left hippocampus in patients with schizophrenia compared to controls and no differences between patients with MDD and controls (Kühn and Gallinat 2013).

The observation that various psychiatric disorders are associated with volumetric and functional alterations of the hippocampus, as well as with a reduction in hippocampal neurogenesis, has strongly highlighted the need to carefully investigate

the mechanisms affecting this structure in both psychiatric and neurological conditions.

Investigating the hippocampus in AN is of great interest for several reasons. Firstly, some evidence suggests that patients with AN present alterations in some hippocampal-related functions, such as episodic memory, decision-making, and food intake regulation (Tenconi et al. 2016, 2021). AN is also characterized by some of those environmental factors that are thought to influence cell proliferation in the hippocampus, including chronic stress, altered nutritional status, and hyperactivity. Furthermore, AN is characterized by alterations in both neurodevelopmental and neuroprogressive processes, thus offering the potential to investigate the role that different pathogenetic conditions may have on this structure (Collantoni et al. 2019).

Hippocampus in Animal Model of AN

Activity-based anorexia (ABA) is a translational rodent model of AN originally proposed in 1967 by Rottenberg and Kuznesof (1967). In this model, adolescent rodents are exposed to food restriction while having access to a running wheel, and it was observed that they further reduce food intake, leading to self-starvation, and increase physical activity. This model allows some of the disorder's key features, such as reduction of food intake, hyperactivity, and weight loss, to be observed in an animal model. Moreover, by varying the degree of food deprivation and physical exercise, it is possible to determine the specific contribution of hyperactivity and low food intake to maintaining the AN phenotype.

In recent years, ABA has been shown to be a particularly useful model for studying some specific neurobiological, molecular, and structural bases of AN, and alterations have also been observed at the level of the hippocampus.

Some studies focused on the expression level of the brain-derived neurotrophic factor (BDNF), a protein that promotes hippocampal neurogenesis, in ABA rodents. Gelegen et al. (2008) observed that rodents that were exposed to a restricted feeding schedule and unlimited access to running wheels presented a reduction in BDNF expression localized in the mice hippocampus. On the contrary, in a more recent observation, Ho et al. (2016) evidenced an increase in BDNF mRNA (but not BDNF protein) expression in the hippocampus of rodents exposed to food restriction, while physical activity seemed to have no effect. Overall, these results suggest that BDNF expression might be altered in ABA rodents. However, the results are quite inconsistent, and further studies are needed to better clarify the involvement of BDNF expression in the neurobiology of ABA, even in light of the variable results observed in human AN (Brandys et al. 2013).

In a study using a rodent model to investigate the effect of ABA on hippocampal neurogenesis, Barbarich-Marsteller et al. (2013) evidenced a significantly reduced cell proliferation in the hilus region of the dentate gyrus and in the dorsal hippocampus after 3 days of ABA, and they also observed a positive correlation between the level of cell proliferation, body weight, and food intake. Interestingly, since proliferating cells in the hilus primarily give rise to glial cells rather than neurons, the effect of ABA on rodents was suggested to be mainly on gliogenesis rather than on

neurogenesis. However, this result was not replicated by Farinetti and colleagues (2020), who reported no differences between ABA and control rats in the degree of dentate gyrus neurogenesis.

In a study conducted to assess structural changes in the ABA hippocampus, Chowdhury et al. (2014a) observed a reduction in dendritic branching and a decrease in total dendritic length in the dorsal hippocampus of ABA rats compared to control rats, while in the ventral hippocampus, they observed that ABA was associated with an increased branching of the stratum radiatum. Since the ventral hippocampus is suggested to mediate anxiety symptoms while the dorsal hippocampus is mainly associated with spatial learning and cognition, the authors suggested that ABA may induce alterations leading to both increased anxiety and reduced behavioral flexibility through changes that occur at different neuroanatomical levels.

Interestingly, by differentiating the experimental groups so that one was specifically characterized by excessive exercise and the other by low-calorie intake, the authors observed that food restriction and hyperactivity were likely to influence different regions of the hippocampus. In particular, excessive exercise was suggested to be mostly associated with changes in the rostral-dorsal stratum radiatum, while food restriction was evidenced to be associated with decreased branching in the stratum lacunosum-moleculare in the dorsal and ventral regions of CA1 (Chowdhury et al. 2014a).

Chowdhury and colleagues (2014b) also investigated possible age-dependent effects of ABA on hippocampal structure, and they observed that while inducing ABA during adolescence was associated with increased branching of pyramidal cells in the ventral hippocampus, ABA induced during adulthood had no effect on dendritic branching.

To date, only one study has assessed changes in hippocampal volume following ABA induction, but it failed to observe any difference between ABA and control rats (Farinetti et al. 2020).

Structural Studies

Several studies have evaluated hippocampal alterations in AN from a structural point of view and using different methodologies. Some of them focused on overall hippocampal volume, while others investigated differences in specific subregions by using different segmentation systems.

However, given the high methodological heterogeneity among studies, results are quite inconsistent, and difficult to compare each other.

As regards alterations in whole hippocampal volume, some studies observed a reduction in gray-matter volume in patients with acute AN compared to healthy controls (Collantoni et al. 2021; Connan et al. 2006; Miles et al. 2018). Other authors, however, reported either no differences between patients and healthy controls (Burkert et al. 2015) or even an increase in whole hippocampal volume in patients with AN (Beadle et al. 2015).

In this regard, though, it is important to note that even if alterations in the whole hippocampal volume have not been consistently pointed out, differences in some of its subregions are likely to be present.

Burkert et al. (2015), for example, observed, in a sample of 21 female patients with acute AN, a reduced volume of the fimbria and an enlargement of the hippocampal fissure compared to healthy controls. Two studies found a reduction in bilateral parahippocampal gyri in patients with acute AN, and Brooks and colleagues (2011) also observed that parahippocampal gyri volume was lower in restrictive-type patients compared to binge-purging ones.

The fact that in some psychiatric disorders, such as MDD, the volume of the hippocampus is negatively associated with the duration of the disease has raised the hypothesis that it might be structurally involved in some neuroprogressive processes concerning the pathophysiology of AN. However, studies testing the hypothesis of a reduction in hippocampal volume alongside AN progression did not find any relationship between volume and duration of the disorder. The only partial exception is represented by a study conducted by Giordano and colleagues (2001), who found a trend-level negative correlation between the duration of the disease and the volume of the hippocampus-amygdala formation. In a recent study, Collantoni and colleagues (2022) evaluated hippocampal volumes in three groups of patients with AN: one with a recent onset (less than 1 year), one with a longer illness duration (more than 1 year), and one of fully recovered patients, with the aim of characterizing the potential role of the hippocampus in the neurobiological trajectories of AN. Although this study showed the presence of significantly reduced hippocampal volume in patients with AN compared to the control group, no significant association was detected between hippocampal volume and the duration of the disorder. Furthermore, a comparison between patients with a duration of the disorder shorter than 1 year and patients with a duration of the disorder longer than 1 year showed no differences between the two groups (Table 1).

As regards other associations between clinical variables and hippocampal volume, one study observed a trend-level negative association between total hippocampal volume and stress in patients with AN, meaning that smaller volumes were related to higher stress levels (Burkert et al. 2015). Age of onset might also determine different structural alterations in patients with AN. Studies conducted on adolescent patients with AN have indeed reported more extensive hippocampal volumetric alterations than research conducted on adult samples. This evidence suggests that one of the factors that may contribute to altering hippocampal morphology in AN may be related to its onset in periods in which brain development is particularly intense, such as in adolescence and early adulthood. Lastly, one of the studies that reported increased hippocampal volume in patients with AN observed that this increase was present only in patients who exercised excessively, suggesting that hyperactivity may compensate for the effects of malnutrition on this structure (Beadle et al. 2015).

At present, four studies have adopted a longitudinal design in order to assess the effects of weight recovery on the hippocampal structure. In the acute phase of the disorder, three of these studies observed a reduced volume of the hippocampus in patients with AN (Bernardoni et al. 2016; Mainz et al. 2012; Martin Monzon et al. 2017), while the other found that patients with AN who exercised excessively presented a larger hippocampus than healthy controls (Beadle et al. 2015). Bernardoni and colleagues (2016) conducted a study on an adolescent sample of patients with AN

Table 1 Hippocampal volumes in patients with short (≤1 year) or long duration of anorexia nervosa (Adapted from Collantoni et al. (2021))

	Short duration (<1 year) (27 AN vs. 24 HW)		Long duration (>1 year) (31 AN vs. 30 HW)	
	F (p)	Effect size d	F (p)	Effect size d
Whole left hippocampus	**7.30 (0.010)**	0.75	**5.65 (0.021)**	0.62
Whole right hippocampus	4.23 (0.045)	0.59	**6.15 (0.016)**	0.65
Left tail	**6.78 (0.012)**	0.54	**8.45 (0.005)**	0.76
Right tail	3.34 (0.074)	0.31	**10.95 (0.002)**	0.86
Left subiculum	4.02 (0.051)	0.64	0.62 (0.436)	0.19
Right subiculum	1.15 (0.289)	0.28	2.74 (0.103)	0.41
Left fimbria	**5.76 (0.020)**	0.64	**5.31 (0.025)**	0.61
Right fimbria	1.70 (0.198)	0.46	**12.55 (0.001)**	0.92
Left CA1_2	3.61 (0.06)	0.56	**5.40 (0.024)**	0.61
Right CA1_2	2.69 (0.108)	0.56	2.17 (0.147)	0.40

AN anorexia nervosa, *HW* healthy women
Statistics adjusted for age and site: threshold of significance according to FDR correction $p < 0.025$

and pointed out a complete normalization of hippocampal volume after a 3-month inpatient treatment program and partial weight normalization. The research conducted by Martin Monzon et al. (2017), instead, found that only the left hippocampus was restored after weight gain, with the right one being persistently reduced in volume. Although Mainz and colleagues did not explicitly assess differences in hippocampal volume between baseline and follow-up, they observed an association between recovery of sex hormones (FSH) and GM increase in the right hippocampus. Lastly, Beadle and colleagues (2015), who, at baseline, reported an increased hippocampal size in patients who exercised excessively, observed that after weight restoration, hippocampal volume was significantly lower than at baseline.

These findings indicate that weight restoration can normalize hippocampal structure in patients with AN, thus suggesting the role of malnutrition as a pathogenetic mechanism modifying the hippocampus' morphology. Moreover, although more longitudinal studies are needed to better clarify the changes occurring in the hippocampal structure during AN progression, the absence of a correlation between the volume of the hippocampus and the duration of the disorder leads to the hypothesis that the hippocampus may be structurally sensitive to disorder-specific alterations without being a useful marker for neuroprogression in AN.

Functional Studies

Most studies that employed functional neuroimaging methodologies to investigate hippocampus activation in patients with AN aimed at examining the role of this structure in the processing of food signals. The findings of these studies, which involve relatively low sample sizes and whose results should therefore be taken with

caution, are quite heterogeneous, mainly due to differences in task designs and methodologies.

Holsen et al. (2012) found lower left hippocampal activation in patients with AN, compared to healthy controls, when viewing high-calorie food images in a hungry state. These results, however, were not confirmed in another study conducted by Sanders and colleagues (2015), who found higher activation in the left hippocampus in both acute and recovered patients with AN than in controls in response to food cues. However, in this study, the comparison was made only for food versus nonfood cues, without specifying responses to high- or low-calorie food separately.

Lastly, Brooks and colleagues (2012) observed a left-sided parahippocampal hyperactivation in response to food images in patients with restrictive AN compared to patients with binge-purge AN, while no differences in hippocampal activation were observed between patients and healthy controls.

Other studies that examined hippocampal activation during specific tasks focused on the neural responses elicited during a set-shifting task and an emotional conflict task.

Sato and colleagues (2013) measured brain activity while participants were performing the Wisconsin Card Sorting Test, a task requiring cognitive flexibility and set-shifting abilities. The authors observed that patients with AN showed lower activation than healthy controls in the bilateral parahippocampal cortices. Furthermore, left parahippocampal activation during task execution has been shown to be negatively correlated with age in the experimental sample.

Bang and colleagues (2016) assessed brain activity in a sample of 22 patients who recovered from AN while performing an emotional conflict task. The task required participants to categorize affective faces while ignoring affective words. Face and word stimuli were either congruent (non-conflict) or incongruent (conflict). Their results during congruent trials evidenced a lower activation of the hippocampus (bilaterally) in patients who recovered from AN than in healthy controls.

A resting-state fMRI study conducted on a sample of 74 patients with acute AN found a higher fractional amplitude of low-frequency fluctuation in the bilateral hippocampus of patients with AN compared to healthy controls, suggesting the presence of a higher spontaneous fluctuation in neuronal activity in patients with acute AN in this area. These results were later confirmed in a recent study conducted on a smaller sample of seven patients with AN (Lai et al. 2020).

To date, two studies have used PET methodology in patients with AN to assess possible alterations in neurotransmitters that affect the hippocampus. A study conducted by Frank and colleagues (2002) found a reduced level of [18F] altanserin binding, a serotonin 2A receptor antagonist, in the amygdala and in the hippocampus of patients who recovered from AN, thus indicating an alteration of serotonin transmission that persists also after weight restoration.

Another study, conducted by Yoshizawa et al. (2009) evidenced an increased binding of [^{11}C]doxepin, which is a radioligand for the histamine H1 receptor, in the hippocampus of female participants as compared to males. However, no differences were observed between patients with AN and healthy women.

Hippocampus in Other Eating Disorders

The studies investigating the functioning of the hippocampus in bulimia nervosa (BN) are few and heterogeneous, as regards both methodology and findings. However, they deserve to be described given that they are of possible interest for future research.

As regards structural alterations, a study conducted using voxel-based morphometry (VBM) in order to characterize brain abnormalities in patients with BN failed to observe any significant difference between patients and healthy controls in hippocampal gray matter volume (Amianto et al. 2013).

The role of the hippocampus in the neurobiology of BN was also investigated by Wang et al. (2017), who explored brain networks in 44 patients with the disorder and in 44 healthy controls using graph theory tools. Interestingly, when analyzing nodal strength, the authors evidenced a decrease in nodal strength in patients with BN in different subcortical regions: in the medial orbitofrontal gyrus, in the left hippocampus, and in the bilateral parahippocampal gyri. Also, the hippocampus and the amygdala showed reduced connectivity in the experimental group compared to the healthy control one. Given the involvement of these regions of reduced strength and connectivity in reward functions, the authors suggest that these results may support the reward hyposensitivity hypothesis in patients with BN.

Reduced integrity of brain networks involved in reward processing was confirmed by a diffusion tensor imaging (DTI) study (Mettler et al. 2013). This study evidenced lower fractional anisotropy in the bilateral corona radiata, corpus callosum, right subinsular white matter, and right fornix in patients with BN compared to healthy controls. Interestingly, the results of this study highlighted that trait anxiety was negatively correlated with the fractional anisotropy of the fornix, corpus callosum, and left corona radiata in healthy women but not in patients with BN.

Another study by Mueller et al. (2017) investigated the neural substrate of catecholaminergic dysfunction in bulimia nervosa and its relationship with symptom relapse. In this investigation, the authors induced catecholamine depletion through the oral administration of alpha-methylparatyrosine (AMPT) for 24 h in 18 women with remitted BN and 22 healthy female participants using a randomized, double-blind, and crossover study design. A continuous arterial spin labeling sequence was used to measure cerebral blood flow. Furthermore, the presence of bulimic symptoms relapse was assessed by means of a follow-up telephone interview. Interestingly, bulimic relapse was found to be associated with a reduction in the cerebral blood flow in the hippocampus and in the parahippocampal gyrus following catecholamine depletion. On the contrary, staying in remission was associated with an AMPT-induced increase in cerebral blood flow in the hippocampus/parahippocampal gyrus.

One study conducted by Cyr and colleagues (2016) used a virtual reality-based paradigm to investigate the neural correlates of reward-based learning in a sample of 27 adolescents with BN and 27 age-matched healthy control participants. While acquiring fMRI data, participants had to navigate a virtual maze and collect monetary rewards. In the learning condition, they could learn the structure of the maze,

while in the control condition, learning was experimentally prevented, and thus reward stimuli were unexpected. The authors observed that patients with BN deactivated the right anterior hippocampus in the learning condition (when receiving expected rewards) and activated it in the control condition (when receiving unexpected rewards). In healthy controls, instead, activation of the hippocampus was greater in the learning condition than in the control condition.

In addition, activation of the right anterior hippocampus in response to unexpected rewards was greater in individuals who reported more bulimic behaviors in the 28 days prior to scanning.

Applications to Other Areas

The involvement of the hippocampus in food-intake regulation, reward-related mechanisms, and memory consolidation, among many other cognitive functions, made the study of this area of particular interest in the context of eating disorders and other psychiatric conditions.

In anorexia nervosa, both functional and structural neuroimaging studies suggested a possible involvement of this area in the neurobiology of the disorder. The findings, however, are inconclusive to date, mainly due to the small size of the experimental samples and to some methodological heterogeneities. Furthermore, only a few assessments of hippocampal structure and function in weight-recovered patients are present, and no longitudinal studies have been conducted to date. Therefore, it is currently not possible to properly evaluate whether the alterations affecting this structure are trait- or state-related phenomena or whether they may represent sequelae of the disorder. Further investigations are needed to better address these research points.

Mini-Dictionary of Terms

Activity-based anorexia nervosa: bio-behavioral phenomenon described in rodents that models the key symptoms of anorexia nervosa.

Diffusion tensor imaging: an imaging technique that provides information about the white matter microstructure.

Voxel-based morphometry: a computational approach that can be applied to MRI data. Employing a voxel-wise comparison of multiple brain images can measure differences in local concentrations of the brain tissue.

Neurogenesis: Process by which new neurons are produced.

Key Facts of Hippocampus in Anorexia Nervosa

Studies evaluating the hippocampus structure and function in eating disorders are still limited and not fully conclusive to date.

Some hippocampal structural and functional alterations have been pointed out in the acute phases of anorexia nervosa.

With weight recovery, the structural alterations affecting this structure seem to improve in patients with anorexia nervosa.

Summary Points

- The hippocampus is an anatomically complex structure that is peculiarly involved in the neurobiology of different brain disorders.
- Different studies have evidenced a role for this structure in the neurobiology of anorexia nervosa, but findings are rather inconsistent and heterogeneous both from a functional and structural point of view.
- Activity-based anorexia models provided important insights into the possible functional, structural, and molecular involvement of the hippocampus in disordered eating behaviors and in excessive physical activity.
- Neuroimaging studies pointed out both structural and functional hippocampal alterations in the acute phases of the disorder.

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Endocrine Disturbances in Anorexia Nervosa

29

Resistance to Hedonic Feeding Hormone Ghrelin

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Contents

Introduction 571
Physiological Functions of Ghrelin 572
Ghrelin and Reward Signaling in AN 573
Clinical Evidence of Ghrelin Resistance 575
Ghrelin Resistance: Antagonism by Other Ghrelin-Derived Peptides? 576
Physical Activity: The Patients' Option to Induce Ghrelin Resistance? 576
Genetic Factors Involved in Ghrelin Resistance 576
Chronicity and Ghrelin Levels in AN 577
Application to Other Eating Disorders 577
Summary Points 577
Mini-Dictionary 578
References 578

Abstract

Anorexia nervosa (AN) is a devastating psychiatric condition associated with a high mortality and chronicity and for which the etiology is unknown. Recent genomic-wide association studies suggest that AN is a psychometabolic disorder, having identified several genes that link AN to both psychiatric disorders and metabolic states. One of the metabolic factors that have since long been of interest in eating disorder pathophysiology is ghrelin, an orexigenic hormone produced by the gut. Ghrelin increases before food intake and stimulates appetite, reducing insulin, and is linked to increase in norepinephrine and growth hormone. Ghrelin exists in different forms in humans, i.e., as acyl-ghrelin, the activated form, and desacyl-ghrelin, a previously presumed inactive form, that may counteract the effects of acyl-ghrelin. Both have consistently been found to be increased in AN

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both in the acute stage and after weight restoration therapy, in spite of a lack of increase in appetite. Some findings indicate that individuals with long-standing AN develop resistance to the increased ghrelin levels, a process where exercise may be involved. This review present some of the most recent findings in the field of ghrelin research, as relevant for the understanding of the pathophysiology of AN.

Keywords

Anorexia nervosa · Ghrelin · Desacyl-ghrelin · Acyl-ghrelin · Eating disorders · Ghrelin resistance · Exercise · Disease model

Abbreviations

AG	Acyl-ghrelin
AgRP	Agouti-related peptide
AN	Anorexia nervosa
BBB	Blood–brain barrier
BED	Binge eating disorder
BMI	Body mass index
BN	Bulimia nervosa
CNS	Central nervous system
D2R	Dopamine 2 receptor
DA	Dopamine
DAG	Desacyl-ghrelin
ED	Eating Disorder
fMRI	Functional magnetic resonance imaging
GH	Growth hormone
GHRL gene	Ghrelin gene
GHSR1a	Growth hormone secretagogues receptor 1a
GOAT	Ghrelin-o-acetylase enzyme
Gαi	Gi protein alpha subunit
Gαq	Gq protein alpha subunit
HC	Healthy controls
IGF-1	Insulin-like growth factor 1
Leu	Leucine
ME	Median eminence
Met	Methionine
NAc	Nucleus accumbens
NPY	Neuropeptide Y
POMC	Proopiomelanocortin
PROLED	PROspective Longitudinal all-comer inclusion study in Eating Disorders
SNP	Single-nucleotide polymorphism
VTA	Ventral tegmental area

Introduction

Anorexia nervosa (AN) is a devastating psychiatric disorder, often having an onset during adolescence, characterized by extreme weight loss or failure to gain weight appropriately for age, associated with an intense fear of weight gain, and a distorted body image (Association 2013). Recent reconceptualization of AN, as of both psychiatric and metabolic etiology, suggests that metabolic circuits linked to hunger may be a critical nexus linking metabolic dysfunction to mood disturbances. During the acute stage of AN, patients display multiple endocrine abnormalities that are commonly associated with starvation, including elevated stress hormones, hypogonadotropic hypogonadism, and adipocytokine disturbances (Singhal et al. 2014; Levine 2002). Upon weight restoration, many of these abnormalities normalize (Brown and Mehler 2015). Of particular interest to AN is ghrelin, a centrally active, unique orexigenic hormone, being peripherally produced, and involved in gut–brain signaling for appetite control and energy balance (Kojima et al. 1999).

Ghrelin is secreted from oxyntic glands in the gastric fundus (Kojima et al. 1999) and primarily acts via the growth hormone secretagogues receptor 1a (GHSR1a), stimulating the release of growth hormone (GH) from the pituitary, which in turn releases insulin-like growth factor 1 (IGF-1) as a response (Warzecha et al. 2006). In addition, ghrelin exerts pleiotropic effects both peripherally and centrally, including the modulation of the dopaminergic reward system (Mequinion et al. 2013).

The GHRL gene is located on the short arm of chromosome 3 (3p25–26), and translation mRNA gives rise to five products of similar structure and function: (a) The first is the 117-amino acid *preproghrelin*, which is homologous to promotilin, both of which are members of the motilin family. Preproghrelin is cleaved to produce (b) *proghrelin* which is cleaved in the next step to produce the 28-amino acid (c) *ghrelin* (unacylated; desacyl-ghrelin) and *C-ghrelin* (acylated) and (d) *obestatin*, which is presumed to be cleaved from C-ghrelin (Seim et al. 2010).

In order for ghrelin to pass the blood–brain barrier and activate the GHSR1a receptor and trigger the release of GH from the pituitary, it must be modified posttranslationally. This is done by the ghrelin-o-acetylase enzyme (GOAT; (Yang et al. 2008)), which forms acyl-ghrelin (AG). In contrast, desacyl-ghrelin (DAG), which is the more abundant form, does not activate the ghrelin receptor (Giovambattista et al. 2007).

The GHSR1a receptor is expressed across the brain (Schellekens et al. 2010; Stengel and Tache 2012) and especially in the arcuate nucleus, in neurons that also express agouti-related peptide (AgRP) and neuropeptide Y (NPY), both of which are involved in regulating food intake (Tschop et al. 2000). AgRP neuron involvement includes regulating a broad range of behaviors that become activated in response to the presence or absence of food availability. These behaviors include motivation, locomotor activity, negative reinforcement, anxiety, and obsession (Mequinion et al. 2019). When AG activates GHSR1a, this stimulates food intake, reduces insulin secretion leading to hyperglycaemia (Gauna et al. 2005), and stimulates gastric motility (Tack et al. 2006). DAG is more abundant in plasma and accounts for 80–90% of total ghrelin (Kojima and Kangawa 2005) and has been described as

anorexigenic and may counterbalance acyl-ghrelin (Inhoff et al. 2008; Fernandez et al. 2016), probably acting as an agonist at the supraphysiological levels (Gauna et al. 2007; Heppner et al. 2014).

Recently, the first meta-analysis of all forms of ghrelin in AN, including analyses of longitudinal changes, confirmed elevated fasting blood levels in acute AN compared to HCs for all forms of ghrelin (Seidel et al. 2021). In addition, although the previous studies have indicated subgroup differences, some finding higher levels in binge/purge AN vs restrictive AN (Tanaka et al. 2003), whereas others have not (Stoving et al. 2007; Westwater et al. 2020), the results did not reveal an effect of AN subtype on ghrelin levels (Seidel et al. 2021). Furthermore, in longitudinal studies, total ghrelin levels in AN showed a significant decrease during treatment, although the levels were still significantly elevated compared to the levels in HC at the same follow-up time points. Since the levels of total ghrelin have been found to be decreased in BMI-matched lean individuals compared to AN (Tolle et al. 2003; Korek et al. 2013; Germain et al. 2007), likely, there are other factors that underlie the elevated ghrelin levels in AN than a low BMI and undernourished state. Instead, explanations to the differences may need to be sought in behavioral and physiologic changes. For example, lean individuals do not exhibit clinical features such as persistent efforts to reduce energy intake, amenorrhea, distorted body image, or fear of weight gain, and lean individuals display an equilibrated energy metabolism similar to that of healthy controls, which might result in normalized ghrelin levels (Korek et al. 2013; Germain et al. 2007).

Physiological Functions of Ghrelin

Ghrelin is known to have many physiological effects such as increasing food intake which historically has been presumed to be via modulating both the homeostatic and hedonic systems. In addition, ghrelin increases gut motility, is involved in stress and reward-oriented behaviors including anxiety, and also influences locomotion (Muller et al. 2015; Perello and Dickson 2015). Studies of ghrelin function in AN have been less conclusive.

In order to map the physiological functions of ghrelin in AN, infusions of ghrelin have been adopted. In one study in AN, intravenous ghrelin infusions during 5 h led to no clear changes in food intake but instead increased sleepiness (Miljic et al. 2006). In another study, a slight sense of hunger was experienced in six of nine patients with AN after a bolus intravenous injection of 1 mg/kg ghrelin (Broglio et al. 2004), at a similar level as in HC (five of seven responders). Yet another study found that administration of ghrelin (3 mg/kg) twice a day led to a decrease in gastrointestinal symptoms and an increase in the sense of hunger, which also led to an increase in daily energy intake (12–36%) in five AN patients (Hotta et al. 2009). Albeit these studies suffer from being experimental and lack statistical power, as well as lack proper controls, and fail to properly evaluate the motivation aspect of AN, namely, to eat (Ueno et al. 2010), they still provide some support for the involvement

of ghrelin in appetite and food intake in AN. Whether this is homeostatic or hedonic is however unsettled by these studies.

Other studies stress that ghrelin influences hedonic food intake rather than homeostatic. For example, in mice with total ghrelin deficiency or selective AG deficiency, food intake is not reduced (Sun et al. 2003, 2004; Zigman et al. 2005; Zhao et al. 2010; Pfluger et al. 2008), which does not support a key role of AG in homeostatic eating. However, suppressed intake of rewarding food in a free choice food paradigm, lack of cue-potentiated feeding, and suppressed motivation for food in an operant responding model rather support a role of the endogenous peptide(s) in hedonic eating (Uchida et al. 2013).

Ghrelin and Reward Signaling in AN

Several findings provide support for the involvement of ghrelin in hedonic eating in AN, for example, as evidenced by research on reward signaling. Using a sucrose taste classic conditioning paradigm, with fMRI to investigate dynamic effective connectivity during expected sweet taste receipt, and where violations of learned associations between conditioned visual and unconditioned taste stimuli evoked dopamine-related prediction error, Frank et al. found an elevated prediction error response in AN compared with HC, BN, and binge eating disorder (BED). Furthermore, this altered reward response in AN was inversely associated with BMI. In addition, they found changed signaling in reward and food intake brain circuits in AN patients compared to healthy controls (Frank et al. 2021).

In another study, using a reward prediction error construct, i.e., a computational model for reward receipt and omission related to motivation and neural dopamine responsiveness, brain function was tested using functional MRI (fMRI) before and after treatment. This study found an increased brain activity of the DA-mediated reward system in AN patients compared to HC when exposing the subjects to situations that require reward-related learning (deGuzman et al. 2017), especially when underweight. After weight restoration, an elevated prediction error response in the striatum and insula was still found, although normalized as compared to before treatment. This replicates another study that also found underweight to be associated with increased dopamine-related reward system responsiveness, which only partially recovered with weight restoration (Carr 2002). In the study by DeGuzman et al. (2017), they especially found elevated brain reward circuits in the nucleus caudate and insula during reward learning, with the caudate being known to respond to salient stimuli and encode prediction error signals during stimulus reward learning (Zink et al. 2004), which thereby may reflect an altered dopamine function in AN, and the insula containing the primary taste cortex and being involved in cognitive control (Cauda et al. 2011; Klein et al. 2013). Prediction error signaling in insula has been associated with flexible behavioral control, and thereby, an increased signaling in insula may indicate altered reversal learning in AN, which may be associated with therapy resistance.

To further support the role of ghrelin as a potential modulator of reward-related behaviors, a study on cognitive functioning such as reward-based decision-making found that high levels of ghrelin were associated with better cognitive performance on the Iowa gambling task (reward sensitivity) (Paslakis et al. 2019) and with decreased delay discounting in AN (patients with high ghrelin more often chose the delayed reward) (Bernardoni et al. 2020).

The role of ghrelin in reward processing is thought to occur via its strong connections to the mesolimbic dopamine system (Stievenard et al. 2017). For example, ghrelin injection was associated with increased dopamine in the nucleus accumbens (Jerlhag et al. 2007) as well as heightened activation in key regions associated with pleasure and reward (Malik et al. 2008). It is via this pathway that ghrelin is able to increase the incentive value of food (Kroemer et al. 2013) and, in the same fashion, also in other reward-motivated behaviors such as alcohol consumption and drug use (Wittekind and Kluge 2015; Dickson et al. 2011).

Another central structure where ghrelin exerts its actions is the ventral tegmental area (VTA), a structure involved in the reward/locomotion behavior, and hypothalamus to modulate appetite, respectively (Jiang et al. 2006; Kern et al. 2012; Sharpe et al. 2016).

A recent fMRI study in women with AN demonstrated that the VTA activity, measured with the blood flow to the VTA, was reduced compared to individuals suffering from bulimic nervosa when exposed to food odors, which may indicate potential dysregulation of VTA activity in AN patients (Jiang et al. 2019). Additionally, a retrograde viral injected, chemogenetic induction of intracellular ghrelin (Gαq) pathway activity, in projections from the VTA to NAc, increased food intake and food anticipatory behavior of activity-based anorexia (ABA) rats, an animal model of AN, mainly as a result of activated dopaminergic neurons (Foldi et al. 2017). The interpretation of these findings suggests that a decreased activation of the dopaminergic projections from VTA to the NAc, which have been consistently found to be activated by ghrelin in the presence of food, may be involved in the etiology of AN. A modulation of these dopaminergic projections may influence and even reduce the development of AN (Kawahara et al. 2009).

On the other hand, others have associated high ghrelin levels not only with increased impulsivity (Anderberg et al. 2016) but also with increased reward sensitivity (Farokhnia et al. 2018; Ralevski et al. 2018) or reduced activity in areas associated with regulatory control (dorsolateral prefrontal cortex, (Bogdanov et al. 2020) in other populations.

There are additional evidence to support an involvement of the DA system in mediating the effects of ghrelin in AN, e.g., from fMRI studies in which individuals with AN showed a high rate of self-control and are less sensitive to rewards and more sensitive to punishment, e.g., during odor-cued food task (Jiang et al. 2019) or increased blood flow oxygenation in the left anterior insula in response to food images (Kim et al. 2012), and in behavioral studies, as an increased activity level (Dalle Grave et al. 2008).

Another evidence of the involvement of reward and dopamine in AN stems from studies on drug use, which have indicated a rather high usage, especially of

amphetamine and cocaine, in this population (Herzog et al. 2006; Aguinaga et al. 2019). Anecdotal reports from my own interviews with patients in the PROspective Longitudinal all-comer inclusion study in Eating Disorders (PROLED; for more info see (Fjeldstad et al. 2021)) suggest that the usage of dopaminergic stimulating drugs helps to suppress hunger signals in AN. Hypothetically, the hedonic reward from the CNS stimulant overrides the drive for feeding. Supporting this is both the clinical experience of refusal to accept medication with antipsychotic drugs (D2R antagonists), i.e., drugs that potentially may drive feeding behavior, and the results of clinical trials which suggest no overall positive effect from treatment with anti-dopaminergic drugs; see meta-analysis (Blanchet et al. 2019). Many of these studies used second-generation antipsychotics, which are known to increase body weight, at least in patients with schizophrenia and bipolar disorders, which raises questions on the compliance in these clinical studies in AN but also whether these drugs influence ghrelin-related hedonic food intake in the way required for changing the course of AN. However, the D2 blockade may also be affecting the dopaminergic system insufficiently or be too crude a mechanism to promote feeding behavior in AN (see below on biased signaling).

Clinical Evidence of Ghrelin Resistance

One potential explanation for the lack of effects of ghrelin infusions on food intake in AN concerns potential ghrelin resistance. Overall, there are a couple of disparate findings that support this:

(a) A reduced ability of ghrelin to be transported to central targets within the hypothalamus (Schaeffer et al. 2013); the transport mechanisms of ghrelin, through the blood–brain barrier (BBB) and into the nucleus arcuatus, is yet vaguely understood, and the current knowledge implies that it may be either via diffusion across fenestrated capillaries in the median eminence (ME) or via saturable receptor-mediated transport across the BBB. One study has demonstrated that ghrelin is able to pass the fenestrated capillaries in ME and that hypothalamic neuronal monitoring of this is possible together with rapid adaptations of the passage of ghrelin (Schaeffer et al. 2013).
(b) A reduced GHSR1a sensitivity or function; this could be related to a dysregulation of hypothalamic NPY/AgRP and POMC neurons, which function as direct or indirect targets of ghrelin effects, thereby leading to opposing actions on food intake (Denis et al. 2014). Overall, GHSR1a signaling is highly complex as reflected in the available four different intracellular pathways that may be triggered as a result of GHSR1a activation: Gαq, Gαi/o, Gα12/13, and the recruitment of β-arrestin. Thus, a biased signaling may enable a partial or complete activation or inhibit one or a subset of intracellular pathways of this pleiotropic receptor (Khelifa et al. 2021).
(c) An alteration in the ghrelin signaling on dopaminergic neurons, in the ventral tegmental area (VTA) (Abizaid et al. 2006). See more below.

Ghrelin Resistance: Antagonism by Other Ghrelin-Derived Peptides?

With regard to altered ghrelin signaling on DA neurons, this may be the effect of other ghrelin-derived peptides, such as those that may modulate the actions of AG. One potential modulator is DAG, which may exert its actions on appetite by counteracting the effects of AG. Evidence of such a counteracting mechanism stems from studies on central and peripheral injections of DAG (Asakawa et al. 2005; Inhoff et al. 2008), where DAG suppresses ghrelin-induced food intake by reducing the ghrelin-induced increase in neuronal activity in the arcuate nucleus. In addition, transgenic mice overexpressing DAG present with a reduced body weight, reduced food intake and reduced body fat mass, and decreased linear growth (Asakawa et al. 2005). Furthermore, DAG exerts several biological actions, independent of the GHSR1a pathway, including regulation of glucose homeostasis and fat metabolism (Delhanty et al. 2012, 2013). Another candidate for opposing the effects of AG is obestatin (Chartrel et al. 2007). For example, in individuals suffering from restrictive subtype of AN, obestatin and the ghrelin/obestatin ratio were found decreased in comparison to constitutionally thin women, who had a normal ratio (Germain et al. 2010). Such changes may participate in the eating restriction despite the hyper-ghrelinemia observed in these patients.

Physical Activity: The Patients' Option to Induce Ghrelin Resistance?

Patients suffering from AN frequently engage in increased physical activities to burn calories and thereby counteract any risk of weight gain. This often becomes a habit in AN, and many patients report several hours of physical activity per day for extended periods of time. The effects of physical activity on ghrelin levels in AN are yet to be fully elucidated, but speaking in favor of an effect on inducing resistance is a systematic review of physical activity that found ghrelin levels are suppressed after acute and increased after chronic physical exercise (Ouerghi et al. 2021).

Genetic Factors Involved in Ghrelin Resistance

Genetic factors may be yet another reason for altered ghrelin levels in AN as proposed by Dardennes et al. (2007), who studied 114 trios (studies in individuals with AN including both of their parents). Transmission disequilibrium was observed for the Leu72Met single-nucleotide polymorphism (SNP) in the preproghrelin gene, which was primarily transmitted in trios in the binge eating/purging subtype of AN (Muller et al. 2011). Studies on a general population have found that Met72GHREL carriers have the lowest BMI and the lowest fat mass including less visceral fat and a lower fasting respiratory quotient, indicating a greater utilization of fat as an energy substrate (Ukkola and Poykko 2002).

Chronicity and Ghrelin Levels in AN

A yet unknown aspect is how ghrelin levels change over time, for example, with development of severe and enduring AN. The development of ghrelin resistance in AN may be part of this treatment-resistant state. Some findings indicate that some individuals with AN suffer progressive disorder, similar to that in schizophrenia and bipolar disorder. This neuroprogressive state changes the clinical features of AN in terms of psychological and clinical symptoms and signs. However, it is unknown how ghrelin resistance may influence or be part of the pathophysiology of this state (Fig. 1).

Application to Other Eating Disorders

In other disorders such as BN, ghrelin levels have mostly been found to be at normal levels (Westwater et al. 2020; Troisi et al. 2005; Monteleone et al. 2008) and increased before food intake and decreased after (Kojima et al. 2005). In addition, acute stress increased ghrelin in AN but not in BN (Westwater et al. 2020). In BED, ghrelin levels in blood are usually comparable to that of healthy controls (Munsch et al. 2009). In addition, while the GHRL gene may be involved in AN and BN, no such association has been found for BED (Palmeira et al. 2019).

Summary Points

Ghrelin is a unique orexigenic hormone, being produced in the periphery, and is involved in feeding behavior. All forms of ghrelin have been found to be increased in blood in AN and still being increased after weight gain. No clear evidence links

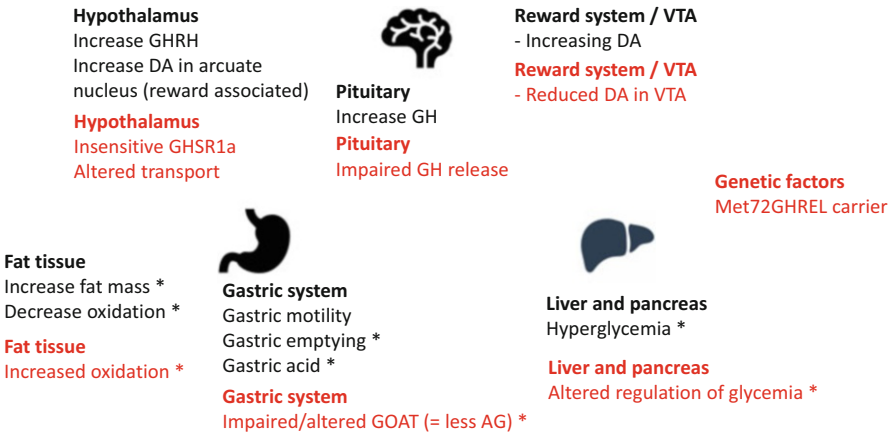


Fig. 1 Ghrelin physiological effects (in black) and signs of resistance to ghrelin (in red)

ghrelin levels in blood to any specific behavior in AN, and in general, most evidence point at ghrelin being involved in hedonic feeding behavior, linked to reward. The actions of the active form of ghrelin, AG, may be counteracted by its sisterpart, DAG, and potentially also by other hormones such as obestatin. The concept of ghrelin resistance has been presented. This is supported by the increased ghrelin levels in AN, while normal in lean individuals, and a lack of effect of ghrelin on feeding in AN. Both genetic factors and physical activity may be involved in ghrelin resistance. No clear evidence of an involvement of ghrelin in other ED exists.

Mini-Dictionary

- **Ghrelin:** A peripherally produced orexigenic hormone involved in feeding behavior.
- **Acyl-ghrelin:** The active form of ghrelin stimulating primarily hedonic feeding behavior.
- **Desacyl-ghrelin:** The previously presumed inactive form, while current concept suggests it is counteracting the effects of AG.
- **Reward system:** Neuroanatomically and neurochemically defined system involved in behaviors linked to a sensation of reward.
- **Reward sensitivity:** Being prone to react to rewarding stimuli.
- **Anorexia nervosa:** An ED characterized by extreme weight loss or failure to gain weight appropriately for age, associated with an intense fear of weight gain, and a distorted body image.

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Anorexia Nervosa and Eye Movements

30

Andrea Phillipou

Contents

Introduction 586
Neurobiology of Saccadic Eye Movements 587
Saccade Characteristics 588
Saccade Tasks 589
Fixation Task 589
Prosaccade Task 591
Antisaccade Task 591
Go/No-Go Saccade Task 592
Memory-Guided Saccade Task 593
Self-Paced Saccade Task 594
Visual Scan Path Tasks 594
Attentional Bias Tasks 596
Conclusions and Implications 597
Applications to Other Eating Disorders 597
Mini-Dictionary of Terms 597
Key Facts of Eye Movements in AN 598
Summary Points 598
References 598

Abstract

Eye movement tasks have been used widely in psychiatric and neurological illnesses to gain a better understanding of cognitive processes and the neurobiology involved in these conditions. A range of different eye movement tasks have been employed, most of which have focused on saccadic eye movements – the fast, "jerky" eye movement humans typically use to view their surroundings. This chapter will provide an overview of the eye movement literature in anorexia

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nervosa (AN) to date and will describe the value of gaining a better understanding of eye movements to inform improved diagnosis, treatment, and prevention of AN.

Keywords

Anorexia nervosa · Eye movements · Saccade · Fixation · Square wave jerk · Prosaccade · Antisaccade · Memory-guided saccade · Self-paced saccade · Smooth pursuit · Scan path · Visual attention · Cognition · Body · Food

Abbreviations

AN	Anorexia nervosa
BMI	Body mass index
DLPFC	Dorsolateral prefrontal cortex
FEF	Frontal eye fields
GABA	gamma-Aminobutyric acid
HC	Healthy control
LIP	Lateral intraparietal lobule
SD	Standard deviation
SEF	Supplementary eye fields

Introduction

The visual system is a complex biological system that processes information gathered from visible light to build a representation of our surrounding environment. Light enters our eyes via the cornea and through the pupil, onto the retina situated at the back of our eyes. The retina is connected to the optic nerve which sends neural signals to our brains. Our eyes move to locate stimuli of interest onto the region of the retina with the greatest visual resolution – the fovea – using four different types of eye movements: saccadic, smooth pursuit, vergence, and slow stabilizing eye movements. Slow stabilizing eye movements – namely, the vestibular-ocular reflex and optokinetic reflex – are reflexive eye movements which help us hold gaze stationary. Vergence describes when our eyes converge or diverge when a target moves toward or away from us, respectively. Smooth pursuit refers to slow eye movements ($<100°/s$) that we use to track moving targets. Saccadic eye movements – or saccades – are the fast jerky eye movements, typically followed by a period of fixation, that redirect gaze. As humans, we use a "saccade and fixate" strategy when viewing our surroundings, making approximately three to four saccades every second of our waking lives. Given that saccades are by far the predominant type of eye movements that we use in everyday life, they are also the most researched. But why would we research saccadic eye movements, and what do differences or deficits in their execution tell us?

Saccadic eye movements are stereotypical and tend to have a characteristic profile, and when saccades do not look like how we would expect, it can suggest neurocognitive or neurobiological deficits. Saccadic eye movements can tell us about higher level processing such as inhibition and memory, as well as visual attention. Examining different characteristics of saccadic eye movements can also tell us about neurological mechanisms that may underlie different conditions, such as anorexia nervosa (AN). As brain regions involved in eye movement production overlap with regions thought to be involved in various psychiatric conditions, deficits in eye movement production have been researched in mental health populations since the early 1900s, providing increased understanding of the neurobiology underlying these conditions.

Neurobiology of Saccadic Eye Movements

Each eye is controlled by six extraocular muscles, with horizontal eye movements controlled by the medial and lateral rectus muscles, and vertical eye movements controlled by the superior and inferior rectus muscles, and superior and inferior oblique muscles. Saccadic eye movements are generated in the brainstem with horizontal saccades generated by neurons in the paramedian pontine reticular formation (Keller 1974) and vertical saccades generated by neurons in the mesencephalic reticular formation (Buttner et al. 1977; Buttner-Ennever and Buttner 1978). A number of other subcortical and cortical brain areas are involved in the production of saccades – which are best understood for horizontal saccades – including the superior colliculus, basal ganglia, thalamus, and parietal and frontal cortices.

The superior colliculus is a midbrain region that plays an important role in the generation of saccades, with caudal regions involved in driving saccades and more rostral regions involved in maintaining fixation between eye movements (Munoz and Wurtz 1993a, b, 1995). Neurons in the intermediate superior colliculus discharge in relation to saccades of different amplitudes, with larger saccades generated in caudal regions and smaller saccades generated in rostral areas (Robinson 1972; Schiller and Stryker 1972). The intermediate superior colliculus receives projections from cortical areas – including the frontal eye field (FEF) (Bruce et al. 1985; Sommer and Wurtz 2000), supplementary eye fields (SEF) (Shook et al. 1990), dorsolateral prefrontal cortex (DLPFC) (Selemon and Goldman-Rakic 1988), and the lateral intraparietal lobule (area LIP) (Clower et al. 2001; Lynch et al. 1985) – as well as subcortical regions – such as the brainstem and basal ganglia, as well as the cerebellum (Edwards et al. 1979; Hikosaka et al. 2000). The superior colliculus itself projects to areas involved in premotor circuitry of eye movements – the paramedian pontine reticular formation and the rostral interstitial nucleus of the medial longitudinal fasciculus (Sparks 2002) – as well as to the FEF, providing a warning of an impending eye movement (Sommer and Wurtz 2008).

Saccade Characteristics

In normal viewing, saccades generally do not exceed an amplitude of 15° (Bahill et al. 1975), with targets further in the periphery usually involving moving the head to redirect the image onto the fovea (Bahill et al. 1975). Saccades can be made in less than 100 ms, with both eyes moving in the same direction with the same amplitude. Saccades begin when the eye is stable, quickly accelerating to a peak velocity followed by a rapid deceleration which then quickly returns to a stable position. In laboratory-based experiments, a number of saccade characteristics are typically examined including the gain, latency, and peak velocity of the saccadic eye movement (see Fig. 1). Gain refers to the accuracy of a saccade onto a target and is calculated by dividing the saccadic amplitude by the amplitude of the target. Latency describes the time from stimulus onset to the initiation of a saccade (saccadic reaction time), whereas peak velocity refers to the fastest point of a saccade, quoted in degrees per second (Liversedge et al. 2011).

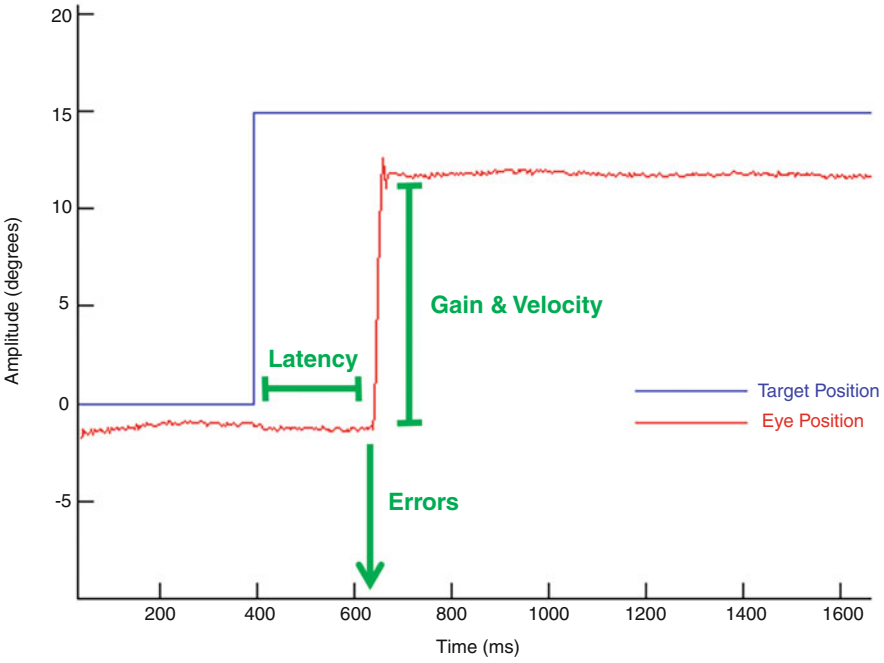


Fig. 1 Saccadic eye movement characteristics typically measured in laboratory-based experiments. Visual representation of eye movement data to a 15° target. The blue line represents the target position, and the red line, the eye position. In this example, a correct prosaccade is shown. An error on this task would result in a saccade made in the opposite direction of the target. Latency refers to the time from the onset of the target to the onset of the saccadic eye movement. Gain refers to the accuracy of the saccade onto a target, calculated by dividing the saccadic amplitude by the amplitude of the target. Peak velocity refers to the fastest point of the saccade, quoted in degrees per second

In laboratory-based experiments, saccades are typically researched in terms of the direction in which they are made, i.e., vertical or horizontal. In everyday life, horizontal saccades are more frequently used and are therefore more frequently researched, and consequently their neurobiology is better understood.

Saccade Tasks

A range of tasks based in the laboratory are typically carried out to examine the various saccade characteristics in different populations. Included among these tasks are the "basic saccade tasks" such as fixation, prosaccade, antisaccade, go/no-go, memory-guided and self-paced saccade tasks, and other types of paradigms in which gaze is examined. Examining performance on these types of tasks has been of increasing interest in the study of AN and has provided valuable insights into possible neurocognitive and neurobiological deficits in this population.

The first study on eye movements in AN did not specifically employ a saccadic eye movement task but a smooth pursuit task (Pallanti et al. 1998). In this study, participants who were weight-restored from AN were required to track a moving dot with their eyes. Unpredictable step-ramp stimuli were utilized, and patients were found to have lower mean peak velocity gains, increased anticipatory saccades, and lower target matching than healthy controls (HC). The authors also reported that 3 of 28 wr-AN participants also exhibited square wave jerks during the smooth pursuit task. The authors suggested that these impairments may represent alterations in cortical-subcortical neuronal circuits that control oculomotor activity and saccadic eye movements. Since this early pioneering study, all the research in AN to date has focused specifically on saccadic eye movements.

Fixation Task

The fixation task is perhaps the simplest of all eye movement tasks to perform but is also perhaps the most interesting in terms of AN. In a fixation task, participants are required to remain fixated on a central stimulus for the entire duration of the task (usually for around 1 min). Performance on this task is determined by the ability to remain fixated on the central stimulus. Intrusive saccades, however, occur at a low rate during fixation. In particular, a type of small, involuntary eye movement – called a square wave jerk – is frequently seen in individuals with AN (see Fig. 2). Square wave jerks involve a pair of small (typically 0.5–5°), involuntary, and unconscious horizontal saccadic eye movements that very briefly (~200 ms) move the eye away from and back to the target, appearing as an eye movement "twitch" (Abadi and Gowen 2004; Abadi et al. 2003). It is typical to make square wave jerks at a low rate during fixation; however, individuals with AN have been reported to make a very large number of these atypical eye movements (Phillipou et al. 2014, 2022). In the first study to identify an increased rate of square wave jerks during fixation in AN, Phillipou et al. (2014) found that individuals with AN made an average of 11.8

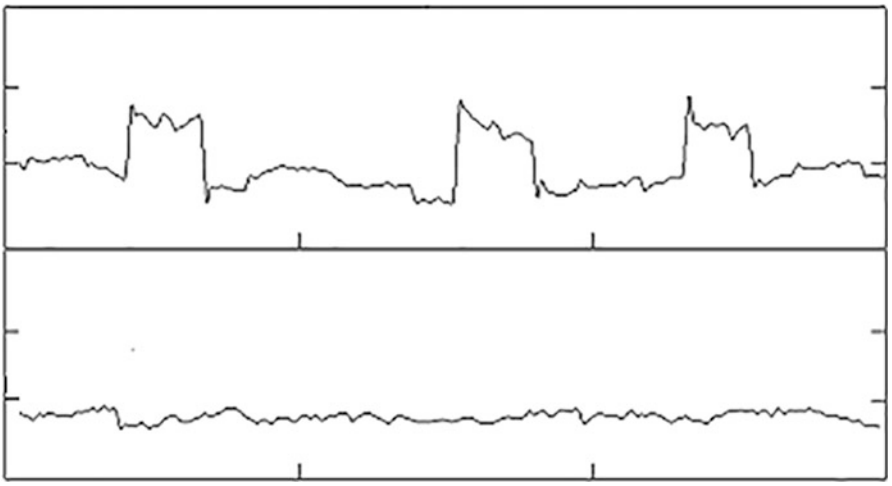


Fig. 2 An example of square wave jerks in an individual with AN (top panel) and stable fixation in a HC (bottom panel) during a fixation task. Visual representation of eye movement data over a three-second period. The vertical axis represents 1° increments

(SD = 12.2) square wave jerks in a 1 min eye tracking recording, compared to an average of only 2.95 (SD = 2.8) in HCs. This study also reported a significant negative correlation between square wave jerk rate and levels of anxiety in the AN group. Square wave jerk rate and anxiety levels, together, were also able to discriminate AN from HCs with exceptionally high accuracy (91.25%), providing a potential biomarker for identifying people with AN. A follow-up study by the same authors replicated this finding in individuals currently with AN compared to HCs (with 92.5% accuracy) and also extended the findings to individuals who were weight-restored from AN and sisters of individuals with AN who could each be discriminated from HCs with 77.5% accuracy, respectively (Phillipou et al. 2022).

In addition to the finding of a new potential biomarker for AN that could potentially be used for diagnosis or as a screening tool for prevention, the presence of these intrusive saccades and their relationship to anxiety levels provide support for the hypothesis that the superior colliculus and gamma-Aminobutyric acid (GABA) may play a role in AN. GABA levels in the superior colliculus have been linked to intrusive saccades (Munoz and Wurtz 1993b), and levels of anxiety are closely related to GABA activity (Tallman et al. 1980). Importantly, the superior colliculus is also involved in multisensory integration, and deficits in this area may be related to the integration of visual and tactile information that contributes to body image disturbances in AN (McFadyen et al. 2020; Meredith and Stein 1986). As this biomarker was also present in individuals who were weight-restored from AN, this suggests that this marker may represent an AN trait. Further to this, as sisters of individuals with AN were also found to show this marker, it indicates that not only may this eye movement suggest an underlying neurobiological trait, but it may also

represent a hereditary endophenotype, suggesting that certain individuals may be predisposed to developing AN.

Prosaccade Task

The prosaccade task – also known as the reflexive saccade task – is a simple task in which a stimulus, such as a black dot on a white background, is simply presented and a participant is required to make a saccade toward this target (Hallett and Lightstone 1976). While minimal effort is required to perform a prosaccade task, performance on this task requires some attention, and the brain mechanisms involved in attentive processes overlap with brain regions involved in eye movements including FEF, SEF, inferior parietal lobule, and cerebellum, among other areas (Beauchamp et al. 2001; Nobre et al. 2000; Corbetta et al. 1998; Perry and Zeki 2000). Gain, latency, and peak velocity of prosaccades are typically examined and are rarely reported to be disrupted in psychiatric conditions. To date, two studies have investigated prosaccades in AN, the earlier of which found significantly shorter latencies in AN relative to HC (Phillipou et al. 2016b) and the latter not reporting a difference in any prosaccade characteristic between AN, weight-restored AN, and sisters of individuals with AN and HC (Phillipou et al. 2020). The lack of consistency in these two studies may be as a consequence of different methods of trial presentation. The earlier study examined prosaccades within a paradigm that also contained antisaccade and no-go trials following a cue period and may have resulted in attention being disengaged before the presentation of the target, enabling faster saccades. This earlier finding of faster initiation of prosaccades also provides support for the potential role of the superior colliculus in AN given the region's involvement in the initiation of eye movements, as well as the potential role of the neurotransmitter GABA in this brain region. However, given the lack of group difference in the latter study, further research into prosaccade task performance is required.

Antisaccade Task

The antisaccade task is a somewhat more complicated task than the prosaccade task. In this task, the participant is asked to fixate on a central stimulus. Similarly to the prosaccade task, a target is presented in the periphery. However, unlike the prosaccade task, the participant is required to suppress making a saccade to the stimulus and instead make a saccade to its mirror image – in other words, they need to make a saccade of the same distance from the center but in the opposite direction – a "correct antisaccade" (Hallett 1978). The antisaccade task is frequently used in psychiatric conditions to assess neurocognitive function because it can provide information on a number of different cognitive processes, including inhibition, attentional focus, working memory, and spatial representation. Correct antisaccades require the participant to inhibit making a prosaccade to the presented stimulus, a process which requires focused attention as well as working memory. While correct antisaccades

tend to by hypometric – meaning that participants tend to "undershoot" the target by making a saccade that is not quite as large as necessary to be a "mirror image" of the target (i.e., have smaller gains) – being excessively hypometric or hypermetric can indicate difficulties with transforming coordinates to spatial representations (Krappmann 1998). The latency of correct antisaccades is also typically longer than that of prosaccades due to the increased cognitive processes required to inhibit the automatic response to make a prosaccade to the target (Everling and Fischer 1998; Hutton and Ettinger 2006; Munoz and Everling 2004; Olk and Kingstone 2003). Errors on the task are common, with two types of errors typically recorded – corrected and uncorrected antisaccade errors. Corrected errors occur when a saccade is made toward the presented target and immediately corrected to make a saccade in the opposite direction, whereas this correction is not made with uncorrected errors. Both types of errors are thought to result because of deficits or lack of maturation of the frontal lobe, particularly the DLPFC (Ford et al. 2005; Curtis and D'esposito 2003; Bowling et al. 2012), but uncorrected antisaccades are rare and are typically only seen in populations with neurological diseases such as Alzheimer's disease and frontal lobe damage (Crawford et al. 2005; Guitton et al. 1985; Abel et al. 2002) and are not typically found in individuals with mental health conditions. Corrected antisaccade errors, however, are common in individuals with mental health conditions, particularly in individuals with schizophrenia where no study to date has failed to find an increased rate of antisaccade errors in this population (Hutton and Ettinger 2006; Myles et al. 2017). In relation to AN, two studies have investigated antisaccade task performance, one using an interleaved design (interleaved with prosaccade and no-go saccade trials) and the other using a block design of just antisaccade trials. The study using an interleaved design failed to find a difference in any antisaccade variable between AN and HC groups (Phillipou et al. 2016b). The blocked design study, however, reported that individuals with AN and sisters of individuals with AN showed higher gains than both HC and individuals who were weight-restored from AN who tended to "undershoot" the target, suggesting discrepancies in visual representations (Phillipou et al. 2020). Furthermore, in the group currently with AN, gain negatively correlated with body mass index (BMI), suggesting that starvation effects may contribute to visual representation difficulties.

Go/No-Go Saccade Task

In the go/no-go saccade task, participants are required to fixate on a central stimulus which will change to indicate whether a saccade should be made to a peripherally presented stimulus (the "go" response/prosaccade) or to remain fixated in the center when the peripherally presented stimulus appears (the "no-go" response/fixation) (Van'T Ent and Apkarian 1999). Similarly to the antisaccade task, the no-go response requires an inhibitory response when the stimulus appears, but unlike the antisaccade task, it does not require the volitional action of generating a saccade (Brown et al. 2006), thereby allowing for the investigation of inhibitory processes regardless of the ability to perform a volitional saccade. In terms of investigations in

AN, only one study to date has examined performance on this task and found no differences in no-go error rate, relative to HC (Phillipou et al. 2016b).

Memory-Guided Saccade Task

The memory-guided saccade task – also known as the oculomotor delayed response task – requires a participant to fixate on a central stimulus while a target is briefly presented in the periphery. The participant is required to maintain fixation on the central stimulus and to not look at the stimulus that has just flashed in their periphery. Only when the central stimulus disappears following a short delay are they required to make a saccade to where the target was briefly presented (Pierrot-Deseilligny et al. 1991). While the memory-guided saccade task assesses short-term memory, it also taps into other cognitive processes, including inhibition and attentional control. Inhibitory errors on this task can result due to a failure to suppress an unwanted reflexive saccade to the briefly presented stimulus or a failure to inhibit a planned saccade to the remembered location during the delay period. Similarly to the antisaccade task, correct memory-guided saccades have longer latencies than prosaccades, indicating increased cognitive demand during this task (Özyurt et al. 2006; Mitchell et al. 2002). Similarly to antisaccades, memory-guided saccades also tend to be hypometric (Gnadt 1991; Krappmann 1998).

In relation to AN, two studies have examined performance on the memory-guided saccade task. The first of these studies presented AN and HC participants with stimulus targets at 5° and 10° (Phillipou et al. 2016b). Group differences were not observed for gain, latency, peak velocity, or directional error rate. The AN group were, however, found to show an increased rate of inhibitory errors, specifically to stimulus targets at 10°. The latter of these studies employed a similar paradigm but also presented stimulus targets at 15° (Phillipou et al. 2020). Interestingly, the only group difference found again was on inhibitory errors to 10° targets. Individuals with a current diagnosis of AN showed increased inhibitory errors to stimuli presented at 10° in comparison to HC, as well as in comparison to individuals weight-restored from AN. The current AN group also showed a trend toward making more inhibitory errors to 10° targets than first-degree relatives (i.e., sisters) of people with AN.

This finding of increased inhibitory errors to a specific target amplitude in AN provides further evidence for the potential role of the superior colliculus in the disorder. Cells producing saccades are topographically mapped on the superior colliculus – with smaller amplitude saccades being initiated by more rostral areas and larger saccades by more caudal areas (Sparks 2002). Hence, there may be dysfunction in a very specific region of the superior colliculus in individuals with AN given that deficits were only present at 10°. As these findings do not appear to extend to individuals who were weight-restored from the illness, it suggests that this dysfunction may represent a state effect that is restored with the restoration of body weight or improved psychological symptoms.

Self-Paced Saccade Task

The self-paced saccade task is considered an almost entirely volitional task in which the participant is required to self-initiate refixations back-and-forth between two stimuli for the entire duration of the task (usually for around 30 s) (Abel and Douglas 2007). Findings from aging and neurodegenerative studies suggest a role of frontal functioning in the production of self-paced saccades (Abel and Douglas 2007; Abel 2009), while traumatic brain injury studies suggest that performance on this task represents an inability to disengage attention and speed of information processing (Heitger et al. 2009; Williams et al. 1997). Only one study to date has examined performance on this task in AN and found no difference to HC on saccade rate, gain, intersaccadic interval or peak velocity (Phillipou et al. 2016b).

Visual Scan Path Tasks

In everyday life, saccades do not occur in isolation but are preceded and followed by a period of fixation, resulting in a continuous sequence of saccade, fixation, saccade, fixation, etc. This sequence is typically referred to as a visual scan path and describes the gaze or pattern of eye movements used to view visual scenes and our surroundings. Visual scan paths are generally controlled by top-down processing – i.e., we make saccades towards locations that provide information for the task at hand. Bottom-up processing is, however, also involved and describes visual attention that is driven by salient stimuli. In terms of scan paths, there are a number of aspects that can be examined. The simplest is examining visual attention to specific elements of a visual scene, such as how long someone spends looking at a face within a scene or how many fixations are made to that face. The other aspect of visual scan paths that is investigated is the scanning behavior – e.g., whether they show a disorganized scan path or tend to hyper- or hypo-scan, reflecting lots of fixations with short duration or few fixations with long durations, respectively.

In terms of AN, several studies have examined scan path behaviors. Individuals currently with AN have been reported to show hyperscanning behaviors to both faces (Phillipou et al. 2015) and bodies (Phillipou et al. 2016a). Hyperscanning behaviors are closely linked with anxiety (Horley et al. 2003), with these results suggestive of anxiety toward social (i.e., faces) and disorder-relevant (i.e., bodies) stimuli. Further, the presence of hyperscanning provides additional support for the presence of saccadic inhibition deficits in people with AN, similarly to the findings in basic saccade and fixation tasks, and provides further evidence for the potential role of brain regions and neurotransmitter systems that underlie saccadic disinhibition in the development of AN (i.e., the superior colliculus and GABA). Research in scanning behaviors is, however, limited, with other studies reporting a lack of hyperscanning when looking at faces in a recovered AN group (Dinkler et al. 2019), as well as in a mixed ED group (Fujiwara et al. 2017). Current AN, weight-restored AN, and sisters of individuals with AN and HC were also found to not differ in scanning behaviors to disorder-irrelevant stimuli (i.e., landscapes and

geometric shapes) (Phillipou et al. 2016b), suggesting that if hyperscanning behaviors are present, they may be specific to stimuli relevant to AN pathology.

Eye movement tasks utilizing disorder-relevant stimuli have been of particular interest to identify differences in attentional biases in individuals with AN, such as areas of a stimulus that are given more or less visual attention, indexed by more frequent and/or longer fixations. Examining these types of attentional biases can provide important information about how visual information is processed in AN, which may contribute to their symptomatology. Of particular interest has been the investigation of where AN patients focus on when presented with stimuli of bodies. Individuals with AN tend to show longer fixation durations to areas of their own body that they perceive to be unattractive or they are dissatisfied with (Bauer et al. 2017a, b; Svaldi et al. 2016; Freeman et al. 1991; Von Wietersheim et al. 2012). When looking at other individuals' bodies, the findings are more mixed, and it is unclear where attentional biases may exist. In a study by Tuschen-Caffier et al. (2015), individuals with AN made more fixations with longer durations to areas of other peoples' bodies that they were more dissatisfied with in themselves and thought were more unattractive. When completing a task which required participants to estimate the body size of stimuli, individuals who were recovering or in recovery from AN showed more attention to the face and torso of stimuli, relative to HC (Cornelissen et al. 2016). In a different study where participants rated bodies on both body size and attractiveness, HC participants made fixations mostly to the stomach, whereas AN participants made more widespread fixations from the breast and collar bone down to the hips and groin (George et al. 2011). Individuals with AN have also been reported to make more fixations and have longer fixation times to thin bodies (Pinhas et al. 2014) but to not differ to HC in the amount of time fixating on overweight bodies (Hartmann et al. 2020). Other studies have, however, failed to find a difference in the number of or durations of fixations to different body areas when presented with different body weights, ranging from very thin to very heavy (Horndasch et al. 2012; Phillipou et al. 2016a). Interestingly, when body stimuli are presented with faces being visible, individuals weight-restored from AN have been reported to be less likely to look at faces, compared to HC (Watson et al. 2010). The same study also reported that when presented with just faces, wr-AN spent less time looking at the eyes than HC (Watson et al. 2010).

AN patients have also been shown to spend less time looking at faces while viewing a naturalistic scene than recovered AN and HC; when looking at faces specifically though, attention to different facial features did not differ between AN and HC in this study (Kerr-Gaffney et al. 2021). Kerr-Gaffney et al. (2020) also reported a lack of group difference between AN, recovered AN, and HC during a facial emotion recognition task in terms of the time spent looking at faces. Similarly, Phillipou et al. (2015) found no difference in the number of or duration of fixations to salient facial features (i.e., eyes, nose, and mouth), compared to HC during an emotion discrimination task. When looking at one's own face, however, the same study reported that HC made more fixations of longer duration to salient features of their own faces, whereas AN did not differ in the amount of attention shown to their own salient and non-salient features. This finding suggests that individuals with AN

may avoid fixating on salient features of their own face as they find looking at these important features of their face anxiety-provoking.

Individuals with AN are frequently reported to have high levels of social anxiety and difficulties with social situations (Kaye et al. 2004). A key aspect of social interactions in Western societies is the level of eye contact held with someone. An early study reported that adolescents with AN made less eye contact with a psychologist than HC, which the authors suggested may be related to social difficulties, depression, or anxiety in AN (Cipolli et al. 1989). In a more recent study, individuals with AN made fewer fixations and spent less time looking at the eyes of static and moving social stimuli and during a real-life social interaction than HC, whereas a recovered AN group demonstrated greater eye contact in the same paradigms than AN but less so than HC (Harrison et al. 2018).

Attentional Bias Tasks

While examining scan paths can tell us about differences in visual attention, other cognitive tasks can also employ eye movements to assess attentional biases. During a visual-probe or a "dot-probe" task, for example, while the participant is fixating on a central fixation cross, they are presented with two images simultaneously to the left and right and are required to make a saccade as quickly as possible to the target stimulus (e.g., circled in red). In these tasks, disorder-relevant (e.g., bodies, food) and disorder-irrelevant stimuli are often presented simultaneously, and examining saccadic latencies to targets can indicate attentional biases to disorder-relevant stimuli. When presented with images of their own body and another individuals' body, people with AN have been shown to have shorter latencies to images of themselves when it was the target than images of others, whereas HC showed similar latencies to self- and other target images (Blechert et al. 2010). This suggests that individuals with AN may have an attentional bias for images of their own bodies. Other studies have used similar paradigms where two stimuli are presented simultaneously, such as image pairs of people undertaking physical activity and people being physically inactive. While both AN and HC have been shown to orient their attention to physically active stimuli first, individuals with AN have been found to gaze longer at images containing physical activity (Giel et al. 2013). Individuals weight-restored from AN, however, have been reported to show less visual attention to images of physical activity than current AN and HC, which may indicate an avoidance of illness-related information during recovery (Giel et al. 2020). The same study also reported that individuals with a current diagnosis of AN spent less time looking at food stimuli than HC and the weight-restored group "fell in between," not significantly differing to either group. This finding of increased visual attention to stimuli of food in AN has been replicated several times (Werthmann et al. 2019; Giel et al. 2011). Increased visual attention has also been shown specifically to high- over low-calorie foods in AN, however, only when stimuli are presented on their own rather than simultaneously (Godier et al. 2016; Horndasch et al. 2020), suggesting

that there may be conflicting mechanisms of attention toward food depending on whether there is another stimulus competing for the viewer's attention.

Conclusions and Implications

Gaining a better understanding of how eye movements differ in individuals with AN has a number of significant implications. While the area of research is still very much in its infancy, the findings to date provide us with a better understanding of the cognitive and neurobiological differences which may underlie the disorder, which consequently provide potential targets for treatment. For example, attentional biases in terms of body regions that are focused excessively on by individuals with AN may be targeted with visual retraining or other cognitive-based therapies (Beilharz et al. 2018). Further, neurobiological deficits, including brain regions and neurotransmitter systems, implicated in AN through saccadic eye movement tasks could be targeted with brain stimulation and pharmacotherapy, respectively (Phillipou et al. 2019). In addition, the identification of a potential biomarker or endophenotype of AN (square wave jerks during fixation) is significant as this type of eye movement may provide an objective diagnostic tool, as well as a tool that could potentially be used for early identification and prevention of AN.

Applications to Other Eating Disorders

In this chapter, we reviewed the literature pertaining to eye movements in AN. The great majority of the eating disorder research in eye movements to date has focused on AN, with little research directed to the other eating disorders. The eye movement literature in AN is still very small but growing. It is still unclear whether many of the findings will replicate in future research and whether we will find similar or different results in other eating disorders. Undertaking similar paradigms in individuals with other eating disorders will be of great value to identify overlapping neurobiological and cognitive processes that may be similar across different eating disorders.

Mini-Dictionary of Terms

- **GABA**: Inhibitory neurotransmitter involved in anxiety and the initiation of saccades.
- **Gain:** The accuracy of a saccade onto a target, calculated by dividing the saccadic amplitude by the amplitude of the target.
- **Latency**: The time from stimulus onset to the initiation of a saccade.
- **Peak velocity**: The fastest point of a saccade, quoted in degrees per second.
- **Saccade:** Fast, jerky eye movement humans frequently use to observe their surroundings.
- **Scan path:** The sequence of saccades and fixations when viewing an image.

- **Square wave jerks:** Small, involuntary, and unconscious eye movement pairs that briefly take the eye away from and return it to fixation.
- **Superior colliculus:** AN area of the midbrain involved in saccade inhibition/disinhibition.

Key Facts of Eye Movements in AN

- Differences in eye movements are found in individuals with AN.
- Key differences include an increased rate of square wave jerks during fixation and increased inhibitory errors to 10° targets on the memory-guided saccade task.
- Eye movement differences in individuals with AN suggest saccadic inhibition deficits.
- Findings also implicate specific neurobiological differences in individuals with AN including brain regions such as the superior colliculus and neurotransmitter systems such as GABA.
- Individuals with AN also show attentional biases to disorder-relevant stimuli such as bodies and food.

Summary Points

- Saccadic eye movement deficits are present in individuals with AN.
- An increased rate of inhibitory errors on the memory-guided saccade task, and an increased rate of square waver jerks, is present in individuals with AN.
- The specific eye movement deficits suggest neurobiological dysfunction which may contribute to the illness.
- The rate of square wave jerks during fixation, together with anxiety, has been proposed as a promising biomarker to identify individuals with AN.
- Individuals with AN show attentional biases to disorder-relevant stimuli which may contribute to illness pathophysiology.

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Anorexia Nervosa: Reproduction and Consequences for Mother and Child

31

Ängla Mantel and Angelica Lindén Hirschberg

Contents

Introduction 605
Anorexia Nervosa and Fertility 605
Functional Hypothalamic Amenorrhea 605
Management and Treatment of Functional Hypothalamic Amenorrhea 607
Long-Term Effect on Fertility 608
The Prevalence of Anorexia Nervosa in Pregnancy 610
Disease Course in Pregnancy 611
Anorexia Nervosa and Pregnancy Complications 611
Anorexia Nervosa and Adverse Perinatal Outcomes 613
The Postpartum Period 614
Children to Mothers with Eating Disorders 615
Management of Pregnant Women with Anorexia Nervosa 615
Applications to Other Eating Disorders 617
Mini-Dictionary of Terms 618
Key Facts 618
Key Facts of Amenorrhea in Anorexia Nervosa 618
Key Facts of Pregnancy and Perinatal Outcomes in Women with Anorexia Nervosa 618
Key Facts of Management of Pregnant Women with Anorexia Nervosa 618
Summary Points 619
References 619

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Abstract

Anorexia nervosa (AN) mainly affects girls and women in adolescence and early adulthood, making it of particular importance to understand the impact of the disease on reproductive function, pregnancy, and postpartum period *and* how children to mothers with eating disorders are affected. Anorexia nervosa is associated with extensive endocrine abnormalities resulting in impaired fertility, which is commonly normalized with weight and nutritional restoration. Although rare, spontaneous pregnancy can occur among women with ongoing AN, and there are no major limitations for women recovered from AN to conceive. Nevertheless, pregnancy constitutes a vulnerable time period and may affect the disease course among women with ongoing disease and possess a relapse risk for women with previous disease. Consequently, it is important to identify women with ongoing or a history of AN in antenatal maternal health care in order to provide adequate support and management to prevent adverse outcomes. Maternal AN is associated with several adverse pregnancy-related outcomes, including anemia, hyperemesis gravidarum, antepartum hemorrhage and preterm delivery, and restricted fetal growth. The children to mothers with AN seem to suffer from an increased risk of developing specific conditions throughout childhood. This chapter reviews available evidence on the impact of maternal anorexia nervosa on fertility, pregnancy, and postpartum period and childhood health.

Keywords

Anorexia nervosa · Undernutrition · Reproduction · Pregnancy · Postpartum · Perinatal · Amenorrhea · Fertility · Functional hypothalamic amenorrhea · Neonatal · Child health · Anemia · Antepartum hemorrhage · Preterm delivery · Small for gestational age

Abbreviations

AN	Anorexia nervosa
BMD	Bone mineral density
CRH	Corticotropin-releasing hormone
CVD	Cardiovascular disease
DXA	Dual-energy X-ray absorptiometry
FHA	Functional hypothalamic amenorrhea
FSH	Follicle-stimulating hormone
GH	Growth hormone
GnRH	Gonadotropin-releasing hormone
hCG	Human chorionic gonadotropin
HG	Hyperemesis gravidarum
ID	Iron deficiency
IGF-1	Insulin-like growth factor 1
LDL	Low-density lipoprotein
LH	Luteinizing hormone

PPROM	Premature rupture of membrane
SGA	Small for gestational age
SHBG	Sex hormone-binding globulin
T3	Triiodothyronine
TSH	Thyroid-stimulating hormone

Introduction

Anorexia nervosa (AN) impacts multiple aspects of the reproductive health. The fertility is impaired among women with AN due to the extensive hormonal aberrations, induced by energy deficit. Pregnancy in women with ongoing AN is rare but can occur sporadically, and women with a history of AN have no major obstacles to conceive in general. Pregnant women with ongoing or previous AN suffer from an increased risk of multiple pregnancy complications and are likewise at an increased risk of impaired outcomes in the postpartum period. Early identification of women with AN in antenatal maternal health care is essential in order to provide adequate and intensified support throughout the pregnancy and postpartum period.

Anorexia Nervosa and Fertility

The reproductive health is compromised in women with AN, mainly as a consequence of functional hypothalamic amenorrhea (FHA). Depending on age at disease onset, AN is associated with either primary amenorrhea (defined as spontaneous menstruation that has never occurred) or secondary amenorrhea (absence of menstruation for at least three consecutive months after menarche). Sporadically, AN is associated with infrequent menstruation with increased menstrual intervals (>35 days) or five to nine periods within the last year (oligomenorrhea).

Functional Hypothalamic Amenorrhea

The specific pathophysiology of FHA is complex. In brief, energy deficit caused by starvation and weight loss, the hallmark of anorexia nervosa, induces an aberration in multiple hormone levels, including increased levels of corticotropin-releasing hormone (CRH), reduced levels of insulin and insulin-like growth factor 1 (IGF-1), and altered levels of appetite-regulating hormones such as leptin and ghrelin, leading to an impairment of the pulsatile release of gonadotropin-releasing hormone (GnRH) from the hypothalamus (Allaway et al. 2016). In turn, the altered GnRH pulsatility leads to disrupted secretion of the gonadotropins follicle-stimulating hormone (FSH) and luteinizing hormone (LH) resulting in reduced ovarian production of estradiol, progesterone, and testosterone and consequently amenorrhea and anovulation (Gordon 2010; Misra and Klibanski 2014). In addition to a suppressed hypothalamic-pituitary-ovarian axis, an overactive hypothalamic-pituitary-adrenal axis and an altered

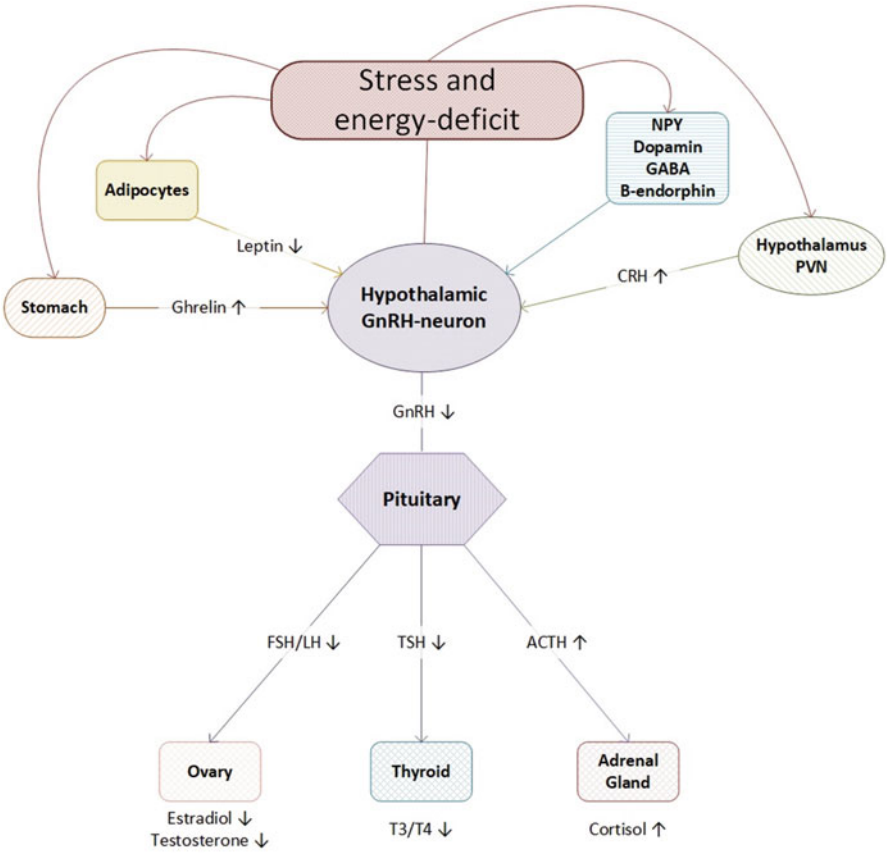


Fig. 1 Overview of hormonal changes in functional hypothalamic amenorrhea. In addition to a suppressed hypothalamic-pituitary-ovarian axis, functional hypothalamic amenorrhea is characterized by an overactive hypothalamic-pituitary-adrenal axis and an altered thyroid hormone regulation. ACTH, adrenocorticotropic hormone; CRH, corticotropin-releasing hormone; FSH, follicle-stimulating hormone; GABA, gamma-aminobutyric acid; GnRH, gonadotropin-releasing hormone; LH, luteinizing hormone; PVN, paraventricular nucleus; TSH, thyroid-stimulating hormone; T4, thyroxine; T3, triiodothyronine

regulation of thyroid hormones are commonly seen in patients with FHA (Misra and Klibanski 2014) (Fig. 1).

Besides impaired reproductive function, AN/FHA has a detrimental effect on bone health by interfering with the bone turnover. The multiple deranged hormonal axes have partially different effect on the complex osteoblast-osteoclast interaction depending on the patient's age. Estrogen is involved in the normal bone formation homeostasis by inhibiting osteoclastic bone resorption, and reduced levels of estrogen accordingly lead to an increased osteoclastic bone resorption (Almeida et al. 2017; Snow et al. 2000). However, estrogen deficiency alone does not explain the overall bone effect in anorectic patients, which is likely to be multifactorial and

involve multiple, presumably interlinked, mechanisms (Legroux and Cortet 2019). Hypercortisolism amplifies the osteoclast activity and bone resorption and additionally impairs the calcium absorption (Tauchmanova et al. 2007). Moreover, the reduced levels of the anabolic growth hormone (GH) and IGF-1 lead to decreased bone formation (Snow et al. 2000). As a consequence of the disrupted bone metabolism, the bone mineral density (BMD) is reduced and bone microarchitecture altered, resulting in an increased prevalence of osteoporosis and increased fracture risk among girls and women with AN (Faje et al. 2014; Legroux-Gerot et al. 2005). The increased risk of fractures in AN persist many years after diagnosis (Vestergaard et al. 2002) and is highest among girls and women with active disease.

Management and Treatment of Functional Hypothalamic Amenorrhea

Regardless of amenorrhea no longer being one of the diagnostic criteria of AN, it is a cardinal feature (Treasure et al. 2020). However, despite amenorrhea being an expected clinical finding among girls and women with AN, it should always be carefully evaluated in order to rule out alternative or concomitant conditions. Importantly, the prevalence of an AN diagnosis is not always known when assessing amenorrhea since some patients with AN may be reluctant to inform health-care professional about the disease, whereas other patients may be in denial of having an eating disorder (Schorr and Miller 2017). Hence, evaluation of amenorrhea should include a careful assessment of comorbidities, including eating disorders, and detailed laboratory assessment of hormone levels, liver function tests, complete blood count, electrolytes, and specific nutritional markers should be performed (Gordon et al. 2017). As expected, suppressed levels of LH, FSH, estradiol, testosterone, and T3 and increased levels of sex hormone-binding globulin (SHBG) are characteristic of FHA (Allaway et al. 2016; Gordon 2010) (Table 1). If nothing points toward alternative conditions requiring physical examination, gynecological

Table 1 Endocrine findings in functional hypothalamic amenorrhea

Hormone or binding protein	
FSH	↓
LH	↓↓
Estradiol	↓
Testosterone	↓
SHBG	↑
Prolactin	↓
TSH	↔
Free T4/T3	↓

FSH, follicle-stimulating hormone; LH, luteinizing hormone; SHBG, sex hormone-binding globulin; TSH, thyroid-stimulating hormone; T4, thyroxine; T3, triiodothyronine

↑ indicates increased levels, ↓ indicates decreased levels, and ↔ indicates no change in levels

examination is not indicated. In order to address the associated risk of bone loss, bone mass should be evaluated in adult patients, using dual-energy X-ray absorptiometry (DXA).

FHA is a functional condition without underlying organic pathology, and with weight and nutritional restoration, the menstrual function usually normalizes. Therefore, treatment of AN and restoring the energy balance should be prioritized. Not surprisingly, the prevalence of eating disorders among women receiving infertility treatment with GnRH pulsatility pharmacotherapy is high (Barbosa-Magalhaes et al. 2021). However, encouraging fertility treatment among women with active AN should be avoided, partially due to the increased risk of impaired pregnancy and neonatal outcomes (Gordon et al. 2017).

In long-term amenorrhea (>1 year), the effects of hypoestrogenism should be evaluated, primarily in relation to the risk of osteoporosis, but also regarding multiple other potential consequences of estrogen deficiency, including urogenital symptoms, adverse lipid profile, and endothelial dysfunction. Estrogen affects the endothelium, including the vascular endothelium, via several mechanisms, by promoting endothelial homeostasis and preventing atherosclerosis. Estrogen deficiency is associated with a deteriorated vascular function as well as a shift toward an atherogenic lipid profile (increased levels of low-density lipoproteins [LDL] and total cholesterol). Consequently, conditions associated with low levels of estrogens, e.g., premature menopause, have been associated with an increased risk of cardiovascular disease (CVD) (Wellons et al. 2012). However, except for a few number of case reports on coronary heart disease in women with AN, no association between AN and long-term risk of CVD has been reported (Birmingham et al. 2003). Weight restoration is central to increase the bone mass and should be prioritized (Legroux and Cortet 2019). Transdermal estrogen in combination with cyclic progesterone, shown to improve bone mass in girls with AN, could be used (Misra et al. 2011). Oral estrogen lowers the levels of IGF-1 and hence amplifies the negative effects on bone formation and should therefore be avoided (Snow et al. 2000). Likewise, the knowledge of the long-term efficacy of bisphosphonates among women with eating disorders of reproductive age is limited, wherefore their use is not recommended (Fig. 2).

Long-Term Effect on Fertility

As the menstrual function commonly normalizes with weight and nutritional restoration, the fertility naturally improves. Girls with FHA prior to, or in relation to, puberty might suffer from delayed menarche, disrupted puberty, and underdevelopment of sex characteristics. In adult women, long-lasting FHA might induce atrophic changes in urogenital mucosa and uterine muscle atrophy, which could reduce reproductive function (Meczekalski et al. 2014). One meta-analysis, investigating the reproduction after recovery from AN, that included five small studies, whereof three uncontrolled, concluded that the birth rate did not differ in women having recovered from AN compared with the general population and that long-term

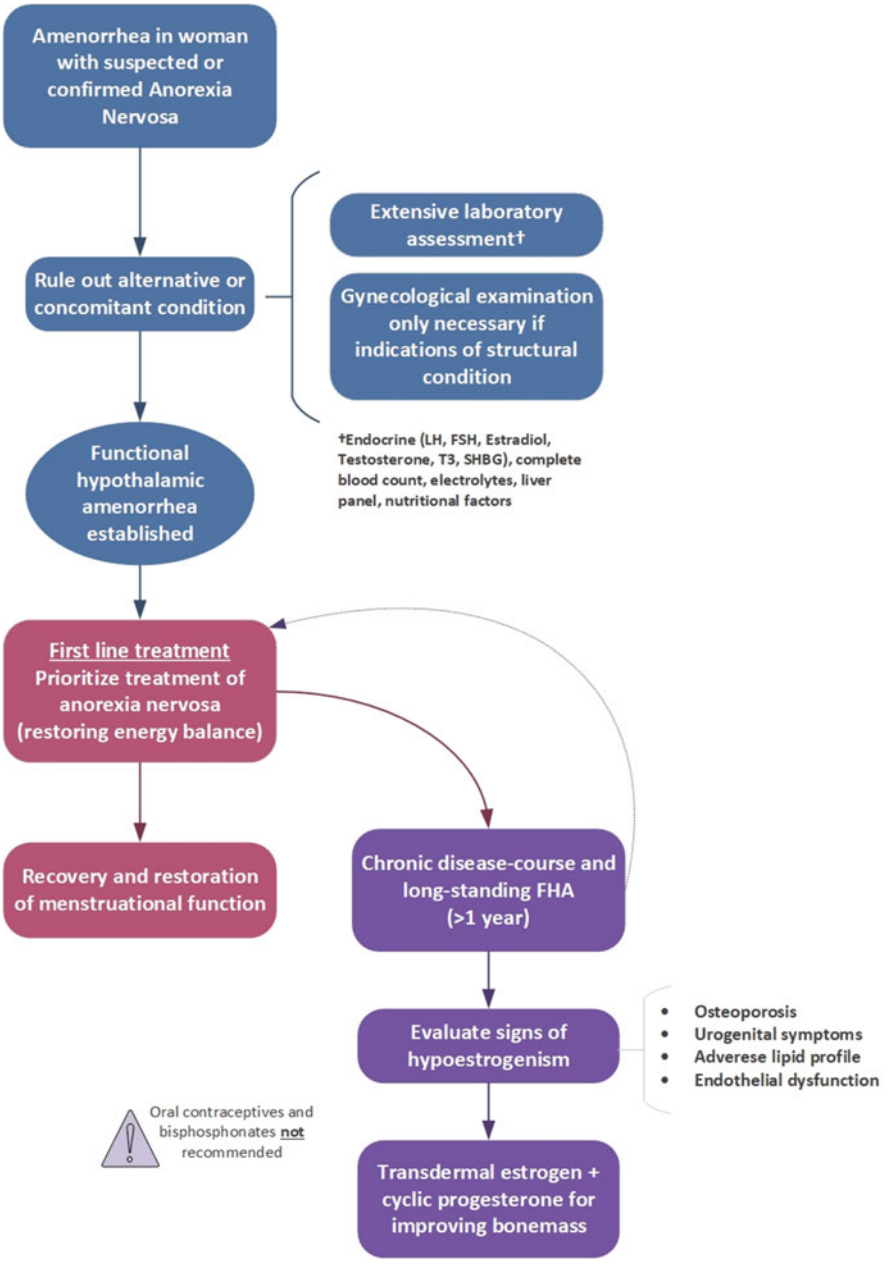


Fig. 2 Evaluation and management of functional hypothalamic amenorrhea in women with anorexia nervosa. FHA, functional hypothalamic amenorrhea; FSH, follicle-stimulating hormone; LH, luteinizing hormone; SHBG, sex hormone-binding globulin; TSH, thyroid-stimulating hormone; T3, triiodothyronine

fertility is unlikely to be affected (Chaer et al. 2020). Yet, other studies have found that adolescents with AN had a lower prevalence of medical abortions compared with adolescents with other eating disorders (Lindeman et al. 2021) and that women with a history of AN are more likely to see a fertility doctor, delayed first birth, and lower parity (Linna et al. 2013).

The Prevalence of Anorexia Nervosa in Pregnancy

The vast majority of individuals affected by AN are girls or women. The reported incidence of AN in women varies considerably depending on study setting and case definition. In a recent meta-analysis, the pooled incidence of AN among women was higher in outpatient care settings (8.8/100,000 person-years [95% CI 7.83–9.80]) compared with the pooled incidence of hospital admissions (5.0/100,000 person-years [95% CI 4.87–5.05]) (Martinez-Gonzalez et al. 2020).

Not surprisingly, the prevalence of AN is much lower among pregnant women than in the general female population. However, ovulation can occur in irregular menstrual cycle, and although rare, spontaneous pregnancy do occur in women with ongoing AN. In fact, AN has been associated with an increased frequency of unplanned pregnancies (Bulik et al. 2010), which could be a consequence of mistaken assumption of reduced reproductive function. Additionally, despite the potential effect of AN history on long-term fertility, naturally there are no major obstacles for women with previous AN to conceive.

In similarity with incidence and prevalence reports based on the general female population, there is extensive variability in the reported prevalence of AN among pregnant women, depending on the case definition. Based on studies on pregnancy-related outcomes in women with AN, where the exposure was self-reported using interviews or questionnaires, the prevalence of a self-reported history of AN was reported between 0.9 and 2.0% (Easter et al. 2014; Micali et al. 2016; Popovic et al. 2018). Studies using a similar case definition have reported a prevalence of ongoing AN between 0.1 and 0.3% (Bye et al. 2020; Micali et al. 2016; Popovic et al. 2018). In general, register-based studies identifying exposure (AN) using registered diagnoses have reported lower AN prevalence compared with self-reported exposure. Based on such studies, a prevalence of previous AN between 0.1 and 0.5% and a substantially lower prevalence of ongoing AN (<0.03%) have been reported (Ante et al. 2020; Eik-Nes et al. 2018; Mantel et al. 2020; Perrin et al. 2015).

Despite controversies regarding temporal changes in the AN incidence in the last decades, there are in fact several indices of an increasing incidence of AN (Martinez-Gonzalez et al. 2020). Whether this reflects an actual increase in disease incidence or rather altered diagnostic criteria, improved diagnostic awareness, and/or expansion of health-care resources to identify cases is not known. There are, up to date, no reports on the temporal variation of anorexia nervosa prevalence among pregnant women, but considering the point prevalence of AN being the highest in adolescence and early adulthood, it is likely to follow the trend of the general female population.

Disease Course in Pregnancy

The recovery from AN is gradual and the long-term disease course heterogeneous. Longitudinal studies suggest that the disease course is chronic for one of five women and that it takes no less than 20 years from disease onset to recover for 60% of all women with AN. Many women experience residual symptoms, and one of four women relapse into disease after treatment (Mitchell and Peterson 2020).

The pregnancy and postpartum period constitute a particularly vulnerable time period, characterized by physiological, psychological, and hormonal changes, which could affect the AN disease course. There seem to be large variations in the inter-individual response to pregnancy, which has been reported to have a protective as well as possessing a risk for relapse, among women with AN. An improvement of eating disorder symptoms, including decreased weight and shape concern, during pregnancy among women with ongoing or recent AN has been described in some studies (Blais et al. 2000; Crow et al. 2008; Micali et al. 2007). Psychological, social, and biological factors have been suggested to mediate the improvement of eating disorder symptoms during pregnancy among women with ongoing or recent AN. Psychologically, a sense of maternal responsibility of recovery and altered body perception have been reported by women with AN as factors influencing improvement during pregnancy. Improved and intensified support from partner and health-care services (Madsen et al. 2009) and placental-induced neuroendocrinal changes are other suggested potential explanations for symptom relief during pregnancy. Importantly, several other studies report an increased frequency of eating disorder symptoms and risk of relapse of AN during pregnancy, in particular among women with a history of AN (Easter et al. 2015; Koubaa et al. 2005; Makino et al. 2020; Micali et al. 2007).

Considering the complexity of the disease course, the frequently persisting symptoms over a long period of time, and the increased relapse risk among women with previous AN, it is important to acknowledge pregnant women with AN in their medical history (in addition to women with ongoing anorexia nervosa) when screening women for psychiatric comorbidities in antenatal maternal health care in order to provide adequate support and management throughout the pregnancy period (Fig. 3).

Anorexia Nervosa and Pregnancy Complications

Recently, several population-based studies have strengthened the evidence on impaired outcomes in women with AN, by adding information on the subject to the previously reported observations from clinical studies. In addition to being a frequent finding among girls and women with AN in general, anemia in pregnancy is a more common finding among pregnant women with ongoing or previous AN compared with pregnant women without eating disorders (Bansil et al. 2008; Koubaa et al. 2005; Linna et al. 2014; Mantel et al. 2020). The underlying pathophysiology of anemia in AN has mainly been attributed to morphological alterations of the bone

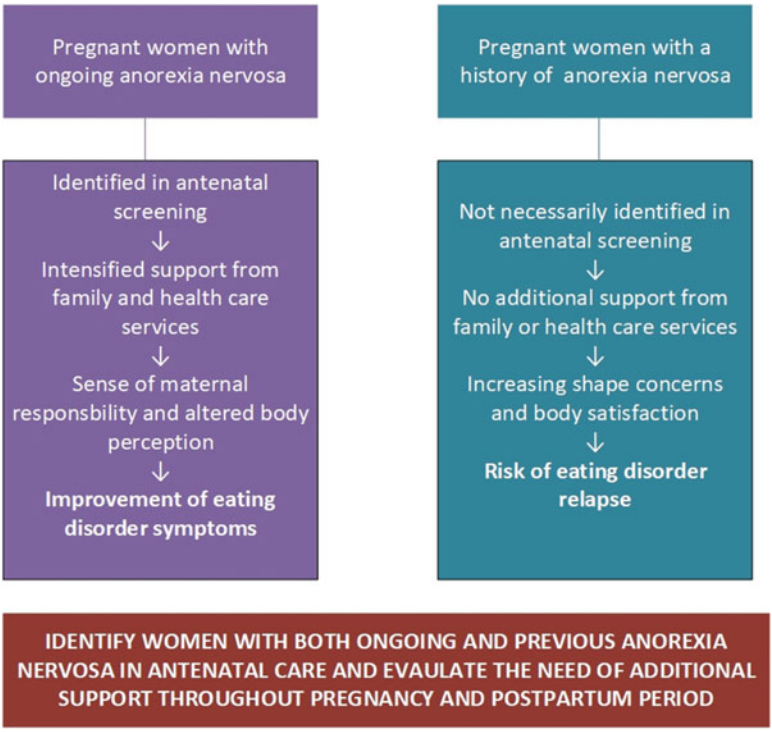


Fig. 3 Schematic flow chart of the pregnancy disease course of ongoing vs. previous anorexia nervosa. Highlighting the importance of recognizing women with both ongoing and previous anorexia nervosa in antenatal care in order to provide adequate support and measurements to improve eating disorder symptoms and decrease the relapse risk

marrow, and laboratory findings are various (Walsh et al. 2020). The most common type of anemia seen among pregnant women in general is iron deficiency (ID) anemia due to an increased iron demand necessary to support the fetoplacental development (Breymann 2015), and one study found lower levels of ferritin in pregnant women with AN (Koubaa et al. 2015). However, unpregnant women with AN commonly have normal iron status and often increased levels of ferritin (biomarker of iron storage), which could be a consequence of increased intake of iron supplements and decreased loss due to amenorrhea or stress-induced inflammation and liver damage (Hutter et al. 2009).

Women with AN are at an increased risk of developing hyperemesis gravidarum (HG), a severe form of nausea and vomiting in pregnancy resulting in dehydration, weight loss, and electrolyte disturbances, often requiring hospital admission (Austin et al. 2019). The etiology of HG is not completely understood but has, inter alia, been associated with low early pregnancy BMI and transient gestational thyrotoxicosis (Nurmi et al. 2020) which presumably could mediate the increased risk of HG among women with AN. The increasing levels of human chorionic gonadotropin

Table 2 Overview of adverse pregnancy and perinatal outcomes in women with anorexia nervosa

Pregnancy outcomes	Perinatal outcomes
Anemia ↑	Stillbirth ↑
Hyperemesis ↑	Preterm delivery ↑
Antepartum hemorrhage ↑	Small for gestational age ↑
Acute liver failure ↑	Microcephaly ↑
Gestational diabetes →	Low Apgar scores ↑
Infections and sepsis →	Admission to NICU ↑
Delivery mode →	Birth trauma →
	Congenital anomalies →

↑ indicates increased risk of outcome in women with anorexia nervosa (or their neonate), and → indicates no difference in outcome in women with anorexia nervosa compared to women without eating disorder

(hCG) in the first trimester stimulate the TSH receptor inducing increased levels of thyroxine and triiodothyronine resulting in transient biochemical hyperthyroidism, observed in approximately one of 10 pregnant women. Importantly, TSH and thyroxine values normalize in mid-pregnancy, and anti-thyroid pharmacotherapies are not warranted. HG is a clinical diagnosis and is managed by supportive care, including usage of antiemetic drugs and monitoring of fluid balance.

Moreover, AN is associated with an increased risk of antepartum hemorrhage (Ante et al. 2020; Mantel et al. 2020) and in particular an increased risk of abruptio placentae (Ante et al. 2020). The mechanism mediating this association is not known, but abruptio placentae is associated with low BMI and specific vitamin and mineral deficiencies, which might explain some of the association. Anorexia nervosa has also been associated with an increased risk of acute liver failure during pregnancy and admission to intensive care unit (ICU). Prolonged starvation in severe AN has been suggested as a potential explanation of the increased risk of acute liver failure (Ante et al. 2020). Most studies have not observed a difference in delivery mode in women with AN compared with women without eating disorders, and likewise, women with AN are not at an increased risk of postpartum hemorrhage (Table 2) (Ante et al. 2020; Mantel et al. 2020).

Anorexia Nervosa and Adverse Perinatal Outcomes

In addition to being associated with several adverse pregnancy outcomes, AN prior to or during pregnancy is also associated with an increased risk of multiple adverse perinatal outcomes. Pregnant women with AN are at an increased risk of delivering prematurely (before 37 gestational weeks) (Ante et al. 2020; Mantel et al. 2020), and this increased risk is similar for moderate preterm birth (between 32 and 37 gestational weeks) and very preterm birth (between 28 and 32 gestational weeks) (Mantel et al. 2020).

The etiology of the increased frequency of preterm births in AN has not been specified but is likely to be diverse since women with AN seem to be at an increased

risk of both premature rupture of membrane (pPROM) and precipitous labor (Ante et al. 2020). Furthermore, the risk of both spontaneous preterm delivery and medically induced preterm delivery is increased among women with AN. Multiple studies have consistently reported a negative impact of maternal AN on neonatal growth outcomes. AN has been associated with an increased risk of stillbirth (Ante et al. 2020) or delivering low birthweight (<2500 grams) (Ante et al. 2020) or small-for-gestational-age neonates (SGA, <2 SDS below median birthweight for gestational age) and neonates with microcephaly (head circumference < 2 SDS of median head circumference for gestational age) (Koubaa et al. 2005; Linna et al. 2014; Mantel et al. 2020; Micali et al. 2016; Watson et al. 2017). As a consequence, neonates to mothers with AN have a lower Apgar scores and are intubated and admitted to neonatal intensive care (NICU) more frequently than neonates to mothers without eating disorders (Ante et al. 2020; Mantel et al. 2020). The prevalence of birth trauma or congenital anomalies is not different in neonates to mothers with AN compared with neonates to healthy mothers (Ante et al. 2020). The risks of adverse neonatal outcomes have been reported to be higher among women with ongoing or recent AN during pregnancy compared with previous AN (Ante et al. 2020; Mantel et al. 2020). Importantly though, the risks of a majority of adverse neonatal outcome are still significantly increased among women with a history of AN.

The rationale for the association between maternal AN and increased risk of adverse neonatal outcomes is not known. Presumably, the key factors poor nutrition, low BMI, and stress can explain some of the association. In fact, one study found that low maternal pre-pregnancy BMI and weight gain mediated a majority of the association between maternal AN and low birthweight neonates (Watson et al. 2017), which is indicative of a nutritional impact. The level of cortisol is increased in women with AN, and increased levels of cortisol have been associated with preterm birth and with microcephaly in children to mothers with AN (Koubaa et al. 2015). Undernutrition and specific vitamin deficiencies are doubtlessly leading to fetal growth restriction due to compromised nutritional transfer to the fetus (Table 2).

The Postpartum Period

Depressive and anxiety symptoms are common among all women during the postpartum period, which in similarity with the pregnancy period is characterized by physiological and psychological changes. Women with AN report a higher frequency of depressive and anxiety symptoms during the postpartum period (as compared with women without a history of eating disorder), which is related to problems of maternal adjustment (Koubaa et al. 2008). An eating disorder history independently predicts the risk of postpartum depression (Johansen et al. 2020; Makino et al. 2020).

Moreover, women with AN have been reported to have a more rapid weight loss compared with healthy mothers within the first postpartum months, and, in contrast to the improvement of eating disorder symptoms during pregnancy, many women

with eating disorders experience eating disorder exacerbation during the postpartum period (Micali et al. 2007).

Several studies with inconsistent results have investigated breastfeeding pattern in women with eating disorder. One large population-based study reported no difference in initiating breastfeeding among women with AN compared with women without eating disorders, but earlier breastfeeding cessation (Micali et al. 2009). Insufficient milk production and concerns about the baby being hungry or not completely satisfied have been suggested to explain the difference in breastfeeding pattern among women with AN.

Children to Mothers with Eating Disorders

Understanding the risk of adverse outcomes in children to mothers with AN and to identify factors mediating these risks are of importance to provide sufficient resources and to identify potential key preventive interventions. There are indications of an increased risk of various adverse health outcomes among children to mothers with AN. A recent systematic review has compiled existing studies on maternal eating disorder and childhood development. Children to mothers with AN seem to have a higher degree of early developmental difficulties, including motor and cognitive development, compared with children to mothers without eating disorder. In contrast, studies on later cognitive development have indicated higher IQ and better working memory capacity in children to mothers with AN. Moreover, studies have shown that children to mothers with AN have an increased risk of emotional difficulties already visible at an early age (3.5 years). Likewise, maternal AN predicts emotional and anxiety disorders in children between 7 and 13 years of age (Martini et al. 2020). A recent large population-based cohort study reported that maternal AN was associated with an increased risk of offspring neuropsychiatric diseases, which could not be explained by coexisting parental comorbidities (Mantel et al. 2022). The mechanism behind the impact of maternal AN on childhood development has been suggested to consist of a complex interplay between genetic and environmental factors.

One study has investigated the impact of maternal AN on childhood respiratory morbidity and found that maternal AN is associated with an increased risk of early childhood wheezing (Popovic et al. 2018).

Additional studies on long-term consequences on childhood health are lacking but warranted.

Management of Pregnant Women with Anorexia Nervosa

Given the complex interplay between AN and reproductive function, the influence of pregnancy on AN disease course, and vice versa the impact of AN on adverse pregnancy and perinatal outcomes, early identification of eating disorders in fertility planning and antenatal maternal health care is fundamental.

Among women with infertility planning to conceive with prevalent eating disorder, focusing on treatment of the eating disorder is essential due to the associated risks in pregnancy. Advice and education on the importance of an adequate weight and nutritional intake and well-being prior to attempting to conceive are recommended to increase the likelihood of conception and promote a healthy pregnancy (NICE 2020).

In many countries, a routine inquiry of ongoing and previous mental illness, including eating disorder, is recommended for all women enrolling in antenatal maternity health care. It is important to acknowledge that women with eating disorder may be reluctant to share their ongoing or previous eating disorder to health professionals. The stigma surrounding eating disorders and feelings of shame are patient-related factors known to impede health-seeking for eating disorders in general (Ali et al. 2017). Additionally, among health professionals in maternal health care, lacking of confidence, due to insufficient professional training, has been reported to hamper the identification of pregnant women with eating disorders (Bye et al. 2018). Keeping the many barriers for acknowledging pregnant women with eating disorders in mind, a focus on a non-judgmental and delicate inquiry when screening for eating disorders is important (Bye et al. 2018).

Women, who disclose an ongoing or previous eating disorder, should be regarded as a risk population during pregnancy and postpartum period and be offered intensified support throughout the pregnancy. An early pregnancy appointment with an obstetrician for assessment of the patient's physical and mental health is recommended. Depending on whether the eating disorder is ongoing or past, the co-occurrence of other psychiatric diseases, the severity of the disease, and the patient's individual need and wish, a tailored follow-up scheme should be developed. A low threshold for referral to specialized eating disorder unit (or perinatal specialist mental health service if not available) is preferable during the pregnancy and postnatal period. Referral to a curator or psychologist, specialized in management of eating disorders, is another alternative. In order to provide information on the importance of adequate nutrition and nutritional support, and pregnancy-adjusted exercise during pregnancy, referral to nutritionist and physiotherapist should also be considered. Intensified frequency of antenatal visits to midwife with a focus on continuity of care in order to facilitate identification of altered patient well-being throughout pregnancy is preferable. In agreement with the patient, frequent weight measurements are recommended in conjunction with the antenatal visits. Underweight patients (BMI <18.5) and patients with insufficient weight gain or patients with weight and shape change preoccupation are alarming signs of relapsing or uncontrolled disease and hence reasons for concern. Due to the association between AN and low fetal gestational weight, extra fetal growth scan is indicated, in particular among women with poor gestational weight gain (Fig. 4). Clearly, women with severe eating disorder presentation during pregnancy should be managed by a multidisciplinary team involving specialized obstetric, internal medicine, and psychiatric care.

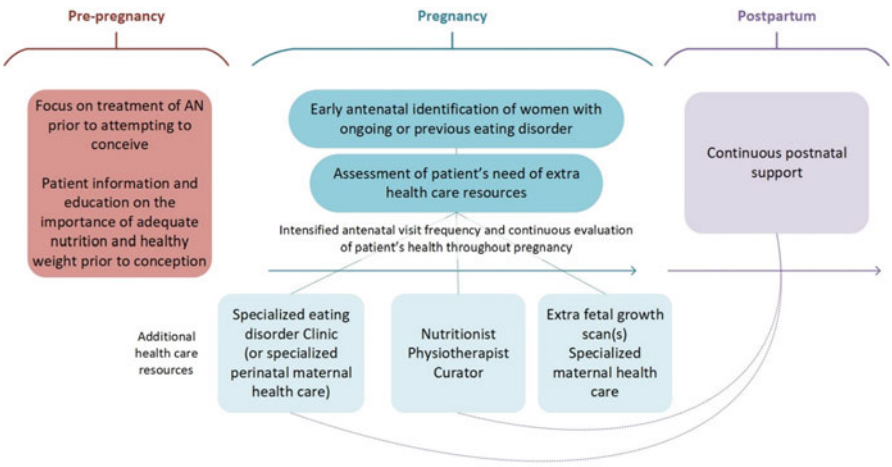


Fig. 4 Overview of clinical management of women with anorexia nervosa prior to pregnancy and during the pregnancy and postpartum period. AN, anorexia nervosa

In light of the increased risk of deteriorated eating disorder symptoms, disease relapse, depression, and anxiety and attachment difficulties postnatally, the intensified support should continue for up to 1 year postpartum (NICE 2020).

Applications to Other Eating Disorders

In this chapter, we have reviewed the impact of anorexia nervosa (AN) on fertility, pregnancy, postpartum period, as well as neonatal and child health. There is a separate chapter reviewing the impact of bulimia nervosa (BN) on fertility, pregnancy, postpartum period, and child health. In brief, the prevalence of amenorrhea and infertility among women with BN is higher compared with the general population but lower compared with women with AN. Periods of starvation in BN could induce functional hypothalamic amenorrhea by similar mechanism as among women with AN, but BN is additionally associated with polycystic ovary syndrome, which similarly is characterized by oligomenorrhea/amenorrhea and infertility. Women with BN are at an increased risk of several adverse pregnancy and perinatal outcomes but in general not to the same extent as women with AN. Moreover, there is evidence of separate distinct neurocognitive phenotypes in AN vs. BN, which is likely to partly explain some of the differences in childhood developmental outcomes. Hence, the information within this chapter can only partly be transferable to women with BN. Moreover, a majority of studies have focused on women with specific eating disorders such AN or BN, wherefore it is difficult to extrapolate results to women with unspecified eating disorders. There are, however, indications of similar rates of adverse pregnancy and perinatal outcomes among women with unspecified eating disorder as women with AN.

Mini-Dictionary of Terms

- **Apgar score** is a structured evaluation of the health of the newborn according to five criteria (tone, pulse, grimace, appearance, and respiration) at 1, 5, and 10 min after birth.

Key Facts

Key Facts of Amenorrhea in Anorexia Nervosa

- Amenorrhea is a cardinal feature in women with anorexia nervosa and is commonlycaused by functional hypothalamic amenorrhea (FHA).
- In FHA, stress and energy deficit induces an aberration in the hormonal regulation of the menstrual cycle, by interfering with the release of regulating hormones from the hypothalamus and pituitary, leading to amenorrhea and consequently infertility.
- First-line treatment of FHA consists of treating underlying eating disorder and restoring the energy balance, which normalized the menstruation and restores fertility.

Key Facts of Pregnancy and Perinatal Outcomes in Women with Anorexia Nervosa

- Women with anorexia nervosa might experience improved or deteriorated eating disorder symptoms throughout pregnancy.
- Anemia, hyperemesis, and antepartum hemorrhage are more common among pregnant women with anorexia nervosa compared with healthy pregnant women.
- Pregnant women with anorexia nervosa are at an increased risk of preterm delivery.
- Neonates born to mothers with anorexia nervosa have lower Apgar score and lower birthweight and more often require intubation and admission to neonatal intensive care units.

Key Facts of Management of Pregnant Women with Anorexia Nervosa

- Among pregnant women, the prevalence of ongoing, recent, or previous anorexia nervosa should be identified and acknowledged early in antenatal screening.
- Given the association between anorexia nervosa and increased risk of adverse pregnancy, neonatal, postpartum, and child outcomes, pregnant women with anorexia nervosa should be considered a high-risk population.

- Individually tailored follow-up schemes for pregnant women with ongoing or previous anorexia nervosa are recommended and may include psychologist or psychiatrist contact, nutritional support, and intensified antenatal visit frequency follow-up, including extra growth ultrasound in the third trimester and earlier postpartum follow-up.

Summary Points

- Amenorrhea is a cardinal feature of anorexia nervosa (AN) and commonly attributed to functional hypothalamic amenorrhea (FHA).
- FHA is diagnosed by careful endocrine evaluation in order to rule out other causes of menstrual dysfunction.
- First-line treatment of FHA consists of restoring energy balance, leading to normalized menstruation and fertility.
- Some women with AN experience improvement of eating disorder symptoms during pregnancy, whereas others experience deterioration of eating disorder symptoms throughout the pregnancy.
- Pregnant women with anorexia nervosa are at an increased risk of several pregnancy complications, including anemia, hyperemesis, antepartum hemorrhage, and acute liver failure.
- Maternal anorexia nervosa is associated with adverse perinatal outcomes, including preterm delivery, delivering small-for-gestational-age or low birthweight neonate.
- Neonates born to mothers with anorexia nervosa have lower Apgar scores at birth and are at an increased risk of being intubated or admitted to neonatal intensive care units.
- Depressive and anxiety symptoms are more common among women with anorexia nervosa in the postpartum period.
- Feeding difficulties are more common in children to mothers with anorexia nervosa, and they have lower weight-for-length growth during the first year of life.
- Children to mothers with anorexia nervosa are at an increased risk of impaired neuropsychiatric and cognitive development and more likely to seek health care for childhood wheezing.
- Pregnant women with recent or previous anorexia nervosa should be recognized as a high-risk population in antenatal screening and offered intensified support and extra health-care resources throughout pregnancy and postpartum period.

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Anorexia Nervosa in the Acute Hospitalization Setting

32

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Contents

Introduction 624
Hospitalization Criteria 625
Integrated Treatment 626
Nutritional Rehabilitation 627
Refeeding Process 628
  Caloric Prescription 629
  Nutrient Quality and Nutrient Supplementation 629
  Nasogastric Feeding and Parenteral Nutrition 630
Psychological Treatment 630
Psychopharmacological Treatment 631
Behavioral Management 631
Motivation to Treatment 632
Treatment Outcomes 632
  Renutrition 632
  Psychopathology 633
  Quality of Life 634
  Rehospitalization 634
Discharge and Follow-up 635
Applications to Other Eating Disorders 635
Mini Dictionary of Terms 636
Summary Points 636
References 636

Abstract

Inpatient treatment for Anorexia Nervosa (AN) is the most intensive level of care, often aimed at emergency renutrition. As per international guidelines, vital signs alterations, psychiatric symptoms, Body Mass Index (BMI) thresholds

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(extreme when <15 kg/m^2), and severe rate of weight loss (>1 kg/week) should all be used as indicators of severity when considering hospitalization. Hospital care must be multidisciplinary and integrated, and caregivers should be involved in the treatment decision whenever possible. Weight gain (0.5–1.4 kg/week) aiming at weight restoration is the main goal of nutritional rehabilitation and is achieved mainly through oral diet, nutritional supplements, and tube feeding, alone or combined. Caloric prescriptions (starting from 5–20 kcal/kg and increasing every 2–4 days) must be balanced to avoid both refeeding and underfeeding syndromes. Psychological treatments during hospitalization are useful in sustaining weight recovery, and clinicians should value therapeutic alliance and interventions fostering patient motivation. The use of psychoactive drugs can be useful in treating psychiatric comorbidities, however not in pursuing weight gain. Clinicians should be aware that rehospitalization is common, mostly due to symptoms' persistence after discharge. On this line, inpatient and outpatient services should collaborate to promote continuity of care.

Keywords

Inpatient · Refeeding · Oral supplements · Psychopathology · Weight gain · Comorbidity · Tube feeding · Renutrition · Eating disorders · Bulimia nervosa · Other specified feeding and eating disorders

Introduction

Although outpatient care is recommended for most patients with EDs, individuals with anorexia nervosa (AN) can require hospital treatment during the course of the illness due to the sometimes rapid worsening of their medical and psychopathological conditions. Quite often, acute hospitalization is needed for reverting severe weight loss and accompanying complications that are no more manageable in the outpatient setting, since renutrition requires specialized care when malnutrition is established. On this line, current evidence agrees on the centrality of weight gain in allowing good treatment outcomes, and in recent years several authors have argued that clinicians should not be overcautious in caloric prescription when closely monitoring the clinical conditions of malnourished patients. It should be borne in mind that patient's motivation to treatment is key to obtaining and maintaining clinical results, and psychological interventions provided in the inpatient setting should foster the patient's will to change.

The present chapter moves from presenting the conditions requiring hospital admission, to describing current refeeding practices and the other components of the integrated treatment provided in inpatient units. Inpatient treatment outcomes are then discussed as well as the factors both related to the patient and to the service organization that are currently recognized as pivotal in enabling longer-term recovery beyond medical stabilization.

Hospitalization Criteria

Inpatient treatment is the most intensive level of care and is usually reserved for those patients who are medically unstable or who fail to benefit from outpatient care (National Institute for Health and Care Excellence (NICE) 2017). International guidelines (listed in Table 1) depict the situations in which hospitalization is most appropriate; however, no stringent criteria are available and clinical expertise is often of great use. Table 2 presents a summary of clinical severity signs and criteria for hospitalization. The decision is also influenced by contingent factors such as the type of treatment facilities available in the region (Royal College of Psychiatrists 2014).

Hospital admission becomes necessary when there are vital signs alterations that can become life-threatening (such as bradycardia below 40 bpm, severe hypotension, hypothermia). Even though body mass index (BMI) <15 kg/m^2 in adults and $<70\%$ mBMI (median BMI) in children and adolescents are used to define the extreme level of malnourishment (American Psychiatric Association 2013), BMI alone should not be used as an indicator of severity in deciding for the hospital admission. For instance, a rate of weight loss exceeding 1 kg/week may warrant hospitalization even at non-extreme BMI, while some patients with a severe enduring course of illness can be safely managed at the outpatient level even at very low BMI (Robinson and Jones 2018). The clinician evaluating the patient's risk and need for hospitalization should carefully assess psychiatric symptoms, both about eating pathology (e.g., frequency of binge purging behaviors, time spent doing compulsive exercise) as well as to non-eating psychopathology (e.g., acute suicidality, self-harm ideation). Resort to compulsory admission for patients with AN is debated in the literature (Elzakkers et al. 2014) and differently regulated based on country legislation; however, involuntary hospitalization needs to be considered when patients with AN refuse treatment while being in life-threatening conditions that can only be managed in the inpatient setting (Atti et al. 2021).

Besides emergency medical and psychiatric care, inpatient treatment in the specialized eating disorders units provide a structured environment that can foster treatment adherence when it becomes difficult for the patient to follow treatment plan at the outpatient level. As stated by NICE guidelines, following admission, inpatient and outpatient services should collaborate in the care management. Whenever possible,

Table 1 Main guidelines with recommendations regarding inpatient treatment for AN

Guideline	Year of publication
National Institute for Health and Clinical Excellence (NICE)	2017
MARSIPAN: Management of Really Sick Patients with Anorexia Nervosa	2014
Royal Australian and New Zealand College of Psychiatrists clinical practice (RANZCP) guidelines for the treatment of eating disorders 2014	2014
Junior MARSIPAN: Management of Really Sick Patients under 18 with Anorexia Nervosa	2012
American Psychiatric Association (APA)	2006

Table 2 AN risk assessment and signs warranting inpatient treatment

Area of assessment	Indices of severity	Comment
BMI (kg/m^2)	Medium risk 13–15 High risk <13	Do not use only BMI thresholds but consider also if the rate of weight loss can be safely managed in a day patient service
Weight loss	Rate of weight loss of more than 1 kg a week	
Blood tests	Hypokalemia: high risk <3.0 mmol/l	Consider vomiting or laxative abuse, especially in case of hypochloremic metabolic alkalosis or metabolic acidosis
	Hyponatremia: high risk <130 mmol/l	Can be due to severe malnutrition, water loading, diuretics abuse, inappropriate antidiuretic hormone secretion associated to occult infection
	Hypoglycemia: blood glucose <3 mmol/l	Especially severe if symptomatic. With low albumin or raised C-reactive protein can be associated with occult infection
	Raised creatinine or urea	Impairment in glomerular filtration rate increases the risks of refeeding syndrome. Reduced protein intake and low muscle mass can however hinder detection of this alterations
	Raised transaminases	Common in severe AN, probably due to hepatocellular autophagy
ECG	Bradycardia Prolonged QTc interval (>450 ms) Hypokalemia-induced alterations T-wave changes	Can lead to atrial and ventricular arrythmias
Physical examination	Low pulse (< 40 beats per minute) Blood pressure < 90/60 mmHg Low body temperature (<35°C) Reduced muscle strength	Due to autonomic nervous systems alteration Severe if associated with postural symptoms
Mental state examination	Suicide ideation Serious comorbid psychiatric illness	In case of acute mental health risk, consider psychiatric crisis or psychiatric inpatient care

Freely modified from NICE and MARSIPAN guidelines

carers should be included in the decision process and kept informed on the treatment plan (National Institute for Health and Care Excellence (NICE) 2017).

Integrated Treatment

It is well established that the treatment of AN requires a multidisciplinary team in which specific professional figures collaborate on the different aspects of the pathology while keeping in sight the individuality of each patient. Even though

the team's composition can differ between centers, specialized eating disorders units generally comprise psychiatrists, dieticians, nurses, clinical psychologists, and internal medicine physicians among others (Braude et al. 2020). It is advised that local protocols are developed and that the professionals meet regularly to discuss advances in the treatment plan and recalibrate the care provided according to the patient's need (Hay et al. 2014). Furthermore, the care of patients with AN is often emotionally demanding and team meetings and supervision are important moments to share difficulties and shortcomings in the therapeutic relationships with patients.

Tenets of inpatient treatment are nutritional rehabilitation and medical management, as well as the delivery of psychological interventions (Cuerda et al. 2019). Psychotropic drugs are often used to treat psychiatric comorbidities. The main aims of the treatment usually are to ameliorate clinical life-threatening conditions, restore weight, foster patient's motivation to engage in subsequent treatment steps, work with the patient to understand and modify their altered cognitions, and the factors that maintain the disorder and lead to its exacerbation (Marzola et al. 2021b). The treating team should be prepared to manage the commonly encountered behavioral problems that can hinder treatment during the inpatient stay.

Nutritional Rehabilitation

The core component of the treatment of inpatients with AN is refeeding with the goal of weight restoration. Weight gain during hospitalization is of pivotal importance for AN recovery and is associated with positive post-discharge outcomes (Baran et al. 1995; Lock and Litt 2003; Lund et al. 2009).

Notwithstanding the centrality of renutrition, current refeeding practices are still based mainly on clinical expertise rather than on randomized control trials (Hale and Logomarsino 2019; Chatelet et al. 2020), resulting in variability among treatment protocols. An important factor in this variability is the need for obtaining an adequate rate of weight gain while at the same time avoiding the refeeding syndrome (RS), which could entail severe and potentially fatal medical complications (Garber et al. 2016). On the other side, the so-called "underfeeding syndrome" (Royal College of Psychiatrists 2014), which coincides with sub-optimal weight gain during hospitalization is also growing in consideration (Cuntz et al. 2021). Table 3 displays the main clinical findings in RS and the measure to put in place to prevent its development. More detailed recommendations on RS prevention and treatment can be found in the recently published consensus paper by the American Society for Parenteral and Enteral Nutrition (da Silva et al. 2020).

According to guidelines, a rate of weight gain of 0.5–1.4 kg/week is considered appropriate in balancing clinical benefits against the risk of RS in hospitalized patients (Yager et al. 2010; Bargiacchi et al. 2019). Regarding caloric prescription, it is currently debated in the literature whether more aggressive procedures ("start higher, advance faster") should be preferred over cautious approaches ("start low and go slow") (Cuerda et al. 2019). Generally, slower rates of refeeding are favored for severely malnourished patients with extreme BMI, even though some groups

Table 3 Characteristics of refeeding syndrome

Biochemical characteristics	Potential clinical consequences	How to prevent it
Hypophosphatemia Hypomagnesemia Hypokalemia Glucose intolerance Sodium retention/fluid overload Thiamine deficiency Hematologic signs: hemolysis, anemia, thrombocytopenia, leukocyte dysfunction, uremia	**Cardiac**: arrhythmias, contraction changes, congestive heart failure **Neurological**: delirium, ataxia, seizures, paresthesias, skeletal-muscle weakness, Wernicke's encephalopathy, coma **Pulmonary**: dyspnea, respiratory failure, pulmonary edema **Gastrointestinal**: Nausea, vomiting, diarrhea or constipation **Others**: Peripheral edema, hypotension, shock, metabolic acidosis	Determine levels of phosphorus, magnesium, potassium, and calcium before initiation of renutrition, every day for the rest of the week and every other day in subsequent weeks Replete low electrolytes (P, K, Mg) Supplement thiamine Gradually increase calories every 1–2 days. In patient at high risk for RS and low levels of electrolyte, consider holding increase of calories until electrolytes are supplemented Monitor ECG and vital signs

advocate for a faster rate of refeeding under close medical surveillance, adequate supplementation, and rapid treatment of complications even for these patients (Cuntz et al. 2021). A recent systematic review (Garber et al. 2016) reached the following evidence-based conclusions on refeeding practices:

- Lower-calorie refeeding is too conservative for mild and moderately malnourished patients (i.e., respectively with 80–90% and 70–79% mBMI according to CDC data).
- Higher calorie refeeding is not associated with increased risk for refeeding syndrome under close medical monitoring with electrolyte correction.
- There is insufficient evidence to change the current standard of care for refeeding in severely malnourished inpatients (i.e., BMI <15 in adults or mBMI <70% in adolescents).
- Total parenteral nutrition is not recommended unless no other form of refeeding is possible.
- Meals and liquid formulas with nutrient compositions within recommended ranges are appropriate for refeeding.
- The impact of approaches to refeeding on long-term outcomes is unknown.

Refeeding Process

Oral diet is the first option for refeeding. Even though some authors advocate for standardization over personalization of caloric prescription (Haynos et al. 2016), in most cases is advisable for each patient to receive a personalized dietary plan which

should take into account the patient's nutritional requirements and be structured following a healthy diet model (Cuerda et al. 2019).

Caloric Prescription

As mentioned above, starting caloric prescription varies among centers and countries (e.g., varying from 1200 kcal/day in the United States to as low as 200 kcal/day in some centers in Europe) (Garber et al. 2016). NICE and MARSIPAN guidelines suggest a range between 5 and 20 kcal/kg at the beginning of treatment. Despite differences in starting prescriptions, the caloric intake needs to be increased gradually over time to sustain weight gain. Indeed, it should be considered that individuals with AN appear to be in a hypermetabolic state during renutrition (Marzola et al. 2013), and require a higher amount of calories compared to healthy individuals to gain 1 kg/week in the refeeding process (Mehler et al. 2010; Gentile 2012). Furthermore, some authors suggested in the past that patients with restricting AN need more calories than patients with binge-purging AN (Kaye et al. 1986). Rather obviously, the number of excess calories needed for weight gain can greatly vary based on the amount of physical exercise that the patient engages in. During refeeding, weight should be monitored with appropriate frequency (e.g., weekly) since daily fluctuations are not necessarily representative of weight gain over time. Table 4 presents theoretical values needed for weight maintenance and weight gain in a 30 kg woman.

Nutrient Quality and Nutrient Supplementation

Little is still known regarding whether specific food products are to be preferred in replenishing essential nutrients (Marzola et al. 2013), and there is no evidence in the literature indicating specific diet type requirement (e.g., diet enriched in polyunsaturated fatty acids or deprived in sodium) (Cuerda et al. 2019).

Oral nutritional supplements (medical foods) are usually introduced when the patient cannot eat enough food to meet caloric prescription but can also be utilized to provide an adequate amount of vitamins and minerals (Marzola et al. 2013). Moreover, since gastric emptying of solid but not of liquid content tends to be delayed in AN (Zipfel et al. 2006), liquid meals can result in more tolerability to patients with AN. On the same line, energy-dense supplements can potentially entail less abdominal bloating compared to regular food, which is relevant since patients with AN often report unpleasant gastroenteric sensations as limiting factors in feeding

Table 4 Example of theorical formula for caloric prescription in a 30 kg woman

Calories needed for weight maintenance	Calories needed for weight gain	
900 kcal/day[a]	+ 500 kcal/day	+ 200–400 kcal/day every 2–4 days

[a] International guidelines suggest starting caloric prescription around 5–20 kcal/kg a day in case of malnourishment

(Kessler et al. 2020). Interestingly, in a study comparing the administration of the same volume of liquid nutritional supplements and fruit juice, patients with AN reported comparable hedonic evaluation for the two conditions, suggesting that liquid supplements could be useful in providing significant energy intake with reduced volumes of food (Marzola et al. 2020a).

Nasogastric Feeding and Parenteral Nutrition

For severely malnourished patients who refuse to eat, a nasogastric tube can be adopted to administer specific formulas. An infusion pump helps in formula delivery allowing for a progressive increase in the rate of administration and avoiding manipulation from the patient. Some authors note that, even if historically the precocious use of tube feeding in the nutritional treatment of AN has been associated with an increased sense of lack of personal control (Hebert and Weingarten 1991; Rizzo et al. 2019), there are studies that show that this treatment modality can be accepted and even recognized as helpful by patients (Halse et al. 2005). A recent systematic review on the subject (Rizzo et al. 2019) analyzed ten studies on nasogastric nutrition in AN and found that this treatment was well tolerated and produced an average weight gain exceeding 1 kg/week without an increase in adverse effects in comparison to enteral nutrition.

Other modalities of renutrition, like parenteral nutrition and percutaneous endoscopic gastrostomy, are used much less frequently (Cuerda et al. 2019), requiring even more specialized care than the other modalities and, for parenteral nutrition, being associated with potentially more severe complications than oral and tube feeding.

Psychological Treatment

Different psychological therapies that were originally developed for the outpatient setting have been adapted to the hospital context (Hay 2020). For children and adolescents, family-based treatment remains the gold standard also when patients are hospitalized (Halvorsen and Rø 2019). For adults, Cognitive Behavioral Therapy is the most recent iteration for EDs, Enhanced Cognitive Behavioral Therapy is currently used in the inpatient setting with good outcomes (Dalle Grave et al. 2016). Other types of manualized psychotherapies are heterogeneously applied in different centers. All these treatments, however, share the psychoeducation and support to the nutritional rehabilitation provided in the inpatient setting.

Different novel treatments are currently under study. For instance, initial studies evaluated interventions focused on emotional difficulties with promising results (Money et al. 2011; Preis et al. 2020). Cognitive remediation therapy (CRT) aims to improve cognitive flexibility and can be seen as a form of treatment that enables further psychological work (Harrison et al. 2018). Studies on inpatients have been

conducted; however, the results appear to be inconsistent (Zuchova et al. 2013; Giombini et al. 2021).

Psychopharmacological Treatment

No medication is approved for AN treatment. Psychopharmacological agents are generally regarded as useful in the treatment of psychiatric comorbidities of AN (preferably after weight restoration); however, clinicians also often use them "off-label" to target symptoms of depression, anxiety, or hyperactivity in the course of weight restoration. There are very few studies conducted on the subject, and the evidence is still mixed. For instance, a 2015 study on the combined use of atypical antipsychotic agents and antidepressants in inpatients with AN found encouraging results regarding the use of aripiprazole in the reduction of eating-related preoccupations and rituals (Marzola et al. 2015). However, a recent metanalysis with a total sample of 99 patients with AN who received pharmacological treatment concluded that there is currently no evidence to support its use neither to treat AN-specific psychopathology nor to pursue weight gain (Cassioli et al. 2020). Furthermore, the scarcity of pharmacological trials in AN should warrant caution when prescribing psychopharmacological agents to severely emaciated inpatients. For instance, a Japanese case report described the onset of extreme hypoglycemia in a woman with AN short after the beginning of the treatment with olanzapine (Haruta et al. 2014).

Behavioral Management

AN being an ego-syntonic disorder, even when hospitalization is accepted by the patient, often treatment sabotaging and behavioral problems occur requiring careful monitoring and management by the hospital team. MARSIPAN guidelines describe the commonly encountered problems in a ward dedicated to AN, which include, but are not limited to, drinking water to falsify weight measurement, emptying nasogastric feed container and hiding food, vomiting in the toilet, wearing little clothing to induce shivering, engaging in excessive walking, or even trying to escape from the ward. As in other psychiatric disorders, also a more common way of self-harm should be assessed, and measures should be put in place to prevent them. The management of these problems is not trivial since they directly impact the clinical treatment, challenge the therapeutic relationship with the patients, and may disrupt the cohesion of the treating staff.

To deal with these problems, often a "contract" is individually agreed with the patient at the beginning of the treatment, specifying treatment goals and modalities and usually involving the patient's family in the discussion (Strik Lievers et al. 2009). Furthermore, specific rules are applied in the specialized eating disorder ward (e.g., locking toilets for some time after meals). Advancement in treatment should be periodically monitored in the staff meeting. Recently, some studies have evaluated

the integration of treatment aiming specifically at the reduction of compulsive exercise into CBT and showed promising results during inpatient treatment and after discharge (Dittmer et al. 2020).

Motivation to Treatment

Motivation to change is increasingly recognized as crucial in the treatment of AN. The transtheoretical model provides a framework for the assessment of motivation in AN, and motivational interviewing techniques are utilized to foster a patient's will to change (Dray and Wade 2012; Mander et al. 2013).

This translates into the importance of planning hospitalization with the patient when it is needed, ideally as a moment in the integrated care that is actively sought and recognized as useful by the patient. Indeed, per international guidelines, inpatient treatment should be considered before the occurrence of serious medical complications; however, in many cases, patients with AN reach clinical attention only when seriously ill and severely malnourished, therefore requiring urgent hospitalization (Fassino and Abbate-Daga 2013).

Kawai and collaborators (2014) compared treatment outcome and psychopathological scores in patients with AN who were urgently hospitalized to patients who underwent a planned inpatient treatment, finding that the first group had a poorer outcome and still after 2 years showed significantly low BMI and poor psychosocial functioning.

Different studies have shown motivational stages to predict inpatient treatment outcome, and motivation to change has been retrospectively pinpointed by remitted patients who underwent hospitalization as a key factor in their recovery (Long et al. 2012). Interestingly, studies like the one by Mander and collaborators show that the stage of contemplation significantly predicts therapeutic alliance in adult inpatients (Mander et al. 2013). Therefore, even though the directionality of this association is not clear, the therapeutic alliance should be highly valued in the course of inpatient treatment (Marzola et al. 2019).

Treatment Outcomes

Renutrition

Outcomes of refeeding programs are first of all weight gain, degree of medical complications, and mortality. The efficacy of inpatient treatment on weight gain is well established (Schlegl et al. 2014) and weight gain during treatment has emerged as a predictor of medium and long-term recovery (Lock et al. 2013). Indeed, some analyses evidence that the greater the weight gained during hospitalization, the better the outcome after discharge. This sometimes leads to longer hospitalization time, especially in the case of patients starting from extreme BMI (Guinhut et al. 2021). Even in centers that predominantly treat extreme cases, the mean length of stay

greatly varies, for example, ranging from 36 (Guinhut et al. 2021) to 72 (Chatelet et al. 2020), and up to 150 days (Born et al. 2015). In the studies reviewed by Cuerda et al. (2019), BMI increased from 1 to 6 points during hospitalization. Regarding medical complications, the incidence of hypophosphatemia has been reported to vary from 0 to 40%; the degree of malnutrition, rather than the rate of refeeding, seems to be a better predictor of the occurrence of this alteration (Garber et al. 2016). Vital signs have different times needed for renormalization, for example, heart rate reverts to normal range faster than others such as hypotension (Garber et al. 2016). The recent review by Cass and collaborators (2020) analyzes in more detail the rate and management of medical complications in the hospital setting.

Even though AN is recognized to be the psychiatric disorder with the highest mortality, studies conducted in specialized eating disorder units underreport mortality rates (Cuerda et al. 2019). It is to be noted however that mortality in intensive care units can be as high as 10%. A nationwide retrospective study conducted in Japan found male sex, age at first hospital admission, the ratio of actual weight to ideal body weight, psychiatric comorbidities, hypotension, and being treated in non-university hospitals as greater predictors of in-hospital mortality (Edakubo and Fushimi 2020).

Psychopathology

Besides weight gain, several studies report amelioration of eating psychopathology during inpatient treatment (Calugi et al. 2018; Waples et al. 2021; Marzola et al. 2021b). However, it is noteworthy that most patients still show clinical range values in eating disorders measures when discharged from inpatient treatment (Goddard et al. 2013), and even in the longer run (Eielsen et al. 2021). To deepen the understanding of psychopathological factors that influence hospitalization outcomes, the role of nonspecific ED psychopathology and its connections to core AN symptoms are increasingly studied also in the inpatient setting (Martini et al. 2021). For instance, Olatunji and collaborators (2018) have shown that the most relevant symptoms at admission to inpatient treatment were interoceptive awareness and feeling of ineffectiveness, while body dissatisfaction and drive for thinness were less central to the network of psychopathological symptoms. In the same sample, ineffectiveness at admission predicted discharge BMI and depression.

Comorbidity with depressive and anxiety disorders is relevant in the scope of inpatient treatment. A recent study (Panero et al. 2021) comparing AN inpatients with and without major depressive disorder highlighted that even though both groups were similar in terms of clinical severity and eating psychopathology at admission, the diagnosis of depressive disorder impacted hospitalization length and response to treatment (i.e., being associated with a lower increase in caloric intake and lower BMI at discharge in comparison to patients without major depression). Inpatient treatment has shown effective in improving body shape concerns despite baseline clinical severity (Marzola et al. 2020b).

Quality of Life

Quality of life measured with an instrument such as the EuroQol in patients with AN at admission to inpatient treatment is comparable with or even worse than that of other debilitating psychiatric and medical diseases, even in the light of a purported poor perception of psychosomatic distress, which poses some challenges in the comparison between ED inpatients and outpatients (Baiano et al. 2014). Nevertheless, hospitalization can result in improvement in both physical (i.e., mobility, pain) and psychological (i.e., anxiety, depression) dimensions (Abbate-Daga et al. 2014). These changes can set the stage for durable results in the outpatient setting. Therapeutic alliance during hospitalization has been shown to correlate to quality-of-life improvement upon discharge (Marzola et al. 2019). Patients with AN (both restrictive and binge-purging phenotypes) can establish acceptable levels of the therapeutic alliance (Marzola et al. 2019). It should be borne in mind, that this remains true even for a patient with a severe and enduring form of the disorder, who can benefit from inpatient treatment like patients with more recent disease onset (Marzola et al. 2021b).

Rehospitalization

Many patients with AN undergo more than one single hospitalization in the course of their illness, and some of them enter a cycle of frequent admission to inpatient treatment which has been indicated as "revolving door" (Marzola et al. 2021a). The determinants of these patterns are to be sought first of all in the high relapse rate, between 30 and 50% for adult patients in the European context (Bryan et al. 2021), which Treasure and collaborators (2021) motivate with the fact that most patients remain symptomatic when discharged from intensive care. Furthermore, it is now established that BMI at discharge is the strongest predictor of readmission in adult AN (el Ghoch et al. 2016). Low BMI at discharge, besides being associated with more severe psychopathology in the year after inpatient treatment, also correlates with an increased rate of hospitalization (Baran et al. 1995; Lund et al. 2009).

A recent analysis on the predictors of rehospitalization in a cohort of extremely severe inpatients confirmed improvement in BMI during the first admission to predict time to readmission (Marzola et al. 2021a). Furthermore, this study found drive for thinness as measured by the Eating Disorders Inventory 2 (EDI-2) to predict early readmission even controlling for all the other clinical and comorbidity-related conditions taken into consideration. The authors argue that if high levels of drive for thinness are still present at discharge, even the BMI improvement achieved during the inpatient treatment could not be sufficient to prevent further hospitalizations.

In children and adolescents, 1-year rehospitalization rate is recognized to be around 20% (Peebles et al. 2017), and an RCT found no difference in rehospitalization rate in adolescent patients treated with family-based therapy

when the first hospitalization was either aimed at medical stabilization (i.e., relatively short) or weight restoration (i.e., longer duration) (Madden et al. 2015).

Discharge and Follow-up

As per NICE guidelines, the care plan developed for each patient should specify how the patient will be discharged and reenter community-based care. In comparison to other medical illnesses, this transition is so much important for AN due to the clinical level of symptomatology still displayed after intensive treatment. Indeed, the goal of inpatient treatment is not to replace outpatient care but rather to make it possible (Giel et al. 2021). Unfortunately, the end of inpatient treatment still too often coincides with discontinuity of care. Very recently, prominent authors in the field of EDs have stressed the importance of favoring the transition from inpatient to outpatient services to provide continuity of care (Treasure et al. 2021). Psychological interventions to support this transition are under study (Treasure et al. 2021). A recent review on the subject found a small trend for better weight maintenance in patients allocated at the time of discharge to intervention adopting guided self-help and social support through the involvement of carers (Bryan et al. 2021), even though these interventions did not seem to improve eating and mood symptomatology.

Applications to Other Eating Disorders

Due to the complications associated with low weight and malnourishment described in this chapter, Anorexia Nervosa is the diagnosis most commonly encountered in inpatients units. However, also patients with other EDs can require acute hospitalization, due to medical and psychiatric emergency conditions. For instance, patients with Bulimia Nervosa (BN) and frequent compensatory episodes can encounter severe electrolytes alterations requiring urgent correction, and hospitalization can serve to break the binge/purge cycle (Atti et al. 2021). Furthermore, regarding urgent psychiatric symptoms, a recent retrospective study analyzing data from hospital admission over a 10-year time span in patients with an ED diagnosis found that among patients diagnosed with AN, BN, or Eating Disorder Otherwise Specified (EDNOS) 331 (6.7% of the total sample) required hospitalization due to a suicide attempt (Cliffe et al. 2020). Some authors report that BN can be treated in the inpatient setting with good outcomes and without engendering excessive weight gain (Hessler et al. 2018). Avoidant Restrictive Food Intake Disorder (ARFID) most often affects young patients and can be associated with weight loss and malnutrition which sometimes are not different from those encountered in patients with Anorexia Nervosa (Brigham et al. 2018). Patients with ARFID can be more compliant to nutritional modalities such as tube feeding also in the outpatient setting; however, sometimes hospitalization is required for medical stabilization and to provide a safe setting to reintroduce feared foods (Brigham et al. 2018).

Mini Dictionary of Terms

Caloric prescription: The amount of energy from food established for individual's requirements during refeeding, commonly expressed in kilocalories per day (kcal/day)

Refeeding: The process of reintroducing nutrition in malnourished individuals

Refeeding syndrome: A severe medical condition associated to shift in electrolytes that can occur during too rapid renutrition of severely malnourished individuals

Nasogastric feeding: A modality of renutrition that involves the positioning of a tube through the nose to reach the stomach allowing for controlled delivery of liquid food

Medical foods: Specific formulations of nutrients used in clinical settings

Summary Points

- Inpatient treatment is the most intensive level of care for AN, often aimed at emergency renutrition.
- Vital signs alterations, psychiatric symptoms, Body Mass Index thresholds (<15 kg/m^2 extreme), and rate of weight loss >1 kg/week should all be used as indicators of severity.
- Hospital care must be multidisciplinary and integrated.
- Weight gain (0.5–1.4 kg/week) aiming at weight restoration is the main goal of nutritional rehabilitation.
- Caloric prescriptions (starting from 5–20 kcal/kg and increasing every 2–4 days) must be balanced to avoid both refeeding and underfeeding syndromes.
- Oral diet, nutritional supplements, and tube feeding, alone or combined, are the main modalities of refeeding.
- Psychological treatments are useful in sustaining weight recovery; motivation to treatment and therapeutic alliance during hospitalization are predictors of good outcomes.
- Psychopharmacological treatment can be useful in treating psychiatric comorbidities, not to achieving weight gain.
- Rehospitalization is common due to symptoms' persistence.
- Discharge from inpatient treatment should be planned to favor the transition to outpatient services.
- Caregivers should receive information and participate in the decision regarding treatment whenever possible.

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Anorexia Nervosa and Comorbidities

33

Linking Autism

Antonia Parmeggiani and Jacopo Pruccoli

Contents

Introduction 642
Feeding and Eating Disorders 642
Anorexia Nervosa 643
Mental Health Comorbidities in Individuals with AN 643
Autism Spectrum Disorder 644
AN and ASD 645
General Considerations 645
Epidemiology 646
Psychodiagnostics 646
Clinical Traits and Theories 648
Treatments and Outcomes 649
Conclusions 650
Applications to Other Eating Disorders 650
Mini Dictionary of Terms 651
Key Facts of Anorexia Nervosa and Comorbidities: Linking Autism 651
Summary Points 651
References 652

Abstract

Anorexia Nervosa (AN) and Autism Spectrum Disorder (ASD) are two mental health conditions sharing a series of clinical features. Epidemiological studies have documented that subjects with AN may present ASD and ASD traits more frequently than the general population. Specific studies have discussed the use of psychodiagnostics tools to investigate ASD traits in individuals with AN. Recent

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research has reported common neuropsychological (i.e., deficits in "Theory of Mind") and psychopathological (i.e., alexithymia) traits between the two conditions. Finally, ASD traits may impact the interventions to treat AN. This chapter examines the recent literature reporting on the link between AN and ASD, and discusses the implications of this link for the development of new screening and treatment protocols.

Keywords

Anorexia nervosa · Feeding and eating disorders · Autism spectrum disorder · Neurodevelopmental disorders · Neuropsychology · ADOS-2 · AQ · Psychopathology · Alexithymia · Theory of mind

Abbreviations

3di-sv	3-developmental dimensional and diagnostic interview short version
AdAS	Adult Autism Subthreshold Spectrum
ADHD	Attention-Deficit/Hyperactivity Disorder
ADOS-2	Autism Diagnostic Observation Schedule-2nd Edition
AN	Anorexia Nervosa
AQ	Autism Spectrum Quotient
ARFID	Avoidant/restrictive food intake disorder
ASD	Autism Spectrum Disorder
BMI	Body Mass Index
CDC	Center for Disease Control and Prevention
DSM-5	Diagnostic and Statistical Manual of Mental Disorders, fifth edition
ED	Eating Disorders
IQ	Intelligence Quotient
NDD	Neurodevelopmental Disorders
OCD	Obsessive-compulsive Disorder
RRB	Restrictive and repetitive behaviors and interests

Introduction

Feeding and Eating Disorders

Eating behavior represents a fundamental regulating factor in normal childhood development. The achievement of adequate eating functions relies on the proper integration of a range of physical and psychological competencies. While transitory feeding problems in infancy are common and considered paraphysiological, 1–5% of infants develop severe feeding and eating disorders (Rybak 2015). A peak in incidence regarding specific eating disorders (ED) is evident in late childhood and especially teenage years (Jagielska and Kacperska 2017). The conceptualization and increased incidence of ED in the past decade have called for standardized research on the topic and the development of specific treatment programs. According to the

Diagnostic and Statistical Manual of Mental Disorders, fifth edition (DSM-5) (APA 2013) Feeding and ED are classified as: Pica, Rumination Disorder, avoidant/restrictive food intake disorder (ARFID), Anorexia Nervosa, Bulimia Nervosa, and Binge-Eating Disorder, Other Specified Feeding or ED, and Unspecified Feeding or ED. Current understanding suggests that both genetic and environmental factors are involved, but the biological mechanisms underlying ED are still not understood compared with other psychiatric disorders. An extensive co-occurrence of other psychiatric disorders is often observed in all ED, which intersect with weight and appetite regulation.

Anorexia Nervosa

Among ED, Anorexia Nervosa (AN) represents one of the most challenging conditions for clinicians and health policymakers worldwide. According to the DSM-5 (APA 2013), AN is defined by A) a restricted-energy intake, resulting in significantly low body weight for the individual's age, gender, development, and medical health; B) intense fear of gaining weight, or behaviors precluding weight gain, despite a significantly low weight; C) a disturbed experience of body weight or shape, and/or an excessive influence of body weight/shape on self-evaluation, or an insufficient recognition of low body weight. The prevalence of AN has been estimated to be as high as 1.4% in women and 0.2% in men in a systematic literature review (Galmiche et al. 2019).

Mental Health Comorbidities in Individuals with AN

A considerable lifetime prevalence of psychiatric comorbidities has been documented among individuals with AN, ranging from 45% to 97% (Herpertz-Dahlmann 2015). Specifically, researchers have documented relevant comorbidity between AN and mood disorders, anxiety disorders, obsessive-compulsive disorder (OCD), and personality disorders (Herpertz-Dahlmann 2015; Mairs and Nicholls 2016). These associations may be due to the specific neurodevelopmental features of the individuals with AN, since they may present a familial liability (transmitted propensity) for generalized anxiety, OCD, separation anxiety disorder, social phobia, panic disorder, and obsessive-compulsive personality disorder (Strober et al. 2007). In addition to the reported evidence of comorbidity between AN and psychopathological conditions, researchers have documented a specific link between AN and neurodevelopmental disorders (NDD).

NDD are a group of mental health conditions affecting the nervous system during early development. These disorders may involve different brain functions, manifest themselves clinically during childhood, and affect the personal, social, academic and occupational life of an individual (Thapar and Rutter 2015). Unlike the frequently remitting and relapsing course of many psychiatric conditions, the core symptoms of NDD are usually stable across the life of an individual, despite undergoing

Table 1 Neurodevelopmental disorders according to DSM-5 criteria

Group	Conditions
Intellectual disability	Intellectual Disability, Global Developmental Delay, Unspecified Intellectual Disability
Communication disorders	Language Disorder, Speech Sound Disorder, Social (Pragmatic) Communication Disorder, Childhood-Onset Fluency Disorder (Stuttering), Unspecified Communication Disorder
Autism spectrum disorder	Autism Spectrum Disorder
Attention-deficit/ hyperactivity disorder	Attention-Deficit/Hyperactivity Disorder, Other Specified Attention-Deficit/Hyperactivity Disorder, Unspecified Attention-Deficit/Hyperactivity Disorder
Specific learning disorder	Specific Learning Disorder
Motor disorders	Developmental Coordination Disorder, Stereotypic Movement Disorder, Tic Disorders, Other Specified Tic Disorder, Unspecified Tic Disorder
Other neurodevelopmental disorders	Other Specified Neurodevelopmental Disorder, Unspecified Neurodevelopmental Disorder

continuous modifications at different developmental stages (Thapar et al. 2017). The DSM-5 recognizes seven groups of NDD, namely Intellectual Disability, Communication Disorders, Autism Spectrum Disorder (ASD), Attention-Deficit/Hyperactivity Disorder (ADHD), Specific Learning Disorders, Motor Disorders, Other NDD (APA 2013). Among those conditions, ASD seems to be associated with AN through major direct and indirect developmental, neuropsychological, and psychopathological links. The NDD recognized by the DSM-5 are reported in Table 1.

Autism Spectrum Disorder

The core features of ASD are represented by A) persistent deficits in social communication and social interaction; B) restricted, repetitive patterns of behavior, interests, or activities; C) symptoms must be present in the early developmental period (but may not become fully manifested until social demands exceed limited capacities, or may be masked by learned strategies in later life); D) symptoms cause clinically significant impairment in social, occupational, or other important areas of current functioning (APA 2013). Patients with ASD usually show deficits in nonverbal communication, social reciprocity, and skills in developing, maintaining, and understanding relationships (Chiang and Carter 2008). Restrictive and repetitive behaviors and interests (RRB) constitute a further key clinical feature of ASD, pertaining to the field of neuropsychology and requiring the diagnosis and treatment of affected individuals (Lanzarini et al. 2021). These behaviors may include stereotyped or repetitive motor movements and use of objects or speech; insistence on sameness, inflexible adherence to routines, or ritualized patterns of verbal or nonverbal behaviors; highly restricted interests, with abnormal intensity or focus; excessive or reduced reactivity to sensory input or unusual interest in sensory elements (APA 2013). The severity of ASD is

recorded as the level of support needed for each of the two reported major psychopathological domains (D'Cruz et al. 2013).

The reported prevalence of ASD in the USA is 24.7 every 1000 children (age 3–17 years) with a reported gender ratio of 3 males to 1 female (Xu et al. 2018). More recent data published by the Center for Disease Control and Prevention (CDC) in the United States indicate a prevalence of 18.5 per 1.000 (one in 54) children aged 8 years (Maenner et al. 2020). The reported male to female ratio does not appear to be constant among different research studies. Classic studies indicate a gender ratio of 2 males to 1 female (Baron-Cohen et al. 2011; Lai et al. 2014). The previously cited CDC data report a diagnosis of ASD 4.3 times more prevalent among boys than among girls (Maenner et al. 2020). It is likely that females affected by ASD with normal high intelligence quotient (IQ) are more difficult to diagnose; biological, psychopathological, and diagnostic factors have been accounted for these gender differences (Baron-Cohen et al. 2011). Moreover, researchers have documented relevant comorbidities between ASD and other mental health conditions such as anxiety disorders (Simonoff et al. 2008) and ADHD (Taurines et al. 2012).

Problematic feeding behaviors have been documented to have a high prevalence in children with ASD, ranging from 46% to 89% (Ledford and Gast 2006, Parmeggiani 2014; Parmeggiani and Pruccoli 2022). The most frequently reported feeding issue is food selectivity, affecting nearly 70% of individuals with ASD. With regard to feeding disorders, the literature has documented a possible comorbidity between ARFID and ASD. It has also been recognized that the differential diagnosis may at times be difficult when considering ARFID and Pervasive Refusal Syndrome (Perrone et al. 2020). Although ARFID and Pervasive Refusal Syndrome are not connected with body weight or shape, recent research has specifically documented a comorbidity between ASD and AN (Adamson et al. 2020).

This chapter will focus on the neuropsychological, clinical, and treatment connections between AN and ASD.

AN and ASD

General Considerations

Gillberg and colleagues were the first to hypothesize the possible existence of an association between AN and ASD (Gillberg 1983). In a seminal clinical study that the group subsequently conducted, the documented prevalence of ASD and autistic traits in a population of adolescents affected by AN was 15% (Gillberg and Rastam 1992). Following this research, different authors have proposed new models to explain the documented clinical associations between AN and ASD. Some have formulated the possibility that undiagnosed ASD females with a high IQ could develop an ED during their lives, manifesting clear ED symptoms which, however, would conceal neurodevelopmental and communicative altered traits (Head et al. 2014; Lai et al. 2014). Others have suggested that occurrences of malnutrition in individuals with AN may induce specific psychopathological features, including

mental rigidity, obsessive behaviors, and RRB; these features resemble core ASD symptoms, but would improve upon restoration of a normal nutritional status (Mandy and Tchanturia 2015). In recent years, consideration of AN and ASD common neuropsychological features has led researchers to examine potential links existing between these conditions in the fields of psychology and psychiatry (Westwood and Tchanturia 2017).

Epidemiology

Little literature exists concerning the epidemiology of individuals with ASD and AN, and the data available is extremely variable. Possible reasons for this variability include inhomogeneous patient samples, evolving diagnostic criteria for the two conditions, and different diagnostic tools to investigate ASD traits in individuals with AN. Huke et al. (2013) have published a systematic review and metanalysis of the prevalence of ASD among individuals with AN. The authors found an average prevalence of 22.9%, but stressed that most of the included studies were conducted by a single research group on the same sample (Huke et al. 2013). These findings have been partially confirmed by more recent reviews (westwood and tchanturia 2017; Nickel et al. 2019). A relevant nationwide study on this topic was conducted by Kock and colleagues in Denmark (Koch et al. 2015). This research documented that individuals with AN present an increased risk of comorbid ASD; moreover, an increased risk for ASD was also documented in individuals with a family history for AN. It should be pointed out that, in this study, individuals with a diagnosis or a family history of any other psychiatric condition showed an increased risk for AN (Koch et al. 2015). The prevalence of ASD traits in individuals with AN, as detected by the autism quotient (AQ) questionnaire (Baron-Cohen et al. 2001) was compared to healthy controls was assessed by a metanalysis of Westwood et al. (2016). The authors documented individuals with AN, who presented higher AQ scores than healthy controls, even though the mean scores did not reach the cutoff values suitable for a diagnosis of ASD. All the reviews consulted for this article appear to agree on a higher prevalence of ASD traits in individuals with AN than in the general population.

Psychodiagnostics

Among the diagnostic instruments to assess ASD traits in individuals with AN which have been reported in literature, we have considered for this study: a) the Autism spectrum Quotient (AQ) (Baron-Cohen et al. 2001), b) the Autism Diagnostic Observation Schedule-2nd Edition (ADOS-2) (Lord et al. 2012), c) the Adult Autism Subthreshold Spectrum (AdAS) (Dell'Osso et al. 2017), and d) the 3-developmental, dimensional and diagnostic interview short version (3di-sv) (Santosh et al. 2009). The AQ is a test exploring five different domains: social skills, attention shifting, attention to detail, communication, and imagination. The AdAS is

a questionnaire tailored to investigate subthreshold ASD in adults. This test shows high internal consistency, and test-retest reliability and strong convergent validity with alternative dimensional measures of ASD (Dell'Osso et al. 2017). The AQ and the AdAS scores of patients affected by AN are significantly more elevated compared to those of control groups, even when they do not reach the threshold for diagnosis of autistic traits (Westwood et al. 2016; Dell'Osso et al. 2018). The 3di represents an accurate tool to assess, in dimensional terms, ASD symptoms in both clinical and nonclinical individuals (Skuse et al. 2004). The ADOS-2 is a key diagnostic tool for the recognition of individuals with ASD (National Institute for Health and Clinical Excellence 2011). Module 4 of the ADOS-2 investigates adolescents and adults with no language impairment by examining language and communication, reciprocal social interaction, imagination, creativity, stereotyped behavior, and restricted interests. The scores obtained in the language and communication and reciprocal social interaction domains produce a final score, possibly leading to a diagnosis of "Autism," "Autistic Spectrum" or "Non-Spectrum" (Lord et al. 2012). In a study by Westwood et al. (2018) 3di-sv, clinical observation and ADOS-2 were used to investigate ASD traits in AN individuals. In 51.2% of the enrolled patients over-threshold ADOS-2 scores were documented, while only 10.0% of them could be clinically diagnosed with ASD. Nevertheless, this result is significantly higher than data referring to the general population (Westwood et al. 2018). (Sedgewick and colleagues 2019a) show that the recently revised ADOS-2 diagnostic algorithm for adults permits to identify ASD cases above the cutoff value established in the previous edition. This result was confirmed in both individuals with active AN and in individuals who have recovered from AN, which suggests that ASD traits are more highly represented in AN, independent of the effect of malnutrition (Sedgewick et al. 2019a).

As for the studies conducted on pediatric samples, a research by Postorino et al. (2017) compared individuals with severe AN (age range 10–17 years) to ASD and healthy controls. The enrolled individuals were tested using ADOS-2 and AQ. In the AN sample, only three individuals (10%) obtained a score above thresholds for ASD. AQ scores did not significantly differ between individuals with AN and controls. However, AN individuals presented obsessive-compulsive, theory of mind and affect recognition scores similar to those obtained by members of the ASD group (Postorino et al. 2017). In a recent study, our group investigated possible associations among ED psychopathology, ASD traits and body-mass index (BMI) in a sample of young individuals with AN, using the EDI-3 (Eating Disorder Inventory-3) test and gold-standard tests for ASD. Twenty-three inpatients were enrolled. ASD traits were assessed administering ADOS-2 and AQ, investigating both present and past autistic traits using different versions of AQ. We found a high frequency of ASD traits in young inpatients with AN. These traits were significantly correlated to four specific EDI-3 subscales and independent of BMI (Pruccoli et al. 2021a). An example of the existing psychodiagnostic tools used to assess ASD traits in individuals with AN is reported in Table 2. Figure 1 reports the potential diagnostic issues in detecting comorbidities between ASD and AN.

Table 2 An example of psychodiagnostic tools used to assess ASD traits in individuals with AN

Psychodiagnostic tools	Description
Autism spectrum Quotient (AQ) (Baron-Cohen et al. 2001)	Questionnaire exploring social skills, attention shifting, attention to detail, communication, and imagination
Adult Autism Subthreshold Spectrum (AdAS) (Dell'Osso et al. 2017)	Questionnaire exploring ASD-related domains: childhood/adolescence, verbal communication, nonverbal communication, empathy, inflexibility and adherence to routine, restricted interests and rumination, hyper-hypo reactivity to sensory input
Autism Diagnostic Observation Schedule-2nd Edition (ADOS-2) (Lord et al. 2012)	Direct observation, assessing the domains of language and communication, reciprocal social interaction, imagination, creativity, stereotyped behavior, and restricted interests
3-developmental, dimensional and diagnostic interview short version (3di-sv) (Santosh et al. 2009)	Parental interview, assessing the domains of reciprocal social interaction, communication, and repetitive and stereotyped behavior

Abbreviations: ASD: Autism Spectrum Disorder

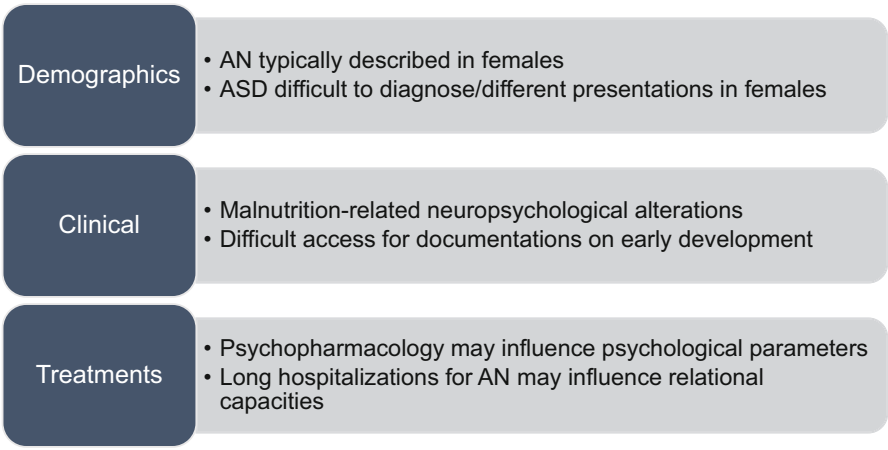


Fig. 1 Potential diagnostic issues in detecting ASD traits in AN individuals. (Abbreviations: AN: Anorexia Nervosa; ASD: Autism Spectrum Disorder)

Clinical Traits and Theories

A series of clinical traits have been documented in individuals with AN and ASD. Alexithymia is defined as a marked impairment in emotional awareness, social attachment, and interpersonal relating. Westwood and colleagues (2017a) have reported that individuals with ASD may present alexithymia in 33–66% of the cases, while this condition can be documented with a prevalence of 74–83% in patients with AN. Empathy and empathy-related measures in subjects with ED may present profiles comparable to individuals with ASD (Kerr-Gaffney et al. 2019). Similarities between ASD and AN were identified for measures related to the theory

Table 3 Main neuropsychological domains linking Anorexia Nervosa and Autism Spectrum Disorder

Domain	Description	Considerations
Alexithymia	Impairment in emotional awareness, social attachment, and interpersonal relating	Documented in 33–66% of subjects with ASD and 74–83% patients with AN.
Theory of Mind (TOM)	Ability to understand the mental states of others	Both individuals with ASD and AN have widely shown poor performances in TOM
Set-shifting	Capacity to change and adapt current thoughts of actions to meet environmental demands	Impaired set shifting in patients with ASD; compromised set shifting after childhood in individuals with ED

Abbreviations: AN: Anorexia Nervosa; ASD: Autism Spectrum Disorder; ED: Eating Disorders; TOM: Theory of Mind

of mind (TOM). TOM represents the ability to understand the mental states of other individuals (Baron-Cohen et al. 1985). Poor performances have been widely documented both in cases with AN and in cases with ASD, while emotional theory of mind seems to be more significantly compromised in individuals with ASD than in those with AN, as documented by a recent metanalytic review (Leppanen et al. 2018). Set shifting, defined as the ability to change and adapt current thoughts of actions to meet environmental demands, has been compared between cases affected by ASD and ED by Westwood et al. (2016). The authors found impaired set shifting in ASD patients, while those affected by ED showed normal set-shifting profiles during childhood but a compromised ability later in their lives (Westwood et al. 2016). Moreover, AN patients with over-threshold ADOS-2 scores may present a significant impairment in set shifting (Westwood et al. 2017b). Other authors, who have used the AQ questionnaire, report nonsignificant differences concerning set shifting between AN subjects with and without ASD features (Sedgewick et al. 2019b). Table 3 reports the main neuropsychological domains linking AN and ASD.

Treatments and Outcomes

AN has the highest mortality rate among mental health conditions (Smink et al. 2012). Clinical interventions typically aim to restore body weight and address social and emotional issues preventing recovery (Treasure and Schmidt 2013). Family-based treatment represents the mainstay of the treatment of children and adolescents with AN in a series of different settings. As for psychopharmacological interventions, selective serotonin reuptake inhibitors and atypical antipsychotics have been widely used in the management of patients with AN. However, medications should not be prescribed as the sole treatment for AN (NICE 2017). Contradictory evidence is available concerning the possible impact of ASD traits on the treatment and outcomes of AN. Individuals with ED and overlapping ASD traits may experience a greater impairment of cognitive flexibility, ritualistic behaviors, mood disorders, and social impairment, but these features do not seem to directly correlate with malnutrition or BMI (Nielsen et al. 2015; Stewart et al. 2017; Tchanturia et al. 2019).

In a recent study, we directly assessed the impact of ASD traits on the treatment of a group of adolescents with AN. Enrolled patients were assessed with ADOS-2 and AQ tests, and outcomes were measured as changes in psychopathology and body weight. When compared to other patients, AN individuals with diagnostic scores for ASD showed overlapping types of treatments, as well as psychopathological and weight outcomes (Pruccoli et al. 2021b). Currently, no specific protocol addresses the management of individuals with AN and comorbid ASD, and new studies on this topic are needed by clinicians (Kinnaird et al. 2017; Kinnaird et al. 2019).

Conclusions

Psychiatric comorbidities are frequent in ED; they may be premorbid, comorbid, or even present after recovery. Thus, the assessment of individuals with ED requires a thorough psychiatric history, and psychodiagnostic testing to define a psychological profile. Obtaining this information is key to programming early interventions in developmental age. AN is a severe ED with many complications and a high mortality. According to an epidemiologic survey (2018–2020) conducted by the Italian Ministry of Health, a 30% increase in the mortality rate for individuals with AN was observed following the COVID-19 pandemic. A considerable lifetime prevalence of psychiatric comorbidities has been documented among individuals with AN; a particularly interesting yet potentially undetectable case is the comorbidity of AN with ASD when considering females with a normal IQ. Patients with comorbid AN and ASD may present specific neuropsychological and clinical features. Clinical evolution of patients with AN, who have not been properly diagnosed with ASD traits, could affect a clinical improvement or facilitate the emergence of other psychopathologies. In the literature, current studies have failed to clearly identify the specific interventions needed to address this particular population. A special effort should be made to deal with the specific diagnostic challenges in order to properly identify ASD traits in girls with AN, given the relevant differences in the clinical expression of ASD between males and females. We believe further research should systematically investigate the biological and hormonal factors that may distinguish this clinical population, in order to propose new interventions and establish new health policy protocols.

Applications to Other Eating Disorders

In this chapter, we have reviewed the available evidence on the links between Anorexia Nervosa (AN) and Autism Spectrum Disorder (ASD), documenting a number of relevant links between these two conditions. However, ASD and ASD traits may also impact other Eating Disorders (ED). Numata and colleagues have evaluated a group of patients with different ED for the presence of ASD traits (Numata et al. 2021). Individuals without self-induced vomiting presented more evident ASD traits than those with self-induced vomiting, while subjects with BED had the most evident ASD traits (Numata et al. 2021). Moreover, in a recent

study by Demartini and colleagues, individuals with ASD showed higher scores than neurotypical controls for the two scales that assessed eating disturbances (EAT-26 and SWEAA), with a higher frequency of both eating disturbances typical of ASDs and ED symptoms, such as a distortion of the body image, a tendency toward bulimic behaviors, and self-control of eating (Demartini et al. 2021). The recognition of this evidence may help researchers to expand the existing body of literature concerning the links between ASD and ED, and to systematically investigate the presence of disorders of eating behaviors and body image in individuals with ASD.

Mini Dictionary of Terms

- ***Autism Spectrum Disorder****: A condition characterized by an altered brain development, with resulting problems in relationship development and communication.*
- ***Alexithymia****: The inability to identify and describe one's feelings, and to distinguish emotional states from physiological perceptions.*
- ***Empathy****: The ability to understand the mood, behavior, and emotions of others.*
- ***Theory of mind****: The capacity to represent one's own and others' mental states.*
- ***Set shifting****: The ability to subconsciously shift attention between different tasks.*

Key Facts of Anorexia Nervosa and Comorbidities: Linking Autism

- The suggestion of a link between Anorexia Nervosa (AN) and Autism Spectrum Disorder (ASD) was first advanced by Gillberg in Gillberg 1983.
- The first systematic review and metanalysis of the prevalence of ASD among individuals with AN found an average prevalence of 22.9%.
- A series of psychodiagnostic tools have been used to identify ASD traits in individuals with AN.
- Alexithymia, defined as difficulty in identifying and describing one's feelings, has been documented in 33–66% of the individuals with ASD, and 74–83% of the patients with AN.
- Individuals with ED and overlapping ASD traits may exhibit greater impairment of cognitive flexibility, ritualistic behaviors, mood disorders, and social impairment.

Summary Points

- *Recent systematic reviews and metanalyses have documented that individuals with Anorexia Nervosa (AN) may present a comorbid Autism Spectrum Disorder (ASD) or ASD traits more frequently than the general population.*
- *The Autism spectrum Quotient (AQ), the Autism Diagnostic Observation Schedule-2nd Edition (ADOS-2), the Adult Autism Subthreshold Spectrum*

(AdAS), and the 3-developmental, dimensional, and diagnostic interview short version (3di-sv) have been used to assess ASD traits in individuals with AN.

- *Psychopathological features, such as alexithymia, have been reported with a high frequency both in individuals with ASD and AN.*
- *Neuropsychological impairments, such as deficits in the Theory of Mind, may link the development and persistence of both AN and ASD symptoms.*
- *No specific treatment protocols have been developed so far to address individuals with AN and comorbid ASD.*

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The Electrocardiogram in Anorexia Nervosa 34

Mikyla Janzen, Julia Raudzus, and Andrew Krahn

Contents

Introduction 656
Background 656
Heart Rate and Heart Rhythm 657
The Electrocardiogram 657
The Electrocardiogram in Anorexia Nervosa 659
The ECG in Anorexia Nervosa 660
Bradycardia 660
Heart Rate Variability 662
QTc Interval 663
T-Wave Changes 664
Special Circumstances 664
Impact of Refeeding 664
The Electrocardiogram during Exercise 664
Psychopharmacotherapy and the Electrocardiogram 665
Sudden Unexpected Death 666
Clinical Use of the ECG in AN 666
Conclusion 668
Applications to Other Eating Disorders 668
Mini-Dictionary of Terms 668

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Key Facts of the Electrocardiogram in Anorexia Nervosa 669
Summary Points 669
References 669

Abstract

The electrocardiogram (ECG) provides important information regarding the heart rate and heart rhythm in patients with anorexia nervosa (AN). Up to one third of deaths in AN are due to cardiac causes, with a subset of those due to arrhythmia. The ECG is an inexpensive, minimally invasive, and widely accessible screening tool to assess the heart's electrical activity. Bradycardia occurs widely in AN, with severity correlating to degree of malnutrition and/or low BMI, attributed to impaired autonomic regulation. Changes in the QT interval and other repolarization parameters are less ubiquitous in patients with AN, and their prognostic and therapeutic implications are less clear. However, a growing field of research supports serial ECG monitoring, especially in acutely unwell patients with AN, for both risk assessment and to monitor regression to normal with treatment.

Keywords

Eating disorders · Anorexia nervosa · Electrocardiogram · Heart rhythm · Arrhythmia · Bradycardia · Heart rate variability · QT interval · T-wave · Sudden unexpected death

Abbreviations

AN	Anorexia nervosa
BN	Bulimia nervosa
BPM	Beats per minute
ECG	Electrocardiogram
HR	Heart rate
HRV	Heart rate variability
QTc	Corrected QT interval
SSRI	Selective serotonin reuptake inhibitor
SUD	Sudden unexpected death

Introduction

Background

Anorexia nervosa (AN) is a complex eating disorder that has the highest mortality of all psychiatric disorders (Arcelus et al. 2011). Up to one third of deaths are due to cardiac manifestations of disease; as such, identifying at-risk patients prior to adverse events is of great importance (Papadopoulos et al. 2009). The most harrowing of these cardiac deaths are sudden unexpected deaths (SUD), which are

precipitated by sudden-onset arrhythmia. In other cardiac conditions, clinical warning signs of arrhythmia and SUD have been identified and are an important risk-assessment and prognostic tool. These warning signs include symptoms such as syncope (fainting) and palpitations or changes seen on cardiac testing of the heart rhythm. While SUD secondary to arrhythmia represents a subset of cardiac deaths, and therefore a fraction of all-cause mortality in AN, arrhythmias remain an important area of clinical concern.

Principles from other known causes of SUD, such as inherited arrhythmia conditions, have helped inform how best to screen and identify patients with AN who may be at risk for arrhythmia and SUD. A mainstay of cardiac screening is the electrocardiogram (ECG), a widely used, quick, and cost-effective test which can provide detailed information regarding the heart rate (HR) and heart rhythm. The utility of the ECG in the setting of AN will be explored in this chapter.

Heart Rate and Heart Rhythm

Each heartbeat is initiated by an electrical signal that travels through the heart to create coordinated, effective muscle contractions which are related to two clinically important variables: heart rate (HR) and heart rhythm. HR is measured as the number of heartbeats per minute (bpm), while heart rhythm is the origin and nature of the cardiac impulse that subsequently leads to electrical and mechanical activation across the heart. Both parameters are measured on the electrocardiogram (ECG).

Both heart rate and heart rhythm are dependent on intracellular and extracellular electrolyte gradients and as such are sensitive to changes in body electrolyte levels. Serum electrolyte imbalances are almost universally observed in AN, including hypokalemia, hyponatremia, hypocalcaemia, and hypomagnesemia (Abed et al. 2014). These imbalances are seen in most subtypes of AN, with both starvation and purging behaviors impacting serum electrolyte levels. As such, deranged serum electrolytes can impact the ECG in ways which will be explored throughout this chapter. Clinical evaluation of serum electrolytes is also indicated during AN treatment, as the nutritional changes associated with refeeding syndrome can increase the risk of cardiac arrhythmia (Hofer et al. 2014; Boateng et al. 2010; Abed et al. 2014). HR is also tightly regulated by the autonomic nervous system, wherein parasympathetic stimulation slows HR. While most studies conclude that parasympathetic predominance is observed in AN, this finding has not been completely reproducible, nor has an ideal measure of autonomic nervous system activity been identified (Mazurak et al. 2011; Jenkins et al. 2021; Farasat et al. 2020).

The Electrocardiogram

The electrocardiogram (ECG) measures the electrical signal of the heart through the placement of skin electrodes. The electrical impulses are then transcribed and recorded to produce the 12-lead ECG (Fig. 1). The ECG recording provides both

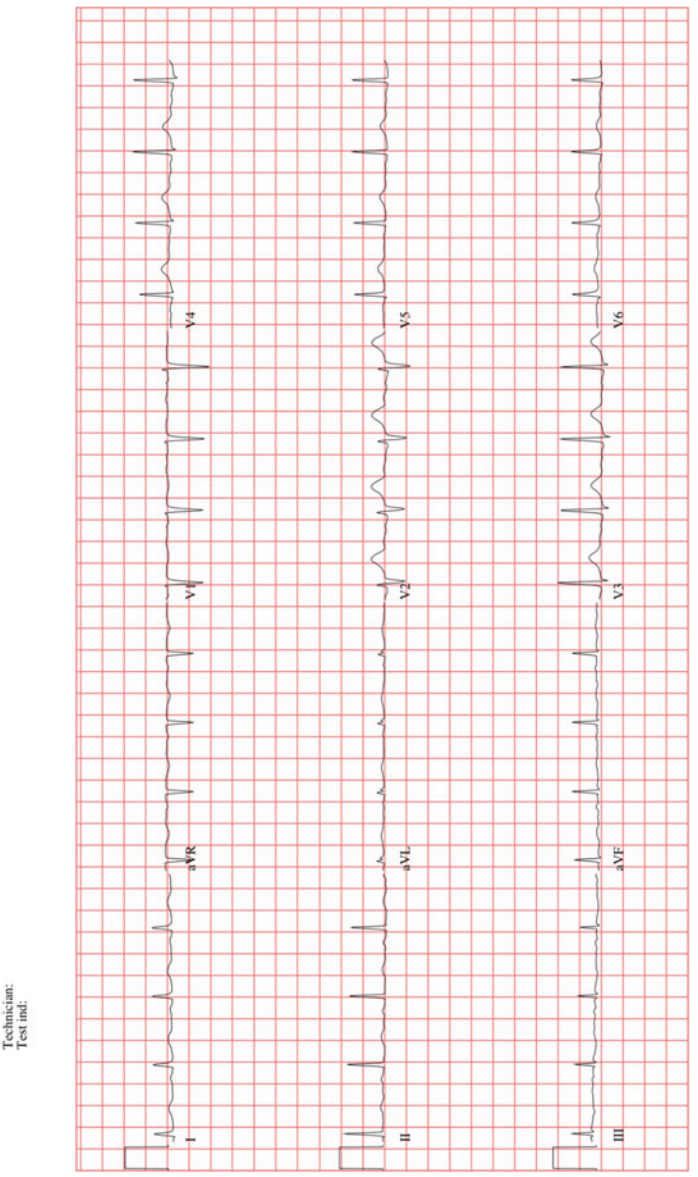


Fig. 1 A normal ECG including computer-generated parameters and interpretation

Table 1 Normal electrocardiogram values

Parameter	Normal range and units	Notes
RR interval	0.6–1.2 s	Heart rate is calculated as 1/(RR/60) [normal value 60–100 bpm]
PR interval	0.12–0.20 s	
QRS duration	0.06–0.10 s	
ST segment	0.08 s	Normally on the isoelectric line
QTc interval	Lower limit: 350 ms Borderline: 450–470 ms (male) 460–480 ms (female) Prolonged: >470 ms (male) >480 ms (female)	The absolute QT interval is corrected for heart rate (QTc)

spatial and temporal information, as waves are plotted with time (seconds) on the x-axis and amplitude (millivolts) on the y-axis. Each waveform corresponds to a specific portion of the cardiac cycle with clinically accepted normal values (Table 1). Of note, the QT interval represents the entire cycle of ventricular depolarization and repolarization and is used clinically to assess ventricular abnormalities as explored below. This "raw" QT interval is also adjusted to a baseline HR of 60 bpm to calculate the corrected QT (QTc) interval. As HR increases, the duration of each cardiac cycle shortens, and the raw QT interval decreases. By adjusting the QT interval for HR (i.e., the QTc interval or value), clinicians are able to accurately compare QTc intervals both within and between patients.

Typical ECG reports include automated measurements of common parameters, such as HR, QRS duration, and QT interval. Algorithms are relatively accurate for most measurements except the QT interval. This is particularly the case when the T-wave has abnormal shape, making it more difficult to measure, which is often the case in AN (Janzen et al. 2019). As such, manual measurement of the QT interval is encouraged to ensure accurate values.

The ECG is an inexpensive, noninvasive, and widely accessible screening tool used to assess for and risk-stratify a multitude of cardiac abnormalities. Specifically, its utility in AN is becoming increasingly better understood as research progresses, with particular interest in the HR and QTc interval.

The Electrocardiogram in Anorexia Nervosa

As AN is a complex and multifactorial disease, clinical presentation and systemic manifestations can vary widely. The underlying etiologies of the binge/purge compared to restrictive subtypes of AN result in drastically different biochemical profiles. Further, refeeding and psychopharmacotherapy can impact the ECG and play a dynamic role in AN treatment and remission. This results in heterogeneity of the ECG, perhaps with the exception of bradycardia (Garber et al. 2021). Nevertheless, the ECG provides important insight into the cardiac status of patients and is commonly used in the clinical setting, especially as part of inpatient care.

The ECG can also be used to identify at-risk markers for SUD. The most widely used is prolongation of the corrected QT (QTc) interval (Table 1). The implication of QTc interval prolongation in SUD in AN was first described in a case report published in 1985, which prompted a flurry of research and clinical interest (Isner et al. 1985). Since this report, many studies have analyzed the QT interval in AN, but a consensus has not been reached regarding resting QT interval prolongation or a definitive link to the increased risk of SUD (Janzen et al. 2018). The most recent evidence does not support a clear link between widespread QTc prolongation and risk of SUD in the AN population. The utility of the QT interval in AN is an incompletely understood, yet important, topic and will be explored in depth later in this chapter.

Specific ECG changes have not been identified globally in the AN population aside from bradycardia, but the ECG remains an important mainstay of care. As this chapter will explore, a myriad of factors may affect the ECG and become important on a patient-level basis.

The ECG in Anorexia Nervosa

Specific ECG parameters of interest include bradycardia, heart rate (HR) variability, and the QTc interval. The ECG can be highly variable, and special considerations in monitoring should be taken in the settings of refeeding, exercise, and psychopharmacotherapy.

Bradycardia

Bradycardia is a slowed heart rate, with definitions varying slightly from HR $<$60 bpm or $<$50 bpm. It is the most consistent ECG change seen in patients with AN, with HR $<$50 bpm reported in up to 80% of acutely unwell patients and likely to be seen in those with more extensive weight loss (Garber et al. 2021; Yahalom et al. 2013; Sachs et al. 2016; Assalone et al. 2021). Figure 2 shows an example of an ECG with sinus (regular) bradycardia. The mechanism underlying this reduction in HR is incompletely understood and likely multifactorial with disease, environmental, and genetic contributors. However, a relatively well-supported overarching hypothesis of the underlying cause of bradycardia in AN is dysregulation of autonomic tone with parasympathetic dominance (Jenkins et al. 2021). Importantly, autonomic dysregulation has not been shown to account for all HR changes, suggesting other, minor factors are at play (Buchhorn et al. 2021). The degree of AN exacerbation, as measured by low BMI, correlates with more extensive bradycardia, supporting the notion that the underlying mechanisms are in part a reflection of the systemic severity of AN. Further, compulsive exercise may be a manifestation of anorexia nervosa. As athletes are known to have a slower resting HR, this may predispose some patients with AN to exhibiting more profound bradycardia. Similarly, genetic

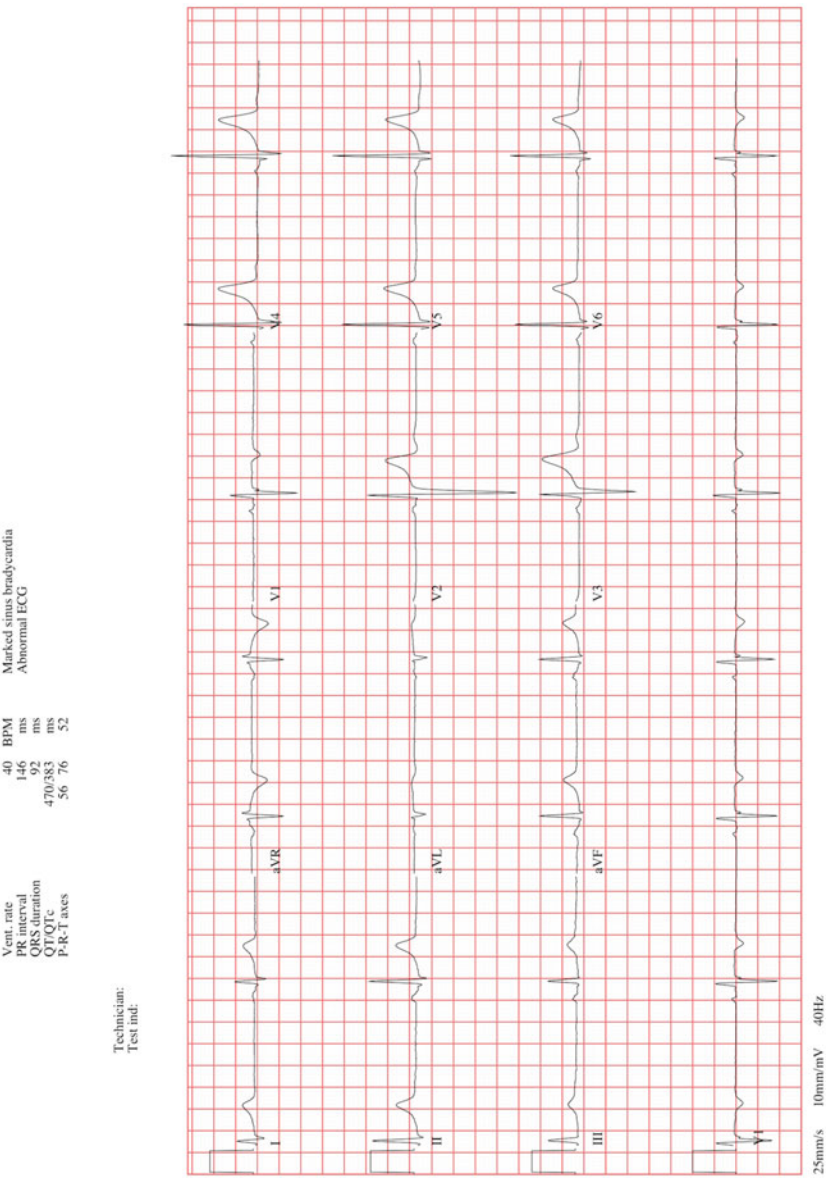


Fig. 2 An ECG showing sinus bradycardia including computer-generated parameters and interpretation

variants likely play a role in nonneural bradycardia in AN, although this is a new area of research awaiting robust studies (Buchhorn et al. 2021).

Although there are no current national guidelines for admission to hospital, physician surveys suggest that most centers implement a bradycardic threshold of HR ≤40–45 bpm to prompt admission (van Son et al. 2014; Schwartz et al. 2008). Local jurisdictions and care centers often follow admission criteria based on clinical experience in the absence of formal evidence-based guidelines. For example, in British Columbia, Canada, emergency room guidelines for admission of adults with AN are risk-stratified by BMI with specific advice regarding prolonged QTc interval and T-wave inversion or flattening on ECG. Similarly, local pediatric guidelines indicate to consider admission for patients with HR <45 bpm, QTc interval < 450 ms, or any heart rhythm disturbance. The complete clinical picture should be taken into account when considering hospital admission for treatment for acute AN, but in the absence of other factors, profound bradycardia is a reasonable indication for admission. Patients with HR <50 bpm should also be placed on a cardiac monitor where available. Heart rates have been reported as slow as 30 bpm on admission, although restoration to normal (60–100 bpm) is often seen with even modest weight gain in the early refeeding period (Farasat et al. 2020; Assalone et al. 2021; Jenkins et al. 2021). As such, the return of HR to normal range is often used as a marker of clinical recovery and stability. Although related to more severe AN, the evidence does not suggest that bradycardia is an independent predictor of death or adverse outcomes in this population (Edakubo and Fushimi 2020). Of note, while periodic heart rate surveillance during admission is effective in monitoring the progression and normalization of bradycardia, cardiac monitoring, including ECG, is not regularly performed.

Heart Rate Variability

With the reproducibility of bradycardia in AN, researchers sought to quantify and better understand the contribution of the autonomic nervous system. HR variability (HRV) is the beat-to-beat variability in HR measured over 24-hour continuous monitoring. Increased HRV reflects parasympathetic nervous system predominance as demonstrated in the general population (Draghici and Taylor 2016). In theory, parasympathetic-mediated bradycardia would also be reflected as increased HRV which may provide further information regarding the underlying systemic changes seen in AN. However, increased HRV has not been consistently reported in AN, suggesting parasympathetic predominance is not the only factor responsible for bradycardia in patients with AN (Mazurak et al. 2011). Sympathovagal balance may also play a role, wherein decreased sympathetic tone synergistically potentiates the impact of increased parasympathetic tone on bradycardia. Reduced sympathetic tone may be a form of evolutionary conservation. Further, even if HRV is only present in a subset of patients with AN, its clinical utility is not clear (Peyser et al. 2021). HRV is cumbersome to record and is not widely used as a clinical tool in the care of patients with AN.

QTc Interval

The QT interval is a measurement of ventricular depolarization and repolarization and is highly dependent on HR. As HR increases, repolarization time and the absolute QT interval decrease to allow effective propagation of the next heartbeat. To adjust for HR changes and create normalized QT interval values, various formulae to calculate the corrected QT (QTc) interval have been developed (also called the QTc value by some). Bazett's formula is by far the most widely used of these formulae ($QTc = QT/\sqrt{RR}$). Most ECG programs utilize a computer algorithm to measure the absolute QT interval, which is then mathematically converted to the QTc interval. However, these algorithms are not particularly accurate, especially in the context of concurrent ECG abnormalities; as such, QT interval measurements should be validated by trained personnel.

The QTc interval has been a point of interest on the ECG of patients with AN since 1985, when Isner et al. recorded QTc interval prolongation in the days preceding the sudden unexpected death of three patients with AN (Isner et al. 1985). While QTc interval prolongation has been definitively linked to fatal arrhythmias in other populations, current evidence for its relevance in AN is inconsistent. While a 2008 meta-analysis reported QTc interval prolongation in patients with AN compared to healthy controls, the majority of subjects had QTc intervals within normal range (Lesinskiene et al. 2008). Conversely, an updated 2018 meta-analysis reported no significant difference between patients with AN and healthy controls but did find significant publication bias in the field (Janzen et al. 2018).

In the setting of bradycardia, Bazett's formula underestimates the QTc interval producing lower than accurate values (Johnson and Ackerman 2009). Given the high prevalence of bradycardia in AN, it was hypothesized that QTc intervals are lower than accurate values in this population, masking prolonged QTc intervals and arrhythmic risk. However, this was not seen in studies which used other QT interval correction formulae and reported no difference between the QTc intervals of AN patients and healthy controls (Janzen et al. 2019; Walter et al. 2015).

In cases where dramatic QTc interval prolongation at rest has been reported, multiple factors are often at play such as severe hypokalemia, extremely low BMI, and/or the presence of QT prolonging drugs (Sachs et al. 2016). However, the individual impact of each confounder is also inconsistent, suggesting perhaps a subset of patients with AN may be more susceptible to QTc interval prolongation than others.

Current evidence suggests the impact of AN on cardiac repolarization and the QTc interval is complex, multifactorial, and incompletely understood. Further, in the vast majority of studies, even if QTc intervals were significantly prolonged compared to healthy controls, mean values were within normal range, and thus any prolongation was likely of negligible clinical impact. It is possible with future research that the QTc interval will play a larger prognostic role in AN as a whole, but the specific subpopulations in which this may be a factor have not yet been identified. While it remains advised to perform ECG on patients with AN, current evidence suggests that the initial perceived clinical importance of the resting QTc interval in AN was overemphasized.

T-Wave Changes

The T-wave measures ventricular repolarization, and its morphology can relay important information regarding the underlying cardiac tissue. For example, in genetic forms of long QT syndrome, flat, notched, or otherwise abnormal T-waves are observed concurrently with or independently of prolonged QT intervals (Porta-Sánchez et al. 2017). Evaluation of the T-wave in patients with AN is an emerging field of research, but flattening of the T-wave appears to occur during both acute and weight-restored AN (Stahi et al. 2020; Janzen et al. 2019). The significance of this finding is uncertain but may play into the multifactorial hypothesis of cardiac risk in the AN population and as such remains a field of active research.

Special Circumstances

Impact of Refeeding

Prompt initiation of refeeding is a hallmark of treatment for acute exacerbations of AN. A sudden influx in caloric intake can result in abrupt changes in serum electrolytes, which as discussed play an important role in the heart rhythm. In a minority of cases, this sudden shift can lead to refeeding syndrome and increase the risk of arrhythmias (Giovinazzo et al. 2019). However, with careful medical monitoring and appropriate electrolyte adjustment, adverse outcomes can be avoided and are not increased with more aggressive refeeding protocols (Garber et al. 2016, 2021).

Importantly, refeeding most often reverses ECG abnormalities seen in acute AN exacerbations (Ulger et al. 2006). As discussed above, the underlying pathophysiology of such abnormalities is often not well understood, but the reproducible finding of normalization with weight gain suggests that low BMI plays an important role. Any risk associated with observed ECG abnormalities is also assumed to normalize with the ECG. From a clinical perspective, this further supports the incentive to pursue aggressive refeeding and treatment as both cardiac stabilization and medical stabilization are achievable.

The Electrocardiogram during Exercise

Many patients with AN have a complex relationship with exercise; this simultaneously supports the importance of understanding any ECG changes with exertion while complicating the ethical and practical aspects of clinical research. However, other conditions with ECG abnormalities, specifically QTc interval prolongation, show changes during exercise which can be imperative to quantifying the clinical risk of arrhythmia. Recent research has demonstrated impaired QTc interval dynamics during exercise in both adults and adolescents with AN (Padfield et al. 2016; Janzen et al. 2020). The repolarization reserve is a marker of the heart rhythm's

ability to appropriately respond to changes in HR; a reduction in reserve is observed in patients with AN and may correspond to an increased risk of arrhythmia at faster HR, in contrast to rest. This field of research is relatively new, and future studies will be important in better understanding the absolute risk conferred by impaired QT interval dynamics during exercise in this population. At present, exercise evaluation is not recommended in AN. Similarly, continuous cardiac monitoring (e.g., 24-hour Holter monitor) is utilized in other states with abnormal cardiac repolarization, but its clinical utility in AN is currently unclear.

Psychopharmacotherapy and the Electrocardiogram

Many patients with AN are concurrently prescribed psychopharmacotherapy such as selective serotonin reuptake inhibitors (SSRIs) and anxiolytic medications, even though evidence does not support their efficacy in treating AN (CROW 2019). Outside of AN, these drugs are well known to prolong the QT interval and predispose patients to ventricular arrhythmias. As such, the risk implications in patients with AN are of interest. Current evidence does not support a link between psychopharmacotherapy use and QT interval prolongation; however, observational studies are difficult given dose and agent alterations throughout treatment (Janzen et al. 2019). A convenient resource for clinicians to determine if drugs prolong the QT interval is available at www.QTDrugs.org, with a user-friendly smartphone app for both major platforms (CredibleMeds Mobile). Figure 3 outlines the

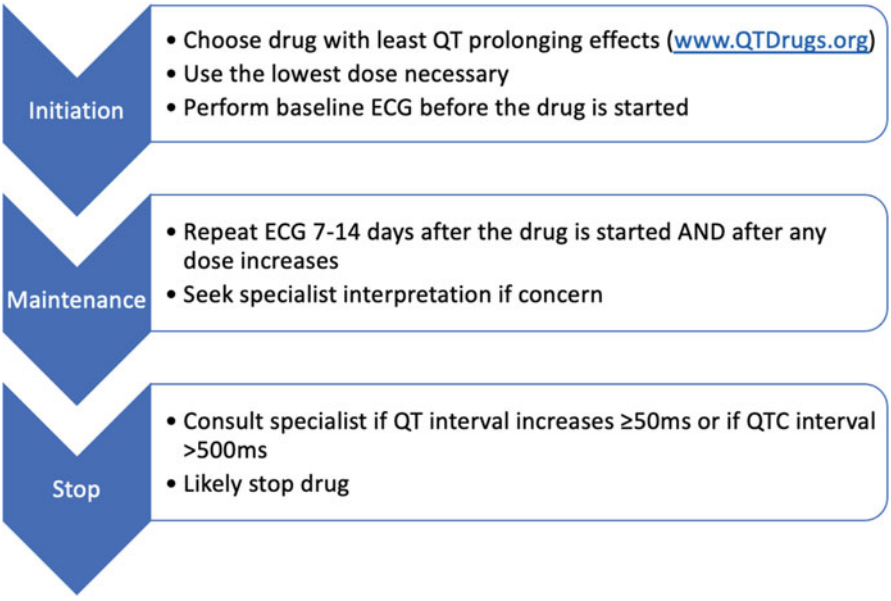


Fig. 3 Approach to prescribing QT-prolonging medications in AN

recommended steps to assess patients at risk of QT prolongation with the initiation and maintenance of QT-prolonging drugs. Once again, it is likely that any additional QT interval prolongation risk conferred by psychopharmacotherapy is dependent on a multitude of factors in patients with AN, from drug dose to current degree of disease exacerbation to underlying genetic predisposition. Nevertheless, it remains best practice to regularly evaluate the indication for these drugs throughout treatment, especially in light of evidence refuting their efficacy in AN.

Sudden Unexpected Death

The first evidence for an arrhythmic cause of sudden unexpected death (SUD) in the AN population was reported in 1985, in a case report of three patients with recorded QT interval prolongation in the days preceding SUD (Isner et al. 1985). Prolongation of the QT interval has been widely implicated in other SUD conditions, perhaps most prominently in the inherited long QT syndrome (Schwartz et al. 1993). As discussed above, QTc interval changes in patients with AN are variable and often within normal range, complicating the clinical implications. So, although this link was logical, in the over 35 years since its publication, a definitive consensus regarding the cause of SUD in AN has not been reached. If the QTc interval was primarily and independently involved in SUD risk, the evidence would reflect this. It is also plausible that inherited long QT, which is present in 1:2000 person, was present in those rare cases on SUD, and AN was a triggering factor in individuals otherwise at risk (Schwartz et al. 2009).

More recently, significant bradyarrhythmias such as sinus pause have been postulated as an etiology of SUD in AN (Farasat et al. 2020). This is a divergence from previous belief that ventricular tachyarrhythmias were the culprit as seen in other conditions, where SUD risk is increased. Nevertheless, given the high prevalence of bradycardia in AN, bradyarrhythmias are an important consideration, and this new hypothesis further supports the pursuit of prompt refeeding to normalize HR and reduce risk.

Clinical Use of the ECG in AN

Guidelines recommend routine ECG monitoring at diagnosis, throughout treatment, and annually in recovery as outlined in Table 2 (National Institute for Health and Care Excellence (NICE) 2017; Royal Colleges of Psychaitrists 2014). Patients with electrolyte imbalances or taking medications that may alter the HR or QTc interval should receive more regular monitoring, especially during acute exacerbations of AN. The ECG is best utilized and evaluated on a patient-specific level, taking all relevant clinical findings into consideration. For example, a prolonged QTc interval in a patient with concurrent hypokalemia would support more urgent electrolyte replenishment compared to a patient with mild hypokalemia without QTc interval prolongation.

For many centers, resolution or improvement of bradycardia is used as a marker of medical improvement during treatment for AN. For this reason alone, serial ECG monitoring is implicated. While a prolonged QTc interval may not be seen consistently

Table 2 Summary of indications to include ECG in clinical care of patients with AN. *Adapted from the 2017 NICE Guidelines and 2014 MARSIPAN Report.*

Primary care	
Baseline physical assessment	*Indicated if any of the following:* Rapid weight loss Excessive exercise Severe purging behavior Bradycardia Hypotension Excessive caffeine Muscular weakness Electrolyte imbalance Previous abnormal heart rhythm Medications that may compromise cardiac function (electrolyte imbalance, bradycardia, hypokalemia, QT prolongation)
Follow-up	Annual ECG recommended if purging behavior and/or significant weight change since last visit
Secondary/tertiary care (inpatient or day patient)	
Admission	All patients
Throughout treatment	*Daily ECG indicated if any of the following:* Bradycardia (HR <40 bpm) QTc interval prolongation (QTc > 450 ms [male] or > 460 ms [female]) Nonspecific T-wave changes Hypokalemia-associated changes
Follow-up	Monthly ECG recommended for seriously ill patients until clinical stability and/or absence of ECG abnormality

Table 3 Summary of ECG abnormalities seen in patients with AN

Parameter	Abnormality	Prevalence	Clinical implications/indications
Heart rate	Bradycardia (HR <50 bpm)	Very common	Monitor as outpatient depending on rest of clinical picture
	Severe bradycardia (HR <40 bpm)	Less common; likely more severe disease	Hospital admission supported
Heart rate variability	Decreased	Inconsistent	Monitor as outpatient depending on rest of clinical picture
QTc interval	Prolonged	Inconsistent	Review potential underlying causes of QT prolongation (e.g., drugs, electrolyte imbalance) and correct where possible
T-wave	Morphology changes	Unclear	Unclear, likely not independent risk factor

in patients with AN, it is important to monitor the ECG throughout treatment given the abundance of confounding factors present which may exacerbate QTc interval abnormalities. Importantly, routine ECG may identify a small, yet high-risk, subset of patients predisposed to ventricular arrhythmia. Common ECG abnormalities should be noted (Table 3), and more nuanced abnormalities such as T-wave morphology

changes may require consultation with experienced personnel, which should be sought with a low threshold of suspected abnormal ECG. In the authors' experiences, cardiology and/or electrophysiology specialists should be urgently consulted when the QTc interval $\geq$ 500 ms, especially in the absence of QT-prolonging factors.

Conclusion

The increased risk of SUD and potentially profound ECG changes, from severe bradycardia to prolonged QTc interval in a subset of patients with AN, have prompted a clinical interest in ECG monitoring. Bradycardia is reported in the majority of patients in part due to autonomic dysregulation, but with no apparent associated direct risk of arrhythmia or adverse events. As the current evidence stands, other definitive and consistent ECG changes have not been identified in the AN population. Nevertheless, the ECG remains an important and useful tool in monitoring individuals on a patient level, and the impact of common patient-specific confounders such as psychopharmacotherapy and electrolyte imbalances should be considered.

Applications to Other Eating Disorders

In this chapter we review the utility and changes seen on the electrocardiogram (ECG) in patients with anorexia nervosa (AN). Aside from bradycardia, the ECG changes described are likely multifactorial and impact only a subset of patients. As such, the underlying pathophysiology is not yet fully understood. Nevertheless, the ECG remains an important tool in the setting of AN to identify the subset of patients who may be at increased risk of adverse cardiac events and sudden death. It is likely that abnormal serum electrolytes and low BMI are significant contributors to the cardiac manifestations of AN. As such, we would expect to observe these complex findings in other eating disorders with similar etiology to anorexia nervosa.

In bulimia nervosa (BN), binge-purge cycles often exacerbate serum electrolyte disturbances. As a result, it was similarly hypothesized that QTc interval prolongation would be observed on the ECG of patients with BN. However, similar to AN, the impact on QTc interval prolongation is likely multifactorial as studies have found contrasting results in the BN population (Krantz et al. 2020; Frederiksen et al. 2018). Interestingly, in the subset of patients with BN who did show changes on their ECGs, these were not associated with worse long-term outcomes.

Mini-Dictionary of Terms

- Electrocardiogram: A minimally invasive test to measure the heart rate and heart rhythm.
- Heart rate: The number of heartbeats per minute.
- Heart rhythm: The pattern of how each heartbeat activates the heart.

- Bradycardia: A heart rate slower than 60 beats per minute.
- QTc interval: A measurement of cardiac repolarization on the electrocardiogram.

Key Facts of the Electrocardiogram in Anorexia Nervosa

- The electrocardiogram measures heart rate and heart rhythm.
- Certain heart rhythm abnormalities predispose patients to cardiac arrest and sudden death.
- Bradycardia is a slow heart rate, often seen in patients with anorexia nervosa.
- Other variations in the electrocardiogram in patients with anorexia nervosa are multifactorial and not fully understood.
- Electrocardiogram abnormalities usually revert to normal with weight restoration.

Summary Points

- Bradycardia (HR <60) is commonly seen in patients with anorexia nervosa.
- Resting QTc interval prolongation is not a reliable marker for cardiac risk in patients with anorexia nervosa.
- Electrocardiogram abnormalities generally return to normal with weight restoration.
- The mechanism underlying increased risk of sudden unexpected death in anorexia nervosa is not fully understood.
- Refeeding and weight restoration normalize ECG changes.

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Anorexia Nervosa and Concurrent Psychiatric Comorbidity

35

Gennaro Catone

Contents

Introduction 675
Psychiatric Comorbidity in Anorexia Nervosa 677
Population-Based Studies 677
Clinical-Based Studies 678
Theoretical Implications 679
Clinical Implications 680
Anorexia Nervosa and Depressive Disorders 681
Anorexia and Bipolar Disorders 683
Anorexia Nervosa and Anxiety Disorders 684
Anorexia and Obsessive-Compulsive Disorder 685
Anorexia Nervosa and Psychosis 686
Anorexia Nervosa and Other Disorders 687
Application to Other Eating Disorders 688
Mini-Dictionary of Terms 689
Key Facts 690
Key Facts of Depressive Disorders 690
Key Facts of Bipolar Disorders 690
Key Facts of Anxiety Disorders 691
Key Facts of Obsessive-Compulsive Disorders 691
Key Facts of Psychosis 691
Summary Points 692
References 693

Abstract

Psychiatric comorbidity indicates the possibility of diagnosing more than one disorder in the same individual. Anorexia nervosa presents a high psychiatric comorbidity with implications both on a theoretical and clinical level.

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Population-based and clinical-based studies provided lifetime and concurrent rate of the main psychiatric comorbidities in anorexia nervosa. In the community sample, anorexia nervosa presented a prevalence of approximately at least one psychiatric comorbidity ranging from 20% to 50%. In the clinical sample, results were oriented toward the search for the most frequent comorbid disorders. They are depressive and bipolar disorders, anxiety disorders, obsessive-compulsive disorders, psychosis, substance abuse disorder, and personality disorders. Concomitant psychiatric comorbidity has strong impact on the onset, course, clinical manifestations, prognosis, and treatment of AN; therefore, it should be carefully assessed and treated. Psychiatric comorbidity can impact on symptom severity, hinder functional recovery, substantially worsen outcome, and be a risk factor for mortality.

Keywords

Anorexia nervosa · Comorbidity · Depression · Bipolar disorder · Anxiety · Psychosis · Obsessive-compulsive disorder · Substance use disorder · Personality disorder · Outcome · Persistence · Relapse · Mortality · Treatment

Abbreviations

ALSPAC	Avon Longitudinal Study of Parents and Children
AN	Anorexia nervosa
BD	Bipolar disorder
BED	Binge eating disorder
BN	Bulimia nervosa
BPD	Borderline personality disorder
CGAS	Clinical global assessment scale
CGI	Clinical global improvement
CI	Confidence interval
CRH	Corticotropin-releasing hormone
DSM	Diagnostic and Statistical Manual of Mental Disorders (III, third edition; III R, third edition revised; IV, fourth edition; IV TR, fourth edition text revision; 5, fifth edition)
EDs	Eating disorders
FFMI	Fat free mass index
FMI	Fat mass index
GAD	Generalized anxiety disorder
GWAS	Genome-wide association study
MDD	Major depressive disorder
NA	Network analysis
NCR-S	National Comorbidity Replication Survey
OCD	Obsessive-compulsive disorder
OR	Odds ratio
OSFED	Other specific feeding and eating disorders
SD	Standard deviation

SGA	Second-generation antipsychotics
SSRIs	Selective serotonin reuptake inhibitors
TCAs	Tricyclic antidepressants

Introduction

Comorbidity is a term originally used in the divisions of internal medicine in order to indicate "any distinct additional clinical entity that has existed or that may occur during the clinical course of a patient who has the index disease under study" (Feinstein 1970). Originally related to epidemiological medicine and biomedical research, the term has progressively gained interest in psychiatry in correspondence with a paradigm shift in psychopathology. Klerman supports the thesis that the progressive introduction of the concept of multiple and discrete mental disorders, operational criteria, structured interviews, diagnostic algorithms, validity, and reliability progressively produced the effect to introduce the topic of comorbidity into psychiatric language (Klerman 1990). This psychopathological paradigm shift coincided with a renewed interest in nosology and diagnosis determined by the increasing demand of objectivity and reliability expressed by mental health professionals and researchers and by the progressive development of psychopharmacology and psychotherapeutic and psychosocial approaches.

In psychiatry, the definition of comorbidity is to be considered extensive; it depends on various factors. Burke introduced the temporal element and defined comorbidity as the presence of two or more disturbances in a given period of time; in a broader sense, this can be transposed to the lifetime, and therefore the temporal element becomes continuous rather than discrete (Burke et al. 1990). In epidemiological psychiatry, the comorbidity relates to the greater or lesser risk of developing a certain disorder or symptoms if you already have one. In a clinical perspective, the comorbidity construct indicates the possibility of diagnosing more than one disorder in the same individual or the coexistence of a disorder and a constellation of symptoms of another category(ies), which, however, do not meet the criteria defined for the diagnosis(es) (Maser and Cloninger 1990).

The increase in comorbid diagnoses began with the publication of the DSM III (1980) and more in detail of the DSM III R (1987). In fact the introduction of the multiaxial system and the subsequent change in hierarchical diagnostic rules allowed multiple diagnoses of comorbid states (Klerman 1990). DSM IV (1990) and DSM IV TR (1994) seem to encourage the coding of multiple diagnoses, underlying a principle that the collection of as much descriptive information as possible responds best to the complexity of clinical presentations. Furthermore, in the clinical setting, the patient with a complex clinical picture can receive specific treatments for each of the problems presented, while in the field of epidemiological research the high amount of information described allows to define more precisely population studies (Pincus et al. 2004).

In DSM 5 (2013), it is possible to grasp a new conceptual framework; the premise of this transition is the idea that an excessively rigid diagnostic classification system

cannot correctly represent the complexity of clinical experience and scientific research data. As a consequence, it has become clear that the boundaries between many categories of disorders are plastic, and therefore many symptoms can be found in more than one disorder, and this was also evident from studies on psychiatric comorbidity. Therefore, the DSM 5 introduces a dimensional approach to mental disorders that interfaces with the categorical one already in use (American Psychiatric Association, DSM-5 Task Force 2013).

Large epidemiological studies revealed that among patients who suffered from a mental disorder, 35% to 45% satisfied the criteria for two or even more psychiatric disorders (Van Loo et al. 2013).

Obviously, there is no lack of elements of critical judgment regarding the rapid expansion of psychiatric comorbidity, especially in the clinical and psychopathological fields.

Pincus et al. stressed that the uncertainty in the question whether the coexistence of symptoms indicates in a patient the presence of two separate clinical entities or on the contrary manifestations of a single disorder derives from the scarce knowledge we have accumulated on the etiology and pathophysiology of mental disorders (Pincus et al. 2004).

Vella et al. raised the issue relating to the problems that may arise in the transposition of the term comorbidity from medicine to psychiatry. They stated that "comorbidity should be the epidemiological descriptive starting point to build hypotheses that must be clear and rigorously defined, with specified usefulness and limits" with the possibility to test these hypotheses with appropriate methodologies (Vella et al. 2000).

Other critical issues that are raised refer to the low sample size, different definitions of time limits attributed to the comorbidity, and the presence of different methodological biases in the studies that have assessed psychiatric comorbidity. These epidemiological studies often suffer from selection bias (patients vs. general population, different clinical characteristics, rejection rates) or the absence of control groups (Siracusano et al. 2003).

Maj in a refined dissertation argues for the thesis that "the use of the term comorbidity to indicate the concomitance of two or more psychiatric diagnoses appears incorrect . . . and the usage of the term 'comorbidity' should probably be avoided." Obviously, the greatest criticism on the idea of psychiatric comorbidity occurs when the concept is handled from a psychopathological perspective, in fact the author affirmed that: "splitting a complex clinical condition into several pieces may prevent a holistic approach to the individual, he also added what is currently conceptualised as the co-occurrence of multiple disorders could be better reformulated as the complexity of many psychiatric conditions" (Maj 2005).

Lilenfield et al. (1994) argued that the term comorbidity is not appropriate to the psychopathological lexicon as it would express a level of knowledge of the categories, etiology, and pathophysiology of mental disorders that is currently lacking. They proposed the term co-occurrence (Lilienfeld et al. 1994).

Krueger and Markon (2006) proposed a conceptual framework to cope with these difficulties. They introduced a liability spectrum model of comorbidity in which

mental disorders are interpreted as the result of latent liability factors. This makes the concept of comorbidity predictable in light of the role of these factors on the onset of specific mental disorders (Krueger and Markon 2006).

Comorbidity has theoretical, research, and clinical implications for those involved in mental health. Rutter proposed that it could have a strong impact on research on current diagnostic constructs (Rutter 1994). Moreover, the concept is applicable to both general population and clinical studies. The accurate evaluation of comorbidity patterns could improve classification systems and answer a series of questions: "Are mental illnesses discrete entities? Are the diagnostic criteria used valid and reliable? What do we know about the course of the disease and the family aggregation of syndromes and symptoms? How do environmental and genetic factors interact with each other?" From a clinical perspective, it is possible to state that the issue of comorbidity has an impact on diagnosis, prognosis, and the choice of appropriate treatments (Maser and Cloninger 1990).

Leaving aside the implications of a psychopathological nature, in this chapter, the concept of comorbidity has primarily a statistical-quantitative significance linked to the methodology of research in epidemiology. The enlightenments of concurrent comorbidity in AN resume what the authors of the studies considered in this review have tried to interpret in an explanatory key based on the data presented. Comorbidities with neurodevelopmental disorders (i.e., autism spectrum disorder, ADHD) are not presented which, although they represent an emerging area of study, deserve a separate discussion.

Psychiatric Comorbidity in Anorexia Nervosa

Early clinical descriptions of AN had highlighted the association with other psychiatric manifestations such as anxiety and depression. Population-based and clinical-based epidemiological studies confirmed these observations.

Population-Based Studies

Hudson et al. examined a subsample ($n = 2980$, aged 18+) of the NCR-S. They found that the 56.2% of respondents who meet DSM IV criteria for AN had at least another DSM IV disorder assessed in the survey. In detail, 8.4% had exactly one disorder, and 14.1% had exactly two disorders, while 33.8% had three or more. The significant comorbidities were those with specific phobia (26.5%, OR = 2.1), MDD and dysthymia (39.1%, OR = 2.7, and 12.8%, OR = 4.5, respectively), and alcohol and/or drug misuse and/or dependence (24.5%, OR = 2.9, and 17.7%, OR = 3.4, respectively) (Hudson et al. 2007).

In the NCR-S adolescent supplement ($n = 10{,}123$, aged 13–18), the data on general comorbidity were quite similar; in fact, 55.2% of respondents with DSM IV criteria for AN showed at least another DSM IV disorder. Of these, the 28.4 had exactly one disorder, and 10.4% had exactly two disorders, while 5.5% had three or more. They diverged in relation to the type of concomitant disorder, as oppositional defiant disorder

was the most frequent and significant one in association with AN (30.4%, OR = 5.1). From these results, it is possible to affirm that the type of concurrent psychiatric comorbidity in the course of AN is age dependent and also in the adolescent range the single comorbidity is more frequent, while in the adult range the opposite occurs because multiple comorbidities are more represented (Swanson et al. 2011).

In a matched Denmark nationwide cohort study of individuals with diagnosis of AN (n = 9985 patients vs. 49,351 controls) with a follow-up analysis, the risk of developing any other psychiatric disorder was about 25% in the first 2 years and 55% in the two decades after the inclusion in the study protocol. Authors found a hazard ratio of seven to receive a concurrent psychiatric comorbidity in the first year after the diagnosis, and this risk was higher for patients aged 8–13 at the diagnosis. The comorbidities most frequent were affective, autism spectrum, personality, and obsessive-compulsive disorders. Interestingly, the rate of psychiatric morbidity tends to decrease over the years, but the risk of developing a psychiatric disorder after 20 years remains double or more than that of the general population (Steinhausen et al. 2021). In another prospective controlled study, 39% and 38% of subjects with adolescent-onset AN had at least the criteria for another concurrent psychiatric diagnoses (affective, anxiety, or psychotic disorders) at 18- and 30-year outcome, respectively (Wentz et al. 2009; Dobrescu et al. 2020).

Clinical-Based Studies

One of the first studies assessing comorbidity in anorexic patients examined a sample of 229 patients, of whom 41 (11%) had AN and 90 (29%) had anorexia/bulimia nervosa. Affective disorder was the most frequent comorbidity in the groups. Authors found also the co-occurrence of personality disorders, anxiety disorders, and substance use disorder. They concluded that treatment-seeking anorexics display a high rate of concurrent comorbidity and this has clinical implications because these patients entail diverse interventions (Herzog et al. 1992).

A clinical study on psychiatric comorbidity in 62 patients with feeding and eating disorders (48ss, 66.7% diagnosed with AN; 24ss, 33.3% diagnosed with OSFED) focused on the relationship between dimensional and categorical approach to comorbidity diagnosis. In this sample, the assessment was carried out with a clinician-rated questionnaire that investigated the categorical diagnoses (DSM based) and different self-report dimensional scales on depression, social anxiety, obsessive-compulsive symptoms, mania, paranoia, and hyperactivity. With the categorical approach, a quarter of patients had a comorbidity, while about half had two psychiatric comorbidities. The most frequent were social anxiety disorder (38ss, 52%), depressive disorder (31ss, 43.1%), and generalized anxiety disorder (14ss, 19.4%). Through the dimensional evaluation, it was possible to demonstrate that other psychiatric symptoms are distributed along a continuum in the course of AN. Moreover, with regard to the two most frequent comorbidities, the results showed that the participants were able to self-report the social anxiety symptoms, but they had difficulty in self-indicating depressive symptoms. This could indicate a tendency to deny depressive symptoms by those suffering from AN (Catone et al. 2020).

In 22-year follow-up study with 38 adolescents who met criteria for AN, 13 (34%) showed persistence of eating symptoms, whereas 25 (66%) had completely recovered. Of interest is the fact that psychiatric comorbidity mainly concerned the group with still active symptoms (Andres-Pepina et al. 2020).

In a Mexican adolescent sample study, the 78.12% ($n = 25$) of subjects with AN presented another psychiatric comorbidity (mood and anxiety disorders, substance-related and addictive disorders, disruptive and impulse control/conduct disorders, and neurodevelopmental disorders) (Ruiz-Ramos et al. 2021).

Theoretical Implications

The psychiatric comorbidity model in AN has been the subject of studies for a long time, and several authors have attempted to understand the nature of the relationship underlying this association. C. Bulik provided a starting point from which to test a series of hypotheses through clinical and community epidemiological studies. She indicated five plausible models to explain the relationship between eating and affective symptoms (Table 1).

Evidence suggests that there is little evidence for models 1, 3, and 4 as the conditions examined are not always found in comorbidities and the data do not converge on the hypothesis of a single shared factor. Rather, the evidence suggests that eating disorders follow the onset of affective disorders (this is especially true for anxiety disorders and AN), and they support the presence of both shared and specific causal factors (Bulik 2005).

A further study model of concurrent psychiatric comorbidity in AN is that related to the NA approach. In other words, the NA hypothesizes that mental disorders are made up of a constellation of symptoms, which in turn self-maintain each other. Therefore, the concurrent comorbidity corresponds to the situation in which the symptoms of different clusters are activated. The NA included nodes, which represent the selected variables, and edges that indicate the connections between the

Table 1 Bulik hypotheses of the nature of association underlying AN and affective disorders (anxiety, depression)

1	*Anxiety and depression are sequelae of eating disorder. The implications of this model are that affective symptoms do not manifest until after the onset of the eating disorder and they may respond to treatment of the underlying disorder*
2	*Eating disorders are sequelae of anxiety and depression. In this model, eating symptoms can improve following the treatment of affective symptoms*
3	*Eating disorders are expression of an underlying affective disorder. In this model, the causal factors are entirely shared among the two groups of disorders, and eating symptoms may be conceptualized as age and gender particular signs of affective disorders (forme fruste model)*
4	*Eating disorders and affective disorders are different manifestations of the same underlying etiological factors*
5	*Eating disorders and affective disorders may share same causal factors although they are to be understood as separate/distinct categories. In this model, there is no prediction of the succession of the various clinical manifestations*

various nodes. Centrality is a measure of the importance of a node within the network. Studies showed the centrality of general psychiatric symptoms (anxiety, depression) as well as core symptoms (drive to thinness and interoceptive awareness) in AN (Monteleone and Cascino 2021). Monteleone et al. explored the potential of the NA approach in studying comorbidity in 405 adolescent inpatients aged 9–18 with diagnosis of AN (duration of illness <3 years). In this sample, depressive symptoms and personal alienation were the nodes with the highest centrality followed by drive to thinness, asceticism, post-traumatic stress symptoms, anxiety physical symptoms, and low self-esteem. Potential maintaining comorbid symptoms belong to two different clusters: (1) negative affect symptoms/internalizing problems and (2) negative self-appraisal problems. This conceptual approach may suggest focusing the intervention on the symptoms that convey the concurrent comorbidity as well as the AN core symptoms, which are notoriously difficult to treat (Monteleone et al. 2019).

Clinical Implications

Clinically, the importance of concomitant psychiatric comorbidity lies in the impact it has on the onset, course, clinical manifestations, prognosis, and treatment of AN.

Psychiatric comorbidity could impact on AN symptom severity (Saccomani et al. 1998). For example, affective and especially anxiety disorders can worsen cognitive-affective eating disorder symptoms such as fixation on underweight, fear of weight gain, and preoccupation with weight and appearance; also dieting has been found to be linked with anxiety disorders, whereas binge/purging behaviors were associated with substance misuse disorders and cluster B personality disorders in addition to anxiety disorders. These findings derive from a study on a mixed population of 277 subjects with eating disorders, of which 84 (30%) had AN, and they confirmed that concurrent psychiatric comorbidity produces an increased severity of the eating disorder symptoms with recurrent patterns of association (Spindler and Milos 2007).

A further clinical aspect is AN recovery. It is not easy to define recovery in this field; in fact, physical, behavioral, and psychological indices should be considered. A group of patients with complete remission ($n = 20$) was compared with a group of subjects (1) in partial remission ($n = 15$), (2) with active disease ($n = 53$), and (3) with a healthy control group ($n = 67$). The complete remission group did not differentiate from the healthy control group in terms of having other non-eating axis I diagnosis (conversely the partial remission group and active disease group showed three and seven times greater risk, respectively). The subjects belonging to the complete recovery group and the healthy control group showed the same low rate of mood disorder comorbidity. The pattern of comorbidity with anxiety disorders was quite different; in this case, the total and partial remission groups showed comparable results, with a concurrent diagnosis rate of anxiety disorder higher than those in the group of healthy controls but lower than those relating to subjects in the active disease phase. The authors interpreted these results as confirming the hypothesis that anxiety disorders precede AN, while mood disorders are consequences (Bardone-Cone et al. 2010).

Comorbidity affects also outcome (Wentz et al. 2009; Dobrescu et al. 2020; Andres-Pepina et al. 2020). The severity of the clinical expression of AN is influenced by the psychiatric comorbidity (Riquin et al. 2021). In children and adolescent sample with AN, the comorbidity with mood disorders and personality disorders was associated with poorer outcome (Saccomani et al. 1998).

AN presents a higher risk of mortality than the general population and also other psychiatric and nonpsychiatric disorders. Comorbidity was considered a risk factor for mortality for AN in association with demographic and socioeconomic factors (Ulfvebrand et al. 2015). Himmerich et al. confirmed these observations in a retrospective study of 1970 subjects diagnosed with AN from the South London and Maudsley Foundation Trust retrieved through a clinical record interactive search. Indeed, mortality in the sample was moderately associated with concomitant substance use and personality disorders (Himmerich et al. 2019). Suicide is a significant element in AN mortality, and suicidality (suicidal ideation and attempts) is augmented in people with EDs compared to the general population especially when a concurrent psychiatric comorbidity occurs (Milos et al. 2004). There is evidence that AN, depression, and suicide attempts may share a strong common genetic predisposition (Thornton et al. 2016). In a sample of 288 ED patients including 87 anorexic patients (about 30%), a quarter admitted a lifetime suicide attempt, and the same proportion stated existing suicide ideation. Patients with a history of suicide attempt had a higher prevalence of mood disorders and cluster b personality disorders than patients who did not report a lifetime suicide attempt. Moreover, anxiety, depressive disorders, and clusters B and C and negativistic depressive disorders significantly increased the rate of concurrent suicidal ideation with an additive effect among various other associated psychiatric disorders. This effect was particularly pronounced for AN (Milos et al. 2004).

Woodside and Staab in a practical review summarized all the prominent aspects of the management of psychiatric comorbidity in AN. The starting point relates to the fact that the treatment of AN is complex, and therefore the concomitant presence of other psychiatric disorders adds further complexity. Furthermore, clinicians must take into consideration the effects of malnutrition and dysfunctional eating behaviors, which can impact on therapeutic choices and modify responses to treatment. The authors pointed out that the effects on concomitant psychiatric comorbidity are modest if there is no parallel improvement in starvation conditions and reduction of AN core symptoms (Woodside and Staab 2006).

Anorexia Nervosa and Depressive Disorders

Numerous evidences indicate that depression is the main comorbidity in the course of AN. Several authors identify shared etiological factors between the two conditions such as temperament, genetic aspects, altered neurotransmitter and neurometabolic profile, cognitive styles and attachment pattern, childhood trauma, and psychosocial functioning (Fernandez-Aranda et al. 2007). Depressive symptoms are often present in the course of AN, and they must be carefully evaluated to decide whether they delineate a depressive disorder according to the DSM 5 criteria; the main ones are

flattened mood, feelings of guilt, hopelessness and worthlessness, reduced self-esteem, difficulty in managing eating patterns, irritability, insomnia, suicide ideation, and attempts. These symptoms often impact on social, school, and work functioning (Siracusano et al. 2003; Bulik 2005). Fernandez-Aranda et al. in a study of 1371 individuals with EDs investigated the temporal relationship between the two diagnoses and looked for a potential clinical profile in the case depression precedes EDs. They found a great prevalence of MDD among EDs and quite high in binge/purging subtypes. Moreover, in one third of the sample, MDD preceded ED, and in this case patients reported a longer duration of depressive symptoms, greater psychomotor agitation, and increased thoughts about death but not increased suicidality (Fernandez-Aranda et al. 2007). In a 10-year controlled follow-up study of 51 adolescent-onset AN, authors found a high prevalence of depression among patients (84%) with respect to the control group (18%). Findings supported the thesis that depression was concomitant or subsequent AN onset, but depression itself predicted further depressive episode in the longitudinal observation (Ivarsson et al. 2000). The prevalence of depressive disorder in AN varies according to epidemiological studies between 20% and 94% (Ivarsson et al. 2000; Kennedy et al. 1994; Blinder et al. 2006; Godart et al. 2007). These studies differ in the choice of diagnostic instruments used ranging from structured interviews to self-report tools (Srober and Katz 1997); furthermore, samples were different between the various studies (in- and outpatients, volunteers in evaluation or treatment phase, follow-up patients), and there are several general methodological limitations (small sample, difference in the assessment procedure, potential selection bias, lack of control group, difference between concurrent and lifetime prevalence, and changing in diagnostic criteria for anorexia nervosa and depressive disorder). In a descriptive review of *methodological issues and prevalence findings*, Godart et al. examined studies of mood disorder comorbidity among anorexic subjects until 2006 (Godart et al. 2007). MDD was present in a range between 9.5% and 64.7% in the restrictive subtype AN and between 50% and 71.3% in the binge/purging subtype in five referred patient sample studies; moreover, MDD concurrent prevalence was about 2.2–35.3% in a seven follow-up studies of anorexic patients. The concomitant dysthymic disorder in AN has been estimated between 13% and 33% with contrasting results in the AN subtypes with unclear results when compared to control groups.

A further issue relates to the possibility that depressive symptoms are linked to the state of malnutrition with conflicting results deriving from the various studies. Pleple et al. demonstrated a positive relationship between markers of nutritional status (BMI, FMI, FFMI) and anxious and depressive symptoms (Pleple et al. 2021). Voderholzer et al. found different results in a study of 418 women with AN (mean age at hospitalization 26.42 years, range 18–62), of whom 152 (36.4%) suffered from a depressive episode and 165 (39.5%) from recurrent depressive episodes. In their analyses, depressive symptoms and BMI are not correlated, and this negative association was evident both at the time of admission and that of discharge (Voderholzer et al. 2016). It is difficult to establish if depressive symptoms precede AN or some effects of eating psychopathology such as starvation and neurometabolic alteration led to chronic depressive state. Some authors indicate that the AN-depression association is multifactorial and therefore not reducible to

the effects of malnutrition; other authors, on the other hand, indicate that malnutrition and caloric restriction can generate an increase in CRH and a reduction in serotonin functioning, both factors implicated in the onset of depression (O'Brien and Vincent 2003). Concomitant mood disorder is associated with a poorer outcome of the underlying AN pattern with worse response to treatment (Halmi et al. 1973). In a 7-year follow-up study of 34 anorexic inpatients, authors found a positive and significant association between depression and AN outcome; therefore, the persistence of one condition entailed the persistence of the other as well (Herpertz-Dahlmann et al. 1995). Finally, AN and depressive disorder are considered two conditions to be at high risk for suicide, and the risk is higher when there is comorbidity between these disorders. In fact, suicide attempts occurred more frequently in patients with AN and depression than in those with only AN, and furthermore suicide attempts were reported mainly during the exacerbation of depressive symptoms (Bulik et al. 2008). A recent community cross-sectional study (8.746 Chinese students, mean age 15.38 years, SD 1.95 years) pointed out that AN is an indicator of suicidal thoughts and depression associated with AN has a synergistic effect on these thoughts (Lian et al. 2017). Thornton et al. in the Swedish Twin Study of Adults: Genes and Environment provide an indication of the common biological disposition to AN, depression, and suicide which is represented by a genetic liability (Thornton et al. 2016).

Anorexia and Bipolar Disorders

The association between AN and BD received less attention than those with unipolar depressive mood disorders. McElroy et al. summarized the few and scattered contributions on the argument (McElroy et al. 2005). In a community controlled longitudinal study of 810 female of which 19 were classified as full eating syndrome ($n = 7$ AN) and 23 as partial eating syndrome ($n = 9$ AN), there was no difference between eating disorder groups and control group regarding the prevalence of bipolar disorder diagnosis; however, the presence of subthreshold bipolarity was significantly greater in the full eating syndrome group (26.3%) and partial eating syndrome group (21.7%) than in the control group without eating disorders (3.8%). At the follow-up point, bipolar disorder period prevalence rate was 10.5% and 8.3%, respectively, in the two groups and significantly higher than in control groups (Lewinsohn et al. 2000). Clinical studies suggested a range of 2.4–16.1% of AN in bipolar disorder patients. In detail, Halmi et al. found ten BD (two mania, two BD, and six atypical BD in a sample of 62 females with AN) (Halmi et al. 1991). AN and BD share several phenomenological similarities. Both disorders start in adolescence and presented an episodic chronic course. Manic symptoms such as elation, irritability, mood swings, hyperactivity, hypertalkativeness, impulsivity, insomnia, poor insight, delusions, and behavioral agitation may occur during AN. Two recent studies showed interesting results. In the first one, the sample was constituted by 288 patients with EDs (aged 18–24). In the AN subsample ($n = 54$), nine subjects (16.7%) had lifetime occurrence of bipolar disorder, a rate significantly higher than in the control group. Furthermore, the comorbidity of EDs and bipolar disorder also

showed increased psychiatric comorbidities with anxiety disorders, impulsivity, suicidality, and increased intensity of body concerns (Tseng et al. 2016). In the second one, the comorbidity with BD worsened the clinical (psychiatric and nutritional) state of AN, extended the duration of AN, and increased the association with other psychopathological symptoms and syndromes, requiring greater use of psychotropic drugs (Radon et al. 2021). A recent review highlighted that the presence of a bipolar disorder had a negative impact on outcome and quality of life and raised reflections on additional treatment modalities (Craba et al. 2021).

Anorexia Nervosa and Anxiety Disorders

The first observations on AN anxiety comorbidity highlighted a similar phenomenology between the two conditions with respect to clinical presentations, familiarity, and response to treatment. Both conditions share essential psychopathological aspects such as the distress of negative evaluation (social phobia) as well as the fear of gaining weight (weight phobia) which is a nuclear symptom of AN; in this light, anxiety is considered an onset and maintenance factor for AN (Bulik 1995). In most epidemiological studies on EDs, the presence of anxiety disorders in both probands and family members is very high, and both conditions respond to treatment with SSRIs.

Several studies assessed the comorbidity between AN and anxiety disorder (Godart et al. 2002; Swinbourne and Touyz 2007).

Kaye et al. found a prevalence of *at least one anxiety disorder* in 55 of 97 (55%) anorexic subjects, of which 21 (22%) had social phobia. The onset of social phobia, specific phobia, and GAD usually preceded AN, whereas panic disorder and agoraphobia were successive. Further findings indicated that the BMI was higher if there was no concomitant anxiety disorder and that various aspects of the eating disorder (perfectionism, avoidance) worsened in the presence of acute state of eating pathology and concomitant anxiety disorder (Kaye et al. 2004). Swinbourne et al. found approximately the same results in a sample of 50 inpatients (mean age 25.4, SD 8.3) which included 33 anorexics (66%). The percentage of those with *at least one anxiety disorder* was around 70% ($n = 23$), and social phobia had a prevalence of 27.3% ($n = 9$) (Swinbourne et al. 2012).

In a controlled cross-sectional study of 271 women seeking treatment (166 anorexics, 111 restrictive subtype, 55 binge/purging subtype), the presence of at least one concomitant anxiety disorder was high (62.2% restrictive subtype, 63.6% binge purging subtype) and greater than in the control group. The most frequent anxiety disorders were generalized anxiety disorder (48.6% and 45.4% in the two subtypes, respectively) and social phobia (30.6% and 32.7% in the two subtypes, respectively). Separation anxiety history was common in AN (18.2% restrictive subtype and 12.7% binge/purging subtype). Less than half of the comorbid cases showed that the anxiety disorder preceded AN and social phobia most regularly respected this pattern (Godart et al. 2003). Lavender et al. in a refined study on 118 anorexic women demonstrated that eating disorder symptoms and behaviors were associated with different daily patterns of anxiety. For example, binge and

vomiting behaviors early in the day were associated with a decrease in anxiety throughout the day or if they showed up late were consequences of an increase in anxiety during the day. Furthermore, high anxiety during the day was associated with concomitant mood disorder, affective lability, self-harm, oppositive behaviors, and social avoidment (Lavender et al. 2013). Several interpretations suggest a contributing role of anxiety in AN. AN have typically onset in mid-late adolescence, whereas anxiety disorders develop in childhood – early adolescence. Some authors propose that cognitive and behavioral symptoms of AN (restrictive diet, prevalent ideation about food and diet) could reduce preexisting anxious symptoms and thus maintain the eating disorder. Lloyd et al. conducted a systematic review of the longitudinal association between anxiety and AN (Lloyd et al. 2019). There was an association between childhood anxiety and AN in retrospective studies, while the prospective studies failed to clearly demonstrate a functional association between a specific anxiety disorder and AN although the authors concluded that this did not imply the absence of a significant correlation between the two conditions. From the analysis of the retrospective studies, it was possible to state that subjects with AN reported anxiety more frequently than control groups in childhood, but there was no evidence that anxiety could be the only factor that could explain the subsequent development of AN. A study by Taborelli et al. highlighted that separation anxiety was more endorsed in childhood by subjects with AN than healthy sister who represented the control group (Taborelli et al. 2013). A prospective study (23 years) by Maier et al. in a childhood cohort of a large community sample ($n = 1{,}664{,}876$) from Danish population registry found that GAD and social anxiety diagnoses increased the risk of developing AN and the AN – social anxiety association was maintained even after control with confounders (age, sex, family psychiatric history, other psychiatric comorbidities excluding anxiety disorders). However, if the analysis was controlled by including the presence of other anxiety disorders as confounders, the results excluded that a single anxiety disorder could have an independent effect on the onset of AN (Meier et al. 2015). A recent longitudinal study using data from the ALSPAC demonstrated a robust association between the presence of an anxiety disorder at age 10 and subsequent develop on AN at age 24, moreover worry had a fundamental impact on a successive AN onset (Lloyd et al. 2020).

Anorexia and Obsessive-Compulsive Disorder

The overlap between OCD and anorexic symptoms was highlighted from the first observations and clinical descriptions of AN. Properly in AN we observe obsessive concerns on the theme of eating, weight and body shape; ritualized behaviors at mealtimes and compulsive physical activity (Bulik 1995). The prevalence of OCD approximately ranged from 6% to 35% (Kaye et al. 2004; Swinbourne et al. 2012; Godart et al. 2003). In children and adolescents, the percentages were higher (50–60%) (Serpell et al. 2002; Blinder et al. 2006).

The present prevalence of OCD in 58 anorexic inpatients and outpatients (mean age 18.6 years, SD ±4) was 19% ($n = 11$), a significantly higher proportion than in the control group. This study evaluated also difference between AN subtypes:

(1) AN restrictive subtype had a prevalence of 16% (7/44) and (2) AN binge/purging subtype had a prevalence of 29% (4/14). These results were in contrast to other results which showed a higher prevalence of OCD in the restrictive subtype (Deep et al. 1995). Finally, the AN-OCD association presented a clinical profile characterized by a lower BMI than AN without this comorbidity (Speranza et al. 2001). In another study, OCD comorbidity was related with a higher duration of AN illness; in this sample constituted by 84 females with AN, the prevalence of concomitant OCD was 28.6% (Milos et al. 2002). In a recent report, results indicated that subjects diagnosed with OCD had a 17 times greater risk of also having AN and this risk was higher for males. Furthermore, in the longitudinal analyses, the risk of OCD in patients with AN was four times greater than in the control population (mean interval between the two diagnoses = 2.2 years), while the risk of developing OCD in AN subjects was ten times greater than in the control group (mean interval between the two diagnoses = 2.4 years) (Cederlof et al. 2015).

Many studies agree on the observation that obsessive traits were present before the onset of eating symptoms and furthermore starvation can worsen these pre-existing aspects. Furthermore, there could be a similar genetic and neurotransmitter profile between the two conditions as they both respond to SSRI treatment (O'Brien and Vincent 2003; Halmi et al. 1991). Ylmaz et al. reviewed the shared genetic basis of AN and OCD using a GWAS meta-analysis that confirmed the elevated genetic correlation between the two conditions (Yilmaz et al. 2020). Finally, the association between AN and OCD has been linked to a clinical profile characterized by excessive physical activity, exercise, and orthorexia (Davis and Kaptein 2006; Dell'Osso et al. 2016; Young et al. 2013).

Anorexia Nervosa and Psychosis

The association between AN and psychosis was less explored than that with affective disorders. Contributions on the topic mainly concern the association of AN with psychotic symptoms and/or schizophrenia or the use of antipsychotic drugs.

In the association studied contributions are mainly case reports or case series (Miotto et al. 2010; Sarro 2009; Grounds 1982). Others studies highlighted the concomitant of AN and schizophrenia (Lyon and Silber 1989; Kouidrat et al. 2014). Looking at several study designs, Hudson et al. found a prevalence of psychotic symptoms in 17 patients among 130 consecutive anorexic patients (Hudson et al. 1984). McGrath et al. were interested in the temporal relationship between the two conditions and whether the anorexic symptoms preceded the psychotic ones or the opposite. They analyzed the bidirectional relationship concerning the DSM-IV-TR diagnostic categories and psychotic symptoms in 31.261 respondents belonging to an international survey. In their analysis, authors showed a significant temporal relationship between AN and psychotic symptoms (OR 2.8, 95% CI = 1.0–7–8) demonstrating that anorexic symptoms preceded psychotic ones. The inverse relationship (psychotic symptoms – AN) was not significant

(McGrath et al. 2016). A recent study investigated the relationship between AN and paranoia. Data showed that paranoia was dimensionally distributed among 92 adolescents (mean age 14.3 years, SD 1.9 years, age range 11–17.8 years) with diagnoses of AN (66, 71.7%) and OSFED (26, 28.3%). Furthermore, in this population, the presence of paranoia was more explained by the concomitant presence of social anxiety and depression rather than by the core symptoms of eating disorder and by body image concerns (Catone et al. 2021). These results support recent cognitive models that attribute an important role to emotional symptoms in the onset and maintenance of paranoia (Garety et al. 2001).

The role of SGA in the treatment of AN is currently controversial. For example, in several studies, these medications appear to improve anxiety-depressive symptoms and some core symptoms of the eating disorder, but generally findings have failed to demonstrate a general improvement and an increase in BMI compared to placebo control group. Authors conclude that further studies are needed with large sample and improved methodology; moreover, antipsychotics may be useful in some patient subgroups or individual cases (McKnight and Park 2010; Lebow et al. 2013; Dold et al. 2015; Kishi et al. 2012; Brewerton 2012; Hagman et al. 2011). Pisano et al. presented a naturalistic clinical data from five patients with AN in treatment with olanzapine that showed an improvement in 6 months of follow-up (Pisano et al. 2014). Clinical data were focused on the clinical presentation of the AN in order to highlight which clinical features should direct toward a pharmacological treatment with SGA. Eligibility criteria were displayed in Table 2.

In a retrospective study of 106 adolescents, treatment with aripiprazole as part of a specialized intervention on eating disorders was associated with an increase in BMI compared to the control group (Frank et al. 2017).

Anorexia Nervosa and Other Disorders

Several clinical and community studies assessed the comorbidity between AN and substance use. There is a substantial convergence of data in favor of the greater predisposition to the use of substances for the AN binge/purging subtype, especially when alcohol is taken into consideration. Root et al. analyzed this association in two different samples. In the first one ($n = 731$ participants), alcohol abuse dependence was 13.7%, 19%, and 23.9%, respectively, in the AN restrictive subtype ($n = 328$),

Table 2 Eligibility criteria for SGA treatment by Pisano et al.

1	*Patient is nonresponder (weight and food intake continue decreasing) for at least 1 month of psychological and psychoeducational interventions*
2	*Is consuming a mean caloric intake < 800 kcal/day*
3	*Has comorbid bipolar (I, II, or NOS) or disruptive mood dysregulation disorder with overactivity*
4	*Has high functional impairment and clinical severity (CGAS < 51, CGI-S ‡4)*
5	*Has low insight*

AN purging subtype ($n = 184$), and AN binge subtype ($n = 109$); drug use was 23.2%, 29.9%, and 25.7%, respectively, in the AN restrictive subtype, AN purging subtype, and AN binge subtype; and drug dependence was 6.4%, 14.1%, and 17.4%, respectively, in the AN restrictive subtype, AN purging subtype, and AN binge subtype (Root et al. 2010a). In the second sample, they confirmed that alcohol abuse/dependence, diet pills weekly, stimulants ever and polysubstance ever were more likely in the AN binge/purging subtype than in the AN restrictive subtype (Root et al. 2010b). Personality disorders are often comorbid with EDs. In summary, there is a close relationship between binge/purging symptoms and BPD and cluster C personality disorder and restrictive symptoms of AN (O'Brien and Vincent 2003). An extensive review of the literature has shown a frequency of 22% of obsessive-compulsive personality disorder in the restrictive subtype and a frequency of 25% of BPD in the binge/purging subtype. In a clinical analysis, the characteristics of obsessive-compulsive personality disorder are frequently found in the AN restrictive subtype. They are concern for details; the tendency to organize through lists and rules; perfectionism; dedication to the task; hyperconscientiousness and moral inflexibility; rigidity, which are found in the restrictive AN in the form of rigid adherence to diet; counting calories and nutrients contained in food; extreme dedication to weight loss; social isolation; perfectionism; and the desire to achieve a culturally defined ideal of thinness. On the other hand, impulsivity, self-harm, emotional instability, a sense of emptiness, irritability, and unstable relationships are the characteristics of borderline personality disorder which are found in the AN binge/purging subtype in the form of episodes of binge eating and elimination conducts (vomiting, use of laxatives and diuretics) (Sansone and Levitt 2006). Moreover, cluster C disorders and depressive negativistic personality disorder were related to fixation to underweight, fear of weight gain, preoccupation with weight and appearance, and dieting; instead, cluster B disorders were associated with binge eating behaviors and vomiting (Spindler and Milos 2007).

Application to Other Eating Disorders

Bulimia nervosa is more common than AN. Its prevalence is approximately 1–2% in the female population (Keski-Rahkonen and Mustelin 2016). Clinically, BN often presents with other psychiatric comorbidities. Several studies have confirmed the concomitance of anxiety disorders (Bulik 2005), mood disorders (Miniati et al. 2018), substance abuse (Fouladi et al. 2015), personality disorders (Himmerich et al. 2019), self-harm, and suicidal ideation (Anderson et al. 2002). The high prevalence of anxiety disorders in bulimia nervosa and the evidence that bulimic symptoms often follow anxious symptoms led researchers to speculate that binge/purging behaviors may have an effect to reduce subjective anxiety. Social phobia and GAD are the most common anxiety disorders in BN (Bulik 2005). Depressive and bipolar disorders are frequent among subjects with BN (Godart et al. 2015; Tseng et al. 2016). Depressive symptoms are considered to be maintenance factors in bulimic behaviors, and they have been associated with persistence of the disease,

relapse, and negative outcome (Linardon et al. 2017). The concomitance of BN and bipolar disorder displayed poorer outcome, lower quality of life, impulsivity, and further psychiatric comorbidity which in turn expose you to greater suicidal risk (Tseng et al. 2016). The relationship between BN and substance abuse has been studied for a long time. Many results converge on the hypothesis that substance abuse is often the result of the concomitance of BN and other psychiatric disorders, especially personality disorders (O'Brien and Vincent 2003). As already mentioned, the personality disorder most associated with the bulimic profile (binge/purging behavior) is BPD. In a recent study, BN BPD comorbidity showed a significant effect on mortality in a sample of 1501 bulimic subjects (Himmerich et al. 2019). The association of impulsive behaviors, substance abuse, and other psychiatric and personality disorders confers a greater suicidal risk than in patients with BN without psychological comorbidities (Spindler and Milos 2004; Milos et al. 2004). BED is often associated with depressive and bipolar disorders, anxiety disorders, substance abuse disorders, and personality disorders. Obviously negative affect may trigger binge eating and loss of control. Another issue is the obesity responsibility in the onset of psychiatric comorbidity. BED showed elevated suicidal risk when it presents with other psychiatric comorbidities (Welch et al. 2016).

Mini-Dictionary of Terms

- **Hierarchical diagnostic rules:** Rules that regulate the process of diagnosis and that do not allow certain diagnoses to be made when certain conditions coexist
- **Diagnostic and Statistical Manual of Mental Disorders fifth edition (DSM 5)**: It is a classification and categorization tool of the main psychiatric disorders published by the American Psychiatric Association in which experts from all over the world collaborate. It has reached its fifth edition published in 2013
- **Dysthymia**: Also called persistent depressive disorder, it is characterized by depressive symptoms for at least 2 years (in children and adolescents, the duration must be at least 1 year)
- **Major depressive disorder**: In the DSM 5, MDD is described such as the presence of depressive symptoms for at least 2 weeks
- **Personality disorders**: In the DSM 5, personality disorder is defined: "a constant pattern of internal experience and behaviour that is profoundly different from what is expected based on the culture of the individual. It is characterized by stability, pervasiveness and inflexibility. This pattern begins in adolescence or early adulthood and causes discomfort". Personality disorders are classified into three groups: *Cluster A personality disorders*, paranoid personality disorder, schizoid personality disorder, and schizotypal personality disorder; *cluster B personality disorders*, antisocial personality disorder, borderline personality disorder, histrionic personality disorder, and narcissistic personality disorder; and *cluster C personality disorders*, avoidant personality disorder, dependent personality disorder, and obsessive-compulsive disorder

- **Psychopathology**: The definition of Schulze-Lutter et al. was provided: "Psychopathology is the scientific exploration of abnormal mental states that, for more than a century, has provided a Gestalt for psychiatric disorders and guided clinical as well as scientific progress in modern psychiatry" (Schultze-Lutter et al. 2018)
- **Recovery**: Suggested operational recovery criteria by Bardon-Cone used in the text were as follows: (1) no longer encounter diagnostic criteria for AN, (2) absence of binge/purging or fasting behavior in the past 3 months, (3) a body mass index not lower than 18.5 mg/kg, and (4) results within 1 *SD* on all the subscales of the Eating Disorder Examination-Questionnaire (EDE-Q; Fairburn and Beglin 1994)
- **Suicidality:** Dimensional concept that starts from the vague and sporadic suicidal ideation up to the complete suicidal act

Key Facts

Key Facts of Depressive Disorders

In the DSM 5, depressive disorders are disruptive mood dysregulation disorder, major depressive disorder, persistent depressive disorder (dysthymia), premenstrual dysphoric disorder, depressive disorder due to another medical condition, and depressive disorder with other specification and without specification. Major depressive disorder is characterized by the presence of depressed mood, loss of interest, and irritability to which changes in appetite and weight, sleep, psychomotor activity, anergy, low self-esteem, and difficulty in attention and concentration can be added. Symptoms must be present daily for at least 2 weeks. Suicidal ideation may be present. The DSM 5 recognizes a 12-month prevalence of the disorder of 7% with greater frequency in women and in the 18–29 age group. The course has frequent relapses. Dysthymia presents persistent depressed mood with at least two additional symptoms described above for major depressive disorder. The 12-month prevalence in the United States is between 0.5% and 1.5%. The treatment of depressive disorder is combined in moderate-severe forms and uses psychotherapy and psychopharmacology

Key Facts of Bipolar Disorders

In the DSM 5, bipolar disorders are bipolar disorder I, bipolar disorder II, cyclothymic disorder, and bipolar disorder substance/drug induced, due to another medical condition or unspecified. Bipolar disorder I is characterized by the presence of a manic episode which may be preceded or followed by hypomanic or major depressive episodes. Manic episode presents elevated or irritable mood lasting at least 1 week, increased activity with associated high self-esteem, reduced need for sleep, increased speed of thought and language with hypertalkativeness, and involvement in potentially harmful activities. The 12-month prevalence of bipolar disorder I is

about 0.6%. Bipolar disorder II is characterized by the presence of hypomanic and depressive episode; hypomanic episodes are of a shorter duration and intensity than manic ones. The course of bipolar II disorder is chronic, characterized by the alternation of episodes. The prevalence at 12 months is estimated at around 0.3%. Cyclothymic disorder is constituted by chronic mood alteration (at least 2 years) with alternating symptoms relating to the two depressive-hypomanic polarities without, however, the criteria for depressive/hypomanic episode being met. In the studies presented above on the association between AN and bipolar disorders, authors usually included not only categorical diagnosis of BD but also those contributions/participants related to the broad bipolar spectrum, including subthreshold presentations. This approach appears to be more inclusive and useful in order to obtain information about this particular comorbidity

Key Facts of Anxiety Disorders

In the DSM 5, anxiety disorders are presented with an order relative to the age of onset. They are separation anxiety disorder, selective mutism, specific phobia, social phobia, panic disorder, agoraphobia, and generalized anxiety disorder. The various disorders differ substantially in the content of the threat and in the intensity and duration of cognitive, somatic, and behavioral symptoms. For example, in separation anxiety disorder, the separation from the reference figure represents the stressful event, while in social phobia it is related to the possible judgment by others. Panic disorder has high intensity and short-duration acute symptoms, while generalized anxiety disorder shows low intensity and long duration symptoms. Anxiety disorders are widespread in the general population and require combined psychoeducative, psychotherapeutic, and psychopharmacological treatments

Key Facts of Obsessive-Compulsive Disorders

Obsessions are recurring and persistent thoughts, impulses, and images, experienced as intrusive and unpleasant; compulsions are repetitive attitudes or mental actions that usually follow an obsession. The annual prevalence in the United States of OCD is 1.2%, and the disorder is more frequent in females, but in males the onset is anticipated. The course is chronic if left untreated. OCD responds to drug treatment with SSRIs and TCAs in combination or not with psychotherapeutic treatments

Key Facts of Psychosis

Psychosis is severe type of psychiatric disorder, expression of an alteration of the psychic stability of the individual, with impairment of reality examination, frequent absence of insight, and frequent presence of thought disorders, delusions, and hallucinations. Psychosis is often accompanied by an altered relationship with

reality, impairment of one or more mental functions, disintegration of the personality, lack of insight, very marked regression, primordial and catastrophic anxieties, and defense mechanisms such as scotomization and external projection. Schizophrenia is characterized by the presence of delusions, hallucinations, speech and disorganized behavior, decreased expression of emotions, and abulia with a chronic and worsening course with remissions and exacerbations of active symptoms. The prevalence of schizophrenia is 0.3–0.7%

Summary Points

- The association of two or more mental disorders, properly psychiatric comorbidity, has increased in recent years, and this is due to multiple factors including introduction of the concept of multiple and discrete mental disorder categories, operational criteria, structured interviews, diagnostic algorithms, validity, and reliability of the diagnosis
- AN displays a high level of psychiatric comorbidities, and this has been confirmed by population-based and clinical-based studies
- Several theories have been attempted to explain the frequent association between AN and other psychiatric disorders. Findings suggest that there may be common causative and maintenance factors or that AN may complicate a preexisting affective disorder. Negative affect symptoms and negative self-appraisal are potentially important as well as eating core symptoms
- Clinically, the presence of psychiatric comorbidities in the AN has an impact on the onset, course, severity of clinical manifestations, recovery, outcome, and prognosis with evidence of increased mortality and suicidal risk
- Treatment of AN is complex, and therefore the presence of psychiatric comorbidity adds further complexity. The effects of malnutrition and dysfunctional eating behaviors must be taken into account as well as the evidence that improvements on the psychological state are usually obtained after improvements on the physical level
- The AN-depression association is the most frequent. The two conditions can potentially share numerous causal and maintenance factors. It is not clear whether depression precedes or follows AN, but an area of investigation is the link between malnutrition and depressive symptoms. Comorbidity AN-depression increases suicidal risk
- Some symptoms of the bipolar spectrum are often present in the course of AN such as hyperactivity, hypertalkativeness, impulsivity, insomnia, and poor insight. Comorbidity AN-bipolar disorder was associated with a negative outcome, worse quality of life, and greater treatment complexity
- Anxiety usually precedes AN. Several authors suggest that anorexic symptoms may have the function of reducing underlying anxiety. The most common anxiety disorders are social phobia and GAD
- Anorexia nervosa and OCD appear to share common psychopathological features and several causative and maintenance factors. This comorbidity is very common

- The association between AN and psychosis has been less studied than the other comorbidities. The most promising area of investigation is that relating to the use of SGAs, in particular populations of patients with severe AN
- Substance abuse is more common in the AN binge/purging subtype
- The binge/purging subtype is often associated with cluster B personality disorders
- The restrictive subtype is often associated with obsessive-compulsive personality disorder

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Part III

Bulimia Nervosa

The Growth Hormone-IGF-1 Axis in Anorexia Nervosa

36

Anamil Khiyami and Pouneh K. Fazeli

Contents

Introduction 703
GH and IGF-1 Levels in Anorexia Nervosa 703
Potential Causes and Mechanisms of GH Resistance in Anorexia Nervosa 705
Protein Deficiency 705
Ghrelin 705
Sirtuin 1 706
CREBH 706
Fibroblast Growth Factor (FGF)-21 707
Insulin 707
Triiodothyronine 707
Leptin 708
Estradiol 709
Testosterone 709
Effects of GH Resistance on Bone Mineral Density 709
Effects of GH and IGF-1 Replacement in Anorexia Nervosa (Table 1) 710
Recombinant Human GH 710
Recombinant Human IGF-1 710

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Applications to Other Eating Disorders 714
Conclusions 714
Mini-Dictionary of Terms 715
Key Facts of the GH/IGF-1 Axis 715
Summary Points 715
Conflict of Interest 716
References 716

Abstract

Anorexia nervosa is a psychiatric disorder characterized by low body weight and serves as a model of chronic human starvation. Humans have evolved hormonal adaptations to survive periods of starvation. One critical response to periods of decreased nutrient intake is growth hormone (GH) resistance. This adaptive response allows for the maintenance of the beneficial counter-regulatory properties of GH during periods of low caloric intake, while minimizing energy expenditure on growth-related processes. This chapter will review the GH-insulin-like growth factor-1 (IGF-1) axis in anorexia nervosa. We will also describe potential mechanisms of GH resistance in this disorder, the effects of GH resistance on bone mass in anorexia nervosa, and the effects of treatment with exogenous GH and IGF-1 in anorexia nervosa.

Keywords

Anorexia nervosa · Growth hormone · IGF-1 · Bone mineral density · Growth hormone resistance · Chronic starvation · Adaptive response · Exogenous GH · rhIGF-1

Abbreviations

AN	Anorexia nervosa
BMD	Bone mineral density
BN	Bulimia nervosa
CREBH	cAMP-responsive element-binding protein H
FGF-21	Fibroblast growth factor-21
GH	Growth hormone
GHSR1a	Growth hormone secretagogue receptor 1a
IGF-1	Insulin-like growth factor-1
kg	Kilograms
mcg	Micrograms
mg	Milligrams
rhGH	Recombinant human growth hormone
rhIGF-1	Recombinant human insulin-like growth factor-1
SIRT1	Sirtuin 1
STAT5	Signal transducer and activator of transcription 5
T3	Triiodothyronine

Introduction

Anorexia nervosa affects up to 2.2% of women (Keski-Rahkonen et al. 2007) and is defined by low body weight due to self-induced starvation. This psychiatric disorder, which affects women more often than men, can serve as a model of chronic starvation in humans. As our evolutionary past was marked by periods of famine, humans have evolved several hormonal adaptations to survive periods of decreased nutrient intake. These responses to undernutrition include functional hypothalamic amenorrhea, an adaption that results in shunting energy away from reproduction, a costly process that is critical for the survival of the species but notably not critical for the survival of an individual (Fazeli and Klibanski 2018). A second crucial adaptive response to a state of chronic undernutrition is growth hormone (GH) resistance (Fazeli and Klibanski 2014).

GH is a hormone secreted by pituitary somatotroph cells and signals the liver to produce insulin-like growth factor (IGF)-1. IGF-1, in turn, mediates many of GH's growth-related processes. GH has other effects, including lipolytic actions (Gahete et al. 2013) and counter-regulatory effects that help maintain euglycemia during periods of fasting (Zhao et al. 2010; Kopchick et al. 2020). Whereas the counter-regulatory effects and lipolytic actions of GH are essential for energy mobilization during periods of low caloric intake, it is not advantageous to utilize energy for growth during such periods (Fazeli and Klibanski 2018). Therefore, a state of GH resistance – robust GH secretion coupled with low or low-normal IGF-1 levels, which would minimize energy expenditure on IGF-1-dependent processes – would be advantageous in states of chronic undernutrition such as anorexia nervosa.

In this chapter, we will review the GH-IGF-1 axis in anorexia nervosa. We will describe potential mechanisms of GH resistance in this disorder, the effects of GH resistance on bone mass in anorexia nervosa, and the effects of treatment with exogenous GH and IGF-1 in anorexia nervosa.

GH and IGF-1 Levels in Anorexia Nervosa

IGF-1, a hormone primarily secreted by the liver in response to GH secretion by the pituitary gland, is also responsive to nutritional status. For example, during an acute fast, IGF-1 levels fall below the normal range (Clemmons et al. 1981) (Fig. 1); IGF-1 levels drop by 40% within 4 days of a fast (Grinspoon et al. 1995), but the decrease in IGF-1 levels are not due to a drop in GH levels (Clemmons et al. 1981). Girls and women with anorexia nervosa, a state of chronic undernutrition, also have lower IGF-1 levels compared to normal-weight girls (Counts et al. 1992). IGF-1 levels in anorexia nervosa are approximately 50% of those of normal-weight individuals (Counts et al. 1992), and these low IGF-1 levels are concomitant with increased GH secretion (Garfinkel et al. 1975; Scacchi et al. 1997; Stoving et al. 1999) and a failure of GH to suppress in the setting of intravenous or oral glucose (Tamai et al. 1991; Misra et al. 2004). Notably, bioactive IGF-1 levels are also decreased compared to normal-weight controls (Støving et al. 2007). The importance of nutritional status on the GH-IGF-1 axis is further underscored by the fact that hyperalimentation

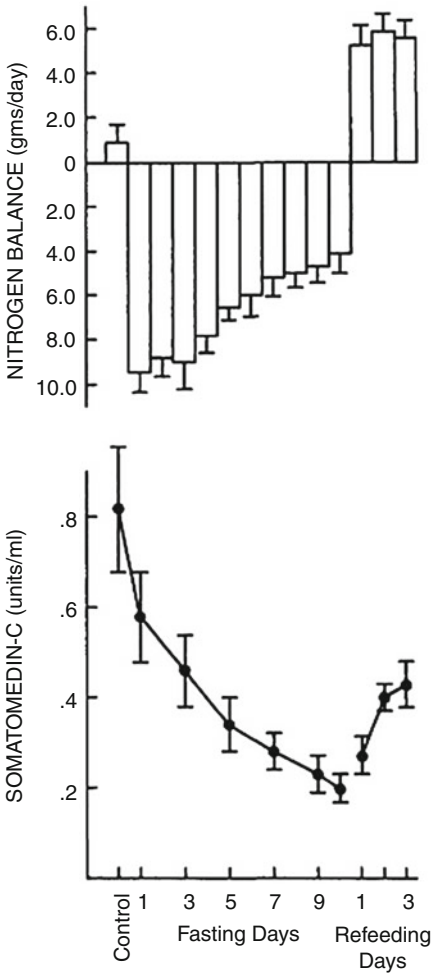


Fig. 1 Plasma somatomedin C [IGF-1] levels decrease during an acute fast. Nitrogen balance and immunoreactive plasma somatomedin C levels in study subjects. Nitrogen balance (top panel) was determined as the nitrogen intake minus daily urinary urea nitrogen plus 2 g nitrogen (2 g nitrogen was estimated to be the loss in stool, skin, and urinary nonurea nitrogen). The mean (±SEM) balance value for all seven subjects is depicted. The mean (±SEM) plasma somatomedin C is depicted in the lower panel. The control day sample represents the mean values for all subjects on 3 consecutive control days. (Reprinted by permission of Oxford University Press on behalf of the Endocrine Society (Clemmons et al. 1981))

therapy in women with anorexia nervosa results in a rapid increase in IGF-1 levels – 3 days of hyperalimentation therapy increases IGF-1 levels by nearly 50% (Hotta et al. 2000). This nutritional regulation of IGF-1 levels in states of fasting and chronic starvation is likely an adaptive response, allowing for decreased energy expenditure on IGF-1-dependent processes, including acquisition and maintenance of bone mass (Dixit et al. 2021) during times of reduced caloric intake. In contrast, given GH's lipolytic and insulin-resistant actions (Kopchick et al. 2020), the robust secretion of GH during periods of decreased caloric intake is also advantageous. Therefore, anorexia nervosa, a state of chronic undernutrition, is biochemically characterized by low IGF-1 levels and normal/elevated GH levels, also known as a state of GH resistance.

Potential Causes and Mechanisms of GH Resistance in Anorexia Nervosa

Although the precise mechanisms of GH resistance in anorexia nervosa have not been elucidated, there are several potential mechanisms (Fig. 2). First, the lack of high IGF-1 levels in the setting of robust secretion of GH suggests either down-regulation of GH receptors in the liver or a post-receptor defect, resulting in a disruption in GH's ability to stimulate IGF-1 production and secretion (Fazeli and Klibanski 2014). Animal studies suggest that GH receptor downregulation may in part contribute to the low IGF-1 levels observed in states of starvation (Baxter et al. 1981; Straus and Takemoto 1990).

Protein Deficiency

Isolated protein deficiency is also associated with GH resistance. This has been shown in studies of children (Olusi et al. 1977; Robinson and Picou 1977; Hintz et al. 1978; Soliman et al. 1986) and adults (Isley et al. 1983). Given the overall inadequate caloric intake in anorexia nervosa, one might hypothesize that protein deficiency contributes to the state of GH resistance in anorexia nervosa also. However, this is not the case, and studies demonstrate that individuals with anorexia nervosa consume similar amounts of protein compared to normal-weight controls (Fernstrom et al. 1994; Misra et al. 2006a, b). Therefore, protein deficiency is not likely to be a primary driver of GH resistance in anorexia nervosa.

Ghrelin

Acylated ghrelin – the active form of the hormone ghrelin, which is an orexigenic hormone secreted by the fundal cells of the stomach – binds to the GH secretagogue

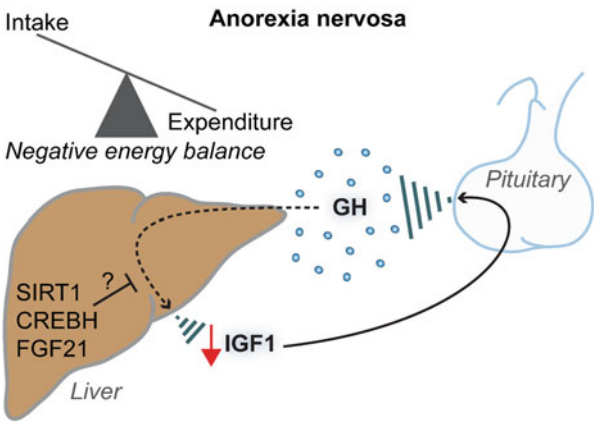


Fig. 2 Possible mediators of growth hormone (GH) resistance in anorexia nervosa include sirtuin 1 (SIRT1), cAMP-responsive element-binding protein H (CREBH), and FGF-21

receptor 1a (GHSR1a). Levels of ghrelin are higher in anorexia nervosa as compared to normal-weight controls (Otto et al. 2001). As ghrelin binds to the GHSR1a and results in GH release, the elevated ghrelin levels likely help maintain GH levels in anorexia nervosa and may be a potential mediator of GH resistance.

Although ghrelin is an orexigenic hormone and levels are higher in anorexia nervosa than normal-weight individuals, levels of hunger are lower in anorexia nervosa than in controls (Halmi et al. 1989). Therefore, women with anorexia nervosa may be resistant to the orexigenic effects of ghrelin. In a randomized, placebo-controlled study investigating the impact of a GHSR1a agonist (a ghrelin agonist) in women with anorexia nervosa, we found a trend in weight gain in women randomized to the GHSR1a agonist as compared to the placebo-treated women (Fazeli et al. 2018). IGF-1 levels also increased significantly in response to 4 weeks of treatment with the GHSR1a agonist even after controlling for changes in weight (Fazeli et al. 2018). This rise in IGF-1 levels was unexpected, given the state of GH resistance in anorexia nervosa and the fact that we would expect a GHSR1a agonist to act on the GH-IGF-1 axis by increasing GH levels. This finding suggests that there may be an alternate means by which a ghrelin agonist increases circulating IGF-1 levels.

Sirtuin 1

Sirtuin 1 (SIRT1) is a deacetylase that promotes gluconeogenesis and fatty acid oxidation in the setting of fasting (Gillum et al. 2010). In murine models, SIRT1 has been shown to be a mediator of GH resistance during starvation (Yamamoto et al. 2013). As compared to controls, mice in whom SIRT1 was knocked down had higher serum levels of IGF-1 after a 48-h fast (Yamamoto et al. 2013), suggesting that SIRT1 may be a mediator of the low IGF-1 levels observed in the setting of starvation (Yamamoto et al. 2013). The proposed mechanism by which SIRT1 reduces IGF-1 levels is through a decrease in STAT5 phosphorylation, a transcription factor that plays a vital role in GH signaling and induction of IGF-1 (Yamamoto et al. 2013).

CREBH

The cAMP-responsive element-binding protein H (CREBH) is a transcription factor induced during fasting. Liver-specific CREBH transgenic mice have a biochemical profile consistent with GH resistance – increased GH levels and decreased IGF-1 levels (Nakagawa et al. 2021). The liver-specific CREBH transgenic mice have reduced liver expression of GH receptor mRNA, suggesting a potential mechanism by which CREBH causes GH resistance (Nakagawa et al. 2021).

Fibroblast Growth Factor (FGF)-21

FGF-21 is a hormone predominantly secreted by the liver during fasting (Badman et al. 2007; Inagaki et al. 2007; Fazeli et al. 2015). FGF-21 is a potential mediator of GH resistance in murine models (Inagaki et al. 2008); FGF-21 transgenic mice have the biochemical profile of GH resistance – compared to wild-type mice, they have higher GH levels and lower IGF-1 levels (Inagaki et al. 2008) (Fig. 3). Similar to SIRT1, the mechanism by which FGF-21 is thought to mediate GH resistance is a reduction in STAT5 phosphorylation (Inagaki et al. 2008). In the human model of chronic starvation, anorexia nervosa, we have also shown that FGF-21 may mediate GH resistance. In a study of adolescent girls with anorexia nervosa, FGF-21 was positively associated with GH area under the curve during 12-h frequent overnight sampling and negatively associated with IGF-1 (Fazeli et al. 2010a). Therefore, FGF-21 may be a potential mediator of GH resistance in anorexia nervosa.

Insulin

GH resistance is observed in type 1 diabetes mellitus – a state of insulin deficiency (Horner et al. 1981; Gutefeldt et al. 2018). In vitro studies and studies in animal models suggest that the GH resistance in insulin-deficient states may be due to a reduction in GH receptors in the liver (Baxter and Turtle 1978; Leung et al. 2000). In conditions of starvation, insulin levels are low due to decreased nutrient intake, and therefore low insulin levels may play a role in mediating GH resistance in anorexia nervosa (Fig. 4).

Triiodothyronine

Anorexia nervosa is characterized by low thyroid hormone levels, including triiodothyronine (T3) (Miyai et al. 1975; Moshang Jr. et al. 1975). In fasted animal

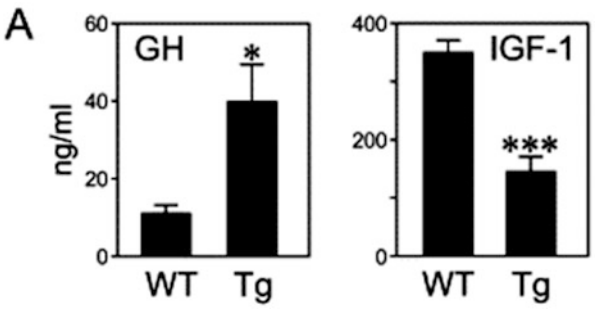


Fig. 3 Levels of GH and IGF-1 in FGF-21 transgenic mice. FGF-21 causes GH resistance. (**a**) GH and IGF-1 concentrations in plasma from wild-type (WT) and *FGF21*-transgenic (Tg) mice. $n = 8$ male mice/WT group, 11 male mice/Tg group. (Reprinted from (Inagaki et al. 2008), Copyright (2008), with permission from Elsevier (Inagaki et al. 2008))

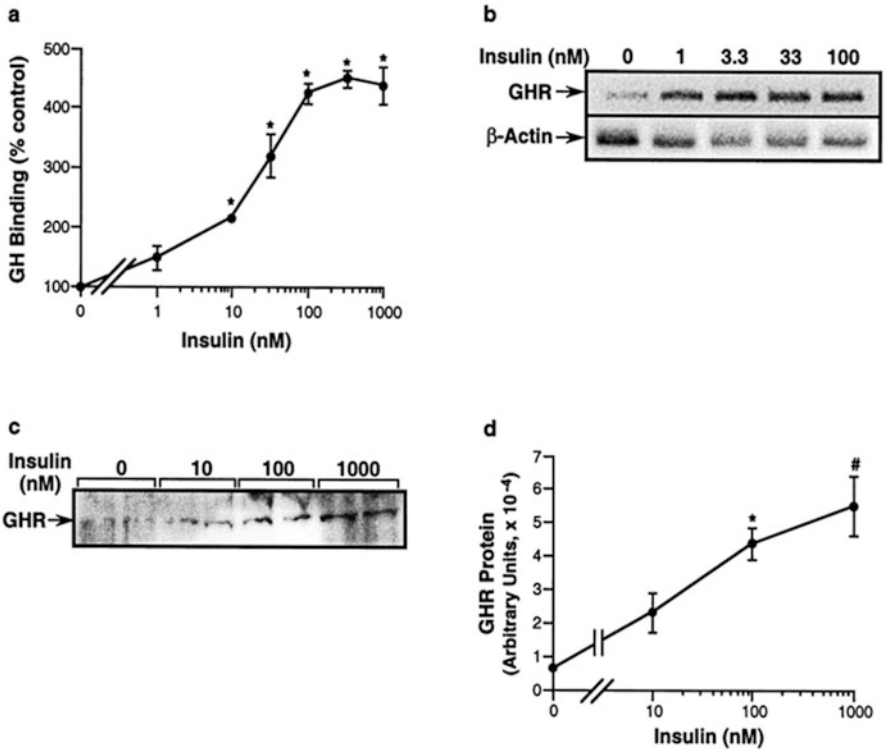


Fig. 4 Relationship between insulin levels and GH binding. GHR biosynthesis. (**a**) Total GH binding. GH binding to total cellular membranes was determined as described in Materials and Methods. The control level was 1676 ± 228 cpm/mg protein. Significance versus control: *, $P < 0.0001$. (**b**) RT-PCR for mRNA of GHR and β-actin. Total RNA was harvested from cultures treated with insulin at the indicated concentrations and used in the RT-PCR for GHR and β-actin mRNA. A representative agarose gel electrophoresis of PCR products stained with ethidium bromide is shown. (**c**) Western blot of GHRs. Immunoprecipitation was performed with a combination of an antiserum (αGHRcyto) and a monoclonal antibody (MAb263) against GHR. The samples were then separated by SDS-PAGE and studied by Western blotting with αGHRcyto. (**d**) Densitometric quantitation of GHR protein from Western analysis. Significance versus control: *, $P = 0.001$; #, $P < 0.005$. (Reprinted by permission of Oxford University Press on behalf of the Endocrine Society (Leung et al. 2000))

models, similar to human models of starvation, IGF-1 and T3 levels are both reduced, but treatment with subcutaneous T3 results in normalization of T3 levels and a significant increase in IGF-I levels (Ikeda et al. 1990). Therefore, the low T3 levels in anorexia nervosa may also mediate GH resistance.

Leptin

Leptin is a hormone secreted predominantly by subcutaneous adipocytes. As subcutaneous adipose tissue stores are reduced in states of chronic starvation such as

anorexia nervosa, leptin levels are also low (Grinspoon et al. 1996a). Low leptin levels are a likely mediator of functional hypothalamic amenorrhea in states of negative energy balance (Welt et al. 2004). In women with functional hypothalamic amenorrhea, treatment with recombinant human methionyl leptin results in normalization of leptin levels and an increase in IGF-1 levels (Chan et al. 2008). Therefore, in addition to being a potential mediator of functional hypothalamic amenorrhea, low leptin levels may also mediate GH resistance in anorexia nervosa.

Estradiol

As a likely result of the low leptin levels, most women with anorexia nervosa have functional hypothalamic amenorrhea (Welt et al. 2004; Miller et al. 2004). To treat the hypoestrogenemia resulting from functional hypothalamic amenorrhea, women with anorexia nervosa are often started on oral contraceptive pills containing oral estrogen, despite multiple prospective, randomized studies which have demonstrated no benefit to oral estrogen compared to placebo with respect to changes in bone mineral density (Klibanski et al. 1995; Golden et al. 2002; Grinspoon et al. 2002). Oral estrogen reduces IGF-1 levels in women in a dose-dependent manner (Kam et al. 2000) and to a greater degree than transdermal estrogen (Weissberger et al. 1991). Therefore, treatment of functional hypothalamic amenorrhea with oral contraceptive pills may lead to a more significant reduction in IGF-1 levels in women with anorexia nervosa than that observed due to GH resistance alone.

Testosterone

Treatment with testosterone increases IGF-1 levels in men (Hobbs et al. 1993; Liu et al. 1987). A similar association is found in women; compared to normal-weight controls, women with anorexia nervosa have lower testosterone levels (van Binsbergen et al. 1990; Miller et al. 2007), and free testosterone levels are positively associated with IGF-I levels (Brick et al. 2010). Therefore, low testosterone levels in anorexia nervosa may also contribute to the low IGF-1 levels observed in this disorder.

Effects of GH Resistance on Bone Mineral Density

Low bone mass is the most prevalent medical complication associated with anorexia nervosa (Miller et al. 2005). More than 85% of women with anorexia nervosa have either osteopenia-range or osteoporosis-range bone mineral density (BMD) values (Miller et al. 2005) and an increased fracture risk, which persists even years after initial diagnosis (Rigotti et al. 1991; Lucas et al. 1999; Vestergaard et al. 2002; Nagata et al. 2017; Frølich et al. 2020). The hormonal adaptations observed in anorexia nervosa, including functional hypothalamic amenorrhea and GH resistance,

are likely integral mediators of this reduction in bone mineral density (Fazeli and Klibanski 2018; Fazeli 2019).

The low IGF-1 levels in anorexia nervosa, which are secondary to GH resistance, are associated with abnormal bone parameters. Low IGF-1 levels are associated with both low markers of bone formation (Hotta et al. 2000; Soyka et al. 1999) and low BMD (Fazeli et al. 2010b; Grinspoon et al. 1999). Low IGF-1 levels are also associated with lower estimates of bone strength in this population (Fazeli et al. 2020).

Effects of GH and IGF-1 Replacement in Anorexia Nervosa (Table 1)

Recombinant Human GH

Treatment with supraphysiologic doses of GH cannot overcome GH resistance in anorexia nervosa (Fazeli et al. 2010c). We randomized 21 women to recombinant human GH or placebo for 12 weeks (Fazeli et al. 2010c). The mean maximum daily dose of recombinant human GH was 1.4 mg/day, which is approximately five times greater than typical doses used to treat adult GH deficiency (Fazeli et al. 2010c). Despite these high doses of recombinant human GH, levels of IGF-1 were similar in the groups receiving recombinant human GH and placebo at the conclusion of the study (Fazeli et al. 2010c). Although IGF-1 levels were similar in both groups after treatment, the study participants with anorexia nervosa who received recombinant human GH had a significant decrease in fat mass compared to the placebo group, demonstrating that the lipolytic effects of GH – a potentially advantageous effect in a state of starvation – remained intact and also suggesting that the lack of a difference in IGF-1 levels between the two groups was not likely due to participant non-compliance with the recombinant human GH treatment (Fazeli et al. 2010c).

Recombinant Human IGF-1

The use of recombinant human IGF-1 has been investigated in both women and adolescent girls with anorexia nervosa. Given the association between low IGF-1 levels and low bone parameters (Hotta et al. 2000; Soyka et al. 1999; Fazeli et al. 2010b, 2020; Grinspoon et al. 1999), the primary outcome for the studies investigating recombinant human IGF-1 in anorexia nervosa is bone parameters including bone turnover markers, bone mineral density, and bone microarchitecture. The results of these studies have differed in adults versus adolescents, with women having a beneficial response with respect to changes in bone mineral density with recombinant human IGF-1 (Grinspoon et al. 2002; Haines et al. 2021), whereas adolescent girls do not have a beneficial response (Singhal et al. 2021).

With respect to adults, there have been three randomized studies investigating the use of recombinant human IGF-1 in women with anorexia nervosa (Grinspoon et al. 1996b, 2002; Haines et al. 2021). In a study looking at short-term use of recombinant

Table 1 Studies assessing the effects of recombinant human growth hormone (rhGH) or recombinant human insulin-like growth factor 1 (rhIGF-1) in anorexia nervosa

Treatment	Design	Participants	Intervention groups	Treatment duration	Results	References
rhIGF-1	Randomized	Women, anorexia nervosa (ages: 18–29 yo)	1. rhIGF-1 30 mcg/kg twice daily 2. rhIGF-1 100 mcg/kg twice daily 3. Placebo	6 days	**rhIGF-1, 30 mcg dose**: Increase in bone formation marker **rhIGF-1, 100 mcg dose**: Increase in bone formation and bone resorption markers	Grinspoon et al. (1996b)
rhIGF-1	Randomized	Women, anorexia nervosa (ages: 18–38 yo)	1. rhIGF-1 2. Oral contraceptive (OCP) 3. rhIGF-1 + OCP 4. Placebo	9 months	**rhIGF-1 + OCP**: 1.8% increase in spine bone mineral density **OCP alone**: No significant change in bone mineral density	Grinspoon et al. (2002)
rhIGF-1	Open-label	Adolescent girls, anorexia nervosa (ages: 12–18 yo)	rhIGF-1 30–40 mcg/kg twice daily	7–9 days	Increase in marker of bone formation No increase in marker of bone resorption	Misra et al. (2009)
rhIGF-1	Randomized	Adolescent girls, anorexia nervosa (ages: 14–22 yo)	1. Transdermal estradiol + rhIGF-1 2. Transdermal estradiol + placebo	12 months	No benefit of IGF-1	Singhal et al. (2021)

(continued)

Table 1 (continued)

Treatment	Design	Participants	Intervention groups	Treatment duration	Results	References
rhIGF-1	Randomized	Women, anorexia nervosa (ages: 18–45 yo)	1. Six months rhIGF-1 followed by 6 months of risedronate 2. 12 months of risedronate 3. Placebo	12 months	**rhIGF-1 followed by risedronate**: 1.9% increase in lumbar spine bone mineral density at 12 months **12 months of risedronate**: 1.7% increase in lumbar spine bone mineral density at 12 months **Placebo**: 0.3% decrease in lumbar spine bone mineral density at 12 months	Haines et al. (2021)
rhGH	Randomized	Women, anorexia nervosa (ages: 18–45 yo)	1. rhGH 2. Placebo	12 weeks	IGF-1 levels similar in rhGH group compared to placebo at 12 weeks Fat mass decreased in rhGH group versus placebo	Fazeli et al. (2010c)

rhIGF-1: recombinant human IGF-1; rhGH: recombinant human growth hormone; yo: years old

human IGF-1 in women with anorexia nervosa, the primary outcome was markers of bone turnover (Grinspoon et al. 1996b). At baseline, women with anorexia nervosa had significantly lower bone formation markers and elevated bone resorption markers compared to women without anorexia nervosa (Grinspoon et al. 1996b). Six days of treatment with 30 mcg/kg twice per day of subcutaneous recombinant human IGF-1 increased bone formation markers, whereas 6 days of treatment with a higher dose (100 mcg/kg twice per day) led to an increase in both bone formation and bone resorption markers in women with anorexia nervosa (Grinspoon et al. 1996b). A subsequent randomized placebo-controlled study investigated the effects of recombinant human IGF-1 on bone mineral density in women with anorexia nervosa and found that those randomized to recombinant human IGF-1 in addition to oral estrogen, in the form of an oral contraceptive pill, had an increase in spine bone mineral density of 1.8% after 9 months of treatment (Grinspoon et al. 2002) (Fig. 5).

In contrast, in a study in adolescents randomized to either subcutaneous recombinant human IGF-1 or placebo in addition to transdermal estradiol, there was no benefit observed with the addition of recombinant IGF-1 to transdermal estradiol after 12 months of treatment with respect to areal or volumetric bone mineral density measures (Singhal et al. 2021). Surprisingly, there was a significantly greater increase in areal bone mineral density at the spine in the adolescent girls randomized to transdermal estradiol alone compared to those randomized to the combination of transdermal estradiol + recombinant human IGF-1 (Singhal et al. 2021). This

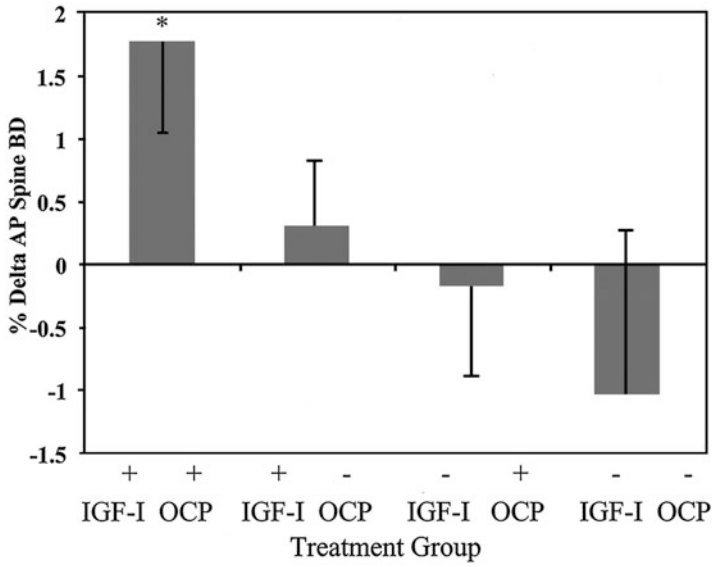


Fig. 5 Spine bone density increases in response to treatment with rhIGF-1 and oral estrogen. Percent change from baseline in AP spinal bone density. *, $P < 0.05$ versus control subjects (group IV). Results are mean ± SEM. (Reprinted by permission of Oxford University Press on behalf of the Endocrine Society (Grinspoon et al. 2002))

difference in the response of adults versus adolescents has been observed in prior treatment studies in anorexia nervosa with respect to treatments for low bone mineral density. For example, when compared to placebo, bisphosphonates increase bone mineral density in adults (Miller et al. 2011) but not in adolescents (Golden et al. 2005). This is likely because bone turnover is distinctly different in adolescents – a time when bone mass is increasing – as compared to adults when peak bone mass has been achieved (Fazeli and Klibanski 2018; Fazeli 2019). These findings underscore the importance of testing therapies to treat low bone mineral density separately in adolescents with anorexia nervosa and adults with the disorder.

Applications to Other Eating Disorders

Anorexia nervosa results in a unique state of GH resistance. Limited conflicting data regarding changes to the GH-IGF-1 axis have been reported in patients with bulimia nervosa (BN), an eating disorder characterized by binge eating and actions to prevent weight gain, such as purging (American Psychiatric Association 2013). Kiriike et al. examined GH levels at baseline and following thyrotropin-releasing hormone stimulation in women with BN and found that 33% of the BN patients had elevated baseline GH levels (Kiriike et al. 1987). Similarly, Levy et al. compared a group of subjects with BN to control subjects and found that IGF-1 levels in BN were comparable to controls despite the fact that the BN group had significantly higher fasting GH levels and the mean GH level after thyrotropin-releasing hormone stimulation was significantly higher in the BN group as compared to controls (Levy and Malarkey 1988). As GH is a counter-regulatory hormone and released in states of physiologic stress, the elevated levels could potentially reflect a stress response, but thus far AN remains the only eating disorder associated with low IGF-1 values in the setting of high GH levels.

Conclusions

Anorexia nervosa is a psychiatric disorder characterized by chronic undernutrition resulting in low body weight. Several hormonal adaptations occur in this state of chronic undernutrition, including functional hypothalamic amenorrhea and GH resistance (Fazeli and Klibanski 2018). The biochemical profile of GH resistance includes normal or elevated GH levels and low IGF-1 levels. This state of GH resistance allows for the lipolytic and insulin-resistant effects of GH (Kopchick et al. 2020) to be maintained while minimizing energy expenditure on costly IGF-1-dependent processes, including the maintenance of bone mass (Dixit et al. 2021). Treatment with supraphysiologic recombinant human GH cannot overcome GH resistance in anorexia nervosa (Fazeli et al. 2010c). Treatment with recombinant human IGF-1, when combined with estrogen, increases bone mineral density in adults with anorexia nervosa (Grinspoon et al. 2002) but not adolescents with anorexia nervosa (Singhal et al. 2021). Further studies are needed to better

understand the mechanisms of GH resistance in states of chronic undernutrition and ways to minimize the negative consequences of long-term GH resistance in anorexia nervosa, namely, loss of bone mass.

Mini-Dictionary of Terms

- *Functional hypothalamic amenorrhea:* A likely adaptive response to states of physiologic stress, including undernutrition and negative energy balance, whereby gonadotropin-releasing hormone secretion from the hypothalamus is disrupted, resulting in amenorrhea.
- *Gluconeogenesis*: A metabolic process that results in the formation of glucose.
- *Lipolysis*: The process by which adipose tissue is broken down into its constituents.
- *Orexigenic*: Hunger-stimulating.
- *Transcription factor:* A protein that binds to specific DNA motifs to regulate gene expression.

Key Facts of the GH/IGF-1 Axis

- The GH/IGF-1 axis is responsible for growth in childhood and is important in the maintenance of bone and muscle mass in adulthood.
- GH-releasing hormone, produced in the hypothalamus, induces secretion of GH from the pituitary gland which stimulates IGF-1 production, primarily from the liver.
- GH deficiency in childhood can result in short stature and can be treated with subcutaneous recombinant human GH.
- In adults, GH deficiency can cause changes in body composition, cardiovascular risk markers, and quality of life.
- Acromegaly is a disorder of pathophysiologic GH excess and elevated IGF-1 levels. Acromegaly is most commonly due to a GH-secreting pituitary tumor. If this pathophysiologic GH excess occurs in a child, before the growth plates are fused, it is called gigantism.

Summary Points

- Anorexia nervosa is a psychiatric disorder that serves as a model of chronic human starvation.
- GH is secreted by the pituitary gland and signals the liver to produce IGF-1, a hormone responsible for most of the growth-mediating effects of GH.
- GH is also a secreted during periods of starvation and may help with the maintenance of euglycemia during periods of decreased caloric intake, in part by mobilizing adipose tissue stores.

- GH resistance, characterized by normal or high GH levels and low IGF-1 levels, is an adaptive response to undernutrition and starvation.
- Potential mediators of GH resistance include FGF-21, SIRT1, and CREBH.
- Treatment with supraphysiologic rhGH does not overcome the state of GH resistance in anorexia nervosa, and IGF-1 levels remain low.
- Bone mineral density is decreased in states of chronic starvation, likely in part due to the hormonal adaptations to undernutrition, including GH resistance.
- Subcutaneous administration of rhIGF-1, when coupled with estrogen, has been shown to improve bone mineral density in adult women with anorexia nervosa but not adolescent girls with this disorder.

Conflict of Interest

PKF is a consultant for Regeneron Pharmaceuticals and Strongbridge Biopharma.

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Relationship Between Bulimia Nervosa and Psychological Problems in Period of Adolescence

37

Perfectionism, Self-Esteem, and Beyond

Gordana Stankovska, Imran Memedi, and Nexhibe Nuhii

Contents

Introduction 724
Adolescence: A Risky Period for the Development of Bulimia Nervosa 725
Psychodynamics of Bulimia Nervosa 727
Bulimia Nervosa, Adolescence, and Psychological Profile of the Person 728
Psychological Problems in Adolescence and Bulimia Nervosa 729
The Image of One's Own Body as a Predictor for the Development of Bulimia Nervosa in the Period of Adolescence 730
Self-Esteem and Bulimia Nervosa 731
Perfectionism and Bulimia Nervosa 732
Anxiety, Depression, and Bulimia Nervosa 733
Other Psychological Problems in Adolescence and Bulimia Nervosa 734
Our Experience 735
What Questionnaires Did We Use for Evaluation? 736
What Do the Obtained Results Show Us? 737
Applications to Other Eating Disorders 739
Mini-Dictionary of Terms 741
Key Facts of Bulimia Nervosa 741
Summary Points 742
References 743

Abstract

Eating disorders, such as bulimia nervosa, develop at the crossroad of childhood and adulthood, between the mental and the somatic, the individual and the social. It is characterized by episodes of increased uncontrolled overeating followed by different types of compensatory behavior. The changes from physical, mental,

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and psychological aspect that occur in the young person – adolescent – affect the person's bulimic behavior. The girl or boy who is strongly focused on the body shape and weight is not satisfied with the image of her/his own body, negative thoughts and emotions are present, and they strive for perfection; therefore, the failure to meet the highly set goals is compensated with an increased desire to eat and overeat, which fosters the pathological patterns of food-related behavior, such as bulimia nervosa. The negative self-image leads to low self-esteem, increased level of perfectionism, fear, anxiety, sadness, increased internal pressure and conflict, and body weight; therefore, the adolescent needs professional help and adequate nutritional, pharmacological, and psychological treatment.

Keywords

Early adolescence · Late adolescence · Overeating · Bulimia nervosa · Image of one's own body · Self-esteem · Perfectionism · Anxiety · Depression · Treatment

Abbreviations

AN	Anorexia nervosa
APA	American Psychiatric Association
BITE	Bulimic Investigatory Test, Edinburgh
BITE-sas	Bulimic symptoms
BITE-ss	Severity of binging and purging behavior
BMI	Body mass index
BN	Bulimia nervosa
CAPS	Child-Adolescent Perfectionism Scale
DSM-V	Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition
ED-NOS	Eating disorder not otherwise specified
KADS	Kutcher Adolescent Depression Scale
RSE	Rosenberg Self-Esteem Scale
STAI	State-Trait Anxiety Inventory
STAI-S	State-Trait Anxiety Inventory – State Scale
STAI-T	State-Trait Anxiety Inventory – Trait Scale

Introduction

Eating disorders in infancy and early childhood are different, such as refusal of food or qualitatively increased food intake. The infant's behavior during the eating process is partly an instinctive and partly a scientific process. Mouth activity and turning toward the source of stimulation are the infant's first activities in relation to the outside world. The child responds to stimuli coming from the mother's arms and breast. While eating, the child ingests food, but simultaneously, this process represents love, pleasure, and tenderness and, on the other hand, dissatisfaction, fear, and sadness. Impaired interaction with parents contributes to the emergence of guilt, decreased self-esteem, and behavioral problems in the child (Vidovic 2009). In

infancy and early childhood, an eating disorder known as pica is most common, while in adolescence, such disorders are anorexia (anorexia nervosa) and bulimia (bulimia nervosa).

Eating disorders have been known since ancient civilizations; however, in the world we live in, we are constantly exposed to information that the number of adolescents with eating disorders is constantly increasing. The mental state that can lead a young person toward dissatisfaction with his/her body is still a mystery in modern medicine and psychology. High levels of hatred of one's own body, self-criticism, self-control, and discipline are required to develop a complex disorder, such as bulimia. Due to preoccupation with the physical appearance, this type of eating disorder in adolescents is an obstacle for the successful performance and focus on daily responsibilities. It is associated with impaired self-esteem and self-image, later on followed by withdrawal, loss of contact with others, and difficulty to establish emotional relationships. The young person with a bulimic disorder experiences changes from psychological aspect, but also in terms of the behavior that is associated with increased dissatisfaction with the appearance and increased body weight. For this reason, psychologists, nutritionists, psychiatrists, and doctors try to penetrate the bulimic person, to recognize the first signs and risk factors for the emergence of this type of eating disorder, its psychological implications for the young person, as well as the development of adequate prevention programs focused on adequate treatment and lifestyle changes.

Adolescence: A Risky Period for the Development of Bulimia Nervosa

Adolescence is a period of life between childhood and adulthood. This interspace in life is an important, decisive period in the life of each individual. Biologically, adolescence begins with the development of reproductive abilities and ends with a deceleration of the physical development. Psychologically, an adolescent is a person in a transitional period between a behavior that is typical of a child and one that is typical of an adult. From a social point of view, it is a period focused on choosing a profession, as well as a period of establishing independence from parents.

The hormonal changes that occur at the onset of puberty strongly and rapidly disrupt the peace from the period of latency. The body becomes an important and decisive developmental segment considering that it reaches maturity and formation. The physical experience largely affects the formation and maintenance of the identity. To be yourself in your big body (strong, powerful, and wise), to feel good and to be harmonized with yourself and different from others, is something that is set before every adolescent. The road is thorny, full of ups and downs, fears, concern, or low mood. The progress in one field of functioning is often accompanied by regression in another field. Therefore, in this developmental period, the feeling of disorder, ambiguity, confusion, and incomprehension of changes often occurs. This is present from the very beginning of the acquisition of psychosexual identity in

early adolescence, when a "painful" hypersensitivity occurs, as well as fear associated with the body (mirror phenomenon, dysmorphic or hypochondriac difficulties), when the adolescent feels "very strong," when the person wants everything to be "immediately and now," and when the process of separation-individualization begins. It is a period when the adolescent starts to rebel, although sometimes he/she does not even know why, but he/she knows that he/she must do that. However, this is related to the awareness of the need for changes that occur with age and development.

The inadequate adaptation of the young person to the conflicting developmental tasks of adolescence, the disturbed realization of the personal synthesis of the individual and the social, and the problems with basic and gender identity all contribute to the development of depressive behavior in the young person, whereby the person's ego becomes fragile and vulnerable. Due to this regression, the person develops nonspecific psychological symptoms, signs and forms of behavior, and characteristic defense mechanisms. Simultaneously, a fear arises regarding the person's own somatic health, fear of specific somatic diseases, behavioral changes, school-related difficulties, emotional difficulties, or mental anorexia or bulimia.

Bulimia most frequently occurs in the transition period from early to middle adolescence and during the transition from adolescence to the early developmental period (Fischer and Le Grande 2007; Sullivan et al. 1998). With the very commencement of secondary school, many girls start dieting, which is a problem because it leads to weight fluctuations and overeating, and any such behavior leads to bulimia and health disorders (Gjurovic 2003).

The dissatisfaction with one's appearance, the adherence to different diets, the increased physical activity, and the inadequate attitudes related to the diet all have different oscillations from one person to another. Many factors are present that contribute to the occurrence of such behavior; however, in the literature, there are two basic models that explain the role of pubertal maturation in the development of bulimia nervosa (Ambrosi-Randic 2004).

The first model is focused on the moment when pubertal maturation begins, so the young person, especially girls, can develop early, on time, or late. The stress and fear of early maturation is a major reason for the development of a psychopathology, including bulimia. Researches have shown that girls who mature early have negative attitudes regarding their own body, so they follow a diet or overeat; therefore, they are at an increased risk of developing bulimia nervosa (Pinel 2002; Pokrajac-Bulian and Kandare 2000).

The second model focuses on the simultaneous action of puberty and transient changes in this period. It is considered that cumulative stress negatively affects the psychosocial functioning, self-esteem is reduced, and it leads to overeating, which contributes to weight gain and mental difficulties – dissatisfaction, low mood, and frustration.

Psychodynamics of Bulimia Nervosa

Over the last few decades, the idea of a single factor as the main cause for the emergence of bulimia nervosa has been replaced by the vision of a "multifactorial" disease, although to this day it is still not entirely clear. In 1980, Paula Garfinkel and David Garner proposed the model of the different predisposing and precipitating factors, the combination of which explains the development of bulimia nervosa in the young person during adolescence (Garfinkel and Garner 1987). It is now known that sociocultural, psychological, biological, and genetic factors make up the genesis of development of bulimia nervosa (Polivy and Herman 2002).

Psychologists and psychiatrists who support the psychodynamic theory of development of bulimia believe that a person's mental rigidity, i.e., reduced flexibility, is the main reason for a sadistic attack of one's own body, which is a major characteristic associated with this disorder. A study by Riviere and Douilliez (2017) shows that adolescence is a "fertile period" for the study of the body image and bodily functions, with an emphasis on food as a means of expressing conflict and aggression, as well as intimacy. Body parts, their shape, and size can metaphorically and symbolically help explain conflict and defend against potential problems. Eating can be a major factor in controlling and regulating urges, due to the guilt and shame that the person experienced in one of the stages of psychosexual development. Dieting or overeating is a "magical" way wherewith a young person attempts to prevent changes in the body or to resolve the existing intrapsychic conflict. According to Marcinko (2013), there are four models that explain self-destruction toward one's own body:

- ***Attack of the pleasure principle***
  The act of eating itself is a satisfaction, an intake of energy, something that is good for the body itself. Dissatisfaction is manifested by blocking the primary potentials through which sensory pleasures occur. Usually this condition occurs due to the inadequate relationship with the mother in the early developmental period which is the basis for the development of potentially aggressive attacks in the future (Stavrou 2018).
- ***Attack of the mother related to the pleasure principle***
  In the dynamics of a person with bulimia, a problem emerges in an event of separation from the mother during the person's developmental path, and a pathological connection with the mother is formed; however, each separation from the mother contributes to the emergence of emotional problems in the young person, such as anxiety and depression. These problems during the growth of the personality can be reactivated and lead to an increased desire to eat as a way to resolve the intrapsychic conflict (Smolak 2011). With the increased food intake, the child compensates for the unsatisfied emotional needs, because the food he/she eats has the same value and meaning as the mother's love. At the same time, increased food intake can be a way to reduce aggression, fear, and depression. Vomiting in a bulimic person also occurs due to the denial of the object – the mother who is a symbol of the food.

- ***Attack of one's own femininity***

  As early as in the initial development of the young person, there are roots that affect the person's understanding and acceptance of her own femininity. The reason is considered to be the inadequate relationship between the child and the mother, due to the emotional and physical absence of the mother, her increased anxiety, and inadequate care, which contribute to the child developing resistance to contact the mother, even when it comes to the eating process (Fairburn and Harrison 2003). During adolescence, girls experience an average increase in body weight, which leads to a departure from the perceived ideal of body weight and thus affects their negative emotions that are associated with their own attractiveness and femininity. Simultaneously, the identification with the mother in many situations in life is substantially blocked, so the young girl feels fear and rejection. Believing that the intrapsychic conflict can be resolved by overeating and vomiting, the feeling of femininity is threatened from both physical and psychological aspects. The very act of overeating in bulimia is a defense against the conflict associated with separation/individualization. In this way, the girl expresses her anger and rage, because of the real or imagined feeling of rejection.
- ***Attack of heterosexuality***

  Psychoanalysts consider that problems with heterosexuality and femininity are related to envy and hatred toward the mother; however, they are also reflected on the father. A characteristic is that girls experience the father, i.e., every male person, in a negative emotional context. The young girl is vulnerable; has an increased threshold of frustration, fear, and anxiety; and directs her own sadistic thoughts toward herself; therefore, a "compulsive," i.e., addictive, need for overeating, clearing, or dieting arises (Gila et al. 2004).

Bulimia Nervosa, Adolescence, and Psychological Profile of the Person

Bulimia nervosa is an eating disorder characterized by episodes of uncontrolled overeating followed by various types of compensatory behavior. The person within a short period of time consumes a large amount of food, with high calorific value, with no control over the act of eating. After an episode of overeating, which is followed by severely reduced self-control, an increased sense of guilt and shame emerges. Guilt usually emerges due to the reduced ability to correct the situation, while shame arises from the negative evaluation of the whole self (French et al. 2001). Now the boy or the girl resorts to compensatory behavior in order to correct the mistake and reduce the feeling of guilt. It is usually self-induced vomiting, but the use of laxatives or diuretics, excessive exercise, dieting, and strict regime are also common.

The young bulimic person is strongly focused on the body shape and weight, and a fear of gaining weight is present, as well as a negative self-esteem in relation to the person's body. In addition to the present developmental difficulties, problems in separation, i.e., separation of the self from the object and denial and fear of

separation and sexuality, are expressed; therefore, bulimia is described as a disorder that occurs due to unsuccessful adaptation to the requirements of adolescence.

There are four empirical models providing us better understanding of the relationship between the psychological characteristics of the person and the bulimic disorder (Marcinko 2013):

1. The first one is the "predisposing model" which refers to the increased risk of developing bulimia in relation to personality traits in adolescence. According to this model, the factors for the occurrence of personality pathology and bulimia are independent of each other.
2. The "shared sample model" also assumes that personality traits and bulimia are independent entities; however, they have a common cause such as the developmental factors, family problems, or problems with peers.
3. The "complication model" refers to the thesis that the changes that occur in a person are the result of bulimia. The personality traits according to this model are a consequence of bulimia.
4. The "pathoplastic model" assumes that the present inadequate psychological characteristics and bulimia affect each other during the developmental path of the person.

The bulimic disorder can occur at all levels during the transition of a person from early to middle and late adolescence; therefore, the adolescent is emotionally unstable and introverted, and he/she reacts to any criticism with violent negative emotions, has a feeling of low value, changes his/her mood in relation to external factors, is ambitious, and strives to be the best (Geller et al. 2000; Keel and Forney 2013).

Psychological Problems in Adolescence and Bulimia Nervosa

Adolescence is not only an overall developmental process, nor a universal developmental process, it has its own path and course, and it all depends on the differences that occur in the environment where the young person grows, the different values and norms that are characteristic of each environment, and the differences in the social role of adults, which for the adolescent are a model of shaping and formation. Thus, the social growth of the person emerges gradually, the person becomes increasingly alert and aware and creates social consciousness and starts to acquire an image and an idea of himself/herself, and self-confidence and self-esteem grow in him/her, which become dominant characteristics of the young person.

Adolescence is a period of intensive intellectual development, a period of gaining great cognitive experiences, concepts, and knowledge, all of which affect the process of cognitive and affective rapprochement with the environment. At the same time, this is a period when young people are facing the world of values, when everywhere they measure their ideals with reality, thereby experiencing conflicts and forming their self-confidence. A characteristic is that the adolescent becomes familiar with

his/her own personality and begins to be objective toward himself/herself and his/her shortcomings, which is especially important for the person's moral and emotional development. Integrating different views into a single homogeneous image of oneself is a difficult process, and therefore, a conflict emerges, which is perceived as stressful, and this often leads to tense relationships between parents and adolescent children. Low self-esteem, intertwined with unfavorable relationships at home, low performance at school, and some stressful events in other social domains all lead to unpleasant experiences in the young person.

Therefore, it is considered that the central notion that develops during adolescence is the identity that should answer numerous questions, such as who am I, why am I, what will happen to me, etc. Prerequisites that lead a young person to develop personal identity are sexual maturation and adequate social functioning. The very process of forming a personal identity takes place in two directions: one of them is the experience of reality and the other is the ideal ego. If during the development of the young person these two directions coincide or are closely related, then the young person is satisfied with himself/herself, will be confident, and will be accepted as he/she is, and this is a prerequisite for harmonious living. However, if there is a discrepancy between these two processes, then the adolescent does not accept his/her physical appearance and bodily ego, and this creates a conflict in the person accompanied by certain psychological and mental reactions, such as low self-esteem, reduced efficiency, conflict between identity and autonomy, depressed mood, and eating disorders (Boone and Leadbeater 2006; Dobmeyer and Stein 2003).

The most problematic types of eating disorders are starvation, dieting, overeating, purgatory behavior, induced vomiting, and abuse of laxatives or diuretics, which are followed by strong emotional distress of the individual and his/her environment.

Psychologically, bulimia nervosa occurs as a reaction to the demands of adolescent development for increased independence and social and sexual functioning. Researches have shown that mental and psychological changes that occur in the young adolescent affect his/her bulimic behavior (Mendelson et al. 2002). The person reacts more intensely to negative events and has low self-esteem and increased feelings of anger, fear, rage, or irritation, problems related to autonomy and personality traits.

The Image of One's Own Body as a Predictor for the Development of Bulimia Nervosa in the Period of Adolescence

The image of one's own body is a subjective perception of one's body (the body's appearance and function), the internalized emotional experience of the body and the reaction of the environment to the subject's body, and the standards and expectations that the person has built for his/her body, so this will determine the person's ideal image of the body (Lackovic-Grgin 2014). Actually, the image of one's body has a strong role in increasing the pathology of bulimia, because young people are not satisfied with their body, and they consider that they are obese and fat and have disproportionate dimensions, especially in some parts of the body. A person believes

only in his/her personal assessment, considering that he/she is obese; therefore, the dissatisfaction with the person's own body is related to problematic eating habits and perception and loss of self-control through food intake, dieting, or overeating. The negative image of one's body is particularly pronounced in adolescents with purgative bulimia nervosa (Patalay and Gage 2019; Vohs et al. (2001)).

According to Erceg-Jugovic (2015), there are four approaches to explaining the occurrence of dissatisfaction with one's own body in adolescents:

- **Social adaptation approach** – the young person who compares his/her appearance with other individuals has an increased risk of dissatisfaction with his/her own appearance.
- **Approach of sociocultural pressure** – the media is a source of strong messages about which bodily disorders are acceptable
- and desirable.
- **Developmental approach** – the body dissatisfaction develops during maturation in adolescence.
- **Approach of negative verbal comment** – negative comments that are associated with dissatisfaction with the body, bulimia nervosa, and generally impaired psychological functioning.

According to the same author, 40–60% of the girls at 6–12 years of age are worried that they are overweight, and this concern continues throughout their entire life (Erceg-Jugovic 2015). When a girl becomes insecure in interpersonal relationships or does not believe in her own abilities, then she uses her disturbed weight self-control as a means to ensure success and acceptance.

The bulimic young person has a negative image of oneself, i.e., a distorted mental image of his/her own appearance. Every day the person seeks evidence to support the false mental image within himself/herself. When a person looks in the mirror, he/she focuses only on those parts of the body for which he/she thinks "something is wrong," self-esteem is decreased, inferiority is increased, and this leads to pronounced psychological disorders (Pesa et al. 2000). The person is prone to self-punishment, so one such form is "compulsive eating." The person is preoccupied with obsessive thoughts related to the diet, he/she cannot control them, and they often transform into compulsive activities. The end result is an increased desire for food, especially when the love the person desires is not available. So it is not hunger that bothers him/her but obsessive thoughts that drive him/her to certain activities, such as overeating, and this leads to a distorted image of his/her own body (Pokrajac-Bulian 2000).

Self-Esteem and Bulimia Nervosa

Self-esteem is a good indicator of an individual's mental health. We usually define it on the basis of the formed notion about ourselves, i.e., valuation or evaluation of ourselves either in a positive or negative way. Actually, it is a multifaceted construct

or a construct of specific domains (Vulic-Prtoric and Cifrek-Kolarcic 2011). From that perspective, the facets of self-esteem are placed in a hierarchical structure where global self-esteem is at the top, followed by the academic, social, emotional, and physical domains of self-esteem (Pazzaglia et al. 2020).

According to Pehar (2016), adolescents with high self-esteem apply a positive way in solving life problems. As life stress increases, self-esteem decreases, so often bulimia nervosa develops as a comorbidity with anxiety and depression. Decreased self-esteem is especially expressed in girls who have an inadequate perception of body weight and body satisfaction. Decreased self-esteem in girls is thought to be related to external factors (such as body appearance) rather than an internalized process, so it is an important precipitating factor in the development of bulimia nervosa (Lebedina-Manzoni 2007). Girls with low self-esteem fear that they will be abandoned because they inadequately assess their body; therefore, they have a negative assessment of their abilities and all aspects of their self-image.

Self-esteem is a primary risk factor that may contribute to the development of other risk factors in bulimia nervosa. Specific research studies have shown that the development of bulimia is more frequent in young people with increased perfectionist tendencies and dissatisfaction with the body, who have low self-esteem, while adolescents with high self-esteem do not have these risk factors and therefore do not develop bulimia (Joiner et al. 1997; Vohs et al. 2001). In addition, studies focusing on the relationship between self-esteem and physical dissatisfaction have shown that a positive correlation between these two variables is present (Mendelson et al. 2002). Decreased self-esteem contributes to the development of an inadequate self-image in boys and girls, which is the cause for the development of bulimic symptoms (Gleason et al. 2000).

According to Mora et al. (2017), the young person with bulimia has increased dissatisfaction with his/her body, as well as the weakest explicit and implicit "I." Explicit self-esteem is the conscious sense of self-evaluation, while implicit self-esteem includes unconscious, automatic self-evaluation. Therefore, Smink et al. (2012) suggest that implicit and explicit self-esteem should be examined separately; however, implicit evaluation is related to impulsive processes, while explicit evaluation is related to reflexive processes. In this way, the two types of self-esteem affect bulimic behavior differently. The act of overeating itself is an impulsive process; hence, implicit self-evaluation plays a greater role in assessing self-esteem (Stavrou 2018; Button et al. (1997)).

Perfectionism and Bulimia Nervosa

Perfectionism is a person's aspiration for high achievements, followed by increased self-evaluation and fear of failure. The perfectionist aspires to be perfect in all areas of life. Perfectionism is easily recognized in the adolescent population, through regular completion of schoolwork, meticulousness, dedication, and the desire to be the best student in the class, to win a competition, etc. And when a young person achieves the desired goal, he/she is usually satisfied, happy, and proud. Then new

endeavors and new pleasures come. If that is the course of the story, it is a matter of a desired (adaptive) perfectionism, because it is a healthy pursuit for high achievements followed by a sense of satisfaction (Flett et al. 2001). However, the story may have a different ending. The adolescent may have high aspirations and therefore inadequately assess his/her own abilities in a particular area. And when he/she is successful, non-adaptive perfectionism comes to the fore, so the person feels dissatisfied, anxious, and obsessed with the thought of being the best and manifests neurotic difficulties and sleep or eating disorders (Boone et al. 2014; Frost et al. 1990; Bardone-Cone et al. 2007).

In the context of bulimia, it is interesting how perfectionists think about the way to be placed in the "all or nothing" category, which limits them in accepting the mediocrity and imperfection that pertain to their physical appearance. The young person primarily sets unrealistic standards for the body appearance and strives for perfection in all areas of his/her life, which affects the person's daily functioning and living (Bardone-Cone et al. 2017). The person has high criteria regarding the ideal of their own appearance and body shape and weight; however, the failure to meet high personal goals is satisfied by increasing the desire to eat and overeat, which encourages pathological patterns of food-related behavior, such as bulimia nervosa (Mennati et al. 2013; Bulic et al. (2003).

In their research, Paulson and Rutledge (2014) indicate that adaptive perfectionism leads to a decrease in bulimia, while non-adaptive perfectionism leads to an increase in the symptoms of bulimia. The same authors indicate adaptive perfectionism as a protective factor and non-adaptive perfectionism as a risk factor for the development of bulimia.

Anxiety, Depression, and Bulimia Nervosa

The primary characteristic of bulimia nervosa is the pathological burden of body weight and body shape, especially during personality development. This affects the developmental course of difficult experiences with shape and weight that lead to the development of a distorted image of one's own body, as well as eating disorders. The bulimic person uses his/her appearance and weight as a response to problems of identity, self-esteem, self-control, and regulation of negative affective states (Prefit et al. 2019).

In the acute phase of the disorder, mood swings are characteristic, which result in overeating and clearing, and this affects the psychological stability of the individual. The most pronounced comorbidity with bulimia is depression or anxiety disorders, such as obsessive-compulsive disorder or social anxiety (Garcia et al. 2020). In early adolescence, the young person begins to reorganize his/her body image; becomes preoccupied with their body self and the reaction of others to it, due to weight gain; and hence loses control of food intake, resulting in episodic overeating which secondarily leads to the onset of anxiety and depression. Fear, anxiety, and sadness are expressed, which indicates that low mood, loneliness, and reduced self-esteem are a central characteristic of anxious and depressive experiences during

adolescence. Negative emotions, such as the feeling of shame, guilt, and dissatisfaction, contribute to a young person becoming withdrawn, sad, or angry because of their above-average weight (Penate et al. 2020).

Cognitive distortion followed by dysfunctional thoughts predominates in adolescents with bulimia nervosa (Gjurovic 2003):

- Logical operation: "Just one more spoon, which means a few more kilos."
- Selective abstraction: "I am 'someone' only if I'm skinny, but what can I do?"
- Personalization: "When I see someone who is fat, I immediately fear about my fat appearance, but that's how I am."
- Generalization: "Fat people are not beautiful"; "I am not happy with a normal weight, so I will not be happy by gaining weight, and still, I am happy."

This way of thinking contributes to the young person being upset, worried, and anxious; there is an increased internal restlessness and conflict, which the individual resolves by overeating or attacks of ingesting large amounts of forbidden food, wherewith the person reduces the feeling of anxiety or depression (Hughes et al. 2013). The mechanism by which food affects these emotional states is not entirely familiar; however, it is considered that increased protein and carbohydrate intake affects the synthesis of brain neurotransmitters, particularly serotonin. Overeating in order to reduce anxiety or depression leads to compulsive overeating or weight gain, i.e., disinhibition of eating control (Gilbert and Meyer 2005).

Other Psychological Problems in Adolescence and Bulimia Nervosa

Eating disorders, such as bulimia nervosa, occur at the crossroad between childhood and adulthood, between the mental and the somatic, the individual and the social. According to the multifactorial model, it is a matter of eating disorders that result from complex relationships between biological, developmental, individual, psychological, and sociocultural factors (Baell and Werheim 1992).

The young person with bulimia is extroverted, acts like a person full of oneself, and is well adapted; however, this person is basically overwhelmed with a sense of low self-esteem and self-worth, dissatisfied with his/her appearance, and dissatisfied with his/her body and with himself/herself in general. The studies by Gander et al. (2015) confirm that the bulimic adolescent perceives food as a symbolic substitute for love and that the relationship with the mother is an issue in the background of the disorder. The feelings of insecurity, anxiety, and sadness are strong; therefore, the adolescent tends to increase food intake, followed by self-induced vomiting due to fear of gaining weight.

Ivarsson et al. (2006) in their research emphasize that narcissism is one of the characteristics of the young bulimic person. The characteristics of narcissism include grandeur, reduced sense of vulnerability, and threat by others. A young girl with expressed narcissistic traits tries to compensate for her low self-esteem by achieving

an ideal body weight and body shape, but at the same time, she has low self-control in terms of eating.

At the same time, there are numerous studies that attempt to explain the impact of sexual, physical, and emotional abuse in childhood of the bulimic person. However, the obtained results are inconsistent. On the one hand, Levinson et al. (2013) in their research confirm that sexual, physical, and psychological abuse in childhood is strongly associated with various psychiatric symptoms, including bulimia. On the other hand, another group of researchers does not confirm this fact but, however, still believes that child abuse in childhood affects the occurrence of specific mental disorders, such as bulimia (Fairburn and Harrison 2003).

Moreover, the relationship with the parents is very important for the adolescent. The lack of "good enough" motherhood during the symbiotic phase and birth problems have a frustrating effect on a child's basic need to be loved and to adequately respond to his or her needs (Eckerd 2005). This is especially evident in the period of adolescence when girls have an insecure style of relationship, especially with the father. This relationship has been shown to be a risk factor for bulimia nervosa, prolonged anxiety, and depressed mood (Fisher et al. 2008). The relationship with the father is very important, because it is related to the late psychosocial adaptation, the secure connection in the friendly and romantic relations, the separation from the parents, the individualization, and the acquisition of autonomy.

Bulimic problems in adolescence are associated with an increased propensity to self-harm which is a conscious and an unintentional infliction of self-harm (Bora and Kose 2016). It is assumed that the individual has an inadequate connection between the psyche and the body which integrate at the moment when something bad and painful is done to the body. Overeating, self-induced vomiting, and increased physical activity are all a part of internal self-harming behavior (Trindade and Ferreira 2014).

Our Experience

We will start this part with a sentence that has profound implications for the psychological problems associated with the complex disorder of bulimia nervosa in adolescence "think globally, act locally." We begin by describing a study conducted at a local level that we believe has global applicability.

The research on this topic provides us with an insight into the prevalence, classification, and characteristics of bulimia nervosa in adolescence. Only in this way we can recognize the disorder from the very beginning and react when an inadequate behavior associated with it occurs. At the same time, this approach allows us to plan and implement primary prevention, to prevent its occurrence. It is known that the disorder itself most commonly occurs in the period of adolescence, i.e., in the school period; therefore, it is necessary to implement preventive programs that will be performed in the very school.

The study includes an analysis of a sample of 300 randomly selected students in the first and fourth year in two secondary schools in Skopje during the winter

semester of the academic year of 2019/2020. The inclusion criteria for the study were subjects between 14 and 19 years of age, while the criteria for exclusion from the study were subjects with severe somatic diseases who are on a special diet and subjects with previous surgeries. The initial idea for this study is the assumption that several key factors are responsible for the occurrence and development of bulimia nervosa. In this study, we examined the relationship between the variables bulimia nervosa, self-esteem, perfectionism, anxiety, and depression. The purpose was to collect data from different, complementary sources; therefore, a battery of questionnaires and scales was used, as well as a survey questionnaire to obtain data on gender, age, height, and body weight.

What Questionnaires Did We Use for Evaluation?

For the purposes of this study, we used the following instruments:

- Bulimia Investigatory Test, Edinburgh (BITE)

  The Bulimia Investigatory Test, Edinburgh (Fairburn and Beglin 1994; Henderson and Freeman 1987), is an assessment scale that consists of 33 statements designed to identify the symptoms of bulimia or overeating in respondents. The scale itself consists of two sub-scales: the Scale of Symptoms (BITE-sas), which measures the degree of present symptoms, and the Scale of Severity (BITE-ss), which shows us the overeating and clearing severity index defined with their frequency of emergence. The Cronbach alpha of the questionnaire is 0.78.
- Child-Adolescent Perfectionism Scale (CAPS)

  We used the Child-Adolescent Perfectionism Scale (Flett et al. 2001) to assess perfectionism, which is a self-assessment scale consisting of 22 statements based on the multidimensional conceptualization of perfectionism. It consists of two sub-scales: Self-Oriented Perfectionism with 12 statements and Socially Oriented Perfectionism with 10 statements. Self-Oriented Perfectionism refers to the unrealistic demands of the person striving for perfection, while Socially Oriented Perfectionism refers to the demands of others in the environment who expect the person to be perfect. The range of possible results is from 22 to 110 points where the higher result favors a higher level of perfectionism. The Cronbach alpha of the whole questionnaire is 0.91.
- Rosenberg Self-Esteem Scale (RSE).

  The Rosenberg Self-Esteem Scale is a scale for the assessment of self-esteem (Rosenberg 1965). The scale measures the global value orientation toward oneself. It consists of ten statements, five in a positive and five in a negative direction. The respondents rate their self-esteem on a 4 point Likert-type scale, ranging from 1 (I strongly disagree) to 4 (I strongly agree). A higher score favors higher self-esteem. The Cronbach alpha is 0.87.
- Kutcher Adolescent Depression Scale (KADS)

  The Kutcher Adolescent Depression Scale (KADS) is a scale for self-assessment of depression in adolescents (LeBlanc et al. 2002). It consists of

11 statements, whereby the answers are scored on a 4 degree scale: from 0 (never) to 4 (always). The range of possible results varies from 1 to 33b where a higher score favors a higher level of depression. The Cronbach alpha for the whole scale is 0.94.

- The State-Trait Anxiety Inventory (STAI)

  The State-Trait Anxiety Inventory (STAI) is a scale for measuring anxiety (Spielberger et al. 1970). It consists of 40 statements where the answers are scored on a 3 degree scale: from 1 (never) to 3 (always). There are two sub-scales: Anxiety as a Trait (Trait Anxiety – STAI-T) and Anxiety as a State (State Anxiety – STAI-S). A higher score favors a higher level of anxiety. The Cronbach alpha for the scale is 0.82.
- Body Mass Index (BMI)

  We get the body mass index when we divide the body weight expressed in kilograms by the square of the body height expressed in meters.

  The statistical analysis of the data was performed with the software package SPSS (Statistical Package for the Social Sciences, version 20).

What Do the Obtained Results Show Us?

The study included 300 respondents, 150 (50%) male and 150 (50%) female respondents, from 15 to 19 years of age, first and fourth year high school students. In our sample, most of the respondents, i.e., 129 (43%), had normal BMI (18.50–24.99 kg/m^2), 41 (13.66%) had reduced BMI (15.00–18.49 kg/m^2), 102 (34.01%) had slightly increased BMI (25.00–29.99 kg/m^2), and 28 (9.33%) had significantly increased BMI (30.00–35.00 kg/m^2).

Table 1 and Fig. 1 show the average value of the examined variables. From the presented table, it can be seen that the mean value for bulimia is $M = 29.52$, for self-esteem $M = 15.32$, for perfectionism $M = 64.21$, for anxiety $M = 74.51$, and for depression $M = 2.45$.

Table 2 and Fig. 2 show the interrelationship of the examined variables of self-esteem, perfectionism, anxiety, and depression in relation to bulimia and BMI. The results show that a significant correlation is present between the body mass index and the total score of BITE, BITE-sas, and BITE-ss in relation to STAI, STAI-T, STAI-S, and KADS at the level of $p < 0.05$ and $p < 0.01$.

As can be seen from Table 3, students between 14 and 15 years of age show lower results of the examined variables compared to students between 18 and 19 years of age.

The research conducted on our sample shows that the young population is at an increased risk of developing bulimic disorders, due to age, the developmental period, and the environment. It is thought that this developmental period may provoke or exacerbate pre-existing risk factors associated with the development of this disorder.

Table 1 Descriptive statistics for bulimic symptoms, self-esteem, perfectionism, anxiety and depression

Construct	Scale	N	Mean ± SD	Theoretical range
Bylimia	**BITE**	300	25.52 ± 1.65	1–48
Bylimic symptoms	**BITE–sas**	300	21.22 ± 1.34	1–30
Severity of binging and purging behavior	**BITE–ss**	300	8.31 ± 0.76	1–18
Self–esteem	**RSE**	300	15.32 ± 6.34	10–40
Perfectionism	**CAPS**	300	64.21 ± 8.56	22–100
The Self – Oriented Perfectionism		300	40.36 ± 7.21	12–60
The Socially Prescribed Perfectionism		300	23.35 ± 5.34	10–40
Anxiety	**STAI**	300	74.51 ± 9.14	40–120
Trait Anxiety	**STAI–T**	300	38.95 ± 6.32	20–60
State Anxiety	**STAI–S**	300	35.56 ± 5.16	20–60
Depression	**KADS**	300	22.45 ± 10.1	11–33

Source: the syrveys, author's own study on the basis of the research on bylimia, perfectionism, anxiety and depression, carried out at secondary school in Skopje
BITE Bulimia Investigatory Test, Edinburgh, *RSE* Rosenberg Self-Esteem Scale, *CAPS* Child-Adolescent Perfectionism Scale, *STAI* The State-Trait Anxiety Inventory, *KADS* Kutcher Adolescent Depression Scale

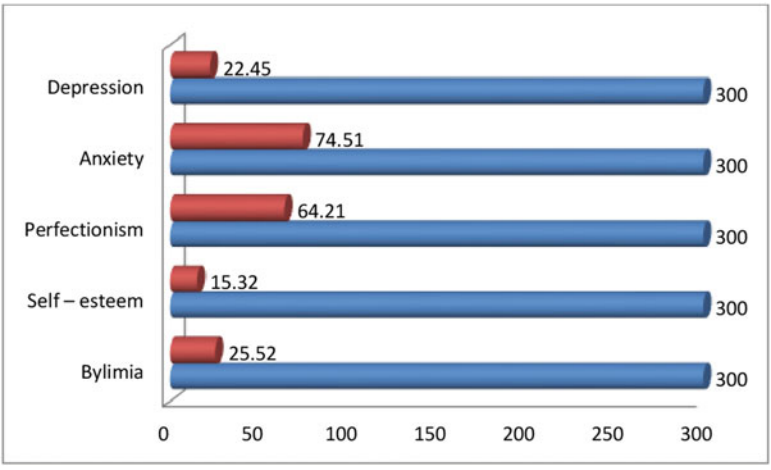


Fig. 1 The level of bylimia, self – esteem, perfectionism, anxiety and depression among adolescents

Through this study, we can see that certain psychological problems in adolescence such as self-esteem, perfectionism, anxiety, and depression play a major role in the development of the bulimic behavior. In accordance with this, it is essential to

Table 2 Pearson's correlation concerning BMI, bylimic symptoms, self-esteem, perfectionism, anxiety and depression

Pearson's correlation	RSE	CAPS	STAI	STAI – T	STAI – T	KADS
BMI	–47**	–45**	–57**	–61**	–53**	–64**
BITE total score	35**	68**	48**	52**	61*	72**
BITE–sas	80[a]	72**	65**	71*	68*	84**
BITE–ss	74*	–74**	81**	62*	82**	71*

BMI Body Mass Index, *BITE* Bulimia Investigatory Test, Edinburgh, *BITE-sas* Bulimic symptoms, *BITE-ss* Severity of binging and purging behavior, *RSE* Rosenberg Self-Esteem Scale, *CAPS* Child-Adolescent Perfectionism Scale, *STAI* The State-Trait Anxiety Inventory, *STAI-T* Trait anxiety, *STAI-S* State anxiety, *KADS* Kutcher Adolescent Depression Scale

*Correlation is significant at the 0.05 level (1-tailed)

**Correlation is significant at the 0.01 level (1-tailed)

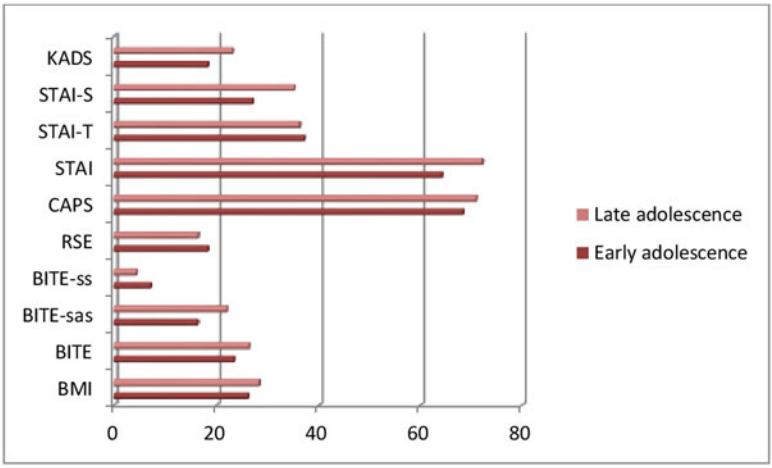


Fig. 2 The level of body mass index, bylimia, self – esteem, perfectionism, anxiety and depression in early and late adolescence. *BMI* Body Mass Index, *BITE* Bulimia Investigatory Test, Edinburgh, *BITE-sas* Bulimic symptoms, *BITE-ss* Severity of binging and purging behavior, *RSE* Rosenberg Self-Esteem Scale, *CAPS* Child-Adolescent Perfectionism Scale, *STAI* The State-Trait Anxiety Inventory, *STAI-T* Trait anxiety, *STAI-S* State anxiety, *KADS* Kutcher Adolescent Depression Scale

confirm or reject the influence of already known predisposing factors but also to discover new ones.

Applications to Other Eating Disorders

In this part, we tried to analyze the relationship between psychological problems that are present in the period of adolescence, such as self-esteem, perfectionism, anxiety, depression, self-image, and suffering caused by the discrepancy between the real and the ideal body weight and eating disorders, including bulimia nervosa. Eating

Table 3 Mean, standard deviations and relationship between body mass index, bylimic symptoms, self-esteem, perfectionism, anxiety and depression in early and late adolescence

Variables	Adolescence (Early) $N = 68$ Mean ± SD	Adolescence (Late) $N = 62$ Mean ± SD	F	p – value
BMI	26.14 ± 1.44	28.32 ± 4.23	72.214	.002
BITE	23.45 ± 8.21	26.34 ± 9.22	77.121	.000
BITE–sas	16.31 ±3.22	21.98 ± 4.79	92.146	.003
BITE–ss	7.14 ± 0.92	4.38 ± 0.64	88.563	.000
RSE	18.31 ± 8.16	16.40 ± 7.32	72.001	.000
CAPS	68.32 ± 7.21	71.02 ± 8.45	94.324	.000
The Self – Oriented Perfectionism	37.17 ± 3.12	36.71 ± 4.81	68.321	.004
The Socially Prescribed Perfectionism	31.15 ± 2.13	34.31 ± 3.53	62.568	.002
STAI	64.15 ± 7.22	72.18 ± 7.56	77.231	.000
STAI–T	37.08 ± 3.31	36.21 ± 3.56	75.243	.000
STAI–S	27.07 ± 2.16	35.17 ± 2.16	69.091	.000
KADS	18.31 ± 5.24	23.15 ± 4.32	89.312	.000

Source: the syrveys, author's own study on the basis of the research on bylimia, perfectionism, anxiety and depression, carried out at secondary school in Skopje
BMI Body Mass Index, *BITE* Bulimia Investigatory Test, Edinburgh, *BITE-sas* Bulimic symptoms, *BITE-ss* Severity of binging and purging behavior, *RSE* Rosenberg Self-Esteem Scale, *CAPS* Child-Adolescent Perfectionism Scale, *STAI* The State-Trait Anxiety Inventory, *STAI-T* Trait anxiety, *STAI-S* State anxiety, *KADS* Kutcher Adolescent Depression Scale

disorders are a group of mental disorders whose common feature is preoccupation with food that leads to somatic, emotional, and behavioral problems (Sambol and Cikac 2015). According to the DSM-V classification, three diagnostic categories of eating disorders are listed: anorexia nervosa (AN), bulimia nervosa (BN), and eating disorder not otherwise specified (ED-NOS) (APA 2013). They are usually transient conditions in the period of adolescence but also part of the clinical features of numerous other mental disorders, such as affective disorders, schizophrenia, and others. They usually occur between 10 and 20 years of age. Anorexia nervosa begins earlier, usually in childhood or early adolescence, when bodily changes occur very rapidly and require extra effort for the young person to accept, process, and incorporate them into his/her physical appearance and identity (Fairburn 1997). Bulimia nervosa usually occurs later in middle and late adolescence when the person enters the adult world (Jurcic 2004). The main characteristic of anorexia nervosa is self-starvation and increased physical activity, while the main characteristic of bulimia nervosa is overeating and self-induced vomiting (Vulic-Prtoric and Cifrek-Kolarcic 2011). The origin of anorexia and bulimia has not been sufficiently studied yet; however, it is known that it is a combination of factors that lead to destabilization of the young person's emotional state. Researches confirm that adolescents with bulimic disorder are pathologically preoccupied and dissatisfied with their body, which affects the emergence of anxiety, depression, and low self-esteem (Halvorsen

and Heyerdahla 2006). Low self-esteem, as a crucial part of identity, is related to other aspects of optimal functioning – self-efficacy, relationship with others and oneself, moral actions, academic success, and attitude toward work and responsibilities (Skoro 2009). Researches have shown that body and weight dissatisfaction affects early pubertal maturation, and negative comments from parents and peers affect the young person in the most vulnerable period of growth and development (Berk 2005). Therefore, the adolescent suffering from this disorder needs professional assistance and adequate nutritional, pharmacological, and psychological treatment. Only in this way one can resolve the problems related to eating habits, binges, vomiting, starvation, dieting, or increased physical activity, but also educating how to regulate negative emotions and the impulses that precede the diet, binges, and/or vomiting (Grilo et al. 2005; Barakat et al. 2017).

Mini-Dictionary of Terms

- **Overeating.** Intake of large amounts of food within a short period of time, followed by reduced self-control
- **Bulimic behavior.** Behavior followed by concerns about the weight and body shape, restrictive diet, overeating, and self-induced vomiting
- **Diet.** An unhealthy and ineffective way to regulate weight, which is followed by a strict and low-calorie diet that, if followed regularly, contributes to weight gain and increases the risk of overeating
- **Perfectionism.** A multidimensional concept that has its own non-adaptive, but also adaptive, desirable functions that are manifested by an increased aspiration for perfection for personal growth and development
- **Negative affect.** A general factor of subjective discomfort, decreased mood, fear, and negative emotions that additionally affect the cognition, worldview, and quality of life
- **Emotional eating.** A pattern of behavior characterized by the intake of increased amounts of food to reduce unpleasant emotions such as depression, anxiety, or loneliness

Key Facts of Bulimia Nervosa

Bulimia nervosa is a developmental disorder that has its latent period that begins in childhood and a manifest, clinical period, which under the influence of precipitating factors manifests itself in the period of adolescence.

Sociocultural, psychological, biological, and genetic factors are part of the genesis of bulimia nervosa.

The young person in the period of adolescence has high criteria related to the index of their own appearance and body shape and weight; therefore, the person satisfies the failure to meet high goals with an increased desire to eat and overeat,

which encourages the psychological patterns of behavior in relation to food, such as bulimia nervosa.

Adolescents with a disturbed self-image develop irrational thoughts about their own body appearance and the importance it has in forming a self-image, which further affects their thoughts, emotions, and behavior.

Low self-esteem and self-assessment, anxiety, and depression are present in the background of bulimia nervosa.

Overeating, self-induced vomiting, and increased physical activity are part of the inner self-harming behavior of a young person with bulimia nervosa.

The main goal in the treatment of bulimia is to enable the person to understand, perceive, and change his/her thoughts that will contribute to setting a new and normal, balanced pattern of a diet and change of personal appearance and food, body, and health.

Summary Points

- The changes from a somatic, mental, and psychological aspect that occur in a young person during the period of adolescence affect the person's bulimic behavior.
- Difficulties with self-esteem, affective self-limitation, impulsivity, perfectionism, inadequate image of one's own body, and reduced social abilities of interaction and communication are the main psychological catalysts for the development of bulimia nervosa.
- The dissatisfaction with the image of one's own body leads to negative attitudes toward a diet, weight concerns, dieting, or overeating, which contributes to the development of bulimia nervosa.
- Low self-esteem in adolescence is a result of the conflict that occurs between the ideal and the real self-image, and the person strives for perfection; however, the person satisfies the failure to meet highly set goals by increasing the desire to eat and overeat.
- Cognitive distortion followed by dysfunctional thoughts contributes to the emergence of concerns, anxiety, depression, overeating, or vomiting in the young person, which are a part of the bulimic behavior.
- Bulimia is a result of increased negative emotional affect, and it affects the self-control of the individual, which contributes to overeating and self-induced vomiting.
- The treatment of a person with bulimia nervosa is a long and complex process; therefore, adequate prevention programs should be implemented by means of which the young person will develop a healthy attitude to food, will learn to control unpleasant emotions and thoughts, and will apply a healthy and appropriate way in relation to the care of his/her health and body.

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Visuospatial Abilities in Eating Disorders

38

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Contents

Introduction 748
Visuospatial Abilities and Mental Rotation 750
Central Coherence 751
Anorexia Nervosa 752
Bulimia Nervosa 753
Binge Eating Disorder 754
Tasks Description 755
Clinical Implications 758
Treatment Implications 758
Conclusion 760
Application to Other Areas 760
Mini-dictionary of Terms 760
Key facts of Visuospatial Abilities in Eating Disorders 761
Summary Points 761
References 762

Abstract

A consistent body of research reports reduced ability in visuospatial processing in the eating disorder population. It has been hypothesized that this neurocognitive alteration may be a consequence of the eating disorder *per se* or an underlying

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trait-marker. Visuospatial difficulties, in particular weak central coherence (a bias towards detail-focusing thinking style), along with executive dysfunctions, have been proposed as endophenotypic traits for anorexia nervosa individuals. In particular, anorexia nervosa patients and their unaffected relatives show a specific detail-focused information processing bias along with a central coherence weakness, with limited ability to gain and integrate contextual information. In bulimia nervosa individuals' visuospatial profile appears less compromised, and, if a dysfunction is present, it seems to characterize specifically bulimia nervosa individuals with a prior history of anorexia nervosa. Visuospatial abilities should be detected and addressed in specific treatment programs due to their potentially negative role in both treatment outcome and body image disturbance, which typically affect individuals on the whole eating disorders spectrum.

Keywords

Visuospatial · Central coherence · Eating disorder · Cognitive functioning · Anorexia nervosa · Bulimia nervosa · Binge-eating disorder

Abbreviations

AN	Anorexia nervosa
ASD	Autism spectrum disorder
BED	Binge eating disorder
BN	Bulimia nervosa
CCI	Central Coherence Index
EDs	Eating disorders
EFT	Embedded Figure test
GEFT	Group Embedded Figures Test
MFFT	Matching Familiar Figures Test
ROCF	Rey-Osterrieth Complex Figure Test
WAIS	Wechsler Adult Intelligence Scale
WISC	Wechsler Intelligence Scale for Children

Introduction

A growing number of studies in the past few years have identified visuospatial difficulties as one of the core features for eating disorders (EDs), especially in the case of anorexia nervosa (AN) and bulimia nervosa (BN). Individuals suffering from AN present a moderate degree of cognitive dysfunction in the visuospatial spectrum, at least partially mediated by specific clinical variables such as BMI, education, and severity of eating symptomatology (Stedal et al. 2021). Indeed, in studies specifically including patients in the acute phase of the illness, clinical severity and lower BMI are factors both associated with poorer visuospatial memory (Zuchova et al. 2013).

AN is one of the most severe mental illnesses. It is a condition characterized by drastic caloric restriction and food avoidance as to induce extreme weight loss or failure to gain weight, along with body weight and shape overestimation (considered

one of the key symptoms) that leads to both meaningful concerns for one's body image, continuous efforts to lose weight, and an intense fear of gaining weight, despite being extremely underweight. Similarly, BN is usually characterized by a radical food-restriction behavior interrupted by episodes of binge eating in turn followed by dysfunctional compensatory behaviors (i.e., vomiting, laxative/diuretic misuse, etc.), more restrictive self-imposed dietary rules, and a very intense "emotional breakdown" increasing the likelihood of running into (i.e., vulnerability of) a new loss of control on food and eating. Lastly, in binge eating disorder (BED), patients exhibit binge eating and very troubled body weight and shape concerns without compensatory behaviors. Usually, as the disease progresses, there is a surge in body weight which, although it is not a diagnostic criterion, takes the role of core symptom for diagnosis, as sufferers express both great distress and pain in dealing with their body weight. Body dissatisfaction and emotional dysregulation are both factors associated with greater vulnerability of incurring in dysfunctional behaviors and of getting stuck in the restriction binge eating loop. Some authors conceptualized body size overestimation characterizing not only AN individuals but also those who are affected by BN and BED, as a direct outcome of visuospatial failure (Lang et al. 2014, 2016). In the non-clinical sample, body size overestimation is associated with poor visual memory (Thompson and Spana 1991). Several authors speculated on the link between body image alteration and a detail-focusing thinking style characterizing AN individuals (Madsen et al. 2013; Urgesi et al. 2012). In particular, it has been proposed that an enhanced attention to local information along with a weakness in the ability to reach global features may predispose to disproportionately focus on detailed body areas, leading to greatest dissatisfaction (Madsen et al. 2013).

Moreover, visuospatial alterations can tie with poor set-shifting, another very peculiar cognitive style observed in ED conditions, leading to a strong cognitive and behavioral rigidity and an extreme need for repetitiveness and keeping to routines (Shott et al. 2012; Steinglass et al. 2006).

Diagnosis, differential diagnosis, clinical classification, and treatment of EDs have traditionally focused on pathological behaviors (i.e., food intake restriction, physical hyperactivity, vomiting, etc.) and typical thoughts and beliefs associated with ED (i.e., fear of gaining weight despite being underweight, body weight overestimation, etc.), while it is only in the last few years that a growing interest towards phenotypic and endophenotypic traits has been observed (Kanakam et al. 2013). This relatively recent focus on cognitive functioning of EDs, in particular on set-shifting and visuospatial abilities, is at least partly supported by some considerations, such as:

- EDs are conditions which are very difficult to treat; to date, elective psychological interventions are very few and for some cases far from effective. Specifically, about half of patients with AN diagnosis recover completely, and 20% remain ill for the rest of their lives (Amianto et al. 2017). Furthermore, relapse rates tend to rise at longer follow-up intervals and appear highly variable (i.e., 9–52%) (Khalsa et al. 2017). Regarding BN, in a recent meta-analysis, over 60% of patients failed to fully overcome eating symptoms despite receiving gold standard treatments (Hagan and Walsh 2021). The long-term outcome studies on the BED population suggest a chronic course of the disorder characterized by a succession of recovery

and relapse phases, with fewer diagnostic migrations than observed in AN and BN (see Hilbert 2019 for a complete overview).
- Neurocognitive weaknesses can have a role in increasing both the vulnerability and the risk of maintaining core symptoms of ED (Connan et al. 2003; Schmidt and Treasure 2006).
- Neuropsychological features can have a negative impact not only on the course of the illness (prognosis) but also on the response to treatment (in terms of both motivation to change and treatment outcome) and, in line with previous considerations, may contribute to maintaining the disorder itself (Harper et al. 2017; Smith et al. 2018).

Studies on cognitive abilities in the ED population are not in line with each other. Alongside those who found a clear visuospatial affection (Lopez et al. 2008a; Tenconi et al. 2010; Weider et al. 2015), there are those who failed to find any cognitive malfunctioning in ED individuals (Jones et al. 1991; Thompson 1993; Øverås et al. 2017), perhaps due to methodological heterogeneity such as experimental design, sample sizes, cognitive tasks employed, and age of the sample (Smith et al. 2018). Moreover, among the studies that found poor visuospatial functioning in the field of ED, it is still unclear whether and to what extent this cognitive alteration represents a premorbid and stable trait-marker rather than a state-characteristic, due to the acute state of the illness. Longitudinal studies on adults (especially in AN) found that visuospatial inefficiencies still persist after recovery (Tchanturia et al. 2002) supporting the trait nature of these inefficiencies. Nevertheless, looking at the duration of the illness, poor cognitive functioning could be considered a consequence of prolonged malnutrition rather than a true trait-marker of the illness (Stedal et al. 2021). Especially in the adolescent population, illness recovery induces cognitive improvement (Lang and Tchanturia 2014; Lozano-Serra et al. 2014; Hemmingsen et al. 2021). The same pattern has been observed with regard to the weak central coherence construct: superior local information processing along with a poorer global thinking style seems to persist despite ED recovery, indicating that both aspects may be stable traits than temporary effects of symptoms, specifically malnutrition and low BMI (Lopez et al. 2009). Furthermore, stronger local processing and weakened global integration appear as relatively independent dimensions (Lopez et al. 2009).

Visuospatial Abilities and Mental Rotation

A promising theoretical framework sees ED individuals enabled in integrating specifically egocentric (vs allocentric) multi-sensory cues, including visuospatial information (Riva 2012). The body image is conceptualized as a construct stored in long-term memory and influenced by implicit and explicit perceptions continuously updated by the perceptual system. The egocentric frame is linked to first-person experiences, perceptions, and short-term memories, with the individual (the body) as the center point of reference, while the allocentric frame refers to a third-person point

of view and relies on long-term memory and schematic representations of space, with spatial orientation gained by external landmarks not associated with the location of the individual's body. This framework conceptualizes AN as a result of a biased perception along with an inability to update the perceptual information in long-term memory. One study found difficulties in processing specifically spatial stimuli from an egocentric perspective in both AN and BN individuals (Serino et al. 2015). Studies which used both mental rotation and object perspective-taking tasks found that AN patients did not perform differently from controls in allocentric perspective tasks, indicating a preserved ability to process the body as an object in the same way as other objects in the environment, while the egocentric perspective tasks (object perspective-taking test) appeared affected. In the object perspective-taking tasks, the task request is a re-estimation of our own position in relation to other objects in space. AN participants show difficulties in updating new locations and a specific difficulty in taking a first-person (egocentric) perspective suggesting an impaired neuronal activity underlying this task (i.e., left inferior parietal lobule and the left somatosensory cortex) (Cipolletta et al. 2017; Lander et al. 2020). Moreover, among individuals with acute AN, measures of detail processing and global integration correlated with connectivity of the left parietal cortex within the somatosensory network, which is involved in the long-term multimodal spatial memory and representation (Favaro et al. 2012). Although perceptual abilities in AN appear to be intact when it is the external world to be processed, things do not work in the same way when it is one's own body that needs to be processed. Egocentric alterations of one's body image would be involved in the body image distortion observed in EDs and may potentially contribute to the development and maintenance of the disorder itself. AN individuals show abnormal egocentric representations along with spared allocentric visual abilities, and the former has been hypothesized to be worsened by visual perception and cognitive flexibility difficulties (Lander et al. 2020).

Central Coherence

Utah Frith in 1989 introduced the term "central coherence" in the context of autism spectrum disorder (ASD) to indicate the natural predisposition to process environmental information integrating features progressively to gain the whole gestalt. Frith named this tendency "weak central coherence" highlighting how at this level information is processed piece by piece, in an extremely detailed way, as opposed to whole perception. Individuals with ASD show a specific cognitive style characterized by strong local processing strategies that keep information fragmented hindering their integration into a meaningful whole (Muth et al. 2014). This phenomenon was already known in the middle of the last century, named field-dependence and field-independence, for individuals with a stronger global and local bias respectively (Witkin et al. 1971). It is the same as that already observed by Navon who found that in the general population, perception is affected by a natural bias from a global to a local processing where the global elements take

precedence over local details (i.e., "a scene is decomposed rather than built up"; Navon 1977, 2003). Weak central coherence is thought to underlie a broad spectrum of skills at both high (i.e., conceptual, abstract, and strategic thinking) and low levels of processing (i.e., visual and perceptive) (Happé and Frith 2006). This pattern of information processing seems to fit the broader autism phenotype well, accounting for the cognitive processing pattern usually adopted in both individuals affected by autism and their relatives (Happé et al. 2001). Lopez et al. (2008a) following Happé and Frith's model of weak central coherence (i.e., poor global processing) in ASD individuals (Happé and Frith 2006) proposed a similar bias towards details in ED individuals. In line with these findings, in the last 20 years, there has been a growth of studies investigating the overlap between EDs, especially AN and ASD (Nickel et al. 2019). The cognitive profile of the two disorders shows some close overlaps, such as both cognitive and behavioral rigidity, the need for repetitiveness, withdrawal from social contacts, and an extreme detail-focused cognitive style at the expense of the contextual information (i.e., global picture). Performance across visuospatial tasks showed an alteration in central coherence in both AN and BN, not only in individuals affected but also in recovered patients and in their unaffected relatives (Lopez et al. 2009; Tenconi et al. 2010; Roberts et al. 2013). The first studies on central coherence found that people affected by an ED show difficulties in global processing, but their superiority in local processing appeared more controversial (Lopez et al. 2009). In particular, its seems that AN individuals and their relatives display high piece-by-piece information processing style (local), while BN patients and their relatives display just a weak central coherence profile, without a local advantage. In line with this, in visuospatial tasks requiring global processing strategies (i.e., the Object Assembly subtest of WISC and WAIS, the Rey-Osterrieth Complex Figure Test, the Bender Gestalt Test), AN individuals perform worse than controls, while in tasks requiring detail-focused strategies (i.e., Block Design, the Matching Familiar Figures Test, the Overlapping Figures Test), their performance appears to be average, if not even above average. In these cases, the better performance has been attributed to a piece-by-piece information processing proneness characterizing both ASD and AN individuals. Regarding the Rey-Osterrieth Complex Figure (ROCF), poor organizational and planning strategies adopted to copy the picture affect copy performance (accuracy score) and immediate (3′) and delayed (10′, 20′, 30′) figure recall (visual memory). Lang et al. (2014) in their systematic review confirmed the involvement of the weak central coherence hypothesis in the ED population.

Anorexia Nervosa

The visuospatial abilities in AN appear altered in both perception and memory. Individuals with current AN perform the copy condition of ROCF, assessing perception and visuospatial planning and organization, significantly worse than healthy controls (Lopez et al. 2008a; Kim et al. 2011), whereas fully recovered AN individuals show improved perception and planning (Lindner et al. 2013). Their ability to

identify the perceptual structure of the complex figure appears preserved, but elements are organized in a fragmented way as a result of a detail-focused thinking style, leading to poor construction abilities. Spatial memory skills also appear deficient in acute AN people (Lopez et al. 2008b), and some authors proposed that a poor visual memory may be a result of the bias towards detail-focused processing (Lopez et al. 2008a; Stedal et al. 2012). As already mentioned, AN individuals show a general weakness in their central coherence, with an information processing style characterized by a strong focus on details along with difficulties in global integration (Smith et al. 2018). This pattern is more evident in the adult population but less consistent in studies on adolescents (Lang et al. 2014). In AN there is some evidence suggesting that the recovered individuals show a higher detail processing along with a better visual coherence (on the ROCF) than acute patients. Therefore, weight loss and malnutrition seem to negatively affect both detail processing and global integration (Lopez et al. 2009). Nevertheless, the literature on these aspects does not appear to be in agreement; indeed, a very recent systematic review reports that factors such as BMI, anxiety, and depression do not affect central coherence abilities in AN (Fuglset 2021).

Bulimia Nervosa

Although BN and AN are clearly distinct disorders, with specific diagnostic criteria (DSM-5), there is a strong overlapping between them in "core" ED distinctive symptoms, such as body weight and shape concerns, overevaluation of one's one body size, and the close interdependence between self-esteem and body weight. This tight bond between BN and AN diagnoses is also highlighted by the very frequent diagnostic migrations within the ED spectrum, particularly from AN to BN, suggesting some biological and psychopathological common processes (Eddy et al. 2008). Studies on BN found poor visuospatial functioning in both visuospatial memory and central coherence (Lopez et al. 2008c). In particular, BN patients showed lower accuracy scores on the copy trial of the ROCF and impaired visuospatial memory (Bosanac et al. 2007). Investigations on information processing approaches in ED found a greater difficulty in global integration (weak central coherence) in BN individuals, whereas a higher detail-focused processing characterizes those with AN diagnosis (Roberts et al. 2013). A weaker performance in tasks which benefit more from a global strategy (i.e., the ROCF) along with a superior detail-focused processing (e.g., shorter times for completing the Embedded Figure Test, lower Central Coherence Index, and a trend for a smaller advantage from Block Design segmentation) appeared to characterize BN individuals. In light of these data, BN shows weak central coherence and some overlaps with the visuospatial profile of individuals with current AN (Lopez et al. 2008b). Both the presence of high levels of anxiety and the severity of BN psychopathology in acutely affected individuals negatively impact the accuracy performance of the ROCF and the CCI (Lopez et al. 2008c); even so it seems to be an aspect that persists at the remission of anxiety symptoms (Lopez et al. 2009). Nevertheless, cognitive impairment in BN

(visuospatial as well as that regarding executive abilities) appears to be less severe and more heterogeneous than in AN (Weider et al. 2015, 2016; Darcy et al. 2014; Lopez et al. 2008c). A possible explanation of this milder cognitive profile characterizing the BN population may be the presence or not of a prior history of AN in individuals with a current BN. The very few studies that differentiated BN patients with "pure" BN (without a prior diagnosis of AN) from those with prior AN found a significative difference compared to healthy controls exclusively in this latter group and specifically for executive abilities, but no differences in visuospatial skills were found (Degortes et al. 2016; Strumila et al. 2020). The only prior investigation on visuospatial functioning in BN that considered the presence or not of a prior diagnosis of AN (in this study the authors assessed 24 "pure" BN and 18 BN with prior AN) found a greater local processing in BN/AN patients than in the "pure" BN (Lopez et al. 2008c), supporting the hypothesis of some impact of prior AN on the thinking style of current BN. The presence of a previous history of AN in BN individuals may have affected cognitive and physical functioning differently from those patients who have never experienced malnutrition and a very low BMI. All these studies support the hypothesis of a residual detrimental role of having had prior AN. In line with this, a poor ICC in the AN study of Weider et al. (2016) no longer differs from controls once it is adjusted for nadir BMI. Although for BN cognitive behavioral therapy is a gold-standard treatment with ample proof of a good efficacy, about one-third of BN patients show poor treatment outcomes. The presence of a prior history of AN implies a greater involvement of physical and cognitive aspects that should receive proper attention, as well as requiring specific care (Strumila et al. 2020).

Binge Eating Disorder

With respect to cognitive functioning, individuals with BED show specific eating disorder-related difficulties and a relative saving of general cognitive abilities. As noted above, the BED condition is usually strongly associated with overweightness and obesity, and some lines of research in both animals and humans support the association between a high-fat and a high-sugar diet, as well as a poor-quality diet and a reduced neural plasticity also associated with alterations in spatial memory (Cordner and Tamashiro 2015; Francis and Stevenson 2011). In a study using the Zoo Map task, in which participants are asked to produce a plan to navigate among a series of positions on a visual map, obese BED individuals made a higher number of errors than non-BED obese participants, providing the first evidence of the link between BED and poor spatial processing (Duchesne et al. 2010). Moreover, there are also insights about relationships between visual memory deficit and being overweight or having binge eating (loss of control) (Calvo et al. 2014; Prickett et al. 2015). Two studies on the obese population found poor performance not only in memory trials but also in the copy trial of the ROCF, a perceptual task usually considered preliminary to the memory test (i.e., the delayed recall part of the ROCF) (Boeka and Lokken 2008; Roberts et al. 2007). In the BED population, visual

memory appears to be deficient, regardless of BMI. According to some studies, as happens in overweight people, also in this population, in addition to poor memory recall, patients reported poorer accuracy scores in the copy trial, again indicating perceptual difficulties (Aloi et al. 2015). Moreover, in a more controlled (i.e., the study considered both normal-weight and overweight BED patients and weight-matched controls) and recent study, BED individuals showed a saving in perceptual skills (i.e., good performance on the coping trial), as well as good visuospatial recognition abilities, along with poor performance on both immediate (3′) and delayed (30′) recall trials compared to controls indicating visual memory deficiency (Eneva et al. 2017). The latter study found an association between BED diagnosis and visual memory difficulties regardless of body weight. It is possible that visuo-spatial memory alterations may affect body size estimations. Future studies of BED using the ROCF should examine central coherence measuring the organizational and perceptive approach strategies for drawing the complex figure.

Tasks Description

Visuospatial abilities are multiple and complex skills consisting in the perceptual analysis of the visual environment by structuring the local elements (details) into a coherent and meaningful perceptual configuration. The literature suggests that the development involves a progressive shift from a local perceptive processing to a global decoding of visuospatial information facilitating global information processing as compared to detail processing. The different but related visuospatial abilities include more "pure" visuospatial functions, such as spatial construction, spatial analysis, and manipulation and visuo-motor coordination, but also the superior executive functions. Spatial analysis consists in the ability to visually perceive the external environment, break it down into sub-elements (local processing), and then integrate details into a coherent whole (global processing). All of these functions lead to organizing and integrating details to perceive a spatial configuration by reproducing spatial patterns. Usually, constructional abilities are assessed by a complex drawing and/or block assembling. The most widely used tasks for spatial construction are the Rey-Osterrieth Complex Figure Test and the Block Design Test. For example, the ROCF is usually employed to assess visuospatial perception and memory but also organizational strategies such as planning and a more local or global cognitive approach. In psychiatry there is a lack of cognitive tests specifically developed and tailored to cognitive alterations characterizing major psychiatric disorders. Neuropsychological tasks were originally conceptualized to detect the effects of focal injury due to brain damage or trauma, and they are not entirely suitable for the psychiatric population, characterized by a different type of damages, usually widespread and enduring. Perhaps, for these reasons they may not be (or not always be) sensitive enough to detect also minor cognitive difficulties (Keefe 1995), which sometimes characterize those who suffer from a psychiatric disorder, especially in the first stages of the illness. A good alternative might be to consider process scores (i.e., considering behaviors and reasoning employed to solve the task) more

Table 1 Visuospatial tests divided according to their local vs global properties

Tasks whose performance benefits more from:	
LOCAL processing	GLOBAL processing
Embedded Figures Test/Group Embedded Figures Test	Rey-Osterrieth Complex Figure test
Matching Familiar Figures Test	Object Assembly
Block Design	Overlapping Figures test
Unsegmented Block Design	Segmented Block Design

than the outcome scores themselves (Stedal et al. 2019). A good example of process scores may be the Central Coherence Index (CCI), an outcome score ranging from 0 to 2 which represents the individual's local vs global natural predisposition (i.e., the bias for detail-focused versus global-synthesis approach in information processing) in copying the ROCF, which appears to well (with a large effect size) differentiate AN individuals from controls.

The tests most commonly used for assessing visuospatial abilities in the field of ED (see Table 1 for a classification of tasks on the basis of their local/global task demand strategies) are:

- The Rey-Osterrieth Complex Figure (ROCF) (Osterrieth 1944), which is no longer regarded as a purely visuospatial test, but is now considered a good task also for the assessment of higher executive functions. Savage et al. (1999), assessing the ROCF performance of obsessive-compulsive individuals, proposed that visual memory deficit could be at least partially explained by difficulties in cognitive planning and organizational strategies activated during the copy trial of the complex figure. The ROCF assesses a variety of cognitive processes such as visual perceptual organization, spatial planning, problem-solving, spatial memory, and motor function. The task consists of two parts: the first assesses perceptual abilities, and participants are asked to copy the complex figure as closely as possible to the template. Successively, without prior warning, they are asked to recall the figure after a temporal delay that may vary from 3 to 30 min (implicit visual memory). The task gives two outcome measures, the perceptual accuracy score and the visual memory accuracy score. The former consists in the correct placement and reproduction of 18 details composing the complex figure, and the latter is the correct placement and production of the same 18 details from memory, after a longer or shorter time interval. In both cases higher scores are indicative of a better performance (range 0–36). The most used scoring system is that proposed by Taylor (1969), adapted from Osterrieth, but there are a lot of different alternatives. Process scoring for organizational strategy and drawing style specifically in the ED population have been developed by Booth (2006). This score system allows us to obtain the CCI, derived from both the order of construction index (the first six global or local elements drawn in the copying trial) and the style index (the degree of continuity of drawing). A higher CCI (the closer the scores are to a score of 2) is indicative of a more coherent drawing style. In

general, a weak central coherence cognitive style (low ICC score) in copying the complex figure adversely impacts on the quality of recall (Lopez et al. 2008a).

- The Object Assembly (a subtest of the Wechsler Adult and Children Intelligence Scales – WAIS and WISC), which is a test assessing the ability to solve five small jigsaw-type puzzles reproducing familiar objects (e.g., a hand, a mannequin). Participants have a time limit to complete and build each object starting from single pieces. Both the time taken to complete the puzzle and the number of pieces correctly assembled are outcome measures. A shorter time suggests a better ability to create an integrated global representation from its parts, indicating stronger global processing.
- The Overlapping Figures Test (Lezak et al. 2004) evaluates the ability to discriminate figures from the background (visual interference), spatial exploration, and denomination abilities. The task consists in a set of overlapping lines which, on closer analysis, hides different types of meaningful shapes (e.g., animals, fruits, words, numbers, etc.). The participant is asked to recognize and correctly denominate the greatest number of figures within a 4 min time limit. Differently from the EFT, in this task the overlapping lines configure many meaningfulness stimuli, and a unified meaningful shape is more difficult to be interpreted in terms of local parts. In this task, a weak central coherence (i.e., difficulties in global processing) is thought to reduce performance (i.e., the detection of as many figures as possible).
- The Block Design (subtest of the WAIS and WISC), which is a construction test assessing the ability to reproduce a complex geometric figure by putting together sets of blocks to replicate the block-design depicted on a two-dimensional template. The outcome score considers both the time taken and the number of block designs correctly reproduced. A higher performance on this task is considered to be indicative of a better detailed visual processing (i.e., higher ability to segment the figure into its constituent elements). Some studies (Tenconi et al. 2010) used a modified version of the Block Design Test, the Unsegmented/Segmented version developed by Shah and Frith in 1993. In the Segmented trials, templates are not presented as a whole (in this case the participants have to split the design into its component elements to solve the task), but are already divided into smaller portions slightly separated from each other. Higher scores in both speed and accuracy are indicative of a better local processing approach, and people usually benefit more from the segmented (vs unsegmented) version. People with weak central coherence should benefit less from segmentation (i.e., should show no difference in performance between unsegmented and segmented trials) (Lopez et al. 2008b).
- The Embedded Figures Test (EFT)/Group Embedded Figures Test (GEFT) (Witkin et al. 1971). This perceptual test measures the time taken to locate and trace 12 (or 18 in the GEFT) simple shapes embedded in complex designs. Scores are expressed in seconds and represent the time taken to locate the hidden shapes and number of errors and false claims. A shorter time and fewer errors/false claims suggest stronger local processing.

- The Matching Familiar Figures Test (MFFT) is a visuo-perceptual test designed to measure reflection-impulsivity. The participant is asked to select from eight very similar alternative items the exact match of a template. The time required to complete all the matches and the number of errors are outcome scores. People who record above-median response times and below-median errors are classified as reflective; people with below-median response times and above-median errors are impulsive. In this task a more detail-focused processing results in better efficiency (i.e., a reduction in both time and errors).

Clinical Implications

The natural tendency to process detail-focused information better in EDs may impact on clinical psychopathology, treatment involvement, and outcome. In particular, the bias towards local processing may prompt and/or maintain maladaptive pattern behaviors as well as make individuals unable to see both the situation as a whole (bigger picture) and the negative effects/outcomes of dysfunctional choices. In line with these considerations, the difficulty in integrating all the data in a bigger picture (context) may limit seeing the long-term consequences of the dysfunctional behaviors triggered by the ED, along with a limitation of the ability to learn from the experience. The strong need observed in EDs for both everything to appear perfect and under strict individual control, combined with an extremely detailed information processing style, may affect eating behavior and other aspects of patient's life (i.e., academic, work, personal and interpersonal life). The extreme detail-focusing processing style risks getting the patient stuck in them, exacerbating core cognitive and behavioral ED symptoms (i.e., perfectionism, rigidity, fears). This bias towards local information over the whole body perception may limit the integration of bodily perceptions and feelings contributing to body image disturbance and distortion, resulting in the overestimation of one's own body size (the peculiar phenomenon of feeling and perceiving oneself as fat despite being severely underweight), or the amount of food intake.

Treatment Implications

The visuospatial difficulties along with the central coherence deficit characterizing information processing in EDs in general, and AN in particular, represent quite stable disorder traits that could contribute to illness onset and maintaining and should be addressed in treatment programs. In particular, some authors developed a specific cognitive treatment (i.e., cognitive remediation therapy) that addresses these aspects directly, helping patients to increase self-awareness about their own thinking style (i.e., the attention is more on the ways than on the contexts of thinking) and stimulating patients to criticize and overcome this specific thinking style promoting the assumption of a broader view (Lindvall and Rø 2014).

CRT is a manualized program, usually employed as an add-on treatment, which addresses the cognitive style underlying both the development and maintenance of AN and other EDs. CRT is a metacognitive intervention considered, with a few exceptions (van Passel et al. 2020), able to increase the effectiveness of traditional treatments and to improve cognitive abilities and quality of life, and in some cases it has also reduced ED symptoms and treatment dropout (Lindvall and Rø 2014; Leppanen et al. 2018). CRT aims to help patients to adopt a new cognitive style through stimulating and engaging in new activities avoiding issues and emotions relating to all that concern the usual eating disorder aspects (e.g., food avoiding, fasting, fear of gaining weight). The key items of CRT are that practicing a determined cognitive skill is thought to improve both the performance itself and the sense of self-efficacy. Moreover, practicing a new cognitive process may increase the neural network (via brain plasticity) involving and activating less-used brain areas. In particular, CRT comprises exercises focusing on enhancing visuospatial abilities and reducing central coherence weakness/extreme attention to detail encouraging patients to "see the wood from the trees," to move on to the whole context by reducing the natural tendency to focus attention on details. CRT also has the key role of indirectly preparing and motivating patients to a more general and eating-addressed psychotherapy. For example, one of the aims would be to help the patient to become more able to manage a full meal without pausing on each single food (e.g., calorie counting or rumination). See Fig. 1 for an example of a CRT exercise in adopting a broader view.

- Task demand: the patient verbally describes the complex figure so that the therapist can draw it without being able to see it. At the end the therapist's drawing is compared with the template, and a metacognitive style discussion follows.
- Reflection questions on the task (e.g., what the patient thinks about the task, which kind of thinking did he/she use, etc.)

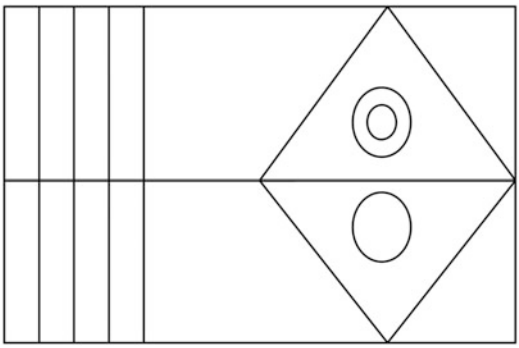


Fig. 1 Complex picture task (Tchanturia et al. 2010 CRT Manual, https://www.katetchanturia.com/_files/ugd/2e1018_f71866481f9f44e5a342fb068b891a8c.pdf)

Conclusion

The literature supports the idea that neurocognitive anomalies characterizing EDs are not a mere consequence of illness state (such as malnutrition, underweight, or purging behaviors) but rather represent a specific and relevant feature to support the diagnosis, involved in the onset, maintenance, and vulnerability to relapse, after a period of recovery. If cognitive alteration can be involved in the maintenance of the illness, it should be specifically addressed in planning treatment interventions, according to the specific processing style shown by the specific patient.

Application to Other Areas

In this chapter, we have dealt with visuospatial abilities and disabilities across the whole spectrum of eating disorders. Anorexia nervosa patients present the greatest impairments in this cognitive area, followed by bulimia nervosa individuals with a previous history of anorexia nervosa (Lopez et al. 2009; Tenconi et al. 2010; Roberts et al. 2013). The "pure" bulimia nervosa patients appear to have slight difficulties, while binge eating patients show deficiencies mainly when the stimuli are specific eating disorder-related (vs. neutral stimuli), although there is growing evidence of some visuospatial fragility (Degortes et al. 2016 for BN and Duchesne et al. 2020; Kittel et al. 2015 and Eneva et al. 2017 for BED). Visuospatial alterations appear to persist after clinical improvement in both anorexia nervosa and bulimia nervosa patients (Tchanturia et al. 2002; Lopez et al. 2009; Tenconi et al. 2010) and seem slightly mediated by psychopathology (i.e., low BMI, illness severity, etc.) (Stedal et al. 2021). The adolescent population needs deeper attention because there are insights of some improvement after initial recovery (Hemmingsen et al. 2021). We should consider visuospatial functioning as a broader construct, as it appears involved not only in eating disorders but also in other psychiatric populations, such as autistic spectrum disorders and schizophrenia. Especially in the latter condition, visuospatial deficiencies already appear to be present in the first episodes and, worsening as the disorder progresses, they seem to worsen the prognosis and it would be very important to disentangle them from the hypothesized negative impact of antipsychotic medications (Happé et al. 2001; Stirling et al. 2003).

Mini-dictionary of Terms

- Visuospatial abilities are multiple and complex skills consisting in the perceptual analysis of the visual environment by structuring local elements (details) into a coherent and meaningful perceptual configuration.

- Central Coherence is the natural predisposition to process environmental information (not only perceptual data) progressively integrating features to gain the whole gestalt (the context, or big picture).
- Weak central coherence indicates a personal tendency to process information piece by piece, in an extremely detailed way, as opposed to processing information as a whole.
- Visuospatial tests are specific tasks employed to both assess and quantify visuospatial skills.
- The Complex Picture Task is an exercise belonging to the Cognitive Remediation Therapy program, designed to address weak central coherence and promote a more global cognitive thinking style.

Key facts of Visuospatial Abilities in Eating Disorders

Visuospatial Abilities

- Visuospatial difficulties affect the eating disorder population.
- Visuospatial difficulties have been proposed as endophenotypic traits for both anorexia and bulimia nervosa.
- Both patients and unaffected relatives may show some visuospatial inefficiencies.
- Weak central coherence is a specific visuospatial alteration and characterized by a bias toward detail-focusing thinking style.
- Clinical improvement does not seem to significantly improve visuospatial cognitive style.

Summary Points

- *Individuals affected by an eating disorder show a reduced ability in visuospatial processing.*
- *Anorexia nervosa patients show a specific detail-focused information processing bias along with a central coherence weakness.*
- *Cognitive alterations consistently associated with AN were less present in BN, especially in those individuals without a previous history of AN.*
- *BED individuals show altered retrieval of a complex visual stimulus, independent of their BMI.*
- *Memory abilities may be negatively affected by unhealthy diet, and memory may affect food intake behavior.*
- *Visuospatial abilities may further affect and worsen body image disturbance observed in the whole eating disorder spectrum.*
- *Visuospatial abilities should be detected and addressed in specific treatment programs due to their role in the development and maintenance of the disorder itself.*

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Androgens and Their Role in Bulimia Nervosa and Eating Disorder Not Otherwise Specified of Purging Type (EDNOS-P)

39

Sabine Naessén

Contents

Introduction 769
Androgens and Their Mechanism of Action 769
The Action of Sex Steroid Hormones in the Pathophysiology of Bulimia Nervosa 772
Binging and Purging: Hormonal Changes 773
Polycystic Ovarian Syndrome: A Hyperandrogenic Condition with Associations with Bulimia Nervosa 774
Antiandrogenic Treatment in Bulimia Nervosa 775
Androgen's Role in Relation to Psychiatric Disorders and Bulimia Nervosa 776
Conclusions 778
Applications to Other Eating Disorders 778
Mini-Dictionary of Terms 778
Key Facts 779
Summary Points 780
References 780

Abstract

The sex steroid hormones, estrogen, progesterone, and androgens, play an essential role in the pathophysiology of bulimia nervosa (BN). The importance of androgens has also been recognized recently. However, the research on androgens' role in bulimic disease, and its psychopathology and comorbidity, is scarce.

Androgens exert direct action on the CNS but also in conjunction with estrogens, and progesterone.

APABulimic women of normal body weight have disturbances in the hypothalamic-pituitary-thyroidal axis and are at increased risk of developing physiologic and endocrine disturbances, including menstrual irregularities. Polycystic ovarian syndrome (PCOS), with features of biochemical hyperandrogenism, menstrual disturbances, and polycystic ovarian morphology, can

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be seen in women with BN. Antiandrogenic oral contraceptives appear to reduce bulimic symptoms, meal-related appetite, and bulimic behavior. Maybe BN is a hormonal rather than primarily a psychiatric illness in some cases.

In a recent study, it has been found that women with BN and the subgroup of Eating Disorder Not Otherwise Specified of Purging type (EDNOS-P) had different origin of androgens, despite similar androgen levels. A direct ovarian testosterone (T) secretion was found in women with EDNOS-P, and peripheral conversion of circulating androstenedione (A2), and dehydroepiandrosterone sulfate (DHEAS) in women with BN.

These findings can perhaps be interpreted as a transition between EDNOS-P to BN and vice versa; the results may also indicate endocrine and psychoendocrine differences between the two groups of bulimic women.

These implications of sex steroid hormones' involvement in the pathophysiology of BN are yet to be understood.

Keywords

Bulimia nervosa · Eating Disorder Not Otherwise Specified · Testosterone · Dihydrotestosterone · DHEA · DHEA-S · Estrogen · Progesterone · Hypothalamic amenorrhea · Polycystic ovarian syndrome · Depression

Abbreviations

A2	Androstenedione
A4	4-Androstene-3,17-dione
BN	Bulimia nervosa
COC	Combined oral contraceptive
DHEA	Dehydroepiandrosterone
DHEAS	Dehydroepiandrosterone sulfate
DHT	Dihydrotestosterone
DSM	*Diagnostic and Statistical Manual of Mental Disorders*
E2	17-ß-Estradiol
EDNOS	Eating Disorder Not Otherwise Specified
EDNOS-P	Eating Disorder Not Otherwise Specified of Purging subtype
FDA	Food and Drug Administration in the United States
FHA	Functional hypothalamic amenorrhea
FSH	Follicle-stimulating hormone
GABA	γ-Aminobutyric acid
GnRH	Gonadotropin-releasing hormone
HDL	High-density lipoproteins
HPA	Hypothalamic-pituitary-adrenal axis
HPG	Hypothalamic-pituitary-gonadal axis
LDL	Low-density lipoprotein
LH	Luteinizing hormone
PCOS	Polycystic ovarian syndrome

PMS	Premenstrual syndrome
T	Testosterone
VLDL	Very-low-density lipoproteins

Introduction

This chapter deals with androgens' role in women with bulimia nervosa (BN) based on studies in the field. There are several proposed biological mechanisms thought to cause and perpetuate BN pathology. However, this chapter will only address the effect of sex steroid hormones' association with BN.

Most of the recent findings concerning androgen's role in BN includes the subgroup of Eating Disorder Not Otherwise Specified (EDNOS), based on the fourth edition of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM) (APA 2000).

The sex steroid hormones, testosterone (T), 5α-dihydrotestosterone (DHT), and 17β-estradiol (E2) influence, among many other factors, the development of eating disorders. Therefore, a background of these hormones' mechanisms of action will be addressed here.

Androgens and Their Mechanism of Action

Cholesterol is the precursor for all steroid hormones, including gluco- and mineralocorticoids, sex hormones, and vitamin D. The production of cholesterol takes place in the liver but most of the supplies come from plasma low-density lipoproteins (LDLs) derived from dietary cholesterol (Gwynne and Strauss 3rd 1982) (Fig. 1).

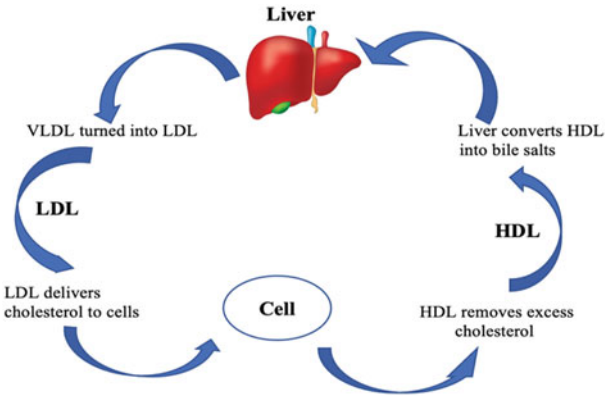


Fig. 1 Production of cholesterol and triglycerides in the liver

Pregnenolone is the main steroid synthesized from cholesterol, which is converted to steroid hormones after a series of enzymatic processes. The biologically active androgens, testosterone (T), and 5-α- dihydrotestosterone (DHT) are formed by de novo synthesis in the ovaries and the adrenal cortex, but the main part arises through peripheral conversion of the adrenal androgens 4-androstene-3,17-dione (A-4), dehydroepiandrosterone (DHEA), and its sulfate (DHEA-S) in the liver, kidneys, muscles, fat, and skin and in the CNS (Miller and Auchus 2011).

Consequently, peripheral testosterone can cross the blood-brain barrier and have various effects on the brain (Melcangi et al. 2008). Dihydrotestosterone has a higher molar potency because of its higher affinity for the androgen receptor, and the androgenic action is diversified by the aromatase (CYP19) mediated conversion of testosterone to estradiol.

The testosterone production in the gonads follows the pulsatile release of luteinizing hormone, and circulating testosterone concentrations result in suppression of gonadotropin (LH and FSH) secretion (Dabbs Jr and La Rue 1991) (Fig. 2).

In the ovaries, androgen formation is performed in LH-stimulated thecal cells, with the synthesis of DHEA and A4. Most of these precursors will be converted to estrogens by granulosa cells, but ovaries will also directly secrete androgens in the circulation, mainly as A4 and T (Burger 2002).

The secretion of testosterone from the ovaries is stimulated by luteinizing hormone, with estradiol exerting negative feedback, while in the adrenal cortex, the secretion of testosterone is stimulated by adrenocorticotropic hormone with negative feedback by cortisol.

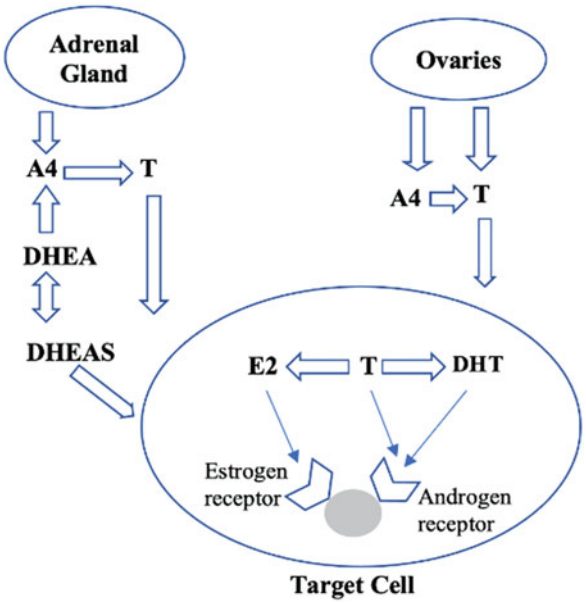


Fig. 2 Testosterone production in women

Testosterone production in premenopausal women is approximately 0.1–0.4 mg per day (Burger 2002), and the circulating testosterone concentrations are stable and not subject to negative feedback by exogenous testosterone (Rothman et al. 2011).

In the circulation, testosterone is specifically bound to sex hormone-binding globulin (SHBG) (∼66%) and to albumin (∼32%), leaving only a small fraction free (∼2%). SHBG is produced and secreted by the liver, binds to testosterone with high affinity, and regulates their bioavailability. In addition, the hepatic production of SHBG is raised by estrogens, and suppressed by androgens.

Testosterone is predominantly bound to SHBG; however, various terms are used to explain the degree of binding grades. *Total testosterone* refers to the sum of the concentrations of protein-bound and unbound testosterone in circulation. The fraction of circulating testosterone that is unbound to any plasma protein is referred to as the *free testosterone fraction* (Manni et al. 1985).

The term *bioavailable testosterone* refers to the fraction of circulating testosterone that is not bound to SHBG and largely represents the sum of free testosterone plus albumin-bound testosterone. However, recent data shows that the bioavailable testosterone also includes SHBG-bound testosterone, which seem to mediate the cellular uptake and biological actions of testosterone (Hammes et al. 2005). One of the most abundant proteins in plasma is albumin. Although it binds testosterone with lower affinity than SHBG does, its high binding capacity and high concentration allow it to buffer fluctuations in testosterone levels (Hammond 2016).

In addition, the hepatic production of SHBG is regulated positively by estradiol, while androgens decrease its production. The androgen DHEAS is the most abundant circulating steroid hormone in the body. It enters the ovarian follicle and can be an important source of ovarian testosterone (Burger 2002). The serum concentrations of androgens in descending order are DHEAS, DHEA, A-4, T, and DHT, though only the latter two bind the androgen receptor (Burger 2002). Both DHEA and DHEAS can be converted in peripheral tissues to androstenedione (A2), testosterone (T), and dihydrotestosterone (DHT), and both are aromatized to estrogens. Compared to T, the daily production rates of DHEA and DHEAS are much higher, approximately 6–8 mg/day and 3.5–20 mg per day, respectively, and both circulate in micromolar concentrations (Burger 2002). The actions of androgens are very complex and may also differ according to the level of androgen receptor (AR) or estrogen receptor (ER) expression, the bioactivity of 5α-reductase and aromatase, the co-activators and co-repressors present in each cell type, and the pattern of interacting in target cells.

Testosterone deficiency and/or increased levels are associated with several health complications including osteoporosis, cardiovascular disease, type 2 diabetes, and metabolic syndrome, among others. However, this is beyond the scope of this chapter.

The actions of androgens are thus important in understanding the normal physiology, pathophysiology, and development of female reproductive system.

The Action of Sex Steroid Hormones in the Pathophysiology of Bulimia Nervosa

Sex steroid hormones comprise testosterone, estrogen, and progesterone. Individuals with BN as well as anorexia are at increased risk of developing physiologic and endocrine disturbances, including menstrual irregularities (Poyastro Pinheiro et al. 2007). The underlying causes of menstrual irregularities are multifaceted and result from a complex interplay of many factors including psychological stressors, frequent purging, and hormonal imbalance (Vyver et al. 2008). Disturbances in the hypothalamic-pituitary-ovarian axis result in impairments of the gonadotropins, follicle-stimulating hormone (FSH), and luteinizing hormone (LH), which in turn leads to functional hypothalamic amenorrhea (FHA) (Genazzani 2005). FHA is classified as hypogonadotropic hypogonadism and is one of the most common causes of amenorrhea in fertile women (Gordon 2010). Furthermore, estrogens' actions and irregular menstrual function are also implicated in the pathophysiology of BN (Hudson et al. 2007), where reduced concentrations of estradiol (E2) and luteinizing hormone (LH) and pulsatile release of luteinizing hormone were observed (Devlin et al. 1989). Thus, in association with other sex steroid hormones and transmitter substances, estrogens have many complex functions.

It is well known that menstrual irregularities are present in women with BN, but the incidence is highly variable (Gendall et al. 2000). Even though amenorrhea occurs in healthy-weight women with BN at a rate of about 5–40%, oligomenorrhea is more common with a frequency of 40–60% (Austin et al. 2008). This variability may be because patients have adequate estrogen secretion and present with an anovulatory syndrome combined with irregular bleeding.

Weight loss, emotional stress, and overexercise mutually or separately can result in complex hormonal changes, i.e., mild hypercortisolemia, low serum insulin levels, low insulin-like growth factor 1 (IGF-1), and low total triiodothyronine, which are manifested by profound hypoestrogenism (Meczekalski et al. 2014). Moreover, high serum beta-hydroxybutyrate and low total triiodothyronine (T3) have been identified in both women with anorexia nervosa (AN) and BN, which can be explained by periods of malnourishment, purging, and/or excessive training (Altemus et al. 1996). Accordingly, normal-weight women with hypothalamic amenorrhea appear to have normal androgen and DHEAS levels (Miller et al. 2007). It is notable that normal-weight women with BN can also have abnormalities in the hypothalamic-pituitary-thyroidal axis, such as low levels of LH and FSH, along with low estradiol, characteristic of emaciated women with anorexia nervosa (Schweiger et al. 1992). Among other properties, the sex steroid hormones, estradiol, progesterone, and testosterone, seem to influence reward circuit alterations that contribute to eating disorders (Ullsperger and Nikolas 2017). Women who have hypothalamic amenorrhea exhibit susceptibility to restrictive disordered eating, depressive traits, and psychosomatic disorders (Meczekalski et al. 2014).

The sex steroid hormones estrogen, progesterone, and androgens are important modulators of food intake and energy balance in humans (Asarian and Geary 2013). They interact with neurotransmitters and gastrointestinal peptides to achieve central

control of appetite and energy expenditure (Asarian and Geary 2013). During the follicular phase of the menstrual cycle, when estrogen is at its peak, the appetite, meal size, and intake of sweets decrease (Asarian and Geary 2013). Just as healthy women may have eating behavior changes during their menstrual cycle, binge eating also varies throughout the menstrual cycle, with low frequencies in the late-luteal phase through the peri-ovulatory phases and high frequencies during the mid-luteal phase in women with BN (Culbert et al. 2016). Animal studies have shown that progesterone, an estrogen receptor antagonist, induces overeating (Roberts et al. 1972). Human studies have confirmed that estrogens reduce food intake during binge-like episodes (Klump et al. 2008; Yu et al. 2011). Whether this is a useful model of binge size or frequency of binging in women, on the other hand, is not known (Yu et al. 2011). Thus, estrogens appear to antagonize androgens' effect concerning eating behavior.

Binging and Purging: Hormonal Changes

Binge eating is a dysregulated form of eating that is rather prevalent in women (Hillbert et al. 2012). It refers to eating an abnormally large amount of food on a single occasion with a feeling of loss of control of eating and can precede even BN (Hillbert et al. 2012). Multiple episodes of binge eating followed by inappropriate weight compensatory behavior, (e.g., diuretic and laxative misuse, self-induced vomiting, fasting, and excessive exercise) are common in bulimics. One of the purging methods used by bulimics is vomiting. The emesis center in the medulla has been suggested to be the chemoreceptor trigger zone in the postrema area known to contain a high density of opioid and dopamine receptors. A rise in dopaminergic and opioid activity has been associated with menstrual dysfunction, hence why vomiting and menstrual irregularity may be linked to dopamine and opioid activity (Gendall et al. 2000).

In addition, craving and binging can result in intake of excess calories, which might promote weight gain and an increase in insulin levels. Elevated insulin levels in turn will stimulate ovarian androgen production, thereby contributing to a vicious circle of androgens and weight gain (Escobar-Morreale and Millán 2007). Further, vomiting itself may result in an increased insulin secretion (Kaye et al. 1989), which appears to mediate hyperandrogenism in young women with polycystic ovarian syndrome (PCOS) (Raphael et al. 1995). Interestingly, high levels of testosterone have also been reported in women with premenstrual syndrome (PMS), as they also have been in bulimic women (Eriksson 2000). Intensified craving for food during the luteal phase of the menstrual cycle means bulimics may experience aggravations of their symptoms (Ferrer-Garcia et al. 2017).

Emotional stress is the primary trigger factor during binge eating. It repeatedly activates the adrenal cortex for cortisol secretion. Activation of the hypothalamic-pituitary-adrenal axis in response to psychological stress results in continuous secretion of cortisol. This consistent stimulation could explain the increase in cortisol levels observed in women with PCOS (Vgontzas et al. 2001). Moreover,

testosterone can suppress activity of the hypothalamic-pituitary-adrenal (HPA) axis, thereby creating opposing interactions between the HPA and hypothalamic-pituitary-gonadal (HPG) axes (Viau 2002). For example, stress inhibits gonadotropins, which in turn precedes suppression of testosterone (Sapolsky 2004). Conversely, testosterone also can attenuate levels of glucocorticoids and other stress hormones (Viau and Meaney 1996). Excess stress can contribute to the major depressive disorder (Holzel et al. 2011). However, the precise mechanisms whereby testosterone inhibits the HPA axis remain unclear. Excess stress might have negative effects on the mental health, and can contribute to major depressive disorder (Holzel et al. 2011). However, the precise mechanisms whereby testosterone inhibits the HPA axis remain unclear.

Polycystic Ovarian Syndrome: A Hyperandrogenic Condition with Associations with Bulimia Nervosa

The pathophysiological actions of androgens in females are also of major importance, particularly as they relate to hyperandrogenic disorders in women. Polycystic ovarian syndrome (PCOS) has typical features of biochemical hyperandrogenism, irregular menstrual cycles, and polycystic ovarian morphology, as well as metabolic traits such as obesity hyperinsulinemia, and insulin resistance (McCartney and Marshall 2016) (Table 1).

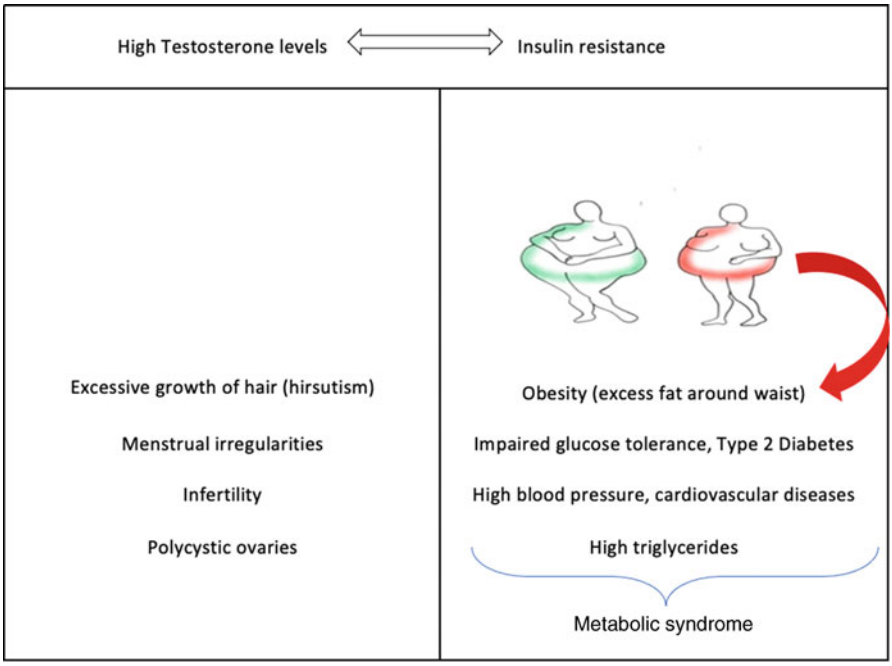
One of the primary pathological changes thought to lead to PCOS is increased ovarian androgen secretion (Lobo 1984), and an affected metabolism of estrogens and androgens (Baptiste et al. 2010). Excess adrenal androgen levels are prevalent in 40–65% of women with PCOS (Lobo 1984). The sources of androgens in women with PCOS are adrenal glands and the ovaries, with most androgens appearing to be formed in the ovaries (60%) and the remainder (40%) contributed by adrenal glands (Cedars et al. 1992).

In healthy women who were submitted to binge eating, hyperinsulinemia and abnormal ovarian morphology have been observed (Taylor et al. 1999). Hyperandrogenic manifestations like PCOS do appear in women with BN and can affect the pathophysiology of the disorder (Naessén et al. 2006; Steegers-Theunissen et al. 2020). Several studies support the hypothesis that androgens are of importance for bulimic behavior and can promote BN by influencing food craving, stimulating appetite, and reducing impulse control in susceptible individuals (Naessén et al. 2006; Baker et al. 2012).

As it has been pointed out, the increased frequency of PCOS in bulimic women may indicate increased androgen sensitivity in these women (Naessén et al. 2006). This susceptibility of androgens maybe reflected in the observed presence of mood and eating disorders in women with PCOS (Steegers-Theunissen et al. 2020).

Disturbances in the function of gonadotropin-releasing hormone (GnRH) in women with PCOS can cause an overproduction of LH, while FSH levels are low, and this in turn increases the androgen production by the theca cells due to a lack of negative feedback from progesterone (Walters et al. 2018).

Table 1 Signs and symptoms of polycystic ovarian syndrome (PCOS)



Binge eating is common among bulimic women and recurrent binge eating can increase insulin levels, by decreasing concentrations of sex hormone-binding globulin (SHBG). This in turn increases the free circulating testosterone levels, thereby negatively impacting follicular maturation and ovulation (Algars et al. 2014). Elevated insulin levels will then stimulate ovarian androgen production, contributing to a vicious circle of androgens and overweight status (Escobar-Morreale and Millán 2007). However, a recent study showed that increased levels of insulin in women with PCOS may lead in turn to BN (Vyver et al. 2008), although this finding could not be supported by a previous study (Raphael et al. 1995).

Antiandrogenic Treatment in Bulimia Nervosa

The fact that elevated testosterone levels and BN could be linked indicates the potential for drugs with antiandrogenic properties to alleviate the bulimic symptoms. There are a few drugs with proven effect on bulimic symptoms that can currently be prescribed.

Fluoxetine, a potent antidepressant, and a selective serotonin reuptake inhibitor (SSRI) (Broekkamp et al. 1980), was approved by the FDA for the treatment of major depressive disorder in 1987 and in 1994 for the treatment of BN. Reduced

symptoms in bulimic women have been obtained with flutamide, and the mechanism of action of the drugs is through the blocking of androgen receptors (Sundblad et al. 1994). Another drug, lisdexamfetamine, a central nervous system stimulant, is also approved by FDA for the treatment of BN (Bello and Yeomans 2018).

A known effect of combined oral contraceptives (COC) in healthy women of reproductive age is a decrease in testosterone, free testosterone, and DHEAS levels (Carlström et al. 2002). Therefore, in one study, a preparation consisting of ethinyl estradiol/drospirenone, widely used as an OC, and well tolerated (Foidart 2000), was administrated to women with BN. Bulimics who responded with a decrease in bulimic behavior had higher pretreatment levels of total and free testosterone and higher frequency of binge eating and of compensatory behavior (Naessén et al. 2007). Therefore, the antiandrogenic oral contraceptives appear to reduce meal-related appetite and bulimic behavior. As a result of that, one may speculate that, in some cases, BN may be a hormonal rather than primarily a psychiatric illness.

Drospirenone is a powerful progestogen with antiandrogen activity and mainly acts by blocking androgen receptors of target organs, in addition to reducing skin activity of 5α-reductase, the enzyme that converts T to 5α-DHT. This significant antiandrogenic effect has been seen even on hyperandrogenic symptoms such as hirsutism and acne (Batukan and Muderris 2006).

Androgen's Role in Relation to Psychiatric Disorders and Bulimia Nervosa

Another area where the role of androgens has been highlighted extensively is depression. Mood and eating disorders are among the most common psychiatric disorders observed in women with PCOS and are most likely the result of complex interactions between different factors. The core symptoms of mood and eating disorders, such as poor self-esteem, and body image dissatisfaction, are shown to be associated with stress (Murray et al. 2011).

The prevalence of depression and depression symptoms is significant in women with PCOS, ranging from 29% (Deeks et al. 2010) to 50% (Hollinrake et al. 2007), although elevated testosterone levels have been found even in premenopausal women without PCOS (Baischer et al. 1995).

Regarding the hypothalamic-pituitary-adrenal (HPA) axis, previous reports indicate a relative hypercortisolism (Bailer and Kaye 2003), and increased circulating concentrations of adrenocorticotropic hormone (ACTH) (Loucks et al. 1989) and of adrenal androgens (Monteleone et al. 2001) in women with BN. However, both normal (Naessén et al. 2006) and low levels of cortisol have been shown in women with BN (Levitan et al. 1997). One possible reason for these findings may be the partial glucocorticoid insensitivity of the HPA axis in women with BN, as described in many reports that show a poor response to dexamethasone in BN (Levy et al. 1989). Hypothetically, this may lead to a compensatory increase in ACTH secretion and thus to increased cortisol levels.

A growing body of research has focused on the notion that depression is the most common comorbid diagnosis in women with eating disorders (Mischoulon et al. 2011). Major depression is frequently noted in bulimics, although it is not clear if the mood disturbance is a function of bulimic disease or a separate phenomenon (Hay et al. 2008). Notably, there are gender differences, with females are more than twice as likely as males to be afflicted by mood disorders (Kessler et al. 2005).

Both androgen insufficiency and hyper-androgen states have been associated with mood disorders and depression (Herzog and Eddy 2007). Clinical evidence suggests that testosterone has anxiolytic and antidepressant benefits, with the potential to promote improved mood and mental health in both sexes. However, the neurobiological mechanisms underlying the protective effects of testosterone remain still poorly understood. Neurotransmitters, γ-aminobutyric acid (GABA), dopamine, and serotonin (5-HT) may underlie some of testosterones' protective benefits on psychological well-being (Dubrovsky 2005).

Testosterone administration has shown to improve the depressive symptoms (Miller et al. 2009) and even the onset of major depressive disorder when higher doses of testosterone were given in a previous study (Rohr 2002). In relation to depression, chronic exposure to T, or to its neuronal metabolites, E2 and DHT, selectively enhances metabolic activity in the mesolimbic system in an animal study (Alderson and Baum 1981).

Taken together, all these findings strengthen the link between androgens and depression.

Androgens have general anabolic effects upon several organ systems including fat distribution and behavior. The role of androgens in BN and its residual categories has not been fully investigated, but recent findings show that, among other functions, steroids play an essential role in eating behavior and are implicated in several major psychiatric disorders in women.

Some of the studies also consider Eating Disorder Not Otherwise Specified of Purging type (EDNOS-P) (APA 2000). The diagnosis EDNOS has often been regarded as a residual category of eating disorders, but it is the most common one in outpatient settings and is like BN in the nature, duration, and severity of psychopathology (Dingemans and van Furth 2015). Since the revision of the fourth edition of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM), there have been substantial changes regarding the classification of eating disorders. The residual diagnosis EDNOS seems to develop multiple subthreshold presentations over time, such that it may occur between the full criteria AN and BN (Fischer et al. 2015).

There are several well-designed studies according to DSM-IV that include the EDNOS diagnosis.

It has been shown that women with BN appear to exhibit greater eating and general psychopathology than those with EDNOS (Thomas et al. 2009). However, EDNOS itself represents a set of disorders associated with substantial psychological and physiological morbidity (Hudson et al. 2007). For example, it has been found that women with EDNOS-P exhibit the hyperandrogenic state to a greater extent and fulfill more criteria for PCOS than women with BN (Naessén et al. 2006, 2007).

Recent investigations have revealed profound differences in the origin of circulating T and the most potent androgen, DHT, in women with BN, EDNOS-P, and healthy control subjects, despite very similar anthrometric data and almost identical androgen and SHBG levels (Naessén et al. 2019). Concerning the origin of T, women with BN and control subjects had positive correlations to DHEAS but not to LH, which suggests peripheral conversion of DHEAS as the main source of T formation in these groups. Thus, not only T but also the major circulating steroid DHEAS serves as precursor to DHT via conversion to T and A-4 (Parker 1989).

However, the production of LH is not regulated by ovarian androgen through the feedback mechanism; hence, in women excess free testosterone or androstenedione (A4) will not reduce ovarian production of these androgens. In women with EDNOS-P, though, a direct ovarian gonadotropin-stimulated secretion was obtained as a main source of circulating testosterone. This knowledge of androgens' origin opens up further research regarding whether the action of androgens has a role in the pathogenesis, course, or treatment of BN.

Conclusions

The role of androgens in the etiology of BN has not been fully elucidated. The actions of androgens are very complex, differing according to the level of androgen receptor (AR) or estrogen receptor (ER) expression, the bioactivity of 5α-reductase and aromatase, the co-activators and co-repressors present in each cell type, and the pattern of interacting in target cells.

The actions of androgens are thus complex but important in understanding normal physiology, pathophysiology, and the involvements of the androgens in development of bulimic symptoms. The available, albeit incomplete, evidence makes it highly likely that the androgens in discourse with other sex steroid hormones seem to play an extensive role in BN. Future studies will hopefully further clarify the role of androgens.

Applications to Other Eating Disorders

- Binge eating
- Eating Disorder Not Otherwise Specified of Purging type (EDNOS-P)

Mini-Dictionary of Terms

- **Amenorrhea:** It is the absence of menstrual periods at least three months or more.
- **Androgens:** These are a group of sex hormones – testosterone (T), androstenedione (A4), dihydrotestosterone (DHT), dehydroepiandrosterone (DHEA), and DHEA sulfate (DHEA-S).

- **Appetite:** It is the desire to eat. Hunger is physiological, and it occurs because of biological changes throughout the body, which signal that you need to eat to maintain energy levels.
- **Binging, and purging:** Binging involves eating much larger portions of food quickly, in a short period of time and feeling a loss of control. Purging is *the act of getting rid of food from the body by* self-induced vomiting or misuse of diuretics, laxatives.
- **Bioavailability of a substance:** The ability of a drug or other substance to be absorbed and used by the body.
- **Gonadotropins:** They include luteinizing hormone (LH) and follicle-stimulating hormone (FSH), and they are made by a part of the brain called the hypothalamus.
- **Gonads:** These are the primary reproductive organs of men, testicles, and the ovaries in the women.
- **Hypothalamic amenorrhea:** It is the functional absence of menstruation. It results in estrogen deficiency in young women, often due to psychological stress, excessive exercise, disordered eating, or a combination of these factors.
- **Metabolic syndrome:** It is a group of disorders – increased blood pressure, high blood sugar, excess body fat around the waist (apple body shape), and abnormal fat levels – that occur together, increasing the risk of heart disease, stroke, and type 2 diabetes.
- **Pathophysiology:** It is the study of the disturbance of normal mechanical, physical, and biochemical functions, either caused by a disease or resulting from a disease.
- **Precursor:** A precursor is a chemical substance that participates in a chemical reaction that produces another compound. For example, cholesterol is the precursor for all steroid hormones.
- **Sex steroid hormones:** The male hormone testosterone and the female hormones progesterone and estradiol.

Key Facts

- The biologically active androgens, T and DHT, are formed by de novo synthesis in the ovaries and adrenal cortex and by peripheral conversion of the adrenal androgens A-4, DHEA, and DHEA-S in the liver, kidneys, muscles, fat, skin, and central nervous system.
- Steroid hormones DHEA and DHEAS can be converted in peripheral tissues to androstenedione (A-2), testosterone (T), and dihydrotestosterone (DHT), and both are aromatized to estrogens.
- Individuals with normal body weight and those with BN are at increased risk of developing physiologic and endocrine disturbances, including menstrual irregularities.
- Normal-weight women with hypothalamic amenorrhea appear to have normal androgen and DHEAS levels attributable to periods of malnourishment and purging.

- Intense ovarian androgen secretion and an affected metabolism of estrogens and androgens can promote PCOS.
- Profound differences in origin of androgens were found in women with BN and EDNOS, although almost identical androgen and SHBG levels were detected in both groups. Perhaps these results reflect the transitional state of the EDNOS to BN.
- The actions of androgens are very complex, and they may differ according to the level of androgen receptor (AR) or estrogen receptor (ER) expression, the bioactivity of 5α-reductase and aromatase, the co-activators and co-repressors present in each cell type, and the pattern of interacting in target cells.

Summary Points

- Androgens exert direct action on the CNS but in conjunction with estrogen and progesterone.
- Testosterone's effects may be explained by its metabolism into two additional bioactive hormones, E2 and DHT.
- Androgens can promote BN by influencing food craving, stimulating appetite, and reducing impulse control in susceptible individuals.
- During the follicular phase of the menstrual cycle, when estrogen is at its peak, the appetite, meal size, and intake of sweets decrease.
- Antiandrogenic oral contraceptives appear to reduce meal-related appetite and bulimic behavior.
- Increased frequency of hyperandrogenic manifestation like PCOS in bulimic women may indicate increased androgen sensitivity in these women.
- Women with EDNOS-P exhibit more clinical features of hyper-androgen state than those with BN.
- Similar levels of T, fT, DHT, DHEAS, and SHBG in BN and EDNOS-P but origin of T, DHT differed.
- T is formed in BN peripherally from DHEAS and by ovarian LH stimulation in EDNOS-P.
- These differences may influence diverging clinical manifestations of BN versus EDNOS-P.

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Bulimic Symptomatology

40

Linking Food Choice and Dentition

Ana Paula Hermont, Isabela Almeida Pordeus, and Sheyla Márcia Auad

Contents

Introduction 786
Understanding the Dental Implications: An Outlook for Erosive Tooth Wear 787
Concepts and Epidemiology 787
Biological and Clinical Aspects 788
Etiology 790
Understanding the Dental Implications: An Outlook for Dental Caries 792
Concepts and Epidemiology 792
Biological and Clinical Aspects 792
Etiology 793
Time to Link Bulimic Symptomatology with Oral Health and Food Choices 794
Food Choices and Erosive Tooth Wear vs. Bulimic Symptomatology 794
Scientific Evidence 794
Hypotheses 795
Food Choices and Dental Caries vs. Bulimic Symptomatology 796
Hypotheses 796
The Role of Professionals Toward Oral Health Preventive Approach 797
Applications to Other Eating Disorders 798
Mini-Dictionary of Terms 799
Key Facts of Bulimic Symptomatology, Food Choices, and Oral Health 799
Summary Points 800
References 800

Abstract

There is consensus that erosive tooth wear is the most prevalent dental implication related to bulimia nervosa, primarily due to frequent self-induced vomiting. However, extensive studies have typically been conducted with patients already diagnosed with the eating disorder, thereby limiting knowledge related to high-

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risk groups and preventive strategies. Furthermore, the evaluation of extrinsic sources of acid seems to have been neglected in studies on dental implications and bulimia nervosa. Assessing risk groups is essential for the development and tailoring of effective strategies to prevent progress toward a full-blown eating disorder and its comorbidities. Raising awareness of dietary preferences, compensatory practices, and the possible association with dental implications among groups with bulimic symptomatology is both clinically and theoretically important. The chapter goes on to discuss dental implications, risk behaviors, and bulimia nervosa, emphasizing the need for considering the compounding effect of extrinsic sources of acids, such as food choices, among risk groups and/or patients already diagnosed with bulimia nervosa.

Keywords

Bulimia nervosa · Tooth erosion · Dental caries · Diet · Risk assessment · Vomiting · Feeding behavior

Abbreviations

APA	American Psychiatric Association
BITE	Bulimic Investigatory Test of Edinburgh
BN	Bulimia nervosa
DC	Dental caries
ED(s)	Eating disorder(s)
ETW	Erosive tooth wear
WHO	World Health Organization

Introduction

Dental implications such as erosive tooth wear (ETW) and dental caries (DC) have been reported as oral manifestations associated with bulimia nervosa (BN), its risk behavior, and purging practices (Hermont et al. 2013; Johansson et al. 2012; Ximenes et al. 2010). The ability to diagnose early clinical signs of oral alterations, associated with a detailed anamnesis, enables the dentist to suspect cases of eating disorders (EDs) and refer patients for specialist care. Consequently, it allows people at risk for EDs to receive a timely, accurate diagnosis and treatment from appropriate professionals, thus preventing the development of severe comorbidities (Hermont et al. 2013). Research on risk behavior for EDs and bulimic symptomatology helps to broaden the understanding of these phenomena among nonclinical populations who have not yet developed a full-blown eating disorder (Fonseca-Pedrero et al. 2011; Hermont et al. 2014).

However, most studies have typically been conducted with patients already diagnosed with an ED and show a well-established link between oral implications and EDs in the presence of self-induced vomiting (Hermont et al. 2014). Conversely, there is less information regarding the occurrence of oral conditions in the absence of

purging practices; and important risk factors such as psychotropic-induced dry mouth, nutritional deficiencies, and/or acidic diet tend to be underestimated (Kisely et al. 2015). Studies tend to neither evaluate nor raise awareness related to extrinsic factors such as dietary habits. In fact, a recent pioneer study on this subject has reported that it was the food choices and not purging practices that differed among the participants with varying severity of bulimic symptomology. Likewise, the dietary habits among the sample were the factors mainly associated to higher prevalence of ETW (Hermont et al. 2021a).

Is this finding a surprise or does the surprise remain in the fact that eating habits of this risky population have been neglected in studies involving dental implications? To answer this question this chapter presents a review addressing dental implications and its association with bulimia nervosa risk behavior. This time, an effort has been made to broaden the knowledge related to the link between food choices and dentition among people with bulimic symptomatology.

Understanding the Dental Implications: An Outlook for Erosive Tooth Wear

Concepts and Epidemiology

According to the last Consensus Report of the European Federation of Conservative Dentistry, dental erosion, referred in a "collective term" as erosive tooth wear, is a chemical-mechanical process caused by an erosive acidic attack without bacterial involvement, resulting in progressive loss of hard tooth tissues (Carvalho et al. 2016; Ganss 2014; Lussi and Carvalho 2014; Schlueter et al. 2020). The sources of acid may be intrinsic factors, such as reflux and vomiting, and extrinsic factors, such as an acidic diet or medications, like acetylic salicylic acid (Hermont et al. 2014; Schlueter and Luka 2018). Diet has a key and complex role in ETW etiology, as its erosive potential relates to the pH, type of acid, buffering capacity of saliva, food consistency (retentiveness in the oral cavity), and frequency of consumption (Barbour and Lussi 2014).

ETW is the third most frequently observed oral condition, after dental caries and periodontal disease (Bartlett et al. 2019). An overview on the data related to the prevalence of ETW detected that heterogeneous methodologies applied within studies turn it difficult to estimate its actual global prevalence. There is an outsized variation in prevalence worldwide ranging between 0% and 100% (Schlueter and Luka 2018). This discrepancy seems to be primarily related to methodological issues such as different indexes used to detect ETW. Even though, Schlueter and Luka (2018) estimated a mean prevalence ranging from 30% to 50% in deciduous teeth, and from 20% to 45% in permanent teeth. In addition, there seems to be an increase in ETW prevalence with age and a gender difference, with a higher prevalence among males (Jaeggi and Lussi 2014).

Instead, differently from the inconsistency reported for global prevalence of ETW, a clear impact on ETW prevalence has been detected in patients with gastroesophageal reflux disease and EDs involving purging practices (Hermont et al. 2014; Schlueter

and Luka 2018). The evidence found in a meta-analysis indicates that patients suffering from anorexia and bulimia have a greater risk of presenting ETW in comparison to individuals without such exposure (Hermont et al. 2014). In addition, it was detected a significant association between bulimia with self-induced vomiting and ETW, but not for bulimia without vomiting practices. It reinforced the hypothesis that the purging practice is a crucial cofactor related to the occurrence of ETW, which results from a chronically acidic oral environment (Johansson et al. 2012).

However, despite the increasing scientific interest about ETW global epidemiology, its awareness is still not widespread. Studies conducted in academic fields worldwide have shown an alarming lack of knowledge of the condition and that it is still not routinely screened during standard dental examination (Al-Ashtal et al. 2015; Bartlett et al. 2019; Dugmore and Rock 2003; Hermont et al. 2011, 2021b; Ngoc and Donovan 2018; Verploegen and Schuller 2019). This may have a negative impact on health, and interventions to minimize the loss of tooth structure might have not been provided at early stages. Dentists usually monitor patients on a regular basis, sometimes throughout childhood up to adulthood. Therefore, they may be the first health professionals to suspect EDs, due to their oral implications. If those professionals are not capable of detecting dental implications such as ETW, patients with possible bulimic symptomatology might go undetected, jeopardizing their early referral to specific treatment (Rosen 2010; Shaughnessy et al. 2008).

Biological and Clinical Aspects

Enamel dissolution occurs both at the enamel/acid interface in the ETW process, as well as within a partly demineralized thin softened layer of enamel, in a process called near-surface demineralization, leading to loss of minerals, and consequently, loss of tooth substance (Shellis et al. 2013). The process starts by initial softening of the enamel surface followed by loss of volume, with a softened layer persisting at the surface of the remaining tissue (Ganss et al. 2014). The rate and severity of erosive wear are determined by the susceptibility of the dental tissues toward dissolution. Since enamel contains less soluble mineral than dentine, it tends to erode more slowly (Ganss et al. 2014).

Typical clinical signs of erosive lesions include a shiny, silky-glazed appearance, excessively smooth tooth surfaces, tooth cupping (small indentations caused by erosion), and a layer of intact enamel along the gingival margin (Ganss and Lussi 2014; Lussi et al. 2011; Shellis et al. 2013). It has been postulated that this preserved enamel band might be due to mechanical protection provided by dental plaque, which could act as a diffusion barrier for acids. In addition, this process could also be due to an acid neutralizing effect of the sulcular fluid (Lussi et al. 2006).

The distribution of ETW lesions among the worldwide population shows a predominance of lesions in occlusal surfaces (mainly on mandibular first molars) followed by facial surfaces (mainly on anterior maxillary teeth), but overall prevalence data are not homogeneous (Jaeggi and Lussi 2014). Clinical features of ETW are shown in Figs. 1 and 2).

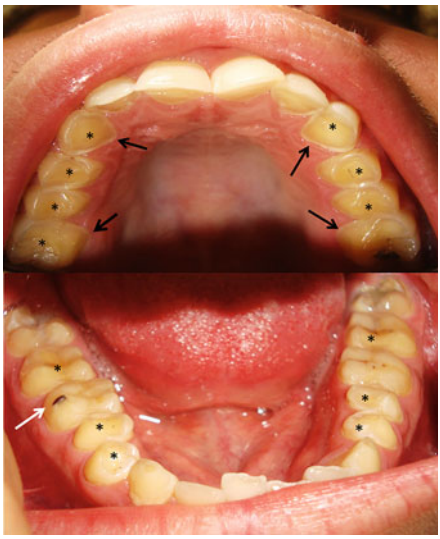


Fig. 1 Erosive tooth wear. Upper and lower dental arches of a 23-year-old male patient. Black arrows point to intact enamel along the gingival margin in permanent teeth secondary to intrinsic factors and daily consumption of acidic beverages (soda). White arrow points to an amalgam restoration rising above the level of the adjacent eroded tooth surface. Asterisks point to affected occlusal surfaces (the yellowish color corresponds to exposed dentin due to the erosive process)



Fig. 2 Erosive tooth wear. (**a**) Upper and lower dental arches of a 26-year-old female patient diagnosed with bulimia nervosa showing erosive tooth wear lesions in permanent teeth. White arrows point to intact enamel along the gingival margin. Black arrows point to affected occlusal surfaces (the yellowish color corresponds to exposed dentin). (**b**) The toothbrush used by the patient had a dual use: brush her teeth and help self-induced vomiting practices. The black circle shows deformed bristles due to excessive brushing force. The patient also presented an acidic diet (citric fruits and diet coke)

Etiology

Erosive tooth wear is a multifactorial condition, resulting from interplay between modifying macro-factors, nutritional, and patient-related factors (Buzalaf et al. 2018; Lussi and Carvalho 2014) (Fig. 3). Recurrent episodes of reflux and/or vomiting are the primary sources of intrinsic acids affecting risk groups, such as people suffering from gastroesophageal reflux disease and/or eating disorders, like bulimia nervosa, whereas diet represents the major etiological factor related to the prevalence and incidence of ETW in worldwide population (Chan et al. 2020; Rosten and Newton 2017; Schlueter and Tveit 2014).

However, it is noteworthy that while some people who consume acidic diets develop erosive lesions, others do not (O'Toole and Mullan 2018). Issues, such as salivary protecting effect (buffering capacity) and deleterious habits, like excessive mechanical force during oral hygiene habits, may account for individual variations (Figs. 2b and 3). Furthermore, other patient-related factors may modulate the erosive potential of foods, like its frequency of consumption. Higher rates of intake of carbonated and sports drinks and natural fruit juices have already been associated with higher prevalence of ETW (Buzalaf et al. 2018; Kitasako et al. 2017; Mafla et al. 2017).

Other important patient-related factors are the contact time of erosive foods/drinks with the teeth (Buzalaf et al. 2018) and the pattern of food consumption. These factors might enhance the erosive potential of dietary substances (e.g., swishing of soft drinks before swallowing, acidic food intake between meals). It has been stated that prolonged intermittent exposure of the teeth to orange juice increases the hazard of erosion progression, irrespective of salivary protective effects (Amaechi et al. 1999). Furthermore, the intake of acidic diets between main meals

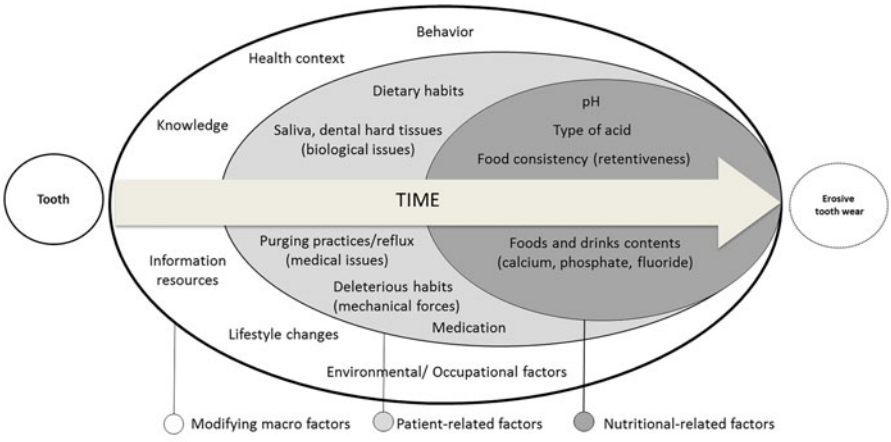


Fig. 3 Determinants related to the etiology of erosive tooth wear throughout life. It is divided in modifying macro-factors, patient-related factors, and nutritional-related factors

and before bedtime is also a risk factor. During these periods, there is a decrease in salivary flow rate that compromises saliva's protective effect against ETW, and the clearance of gastric acids in the esophagus (Buzalaf et al. 2018; Saads Carvalho and Lussi 2020).

Likewise, nutritional and dietary factors such as the type of acid (e.g., citric, acetic, or malic acid) or even the food or drink viscosity/consistency and content influence its erosive potential. While acidic food products, like fruit-based candies, are highly erosive due to an extended contact time with the tooth before oral clearance, high concentrations of minerals, such as calcium and phosphate, may reduce the erosive potential of low pH foods, like yoghurt (Saads Carvalho and Lussi 2020; O'Toole et al. 2017; Shrestha and Rajbhandari 2018). In addition, it is known that the temperature of an acidic drink might influence its erosive potential, which is less pronounced when the drink is consumed at lower temperatures (Amaechi et al. 1999).

Finally, it is important to mention the modifying macro-factors. ETW risk factors comprise not only patient and nutritional-related factors, but also broader social and environmental determinants such as occupational factors, health context, behavioral changes, and knowledge related to this dental implication. Individuals with occupations that predispose them to a regular and sustained acid contact (e.g., wine tasters) may be particularly prone to ETW (Barbour and Lussi 2014). It has also been reported that knowledge about ETW is not being shared with patients, especially concerning information related to preventive measures. Thus, it might corroborate to this dental implication occurrence and progression (Hermont et al. 2011, 2021a). The influence of all the factors described above determines whether the erosive process will proceed or not. The following infographic shows an easy-to-understand overview of this topic (Fig. 3).

Location of erosive lesions is strongly related to the source of acid. Among patients who vomit regularly, the distribution of erosive wear is typically on palatal surfaces of anterior maxillary anterior teeth (Rosten and Newton 2017) as shown in Figs. 1 and 2, whereas extrinsic sources of acid, such as acidic diets, usually affect the facial surfaces of teeth, especially the incisors. It is interesting to notice that while good oral hygiene has proven to be effective for dental caries prevention, deleterious brushing habits, like the application of excessive pressure during tooth brushing (Fig. 2b), may corroborate to ETW when it is carried out along with an ongoing acidic attack on teeth surfaces (Wang and Lussi 2012). This happens because the softened tooth surface resulting from the acidic challenge needs about an hour in the presence of saliva to remineralize, and mitigate the abrasion triggered by tooth brushing (Hemingway et al. 2006). Therefore, a possible correlation between tooth brushing shortly after eating and self-induced vomiting has to be considered, especially considering that it might occur during bulimic episodes (Hermont et al. 2013; Herpertz-Dahlmann et al. 2012; Riddlesberger Jr et al. 1991). In addition, it has been reported that the toothbrush may be used in two different ways. This tool can be employed to help vomit induction and subsequently to clean off vomiting breath and smell, through tooth brushing (Fig. 2b) (Faust and Schreiner 2001; Riddlesberger Jr et al. 1991).

Understanding the Dental Implications: An Outlook for Dental Caries

Concepts and Epidemiology

Dental caries is a multifactorial, diet-modulated disease, resulting in mineral loss of dental hard tissues (demineralization), which is reversible in its early stages. Unlike ETW, it is a biofilm-mediated disease and is the most prevalent non-communicable chronic disease, affecting up to 80% of the world's population from all age groups (Frencken 2018; Moynihan 2016; Selwitz et al. 2007). Unlike the direct association between ETW, purging practices, and acidic food choices (Hermont et al. 2014, 2021a; Rosten and Newton 2017), there is no consensus with respect to the link between bulimia nervosa and dental caries, even though an association has been reported by some researchers (Johansson et al. 2012; Romanos et al. 2012; Rosten and Newton 2017).

Biological and Clinical Aspects

The caries lesion is the cumulative result of an imbalance in the dynamic demineralization and remineralization process, caused by microbial metabolism on the tooth surface, which may result in a net loss of minerals (Fejerskov 1997; Young et al. 2015). Demineralization is the loss of tooth mineral due to acids, while remineralization is the net gain of mineral in previously demineralized tissue. However, the terminology "remineralization" might be misleading since it does not imply that the lesion has regained its original mineral content, and the tooth does not return to its original appearance (Machiulskiene et al. 2020).

Based on clinical parameters, caries lesions are categorized as non-cavitated or cavitated (Young et al. 2015). Non-cavitated lesions refer to the initial stages of the disease, being characterized by a change in color, with loss of glossiness resulting from demineralization, before macroscopic breakdown in tooth surface structure (Longbottom et al. 2009; Young et al. 2015) (Fig. 4a). Due to histological features, those lesions are more prone to be reversed (remineralized), but this process needs key elements such as dietary modification and good oral hygiene practices, including use of fluoride toothpaste (Machiulskiene et al. 2020).

Cavitated lesions are the result of loss of surface integrity, not necessarily restricted to enamel surface, since it can affect the dentin or even the tooth pulp (Longbottom et al. 2009). Commonly, cavitation refers to the total loss of enamel and, consequently, to the exposure of the underlying tooth structure, the dentin (Fig. 4b). The clinical sign of cavitation denotes the failure to biologically replace the loss of hard tissues (Young et al. 2015). The number and extent of carious lesions are related to the disease severity, which may affect both the crowns and roots of teeth, and develop in early childhood as aggressive tooth decay (Selwitz et al. 2007). Fissures and pits in occlusal surfaces of first molars and pits in facial surfaces of lower first molars are the most vulnerable sites for developing a carious lesion (Frencken 2018).



Fig. 4 Dental caries (cavitated and non-cavitated lesions). Dental arch of a 6-year-old female patient. (**a**) Black arrows point to non-cavitated white spots lesions (incipient dental enamel caries). (**b**) White arrows point to cavitated caries lesions (exposed dentin)

Etiology

The combination of behavioral, biological, psychosocial, and environmental determinants corroborates to the dental caries dynamic process (Fejerskov 1997; Pitts et al. 2017; Zero 1999). Consequently, this lifelong progressive and cumulative disease tracks to adulthood, even with exposure to fluoride through mouth-care products or water (Bernabé and Sheiham 2014). Dental caries forms through a complex interaction of multiple factors over time, such as the association between acid-producing bacteria and fermentable carbohydrate, lifestyle, and behavioral-related issues, such as oral hygiene, and host factors, like inadequate salivary flow rate (Selwitz et al. 2007).

However, as a diet-mediated disease, the intake of dietary sugars seems to be the most important risk factor for dental caries (Moynihan and Kelly 2014; WHO 2015), since the cariogenic bacteria produce organic acids as a by-product of their metabolism of fermentable carbohydrates (Selwitz et al. 2007). Therefore, the demineralization process is biofilm-mediated, while in ETW, the acidic attack is not related to bacterial involvement (Machiulskiene et al. 2020).

It is interesting to notice that dental caries seems to be less common than ETW among patients with EDs, since those patients are more prone to obsessional personality traits, and consequently, are more demanding in their oral hygiene (Kisely 2016). In addition, whereas ETW lesions tend to be found on plaque-free tooth surfaces, the presence of plaque is essential for the development of dental caries (Burgard et al. 2003; Huew et al. 2012). Despite having different etiologies, dental caries and ETW might coexist, since the determinants that corroborate to the erosive wear might change during life course, being replaced by risk factors related to dental caries and vice versa. In fact, at sites susceptible to plaque accumulation, dental caries may also occur among patients with ETW, and this is more commonly observed in the occlusal surfaces of molar teeth (Lussi et al. 2006). Figure 5 shows a tooth affected by both conditions. It must be stressed that the cupping lesions caused by erosive wear may represent risk factors for dental caries, since those sites are characterized by cavities that can favor plaque accumulation.

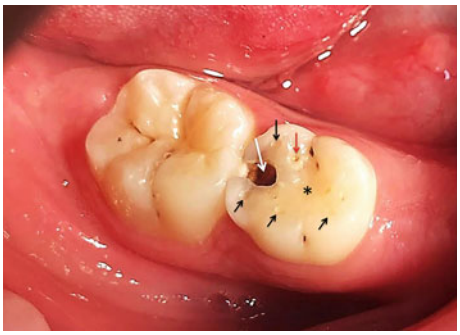


Fig. 5 Dental caries and erosive tooth wear. Lower hemiarch of a 7-year-old female patient. White arrow points to a cavitated caries lesion. Black arrows point to cup-shaped erosive tooth wear lesions (small indentations). Red arrow points to a cup-shaped erosive tooth wear lesion surrounded by a white spot lesion (non-cavitated tooth decay lesion). The asterisk shows an eroded molar occlusal surface with a polished and shiny appearance

Time to Link Bulimic Symptomatology with Oral Health and Food Choices

Food Choices and Erosive Tooth Wear vs. Bulimic Symptomatology

As previously reported, there is strong evidence supporting the association between ETW and bulimia nervosa, especially related to purging practices (Hermont et al. 2014; Schlueter and Luka 2018). However, less attention has been driven to evaluate the role of dietary habits as sources of acid contributing to ETW in patients with bulimia nervosa. It is not uncommon in the literature within the field of oral epidemiology and eating disorders, to see discussions in which authors interpret their data by quoting "known established facts," often derived from "significant associations," without the necessary reflection on the impact among the population addressed.

Few preceding researches have already detected that individuals with bulimic symptomatology presented regular consumption of acidic foods and that patients with EDs, who eat more acidic and sweetened foods, had higher prevalence and severity of ETW (Otsu et al. 2014; Rosten and Newton 2017). However, two questions need to be answered: is there scientific evidence supporting a high consumption of acidic foods among people with bulimic symptomatology? Which aspects contribute to this possible food choice?

Scientific Evidence

Regarding the first question, there is few data in the dentistry field pointing that individuals with bulimic symptomatology have a preference for an acidic diet. It has

been detected that dietary choices of patients with bulimia nervosa have an impact on their oral health, whether associated or not to vomiting practices (Rosten and Newton 2017). In a recent study, female adolescents with bulimic symptomatology, who were evaluated through the Bulimic Investigatory Test of Edinburg (BITE), differed with respect to the occurrence of dental implications and dietary habits (Hermont et al. 2021a). The prevalence of ETW increased along with the severity of BN symptomatology. Despite strong scientific evidence signalizing that the primary factor leading to ETW among patients with EDs is frequent self-induced vomiting (Hermont et al. 2014), and although this habit has been associated with ETW in the aforementioned study, no difference was detected between groups in relation to the self-reported frequency of purging practices (Hermont et al. 2021a). On the other hand, dietary habits differed significantly between groups. Female adolescents with severe bulimic symptomatology reported higher daily consumption of acidic foods and drinks. In fact, higher consumption of diet soda and citric fruits were the factors mainly associated with higher prevalence of ETW (Hermont et al. 2021a). Other researchers observed mild ETW lesions among EDs patients consuming significant amounts of water before self-inducing vomit, while those who routinely consumed sugar-sweetened food or carbonated beverages presented more severe lesions (Otsu et al. 2014).

Hypotheses

Concerning the second question, the intake of carbonated beverages has been identified to help decreasing hunger reflex stimulus in patients with EDs, probably by increasing dilation of the stomach (Gokul 2016; Klein et al. 2006; Lo Russo et al. 2008). Indeed, excessive diet soda intake is common in those patients, particularly the ones with lifetime diagnosis of BN. This dietary pattern could be explained by the combination between high appetitive drive and high weight concerns among patients with BN (Brown and Keel 2013). Not only carbonated drinks, but a preference for citric fruits, such as lemon juice or even slices of lemon, have been linked to people with EDs, since these contribute to eliminate or reduce the gustatory mechanism phase of hunger regulation (Lo Russo et al. 2008).

It is also important to consider foods that might be linked to vomiting/reflux effects. This hypothesis has not been addressed in the field of bulimic symptomology, but the question is worth discussing: does this risk group "learn" which foods might trigger reflux and consume them more frequently to assist purging behaviors? According to Mehta et al. (2020), some types of drinks are known to boost symptoms of gastroesophageal reflux, such as tea and fizzy beverages. Those drinks cause gaseous distension of the stomach and increase the pressure on the lower esophageal sphincter, corroborating to acid reflux (Mehta et al. 2020). Another overarching hypothesis for how these beverages might trigger reflux symptoms is through changes in the pH. An experimental study measured pH and esophageal impedance among healthy individuals when consuming several

beverages and detected that consumption of carbonated beverages decreased intra-esophageal pH (Jarosz and Taraszewska 2014).

Food Choices and Dental Caries vs. Bulimic Symptomatology

The occurrence of dental caries can be enhanced by bulimic episodes due to the uncontrolled events of overeating, which comprise the ingestion of high-carb fermentable foods (Kisely 2016; Rytomaa et al. 1998). In addition, it has been stated that nutritional deficiency might also corroborate to oral implications (Monda et al. 2021; Sheetal et al. 2013). However, there is still no consensus in the literature, since the association between caries, purging practices, and nutritional deficiency among patients with EDs is not clear (Hermont et al. 2013; Johansson et al. 2012; Lo Russo et al. 2008; Monda et al. 2021; Sheetal et al. 2013; Ximenes et al. 2010).

Hypotheses

A review about the impact of BN on oral health concluded that dental caries is a common oral implication in patients with bulimia (Rosten and Newton 2017). Differently from the majority of studies published in this field that mainly focuses on the effects of purging practices, the review detected that binge eating and other dietary habits, as well as antidepressant medication, can also have an effect on oral health among individuals with bulimic symptomatology (Rosten and Newton 2017). Indeed, as it was illustrated in Fig. 3, medication use and salivary issues are patient-related factors related to dental implications. This is applicable not only to ETW, but also for dental caries.

Individuals who use antidepressant drugs may suffer from dry mouth. Saliva acts to buffer organic acids produced by oral bacteria, corroborating to the maintenance of a remineralizing environment within the oral cavity, preserving the teeth from demineralization. Thus, a reduction in salivary flow rates might increase the risk of dental caries (Hopcraft and Tan 2010). Furthermore, patients with dry mouth might try to relieve their symptoms by chewing sugar-containing gums, sucking sweet confectionery, or consuming acidic and cariogenic drinks (Daly 2016). All these “palliative alternatives” are risk factors for dental caries. While some researchers indicate that the risk for dental caries is higher among those patients who also have a change in salivary flow (Moazzez and Bartlett 2014), there are authors pointing to an increased prevalence of this dental implication, due to the consumption of sugary foodstuff to “control” the constant feeling of hunger (Lo Russo et al. 2008). The fact is that both conditions contribute to dental caries; thus the risk may be enhanced in patients who present multiple risk factors.

The Role of Professionals Toward Oral Health Preventive Approach

As it was illustrated in Fig. 3, patient-related factors such as dietary habits (frequency and pattern of consumption) corroborate to the prevalence and incidence of ETW (Huang et al. 2015; O'Toole and Mullan 2018; Shahbaz et al. 2016). Therefore, nutritional-related factors must be considered in preventive measures planning, since some dietary contents such as acidic sweets, carbonated drinks, and acidic fruit juices might increase the prevalence of ETW, whereas calcium-enriched drinks and foods present a protective effect against this dental implication (Salas et al. 2015). With respect to food choices, it must be emphasized that despite their erosive potential, the consumption of healthy food, such as fruits, should be encouraged; instead the patient should be advised to reduce the intake of non-nutritious acidic foods and beverages. The World Health Organization recommends the daily consumption of at least 400 grams of fruits and vegetables to prevent the onset of chronic conditions. Therefore, dietary counseling toward oral health is in line with that of general health (Li et al. 2012).

Oral hygiene practices also have an important role in preventive measures, and good oral hygiene is of proven value in the prevention of DC. However, tooth brushing carried out in conjunction with an ongoing acidic attack may contribute to the loss of tooth surface. In addition, deleterious habits, such as excessive mechanical force during tooth brushing, enhance the occurrence of ETW and must be avoided (Hemingway et al. 2006). The following box (Fig. 6) presents a summary

Box 1- Strategies related to food choices, eating habits and oral hygiene practices that can be adopted to help preventing oral health implications

- Reduce the intake of non-nutritious acidic and sugary foods and beverages;
- Encourage the intake of safer food alternatives, such as milk products and calcium- enriched diets, particularly after an acidic intake;
- Discourage dietary acids and sugary food intake between meals and/or near/at bedtime;
- In case an acidic drink is consumed, it should preferably be chilled;
- Avoid deleterious habits that increase the contact time of the acid with oral cavity, such as swishing or holding acidic drinks in the mouth, before swallowing;
- Encourage the correct use of straws, properly positioned toward the back of the mouth, especially considering the intake of an acidic or sugary food/drink;
- Encourage oral hygiene practices to prevent dental caries;
- Teach patients how to properly conduct oral hygiene, avoiding deleterious habits, such as excessive mechanical force.

Fig. 6 Patient-related preventive measures toward oral health. A box with summary points about possible strategies related to food choices, eating habits, and oral hygiene practices that can be adopted to help preventing oral health implications

of possible patient-related preventive practices that might help preventing oral health implications. The box was based in all etiological factors previously mentioned in the chapter. The advices are applicable not only to risk groups with bulimic symptomology or other EDs, but also to the general population.

Applications to Other Eating Disorders

Scientific evidence points to an association between purging types of other eating disorders, such as anorexia nervosa, and the occurrence of erosive tooth wear, due to the practice of compensatory methods, such as self-induced vomiting and, consequently, to greater acidity in oral cavity (Hermont et al. 2014). Patients with avoidant/restrictive food intake disorder may also show a negative response associated with food intake, following or anticipating an aversive experience such as choking or vomiting. Furthermore, medical conditions such as gastrointestinal implications (gastroesophageal reflux) and persistent symptoms such as vomiting are associated with characteristic eating behaviors of this disorder (APA 2013; Eddy et al. 2015). Thus, it is possible to speculate that individuals with avoidant/restrictive food intake disorder may present greater risk of developing erosive tooth wear.

In addition to this direct association resulting from purgative habits, the occurrence of eating disorders, such as anorexia nervosa or unspecified feeding or eating disorder, can also compromise the function of the salivary glands and, consequently, the mechanisms of self-cleaning and neutralization of acids in oral cavity (Johansson et al. 2012; Kisely et al. 2015). As a result, individuals affected by these disorders could also be at increased risk of oral health implications, such as dental caries.

A literature review stated that the most common food choices among individuals with night eating syndrome include the intake of breads, sweets, and sandwiches (Vander Wal 2012). Considering the reduction in salivary flow at night, the ingestion of cariogenic and/or erosive foods could potentially expose these individuals to a greater risk of developing dental caries and/or erosive tooth wear (Vander Wal 2012).

Food preferences potentially harmful to oral health have also been identified in individuals with binge-eating disorder. The ones who preferred the sweet taste had monthly binge episodes six times higher compared to individuals with preferences for other flavors, as well as higher daily consumption of carbohydrates and calories (Goodman et al. 2018). Therefore, it is possible that, not only individuals with binge-eating disorder, but also people with the binge-eating type of anorexia nervosa, might also be at increased risk for dental implications. In addition, it has also been detected that individuals with avoidant/restrictive food intake disorder had an intake of added sugars and carbohydrates significantly higher than that of healthy individuals (Harshman et al. 2019), which could potentially imply a greater risk of dental caries.

Mini-Dictionary of Terms

- **Buffering capacity.** The measure of a buffer's ability to resist pH change. Refers to the amount of added acid or added base that can be neutralized by a buffer.
- **Cup-shaped lesions.** Small indentations in tooth surface caused by a chemical process of acid dissolution without bacterial involvement.
- **Tooth demineralization process.** The loss of minerals from dental hard tissues (e.g., enamel, dentine).
- **Dental caries.** A multifactorial dynamic disease, biofilm-mediated and sugar-driven. It happens when tooth is more susceptible to demineralization in comparison to remineralization, resulting in the destruction of dental hard tissues.
- **Erosive tooth wear.** The loss of dental hard tissues due to acids without bacterial involvement. It might happen simultaneous or subsequent to the exposure to mechanical forces.
- **Extrinsic acid.** Acids that come from sources other than human body.
- **Facial tooth surface.** A collective term referring to the teeth surfaces that face the cheeks or lips. The term "buccal surface" is used when referring to posterior teeth because it lies next to the buccinator (cheek muscle), and it is referred to as "labial surface" when referring to the anterior (front) teeth surfaces because it lies next to the lips.
- **Intrinsic acid.** Acids that come from gastric contents (produced by the human body).
- **Occlusal tooth surface.** The surface of the teeth that comes in contact with those of the opposite jaw during occlusion. It is the tooth surface used for chewing or grinding.
- **Palatal tooth surface.** It refers to the tooth surface that is directed toward the palate in maxillary teeth. The term "lingual surface" refers to tooth surface that is closest or next to the tongue in mandibular teeth.
- **Tooth remineralization process.** A biological repair mechanism that restores tooth minerals' gain. The remineralization process repairs the outer layer of tooth structure.
- **White spot lesion.** Incipient dental caries lesions characterized by a non-cavitated lesion, usually with a whitish coloration due to the demineralization of the tooth surface.

Key Facts of Bulimic Symptomatology, Food Choices, and Oral Health

- Erosive tooth wear is an irreversible loss of tooth structure, and the most common oral condition associated with bulimic symptomatology.
- Erosive lesions are characterized by a smooth, shiny, silky-glazed appearance, and usually affect the palatal surfaces of anterior teeth in patients with bulimia nervosa.

- Recurrent episodes of vomiting and/or reflux are the primary source of intrinsic acids among patients with bulimia nervosa.
- Acidic food choices may contribute to erosive tooth wear in patients with bulimia nervosa, in addition to purgative practices.
- Acids from dietary sources typically affect the facial surfaces of teeth, especially of the upper incisors.
- Bulimic episodes, with intake of foods rich in fermentable carbohydrates, may contribute to dental caries among people with bulimic symptomatology, but this association is not clear.

Summary Points

- Erosive tooth wear is the most prevalent dental implication related to bulimia nervosa, primarily due to frequent self-induced vomiting, but food choices might have an important role as well.
- The scientific evidence about the occurrence of dental caries among patients with bulimic symptomatology is not as clear as the one for erosive tooth wear.
- Studies on oral health have typically been conducted with patients already diagnosed with bulimia nervosa or other eating disorders, thereby limiting knowledge related to high-risk groups and preventive strategies.
- The evaluation of extrinsic sources of acid, such as dietary habits, has been neglected in studies on dental implications and bulimia nervosa.
- Awareness of dietary preferences, compensatory practices, and the possible association with dental implications among groups with bulimic symptomatology is both clinically and theoretically important.
- Dentists usually monitor patients on a regular basis. Therefore, they may be the first health professionals to suspect EDs, due to their oral implications.

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Emotion Regulation in Bulimia Nervosa and Purging Disorder

41

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Contents

Introduction 807
Conceptual and Theoretical Underpinnings 807
Clinical Observation and Comorbidity 807
Theoretical Models of Bulimia Nervosa as a Disorder of Emotion Regulation 808

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Affect Regulation Model 808
Escape Theory 808
Mood Intolerance and the Transdiagnostic Cognitive Behavioral Model of Eating Disorder Maintenance 809
Manifestations of Emotion Regulation Difficulties in Bulimia Nervosa and Purging Disorder 810
Relationship Between State Negative Affect and Binge Eating/Purging Behaviors: Ecological Momentary Assessment Research 811
Interventions Targeting Emotion Regulation Difficulties for Bulimia Nervosa and Purging Disorder 812
Cognitive Behavioral Therapy (CBT) and CBT-Based Intensive Treatments 812
Dialectical Behavior Therapy 814
Integrative Cognitive-Affective Therapy for Bulimia Nervosa 815
Conclusions 815
Applications to Other Eating Disorders 816
Mini-Dictionary of Terms 816
Key Facts of Emotion Regulation in Bulimia Nervosa and Purging Disorder 817
Summary Points 817
References 818

Abstract

Individuals with bulimia nervosa and purging disorder often experience a range of difficulties effectively regulating their emotions, and eating disorder behaviors such as binge eating and purging often function as maladaptive emotion regulation strategies. A number of theoretical models are premised on or include the idea that eating disorder behaviors such as binge eating and purging function in large part to regulate negative emotions, and these models have been well supported by empirical research. Specific facets of emotion regulation that appear to be particularly challenging for many individuals with bulimia nervosa and purging disorder include accepting negative affective states, difficulties with impulse control during negative emotional states, and difficulty accessing and using emotion regulation strategies at such times. Research also shows a clear temporal and functional relationship between state negative affect and eating disorder behaviors. Several treatments including enhanced cognitive behavioral therapy for eating disorders, dialectical behavior therapy, and integrative cognitive-affective therapy for eating disorders include a focus on improving individuals' ability to more effectively regulate emotions.

Keywords

Bulimia nervosa · Purging disorder · Other specified feeding or eating disorder · Eating disorders · Emotion regulation · Emotion dysregulation · Distress tolerance · Mood intolerance · Negative affect · Impulsivity · Ecological momentary assessment · Dialectical behavior therapy · Cognitive behavioral therapy · Integrative cognitive-affective therapy

Abbreviations

AN-BP	Anorexia nervosa, binge eating/purging type
AN-R	Anorexia nervosa, restricting type

CBT	Cognitive behavioral therapy
CBT-E	Enhanced cognitive behavioral therapy for eating disorders
DBT	Dialectical behavior therapy
EMA	Ecological momentary assessment
ICAT-BN	Integrative cognitive-affective therapy for bulimia nervosa
OSFED	Other specified feeding or eating disorder

Introduction

Difficulties with emotion regulation are common in individuals with eating disorders. Eating disorder behaviors, such as binge eating and purging, often function as maladaptive emotion regulation strategies. Clinical experience and research show that negative emotions often directly precede binge eating and purging behaviors and that individuals commonly report relief from negative emotions afterward. This chapter focuses on issues related to emotion regulation difficulties in individuals with bulimia nervosa and other specified feeding and eating disorder (OSFED) – purging disorder (subsequently referred to in this chapter simply as purging disorder). Although separate diagnostic categories, there is considerable overlap in their presentation and psychopathology – and, as a result, much of the relevant research has grouped them together. However, purging disorder is a more recently defined disorder, and therefore, some of the research focuses only on bulimia nervosa. The chapter starts by considering conceptual and theoretical underpinnings of emotion regulation difficulties in individuals with bulimia nervosa and purging disorder, followed by a description of the ways these problems may manifest. Next, the chapter describes research demonstrating that binge eating and purging behaviors often function to regulate state negative affect, and finally, it reviews treatments and interventions that target these concerns.

Conceptual and Theoretical Underpinnings

Clinical Observation and Comorbidity

Clinicians who work with individuals with bulimia nervosa and/or purging disorder will be familiar with the fact that many such individuals appear to have difficulty tolerating distress and managing their emotions. Clinicians with experience working with clients with these disorders frequently hear individuals describe their emotions as intense and difficult to tolerate, and they often report using eating disorder behaviors – such as binge eating, self-induced vomiting, laxatives, exercise, and food restriction – to help them suppress, escape, numb, or otherwise feel in control of their emotions. In other words, they are using eating disorder behaviors as maladaptive emotion regulation strategies. *Emotion regulation* refers to a complex constellation of related concepts focused on awareness of emotions, acceptance of emotions, the ability to inhibit impulsivity and maintain goal-directed behavior during negative affective states, and the ability to engage in functional behaviors to modulate negative emotional states in a manner that is appropriate to the situation (Gratz and Roemer 2004). A significant body of literature

supports these clinical observations and has also informed the development of treatments targeting these concerns.

The types of mental health concerns that commonly co-occur with bulimia nervosa and purging disorder also suggest the presence of emotion regulation difficulties in this group. Mood and anxiety disorders are the most common comorbid mental health conditions (Ulfvebrand et al. 2015). Additionally, at least 20% of those with bulimia nervosa have symptoms of posttraumatic stress disorder (Ferrell et al. 2020), in which difficulty regulating emotions is highly characteristic. Substance use disorders as well as suicidal ideation and non-suicidal self-injury (e.g., cutting, burning) are common in those with bulimia nervosa and related eating disorders, and these problems may similarly function as ways to manage distress or reflect problems with impulsivity (a dimension of emotion dysregulation; Bahji et al. 2019; Cucchi et al. 2016; Goldstein and Gvion 2019). Finally, borderline personality disorder, which is a psychiatric condition characterized by extreme difficulties with emotion dysregulation, impulsivity, and interpersonal difficulties, is relatively common in individuals with bulimia nervosa and other specified eating disorder presentations (Farstad et al. 2016). The fact that bulimia nervosa and purging disorder are predominantly comorbid with other mental health concerns characterized by emotional difficulties supports the notion that problems with emotion regulation may be a central component of these eating disorders.

Theoretical Models of Bulimia Nervosa as a Disorder of Emotion Regulation

Affect Regulation Model

Although difficulties with emotion regulation are common to many types of mental health disorders, these problems may present or function in a particular way in individuals with eating disorders. According to the affect regulation model, binge eating commonly occurs in response to negative affective states, and is maintained through negative reinforcement, which occurs via an immediate decrease in negative affect following binge eating (Haedt-Matt and Keel 2011; Hawkins and Clement 1984; Polivy and Herman 1993). Since this model was first introduced, a wealth of empirical evidence has provided support for its tenets (Schaefer et al. 2020). For example, Smyth and colleagues (2007) showed a clear temporal relationship between negative emotions intensifying prior to and decreasing following binge/purge episodes. These processes will be further elaborated on later in this chapter, when ecological momentary assessment (EMA) research is reviewed.

Escape Theory

Heatherton and Baumeister's (1991) escape theory of bulimia nervosa shares similarities with the affect regulation model but extends further by suggesting a

functional relationship between negative affect related to perceived personal failures and binge eating. According to escape theory, individuals with bulimia nervosa engage in binge eating as a way to escape from self-awareness of perceived failures relative to their own self-imposed high standards. Awareness of perceived failures is aversive and highly distressing for individuals with bulimia nervosa, and during binge eating episodes, individuals focus their attention on eating and its sensations, which provides a cognitive escape from longer-term or bigger picture concerns (Heatherton and Baumeister 1991). According to escape theory, state negative affect escalates prior to binge eating and lessens after purging. Subsequent research has supported this model (Burton and Abbott 2017). For example, Blackburn and colleagues (2006) used structural equation modelling to provide support for escape theory, by demonstrating that perfectionism predicted aversive levels of self-awareness, which predicted negative affect. Negative affect predicted avoidant coping, and this coping style predicted binge eating (Blackburn et al. 2006). Both escape theory and the affect regulation model are important foundations for the now widely understood notion that emotion regulation concerns are a central problem for individuals with bulimia nervosa (and other eating disorders, including purging disorder).

Mood Intolerance and the Transdiagnostic Cognitive Behavioral Model of Eating Disorder Maintenance

More contemporaneous is Fairburn and colleagues' (2003) transdiagnostic cognitive behavioral model of eating disorder maintenance. The model is "transdiagnostic" in that it applies to the maintenance of all eating disorders, including bulimia nervosa, anorexia nervosa, binge eating disorder, and OSFED presentations. This model also forms the basis for enhanced cognitive behavioral therapy for eating disorders (CBT-E; Fairburn et al. 2008), the current leading evidence-based treatment approach for adults with eating disorders, including bulimia nervosa and related eating disorders such as purging disorder.

Although Fairburn and colleagues' cognitive behavioral model of eating disorder maintenance focuses on overvaluing eating, weight, and shape as the primary cognitive psychopathology driving behavioral eating disorder symptoms and therefore eating disorder maintenance, the role of *mood intolerance* is also highlighted as a key maintaining factor. Mood intolerance is defined as the inability to effectively cope with particular emotional states (typically aversive negative affective states, although for some individuals any intense emotions, including positive ones, may be difficult to regulate). These individuals may mentally disengage from the negative affective state by engaging in a maladaptive behavior, such as self-injury, substance abuse, or eating disorder behaviors like binge eating, vomiting, or driven exercise. Once the eating disorder is established, eating disorder behaviors, and in particular, binge eating, may become a regular or habitual way of managing negative affective states (Fairburn et al. 2003). Individuals with mood intolerance may experience more intense negative emotions compared to others, or they may be more sensitive to

these emotions, or both. Beliefs that one cannot effectively manage their emotions may further exacerbate the intensity of the emotions (Fairburn et al. 2003).

Manifestations of Emotion Regulation Difficulties in Bulimia Nervosa and Purging Disorder

All people use strategies to regulate emotions; however, some coping strategies are less adaptive than others. Those who rely on maladaptive emotion regulation behaviors (e.g., binge eating or purging, self-injury, substance abuse, or other avoidant coping behaviors), including many individuals with bulimia nervosa and purging disorder, are considered high on emotion *dys*regulation. Not only is emotion dysregulation an important correlate of psychopathology in general (Sloan et al. 2017), but emotion dysregulation also plays a critical role in the development and maintenance of eating disorders specifically (Lavender et al. 2015; Prefit et al. 2019; Puttevils et al. 2021). Importantly, it is likely not the experience of having negative emotions that influences eating disorder symptomatology as much as it is difficulty in effectively *regulating* one's negative emotions specifically that is most relevant (Mallorquí-Bagué et al. 2018).

It is well documented that individuals with bulimia nervosa tend to have significant difficulty with effectively regulating their behavior when experiencing distress (Lavender et al. 2014). In this group, severity of eating disorder psychopathology is associated with greater overall difficulties with emotion regulation, as well as problems specifically with nonacceptance of emotional states, difficulties with impulse control, and limited access to strategies to effectively modulate negative affect (Lavender et al. 2014, 2015). Furthermore, individuals with bulimia nervosa may also have problems with alexithymia (i.e., difficulties identifying and describing one's emotions; Lavender et al. 2015). Additionally, more frequent purging behaviors (and other compensatory behaviors such as driven exercise) are associated with greater difficulties staying focused on one's goals or the task at hand during negative affective states (Lavender et al. 2014). When examining the relationship between difficulties with emotion regulation and specific eating disorder symptoms, objective binge eating episodes are uniquely related to difficulties with impulse control, whereas purging behaviors may not be uniquely related to any particular facet of emotion dysregulation (Monell et al. 2018) and may therefore reflect more general problems with regulating emotions. Though the literature on purging disorder is more limited, there is preliminary evidence that individuals with purging disorder demonstrate fewer difficulties with emotion regulation compared to individuals with bulimia nervosa (Smith and Crowther 2013), suggesting that the presence of both binge eating and purging behaviors may reflect a pattern of greater difficulties with emotion dysregulation generally.

Individuals with eating disorders may also engage in other maladaptive emotion regulation behaviors (besides eating disorder symptoms like binge eating or purging). For example, cognitive rumination (i.e., hyper-focusing on negative emotions and thoughts) and suppression (i.e., attempting to push away negative thoughts

and/or emotional expressions) are maladaptive emotion regulation behaviors that are strongly associated with eating disorders including bulimia nervosa (Aldao et al. 2010). Rumination appears to play an especially important role in the maintenance of bulimia nervosa in particular, as binge eating and purging may serve to escape rumination (Prefit et al. 2019). Additionally, cognitive rumination predicts the onset of binge eating as well as increases in binge eating and purging frequency among adolescent girls (Nolen-Hoeksema et al. 2007).

In summary, it is clear that individuals with bulimia nervosa and purging disorder experience a broad constellation of difficulties with emotion regulation. Accordingly, one conceptualization is that it is difficulties with effectively *regulating* one's negative emotions generally (rather than simply the experience of having negative emotions) that may be the important antecedent to binge eating and purging behaviors (Mallorquí-Bagué et al. 2018). Therefore, learning and practicing adaptive emotion regulation skills is an important treatment target for any individual whose eating disorder is characterized by binge eating and/or purging. In fact, improvements in emotion regulation are directly related to positive treatment outcomes for individuals with eating disorders (Peterson et al. 2017), especially if improvements in access to emotion regulation skills occur rapidly during the initial weeks of treatment (MacDonald et al. 2017; MacDonald and Trottier 2019). Interventions targeting emotion regulation difficulties for individuals with eating disorders will be discussed in more detail later in this chapter.

Relationship Between State Negative Affect and Binge Eating/Purging Behaviors: Ecological Momentary Assessment Research

As discussed, bulimia nervosa and purging disorder are associated with emotion regulation difficulties. Although this suggests that eating disorders may function to regulate emotions, it does not demonstrate that eating disorder behaviors *specifically* serve this function or that there is an in-the-moment relationship between distressing emotions and eating disorder behaviors. In order to demonstrate an in-the-moment functional relationship between eating disorder behaviors and emotion regulation, research must reliably demonstrate a temporal association between intensifying negative emotions, engagement in an eating disorder behavior (e.g., binge eating or purging), and the subsequent attenuation of negative affect.

Ecological momentary assessment (EMA) is a methodology that has significantly advanced research on understanding the role of eating disorder behaviors as maladaptive emotion regulation strategies (Schaefer et al. 2020). EMA allows for nuanced examination of temporal relationships between state-level (i.e., in the moment) variables by using real-time assessments in an individual's natural environment multiple times per day for several days or weeks, typically using brief questionnaires completed on a smartphone or biometric data collected using activity trackers or heart rate monitors. In emotion research, EMA can be used to analyze state-level patterns of emotion and emotion intensity across time and examine the relationship between temporal patterns of emotion and behavior. This allows

researchers to draw conclusions about the temporal relationships between affect and behaviors such as binge eating and vomiting (Schaefer et al. 2020).

To date, EMA research has demonstrated a strong temporal relationship between state negative affect and eating disorder behaviors. In an early study in this area, Smyth et al. (2007) used EMA to show that individuals with bulimia nervosa experienced less positive affect, more negative affect generally, more anger and hostility specifically, and more stress on days when binge eating and purging occurred. Additionally, positive affect decreased, and both negative affect generally and anger/hostility increased in a reliable way, shortly prior to binge/purge episodes. Following binge/purge episodes, negative affect generally and anger/hostility both decreased, and positive affect increased (Smyth et al. 2007). Moreover, in an early meta-analysis of EMA research on binge eating, negative affect reliably increased prior to binge eating episodes, increased further after the binge, and then decreased after purging for those with bulimia nervosa (Haedt-Matt and Keel 2011). For individuals with purging disorder, negative affect increased prior to purging on purge days (compared to non-purge days) and was initially higher shortly after the purging episode but then followed a downward trajectory in the hours that followed (Haedt-Matt and Keel 2015). Additionally, among women with bulimia nervosa, guilt (a facet of negative affect) increased prior to, and decreased after, episodes of binge eating and purging as well as after episodes of purging only (Berg et al. 2013). Overall, the body of EMA research on this topic clearly demonstrates that eating disorder behaviors (such as binge eating and purging) often occur in the context of elevated state negative affect, and that negative affect often temporarily improves following these behaviors, and is consistent with the affect regulation model of eating disorders (Shaefer et al. 2020).

Interventions Targeting Emotion Regulation Difficulties for Bulimia Nervosa and Purging Disorder

Cognitive Behavioral Therapy (CBT) and CBT-Based Intensive Treatments

Given that binge eating and purging behaviors appear to function to regulate emotions in individuals with bulimia nervosa and purging disorder, it is important to consider how treatments for these disorders address emotion regulation difficulties. Enhanced cognitive behavioral therapy for eating disorders (CBT-E; Fairburn et al. 2008) is a transdiagnostic treatment based on the cognitive behavioral theory described earlier (Fairburn et al. 2003) and is the current leading evidence-based intervention for adults with eating disorders including bulimia nervosa and purging disorder (Fairburn et al. 2009, 2015). The main foci of CBT-E include behavioral changes (i.e., establishing regular eating, eliminating binge eating, purging, and

other weight control behaviors); reducing overvaluation of eating, weight and shape, and their control; and addressing event- and mood-related concerns, including mood intolerance, defined as the inability to effectively cope with intense mood states (Fairburn et al. 2003).

CBT-E targets event- and mood-related concerns using a cognitive-behavioral approach to help the client become more aware of how, and in what situations, triggering events, negative mood states, and intense emotions may lead to eating disorder behaviors and how to replace these with more functional mood modulation strategies. For example, individuals learn proactive problem-solving to address event-related disruptions in eating, and binge analysis helps them to analyze the antecedents of residual binge eating episodes to help them prevent these episodes. Furthermore, individuals learn to recognize the relationship between their cognitive appraisals of events, escalating negative emotions, and their use of maladaptive behaviors (e.g., binge eating) to modulate negative emotions. By learning to recognize this process early, clients can be taught to slow down, observe and analyze it unfolding, and intervene with more skillful behavior as early as possible (Fairburn et al. 2008). Interestingly, the initial version of CBT-E conceptualized mood intolerance as one of the several potential eating disorder maintenance mechanisms (along with perfectionism, core low self-esteem, and interpersonal difficulties), which could be addressed using a supplementary mood intolerance module. However, mood intolerance is now considered a core treatment target, and therefore this material is currently part of the core CBT-E protocol (Dahlenburg et al. 2019).

In addition to being effective for treating core eating disorder symptoms (Atwood and Friedman 2020), CBT-E is efficacious in reducing emotion regulation difficulties in individuals with bulimia nervosa (Wonderlich et al. 2014). Furthermore, improvements in emotion regulation during CBT-E are associated with improvements in overall eating disorder psychopathology at posttreatment and in binge eating and purging frequency four months posttreatment in a sample of individuals with bulimia nervosa (Peterson et al. 2017).

Many intensive treatment programs for moderate to severe presentations of bulimia nervosa, purging disorder, and other eating disorders also use cognitive behavioral approaches and include interventions aimed at improving clients' emotion regulation capacities (MacDonald et al. 2017; McFarlane et al. 2015; Olmsted et al. 2013). These typically include learning strategies to tolerate intense emotions and resist urges to engage in eating disorder behaviors in response to negative emotions. Research indicates that individuals' emotion regulation skills improve during intensive treatment. Importantly, increased access to emotion regulation strategies early in treatment (i.e., during the first four weeks) predicts abstinence from binge eating and purging and lower cognitive eating disorder psychopathology at posttreatment (MacDonald et al. 2017), as well as lower eating disorder psychopathology and lower impairment due to the eating disorder six months after treatment (MacDonald and Trottier 2019).

Dialectical Behavior Therapy

Dialectical behavior therapy (DBT) was originally designed for the treatment of individuals with borderline personality disorder and includes a primary focus on teaching skills to regulate intense emotions and tolerate distress (Linehan 1993). The fact that individuals with bulimia nervosa and other eating disorders often have difficulties with emotion regulation provided a strong rationale for applying DBT in this group (e.g., Safer et al. 2009). DBT approaches have been examined as a stand-alone treatment for bulimia nervosa (Safer et al. 2001; Brown et al. 2020), as well as an adjunct intervention to target emotion regulation difficulties within CBT-based treatment programs (Ben-Porath et al. 2014). DBT interventions have received preliminary research support, both for their impact on core eating disorder symptoms and emotion regulation (Linardon et al. 2017). Standard DBT typically includes four components: protocolized individual psychotherapy; group skills training (in which mindfulness, distress tolerance, interpersonal effectiveness, and emotion regulation modules are taught); therapist consultation teams; and 24-hour phone coaching (Linehan 1993). Stand-alone DBT for eating disorders may include all or several of these components (or iterations of them; e.g., the adapted DBT manual for bulimia nervosa by Safer and colleagues (2009) includes three of the four DBT skills training modules, with the interpersonal effectiveness module omitted). When DBT is included as a supplement to CBT-based eating disorder treatment, it is often implemented as a DBT skills group in which some or all of the core DBT skills are taught, whereas the other components of standard DBT (i.e., phone coaching, therapist consultation teams, and/or individual DBT sessions) might be omitted (Ben-Porath et al. 2014). There is also an adaptation of DBT for patients with multi-diagnostic presentations who have a primary eating disorder diagnosis as well as significant comorbid psychopathology, often including borderline personality disorder (Ben-Porath et al. 2020). This version of DBT combines components of CBT for eating disorders and DBT to concurrently manage both the eating disorder and other high-risk behaviors (e.g., suicidality, self-injury; Ben-Porath et al. 2020). Regardless of the format, the aim of using a DBT approach to treat eating disorders is to help individuals learn to understand, tolerate, and more adaptively regulate intense emotions, thereby eliminating the use of binge eating and purging behaviors as a maladaptive emotion regulation strategy (Brown et al. 2020; Safer et al. 2001).

Research on the effectiveness of DBT and DBT-informed treatments for individuals with bulimia nervosa has shown that integrating DBT into day treatment leads to significant improvements in patients' emotion regulation capacities (Brown et al. 2020). Similarly, the addition of a weekly DBT skills group to a CBT-based intensive eating disorder program was associated with small improvements in emotion regulation capacities in a mixed sample of individuals with anorexia nervosa and bulimia nervosa (Ben-Porath et al. 2014). Research has not specifically examined the impact of DBT interventions on emotion regulation difficulties in individuals diagnosed with purging disorder.

Integrative Cognitive-Affective Therapy for Bulimia Nervosa

Integrative cognitive-affective therapy for bulimia nervosa (ICAT-BN; Wonderlich et al. 2015) is a psychotherapy intervention with research support for its efficacy in treating individuals with bulimia nervosa (Wonderlich et al. 2014). It was designed with the aim of specifically targeting emotion dysregulation in this population and is based on the theory that momentary experiences of negative emotions play a primary role in the maintenance of bulimia nervosa (Wonderlich et al. 2015). Binge eating and purging symptoms are considered to play a significant role in regulating these emotion states and thus become positively reinforced. ICAT-BN shares some features with CBT-E (including self-monitoring of eating and learning how to plan and implement regular eating); however, the majority of the treatment focuses on modifying and tolerating momentary emotion-related experiences (Accurso et al. 2016; Peterson et al. 2017). Interventions aimed at addressing emotion dysregulation and eating disorder symptoms include improving awareness and tolerance of emotions, developing skills to reduce impulsive behaviors in response to negative emotions, and modifying sources of negative emotions and a lack of positive emotions in the individual's life (Wonderlich et al. 2015).

ICAT-BN led to similar improvements in eating disorder symptoms to CBT-E in a rigorous randomized controlled trial of individuals with bulimia nervosa (Wonderlich et al. 2014), and both interventions had comparable and positive impacts on emotion regulation capacities (Peterson et al. 2017). ICAT-BN may be particularly effective for individuals with bulimia nervosa who experience a high degree of emotion dysregulation before starting treatment. Accurso et al. (2016) found that individuals with higher affective lability (i.e., the tendency to frequently experience intense and unstable emotions) experienced greater improvements in symptom reduction and overall eating disorder psychopathology when treated with ICAT-BN versus CBT-E.

Conclusions

This chapter described the types of emotion regulation difficulties that are commonly experienced by individuals with bulimia nervosa and purging disorder. A number of theoretical models have been put forth to explain the role of negative affect in these disorders, and these models converge in their explanations of binge eating and purging behaviors as maladaptive efforts to regulate emotions. The nuanced temporal relationships that are elucidated by recent EMA research clearly demonstrate the functional relationship between eating disorder behaviors and negative emotions. Finally, the chapter reviewed several treatments for bulimia nervosa and purging disorder that include attention to difficulties with emotion regulation. Although CBT-E is currently the leading evidence-based treatment for eating disorders overall, DBT and ICAT both target emotion-related difficulties as core treatment targets and have accumulating evidence supporting them, making them important treatment options for this group.

Applications to Other Eating Disorders

Anorexia nervosa. Individuals with anorexia nervosa also experience difficulties with emotion regulation (Lavender et al. 2015). There are two subcategories of anorexia nervosa: restricting type (AN-R) and binge eating/purging type (AN-BP). In both types the individual maintains a low weight and restricts energy intake (i.e., via restrictive eating, fasting, and/or excessive exercise). Individuals with AN-R engage exclusively in restrictive behaviors, whereas individuals with AN-BP also engage in regular episodes of binge eating and/or purging behaviors. According to a recent review, individuals with AN-R, AN-BP, and bulimia nervosa do not differ in their use of maladaptive emotion regulation strategies, but individuals with anorexia nervosa are less likely to use adaptive (i.e., skillful) methods of emotion regulation, compared to those with bulimia nervosa (Puttevils et al. 2021). The authors explain that this may be due to the effects of underweight and greater alexithymia in individuals with anorexia nervosa (Puttevils et al. 2021). Other research has demonstrated that individuals with AN-BP tend to use fewer adaptive emotion regulation strategies relative to individuals with AN-R (Rowsell et al. 2016), providing support that emotion dysregulation and binge eating and purging behaviors are strongly related. In fact, one study showed that difficulties inhibiting impulsivity when distressed is the only facet of emotion regulation that was significantly related to binge eating/purging behaviors among individuals with anorexia nervosa (Racine and Wildes 2013).

Binge eating disorder. Binge eating disorder is characterized by recurrent episodes of binge eating without engaging in compensatory behaviors such as purging, fasting, or exercise. As reviewed earlier in the chapter, according to the affect regulation model of binge eating, binge eating is believed to often function as a way to regulate negative affective states. Therefore, it is not surprising that individuals with binge eating disorder report greater difficulty with emotion regulation relative to healthy controls (Brockmeyer et al. 2014). However, there is also evidence to suggest that individuals with binge eating disorder generally report less emotion regulation difficulties relative to individuals with anorexia nervosa and bulimia nervosa (Brockmeyer et al. 2014).

Mini-Dictionary of Terms

- **Affect regulation model:** A theoretical model that suggests binge eating functions to reduce negative affective states. According to this model, binge eating is maintained via negative reinforcement.
- **Cognitive behavioral model:** A transdiagnostic theoretical model of eating disorder maintenance. According to this model, overevaluation of eating, weight, and shape is considered the core cognitive psychopathology of eating disorder behaviors. This model also considers the role of mood intolerance as an important eating disorder maintaining mechanism.

- **Ecological momentary assessment:** A research methodology that uses repeated sampling of participants' real-time emotions, behaviors, and experiences in their natural environments, often using a device such as a smartphone.
- **Emotion dysregulation:** Difficulty with effectively modulating emotions using skillful or adaptive behaviors and/or the overreliance on maladaptive behaviors (e.g., eating disorder behaviors, self-harm, substance use) to manage emotions.
- **Emotion regulation:** A constellation of constructs related to one's ability to effectively modulate and manage emotions. Emotion regulation includes (but is not limited to) sub-constructs such as degree of emotion awareness, the abilities to inhibit impulsivity and maintain goal-directed behavior while experiencing negative emotions, and the ability to flexibly adapt behavior in emotional situations.
- **Escape theory:** A theoretical conceptualization of bulimia nervosa in which binge eating is viewed as a way to escape from states of self-awareness, which may be experienced as aversive and distressing.
- **Mood intolerance:** A central component of the transdiagnostic cognitive behavioral model of eating disorders, in which difficulty effectively tolerating emotions is considered an important eating disorder maintaining factor.

Key Facts of Emotion Regulation in Bulimia Nervosa and Purging Disorder

- Emotion regulation refers to the ability to effectively and adaptively modulate one's emotions
- Emotion regulation includes elements such as awareness of one's emotions, the ability to prevent impulsive behaviors and remain goal-directed during elevated affective states, and the ability to implement strategies aimed at modulating emotions
- Individuals with bulimia nervosa and related eating disorders such as purging disorder often experience difficulties with emotion regulation
- Eating disorder behaviors such as binge eating often function as maladaptive emotion regulation strategies
- During negative emotional states, eating disorder behaviors may help the individual bring down or escape from negative emotions
- This process also contributes to the persistence of eating disorder behaviors over time

Summary Points

- Difficulties with regulating emotions are characteristic of individuals with bulimia nervosa and purging disorder
- There are several theoretical models that include difficulty regulating emotions or tolerating distress as key to understanding the occurrence and maintenance of binge eating and/or purging behaviors

- Difficulties with emotion regulation may include nonacceptance of emotional states, difficulties with impulse control, limited access to emotion regulation strategies, and difficulties engaging in goal-directed behavior during negative affective states
- Ecological momentary assessment (EMA) research has clearly demonstrated a temporal relationship between state negative affect, the occurrence of binge eating and/or purging behaviors, and subsequent decreases in state negative affect
- There are several interventions for individuals with eating disorders that target difficulties with emotion regulation

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Pharmacology Options for Bulimia Nervosa 42

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Contents

Introduction 823
Antidepressants 823
Antiepileptics 824
Stimulants 827
Other Medications 829
  Hormonal 829
  Other Medications with Mixed/Negative Findings 831
Pharmacology Youth with BN 833
Psychotherapy and Pharmacology Combination in BN 834
Conclusions 835
Mini-Dictionary of Terms 836

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Key Facts of Pharmacology Options for Bulimia Nervosa 837
Summary Points 837
References 838

Abstract

Although psychotherapy is effective for bulimia nervosa (BN), many individuals remain symptomatic after treatment. Therefore, pharmacotherapies have been studied as stand-alone treatments, and as adjuncts for psychotherapy, with the goal of improving outcomes for BN. Despite much research in this area, fluoxetine remains the only medication with regulatory approval. However, there are off-label options and several medications in development. The goal of this chapter is to review the literature related to the following pharmacotherapies for BN: a) antidepressants, b) antiepileptics, c) stimulants, and d) other medications. We will also review the literature related to combining pharmacotherapy and psychotherapy for those with BN and present the evidence for medication treatment in youth with this disorder.

Keywords

Bulimia nervosa · Eating disorders · Pharmacotherapy · Medications · Review · Antidepressant · Fluoxetine · Antiepileptic · Anticonvulsant · Topiramate · Stimulant · Lisdexamfetamine · Psychotherapy

Abbreviations

ADHD	Attention deficit hyperactivity disorder
AN	Anorexia nervosa
BED	Binge eating disorder
BMI	Body mass index
BN	Bulimia nervosa
CBT	Cognitive behavior therapy
DBT	Dialectical behavior therapy
ED	Eating disorder
EDNOS	Eating disorder not otherwise specified
IPT	Interpersonal therapy
IU	International units
LDX	Lisdexamfetamine dimesylate
MA	Methylamphetamine
MAOI	Monoamine oxidase inhibitors
MPH	Methylphenidate
Phen/Top ER	Phentermine/topiramate extended release
RCT	Randomized control trial
SSRI	Selective serotonin reuptake inhibitors
TCA	Tricyclic antidepressants

Introduction

Bulimia nervosa (BN) is a serious medical condition characterized by episodes of eating objectively large amounts of food in a discrete period of time and feeling a sense of loss of control during the episode. The shame and guilt associated with these binge episodes then triggers compensatory behaviors (e.g., self-induced vomiting) aimed at alleviating the negative feelings (American Psychiatric Association 2013). The lifetime prevalence of BN is approximately 2% and is associated with increased mortality rates from all causes, including elevated rates of suicide (Hudson et al. 2007; Crow et al. 2009). Although psychotherapy is effective for BN, approximately 40% of individuals remain symptomatic after treatment (Hilbert et al. 2019). As a result, pharmacotherapies have been extensively studied as stand-alone treatments, and as adjuncts for psychotherapy, with the goal of improving outcomes for BN. Despite many clinical trials aimed at developing medications for BN, fluoxetine remains the only option with regulatory approval. Even though fluoxetine is the only approved medication, there are some off-label options and medications in development. The goal of this chapter is to review the literature related to the following pharmacotherapies for BN: a) antidepressants, b) antiepileptics, c) stimulants, and d) other medications. We will also review the literature related to combining pharmacotherapy and psychotherapy in BN and present the evidence for medication treatment in youth with this disorder.

Applications to Other Eating Disorders – In this chapter, we review the evidence for treating BN with pharmacotherapy. Although the research described here relates specifically to BN, there is overlap with binge eating disorder (BED). BED is a distinct disorder, but there are symptom and neurobiological parallels between the two illnesses. As such, there are also similarities between the medications recommended for each disorder. For example, similar to BN, a meta-analysis showed that antidepressants are moderately effective for reducing binge episodes in BED (Stefano et al. 2008), though unlike in BN, fluoxetine does not have regulatory approval for BED. Similarly, as described in the BN literature, there are several randomized controlled trials supporting the use of topiramate in BED (Frank and Berner 2020). Another parallel between pharmacotherapy options for BN and BED is the use of stimulants. In North America, the stimulant prodrug lisdexamfetamine is approved for the treatment of moderate to severe BED in adults (McElroy et al. 2016). Although the same degree of evidence does not exist for using stimulants in BN, we will discuss the emerging evidence for this medication (in BN) later in the chapter. Finally, there is little overlap between pharmacotherapy options for BN and anorexia nervosa.

Antidepressants

Research and guidelines suggest antidepressants are the pharmacological treatment of choice for BN (American Psychological Association 2006; Hagan and Walsh 2021; Hilbert et al. 2017). Currently, fluoxetine (serotonin reuptake inhibitor; SSRI)

is the only approved medication for BN in North America. Several randomized controlled trials suggest that a dose of 60 mg of fluoxetine can reduce frequency of vomiting, binge eating, and purging, as well as improve eating attitudes and comorbid symptoms of depression relative to a dose of 20 mg and/or placebo (Fluoxetine BN Collaborative Study Group 1992; Goldstein et al. 1995; Romano et al. 2002). Notably, fluoxetine appears to result in reductions of BN symptoms in both adult and adolescent populations (Kotler et al. 2003), and in BN patients with or without comorbid depression (e.g., Goldstein et al. 1999). Fluoxetine appears to have low occurrences of adverse events (see Bello and Yeomans 2018 review of safety of fluoxetine for BN); however, it has been cautioned that higher doses of SSRIs like fluoxetine may trigger suicidal behaviors, which may be particularly noteworthy for adolescent populations (Frank 2020). Despite these promising findings, there is evidence of symptomatic regression over time in patients with BN treated with fluoxetine (Romano et al. 2002). As such, it has been suggested that fluoxetine alone may not be a sufficient treatment for BN.

In addition to fluoxetine, other antidepressants have been examined as potential treatments for BN. These include other SSRIs, tricyclic antidepressants (TCA), monoamine oxidase inhibitors (MAOI), and atypical antidepressants (e.g., trazodone; McElroy et al. 2019). While there are fewer randomized, placebo-controlled trials with antidepressants other than fluoxetine (McElroy et al. 2019), a recent meta-analysis found SSRIs, TCAs, and MAOIs have moderate efficacy for reducing binge eating and purging episodes (Svaldi et al. 2019). While these results are encouraging, there is substantial heterogeneity across RCTs with antidepressants (Svaldi et al. 2019). As such, additional research is required before concrete conclusions can be drawn about the effectiveness of classes of antidepressants on BN symptoms. In terms of safety, antidepressants are generally considered safe except for bupropion, which has been associated with seizures in those with BN (Horne et al. 1988).

Overall, the broader literature does not recommend antidepressants as the sole treatment for BN (National Institute for Health and Care Excellence 2017; Reas and Grilo 2021) unless the first line treatment of cognitive behavior therapy (CBT) is unavailable, there has been a poor response to psychotherapy, or patients prefer medication to psychotherapy (Hagan and Walsh 2021; Svaldi et al. 2019; Walsh et al. 2000; Table 1).

Antiepileptics

Of the antiepileptics, topiramate is the most studied as a treatment for BN. In 2003, Hoopes et al. conducted a 10-week RCT in which BN participants received either topiramate ($n = 35$) or placebo ($n = 34$). The study revealed that patients administered topiramate (median dose 100 mg/day) exhibited a 44.8% decrease in mean weekly binge and/or purge days, while those in the placebo group demonstrated a 10.7% reduction. In another RCT by Nickel et al. (2005), 60 participants received topiramate (titrated to 250 mg/day by 6 weeks), or placebo, over 10 weeks. 36.7% ($n = 11$) of the topiramate group experienced a greater than 50% reduction in the

Table 1 Selection of studies examining the use of SSRIs in bulimia nervosa

Authors	Study design duration	Sample size	Medication (daily dose)	Outcomes
Blouin et al. (1988)	Desipramine vs. fenfluramine in 15-week double-blind, placebo-controlled crossover design	22	Desipramine and fenfluramine	Both desipramine and fenfluramine associated with decreased binge eating and vomiting frequency
Fichter et al. (1991)	Fluoxetine vs. placebo in 4-week double-blind trial (patients simultaneously in psychotherapy)	40	Fluoxetine (60 mg/day)	Fluoxetine associated with significant weight loss. No significant improvement in eating attitudes or behavior beyond intensive inpatient psychotherapy
Agras et al. (1992)	Desipramine vs. CBT vs. combined for 16–24 weeks	71	Desipramine	At 16 weeks, CBT and combined > desipramine for binge eating and purging. At 32 weeks combined > desipramine
Fluoxetine Bulimia Nervosa Collaborative Study Group (1992)	Fluoxetine hydrochloride vs. placebo for 8 weeks in double-blind trial	387	Fluoxetine hydrochloride (20 and 60 mg/day)	Fluoxetine 60 mg/day > placebo in decreasing weekly binge eating and vomiting, carbohydrate craving, pathological eating attitudes and behaviors. Fluoxetine 20 mg/day effect between that of 60 mg/day and placebo
Goldstein et al. (1995)	Fluoxetine vs. placebo in 16-week double-blind trial	398	Fluoxetine (60 mg/day)	Fluoxetine > placebo for reduction in binge eating and vomiting
Kanerva et al. (1995)	Fluoxetine vs. placebo in 8-week double-blind trial	46	Fluoxetine (60 mg/day)	Fluoxetine > placebo for eating-related, depressive, and anxiety symptoms, as well as weight loss

(continued)

Table 1 (continued)

Authors	Study design duration	Sample size	Medication (daily dose)	Outcomes
Goldbloom et al. (1997)	Fluoxetine vs. CBT vs. combined in 16-week trial	76	Fluoxetine (60 mg/day)	All three conditions associated with reduction in binge eating, vomiting, and dietary restraint. CBT and combined > fluoxetine. Combined offered no statistically significant advantaged to CBT alone
Beumont et al. (1997)	Fluoxetine vs. nutritional counselling vs. combined for 8 weeks	67	Fluoxetine (60 mg/day)	Fluoxetine > other conditions on Eating Disorder Examination subscales. Some recurrence of symptoms following cessation of fluoxetine
Walsh et al. (2000)	Fluoxetine vs. placebo in non-responders to, or those who had relapsed following, CBT or IPT	22	Fluoxetine (60 mg/day)	Fluoxetine > placebo in reducing binge eating and purge frequency
Mitchell et al. (2002)	Fluoxetine vs. interpersonal psychotherapy (IPT) in CBT non-responders for 15 weeks	62	Fluoxetine (60 mg/day)	Abstinence from eating disorder behaviors did not differ between fluoxetine and IPT conditions in CBT non-responders
Romano et al. (2002)	Fluoxetine vs. placebo in a 52-week single-blind trial of responders to fluoxetine	150	Fluoxetine (60 mg/day)	In those who initially responded to fluoxetine, fluoxetine > placebo for time to relapse. Fluoxetine > placebo for reduction of binge eating and vomiting
Jacobi et al. (2002)	Fluoxetine vs. CBT vs. combined in 16-week trial	53	Fluoxetine (60 mg/day)	All three conditions associated with reduction in binge eating and vomiting, body dissatisfaction, and restrained eating Conditions were not significantly different in effectiveness

(continued)

Table 1 (continued)

Authors	Study design duration	Sample size	Medication (daily dose)	Outcomes
Schmidt et al. (2004)	Fluvoxamine 8-week vs. fluvoxamine 52-week vs. placebo double-blind trial	267	Fluvoxamine (50–300 mg/day)	Fluvoxamine = placebo
Sundblad et al. (2005)	Flutamide vs. citalopram vs. flutamide +citalopram vs. placebo in 3-month double-blind trial	46	Flutamide (250–500 mg/day) Citalopram (20–40 mg/day)	Flutamide and flutamide + citalopram demonstrated a reduction in binge eating. Citalopram only and placebo groups did not demonstrate reduction in binge eating
Leombruni et al. (2006)	Fluoxetine vs. citalopram	37	Fluoxetine (20–60 mg/day) Citalopram (20–40 mg/day)	Both fluoxetine and citalopram were associated with improvements in eating psychopathology

CBT Cognitive behavioral therapy, *IPT* Interpersonal therapy

frequency of binge-purge compared to 3.3% (n = 1) of the control group. Topiramate also produced a significantly greater decrease in body weight relative to placebo, and significantly improved health-related quality of life. Topiramate is also effective in reducing binging and purging in BN patients with comorbid affective and anxiety disorders, and in those being concurrently treated with antipsychotics, antidepressants, and mood stabilizers (Barbee 2003; Bruno et al. 2009).

In a prospective flexible-dose study, 12 BN participants were treated with open-label zonisamide over a 12-week period (Guerdjikova et al. 2013). It was found that zonisamide use was associated with significant decreases in binge-purge episodes, binge-purge days, global illness severity, depressive symptoms, and obsessive-compulsive features of BN. Two participants achieved complete remission from BN prior to the last 4 weeks of the study. Finally, in several case studies, lamotrigine and valproate were associated with a reduction in ED symptoms and in-patients with comorbid affect or impulse dysregulation (McElroy et al. 2019; Table 2).

Stimulants

Similarities between BN and attention deficit hyperactivity disorder (ADHD), including executive dysfunction, have warranted growing interest in the use of stimulants for the management of BN (Keshen et al. 2022). To date, the only RCT

Table 2 Studies using antiepileptics to treat bulimia nervosa

Authors	Study design duration	Sample size	Medication (daily dose)	Outcomes
Barbee (2003)	Case reports of individuals with BN and comorbid mood and/or anxiety disorders	5	Topiramate (25–400 mg)	Topiramate associated with a marked reduction or complete cessation of binging and purging behaviors. This was often sustained for a period of many months, except in one individual who showed a temporary response
Hoopes et al. (2003)	Randomized, double-blind placebo-controlled trial measuring the efficacy and safety of topiramate in BN	69	Topiramate (25–400 mg)	Topiramate associated with a significant improvement in binging and purging symptoms
Nickel et al. (2005)	Randomized, double-blind placebo-controlled trial testing the influence of topiramate on behavior and body weight among patients with BN	60	Topiramate (25–250 mg)	Topiramate associated with a greater difference of change in decreasing binging/purging relative to the placebo Topiramate also resulted in a reduction in body weight that was significantly greater than the placebo
Bruno et al. (2009)	Case report of an individual with BPD, obsessive-compulsive symptoms, and BN treated with aripiprazole and topiramate	1	Topiramate (250 mg); aripiprazole (5 mg)	Co-administration of aripiprazole plus topiramate associated with a reduction in BPD symptoms, obsessive behavior, and frequency of binge episodes. Patient socio-relational functioning was also improved
Guerdjikova et al. (2013)	Open-label, pilot, prospective study investigating the potential effectiveness of zonisamide in BN	12	Zonisamide (100–600 mg)	Zonisamide associated with a significant reduction in binge-purge episodes, obsessive-compulsive behavior, global illness severity, and depressive symptoms

BN Bulimia nervosa, *BPD* Borderline personality disorder

using a stimulant for BN included four patients randomized to phentermine/topiramate extended release (Phen/Top ER; 3.75 mg/23 mg–15 mg/92 mg) or placebo over a 12-week period (Safer et al. 2020). Phen/Top ER was found to significantly reduce objective binge eating days, significantly increase abstinence rates, and reduce weight. There were no serious adverse events reported, and differences in heart rate and blood pressure between the Phen/Top ER and placebo groups were minimal. Considering the sample size of patients with BN was only four, the safety of Phen/Top ER for the treatment of BN still needs to be assessed.

Lisdexamfetamine dimesylate (LDX) has been approved for the treatment of ADHD in adults and children and for BED in adults. A Health Canada approved open-label feasibility study examining LDX (50–70 mg/day) as a treatment for adults with BN concluded that, over an 8-week period, there were reductions in objective binge episodes and compensatory behaviors (N = 23; Keshen et al. 2021). There was a clinically significant mean increase in heart rate observed and a decrease in BMI (which could be problematic if BN patients lose weight due to increased restriction from appetite suppression). These results indicate that an RCT using LDX for patients with BN is feasible, but that clinicians should not prescribe the drug until efficacy and safety are tested on a larger sample size over a longer study period.

Another study involved a one-time administration of either methylamphetamine (MA; 15 mg/75 kg body weight) or placebo intravenously, under double-blinded conditions (N = 8; Ong et al. 1983). Following administration of MA or placebo, patients were left alone with a large amount of food. The frequency of bulimic symptoms was significantly lower for those in the MA group compared to the placebo group.

Several case reports have described the successful use of stimulants in treating individuals with BN, including methylphenidate (Schweickert et al. 1997; Sokol et al. 1999; Guerdjikova and McElroy 2013), dextroamphetamine (Dukarm 2005), amphetamine/dextroamphetamine extended release or dextroamphetamine (Keshen and Ivanova 2013), and LDX or amphetamine/dextroamphetamine ER (Keshen and Helson 2017). Although there are no approved stimulants to reduce BN symptoms, these results support the need to explore further. Future controlled studies are required to better evaluate the efficacy and safety of stimulants for the treatment of BN (Keshen et al. 2022; Table 3).

Other Medications

Hormonal

Oxytocin and anti-androgens have been studied as potential hormonal treatments for BN. Two randomized, cross-over design experiments analyzed the effects of oxytocin on women with BN. In the first study, 34 BN patients, 35 AN patients, and 33 healthy controls received 40 international units (IU) of intranasal oxytocin or

Table 3 Studies using stimulants to treat bulimia nervosa

Authors	Study design duration	Sample size	Medication (daily dose)	Outcomes
Ong et al. (1983)	Administration of MA vs. placebo	8	MA (15 mg/75 kg body weight)	MA > placebo in immediate binge eating/ compensation
Schweickert et al. (1997)	Case report of an individual with comorbid BN and ADHD	1	MPH (15 mg)	MPH associated with cessation of binge eating episodes
Sokol et al. (1999)	Case reports of individuals with BN and cluster B traits	2	MPH (10–15 mg)	MPH associated with reduction in episodes of binge eating/ compensation
Dukarm (2005)	Case reports of patients with comorbid BN and ADHD	6	Dextroamphet (15 mg–30 mg)	Dextroamphet associated with cessation of binge eating/compensation
Guerdjikova and McElroy (2013)	Case report of an individual with comorbid BN, bipolar I disorder, and ADHD	1	MPH (72 mg)	MPH associated with complete remission of BN symptoms and improvement in ADHD symptoms
Keshen and Ivanova (2013)	Case reports of individuals with comorbid BN and ADHD	5	Amphet/ dextroamphet XR (20–40 mg) or Dextroamphet (20 mg)	Amphet/dextroamphet XR and Dextroamphet associated with decrease in episodes of binge eating and purging
Keshen and Helson (2017)	Case reports of individuals with BN (but not ADHD)	6	LDX (50–70 mg) or Amphet/ dextroamphet XR (40 mg)	LDX and Amphet/ Dextroamphet XR were associated with reduction in episodes of binge eating/compensation
Safer et al. (2020)	Placebo-controlled crossover trial of Phen/Top ER 12 weeks	4	Phen/Top ER (15 mg/92 mg)	Phen/Top > placebo for reducing objective binge eating days, binge abstinence rates, and weight
Keshen et al. (2021)	Open-label feasibility study 8 weeks	23	LDX (50–70 mg)	LDX was associated with reductions in objective binge eating episodes and compensatory behaviors. Safety and tolerability were generally acceptable. There was a mean increase in heart rate and decrease in BMI

LDX Lisdexamfetamine, *MPH* Methylphenidate, *Phen* Phentermine, *Top ER* Topiramate extended release, *Amphet/Dextroamphet XR* Amphetamine/dextroamphetamine extended release, *MA* Methamphetamine, *Dextroamphet* Dextroamphetamine

placebo, followed by an emotion recognition task (Kim et al. 2015). There was no significant change in appetite among healthy controls, while those with BN demonstrated a decrease in calorie consumption over 24 h. The second study compared 25 patients with BN or BED and 27 healthy controls who received 64 IU of intranasal oxytocin or placebo (Leslie et al. 2019). Oxytocin had no significant effect on eating behavior. A systematic review and meta-analysis of 12 controlled trials on the use of intranasal oxytocin to decrease food intake concluded that whether oxytocin is a viable treatment option for patients with eating disorders is yet to be determined (Chen et al. 2021).

Increased androgen levels in women may promote bulimic behaviors (Cotrufo et al. 2000; McCluskey et al. 1991; Naessén et al. 2007; Sundblad et al. 1994). Two RCTs have evaluated the use of anti-androgens in treating women with BN. In the first study, 46 BN patients received flutamide (an androgen antagonist), citalopram, flutamide plus citalopram, or placebo for 3 months (Sundblad et al. 2005). Final doses were 500 mg/day of flutamide and 40 mg/day of citalopram. Only the flutamide groups demonstrated a statistically significant reduction in binge eating from baseline. There was no significant decrease in vomiting in any group. In the second study, 93 BN patients received the androgen antagonist spironolactone or placebo (von Wietersheim et al. 2008). Spironolactone demonstrated no therapeutic effect. An ongoing RCT in Sweden is evaluating the use of the anti-androgenic oral contraceptive drospirenone/ethinyl estradiol in women with BN or EDNOS of bulimic type (EudraCT number 2011-006099-38).

Other Medications with Mixed/Negative Findings

Four small RCTs found mostly negative results for treating BN with opioid antagonists (e.g., naltrexone; McElroy et al. 2019); however, one open-label study determined that high dose naltrexone (200–300 mg/day) led to significant reductions in binge/purge symptoms relative to standard dose (50–100 mg/day; Jonas and Gold 1988). One RCT has examined the use of a prokinetic agent to treat BN. For 6 weeks, 39 women with BN and 22 healthy controls received erythromycin (up to 500 mg three times daily) or placebo (Devlin et al. 2012). Erythromycin did not significantly decrease binge eating or vomiting. The use of lithium to treat BN was studied in one 8-week RCT with 91 patients (Hsu et al. 1991). In comparison to placebo, lithium had no significant impact on decreasing binge eating. Conversely, case reports from open trials have demonstrated the successful reduction of binge/purge episodes in BN patients (Hsu 1984, 1987). Case reports on the use of second-generation antipsychotics, specifically clozapine and olanzapine, have noted their potential to induce binge eating or worsen bulimic behaviors (Brewerton and Shannon 1992; Gebhardt et al. 2007; Theisen et al. 2003); however, the use of aripiprazole to successfully treat BN has been reported in case series (Takaki and Okabe 2015; Trunko et al. 2011). Finally, in a case series examining baclofen 60 mg/day, two participants experienced a reduction in binge eating (N = 3) (Table 4).

Table 4 Studies using other medications to treat bulimia nervosa

Authors	Study design duration	Sample size	Medication (daily dose)	Outcomes
Hsu (1984)	Case reports of lithium following or concurrent with CBT Up to 16 months	14	Lithium (450–2350 mg)	Lithium associated with reduction in bulimia symptoms for 12 of 14 patients
Hsu et al. (1991)	Double-blind, randomized controlled trial of lithium vs. placebo 8 weeks	91	Lithium (600–1200 mg)	Lithium = placebo for reduction in bulimia symptoms
Brewerton and Shannon (1992)	Case report of 29-year-old female with BN and schizophrenia	1	Clozapine (up to 350 mg)	Patient was abstinent from binge eating/ purging for several months after beginning daily thiothixene (10 mg) and fluoxetine (80 mg). Six weeks after clozapine was added, binge-purge episodes returned
Jonas and Gold (1988)	Open-label trial of standard vs. high dose of opioid antagonist 6 weeks	16	Naltrexone: low dose (50–100 mg), high dose (200–300 mg)	High dose naltrexone associated with significant reduction in binge eating and purging
Sundblad et al. (2005)	Double-blind, randomized controlled trial of androgen antagonist vs. SSRI vs. androgen antagonist plus SSRI vs. placebo 3 months	44	Final doses: flutamide (500 mg), citalopram (40 mg)	Flutamide (with or without citalopram) associated with significant reduction in binge eating. Treatment groups = placebo for reduction in vomiting
Broft et al. (2007)	Open-label trial of a GABA-B agonist 10 weeks	3	Baclofen (60 mg)	Baclofen associated with reduction of binge eating frequency
von Wietersheim et al. (2008)	Double-blind, randomized controlled trial of androgen antagonist vs. placebo 8 weeks	93	Final dose: spironolactone (150 mg)	Spironolactone not associated with a reduction in binge eating or bulimic behavior
Trunko et al. (2011)	Case reports of aripiprazole	3	Aripiprazole (7.5–10 mg)	Aripiprazole associated with reduction of bulimia symptoms, anxiety, and depression
	Case reports of aripiprazole in	5	Aripiprazole (3–12 mg)	Aripiprazole associated with reduction of binge

(continued)

Table 4 (continued)

Authors	Study design duration	Sample size	Medication (daily dose)	Outcomes
Takaki and Okabe (2015)	patients resistant to antidepressants 8–26 months			eating and purging episodes, anxiety, and depression
Kim et al. (2015)	Double-blind, placebo-controlled, crossover trial of oxytocin 24 h	67	Intranasal oxytocin (40 IU single dose)	Oxytocin associated with a decrease in calorie consumption over 24 h in BN patients; healthy controls and BN patients showed a small increase in emotion recognition sensitivity
Leslie et al. (2019)	Double-blind, placebo-controlled, crossover trial of oxytocin 24 h	52	Intranasal (64 IU single dose)	Oxytocin not associated with a reduction in subjective hunger, immediate consumption of food, 24-h calorie consumption, or binge eating incidence
Chen et al. (2021)	Systematic review and meta-analysis of 12 controlled trials of oxytocin	423	Intranasal oxytocin (single dose)	Oxytocin not associated with a reduction in food intake in psychiatric patients. Oxytocin = placebo for reduction of food craving and hunger
Devlin et al. (2012)	Double-blind, randomized controlled trial of prokinetic agent vs. placebo 6 weeks	29	Erythromycin (up to 500 mg, TID)	Erythromycin not associated with reduction in binge eating or vomiting

Pharmacology Youth with BN

There is a paucity of literature examining the use of medications to treat EDs in youth, with most published studies investigating antipsychotics in adolescents with anorexia nervosa (Couturier et al. 2019; Gorrell and Le Grange 2019). The current evidence for medication use in children and adolescents with BN is insufficient to inform clinical treatment guidelines beyond the statement that medications should not be the only treatment offered (Gorrell and Le Grange 2019). There is a need for randomized controlled trials, yet the completion of these types of studies in youth remains challenging due to issues with recruitment and retention (Couturier et al. 2019).

Although there is a dearth of pharmacotherapy trials in youth with BN, recent studies indicate that use of psychotropic medications in pediatric ED clinical settings is common (Couturier et al. 2019; Garner et al. 2016). In a study of over 600 adolescents with EDs, 20% of participants were already using psychotropic medications at intake, and 1 year later this percentage had almost tripled (Monge et al. 2015). In a different study of youth attending eating disorder programs in school settings, Mizusaki et al. (2018) found almost 50% were taking psychotropic medications upon presentation, with increased likelihood associated with longer histories of ED symptoms and self-harm behaviors.

In addition to these observational studies (Monge et al. 2015; Mizusaki et al. 2018), there are several case series examining the use of medication in youth with BN. Kotler et al. (2003) conducted an 8-week trial of fluoxetine in 12–18-year-olds with BN (N = 10). A dose of up to 60 mg combined with supportive therapy showed improvement in seventy percent of patients with no adverse side effects. Encouragingly, average weekly binge episodes were reduced from 4.1 to 0 and purge episodes from 6.4 to 0.4. Limitations of the study include the small sample size, open-label design, and the lack of long-term follow-up (Kotler et al. 2003).

In a case study by Tor and Lee (2008), fluoxetine may have induced manic symptoms in a teenage girl with BN. Fluoxetine was discontinued, and valproate 200 mg was initiated to effectively treat both her mood instability and binge/purge symptoms. Dukarm (2005) proposed a possible role for stimulant medication in youth with comorbid BN and ADHD, after two adolescents reported rapid and complete cessation of binge/purge episodes with initiation of dextroamphetamine 5–10 mg three times daily.

Psychotherapy and Pharmacology Combination in BN

The two psychotherapies with demonstrated efficacy in the treatment of BN are CBT (Linardon et al. 2017) and interpersonal therapy (IPT; Fairburn et al. 2009). More recently, dialectical behavior therapy (DBT) has been investigated with some promising results (Hill et al. 2011). While psychotherapy is efficacious for some, only about 30–40% of treatment completers with BN achieve symptom abstinence (Linardon and Wade 2018).

In an attempt to improve outcomes, many clinicians prescribe medications in combination with psychotherapy for BN (Cooper and Kelland 2015). Despite the high numbers of people who are prescribed a combination of medication and psychotherapy, the evidence is lagging. Reas and Grilo (2021) conducted a comprehensive review of RCTs that investigated the use of combined treatment for EDs. For BN specifically, they found 12 RCTS that tested the combination of psychotherapy with 1) appetite suppressants, 2) tricyclic antidepressants, and 3) SSRI antidepressants. There was no benefit to adding an appetite suppressant (D-fenfluramine) to CBT treatment for 43 women with BN (Fahy et al. 1993). Similarly, three separate RCTs examined the combination of tricyclic antidepressants (imipramine or desipramine) with either CBT individual or CBT group therapy and found no additive

effects. For 171 patients with BN, all three active treatments were better than placebo; however, adding imipramine to group therapy offered no additional benefit (Mitchell et al. 1990). For 71 patients with BN, the combination of CBT (individual) and desipramine was only superior to desipramine alone (Agras et al. 1992). For 21 patients with BN, the combination of CBT and desipramine was not superior to CBT alone (Leitenberg et al. 1994).

Eight RCTs examined the combination of SSRI antidepressants with psychotherapy for BN. There was no benefit to adding fluoxetine to an in-patient behavioral psychotherapy program for 40 patients (Fichter et al. 1991). In an RCT with 76 patients, CBT and fluoxetine were superior to fluoxetine alone, but it did not differ from CBT alone (Goldbloom et al. 1997). For 67 patients with BN treated with either nutritional counselling and placebo, or nutrition and fluoxetine, no significant differences were found between the two groups (Beumont et al. 1997). Jacobi et al. (2002) examined the effectiveness of fluoxetine alone, CBT alone, and their combination. Adding fluoxetine did not produce supplementary benefit relative to CBT delivered alone. Walsh et al. (1997) compared two modalities of psychotherapy (psychodynamically oriented therapy and CBT), and added fluoxetine to both conditions if desipramine did not offer effects. Results showed that combining CBT (but not psychodynamically oriented therapy) with antidepressant medication was superior to medication alone.

Two of the RCTs examined the use of guided self-help in combination with medication. For 91 women with BN, researchers tested fluoxetine alone, self-help CBT and fluoxetine, and self-help CBT and placebo. Binge/purge abstinence rates did not significantly differ among the active treatment conditions; however, the self-help CBT and fluoxetine condition had greatest reductions in vomiting episodes (Mitchell et al. 2001). Walsh et al. (2004) tested the effects of guided self-help and fluoxetine in 91 women with BN. No significant differences were found across treatment conditions.

In the largest trial (293 patients with BN), Mitchell et al. (2011) compared standard CBT with a stepped-care condition (self-help first, followed by standard CBT in non-responders). Fluoxetine was added to both groups for non-responders (by session 6). The standard CBT and the stepped-care conditions did not differ at post-treatment, but the stepped-care condition was superior at 1-year follow-up. The stepped-care approach also improved outcomes at the end of treatment for those who had fluoxetine added to their treatment.

Conclusions

Many trials have examined pharmacotherapies for BN, but fluoxetine remains the only approved medication treatment. Although meta-analyses suggest that antidepressants other than fluoxetine have moderate efficacy for treating BN (Svaldi et al. 2019), many of these medications are no longer widely used in clinical practice (e.g., TCAs and MAOIs). Of the non-antidepressant medications studied for BN, topiramate could be considered the only practical alternative to fluoxetine as there

have been two small RCTs supporting its efficacy (Hoopes et al. 2003; Nickel et al. 2005). Topiramate can be prescribed as a second line option, or first line option, especially in patients with affective instability (e.g., borderline personality disorder and bipolar disorder). Of the medications in an experimental phase (see McElroy et al. 2019 for a description of medications in clinical trial phases), stimulants offer an interesting route for further exploration. In their review paper, Keshen et al. (2022) present a rationale for further stimulant-based research based on neurobiology, the relationship between ADHD and BN, and the preliminary evidence from a recent feasibility study (Keshen et al. 2021). The authors also summarize the potential risks of treating BN with stimulants, and based on those risks, do not *currently* recommend stimulants as a treatment for BN, but rather propose specific avenues for future research.

Another area that requires further research is pharmacotherapy in youth with BN. Initiation of effective and safe treatments earlier in the course of illness may prevent disease progression before the symptoms become more compulsive and difficult to treat. Finally, future research should explore how medications can augment psychotherapy, though evidence to date suggests that medications do not provide an additive effect.

Mini-Dictionary of Terms

Androgens. A class of steroid hormones, including testosterone, primarily involved in male reproductive development. While also produced in females, to a lesser extent, and needed for estrogen production, increased levels in females can cause a range of symptoms from excessive hair growth to virilism.

MAOIs. The first class of antidepressant developed. MAOIs prevent the enzyme monoamine oxidase from clearing the neurotransmitters serotonin, norepinephrine, and dopamine from the brain. Less frequently prescribed than SSRIs due to their potential side effects and interactions with other substances.

Open-label trial. An "unblinded" study in which researchers and participants are made aware of which treatment is being administered.

Oxytocin. A peptide hormone produced by the hypothalamus. Synthetic oxytocin is commonly used to induce labor by stimulating uterine contractions.

Prokinetic agent. A class of medications typically used to treat gastrointestinal symptoms, such as dyspepsia. Prokinetic agents work by increasing gastrointestinal motility and increasing the strength of the lower esophageal sphincter.

SSRIs. The most commonly prescribed type of antidepressant. SSRIs prevent serotonin (a neurotransmitter) from being reabsorbed into neurons, which increases serotonin levels in the brain and, in turn, stabilizes mood and increases a sense of well-being.

TCAs. A type of antidepressant that prevents the neurotransmitters serotonin and norepinephrine from being reabsorbed into neurons to increase their levels in the brain.

Key Facts of Pharmacology Options for Bulimia Nervosa

- Fluoxetine can reduce binge/purge frequency and cognitive symptoms of BN and remains the only approved medication to treat the disorder.
- Meta-analyses suggest that other antidepressants may also be effective for treating BN, but many of these medications are no longer being widely used (e.g., TCAs and MAOIs).
- Topiramate can decrease binge/purge frequency and may be most useful in those with comorbid mood symptoms.
- There are other medications (e.g., stimulants) that have preliminary support for BN, but these options are still in experimental phases.
- There is minimal support for using medications to treat BN in youth; however, there is some evidence for using fluoxetine.
- There is minimal evidence that adding medication to psychotherapy enhances the efficacy of talk therapy.

Summary Points

- Psychotherapy is effective for BN, but approximately 40% of individuals remain symptomatic after treatment.
- Therefore, pharmacotherapies have been studied as stand-alone treatments, and adjuncts for psychotherapy, with the goal of improving outcomes for BN.
- Despite many clinical trials aimed at developing medications for BN, fluoxetine remains the only option with regulatory approval.
- Several randomized controlled trials suggest that a dose of 60 mg of fluoxetine can reduce frequency of vomiting, binge eating, and purging, as well as improve eating attitudes and comorbid symptoms of depression relative to a dose of 20 mg and/or placebo.
- While there are fewer RCTs with antidepressants other than fluoxetine, a recent meta-analysis found SSRIs, TCAs, and MAOIs have moderate efficacy for reducing binge eating and purging episodes.
- Of the antiepileptics, topiramate is the most studied as a treatment for BN with two RCTs supporting its efficacy.
- There is emerging evidence supporting the use of stimulants and other experimental medications for BN, but the research is too preliminary to justify recommending these treatments.
- There are observational studies and several case series examining the use of fluoxetine in youth with BN (including an open-label clinical trial).
- Adding pharmacotherapy to psychotherapy does not appear to enhance the effects of psychotherapy alone.

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Linking Embodiment Disorder and Bulimia Nervosa

43

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Contents

Introduction 844
The Lived Body, The Embodied Being 845
Bulimia Nervosa as a Disorder of Embodiment 846
Visceral Interoception 847
Neural Correlates 847
Attachment Style 848
Tempo-spatial Dynamics 849
Embodiment and the Definition of the Self 850
Embodiment and Sexuality 852
Embodiment, Clinical Perspectives 853
Applications to Other Areas 854
Mini-Dictionary of Terms 855
Key Facts 856
References 856

Abstract

In this chapter, we provide an overview of the link between embodiment disturbances and bulimia nervosa. According to the cognitive behavioral perspective, the undue influence of body weight and shape concerns can lead to abnormal eating practices, such as binge eating, frequent body checks, and subsequent compensatory behaviors. In the phenomenological perspective, the classic symptoms of bulimia nervosa, including the overvaluation of body shapes and weight for self-esteem, are epiphenomena of a deeper core nucleus represented by a disorder of the embodiment, which consists in an alteration of the way that people experience their own body and shape their personal identity. According to the optical-cenesthetic hypothesis, the embodiment disorder derives from a disproportion between the optical and the cenesthetic perception of one's body, as a

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consequence of the interoceptive deficits that characterize patients with bulimia nervosa. As an effect of the incapacity to experience one's body from within, patients with bulimia nervosa adopt a maladaptive coping mechanism focused on external means of self-definition, and the body becomes just an object that is looked at by others. The implications of embodiment disturbances regard not just eating behaviors but also many other domains of life in patients with bulimia nervosa, including the evaluation of time or space dimensions and sexuality. Beyond bulimia nervosa, embodiment disturbances were shown to influence body image concerns and sexuality in other clinical samples, as well as in the general population.

Keywords

Cognitive behavioral · Phenomenology · Sexuality · Lived corporeality · Cenesthesia · Optical cenesthetic · Interoception · Exteroception · Attachment · Body image · Bulimia nervosa · Embodiment

Introduction

Bulimia nervosa is defined, according to DSM-5, as a recurrent pattern of binge-eating and subsequent compensatory behaviors. Bulimia nervosa is also described as a disorder with a specific and persistent influence of body weight and shape on the self-evaluation of the individual (American Psychiatric Association 2013). As for anorexia nervosa, in bulimia nervosa, the adoption of compensatory behaviors is secondary to binge-eating episodes, as a feeling of guilt and ruin pervades the individual that has a subjective feedback of inadequacy after interrupting the rigid dietary restrictions pursued. Furthermore, both disorders are characterized by a persistent and undue influence of body weight or shape on the self-evaluation of the individual, which multiple sources highlighted as both the initiating and maintaining factor across eating disorders irrespective of the specific diagnosis (Fairburn et al. 2008). Other similarities are shared between the two disorders, namely, the higher prevalence among females and a common onset during puberty (with rare to null novel presentations after reaching adulthood, American Psychiatric Association 2013). In support of a relevant overlap between these conditions, which may rather represent different phases of the same disorder, research has highlighted a high rate of diagnostic crossover in longitudinal studies (Castellini et al. 2011). In other words, DSM-5 diagnoses for anorexia and bulimia nervosa tend to be unstable and change across time (American Psychiatric Association 2013). Clinically, menstrual irregularities or amenorrhea is commonly found among individuals with a diagnosis of eating disorder, and the causal relationship between hormonal alterations and symptomatic severity is difficult identification (Castellini et al. 2019; Berner et al. 2019). In addition to binge-eating episodes, tentative dietary restrictions, and compensatory behaviors, an additional symptom commonly associated with bulimia nervosa is represented by emotional eating. Emotional eating is

described as the tendency to seek food in response to unpleasant feelings, as a modulation of anxiety, or as a reaction to placate feelings of emptiness and boredom (Stark and Lindeman 2001).

In both disorders, binge-eating episodes are subjectively interpreted not as neutral events in the life of the individual but rather as meaningful indicators of personal inadequacy and incompetence, as the main goal of most individuals suffering from an eating disorder is successfully adhering to dietary restrictions. Even in restrictive subtypes of anorexia nervosa, patients often report a subjective experience of loss of control secondary to food intake (Sassaroli et al. 2008). Dietary restriction itself, while the most recognized symptom of eating disorder, is not considered its core psychopathological feature. On the other hand, it is conceptually theorized to be an epiphenomenon of the underlying cognitive bias found across diagnostic labels, namely, the before-mentioned overreliance on body shape and weight for the appraisal of self-worth (Fairburn et al. 2008). In fact, empirical studies often fail to detect significant differences in the psychopathology of individuals with anorexia and bulimia nervosa, while current nutritional status and degree of adherence to dietary restrictions represent their main difference (Alvarenga et al. 2014). Indeed, nutritional status is a useful clinical observation, as medical and psychotherapy guidelines derive the urgency of their interventions based on both body mass index and overall clinical status of patients (Fairburn et al. 2008).

It should be noted that several theories attempted to elucidate the mechanisms of initiating coping mechanisms oriented to the control of body shape and weight. Primarily, they rely on findings of decreased visceral interoceptive capabilities across eating disorders (Klabunde et al. 2017), as well as reduced haptic response, negative feedbacks to social physical contact, and visual perception disturbances in patients (Engel and Keizer 2017; Engel et al. 2021). For these reasons, a specific disturbance in lived corporeality has been proposed in order to explain the over-evaluation of body weight and shape, as well as the decreased homeostatic response from hunger and physical fatigue.

The Lived Body, The Embodied Being

Embodiment has been broadly defined as the subjective preconscious experience of one's own body (Stanghellini et al. 2012). This definition has its philosophical roots in the work of Jean-Paul Sartre, who wrote about "lived corporeality," distinguishing the *lived* body (i.e., the way people experience their bodies in the first person, which is mainly based on cenesthesia, or common individual sensorium) from the *physical* body (i.e., what is objectively noticeable about one person's body, both aesthetically and anatomically, which is based on sight and measure). It has been hypothesized that people with bulimia nervosa, as well as other eating disorders, experience their own body first as an object looked by another person, rather than cenesthetically or from a first-person perspective. In particular, the main features of this disorder seem to be alienation from one person's own body and emotions, feelings of shame and aversion to it, and a disproportionate worry for the way one appears to the others

(Stanghellini et al. 2015). Phenomenological research has recently highlighted the importance of the gaze of the other in determining the symptoms of eating disorders. Indeed, while normally the constitution of one's own body (and consequently of one's own self and identity) depends on the dialectic integration between the *lived* body and the *physical* body, people with bulimia nervosa have difficulties in experiencing their own body from within or from the cenesthetic; for this reason, they tend to understand it from the perspective of another person (the so-called lived body for others, Mancini and Esposito 2021). When the dialectic is unbalanced toward the pole of the lived body for others, experienced from without, the symptom occurs (Mancini and Esposito 2021). Embodiment shows a complex interplay between the preconscious appraisal of one's own body and the conscious experience of it. In fact, embodiment is characterized as a significant factor in influencing cognition (Edelman 2005), perception (Nathan et al. 2021; Tversky and Hard 2009; Witt et al. 2009), memory (Dijkstra et al. 2007), and affective state (Damasio 1999).

As a primary alteration in embodiment is found in individuals with a diagnosis of bulimia nervosa, all behaviors and psychopathological correlates of the disorder can be better appreciated as compensatory strategies adopted to reduce the distress relative to insecurity and distrust toward one's body.

Bulimia Nervosa as a Disorder of Embodiment

According to a line of research embedded in phenomenology, the main features of bulimia nervosa (represented by shape and weight concern) are actually the result of a deeper alteration in the lived corporeality of these patients, a disturbance in embodiment (Castellini et al. 2014). In particular, embodiment alterations may be elicited by bodily modification experiences during puberty and adolescence, as the individual has a first subjective experience of significant physical changes (Striegel-Moore et al. 2001). This first occurrence may be lived with particular distress, as secondary sexual characteristics emphasize both body weight and body shape modifications (Corcos et al. 2000). Puberty can therefore be the first lived and cognitively conscious experience of a body that changes, in which the individual does not recognize its true self. In fact, embodiment has been observed to be significantly shaped and modified by puberty in women and girls (Piran 2016). The development of distress secondary to body changes can be conceptually assessed through two main factors: the biological components and the social environmental characteristics. For what concerns these components, most of the literature focused on body image disturbances rather than embodiment disturbances. Although both concepts apply to the body, the first is the conscious representation of one's own appearance, shape, and the weight, and embodiment is the actual lived experience of it (McBride 2018). For what concerns lived corporeality in bulimia nervosa, researchers mainly converged on the subsequent features:

Visceral Interoception

Abnormal bodily phenomena have been observed to represent a significant clinical feature of bulimia nervosa; this category pertaining to body image disturbances embraces various concepts relative to negative body image, such as body dissatisfaction, avoidance, or, on the contrary, compulsive control of one's body associated with pervasive worries about specific body parts, shapes or functions, and depersonalization (Cuzzolaro et al. 2006). These symptoms seem to be related to a psychopathological core (called *body image disturbance*) that often anticipates the onset of pathological eating behavior and persists even after its remission (Eshkevari et al. 2014), being associated with a worse prognosis and a higher risk of relapse (McLean and Paxton 2019). However, while scholars have traditionally focused on problems with body experience and visual alterations (such as seeing oneself fat while being significantly underweight), more recent research pointed out that those visual alterations involve something more complex than just a sensory deficit. Firstly, in support of the notion that sensory deficits underlie alterations in body image, the degree of body dissatisfaction was found to be directly proportional to deficits in proprioception and tactile perception (Eshkevari et al. 2012; Fontana et al. 2009). Secondly, these patients have been reported to often report poor interoceptive awareness (Jenkinson et al. 2018). In addition to sensory deficit, the conscious appraisal of visceral stimuli (such as the physical sensation of heartbeat, temperature, intestinal tension, hunger, and pain) could also be elicited by feelings and emotions. By now, several studies have documented that patients with bulimia nervosa often have difficulties in discriminating visceral perceptions related to hunger and satiety with sensations determined by emotional arousal (Khalsa et al. 2022). These results could represent a rational basis to explain why these patients exhibit more often than the general population signs of emotional noncompetence, such as emotion dysregulation, alexithymia, and impulsivity. According to the optical-cenesthetic hypothesis (Stanghellini et al. 2019), these deficits in the capacity to experience one's own body from within force patients to adopt maladaptive mechanisms to define the self, in particular for what concerns the perceptual (e.g., visual, haptic) and identity boundaries (e.g., core beliefs, core values) between the self and the other (Stanghellini et al. 2019). As a consequence of the impaired cenesthesia, the gaze of the others becomes a device for self-definition, and the body becomes just an object to be looked at by the others. Living one's own body, the *lived body*, or *body as subject*, as a function of the gaze of the other, and the *lived body for others*, or *body for others*, is then appreciated as a tentative resolution for embodiment disturbances at the basis of the preconscious feelings of anguish and alienation from one's own bodily experiences (Fuchs 2022).

Neural Correlates

Bulimia nervosa has been associated with modification of basal metabolism in specific regions of the brain, such as the striatum, which pertains to the reward

system (Broft et al. 2012). These findings support the hypothesis that reward sensitivity might underlie the symptomatology of bulimia nervosa. However, other brain structures have been shown to exhibit alterations in functional connectivity for bulimia nervosa, namely, the anterior dorsal cingulate cortex and the medial prefrontal cortex (Stopyra et al. 2019). These two structures pertain to the salience and default mode brain network, respectively, which are involved in salience attribution, self-referential processing, and cognitive control. Furthermore, investigations of neural correlates of body image dissatisfaction highlighted a relevant contribution by functional and structural alterations in the insular cortex (Mohr et al. 2011), which other sources described as relevant for the processing of interoceptive stimuli (Kuehn et al. 2016), reward (Monteleone et al. 2017b), and decision-making (Naqvi and Bechara 2010). Therefore, the insula seems central to an effective integration of visceral sensations, environmental factors, and emotional awareness (Simmons et al. 2013), which establishes the insular cortex as a relevant landmark for the embodiment of the self (Stanghellini et al. 2019), and with early evidence of functional and structural alterations in bulimia nervosa. Furthermore, embodiment disturbances in bulimia nervosa also entail internal perceptions of one's own body, the sensation coming from within one's own body. Neuroimaging evidence suggests that both body image and bodily self-consciousness are impaired in patients with bulimia nervosa, with findings of decreased integration between interoceptive and exteroceptive signals (Stanghellini et al. 2019). In particular, visual afferents appear to predominate over interoceptive stimuli, which favors the adoption of an objective stance toward one's own body as a mechanism to cope with the reduced feelings from within (Riva et al. 2015). A lived corporeality based on objective, external appraisal then can ensue, as a maladaptive mechanism in order to compensate visceral and interoceptive afferent deficits. These observations seem to confirm the optical-cenesthetic model previously described. In fact, deficits in integrating the perceptual experience from within (by the insular cortex) can also inhibit the functional coalescence of interoception, exteroception, and mental layers (as processed by the same brain region, Scalabrini, Wolman, and Northoff 2021; Simmons et al. 2013; Kuehn et al. 2016; Riva et al. 2015).

Attachment Style

Attachment styles seem to be of particular interest for what concerns embodiment. In fact, the relationship between attachment and embodiment can be understood in light of an alteration in preconscious subjective experiences of one's body as the most primitive form of self-awareness, acquired during the first interactions with the primary caregiver (Stanghellini et al. 2012; Needham and Libertus 2011). Moreover, the phenomena of attachment and emotional regulation are relevant for the development of a basic form of selfhood during early childhood. Higher levels of embodiment disturbances were observed in patients with anxious or avoidant attachment, and embodiment disturbances mediated the relationship between avoidant attachment and the eating disorder psychopathology (Monteleone et al. 2017a).

According to attachment theory, avoidance is defined as the tendency to distract oneself from emotional contents, which in time results in a reduced capacity to recognize and regulate internal feelings (Fuendeling 1998). This reduced capacity to recognize and moderate feelings appears not to be specific to the affective domain. In fact, patients with bulimia nervosa are observed to be less prone to correctly identify basic bodily signals such as hunger, satiety, and fatigue. Dysfunctional attachment styles are thus associated with a greater susceptibility to exteroceptive signals about the body, rather than interoceptive, and with a higher reliance on bottom-up attentional processes (Eshkevari et al. 2014). Furthermore, worse symptomatic presentations and clinical outcomes have been observed in those individuals with insecure attachment styles (Tasca and Balfour 2014). Significant bodily changes can also precipitate bodily distress secondary to physical or sexual traumatic experiences (Meneguzzo et al. 2021). The body can be the source of constant reminders of a traumatic past, and the persistent state of alertness in traumatized individuals facilitates the misinterpretation of even the most innocuous stimulus as a potential threat (van der Kolk 2015).

Tempo-spatial Dynamics

Patients with bulimia nervosa often report subjective feelings of fatness and heaviness. In addition to feelings directly associated with body shape and weight, patients describe a less defined sensation of "largeness" or distention. Their visual and spatial capacities are often characterized by a high degree of imprecision, and their ability to correctly estimate temporal or spatial dimensions seems to be impaired (Li et al. 2015). Lower abilities to shift between tasks and conditions have also been reported. This lower degree of cognitive flexibility can be conceptualized as the result of an altered perception of time. Some studies found that while time duration might be subjectively underestimated by individuals affected by anorexia nervosa, this is not the case for patients with bulimia nervosa. For this reason, restrictive subtypes of anorexia nervosa show an increased capacity to delay reward compared to individuals with bulimia nervosa or binge-eating disorder, as the first can discount a lower subjective time span (Vicario and Felmingham 2018). This disparity between subtypes is possibly related to differences in dopaminergic neurotransmission (Fung et al. 2021). Impairment in time perception, a critical component of decision-making, represents a crucial factor for the development and maintenance of binge-eating episodes through the enhancement of impulsivity (Mitchell et al. 2018).

For what concerns the spatial domain, early observations described how body schema can affect spatial perception and the perception of objects. Physical exercise, dance, or other tasks involving neuromuscular coordination have been found to shape the subjective appraisal of one's body, both during and after conditioning. Additionally, as an individual gains strength and endurance, a higher perceived self-efficacy can ensue. The lived body can thus be thought of as a dynamic system, undergoing constant change in all its components: from its preconscious awareness to its objective functioning and its subjective correlates. In bulimia nervosa,

mindfulness-oriented activities (e.g., yoga) have been found to facilitate a positive assessment of one's own body and to provide long-sought comfort in critical body areas (such as the lower abdomen, or thighs), as focusing on breathing or posture can reduce the level of distress experienced by these patients and establish a positive cycle of reinforcement learning toward one's own body (Perey and Cook-Cottone 2020). However, while approaches based on *positive embodiment* have been described (Cook-Cottone et al. 2020), *embodiment* rooted in negative affect consistently dominates the experiential landscape of individuals with bulimia nervosa. Spatial relationships with one's own body parts produce intense fear, a subjective feeling of vulnerability, and a high degree of disgust (Clancy 2022). A sense of alienation from one's body is often reported, which, in addition to visceral or interoceptive afferent alterations, can be conceptualized as a result of repeated insecurities experienced by or from one's body. This is the example of those patients where bulimia nervosa is deeply intertwined with histories of trauma, as the fear of exposure and unsafety can dominate the lived corporeality of individuals (Madowitz et al. 2015; Vanderlinden et al. 1993).

Embodiment and the Definition of the Self

Finally, it is well recognized that a significant proportion of patients with a diagnosis of eating disorder tends to develop chronic and ego-syntonic symptoms. Individuals with a diagnosis of eating disorder often have difficulties to define themselves through ordinary life domains, even before the onset of the disorder. These difficulties can be interpreted in light of the optical-cenesthetic model, according to which patients engage in external modes of defining themselves as a response to interoceptive deficits. In other words, this external definition of one's self, through compulsive body check, control over weight or food, starvation, or the gaze of the other, can be a response to an underlying embodiment disturbance (Stanghellini et al. 2012). Patients with embodiment disturbances can then engage in maladaptive habits in order to define one's self, since customary boundaries of one's own self are less detailed (*perceptual*, such as visual/haptic stimuli about one's own body, or *identity-based*, as answering fundamental questions on core beliefs or values) (Stanghellini et al. 2019). Moreover, patients with bulimia nervosa tend to value personality aspects such as perfectionism, rigidity, and control and frequently suffer from subjective or objective feedbacks of their deficit in these values (Silgado et al. 2010; Boone et al. 2012; Steele and Wade 2008). Episodes of restriction or binge eating may be interpreted cognitively in function of these values, as positive or negative feedbacks, respectively. These premises mean that patients with bulimia nervosa often value the thoughts and behaviors associated with their illness as aligned with their core selves. Especially when ill for extended periods of time, people can become stuck in a sick role, reinforcing a sense of self that is dominated by illness ("Who am I? I am my disorder"). In this picture, efforts made to achieve and maintain harsh diet rules and caloric restriction tend to enhance the marginalization of alternative domains of life. Hence, identification with the disorder acts as a

mechanism of avoidance to escape the doom of defining one's self through other life domains (Koskina and Schmidt 2019).

One of the core negative feelings experienced by patients with bulimia nervosa is shame. Shame is commonly experienced only as a function of social relations, as the resulting emotion subsequent to moral or social expulsion (Tracy and Robins 2007). However, patients with bulimia nervosa experience a more general and intimate feeling of shame, that of "wrongly" being, in general (Clancy 2022). Furthermore, patients with bulimia nervosa tend to exhibit particularly pronounced negative cognitive biases in their internal self-talk, such as overgeneralization, with the result that any perceived "failure" is interpreted as a confirmation of low self-worth (Fairburn et al. 1993). This tendency to negativity in the conversation with oneself worsens the core low self-esteem that most patients with bulimia nervosa have, with the result of an inhibition in the exploration of different domains of life. The relative scarcity of life experience in different domains, such as a wide range of interests, reinforces a cycle of negative self-appraisal, suffering the comparison with peers or significant others. For these reasons, fatness and failure acquire a specific moral value in bulimia nervosa, as the main domain in which the patient feels control and self-efficacy (Skårderud 2007).

Moreover, embodiment can refer to two distinct processes, simultaneous and synergic, that is, the phenomenon of being a living being, *being embodied*, and being a living being in a living society, *embodying the social aspect of human nature* (Tolman et al. 2014). While the first focuses on the experiential process of being both consciously aware and unconsciously influenced by one's own body, the second entails the social and historical implications of lived corporeality. This second aspect of corporeality, that is, being alive for others, with others, as a function of others, either as an active agent or as a passive medium, can either empower or isolate individuals, with a special interest by society on normalizing ways of being, ways of feeling, and ways of thinking (Foucault 1978). Thus, social components impose direct or indirect demands on individuals, potentially marginalizing those lived bodies that do not conform to societal standards. The high distress experienced by patients with bulimia nervosa to conform and seek social assessment can then be appreciated as a mechanism to pursue reintegration into a "standard" (Eli 2018). Cultural influences are also thought to influence the interaction between embodiment and personal identity, in line with a social constructionist perspective of lived corporeality (Musolino et al. 2020; Becker 2004). The socially derived concept of "femininity" seems to be relevant for the disturbances observed in bulimia nervosa (Musolino et al. 2020). In particular, "femininity" can be deflated to a simple concept of beauty and a reference to a standardized canon, with adolescent girls actuating mimic behaviors in order to obtain competitive advantages during a period of rapid social transitions (Becker 2004). To be noted, ritualized social practices and social influences seem to shape embodiment and its disturbances, as the collective imaginary and conceptual background aligns individual perceptions and behaviors to social normative types in a cognitively driven but preconscious manner (Durkheim and Cladis 2008; Bell 2009).

In light of the importance of restructuring one's identity around the control of one's shape and weight (Ip and Jarry 2008), the IDentity and EAting disorders (IDEA) questionnaire has been proposed (Stanghellini et al. 2012) to assess alterations in embodiment and personal identity. The IDEA questionnaire can identify significant psychopathological phenomena related to bulimia nervosa, such as the need to define oneself objectively through the gaze of the other or through objective measurements (e.g., weight scale, social media), feeling extraneous from one's own body, or feeling oneself predominantly through starvation. Importantly, IDEA was able to discriminate not only between patients and controls but also capable of identifying vulnerable individuals (Stanghellini et al. 2015).

Embodiment and Sexuality

Beyond psychiatric disorders, embodiment seems to be relevantly involved in sexuality and its functioning in the general population. In fact, the link between body image and sexual well-being is increasingly investigated in scientific and psychological research; recent studies hypothesized that disturbances in body image or embodiment may play a significant role in maintaining abnormal sexual functioning among women and men (Cash 2012). Although most of the research focused on the influence of intrusive thoughts and body image disturbances on sexuality (such as concerns about body weight and shape during a sex), recent approaches elucidated how, in turn, cognition itself can be shaped by sexuality. For instance, arousal has been observed to associate with higher rates of delay discounting, as well as higher propensity to risk-taking behaviors (Wilson and Daly 2004; Skakoon-Sparling et al. 2016). An embodied mind, integrating bodily stimuli with affective or cognitive content, thus seems to mediate sexuality, and an account of a lived corporeality seems to better describe human behaviors and thoughts in comparison to previous approaches (Tolman et al. 2014). In particular, social constructs have progressively interested scholars in the field, with ongoing debates on their role in shaping sexual desire, sexual identities, and sexual relationships (Angel 2010). Novel methods allowed promising findings on the topic, and the concept of "natural," "innate," or "true self" also emerged when describing the lived experience of sexuality (Plante 2006). This more contemporary approach is characterized by a complex definition of the *experienced* and *experiencing body*, defined as the outcome of multiple concurrent demands, in other words an embodied entity. In sexuality, both feelings of disembodiment and generalized shame can be observed in patients with bulimia nervosa. While the first has been more commonly reported in association with previous traumatic experiences, with dissociative or depersonalization episodes during sexual intercourses, impulsiveness can partially explain, and the pursuit of self-harming practices partially underlie, sexual promiscuity and risk-taking behaviors in bulimia nervosa (Swirsky and Mitchell 1996; Castellini et al. 2019). Recent research has also focused on the relationship between dietary restraint and reduced sexual desire and found that embodiment alterations significantly explained their association (Cassioli et al. 2020). These alterations in lived

corporeality, specifically impairments in interception, identity focus on dysfunctional eating behaviors, and the adoption of a third-person perspective in defying oneself, can integrate in predisposing to disturbing experiences during sexuality, with feelings of loss of control, objectification, lack of pleasure, shame during the encounter, and ultimately feelings of coercion or passivity (Castellini et al. 2016; Moradi et al. 2005; Spivak-Lavi and Gewirtz-Meydan 2022).

Embodiment, Clinical Perspectives

According to clinical guidelines, at the present time, only two types of therapies seem warranted in bulimia nervosa (NICE guideline [NG69] 2017), namely, family-focused interventions (Zipfel et al. 2014), and cognitive behavioral therapy – enhanced (CBT-E, Fairburn et al. 2008). Family-focused interventions focus on disrupting the family dynamics supporting and triggering eating symptoms (Zipfel et al. 2014). On the other hand, in CBT-E therapy, the aim is to disturb abnormal behaviors by challenging distorted beliefs about body shape and weight (Fairburn et al. 2008). CBT-E has shown evidence in superiority in comparison to the former type of interventions (Zipfel et al. 2014). However, there is high variability in individual responses, long-term remission rates are currently attested below 50%, and a high relapse rate has also been observed (Calugi et al. 2017). Therefore, targeting embodiment disturbances in bulimia nervosa, as well as in other kinds of eating disorders, can be expected to deliver promising results. Indeed, since a disturbance in lived corporeality can represent a core feature in these disorders, integrating ordinary clinical practice with specific embodiment-focused psychotherapeutic treatments could be crucial to improve prognosis in this category of patients (Rossi et al. 2021). In fact, empirical studies showed that in a multidisciplinary treatment of eating disorders, built on a CBT-E foundation, the variation of embodiment disturbances correlated to response to therapy (Rossi et al. 2021). To target these disturbances effectively, an approach that incorporates cognitive, psychodynamic, and phenomenological perspective seems warranted (Castellini et al. 2022). This integration could lead to a new psychotherapeutic model of intervention, directed not only toward the behavioral, cognitive, and ideational domains of eating psychopathology but also to the emotional, experiential, perceptual, and identity-related domains, which contribute to a large extent to the maintenance of illness (Castellini et al. 2022). In pursuit of this integration, a number of prescriptions for clinical practice derive from considering embodiment disturbances as the basis of bulimia nervosa. First and foremost, the initial assessment of patients should include an evaluation of the subjective lived experience, in order to overcome the limitations given by behavior-informed diagnoses (Stanghellini 2019). All dimensions of corporeality should be assessed: the *lived body*, or the *body as subject*; the *objective body* as appraised by sight or haptic feedback, or the *body as object*; and the body as lived by the *gaze of the other*, or the *body for others* (Fuchs 2022). Therapeutic approaches should be focused on all three of these dimensions of corporeality; in particular, clinicians should inform behavioral counseling based on the dynamic

changes in corporeality in correspondence to binge-eating episodes or compensatory practice (Castellini et al. 2022). In other words, changes in these dimensions of corporeality could efficaciously function as a functional access to otherwise unapproachable internal states of emotions, feelings, or beliefs (Nowakowski et al. 2013). Deficits in interoception should be specifically targeted. Indeed, the recovery of a healthy but critical appraisal of inner bodily signals could represent the first step in the complicated process of recovering a more functional contact with one's own body (Castellini et al. 2022). Furthermore, the impact of the gaze of the other and of defying one's own identity in adherence to an eating disorder should not be underestimated (Stanghellini et al. 2012). Recovering a healthy contact with one's own embodiment can facilitate the redefinition of one's own desires and values, allowing the patients to overcome the definition of one's own self strictly according to illness (Koskina and Schmidt 2019). In this field, new therapeutic interventions might be promising (Stanghellini 2019). Trauma-focused interventions should be implemented in selected patients, taking into account the decisive role of adverse childhood experiences and insecure attachment styles in the development of embodiment disturbances (Swirsky and Mitchell 1996; Madowitz et al. 2015). In conclusion, future developments could enhance recovery rates and reduce clinical relapses, overcoming the limitations of existing treatments, by taking the experience of patients into account in a single, multidimensional model of psychopathology and treatment.

Applications to Other Areas

In this chapter, we described the role of the embodiment disorder in the phenomenology of bulimia nervosa. However, the evidence about this psychopathological dimension shows that the alteration of lived corporeity is a transdiagnostic phenomenon in eating disorders, regardless of clinical subtype (Castellini et al. 2014). Because of that, it has been hypothesized that the different types of eating disorders are, in fact, epiphenomena of a common psychopathological core, represented by an optical-cenesthetic disproportion (Stanghellini et al. 2019). The inability to "feel oneself" seems to be a peculiar characteristic of these illnesses when compared to other psychiatric disorders. The different patterns of coping mechanisms implemented in response to this deficit shape their behavioral and clinical presentation (e.g., starvation as a way to feel oneself in restrictive subtypes of anorexia nervosa or binge eating in bulimia nervosa and binge-eating disorder). This model is also consistent with the high rates of diagnostic crossover and symptom fluctuation that occurs longitudinally in patients with eating disorders (Eddy et al. 2008). Furthermore, we must emphasize that the notion of embodiment is not limited to the field of eating disorders. For instance, embodiment disorders seem to be associated with emotional eating, a phenomenon often reported not just by patients with eating disorders but also by obese subjects, as well as patients with mood or anxiety disorders (Ricca et al. 2009). Moreover, embodiment disturbances can also be observed in other mental disorders, such as schizophrenia and depression. However,

previous research and clinical experience have demonstrated that, while the embodiment disturbance reveals itself in the context of eating disorders as an optical-cenesthetic disproportion, this is not the case for other disorders. For example, the essential characteristic of the alterations in lived corporeality for patients with schizophrenia has been called "disembodiment." Patients with schizophrenia experience their body as a de-animated object, losing the overarching sense of "personally belonging" to their embodied experience (Stanghellini 2009). In other words, patients with schizophrenia lose the ability to represent themselves from a first-person perspective (Doerr-Zegers et al. 2017). On the contrary, patients undergoing depressive episodes or suffering from a depressive disorder preserve the capacity to feel their body as their own from a first-person perspective, but they tend to represent it as an object from within (as their own objectified body). This feature, which has been called "objectification" or "corporealization," would be the causative phenomenon explaining the reduction of the body's feelings of being alive (Doerr-Zegers et al. 2017).

Therefore, the characterization of embodiment becomes of fundamental importance in the assessment of most mental disorders. The presentation of embodiment disturbances between disorders can vary and may sometimes overlap in their characteristics, determining the complex pathway of symptoms and clinical presentations in each different person. Although current practice suggests using the concept of comorbidity to explain the concurrent existence of these psychopathological features, an alternative explanation could be that the specificity and boundaries between the described disorders are not lacking; rather, they depend on the level of assessment. At last, adopting a phenomenological perspective to explore the core of lived experience in these patients reminds us that, while the behavioral level is certainly useful in informing clinical practice and research, estimating clinical severity in an objective and replicable manner, it may not adequately inform individual etiology, prognosis, or therapeutic outcomes, hence the need for integrated and multidimensional models, even beyond the boundaries of disordered eating.

Mini-Dictionary of Terms

- **Attachment style**: The systematic pattern of interpersonal expectations, emotions, and behaviors that result from the internalization of previous relational experiences, with the consequent reliance on a specific strategy to regulate emotions (Fraley and Shaver 2000; Shaver and Mikulincer 2002). For further information on the importance of the functional imprinting of early attachment experiences, as well as the role of adult attachment style in eating disorders, see the other chapters in the current book and the references offered in the present chapter.
- **Body image** is a complex construct that is often used in the clinical context to evaluate the patient's perception of its own corporeality. It is described as "the mental picture one forms of one's body as a whole, including its physical

characteristics and one's attitude toward them" (APA Dictionary of Clinical Psychology 2013). Body image encompasses thoughts, feelings, evaluations, and behaviors toward one's own body, which may range between positive and negative experiences, under the influence of both internal (e.g., personality) and external (e.g., social environment) factors (Tylka and Wood-Barcalow 2015; Tiggemann 2004). There are four fundamental aspects of body image: *perceptual*, the aspect that is about the way one person sees his own body; *affective*, the aspect that concerns the degree of satisfaction or dissatisfaction one person feels about his body shape, weight, or individual body parts; *cognitive*, the aspect that is about the way one person thinks about his own body and can lead to excessive preoccupation about body shape and weight; and *behavioral*, which embraces the behaviors that one person engages in as a result of his perceived body image (e.g., starvation as a way to cope with the persistent sensation of being fat). Body image misperceptions are the result of an alteration of one (or more) of the main elements described above; they represent the core component of body image disturbance and could be present in various types of psychiatric disorders, as well as, at a subclinical level, in healthy subjects (Fuentes et al. 2013).

Key Facts

- Bulimia nervosa is a severe psychiatric disorder, characterized by a disproportionate influence of body weight and shape on the self-evaluation of the individual.
- The undue influence of body weight and shape concerns leads to abnormal eating behaviors such as binge eating and vomiting.
- The onset and course of bulimia nervosa are determined by both biological and psychosocial factors.
- Embodiment disorder is a crucial primary alteration in individuals affected by bulimia nervosa.

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Treating Adolescent Bulimia Nervosa

44

An Overview

Sasha Gorrell, Leigh Brosof, Lisa Hail, and Daniel Le Grange

Contents

Introduction 864
BN Diagnostic Criteria 865
Prevalence, Onset, and Demographics 866
Transdiagnostic View of BN 866
Comorbidity 867
BN Treatment 868
Other Promising Avenues for Psychotherapy Treatments in Youth 873
Pharmacotherapy for BN 874
Treatment Moderators 874
Research and Clinical Future Directions 877
Summary/Conclusions 880
Applications to Other Eating Disorders 880
Mini-Dictionary of Terms 881
Key Facts of Treatment for Bulimia Nervosa 881
Summary Points 882
References 882

Abstract

In this chapter, we provide a broad overview of the treatment of bulimia nervosa among adolescents. First, we describe the disorder prevalence and diagnostic criteria, along with commonly comorbid conditions. We then detail evidence regarding the most efficacious treatments for this disorder and some treatments that show promise and warrant further investigation. Finally, we provide discussion of challenges associated with the treatment of bulimia nervosa among youth and suggest future directions in clinical practice and research.

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Keywords

Eating disorders · Bulimia nervosa · Family-based treatment · Adolescents · Adolescent eating disorders · Cognitive-behavioral therapy · Anorexia nervosa · Restrictive eating · Purging · Compensatory behavior

Abbreviations

ACT	Acceptance and commitment therapy
AN	Anorexia nervosa
ARFID	Avoidant-restrictive food intake disorder
BN	Bulimia nervosa
BED	Binge eating disorder
CBT	Cognitive-behavioral therapy
CBT-E	Cognitive-behavioral therapy enhanced for eating disorders
DBT	Dialectical behavior therapy
DBT	Dialectical behavioral therapy
DSM	*Diagnostic and Statistical Manual of Mental Disorders*
ED	Eating disorder
EDE	Eating disorder examination
EDE-Q	Eating disorder examination-questionnaire
EDNOS	Eating disorder not otherwise specified
EOT	End of treatment
FBT	Family-based treatment
IPT	Interpersonal therapy
ICAT	Integrative cognitive-affective therapy
OSFED	Other specified feeding or eating disorder
RCT	Randomized control trial
RO-DBT	Radically open dialectical behavior therapy
SPT	Individual supportive therapy

Introduction

Bulimia nervosa (BN) is a serious psychiatric disorder that typically has a chronic course of illness (Steinhausen and Weber 2009) and multifactorial etiology (American Psychiatric Association 2013). Accounts of binge eating and purging behavior reach all the way back to Greek and Roman antiquity, and also appear in recorded practices of saints in the Middle Ages (Gordon 2015). Current conceptualizations of the disorder in this century date from 1979, when Gerald Russell first published an account of BN, in which he described patients reporting a "morbid fear of becoming fat" who overate and purged afterward (Russell 1979). Individuals with BN typically do not present as underweight relative to population norms for age, height, and gender (American Psychiatric Association 2013). And yet, eating disorder (ED) pathology and medical complications for youth with BN can be severe

(Peebles and Sieke 2019) with striking levels of suicide (Crow et al. 2014) and psychological comorbidity (Thompson-Brenner and Westen 2005).

To date, less is known about treating BN in youth compared to adults, where findings across the literature support the efficacy of outpatient psychotherapy, and in particular, evidence-based treatments such as cognitive-behavioral therapy (CBT) (Lundgren et al. 2004). For youth and adolescents with BN, the current evidence base principally supports family-based treatment (FBT) (Le Grange et al. 2015; Lock and Le Grange 2019) and CBT enhanced for EDs (CBT-E) (Dalle Grave et al. 2013; Le Grange et al. 2020). Given the severity of this disorder, and the pressing need for early identification and intervention for this patient population, this chapter is focused on BN in youth and adolescence. First, we describe the clinical syndrome and its diagnostic criteria, with associated prevalence rates. This is followed by a description of current evidence-based treatment approaches, along with newer intervention efforts that are promising and warrant further investigation to determine their relative efficacy. Finally, we highlight future research directions that may help to determine where our resources should ideally be devoted to improve treatment outcomes for this high-priority clinical population.

BN Diagnostic Criteria

According to the latest edition of the *Diagnostic and Statistical Manual for Mental Disorders* (DSM-5; American Psychiatric Association 2013), BN is characterized by (1) episodes of eating an objectively large amount of food accompanied with a loss of control (i.e., objective binge eating), (2) inappropriate compensatory behaviors, as well as (3) overvaluation of weight and shape that unduly influences self-evaluation (American Psychiatric Association 2013). Compensatory behaviors may include purging (i.e., self-induced vomiting, laxative or diuretic misuse) or non-purging behaviors (i.e., excessive exercise, or significant restriction behaviors, such as fasting and skipping meals), which are symptoms that do not occur only within the context of anorexia nervosa (AN).

According to DSM-5 criteria, both binge eating and compensatory behaviors must occur at least *once per week* for a period of 3 months (American Psychiatric Association 2013). This frequency requirement was changed from DSM-IV-TR criteria, which required both binge eating and compensatory behaviors to occur at least *twice a week* for a period of 3 months (American Psychiatric Association 2000). Diagnosis is usually determined through clinical interview and self-reported symptoms by the patient, in conjunction with parental report of their observations. Due to the shame and secrecy associated with bulimic behaviors (Bottera et al. 2020), symptoms may be underreported and prevent treatment-seeking. In addition, adolescent patients may have more difficulty endorsing cognitions associated with BN (i.e., undue influence of weight and shape) compared with other EDs that are characterized by low weight such as AN (Le Grange et al. 2004; Le Grange and Loeb 2007), which may potentially further hinder determination of a diagnosis.

Prevalence, Onset, and Demographics

Prevalence estimates for BN vary widely based on whether studies have focused on those who meet full-threshold criteria versus those who fall below diagnostic threshold but have clinically significant presentations. In adolescents, estimates for full-threshold BN fall between 1% and 1.5% (Smink et al. 2012), whereas estimates that include subthreshold presentations fall between 14% and 22% (Swanson 2011). Prevalence of BN in adolescents is twice that of AN (Swanson 2011), and diagnostic crossover is relatively common (Eddy et al. 2008). It should be noted that many of these studies are based on DSM-IV-TR, rather than DSM-5 criteria, and thus these rates may underestimate the prevalence of BN. More recent studies applying DSM-5 criteria found that lifetime prevalence of BN falls between 2.4% and 2.6% (Stice et al. 2013; Bagaric et al. 2020; Silén et al. 2020), and in adolescents specifically, point prevalence is estimated at 4.6% (Mitchison et al. 2020).

According to DSM-IV-TR criteria, the median age of onset for BN is in preadolescence: 12.4 years (interquartile range 11.1–13.5 years) (Swanson 2011). A more recent meta-analysis of 8 epidemiological studies identified peak onset of BN at 15.5 years old (Solmi et al. 2021). In the United States, lifetime prevalence rates of BN are similar among different racial and ethnic groups, although Hispanic women may be at slightly higher risk for disorder development (Nicdao et al. 2007; Levinson and Brosof 2016). Prevalence estimates by gender show a lower rate for boys (1.21%) compared to girls (2.6%) (Bagaric et al. 2020). However, transgender individuals are at higher risk for developing BN (2.9–3.2%) compared to cisgender peers, and sexual minorities have also been shown to have higher lifetime prevalence rates than their heterosexual counterparts (Nagata et al. 2020; Kamody et al. 2020).

Transdiagnostic View of BN

BN has more similarities than differences with other ED presentations (e.g., Forbush et al. 2017). For instance, binge eating and purging are symptoms that may be characteristic of other ED diagnoses, including AN binge-purge subtype, atypical AN (i.e., meeting all criteria for AN except underweight BMI), and other specified feeding or eating disorder (OSFED) (American Psychiatric Association 2013). Further, diagnostic crossover between disorders is common, particularly between subthreshold and full-threshold BN in adolescents (Le Grange et al. 2004; Le Grange and Loeb 2007).

Subthreshold presentations may include not meeting the frequency criteria (i.e., one binge eating episode and compensatory behavior per week; American Psychiatric Association 2013). Individuals with subthreshold symptoms endorse similar levels of impairment to individuals with full-threshold symptoms (Le Grange et al. 2004) and thus should be treated similarly. Another common subthreshold presentation is the presence of subjective binge eating, where individuals endorse loss of control around eating but do not eat an objectively large amount of food (American Psychiatric Association 2013). Particularly among children and

adolescents, psychological impairment stems from the experience of loss of control, rather than amount of food consumed (Tanofsky-Kraff et al. 2011). Individuals with subjective binge eating endorse a similar frequency of binge eating and purging episodes as those with objective binge eating (Le Grange et al. 2004). Given that interventions for binge eating and purging behaviors generally appear the same regardless of diagnosis (Fairburn 2008), it may therefore be clinically useful to consider and treat symptoms transdiagnostically, rather than maintaining focus on a specific diagnosis.

Comorbidity

The vast majority of cases of BN present with a co-occurring psychiatric disorder, up to 88% (Hudson et al. 2007). The most common comorbid disorders are anxiety (66.2%) and mood (49.9%) disorders (see Fig. 1 for more information about BN comorbidity). In addition, 20% of adolescents with BN also endorse misuse of substances (Calero-Elvira et al. 2009) as well as attention-deficit and hyperactivity disorder (Seitz et al. 2013). It should be noted that these rates of comorbidity are based on DSM-IV-TR diagnostic criteria and thus may underestimate true rates of overlap. In a study of adults with DSM-5 EDs, lifetime estimates of BN and comorbid psychiatric disorders were 94.4%, with major depressive disorder (76.3%) and alcohol use disorder (61.0%) recorded most frequently (Udo and Grilo 2019). It is imperative that new prevalence studies using DSM-5 criteria continue to investigate rates of comorbidity in adolescents with BN, as the presence of a co-occurring disorder is associated with longer duration of illness, poorer outcomes, and increased psychosocial impairment (Fichter et al. 2008; Bodell et al. 2011; Quadflieg and Fichter 2019; Van Alsten and Duncan 2020).

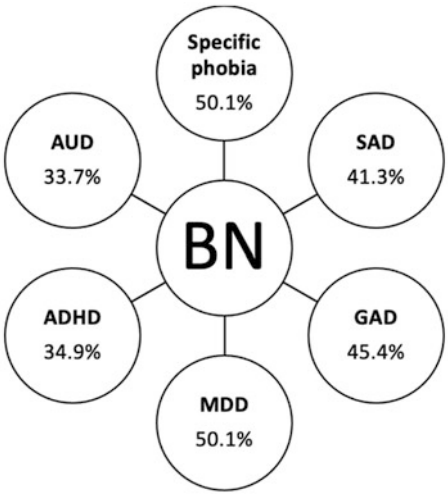


Fig. 1 Most frequently comorbid psychiatric disorders in BN: lifetime prevalence rates. BN, bulimia nervosa; AUD, alcohol use disorder; ADHD, attention deficit-hyperactivity disorder; MDD, major depressive disorder; GAD, generalized anxiety disorder; SAD, social anxiety disorder

Perhaps most concerning, adolescents with BN are at particular risk for suicide, endorsing higher rates than adults with BN or adolescents with another ED diagnosis, with over half reporting suicidal ideation (53%), and 25% reporting having a suicide plan (Swanson 2011; Crow et al. 2014). In addition, 34% report having made a suicide attempt, with 17.1% reporting multiple past attempts.

BN Treatment

Despite the severity of BN and its typical onset in adolescence, there continues to be a lack of systematic study of treatments for adolescent BN. The two main treatments are based in family-based and CBT approaches (see Table 1 for their comparison). At this time, there have only been four published randomized control trials (RCTs) for adolescent BN treatment, worldwide (Le Grange et al. 2007, 2015; Schmidt et al. 2007; Stefini et al. 2017). Most recently, an effectiveness study compared FBT and CBT-E in a transdiagnostic sample of adolescents presenting for treatment in an academic medical center (Le Grange et al. 2020).

Family-based approaches. FBT-BN (see Le Grange and Lock 2007 for treatment manual) uses the same core tenants as those for FBT for AN (see Table 2). In this behavioral treatment approach, parents are mobilized to intervene on the disordered behaviors with the adolescent enlisted to collaborate with parents in the process. In the first phase of treatment, parents are empowered to support their child in establishing a regular pattern of eating while also disrupting the pattern of binge eating and compensatory behaviors. A core intervention is externalization of the illness with the aim of promoting parental action while also reducing blame on the child. If the child is able to engage effectively in treatment, the clinician guides parents to be more collaborative with their child, more so than they might be in the context of FBT for AN. As abstinence from disordered eating and compensatory behaviors is achieved, the second phase of treatment centers on shifting developmentally appropriate control of eating back to the child. The final phase focuses on returning to normative adolescent development and addressing ways in which the ED may have disrupted typical development. An example FBT treatment formulation is presented in Fig. 2. The typical dose of treatment varies across studies, but usually concludes within 6 months from initiation of treatment with the expectation that caregivers remain empowered with their understanding of how to effectively intervene if their child exhibits symptoms of disordered eating again during their recovery journey.

Individual approaches. CBT is the most efficacious individual therapy and therefore a first-line treatment approach for adults with BN (Slade et al. 2018). Specifically, CBT-E is an individual therapy that focuses on interrupting disordered eating (e.g., restriction and binge eating) and compensatory behavior, and also targets distorted cognitions associated with body image concerns (see Fig. 3 for an example CBT-E treatment formulation). Similar to FBT, CBT-E is conceptualized with three stages. Treatment begins with engagement work between the clinician and patient, in an effort to build motivation while establishing rapport. This initial stage

Table 1 FBT-BN versus CBT-E. FBT-BN, family-based treatment for bulimia nervosa; CBT-E, cognitive behavior therapy enhanced for eating disorders; ED eating disorder

	FBT-BN	CBT-E
Structure of session	Brief individual check in with adolescent and therapist at start of session. During this time, weight is taken, and episodes of binge eating and purging are logged. Family joins and participates in remainder of the session	Agenda is set in collaboration with adolescent each session. Includes review of weight and ED symptoms, review of self-monitoring, and other relevant topics such as body image concerns. Sessions are individual with the adolescent who is encouraged to be active in making changes
Phases of treatment	Phase 1 (Sessions 1–10; meeting weekly): Parents take an active role ensuring that their child is eating regularly and not engaged in compensatory behavior. Phase 2 (Sessions 11–16; meeting every 2–3 weeks) Phase 3 (Sessions 17–20; meeting 3–4 weeks apart): Presuming that ED symptoms no longer occur, focus shifts to fostering healthy parent-adolescent relationship, general adolescent issues, relapse prevention	Phase 1 (~10 sessions): Focused on normalizing eating patterns using self-monitoring as a therapeutic tool. With adolescents, there is additional emphasis on bolstering motivation and establishing a collaborative relationship Stage 2 (7–8 sessions): Focus on targeting distorted cognitions Stage 3 (2–3 sessions): Brief stage focused on relapse prevention through anticipatory problem-solving
Role of the family	Parents take a very active role in each session to support their child in reestablishing regular eating without compensatory behavior. Siblings are invited to participate as well	Parents play an adjunctive role and may be asked to join a session for a specific reason. For example, they may support behavioral experiments
Relationship with therapist	Initially, the therapeutic alliance between parents is the priority over the relationship with the adolescent	Therapeutic alliance is between adolescent and therapist
Dose of treatment	Typically 20 sessions over 6–9 months	Typically 20 sessions over 6 months
Suitability for treatment	Parents' active role supports progress in treatment for adolescents who may be ambivalent about recovery. If there is a history of abuse between the parent and child, careful consideration should be taken to determine if it is appropriate for parent to be placed in this role	Adolescent must be able and willing to actively engage in the treatment; they are encouraged to take control of the problem. It is expected that the adolescent will be able to make progress with limited involvement by parents

Legend. FBT-BN, FBT for bulimia nervosa; CBT-E, cognitive behavior therapy enhanced for eating disorders; ED, eating disorder

includes self-monitoring homework (i.e., what is eaten and when, with associated behaviors, thoughts, and feelings) and is focused on normalizing patterns of eating while also interrupting compensatory behaviors. The second stage of treatment focuses on cognitive symptoms including specific integration of feared or avoided foods while using strategies to address triggers for binge eating and purging. In this

Table 2 Core principles and strategies of FBT-BN. FBT-BN, family-based treatment for bulimia nervosa; ED, eating disorder

Tenant	Description
Agnostic view of illness	No assumptions are made about the cause of the illness, and the focus is not on analyzing "why" the ED developed. Instead, the focus is on addressing potential maintaining factors or aspects which would leave someone vulnerable to relapse. This also serves to reduce blame
Caregiver empowerment	It is believed that parents are competent agents for reestablishing healthy eating patterns. Caregivers are charged with ensuring their child is eating appropriately to nourish their body and preventing compensatory behavior
Role of family	Members of the entire family system are important participants in the recovery process
Respect of adolescent development	The adolescent should be allowed to maintain control and autonomy in their life in areas that are unrelated to eating and weight
Externalization of the illness	The illness is viewed as an external force influencing the thoughts and actions of the teen. Caregivers and the therapist join forces to support the healthy part of the teen in fighting against the illness
Initial symptom focus	Treatment starts with a pragmatic focus on interrupting the pattern of restriction, binge eating, and compensatory behaviors including purging. The initial focus is on urgently restoring physical health with consistent nourishment
Non-authoritarian stance	Therapists take an active role guiding the family through the recovery process, without telling them exactly how to do it. The therapist partners with the caregivers to help them determine how to best support their child in breaking the cycle of the ED

Legend. FBT-BN, family-based treatment for bulimia nervosa; ED, eating disorderLegend. FBT-BN, family-based treatment for bulimia nervosa; ED, eating disorder

phase, the self-monitoring records include more intentional focus on cognitive symptoms. The third and final stage of CBT-E is focused on maintaining progress and relapse prevention. Throughout treatment, parents may be included in session for collateral information and to clarify ways in which they can support their child.

A modified CBT approach is in the guided self-care format which is the first-line intervention for adults with BN in the United Kingdom (National Collaborating Centre for Mental Health [UK] 2004). In this approach, a workbook or manual is provided with assigned homework. These modalities incorporate both psychoeducation and a practical focus on the key interventions. The therapist's role is to build motivation while also guiding patients through the workbook. Similar to clinician-guided CBT, core elements of the self-guided format include psychoeducation regarding the conceptual model of how ED symptoms are maintained with a personalized case formulation. Self-monitoring is used to track eating and cognitive symptoms. There is a focus on establishing regular eating and utilizing skills such as problem-solving, goal setting, and behavioral experiments.

RCTs. As mentioned above, there have been four randomized clinical trials evaluating treatment for adolescents with BN to date. All of these studies were

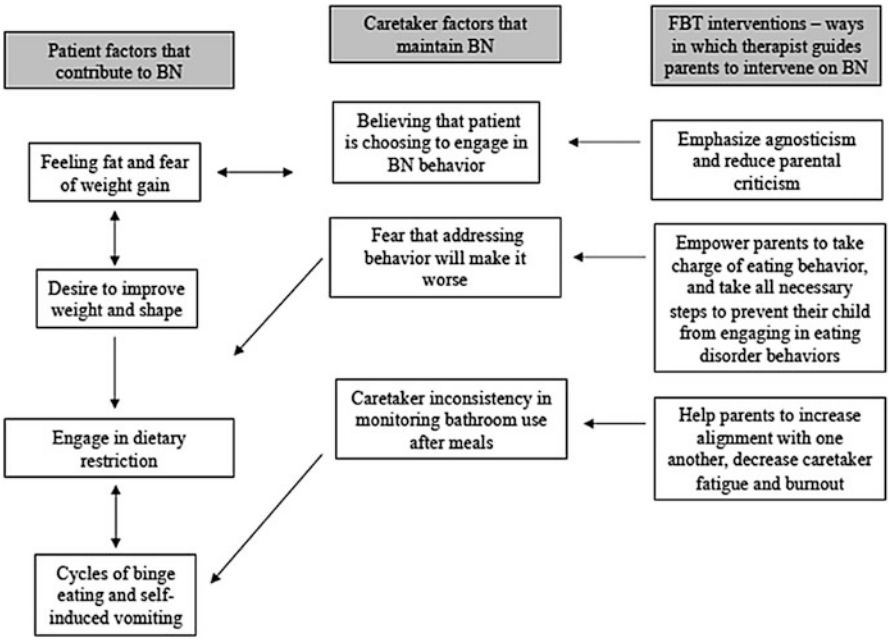


Fig. 2 Sample FBT formulation. BN, bulimia nervosa; FBT, family-based treatment

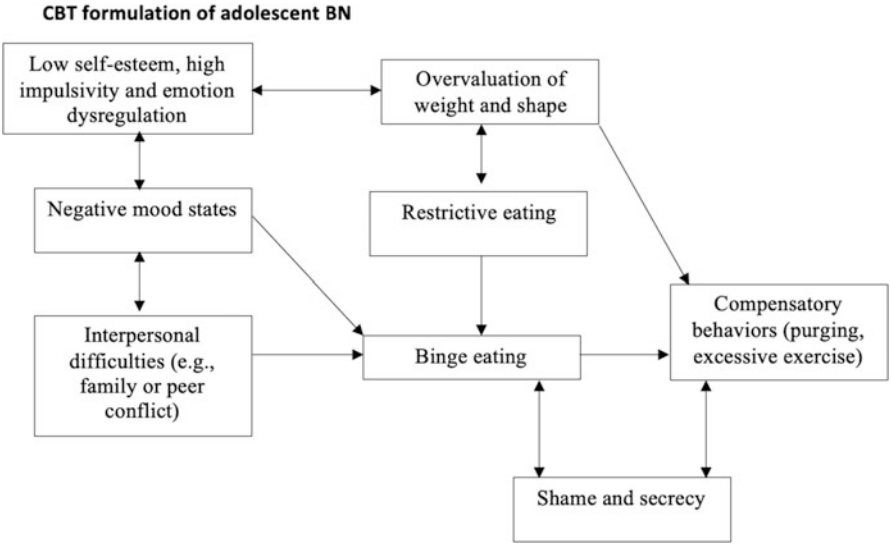


Fig. 3 CBT formulation of adolescent BN. BN, bulimia nervosa

based on DSM-IV-TR criteria for a diagnosis with additional, more flexible criteria that are generally consistent with revised DSM-5 criteria allowing those who endorsed behavioral symptoms less frequently to be included. Three of the four studies have evaluated the efficacy of a family-based approach with another treatment. In the United Kingdom, (Schmidt et al. 2007) compared family therapy with the leading treatment for adults with BN–CBT-guided self-care. This study provided up to 15 sessions of treatment for adolescents with DSM-IV-TR BN or ED not otherwise specified (EDNOS). EDNOS in this study was defined as binge eating and/or purging less than twice per week over 3 months or inappropriate compensatory behaviors without binge eating in patients who were not underweight. The primary outcome was measured by the abstinence from binge eating and self-induced vomiting at end-of-treatment (EOT; 6 months) and follow-up at 1 year, with results indicating no differences between the groups. However, when examining objective binge eating episodes in isolation at EOT, CBT-guided self-care was more effective than family therapy, though this difference was not upheld at follow-up.

In the United States, Le Grange et al. (2007) first compared 20 sessions of FBT to individual supportive therapy (SPT) in youths with BN as defined by DSM-IV-TR, also including those who endorsed binge eating or purge episodes at least once per week over 6 months. Results were defined by abstinence of binge eating and purging 1 month prior to EOT, reevaluated again 6 months later, 1 year from the start of the treatment. At EOT, FBT-BN had higher rates of abstinence, but the rates declined across both treatments at the follow-up time point. Following the comparison against SPT, another RCT compared FBT-BN to CBT for adolescents, offering 18 sessions over 6 months with the same inclusion criteria (Le Grange et al. 2015). As with the prior study, outcome was assessed by abstinence from binge eating and purging for the month prior to EOT, 1-year, and 18-month follow-up. In this study, FBT-BN achieved higher rates of abstinence at EOT. Unlike the prior study, both groups continued to improve with increased rates of abstinence across the 1-year follow-up period at both time points, with FBT-BN remaining more efficacious.

The final RCT by Stefini et al. (2017) did not examine family-based approaches, instead comparing CBT to psychodynamic therapy, the standard of care in Germany. To be in alignment with the longer duration of psychodynamic therapy, the dose of treatment was notably higher than the other studies, providing up to 60 sessions of either therapy over the course of a year. Similar to the prior studies, inclusion criteria comprised those meeting DSM-IV-TR BN criteria, extending to include those reporting binge eating and purging less than twice per week over the prior 3 months. Rather than determining abstinence as the outcome measure, Stefini et al. (2017) evaluated the proportion of participants who no longer met criteria for an ED diagnosis (based on DSM-IV-TR), finding no significant differences between groups.

Effectiveness trial. More recently, Le Grange and colleagues published the results of a non-randomized effectiveness trial which compared FBT to CBT-E on measures of weight and ED symptomatology (Le Grange et al. 2020). This study was transdiagnostic and included adolescents with a DSM-5 ED diagnosis (excluding avoidant-restrictive food intake disorder; ARFID), with 20% of participants meeting criteria for BN, binge eating disorder, or purging disorder. Within this

transdiagnostic sample, adolescents were classified into lower versus higher weight rather than specific ED diagnosis. Treatment effectiveness was measured based on improvement in ED psychopathology as measured by the Eating Disorder Examination interview (EDE) or questionnaire (EDE-Q) (Fairburn 2008) and weight gain, if relevant. Adolescents with BN would most likely be classified in the higher weight group as weight loss is not a core diagnostic feature of the illness. For this group, both FBT and CBT-E demonstrated improvements in the global scores on the EDE without significant differences between groups across time. These findings suggest that a larger higher-powered RCT is warranted.

Other Promising Avenues for Psychotherapy Treatments in Youth

As detailed just above, FBT and CBT are consistently recommended treatment approaches for adolescents with BN (Couturier et al. 2020). However, several "third wave" psychotherapy modalities (i.e., treatments that have evolved and extended from traditional CBT approaches [Hayes 2004]) have demonstrated reasonable efficacy among adults with BN (Hagan and Walsh 2021) and warrant further evaluation among youth. Specifically, research in the last two decades highlights the effective use of interpersonal therapy (IPT) (Agras et al. 2000), dialectical behavioral therapy (DBT) (e.g., Wisniewski and Kelly 2003), acceptance and commitment therapy (ACT) (e.g., Merwin et al. 2013), and integrative cognitive-affective therapy (ICAT-BN) (Wonderlich et al. 2014) for adults with BN.

To consider just a bit more detail on these approaches, IPT rests on the foundation that interpersonal functioning is a critical component of psychological well-being (Markowitz and Weissman 2004) and has been implemented as a focused treatment for EDs (Wilfley et al. 2002; Karam et al. 2019). Although CBT appears to work more efficiently than IPT among adults with BN at EOT, these two treatments demonstrated comparable efficacy when remission rates were compared at 1 year post treatment (Agras et al. 2000), and IPT may be particularly useful for those with marked interpersonal difficulties. DBT enhances skills in the domains of interpersonal effectiveness, distress tolerance, mindfulness, and emotion regulation, with the goal of reducing affective lability and engagement in ED behaviors (Eist 2015). DBT has demonstrated efficacy for treating BN among adults (Hill et al. 2011), and a recent uncontrolled case series of Radically Open DBT (RO-DBT) demonstrated preliminary efficacy in targeting overcontrol among adolescents with restrictive EDs (Baudinet et al. 2020). An ACT approach is intended to increase cognitive and behavioral flexibility, and to reduce experiential avoidance and illness accommodation (Hayes 2004). It has demonstrated efficacy for treating binge-spectrum EDs among adults (Juarascio et al. 2021), and in a recent trial that integrated ACT with a separated family approach (i.e., Acceptance-Based Separated Family Treatment) for adolescents with AN, results demonstrated preliminary feasibility, acceptability, and efficacy for improving weight gain and reducing ED pathology (Timko et al. 2015). Finally, ICAT-BN emphasizes coping and emotion regulation, intrapersonal factors (e.g., nutrition), and interpersonal relationships (Wonderlich et al. 2014). To date, it

has been tested in one RCT in a sample of adults with BN, demonstrating promising efficacy in reducing symptoms. Together, all four of these third wave treatments suggest promising avenues for future study in adolescent samples with BN.

Pharmacotherapy for BN

The use of pharmacology is one area of research that is greatly needed among adolescents with transdiagnostic EDs, particularly given how common medication use is among these youth (Gorrell et al. 2020). Due to the limited number of published studies, evidence-based pharmacological treatment for adolescents with BN is not yet possible, and current clinical guidelines for treating BN in adolescents do not include the use of psychopharmacology, other than to indicate that medication should not be offered as the only treatment option (Couturier et al. 2020). This is surprising, particularly given approval of fluoxetine by the United States Food and Drug Administration and the United Kingdom National Institute for Clinical Excellence for adults with BN (Crow 2019).

In adolescents with a DSM-IV-TR diagnosis of BN or EDNOS, one clinical trial has been published that investigated the feasibility, tolerability, and preliminary efficacy of fluoxetine in conjunction with psychotherapy (Kotler et al. 2003). In this trial, 10 female adolescents (aged 12–18 years) received an adult dose of fluoxetine (60 mg) over 8 weeks, with results indicating that the medication was well tolerated, no participants discontinued the trial, and on the whole, participants demonstrated a significant reduction in binge eating and purging episodes. Although these results suggest that antidepressants are similarly useful and well tolerated for the treatment of adolescent BN as with adults, in nearly two decades no systematic studies since this open trial have been conducted (Couturier et al. 2019). With either mechanistic or effectiveness trials, delineating the specific use of medications for either BN pathology, comorbid psychopathology (e.g., depression; anxiety), or their combination would greatly inform future prescribing practices.

Treatment Moderators

In order to improve treatment outcomes for BN, some research has investigated *how* these treatments work and for *whom* they may be more or less efficacious. Treatment mediators identify the mechanisms through which treatments affect change, or the key ingredients that make treatments effective (Kraemer et al. 2002). In contrast, treatment moderators are characteristics that predict who is more or less likely to benefit from a given treatment; moderators can be differentiated from nonspecific moderators, which are baseline traits that predict treatment outcomes (i.e., main effect on outcome), regardless of patient characteristics (i.e., no interaction effect) (Kraemer et al. 2002). For example, prior hospitalization related to medical complications of EDs is a non-specific predictor of treatment, in that it predicts worse outcomes across all individuals (Le Grange et al. 2012). Compared to AN, our

Table 3 Evidenced moderators of FBT outcomes in adolescents with BN. FBT, family-based treatment; RCT, randomized control trial; SPT, supportive psychotherapy; EDE, Eating Disorders Examination; CBT, cognitive-behavioral therapy

Study (year)	Treatment sample	Summary of moderation findings
Le Grange et al. (2008)	RCT with two treatment groups, FBT v. SPT	No moderators of remission (i.e., absence of binge eating and compensatory behaviors in the previous 4 weeks) or partial remission (i.e., no longer meeting diagnostic criteria) at end-of-treatment when comparing outcomes for treatment with FBT v. SPT At 6-m follow-up, baseline EDE global scores moderated the effects of treatment on partial remission such that individuals with *less* severe baseline global EDE scores had greater partial remission when treated with FBT relative to SPT
Ciao et al. (2015)	Secondary data analysis of data from Le Grange et al. (2008)	Using growth model analyses, participants with *greater* baseline purging had faster change in eating concerns when receiving FBT v. SPT, whereas when baseline purging was low, participants did comparably well in both treatments Age was also a significant moderator such that greater change in eating concerns was demonstrated for younger adolescents receiving FBT v. SPT, whereas those who were older showed an equal rate of change in both treatments; age did not moderate any other outcomes
Le Grange et al. (2015)	RCT with two treatment groups, FBT v. CBT, and one active control group, SPT	Family conflict emerged as a significant moderator such that participants with lower Family Environment Scale – *conflict subscale* scores responded better to FBT than CBT, but there was no differentiation between the treatments in families with higher conflict scores

Legend. FBT, family-based treatment; RCT, randomized control trial; SPT, supportive psychotherapy; EDE, Eating Disorders Examination; CBT, cognitive-behavioral therapy

understanding of treatment mediators and moderators for treatments for BN is limited, particularly in adolescents (see Table 3 for a summary of moderators of BN treatment). For instance, in a recent systematic review of mediators and moderators of ED treatment in adolescents, 16 papers were devoted to AN, whereas only 5 were devoted to BN (Hamadi and Holliday 2020). Further, out of 8 RCTs that have included analyses of moderators and mediators in ED treatments for adolescents, only two investigated BN (Le Grange et al. 2007, 2015). More recently, there has been one additional published treatment study investigating possible moderators in a transdiagnostic sample of EDs, including BN (Le Grange et al. 2020). There have

been no mediators of treatment identified in the current literature on BN in adolescents.

In one trial comparing FBT-BN to SPT that determined that FBT-BN was superior to SPT in reducing core bulimic symptoms (Le Grange et al. 2007), the authors also examined how ED pathology at baseline and throughout the treatment affected outcomes. In this study, remission was defined as abstinence of binge eating (both subjective and objective) and compensatory behavior during the one month prior to EOT. In terms of moderators, participants with less severe eating pathology (as measured by the EDE-Q global score) who were randomized to receive FBT were more likely to reach partial remission at 6-month follow-up compared to those randomized to receive individual supportive therapy (Le Grange et al. 2008). In addition, all EDE-Q subscales (*Restraint, Eating Concerns, Weight Concerns, Shape Concerns*) moderated treatment outcome. For those in the FBT group, lower eating psychopathology early in treatment was predictive of reaching partial remission at EOT. Mediators of treatment, including the mechanism through which FBT brings about change, were not investigated in this study.

A secondary data analysis of additional potential moderators of psychological outcomes in this original trial (Le Grange et al. 2007) included age, purging severity, and use of psychotropic medication (Ciao et al. 2015). The psychological outcomes investigated were cognitive ED symptoms, depression, and self-esteem. Only age and baseline purging severity were identified as moderators such that younger adolescents and those with greater baseline purging severity had larger changes in bulimic symptomatology in the FBT group compared to the SPT group. There were no other moderators of other psychological outcomes.

In the second trial comparing FBT-BN and CBT for adolescents (Le Grange et al. 2015), FBT for BN was found to be more effective in promoting abstinence from binge eating and purging behaviors compared to CBT for adolescents. Similar to a prior trial conducted by Le Grange et al. (2007), remission was defined as abstinence of binge eating (both subjective and objective) and compensatory behavior during the 1 month prior to EOT. In total, 29 moderators were investigated; however, only one moderator was identified such that participants with lower family conflict who received FBT-BN were more likely to reach partial remission by EOT compared to those who received CBT. These findings suggest that individuals with lower family conflict may be better suited that those with higher family conflict for FBT-BN. Interestingly, no other moderators were found, including ED symptom severity, depression, self-esteem, or obsessive-compulsive symptoms.

In the most recent study comparing the effectiveness of FBT versus CBT-E in a transdiagnostic sample (i.e., spanning across EDs) (Le Grange et al. 2020), several moderators were identified. At baseline, participants in the lower weight group (i.e., individuals $<$90% of their expected body weight), depressive symptoms, age, prior hospitalization for co-occurring psychiatric disorders, and family status (i.e., whether individuals lived with their family of origin or a reconstituted family) moderated weight gain at EOT. Specifically, adolescents with higher levels of depression gained comparable rates of weight to those with lower levels over the course of treatment in FBT, but adolescents with higher levels of depression gained

less weight than those with lower levels in CBT-E. Overall, adolescents in FBT gained weight faster than those in CBT-E. In addition, younger adolescents gained more weight than older adolescents in FBT, but older adolescents gained more weight than younger adolescents in CBT-E. Further, adolescents with a prior psychiatric hospitalization were more likely to gain weight in FBT, but lose weight in CBT-E. Overall, adolescents without a prior hospitalization were more likely to gain weight than those with in both treatments. Finally, adolescents living with their family of origin had poorer weight gain compared to those living in reconstituted families more so in CBT-E than FBT. Of note, these factors did not emerge as moderators in the higher weight group, which included individuals with BN. Overall, these findings suggest that younger adolescents, adolescents with higher levels of depression, a prior psychiatric hospitalization, or living in their family of origin may benefit more from FBT, particularly those who need to gain weight as part of their treatment. These moderators should continue to be investigated in adolescents with BN and in the context of binge eating and purging behaviors.

These preliminary studies provide initial evidence that may help guide clinical recommendations for treatment assignment, based on differential treatment response among adolescents for BN. Specifically, individuals with lower eating pathology at the start of treatment or those with less family conflict may respond particularly well to FBT compared to other treatments. However, more rigorous, larger studies will be needed to replicate these findings and to specifically test mediators and moderators of treatment with sufficient statistical power before reaching definitive conclusions (Hamadi and Holliday 2020). Identification of potential moderators and mediators has been quite limited thus far in BN and have to date been a secondary outcome to the main results comparing two treatments. In the future, it will be useful to conduct trials focusing on the mechanisms of action of treatments for BN and taking a stepwise approach to treatment to see who benefits the most.

Research and Clinical Future Directions

There are several domains of future research that are suggested by the current state of evidence reviewed within this chapter. In addition, there are features specific to the BN disorder that suggest shifts in the way that we screen and treat adolescents within our clinical practice. Here, we weave together both research suggestions and recommendations for practice – considering that a discussion of needed clinical research may help to determine where our resources should ideally be devoted to improve treatment outcomes for this high-priority clinical population.

Awareness of diagnostic crossover. As mentioned above, the criteria to meet a diagnosis of BN in DSM-5 is less stringent than the criteria required to meet a diagnosis for BN per DSM-IV-TR (prior to 2013). A majority of our current evidence base of clinical treatment trials for adolescents with BN is therefore based on participants who met DSM-IV-TR inclusion criteria. Arguably, it is "easier" to meet criteria for BN now than it was when these RCTs enrolled. However, much of these RCTS also included partial BN (i.e., subclinical) which naturally

would include youth who would now meet criteria for BN based on today's standards. Regardless of how we interpret the primary outcomes of these trials based on a now outdated definition of BN, it seems important to consider who should be considered for enrollment in future clinical trials to maximize the knowledge gained, based on a potentially shifting definition of this disorder.

"Diagnostic crossover" is a phrase that has been used to refer to the clinical phenomenon of a transition from one ED diagnosis or presentation to another (Eddy et al. 2008). For example, a young person who has been restricting their intake may meet criteria for AN for a certain period of time, but as their illness progresses, this individual may eventually develop binge eating and purging behavior. In a recent meta-analytic review specifically investigating this transition from restricting AN to a presentation that includes binge eating and purging behavior, over 40% of patients reported bulimic behavior at some point during follow-up (Serra et al. 2021). This specific type of diagnostic crossover appears to happen frequently, and it may also help to explain why there are higher rates of BN among adolescents compared to AN. Of note, in one 7-year study, women with BN were less likely to return to AN, supporting the distinction of BN as a separate diagnosis over time (Eddy et al. 2008). The conundrum remains however, that whether one begins with BN or "crosses over" from AN to BN, it is still not particularly clear as to how we might optimally prevent the disorder.

Building awareness among providers that diagnostic crossover from AN to BN is likely, and even more likely with a longer course of illness (Eddy et al. 2008; Serra et al. 2021), is important. In particular, building awareness may be helpful not only in encouraging providers to remain vigilant to screening for new behaviors over time, but also to help to inform patients and families of this compounded risk. Further, although testing interventions that are designed to treat BN are critical, we must also consider that subclinical presentations of this disorder – potentially just as they begin to represent diagnostic crossover – may be particularly important to address in a preventative fashion. In this way, future trials may benefit from including individuals across a diagnostic spectrum (i.e., AN with binge-purge behavior, subclinical BN, and BN).

Weight bias. Recent work describing prodromal symptoms that predict specific EDs found that overvaluation of shape and weight *and* simultaneously feeling fat and fear of weight gain – together were predictive of BN onset (Stice et al. 2021). This was in contrast to onset of AN, which was first predicted by overvaluation of shape and weight without report of a feeling of fatness or fear of weight gain. It is typical for youth with BN to present at a weight that may be lower than their historical weight, but still within the range of expected weight given their height, age, and gender.

Unfortunately, weight status is intricately linked with poor illness detection; specifically, we refer to the (errant) perception that normal weight status is synonymous with lower ED severity (Gaudiani 2018). As a consequence, highly symptomatic youth with BN are less often identified by medical professionals in standard screening, or less often suspected to be struggling with an ED by their caretakers or others who might facilitate treatment referral. A good amount of research has been

focused on low-weight disorders such as AN, and while low weight suggests greater medical acuity for some individuals, this weight-based bias in research has prevented expansion of research into the fuller spectrum of transdiagnostic EDs. Further, insurance companies may deny access to higher levels of care due to weight bias or perceiving that the patients' electrolytes are not "abnormal enough" (Gaudiani 2018). Assumptions based on weight collectively prevent many providers and parents from feeling that treatment for BN is urgently needed.

Adolescents with this disorder may certainly seek treatment on their own, the prospect of which is supported by the ego-dystonic nature of the disorder (e.g., distress caused by one's binge eating and purging) (Bottera et al. 2020). However, among young adults with BN, recent evidence indicates that sentiments reflecting self-criticism and fear of external judgment *decrease* help-seeking and self-referral for treatment (Ali et al. 2020), a problem that we can assume may be even more prevalent among adolescents. Further, prior weight status and stigma directly related to BN (e.g., that individuals with BN lack self-discipline, or are self-destructive) may also contribute to decreased help-seeking (Puhl and Suh 2015).

To offset these issues, we may again turn to the need for increased awareness among providers, but also among caretakers, educators, and individuals who interface with adolescents (e.g., athletic coaches), that EDs can occur in individuals of all sizes, and that screening for ED symptoms should be performed regardless of a presenting weight.

Testing treatments. So far, the evidence from RCTs testing FBT and CBT for BN in adolescents demonstrate relative robustness in their efficacy. However, even the best RCT outcomes leave a majority (nearly 60%) of youth as still partially symptomatic at the conclusion of treatment (Steiger 2017; Lock and Le Grange 2019). It is essential that we continue to study treatment for adolescents with bulimic symptoms in an effort to improve remission rates. We acknowledge that it is a departure to advocate for *not* studying BN as a singular diagnostic sample when calling for increased study of this disorder among adolescents. However, a diagnostically siloed approach to studying restrictive EDs has left us with little understanding of the complexity of these disorders, including mechanisms that drive cycles of binge eating and compensatory behaviors across weight status. Further, given the frequency of diagnostic drift (Eddy et al. 2008; Stice et al. 2009), it is untenable to maintain that a weight criterion or a given frequency of a behavior should determine the delineation of a study sample, diagnostic category, or indication of necessity to receive clinical resources. Therefore, although heterogeneity in a sample must be considered, we advocate for a less siloed approach in future study proposals, and appeal to reviewers in the grant and manuscript review process to recognize the importance of considering BN within a broader transdiagnostic context. Studying BN, atypical AN, and OSFED in tandem will undoubtedly facilitate improved identification of mechanisms that maintain BN behaviors across the weight spectrum and will ultimately translate to more inclusive and effective approaches in screening and treatment assignment.

We further advocate for studying youth with transdiagnostic binge eating and purging behavior with *both* an experimental therapeutics approach *and* with

effectiveness trials. Delineating the mechanisms by which behavior is either maintained or mitigated is critically important. It is equally important that we improve the effectiveness of BN treatment, in the context in which it is delivered. With either mechanistic or effectiveness trials, delineating the specific use of medications for either BN pathology, comorbid psychopathology (e.g., depression; anxiety), or their combination would greatly inform future prescribing practices.

In addition to medication trials and as mentioned earlier in this chapter, there are several third wave therapeutic treatments that show promise for BN in open trials among adolescents (e.g., ACT, Timko et al. 2015), but still require testing in larger-scale clinical trials. In conducting larger trials, more recent work has specified that policy and system changes must be made to improve the reach and ability to disseminate any type of ED treatment (Taylor et al. 2020). Given the burgeoning prevalence rates of ED behaviors in the past year (Phillipou et al. 2020), and the existing critical need for the dissemination of evidenced-based care for youth with EDs (Lock and Le Grange 2019), we do not have a luxury of time in closing a research-to-practice gap.

Summary/Conclusions

In summary, in this chapter, we provide an overview of the current evidence base for research and clinical practice among youth and adolescents with BN. We include prevalence rates and diagnostic criterion, common comorbidities, and the treatments that show the most robust evidence base to date. We also point to the perplexing finding that BN has nearly a twofold greater prevalence rate compared to AN, and yet clinical services do not represent this proportion. We discuss reasons for this phenomenon and provide ideas for moving forward. The symptoms of BN are present across ED diagnoses; therefore, in moving toward studying these phenomena mechanistically across diagnostic siloes, we will more efficiently be able to understand for whom and why these symptoms arise and are maintained. Increased study of BN symptoms (both in mechanistic and effectiveness trials) will help to determine where our resources should ideally be devoted to improve treatment outcomes for this high-priority clinical population.

Applications to Other Eating Disorders

As noted above, BN has significant overlap with the other EDs (e.g., Forbush et al. 2017). Given the shift toward dimensional approaches of psychopathology and the considerable diagnostic crossover that occurs, it follows that many of the considerations discussed above apply to other EDs (Le Grange et al. 2004; Le Grange and Loeb 2007). First and foremost, early detection is the most important indicator for full recovery (Treasure et al. 2015). Thus, screening among pre-adolescents and adolescents is imperative to identify early-onset EDs and refer individuals to appropriate treatment.

Further, treatment among the EDs in adolescents is relatively similar. FBT and CBT-E are the two gold-standard, first-line evidence-based treatments for adolescent EDs, regardless of diagnosis (Couturier et al. 2013; Lock 2015). Both treatments support regular eating and reduce of symptoms of restriction, binge eating, and purging and have been shown to be effective transdiagnostically (Le Grange et al. 2020).

Finally, similar challenges are common across EDs, such as weight bias and need for novel treatments, emphasizing the need for future research in these areas. Similar to BN, weight bias delays time to diagnosis for atypical AN and binge eating disorder (Puhl and Suh 2015). In addition, at least half of youth remain partially symptomatic after treatment (Steiger 2017). There is an urgent need to develop augmented or novel treatments to increase the number of individuals who achieve full recovery.

Thus, in conclusion, the ED field may be better served moving forward in treating these disorders as dimensional, composed of different symptoms, rather than as discrete, categorical disorders. Such an approach may streamline future research efforts to improve treatment outcomes for all EDs across the lifespan.

Mini-Dictionary of Terms

CBT	Cognitive-behavioral therapy is an evidence-based approach to psychotherapy focused on thoughts, behaviors, and emotions.
FBT	Family-based treatment is an empirically based approach where families are a key part of treatment for youth and adolescents with EDs.
Clinical trial	A clinical trial is a systematic study of a specific subject whereby response to an intervention is tested.
Bulimia nervosa	Bulimia nervosa is an eating disorder characterized by engagement in binge eating and compensatory behaviors (e.g., self-induced vomiting).
Self-efficacy	Self-efficacy in FBT refers to parental empowerment in being able to effectively engage with challenging the ED.
Agnosticism	Agnosticism is a term used to describe an attitude where there is no blame placed on any one individual, or any identified cause of a specific issue (e.g., the ED).
Externalization	Externalization refers to the stance where the ED is not identified as belonging to, or being the child.

Key Facts of Treatment for Bulimia Nervosa

- The core symptoms of BN (i.e., binge eating, compensatory behavior, and body image concerns) are present across ED diagnoses.

- BN has nearly a twofold greater prevalence rate compared to AN, and yet clinical services do not represent this proportion.
- FBT and CBT are currently the most efficacious treatments for youth with BN.
- FBT involves family members in treatment as important resources in interrupting the ED, and helping the child to recover.
- In FBT, parents initially take charge of eating and exercise and work to prevent ED behavior, and independence is gradually restored to the child over time.
- CBT is an individual approach to treatment where the child is responsible for making behavior change in the context of treatment. Even in CBT, parents can be a key part of supporting a child's recovery from BN.
- There is an urgent need to develop augmented or additional novel treatments to increase the number of individuals who achieve full recovery from bulimia nervosa and other eating disorders.

Summary Points

- In adolescents, point prevalence of BN is 4.6% though estimates vary based on the inclusion of individuals who fall below diagnostic threshold.
- There is a high rate of comorbidity for BN with anxiety and mood disorders along with substance misuse; suicidal ideation and attempts are also high.
- There is a lack of systematic study of treatment for BN in youth; family-based and cognitive-behavioral approaches have been the focus of the limited number of RCTs.
- There is reasonable efficacy of several "third wave" treatments extending from CBT in adults with BN which may also benefit adolescents.
- Although psychotropic medications are commonly prescribed for youth, current guidelines for treating BN in adolescents do not include the use of psychopharmacology with only one open trial of 10 female adolescents to date.
- There are several domains of future research in adolescent BN including awareness of diagnostic crossover, weight bias, and additional systematic testing of treatments.

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A Narrative Review on the Dual Pathway Model of Bulimic Pathology

45

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Contents

Introduction 888
The Risk Factors Included in the DPM for BN 890
Body Mass Index 890
Sociocultural Pressures to Be Thin 890
Thin-Ideal Internalization 891
Body Dissatisfaction 891
Dietary Restraint 892
Negative Affect 892
Dietary Restraint and Negative Affect 893
Empirical Studies Assessing the Dual Pathway Model 893
Cross-Sectional Studies 893
Longitudinal Studies 902
A Note on the Predictive Utility of the DPM for BN 914
Limitations of Previous Studies and Future Directions 914
Clinical and Prevention Implications 916
Conclusions 916
Applications to Other Eating Disorders 917
Mini-Dictionary of Terms 917
Key Facts 918
Summary Points 918
References 919

Abstract

The dual pathway model (DPM) for bulimia nervosa (BN) symptoms proposes that increased body mass index (BMI) leads to pressures to be thin, and body dissatisfaction. Pressures to be thin are also thought to lead to thin-ideal

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internalization and body dissatisfaction. According to the model, the effects of body dissatisfaction on BN symptoms are mediated via two pathways: dietary restraint and negative affect. Despite its theoretical appeal in being able to capture the multifaceted etiology of BN symptoms, only a few studies have been able to capture the DPM empirically. This chapter aimed to review all the cross-sectional and longitudinal studies to date that have assessed the DPM empirically in its entirety using path analyses or structural equation modeling (SEM). A total of ten studies were retrieved (five cross-sectional and five longitudinal). Overall, there was decent support for most of the paths included in the DPM both cross-sectionally and longitudinally. Understanding the processes that lead to BN symptoms has the potential to prevent and reduce the deleterious effects of BN symptoms.

Keywords

Dual pathway model · Bulimia nervosa · Eating disorders · Dietary restraint · Negative affect · Body dissatisfaction · Pressures to be thin · Thin-ideal internalization · Risk factors · Review · Path-model · Structural equation modeling

Abbreviations

BMI	Body mass index
BN	Bulimia nervosa
DPM	Dual pathway model
SEM	Structural equation modeling

Introduction

Bulimia nervosa (BN) is a debilitating eating disorder that is linked to poor health, psychosocial dysfunction, and comorbid mood disorders (APA 2013). Body mass index (BMI), sociocultural pressure to be thin, internalization of the thin ideal, body dissatisfaction, dietary restraint, and symptoms of negative mood (e.g., depression, anxiety, and negative affect, e.g., Puccio et al. 2016a) have all been identified as risk factors for the development and maintenance of BN symptoms (Stice et al. 2017). The dual pathway model (DPM) for BN (Stice et al. 1996) suggests that a series of recognized BN risk factors are causally connected, and hence generate and perpetuate the disease (see Fig. 1)

The DPM examines the mediating pathways that give rise to BN symptoms. Recurrent episodes of binge eating and compensatory behaviors which can be either purging (i.e., self-induced vomiting) or non-purging (i.e., excessive exercise; APA 2013) are symptoms of BN. Stice et al.'s (1996) DPM model hypothesizes that external pressures to be thin (e.g., the media, family, and peers) lead to the thin-ideal internalization (the extent to which an individual subscribes/aspires to the cultural standard of thinness). Furthermore, comparing one's body to this thin ideal can then

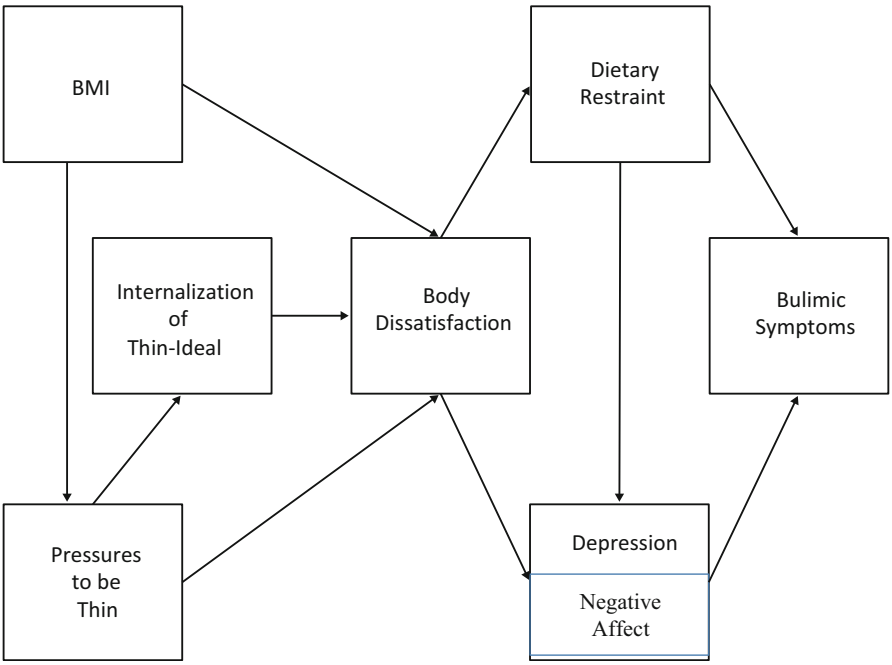


Fig. 1 The original conceptualisation of the DPM according to Stice et al. (1996). (*Notes*: BMI = body mass index. The original DPM model proposed by Stice et al. (1996) includes negative affect as the mood variable. However, other DPM studies have used depression and negative affect interchangeably. It should however be noted that these are different concepts. While depression is a mood disorder that is characterized by persistent feeling of sadness and loss of interest that affect everyday functioning, negative affect is an internal feeling that takes place when one has failed to achieve a goal or has avoided a threat)

lead to an increase in body dissatisfaction (dissatisfaction with one's weight, shape, and/or size) since this thin ideal offers an unachievable objective of thinness. Body dissatisfaction is at the heart of the DPM, and it is thought to cause BN symptoms via two paths. The first pathway is via dietary restraint: Binge eating, a core symptom of BN, is thought to be a compensatory mechanism for caloric deprivation associated with dietary restraint (Polivy et al. 2005). Dietary restraint is also proposed to lead to negative affect. The second pathway is therefore via negative affect: Increased body dissatisfaction, in turn, leads to feelings of disgust, depression, and anger, whereby bingeing and purging are believed to be coping mechanisms to distract attention from this negative mood state (Heatherton and Baumeister 1991). Since the DPM was first proposed, it has been examined in both cross-sectional (e.g., Stice et al. 1996) and longitudinal studies (e.g., Stice et al. 1998). However, to our knowledge, no study to date has systematically reviewed the studies that have assessed the DPM model empirically. Hence, the validity and predictive utility of the model remains unclear.

The aims of the current narrative review of the DPM were therefore to (a) outline the relevance of each of the key constructs included in the DPM and (b) provide

details on the studies that have attempted to validate the model empirically. Understanding if the proposed risk factors outlined in the DPM have meaningful causal relationships for BN symptoms and whether they have predictive power is crucial because they could influence early prevention efforts aimed at preventing individuals who are "at risk" from reaching a clinical BN diagnosis.

The Risk Factors Included in the DPM for BN

The DPM as originally proposed by Stice et al. (1996) outlines a multifaceted interchange among several putative risk factors (i.e., BMI, pressures to be thin, thin-ideal internalization, body dissatisfaction, negative mood/affect, and dietary restraint) that conclude in the experience of BN symptoms. Each of these risk variables will be introduced in the following section, as well as the background for its inclusion in the DPM.

Body Mass Index

BMI is a measurement of a person's weight and height. The BMI is calculated by dividing the body mass by the square of the body height and is given in kilograms per square meter. It is hence expressed in units of kg/m^2. According to the World Health Organization, the following BMI categories have been suggested: <18.5 = underweight, ≥ 18.5–24.9 = normal, ≥ 25–29.9 = overweight, and ≥ 30 = obese. A higher BMI is supposed to increase one's chance of developing disordered eating symptoms as it moves individuals further away from the slender ideal body image (e.g., Stice and Shaw 2002). BMI has been prospectively associated with the onset of BN symptoms (e.g., Abebe et al. 2012), sub-threshold binge eating disorder (Hilbert 2013), disordered eating symptoms (e.g., Ferreiro et al. 2012), and binge eating symptoms (e.g., Ferreiro et al. 2012) in male and female community samples. As a result, previous studies have revealed that having a higher BMI is a risk factor for developing eating disordered symptoms, including BN.

Sociocultural Pressures to Be Thin

Sociocultural pressures to be thin are defined as external media and interpersonal (parents and peers) influences which generate and diffuse unrealistic body-shape ideals that promote the desirability of the thin ideal (Rodgers et al. 2010). Parents, peers, and others who support media-portrayed body-shape ideals are thought to perpetuate these pressures. This is believed to occur through dieting-related encouragement or criticism, as well as modeling of behaviors and attitudes congruent with achieving the thin ideal, which ultimately might lead to a clinically significant eating disorder (Rodgers and Chabrol 2009). Peer pressure to be thin has been linked cross-sectionally to BN symptoms and negative affect (e.g., Hutchinson et al. 2010), body

dissatisfaction (e.g., Ruisoto et al. 2015), and disordered eating (e.g., Ruisoto et al. 2015). Pressures to be thin have also been connected to more severe dietary restriction and poorer teenage weight outcomes (i.e., being overweight; Blodgett Salafia and Gondoli 2011), hence emphasizing the negative impact of societal pressures to be thin on eating disorders.

Thin-Ideal Internalization

The thin ideal is a culturally sanctioned image purporting that a female's attractiveness is primarily based on having an "ultrathin" body (Pidgeon and Harker 2013). A figure with slender hips, buttocks, shoulders, arms, and thighs is regarded as a characteristic of this ultrathin shape and size (Furnham et al. 2002). Given that the thin ideal is a biological oddity, obtaining and/or maintaining this thin ideal is largely unattainable.

The degree to which an individual cognitively adopts the socially imposed beliefs and norms of attractiveness is termed thin-ideal internalization (Pidgeon and Harker 2013). In other words, thin-ideal internalization refers to a person's belief that the thin ideal is a desirable end state to strive for. This internalization process is assumed to take place over time because of frequent exposure to images and messages that purport the thin ideal (Rogers Wood and Petrie 2010).

A meta-analysis by Stice and Shaw (2002) found that the thin-ideal internalization was associated with body dissatisfaction, dieting, negative affect, the onset and maintenance of BN symptoms, and the onset of binge eating. Other research has linked the slim ideal internalization to body-focused anxiety and dissatisfaction (Peterson et al. 2006), dieting (Pidgeon and Harker 2013), and disordered eating (Pidgeon and Harker 2013). Internalization of the thin ideal has also been argued to maintain eating disorders (e.g., Paterna et al. 2021), presumably through social reinforcement mechanisms that signal to individuals that the ideal is desirable. Consequently, the thin-ideal internalization has been identified as a risk factor for the development of eating disorders.

Body Dissatisfaction

Body dissatisfaction has been coined as the subjective negative judgment of one's physique or bodily components (Stice and Shaw 2002). Body dissatisfaction is thought to comprise of two parts: evaluative body dissatisfaction, which is the difference between one's perceived body shape or size and one's ideal body shape or size, and affective body dissatisfaction, which are the negative affective states caused by dissatisfaction with one's shape or size (Bearman et al. 2006). Body dissatisfaction is also referred to as either general unhappiness with one's body or specific discontent with specific bodily parts (Allen et al. 2012). Body dissatisfaction has a high prevalence rate, with over 30% of boys and 60% of girls wanting to change their body shape and size (Lawler and Nixon 2011).

Restrained eating (Neumark-Sztainer et al. 2006), BN symptoms (Stice 2002), and depressive symptoms (Neumark-Sztainer et al. 2006) have all been associated with body dissatisfaction (Mond et al. 2011). Unsurprisingly, body dissatisfaction was found as a main risk factor for dieting, negative affect, and BN symptoms in Stice and Shaw's (2002) meta-analysis.

In terms of the trajectory of body dissatisfaction as a function of sex, Bucchianeri et al. (2013) examined 1902 participants in a sample that was designed to reflect culturally different ethnic/racial and socioeconomic origins. The study's findings revealed that between middle adolescence and early adulthood (10 year follow-up), both girls' and boys' body dissatisfaction grew significantly and that this rise was linked to an increase in BMI over time. When BMI was adjusted, increases in body dissatisfaction became nonsignificant, demonstrating that BMI has a major impact on body dissatisfaction.

Dietary Restraint

The DPM asserts that body dissatisfaction may lead to BN symptoms through two mechanisms: dietary restraint and negative affect (Stice et al. 1996). Dietary restraint refers to conscious efforts to lose weight by achieving a negative energy balance between calorie intake and expenditure (Allen et al. 2013). Dietary restraint is hypothesized to trigger binge eating episodes, which then precipitate BN symptoms (e.g., purging). Caloric restriction and dieting failures can then lead to disordered eating, particularly when people break their rigid and unrealistic dietary restrictions (Polivy and Herman 1985).

The meta-analysis by Stice and Shaw (2002) found that dietary restraint was a risk factor for negative affect and overall disordered eating. However, it should be noted that only a limited number of studies assessed this relationship (i.e., $N = 2$ for dietary restraint and $N = 9$ for negative affect). The idea that dietary restraint is a risk factor for BN symptoms has also been consistently explored in recent studies (Stice et al. 2017, 2021). Restraint eating has also been found to lead to uninhibited eating in a laboratory setting (Bottera et al. 2021). Finally, most BN patients claimed that their BN symptoms began after a period of dieting, and dieting has been identified as the most powerful risk factor for any type of eating disorder (Kabakuş Aykut and Bilici 2022; Stice et al. 2011).

Negative Affect

Negative affect is the second suggested pathway from body dissatisfaction to BN symptoms. Empirical research has suggested that negative affect plays a role in the development, occurrence, and maintenance of BN symptoms. Negative affect, for example, has been revealed to be a risk factor for eating disorders as well as a causal maintenance factor for binge eating (Stice and Shaw 2002). Furthermore, issues regulating negative emotional states have been observed to be more prevalent in

individuals with BN compared to controls and are linked to total symptom severity (Lavender et al. 2014).

Dietary Restraint and Negative Affect

Dieting and dietary restriction have also been linked to a low mood (da Luz et al. 2018). The DPM hypothesizes that dietary restraint has a direct impact on negative affect, which subsequently leads to BN symptoms. However, the literature on the longitudinal effects between depression and dietary restraint is inconclusive, and no study has assessed these relationships bidirectionally. Therefore, it remains unclear whether dietary restraint causes depression (e.g., Hilbert et al. 2013), whether depression causes dietary restraint (e.g., Allen et al. 2013), or whether the relationship between these variables is bidirectional. Therefore, further research is needed to determine the direction of effects between these dimensions.

Empirical Studies Assessing the Dual Pathway Model

While the DPM has received empirical support since its establishment, most of this literature has failed to replicate the model in its entirety, with many studies (e.g., Burton and Abbott 2019) only assessing individual paths by looking at bivariate relationships, and thus not examining the mediating processes by which these pressures ultimately lead to BN symptoms. Other studies have utilized path-analyses or structural equation modeling (SEM) to test alternative variations of the DPM (e.g., Dakanalis et al. 2014; Maraldo et al. 2016), and thus the specific results from these studies are somewhat difficult to compare to the original model proposed by Stice et al. (1996). The subsequent sections, therefore, outline all the cross-sectional and longitudinal studies that have assessed the DPM in its entirety. The inclusion criteria for this narrative review entailed those studies which (i) assessed the core proposition of the model, with flexibility only allowed for the BMI variable and one other missing variable (predominately, the thin-ideal internalization variable), and (ii) used path-modeling and/or SEM to assess the DPM model empirically.

We decided to only include studies that used either path analyses and/or SEM because these statistical techniques can analyze the structural relationship between the proposed constructs in the DPM. These methods are preferred since they assess numerous and interconnected dependencies in a single investigation. Path analyses differ from SEMs in that they employ observed variables, whereas SEMs may use a combination of observed and latent factors.

Cross-Sectional Studies

Cross-sectional research has provided support for the DPM from five studies that have utilized path-modeling or SEM (Anbari et al. 2020; Duemm et al. 2003;

Hutchinson et al. 2010; Maraldo et al. 2016; Stice et al. 1996). Table 1 presents an overview of these studies and the relevant findings.

As shown in Table 1, Stice et al. (1996) used a cross-sectional design to evaluate the DPM in a group of adolescent females. Using subscales from the Bulimia Test Revised (Thelen et al. 1991) and the Eating Attitudes Test-26, they were able to operationalize BN symptoms as a latent variable (Garner et al. 1982. The model was shown to be a good match to the observed data, accounting for 71% of the variance in BN pathology using SEM. All paths were significant, as predicted, demonstrating the model's validity. Although it was not hypothesized, Stice et al. (1996) also discovered that pressures to be thin had a direct effect on BN symptoms. This finding underlined the importance of social pressures, as such effects appear to lead to BN symptoms even when an individual does not internalize the thin ideal.

Duemm et al. (2003) conducted the second cross-sectional study that examined the DPM in its entirety. Duemm et al. (2003) tested whether the model could predict the commencement of BN behaviors using the Bulimia Test Revised (Thelen et al. 1991). Duemm et al. (2003) also looked at sociotropy as a personality trait to see if it had predictive value for the DPM, specifically for thin-ideal internalization and negative affect. Sociotropy is defined as a desire to rely on and/or be approved by others (Duemm et al. 2003). An individual with a high level of sociotropy is supposed to avoid social rejection by displaying signs of striving to please others and is focused on maintaining personal relationships.

Apart from the pressures to be thin → body dissatisfaction, and body dissatisfaction → negative affect pathways, Duemm et al.'s (2003) model was an excellent fit for the data, and most of the hypothesized pathways were supported. The variance accounted for in BN symptoms was 56%. Contrary to the model's primary claim, Duemm et al. (2003) discovered that body dissatisfaction had a direct influence on BN symptoms and was not fully mediated through the negative affect and dieting restraint pathways. According to Duemm et al. (2003), this direct effect may have been caused in part by weight loss that can occur because of purging behaviors. As such, the authors proposed that body dissatisfaction may have resulted in a direct effect on BN symptoms because purging behaviors may have acted as a mechanism for weight loss to alleviate body dissatisfaction.

Duemm et al.'s (2003) findings also revealed that sociotropy – the additional variable – had a direct effect on BN symptoms and was also associated with the thin-ideal internalization and negative affect. The authors concluded that individuals with higher levels of sociotropy may experience greater pressure from their environment to conform to cultural expectations of thinness. While Duemm et al. (2003) provide preliminary evidence for the inclusion of sociotropy in the DPM, more studies are needed to assess whether sociotropy interacts with other BN risk variables in the DPM.

Hutchinson et al. (2010) conducted a third study with 1094 Australian female adolescents to evaluate the model's core paths, without thin-ideal internalization. They also included additional paths of peer perception of weight-related attitudes and behaviors, teasing, and peer-related eating behaviors. According to Hutchinson et al. (2010), peer influence had a significant relationship with body dissatisfaction

Table 1 Overview of the cross-sectional DPM studies

Author	Aim(s)	Sample	Age – Yrs SD (M)	Female (*N*)	Ethnicity (*N*)	Sample	Measures	Significant pathways	Main findings
Stice et al. (1996)	Tested the DPM while incorporating perceived sociocultural pressures, body mass, ideal body internalization, and BD	257	N/A – age range 17–52	257 (100%)	Caucasian (189; 73.54%)	Community	Perceived Sociocultural Pressure Ideal Body Stereotype Scale Body Esteem Scale Eating Attitudes Test-26 Beck Depression Inventory	Perceived sociocultural pressure → BN Perceived sociocultural pressure → ideal body internalization Perceived sociocultural pressure → DR Perceived sociocultural pressure → NA Ideal body internalization → BN DR → BN NA → BN	***Support for the DPM***
Duemm et al. (2003)	Examined the fit of the expanded DPM: adding need for approval and	184	N/A Age ranged from 18 to 22	184 (100)	North America (113; 61.8%)	Community	Sociocultural Attitudes Toward Appearance Questionnaire Eating Disorder Inventory	Sociotropy → NA Sociotropy → ideal body internalization Sociotropy → BN	***Support for the original and extended DPM***

(continued)

Table 1 (continued)

Author	Aim(s)	Sample	Age – Yrs SD (M)	Female (*N*)	Ethnicity (*N*)	Sample	Measures	Significant pathways	Main findings
	fear of social rejection (sociotropy)						Dietary Intent Scale Depression Anxiety Stress Scales The Revised Personal Style Inventory Bulimia Test Revised	Perceived pressure → ideal body internalization Ideal body internalization → BD Ideal body internalization → DR BD → BN BD → DR DR → BN DR → NA NA → BN	
Hutchinson et al. (2010)	Examined the direct and mediational pathwaysof the DPM via which NA and peer factors that are theorized to promote eating problems	1094	12.3 (0.52)	1094 (100%)	N/A	Community	Eating Disorder Inventory Body Attitudes Questionnaire Dutch Eating Behaviour Questionnaire Extreme Weight Loss Behaviours Checklist Multidimensional Personality Questionnaire	**Extended model** Teasing → BD Teasing → NA Teasing → friendship clique eating behaviors Teasing → peer influence Friendship	***Partial support forthe DPM*** The proposed pathways from DR to NA and DR to BN were not supported

							Friends' Concern with Thinness and Dieting Scale Perception of Teasing Scale	clique eating behaviors → DR Friendship clique eating behaviors → BN Friendship clique eating behaviors → Peer influence DR → BN DR → NA NA → BN BD → NA BD → DR BD → BN Peer influence → BD Peer influence → teasing Peer influence → friendship clique eating behaviors Peer influence → DR	
		609		609 (100%)		Community			

(continued)

Table 1 (continued)

Author	Aim(s)	Sample	Age – Yrs SD (M)	Female (*N*)	Ethnicity (*N*)	Sample	Measures	Significant pathways	Main findings
Maraldo et al. (2016)	Replicated and extended the DPM by (a) adding fear of negative evaluation and suggestibility as precursors to thin-ideal internalization, (b) examining the role of rumination as a predictor of BD and NA or a mediator of their association, and (c) examining the role of self-compassion as a predictor of BD and DR or a mediator of their association		27.30 (11.24)		Caucasian (468; 76.7%)		Eating Disorder Examination -Questionnaire The Bulimia Test -Revised Positive And Negative Affect Schedule-Expanded Form Dutch Eating Behaviour Questionnaire-Restrained Eating Subscale The Ideal Body Stereotype Scale-Revised The Body Shape Questionnaire-8B The Brief Fear Of Negative Evaluation Scale - The Multi-Dimensional Iowa Suggestibility Scale The Ruminative	Self-compassion → BD Self-compassion → NA Thin-ideal internalization → BD BD → DR BD → NA DR → DE NA → DE	***Support for the revised DPM***

							Responses Scale Self-Compassion Scale-Short Form		
Anbari et al. (2020)	To determine the DPM for binge eating with two suggested additions: self-esteem and fear of negative evaluation	252	21.59 (2.87)	131 (52%)	N/A	Community	Fear of Negative Evaluation Perceived Sociocultural Pressure Scale Ideal-Body Stereotype Scale Revised Body Shape Questionnaire Dutch Eating Behaviour Questionnaire-Restrained Eating Subscale Rosenberg Self-Esteem Scale Binge Eating Scale	**Modified model:** BMI → perceived sociocultural pressure BMI → fear of negative evaluation BMI → ideal body internalization Perceived sociocultural pressure →BD Perceived sociocultural pressure → self-esteem Perceived sociocultural pressure →DR Fear of negative evaluation →BD Fear of negative evaluation → DR	***Partial support for the DPM*** Supported the DPM's hypothesis that BD is a predictor of DR. However, neither self-esteem nor binge eating was predicted by DR

(continued)

Table 1 (continued)

Author	Aim(s)	Sample	Age – Yrs SD (M)	Female (*N*)	Ethnicity (*N*)	Sample	Measures	Significant pathways	Main findings
								Fear of negative evaluation → self-esteem BD → DR BD → self-esteem DR → self-esteem DR → binge eating disorder Ideal body internalization → BD Self-esteem → binge eating disorder	

Note: DPM = dual pathway model; BMI = body mass index; DR = dietary restraint; NA = negative affect; BD = body dissatisfaction; BN = bulimia symptoms

and dietary constraint. As hypothesized, negative affect mediated the pathway from body dissatisfaction to BN symptoms. However, contrary to predictions, dietary restraint did not predict BN symptoms, and hence body dissatisfaction was not linked to BN symptoms via the restrained eating pathway. Furthermore, Hutchinson et al. (2010) found no evidence of a connection between dietary restraint and negative affect. This null result, according to Hutchinson et al. (2010), may reflect the possibility that restrained eating may cause negative emotional states in some people, but that if restrained eating is maintained and weight loss is achieved, others may experience a heightened sense of self-control and positive affect. A noteworthy limitation of Hutchinson et al.'s (2010) study was that the observed variance in the BN outcome variable was not reported.

The last two studies by Maraldo et al. (2016); Anbari et al. (2020) undertook considerable additions to the original DPM. The study by Maraldo et al. (2016) replicated and extended the DPM by considering additional constructs that may predict and/or precipitate thin-ideal internalization, namely, fear of negative evaluation, suggestibility, rumination, and self-compassion. Fear of negative evaluation and suggestibility were examined as precursors to thin-ideal internalization, given the substantiated role of fear of negative evaluation in the prediction of disordered eating symptoms (DeBoer et al. 2013), and the role of suggestibility in increasing ones' tendency to be influenced by sociocultural messages purporting the thin ideal (Davison et al. 2000). Furthermore, given that individuals with a ruminative response style may use maladaptive behaviors such as disordered eating to avoid self-directed rumination (Etu and Gray 2010), rumination was examined as a predictor of body dissatisfaction and negative affect, and as a mediator of their associations. Lastly, self-compassion, which has been shown to negatively predict body image and disordered eating concerns (Ferreira et al. 2013), was investigated as a predictor of BD and dietary restraint and as a mediator of their associations.

The study was conducted among 609 women recruited from the community and a university sample. The findings demonstrated that fear of negative evaluation and suggestibility predicted thin-ideal internalization, while rumination and self-compassion (inversely) predicted BD. Fear of negative evaluation, rumination, and self-compassion (inversely) predicted negative affect. Overall, this highlights the need to consider these constructs as individual vulnerability factors that increase the influence of ones' susceptibility to the thin-ideal internalization. One limitation of this study, like Hutchinson et al. (2010), was that the observed variances for each of the outcome variables were unclear.

The final study by Anbari et al. (2020) aimed to determine the DPM of binge eating based on Stice et al.'s (1996) original framework with two proposed additions: self-esteem and fear of negative evaluation. Low self-esteem and fear of negative self-evaluation have been suggested to motivate individuals to seek achievements in a valued domain such as weight and shape, which in turn may lead to unhealthy weight control behaviors (Trompeter et al. 2018). Binge eating occurs when cognitive control of overeating is disrupted.

This extended DPM was tested on 252 female university students with a BMI higher than 25. It was found that neither binge eating nor self-esteem predicted

restrained eating. Fear of negative evaluation predicted binge eating through body dissatisfaction. Binge eating was inversely predicted by self-esteem. The authors concluded that fear of negative evaluation is a vulnerability factor that enhances body image concerns, decreases self-esteem, and leads to binge eating. Once again, the variance accounted for in the binge eating outcome variable was not assessed.

In summary, the five cross-sectional studies have found evidence for the DPM, accounted for between 56% (Duemm et al. 2003) and 71% (Stice et al. 1996) of the variance in the BN outcome measures. However, only two out of the five studies provided data on the variance accounted for by the model in the BN or binge eating outcome variable. While these studies provide preliminary support for the DPM, there are some inconsistencies among them, most notably, regarding the influence of dietary constraint, as noted above. The next section of this review will look at longitudinal research that has investigated the DPM.

Longitudinal Studies

To our knowledge, only five studies (Allen et al. 2012; Puccio et al. 2016b; Puccio et al. 2019; Blodgett Salafia and Gondoli 2011; Stice et al. 1998) to date have employed a longitudinal design using either SEM or path-analysis to assess the validity of the DPM. Table 2 provides an overview of these longitudinal studies.

The model was initially examined longitudinally by Stice et al. (1998). A sample of 218 adolescent females was examined at Time 1 and then again 9 months later at Time 2 to assess BN symptoms. The results showed that the model explained 33% of the variation in BN symptoms, and all paths were significant except for BMI and pressures to be thin. While this study found that dietary restraint and negative affect predicted BN symptoms at follow-up, all the other pathways investigated in the model were cross-sectional. As such, Stice et al.'s (1998) study can only give limited evidence for the original DPM's predictive value.

In a later study, Blodgett Salafia and Gondoli (2011) prospectively investigated the DPM in a sample of grade 5 females over a 4 year period including four assessment points, including baseline. The authors evaluated all factors in Stice et al.'s (1996) original DPM, except for internalization of the thin ideal. Blodgett Salafia and Gondoli (2011) also investigated the impact of mothers, dads, and peers on the emergence of BN symptoms. The DPM was supported in this study, except for the path from T3 dietary restraint to T3 depression, which was not significant. Furthermore, different forms of sociocultural influences (e.g., peers, mothers, and fathers) were associated with a greater risk of developing BN symptoms, with peers having the greatest influence in the model. Because the average age of this sample at baseline was around 10 years, analyses from this study also revealed that these putative risk variables had predictive value during childhood. A limitation of this study was that the study did not provide any data with regard to how much variance was accounted for by each of the outcome variables.

The third longitudinal study of the DPM was conducted by Allen et al. (2012), which evaluated 236 children (48% male, ages 8–13) at baseline (T1), 1 year after

Table 2 Overview of the longitudinal DPM studies

Author	Aim(s)	Sample	Age – Yrs SD (M)	Female (*N*)	Ethnicity (*N*)	Sample	Measures	Longitudinal	Significant pathways	Main findings
Stice et al. (1998)	Tested the predictors in the DPM at T1, and BN at T2, to provide evidence of temporal precedence, and hence, for the directionality of the effects	218	N/A–Age ranged from 16 to 18	218 (100%)	Caucasian (169; 77.52%)	Community	Perceived Sociocultural Pressure Ideal Body Stereotype Scale Body Areas Satisfaction Scale Dutch Restrained Eating Scale Positive and Negative Affect Schedule – Expanded Form Eating Attitudes Test-26 The Bulimia Test Revised	**T1 (baseline)** Perceived pressure to be thin BMI BD Ideal body internalization DR NA **T2 (9 months)** BN	BMI T1 → BD T1- BMI T1 → perceived pressure to be thin T1 Perceived pressure to be thin T1 → ideal body internalization T1 Perceived pressure to be thin T1 → BD T1 Perceived pressure to be thin T1 → DR T1 Ideal body internalization T1 → BD T1 BD T1 → DR T1 BD T1 → NA T1 DR T1 → NA T1 DR T1 → BN T2	***Longitudinal support for the DPM***

(continued)

Table 2 (continued)

Author	Aim(s)	Sample	Age – Yrs SD (M)	Female (*N*)	Ethnicity (*N*)	Sample	Measures	Longitudinal	Significant pathways	Main findings
									NA T1 → BN T2	
Blodgett Salafia and Gondoli (2011)	(1) Longitudinally examined the DPM and (2) assessed the relative contribution of parents and peers (via direct encouragement or pressure to be thin and indirect discussion of dieting)	85	10.59 (0.52)	85 (100%)	Caucasian (79; 92.94%)	Community	Family History of Eating Peer Pressure to be Thin Scale Eating Disorders Inventory Dieting Behaviours Scale Children's Depression Inventory	**T1 (baseline)** Paternal encouragement to lose weight Parental discussion of dieting Peer pressure to be thin Peer discussion of dieting BMI BD DR NA (depression) BN **T2 (1 year after baseline)** Paternal encouragement to lose weight Parental discussion of dieting Peer pressure to be thin	Paternal encouragement to lose weight grade 5 → peer pressure to be thin grade 5 Peer pressure to be thin grade 5 → paternal encouragement to lose weight grade 5 BN grade 5 → peer pressure to be thin grade 5 Peer pressure to be thin grade 5 → BN grade 5 Peer pressure to be thin grade 5 → BD grade 6 BD grade 6 → BMI grade 6 BD grade 6 → DR grade 7 BD grade 6 → depression grade 7	***Longitudinal support for the DPM***

					Peer discussion of dieting BMI BD DR Depression BN **T3 (1 year after T1)** Paternal encouragement to lose weight Parental discussion of dieting Peer pressure to be thin Peer discussion of dieting BMI BD DR Depression BN **T4 (1 year after T3)** Paternal encouragement to lose weight Parental discussion of dieting	Depression symptoms grade 7 → BN grade 8 DR grade 7 → BN grade 8 BMI grade 6 → BD grade 6 BMI grade 6 → DR grade 7

(continued)

Table 2 (continued)

Author	Aim(s)	Sample	Age – Yrs SD (M)	Female (*N*)	Ethnicity (*N*)	Sample	Measures	Longitudinal	Significant pathways	Main findings
								Peer pressure to be thin Peer discussion of dieting BMI BD DR Depression BN		
Allen et al. (2012)	Evaluated and compared the DPM, original cognitive-behavioral, and enhanced "transdiagnostic" cognitive-behavioral models of binge eating	236	10.05 (1.41)	122 (51.69%)	N/A	Community	Multidimensional Media Influence Scale Self-Perception Profile for Children Oxford Risk Factor Students' Life Satisfaction Scale Child Eating Disorder Examination Child Depression Inventory Binge Eating Scale	**T1 (baseline)** BMI Media influences **T2 (1 year after baseline)** Weight and shape concern **T3 (1 year after T2)** DR Depression Binge eating	BMI T1 → media influences T1 BMI T1 → weight and shape concern T2 Media influences T1 → weight and shape concern T2 Weight and shape concern T2 → DR T3 Weight and shape concern	***Longitudinal support for the DPM***

									T2 → depression T3 Depression T2 → NA depression T3 Depression T3 → binge eating T3 DR T3 → binge eating T3 DR T2 → DR T3	
Puccio et al. (2016)	Examined the original DPMlongitudinally and assessed whether social comparisons made on Facebook and sociotropy assessed at T1 influenced the model	245	23.77 (7.10)	245 (100%)	N/A	Community	Body Stereotype Scale-Revised Perceived Sociocultural Pressure Scale Body PartsSatisfaction Scale-Revised Centre for Epidemiologic Studies DepressionScale Eating Attitudes Test-26 Personal Style Inventory-II	**T1 (baseline)** Pressure to be thin Thin-ideal internalization BD Sociotropy Social comparison made on FB **T2 (4 weeks)** DR BN Depression	**OriginalDPM model** Pressure to be thin T1→ thin-ideal internalization T1 Pressure to be thin T1 → BD T1 Thin-ideal internalization T1→ BD T1 BD T1 → BN T2 BD T1→ depression T2 DR T2 → BN T2 DR T2 →	***Longitudinal support for the original and the extended DPM.***

(continued)

Table 2 (continued)

Author	Aim(s)	Sample	Age – Yrs SD (M)	Female (*N*)	Ethnicity (*N*)	Sample	Measures	Longitudinal	Significant pathways	Main findings
									depression T2 **Extended DPM model** Sociotropy T1 → social comparison made on FB T1 Sociotropy T1 → pressures to be thin T1 Sociotropy T1 → BD T1 Sociotropy T1 → BN T1 Pressure to be thin T1 → BD T1 Social comparison made on FB T1 → BD T1 Social comparison made on FB T1 → BN T2 Social comparison made on FB T1→ pressures to be thin T1 BD T1 → BN	

									T2 BD T1 → depression T2 DR T2 → BN T2 DR T2 → depression T2	
Puccio et al. (2019)	(1) Examined the bidirectional effects among symptoms of depression, DR, and BN in the DPM (2) Assessed the influence of negative urgency, a personality construct associated with BN symptoms, on the DPM	244	23.90 (7.19)	244 (100%)	Caucasian (140; 57.37%)	Community	Ideal Body Stereotype Scale-Revised Perceived Sociocultural Pressure Scale Body Parts Satisfaction Scale-Revised Urgency, Premeditation, Perseverance, Sensation Seeking Scale Centre for Epidemiologic Studies Depression Scale Eating Attitudes Test-26	**T1 (baseline)** Pressure to be thin Thin-ideal internalization BMI Depression BD BN DR Negative urgency **T2 (1 month)** Depression DR BN Negative urgency	**Variables in the original DPM model** Thin-ideal internalization T1 → BD T1 BMI T1 → pressure to be thin T1 BD T1 → DR T1 BD T1 → depression T1 BD T1 → depression T2 DR T1 → BN T1 DR T1 → DR T2 DR T2 → depression T2 BN T1 → BN T2 Depression T1 → BN T1 Depression T1 →	***Longitudinal support for the original and the extended DPM***

(continued)

Table 2 (continued)

Author	Aim(s)	Sample	Age – Yrs SD (M)	Female (*N*)	Ethnicity (*N*)	Sample	Measures	Longitudinal	Significant pathways	Main findings
									depression T2 Depression T1 → DR T2 Depression T2 → BN T2 **New variable** Negative urgency T1 → BD T1 Negative urgency T1 → BN T2 Negative urgency T1 → depression T1 Negative urgency T1)→ depression T2	

Note: DPM = dual pathway model; BMI = body mass index; DR = dietary restraint; NA = negative affect; BD = body dissatisfaction; BN = bulimia symptoms

baseline (T2), and then 2 years after baseline (T3). Allen et al. (2012) assessed all factors in the original DPM (Stice et al. 1996), apart from thin-ideal internalization, as did Blodgett Salafia and Gondoli (2011). While Allen et al. (2012) found their model to have an acceptable fit for the data, the following paths were found to be nonsignificant: BMI T1 → pressures to be thin T1 and body dissatisfaction T2 → depressed symptoms T3. It is worth mentioning that Allen et al. (2012) did not examine the effect of T3 dietary restraint on T3 depression. Their model explained 54% of the variance in binge eating symptoms at T3; however, they did not consider compensatory behaviors in their analyses. Therefore, their findings could not be generalized as an etiological model for BN symptoms.

The fourth study by Puccio et al. (2016) aimed to assess the validity of the original DPM (Stice et al. 1996) longitudinally. A total of 247 young females participated in the baseline (T1) and at 1-month follow-up (T2) assessments. A shorter 1-month follow-up timeframe than the previous studies was used in Puccio et al.'s (2016) study to further understand the mediating processes that may contribute to BN symptoms. This decision was made because previous research (Dormann and Griffin 2015) has identified that the optimal time-lags might in fact be shorter (e.g., within the vicinity of months) rather than longer [e.g., within the vicinity of a year(s)]. The aims of Puccio et al.'s (2016) study were twofold: (1) to evaluate the DPM prospectively, considering all components as described by Stice et al. (1996), by looking at the model at baseline (time 1; T1) and dietary constraint, depressive symptoms, and BN symptoms 1 month later (time 2; T2). (2) to test a revised DPM with two additional variables Facebook social comparison and sociotrophy, had an impact on the BN risk factors reported in the model.

Social comparisons made on Facebook were included since previous DPM research was constrained by not measuring modern pressures that women are exposed to, including social media. Given Facebook's apparent global ubiquity, Puccio et al. (2016) contended that it was vital to investigate whether this factor is etiological to BN symptomology by including it in the DPM. In this redesigned DPM, Puccio et al. (2016) examined whether social comparisons on Facebook were associated with body dissatisfaction and thin-ideal internalization. The researchers also aimed to explore whether sociotropy was linked to pressures to be thin, thin-ideal internalization, and Facebook social comparisons. This study was the second study to include the cognitive bias of sociotropy in the DPM, and the authors' rationale for this inclusion was guided by the findings obtained by Duemm et al. (2003) which found sociotropy to be an important variable influencing the DPM.

The findings of Puccio et al.'s (2016) path-analyses revealed that the original and revised DPMs had excellent fit to the data once the respective models were modified. T1 pressures to be thin and T1 thin-ideal internalization were both linked to T1 body dissatisfaction in both DPMs. T1 body dissatisfaction, but not T2 dietary restraint, predicted T2 depressed symptoms and T2 BN symptoms prospectively. Furthermore, T2 dietary restraint was related to T2 BN symptoms, but not T2 depressed symptoms. T2 dietary restraint was also linked to T2 depressive symptoms. For the revised DPM, T1 social comparisons on Facebook were linked to T1 body dissatisfaction, T1 pressured to be thin, and T2 BN symptoms. T1 social comparisons on

Facebook were also related to T1 sociotropy, and T1 social comparisons on Facebook were related to T1 sociotropy. Like Stice et al.'s (1998) study, this study was limited by only assessing certain variables (dietary restraint, depression, and BN symptoms) at T2.

The second study by Puccio et al. (2019) assessed the DPM using the same sample as in their 2016 study but employing a different type of analysis. The first aim of this study was to assess the original DPM (Stice et al. 1996) cross-sectionally and to include a longitudinal extension of the model that examined the bidirectional effects among T1 and T2 symptoms of BN, depression, and dietary restraint. To assess these bidirectional effects, cross-lagged modeling was used to determine if two or more constructs were unidirectionally or bidirectionally connected over time. Cross-lagged modeling is a type of SEM that allows researchers to evaluate non-recursive models (i.e., a postulated relationship between two or more variables assessed at two or more time points and assumed to be reciprocally causal) (Martens and Haase 2006), to look at the stability of constructs over time, simultaneously (cross-sectional) and cross-lagged (longitudinal) direction of effects. This type of analysis is crucial when determining whether the relationship between depression and eating disorders is bidirectional. Figure 2 depicts the cross-lagged DPM model used in Puccio et al.'s (2019) study.

The second goal of Puccio et al.'s (2019) study was to examine whether negative urgency improved the DPM's predictive value over and above the initial bidirectional model described in Fig. 2. A previous meta-analysis by Fischer et al. (2008) found that negative urgency had the strongest association with impulsivity. Furthermore, numerous studies have shown that behaving rashly when experiencing psychological distress/poor affect (i.e., negative urgency) increases the risk of binge eating and purging behavior (Hagan et al. 2021; Magel and von Ranson 2021).

Except for T1 BMI and body dissatisfaction, Puccio et al.'s (2019) model had an excellent fit to the data, indicating that all paths of the DPM described by Stice et al. (1996) were positive and significant. The following paths were also found to be positive and significant in improving the model fit: T1 pressures to be thin → T1 dietary restraint, T1 pressures to be thin → T2 depression, T1 body dissatisfaction → T2 depression, T1 body dissatisfaction →T2 depression, T1 body dissatisfaction →T2 BN symptoms. As a result, the outcomes of this research provided reasonable evidence for the validity of the DPM. There were no bidirectional effects between BN, depression, and dietary restraint in this first model that was evaluated; nevertheless, T1 dietary restraint predicted T2 BN symptoms, and T1 depression predicted T2 dietary restraint. The results for the second goal showed that T1 negative urgency was strongly related to T1 pressures to be thin, T1 body dissatisfaction, and T2 depression, indicating a good model fit for the second model that was examined.

Overall, Puccio et al.'s (2019) model explained 59% and 44% of the variance in T1 and T2 BN symptoms, respectively. These findings suggest that T1 BN symptoms were significantly more explanatory than T2 BN symptoms when considered longitudinally. Regardless, the findings of this study imply that the DPM is a relevant paradigm for BN symptom onset and persistence. The model was also found to

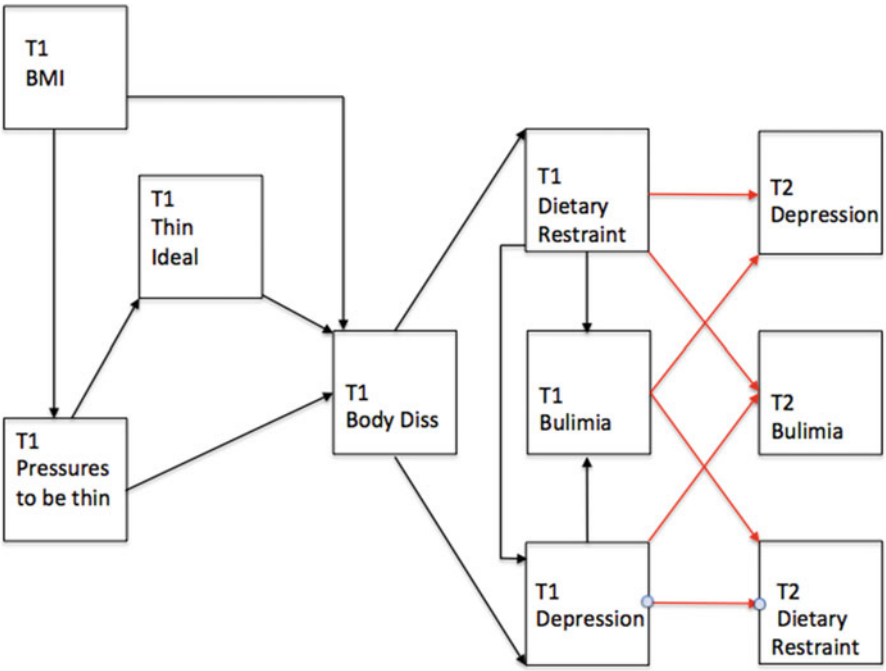


Fig. 2 Cross-lagged model of the DPM assessed in Puccio et al.'s (2019) study. *(Note.* BMI = body mass index; thin ideal = thin-ideal internalization; body diss = body dissatisfaction; bulimia = bulimic symptoms; depression = depressive symptoms; T1 = time 1; T2 = time 2. Black lines represent the original DPM as proposed by Stice et al. (1996). Red lines represent the extended conceptualization of the DPM that includes longitudinal bidirectional effects between symptoms of depression, bulimia, and dietary restraint at T1 and T2)

explain 44% and 63% of the variance in T2 symptoms of depression and dietary constraint, respectively.

Overall, the findings of this study show that early social pressures to be thin, thin-ideal internalization, and higher BMI and body dissatisfaction lead to symptoms of depression, constrained eating, and BN both cross-sectionally and longitudinally. The findings of this study also imply that depression and dietary restraint symptoms occur simultaneously, and that these symptoms lead to BN symptoms, which predict later BN and dietary restraint symptoms.

In conclusion, only a small number of studies ($n = 5$) have used path-models or SEM to examine the DPM over time. Despite differences in conceptualization and assessment of the DPM among individual studies, these studies provide reasonable support for the DPM's central proposition: that the effects of body dissatisfaction on eating pathology are mediated by depression/negative affect and dietary restraint. The overall variance accounted for in BN/binge eating symptoms in these studies ranged from 33% (Stice et al. 1998) for BN symptoms to 54% (Allen et al. 2012) for binge eating symptoms. However, as only three longitudinal studies (Puccio et al.

2016, 2019; Stice et al. 1998) evaluated the full DPM model, further research is needed to see if the model can predict outcomes in a longitudinal design.

A Note on the Predictive Utility of the DPM for BN

As previously stated, preliminary evidence supports the DPM's (Stice et al. 1996) predictive value. The five longitudinal studies that have examined the model using SEMs or path-models (Allen et al. 2012; Puccio et al. 2016b, 2019; Salafia and Gondoli 2010; Stice et al. 1998) have explained between 33% (Stice et al. 1998) and 54% (Allen et al. 2012) of the variation in their individual measures of eating disorder symptoms. This conclusion shows that there are other key risk variables for eating disorders that have yet to be included in the DPM. According to the DPM, BN symptoms are caused by a cascade of cognitive and psychological processes triggered by sociocultural expectations to be thin. While the DPM has shown some predictive utility in limited research, there is a theoretical gap in the model that needs to be addressed: The DPM is unable to explain why only some people who are exposed to sociocultural pressures to be thin develop BN pathology, while most people who are exposed to similar pressures do not.

It is arguable that most, if not all, people in Western civilization are subjected to sociocultural pressure to follow the thin ideal. Despite this, only a small percentage of people will develop eating disorders. The DPM's central hypothesis is that negative affect and dietary restraint mediate the relationship between body dissatisfaction and BN symptoms; however, the model makes no predictions about the factors that predispose a person to transition from body dissatisfaction to restrained eating and/or negative affect. Understanding why only some people with body dissatisfaction develop restrained eating behaviors and negative affect will not only help to improve the model's validity and predictive utility but provide insight into the etiology of BN and therefore, assist in the development of treatment interventions designed to alleviate these eating pathology symptoms.

Limitations of Previous Studies and Future Directions

While the research detailed above has shown support for the predictive utility of the DPM for BN symptoms, these studies are not without limitations.

First, as highlighted above, only five cross-sectional studies (e.g., Duemm et al. 2003; Stice et al. 1996) and five longitudinal studies (e.g., Puccio et al. 2016b, 2019; Stice et al. 1998) have assessed the DPM in its entirety. Given these low numbers, further research is required to assess the entire DPM to determine evidence for its validity and predictive utility.

Second, despite the use of well-validated self-report measures, social desirability bias and mood at the time of assessment may have hindered the validity of the results reported in the different studies. Multiple report methods and/or clinical interviews should be used in future studies to strengthen the current findings.

Third, to date, only a paucity of studies (e.g., Allen et al. 2012; Blodgett Salafia and Gondoli 2011; Stice et al. 1996) have examined the influence of BMI on specific paths within the DPM.Therefore, it is difficult to draw firm conclusions regarding the influence of BMI within the DPM. As such, future studies are required to assess the influence of BMI on the DPM.

Fourth, most studies have relied on female studies, limiting generalizability. As BN symptoms are also prevalent among males (van Eeden et al. 2021), future research should determine whether the revised DPM is also applicable in this sample. Moreover, while the DPM has been associated with a desire to obtain the thin ideal, past research (Yelland and Tiggemann 2003) has identified that many males might also engage in eating pathology behaviors to achieve a muscular physique. Therefore, future research utilizing males as well as females would be beneficial. Such research into the links between the risk factors outlined in the DPM for males might also benefit from utilizing measures that assess eating pathology cognitions and behaviors that focus on the pursuit of muscularity (e.g., the drive for muscularity scale; Yelland and Tiggemann 2003).

Fifth, most studies that examined the DPM assessed either children, adolescents, or very young adults. Thus, to date no study has examined whether the model applies to an older age range of individuals. As research (e.g., Jaite et al. 2013) has found that the age range of onset for meeting criteria for BN is between 20 and 24 years of age, the current literature is limited in that is has yet to examine the validity of the DPM in a sample of older individuals (e.g., aged 40 years and above).

Sixth, while the DPM was originally proposed to be a model that accounts for the development and maintenance of BN symptoms, some studieshave only assessed binge eating (e.g., Allen et al. 2012) and not complete BN symptoms. While these studies have contributed important findings regarding the factors that influence the etiology of eating pathology as assessed via the DPM, further research is required to test the original proposition that the DPM is a model that accounts for the etiology of BN symptoms. Hence, further studies that utilize BN symptoms as the outcome measure for the DPM are required.

Seventh, all cross-sectional and longitudinal studies to date that have assessed the DPM have been nonclinical in nature. It is therefore essential to replicate the DPM model in clinical populations. However, since SEM and path-models require relatively large sample sizes, it can be difficult to obtain these sample sizes through recruitment of tertiary treatment facilities.

Eighth, only one of the longitudinal studies (Puccio et al. 2019) examined the bidirectional relationship between BN symptoms and depression. Given that each of these constructs might be a risk factor for the other (Puccio et al. 2016a), future research should test such bidirectional effects. Future research might also attempt to map more specific affective states onto specific BN behaviors. For instance, depression may be particularly related to binge eating, whereas anxiety is more associated with purging.

Ninth, although some predictive pathways were found in the revised longitudinal DPMs (e.g., Puccio et al. 2016b), many of the conclusions drawn regarding the new constructs were based on cross-sectional data, which precluded causal

understanding. A prospective design with multiple time points might assist in confirming the hypothesized direction of the pathways in these revised DPMs.

Finally, only one study (Puccio et al. 2019) assessed negative urgency as a potential moderating variable. More research should begin to examine factors that might moderate the proposed pathways. Future research should also attempt to provide more integrative analyses of the probably mediational and interactive relations among the putative risk factors for BN.

Clinical and Prevention Implications

The findings of the reviewed studies suggest important implications for future BN preventive efforts. Specifically, since most of the factors in the original and revised DPM have been found to direct or indirect effects on BN risk factors or symptoms, an integrative prevention approach may be required. Indeed, randomized control trials that have focused on the prevention of various BN risk factors (i.e., healthy weight control behaviors, coping skills to challenge pressures, media literacy, and body satisfaction) have shown to reduce BN symptoms in females at 12-month follow-ups (e.g., McVey et al. 2003; Stice et al. 2012). Based on the results from the revised DPMs (e.g., Anbari et al. 2020; Maraldo et al. 2016; Puccio et al. 2016b), future iterations of such preventative efforts could educate women on the deleterious effects of these additional risk factors (e.g., social comparisons on Facebook, fear of negative evaluation, rumination, etc.) may have on body dissatisfaction, dieting, negative affect, and BN symptoms.

In addition, the current findings also highlight the need for preventative efforts to identify individuals scoring high on certain personality traits (e.g., sociotropy and negative urgency) to assess which individuals might be more susceptible for these BN risk factors and tailor prevention efforts accordingly. For instance, people scoring high on sociotropy could learn to become less dependent on others for approval and challenge peer-related pressures to be thin (Puccio et al. 2016b). In terms of negative urgency, interventions could help individuals to regulate negative emotions efficiently to prevent them to act rashly during times of distress and therefore reduce bingeing/purging symptomatology (Puccio et al. 2019). Overall, lowering all these different facets of the DPM could be instrumental in helping reduce the risk of future BN symptoms in women.

Conclusions

The present chapter provides a review of the DPM for BN symptoms by first outlining the key risk factors included in the DPM and then presenting a narrative review of the studies that have empirically assessed the DPM using either path-analyses or SEMs. A total of ten studies were retrieved that have assessed the DPM in its entirety, five of which were cross-sectional and five longitudinal. Overall, the findings from the identified studies provide support for most of the pathways

outlined in the DPM; however, the predictive capacity of the assessed models suggests that the DPM is not able to explain the full occurrence of BN symptoms. It is hoped that upcoming research can assist in informing future preventive efforts for BN risk factors, with the hope that the DPM might become broader. Some promising extensions of the DPM have already been suggested and tested. It would be important for future studies to agree on the additional key factors so that standardized research on these new facets in addition to the original DPM can be conducted. Finally, for our understanding of the development of BN symptomology to progress, further research is needed to clarify the direction of effects between the risk factors outlined in the original and revised versions of DPM.

Applications to Other Eating Disorders

In the current chapter, we reviewed studies that replicated and/or extended the original DPM of BN (Stice et al. 1996). Empirical evidence has shown that variables within the DPM (i.e., sociocultural pressure to thin, thin-ideal internalization, body dissatisfaction, negative affect, and dietary restraint) are risk factors not only for BN but also for other eating disorders such as anorexia nervosa (Ahern et al. 2008; Urvelyte and Perminas 2015), binge eating disorders (Allen et al. 2012), and other specified feeding and eating disorders [which have many features in common and high rates of diagnostic crossover (Fairburn and Harrison 2003)]. These variables are also known risk factors for subclinical forms of eating disorders among community/nonclinical samples (Quick and Byrd-Bredbenner 2013). Specifically, both thin-ideal internalization and initial pressure to be thin predicted subsequent increase in body dissatisfaction, initial body dissatisfaction is a precursor for dieting and negative affect, and initial dieting and negative affect predicted growth in anorexia nervosa, BN, and binge eating disorder symptoms. Hence, it is tempting to speculate that Stice et al.'s (1996) original DPM may also be applicable to a broader range of clinical eating disorders and disordered eating symptoms beyond BN. This has implications for enhancing understandings of the etiology of all type of eating disorders and disordered eating symptoms, as well as the factors underpinning their diagnostic crossover,therefore informing potential prevention and early intervention strategies that prevent against the likelihood of ominous consequences associated with eating pathology.

Mini-Dictionary of Terms

Body dissatisfaction – dissatisfaction with one's weight, shape, and/or size.

Body mass index – is calculated by dividing the body mass by the square of the body height and is given in kilograms per square meter.

Bulimia nervosa – is an eating disorder characterized by binge eating and purging behaviors.

Depression – is a mood disorder characterized by persistent feeling of sadness and loss of interest that affect everyday functioning.

Dietary restraint – the conscious efforts to lose weight by achieving a negative energy balance between calorie intake and expenditure.

Negative affect – an internal feeling that takes place when one has failed to achieve a goal or has avoided a threat.

Path-analyses – is a statistical analysis used to assess the interrelationship among observed variables.

Structural equation modeling – is a statistical analysis used to assess the interrelationship among observed and latent variables.

Sociocultural pressures – external media and interpersonal (parents and peers) influences which generate and diffuse unrealistic body-shape ideals.

Thin-ideal internalization – the extent to which an individual subscribes/aspires to the cultural standard of thinness.

Key Facts

- A higher BMI is supposed to increase one's chance of developing disordered eating symptoms.
- Pressures to be thin from peers, parents, and the media have been linked to all variables included in the DPM.
- Thin-ideal internalization, body dissatisfaction, and dietary restraint are the most prominent risk factors for eating disorders.
- Disordered eating symptoms lead to negative affect/mood and negative affect/mood to disorder eating symptoms.
- The dual pathway model is an etiological model for BN.

Summary Points

- The DPM is a prominent model to explain the multifaceted etiological relationship of various BN risk factors.
- The current review found a total of ten studies that assessed the DPM in its entirety, five of which were cross-sectional and five longitudinal.
- The findings from the identified studies provide support for most of the pathways outlined in the DPM for the cross-sectional and longitudinal studies.
- The predictive capacity of the assessed models suggests that the DPM is not able to explain the full occurrence of BN symptoms.
- Some promising extensions of the DPM have already been suggested and successfully tested.

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Bulimia Nervosa: Reproduction and Consequences for Mother and Child

46

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Contents

Introduction 924
Bulimia Nervosa and Fertility 925
Polycystic Ovary Syndrome 925
Polycystic Ovary Syndrome in Bulimia Nervosa 926
Management and Treatment of Amenorrhea in Bulimia Nervosa 927
Long-Term Effect on Fertility 928
The Prevalence of Bulimia Nervosa in Pregnancy 929
Disease Course in Pregnancy and Pregnancy and Perinatal Outcomes in BN 929
The Postpartum Period 930
Children to Mothers with Eating Disorders 931
Management of Pregnant Women with Bulimia Nervosa 931
Applications to Other Eating Disorders 932
Key Facts 933
Key Facts of Amenorrhea in Bulimia Nervosa 933
Key Facts of Pregnancy and Perinatal Outcomes in Women with Bulimia Nervosa 934
Key Facts of Management of Pregnant Women with Bulimia Nervosa 934
Summary Points 934
References 935

Abstract

Bulimia nervosa (BN) is characterized by cycles of recurrent episodes of binge eating and compensatory behavior, i.e., vomiting, in order to prevent weight gain. In women, the peak incidence of BN is between 15 and 29 years of age, signifying

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the importance to understand the impact of the disease on reproductive function, pregnancy, and postpartum period *and* how children to mothers with eating disorders are affected. Bulimia nervosa is associated with menstrual disturbances, which commonly are attributed to either functional hypothalamic amenorrhea or polycystic ovary syndrome, and hence impaired fertility.

On long term, women with BN seem to have similar reproductive outcomes as healthy women. Importantly, pregnancy constitutes a vulnerable time period and could affect the disease course among women with ongoing disease and possess a relapse risk for women with previous disease. Consequently, it is important to identify these women in maternal healthcare in order to provide adequate support and management to prevent adverse outcomes. Maternal bulimia nervosa is associated with several adverse pregnancy-related outcomes, including anemia, hyperemesis gravidarum, gestational diabetes, and premature delivery. Children to mothers with eating disorders seem to suffer from an increased risk of developing specific conditions throughout childhood. This chapter reviews available evidence on the impact of bulimia nervosa on fertility, pregnancy, and postpartum period and childhood health.

Keywords

Bulimia nervosa · Reproduction · Pregnancy · Postpartum · Amenorrhea · Fertility · Functional hypothalamic amenorrhea · Neonatal · Child health · Anemia · Preterm delivery · Head circumference

Abbreviations

AN	Anorexia nervosa
BN	Bulimia nervosa
FHA	Functional hypothalamic amenorrhea
FSH	Follicle-stimulating hormone
GH	Growth hormone
GnRH	Gonadotropin-releasing hormone
HG	Hyperemesis gravidarum
LH	Luteinizing hormone
PCOS	Polycystic ovary syndrome
SGA	Small for gestational age
SHBG	Sex hormone-binding globulin

Introduction

Despite that women with bulimia nervosa (BN) commonly are of normal weight, the prevalence of menstrual dysfunction in BN is high. Periods of starvation can induce functional hypothalamic amenorrhea (FHA) by a similar mechanism as seen in women with anorexia nervosa (AN). BN is additionally linked to polycystic ovary syndrome (PCOS), characterized by hyperandrogenism and oligo- or anovulation.

Pregnant women with ongoing or previous BN suffer from an increased risk of multiple pregnancy complications and are likewise at increased risk of impaired exacerbation of eating disorder symptoms and depression in the postpartum period. Therefore, early identification of women with BN in fertility and antenatal maternal healthcare is essential in order to provide adequate advice, treatment, and intensified support throughout the pregnancy and postpartum period.

Bulimia Nervosa and Fertility

The prevalence of secondary amenorrhea among women with bulimia nervosa (BN) is higher (between 7% and 40%) (Kimmel et al. 2016) compared with the general population, and many bulimic women suffer from oligomenorrhea (irregular menstruations with long intervals). Whereas the amenorrhea among women with anorexia nervosa (AN) is mainly explained by functional hypothalamic amenorrhea (FHA), amenorrhea in BN may have various etiologies. FHA is characterized by a hypothalamic inhibition of the reproductive system induced by energy deficit and is described in detail in chapter "Anorexia Nervosa and Reproductive Health". The temporary starvation periods between binge-eating episodes, which are characteristic of BN, may result in FHA and consequently amenorrhea and infertility. In fact, endocrine disturbances, including low levels of estradiol, gonadotropins, and thyroid hormones, have been observed in women with BN. In addition to FHA, BN has been associated with polycystic ovary syndrome (PCOS), a hormonal aberration characterized by oligo- or amenorrhea.

Polycystic Ovary Syndrome

PCOS is a common endocrinopathy in reproductive-aged women, with a reported prevalence of between 6 and 16% in population-based studies (Li et al. 2013; Lizneva et al. 2016). PCOS is characterized by oligo- or anovulation, hyperandrogenism, and numerous small ovarian cysts (Goodarzi et al. 2011). The Rotterdam consensus diagnostic criteria are used for diagnosis and include (i) oligo- or anovulation, (ii) clinical or biochemical hyperandrogenism, and (iii) polycystic ovarian morphology (Table 1). Fulfilment of two out of three diagnostic criteria is

Table 1 Diagnostic criteria of PCOS according to Rotterdam consensus

Two of three criteria necessary for PCOS diagnosis
I. Oligo- or anovulation.
II. Clinical and/or biochemical hyperandrogenism. *Clinical signs = hirsutism, acne* *Biochemical = elevated FAI (S-testosterone > SHBG)*
III. Polycystic ovarian morphology (PCOM) on ultrasound.

PCOS, polycystic ovary syndrome; FAI, free androgen index; PCOM, polycystic ovary morphology; SHBG, sex hormone-binding globulin

needed for diagnosis (Rotterdam 2004). Given the heterogenous presentation of PCOS, further stratification into distinct phenotypes based on prevalent Rotterdam criteria is recommended (The not fully known etiology of PCOS is presumably multifactorial and involving both environmental and genetic factors. A reported aggregation of PCOS within families and first-degree relatives implies a genetic predisposition (Yildiz et al. 2003). The syndrome is frequently associated with the metabolic syndrome, including insulin resistance, abdominal obesity, and dyslipidemia (McCartney and Marshall 2016).

PCOS is characterized by hypothalamic dysfunction, but it is not known whether the dysfunction is primary or rather secondary as a consequence of abnormal steroid feedback. Regardless of etiology, the altered GnRH pulsatility in PCOS leads to increased levels of luteinizing hormone (LH) in relation to follicle-stimulating hormone (FSH). The altered LH:FSH ratio results in an increased production of androgens within the ovaries and a decreased ovarian conversion of androgens into estradiol (Goodarzi et al. 2011). High intraovarian levels of androgens lead to follicular atresia and anovulation. Circulating high levels of androgens leads to dyslipidemia (increased levels of low-density lipoprotein [LDL], triglycerides, and total cholesterol and decreased levels of high-density lipoprotein [HDL]), acne, and hirsutism. In the periphery, circulating androgens are converted into estrogens, in particular in adipose tissue, and conversion is therefore amplified in obese patients. Hyperinsulinemia further stimulates the androgen production and suppresses the production of sex hormone-binding globulin (SHBG) in the liver, resulting in even higher androgen levels. The constant conversion of androgens into estrogens leads to unfluctuating high estrogen levels and a constant, nonfluctuating feedback to the hypothalamus and pituitary gland, which further disrupts the secretion of gonadotropins. Constant increased levels of estrogens promote endometrium hyperplasia resulting in an increased risk of endometrial abnormalities, including malignancies (Goodarzi et al. 2011; McCartney and Marshall 2016) (Fig. 1).

Polycystic Ovary Syndrome in Bulimia Nervosa

Bulimia nervosa is associated with PCOS, but the direction of the association is unclear. PCOS could be a consequence of the abnormal eating behavior in BN; alternatively, hyperandrogenism may predispose of the key symptoms of BN. In fact, appetite regulation is frequently disturbed among women with PCOS, and the prevalence of eating disorders in PCOS is increased (Hirschberg et al. 2004; Thannickal et al. 2020). Vice versa, there is an increased prevalence of PCOS features, including polycystic ovaries, acne hirsutism, and biochemical hyperandrogenism, in women with BN (McCluskey et al. 1992; Naessen et al. 2006).

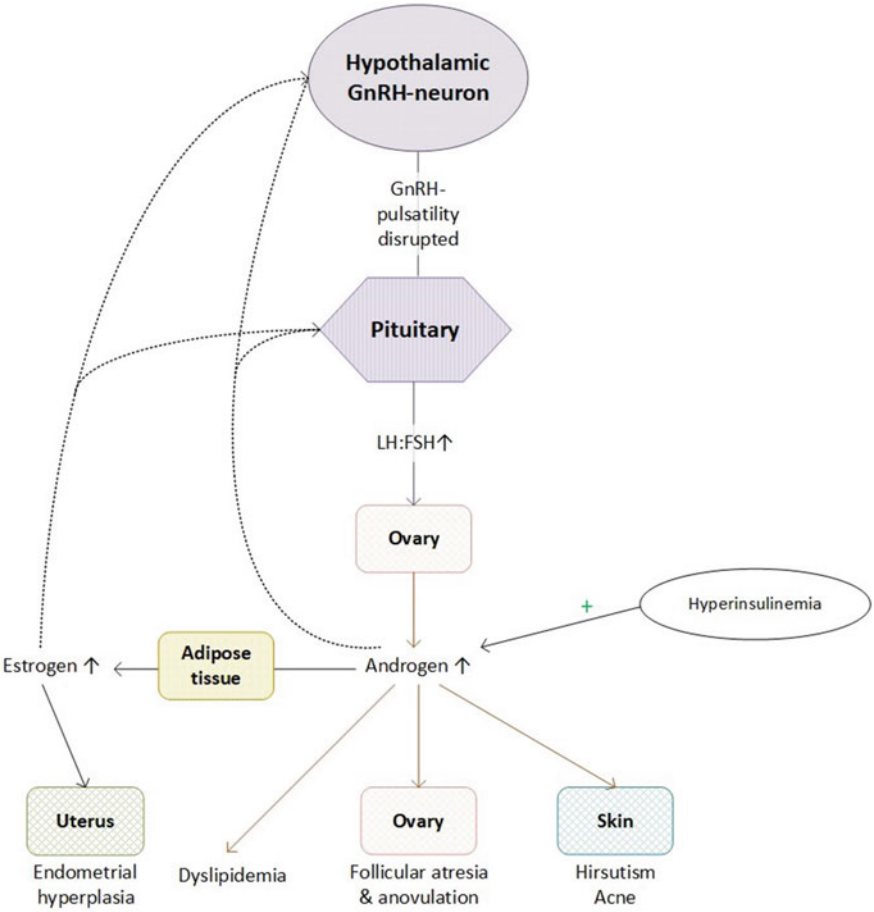


Fig. 1 Overview of pathophysiology in PCOS

Management and Treatment of Amenorrhea in Bulimia Nervosa

Oligo- or amenorrhea occurs frequently in women with BN, and as previously discussed, the most common underlying conditions are FHA and PCOS. In order to distinguish between the two and to rule out alternative or concomitant conditions, medical assessment including endocrine evaluation is necessary. FHA, which is described in detail in chapter on "Anorexia Nervosa and Reproductive Health," is characterized by low levels of gonadotropins, estradiol, and thyroid hormones, whereas PCOS is characterized by an increased LH:FSH ratio, high testosterone level, and low levels of SHBG (Phylactou et al. 2021). The endocrine differences between FHA and PCOS are summarized in Table 2.

Women with BN and FHA should be managed as women with AN and FHA (chapter "Anorexia Nervosa and Reproductive Health"), i.e., focusing on

Table 2 Clinical and biochemical differences between functional hypothalamic amenorrhea and polycystic ovary syndrome

	Polycystic ovary syndrome	Functional hypothalamic amenorrhea
Primary symptom	Oligo- or amenorrhea	Amenorrhea more common than oligomenorrhea
BMI	↑→	↓
Ovary morphology	Polycystic	N/A
Endometrial thickness	↑	↓
LH:FSH ratio	↑	↓
Estradiol	↑	↓
Testosterone	↑	↓
SHBG	↓	↑

BMI, body mass index; FSH, follicle-stimulating hormone; LH, luteinizing hormone; SHBG, sex hormone-binding globulin. ↑ indicates increased levels and ↓ indicates decreased levels

management of disordered eating and restoring energy balance. In women with BN and PCOS, treatment depends on the woman's goal in combination with endocrine aberrations and BN disease severity. Focusing on recovery from BN should be prioritized. Antiandrogenic combined oral contraceptives regulate menstruation, improve hirsutism and acne, and may additionally improve bulimic symptoms. Antiandrogenic oral contraceptives have been reported to improve eating behavior in women with BN (Naessen et al. 2007). In anovulatory infertility, ovulation could be stimulated using letrozole or clomiphene citrate (Legro et al. 2013). Metformin may improve ovulatory function and is recommended for women with PCOS and type 2 diabetes or insulin resistance (Conway et al. 2014).

Long-Term Effect on Fertility

In FHA, the menstrual function commonly normalizes with nutritional restoration and fertility naturally restores. PCOS expression seems to decline with increasing age and leading to normalized menstruation (Welt and Carmina 2013). It has been reported that women with PCOS have similar birth rates as women with normal ovulation (Forslund et al. 2019), but one study reported a lower rate of ≥2 deliveries in women with a PCOS history compared to PCOS-free controls (West et al. 2014). The specific long-term effect of FHA or PCOS in combination with BN has not been investigated. Compared to women with AN, women with BN seem to experience a more moderate reduction and delay in reproduction, and one study has reported that women with BN have similar reproductive outcomes as their discordant sisters (Tabler et al. 2018).

The Prevalence of Bulimia Nervosa in Pregnancy

Few studies have investigated the incidence of BN. Depending on the study setting and case definition, the reported incidence varies between 20 and 180 BN cases per 100,000 person-years in the general population, and the peak age of incidence is between 15 and 29 years (van Eeden et al. 2021). In contrast to AN, which seems to be increasing over time, the incidence of BN has reported to be declining in all age groups, except among girls between 10 and 14 years of age where an increasing trend has been observed (Reas and Ro 2018).

The lifetime prevalence of BN is between 0.3% and 4.6% (Galmiche et al. 2019).

The prevalence of BN in pregnancy has not been addressed specifically, but based on studies on eating disorders and pregnancy outcomes, the estimated prevalence of BN (past or current) in pregnancy is between 0.1% and 0.9% in studies using registered diagnosis as case definition (Ante et al. 2020; Eik-Nes et al. 2018; Mantel et al. 2020; Perrin et al. 2015). In studies identifying BN using diagnostic interviews or questionnaires, the self-reported prevalence is, slightly higher, between 0.7% and 1.3% (Easter et al. 2014; Micali et al. 2016; Popovic et al. 2018).

Disease Course in Pregnancy and Pregnancy and Perinatal Outcomes in BN

In similarity with AN, the recovery from BN is gradual, and one third of bulimic women have persistent eating disorder (Treasure et al. 2020). A high frequency of BN relapse in pregnancy among women with disease remission prior to pregnancy has been reported (Koubaa et al. 2005; Makino et al. 2020). In contrast, other studies have reported a continuation of eating disorder symptoms during pregnancy, but an improvement of symptom severity, in pregnancy among women with ongoing eating disorder (Blais et al. 2000; Micali et al. 2007b). Pregnant women with eating disorders, including BN, have a high prevalence of coexisting psychiatric disorders, including depression and anxiety (Bye et al. 2020; Mantel et al. 2020).

Maternal eating disorder is associated with several adverse pregnancy outcomes. Multiple studies have assessed the impact of AN or composite eating disorder exposure on pregnancy and perinatal outcomes, making it difficult to extrapolate these results to BN. In general, the increased risks of adverse pregnancy and perinatal outcomes seem to be more moderate in maternal BN compared with maternal AN, but still the risks of several outcomes are significantly increased. Women with BN are at increased risk of miscarriage (Micali et al. 2007a; Morgan et al. 2006).

Anemia during pregnancy is a more common finding in women with current or past BN compared to healthy pregnant women (Mantel et al. 2020), as is gestational diabetes (Morgan et al. 2006; Watson et al. 2017). Some studies have found an association between maternal BN and risk of preeclampsia (Eik-Nes et al. 2018), while others have not (Mantel et al. 2020).

Women with BN are at increased risk of developing hyperemesis gravidarum (HG) (Koubaa et al. 2005; Mantel et al. 2020; Morgan et al. 2006), a severe form of

Table 3 Overview of adverse pregnancy and perinatal outcomes in women with bulimia nervosa and anorexia nervosa

	Pregnancy outcomes			Perinatal outcomes	
	Bulimia nervosa	Anorexia nervosa		Bulimia nervosa	Anorexia nervosa
Miscarriage	↑	→	Stillbirth	→	↑
Anemia	↑	↑	Preterm delivery	↑	↑
Hyperemesis gravidarum	↑	↑	Fetal growth restriction	↑	↑
Antepartum hemorrhage	→	↑	Microcephaly	↑	↑
Acute liver failure	N/A	↑	Low Apgar scores	→	↑
Gestational diabetes	↑	→	Admission NICU	N/A	↑
Infections and sepsis	N/A	→	Birth trauma	N/A	→
Delivery mode	→	→	Congenital anomalies	N/A	→

↑ indicates increased risk of outcome in women with bulimia nervosa (or their neonate), and → indicates no difference in outcome in women with bulimia nervosa compared to women without eating disorder

nausea and vomiting in pregnancy, which is described in detail in the chapter on "Anorexia Nervosa and Reproductive Health".

In contrast to AN, which has been associated with antepartum hemorrhage, placenta abruptio, and acute liver failure (Ante et al. 2020; Mantel et al. 2020), BN has not. In similarity with AN, mode of delivery does not seem to differ between women with BN and women without eating disorders, and likewise, women with BN are not at increased risk of postpartum hemorrhage.

Pregnant women with BN are at moderately increased risk of delivering prematurely (before 37 gestational weeks) (Mantel et al. 2020; Morgan et al. 2006). BN does not seem to be associated with fetal growth restriction in general, but is associated with an increased risk of delivering neonates with a small head circumference (Eik-Nes et al. 2018; Koubaa et al. 2005; Mantel et al. 2020; Micali et al. 2016).

Neonates to mothers with BN have similar Apgar scores as neonates to healthy mothers (Mantel et al. 2020) (Table 3).

The Postpartum Period

The postpartum period has been reported to constitute a high-risk time for relapsing or experience deterioration of eating disorder symptoms (Micali et al. 2007b), and eating disorder history independently predicts the risk of developing postpartum depression (Johansen et al. 2020).

Several studies with conflicting results have investigated breastfeeding pattern in women with eating disorder. Most studies have not observed a major difference in initiation or cessation of breastfeeding in mothers with BN (Micali et al. 2007b; Torgersen et al. 2010) compared with healthy mothers. However, feeding difficulties seem to be more common in infants to bulimic mothers (Micali et al. 2009), and maternal BN has been associated with infant overweight (Micali et al. 2009).

Children to Mothers with Eating Disorders

Understanding the risk of adverse outcomes in children to mothers with eating disorders and identifying factors mediating these risks are of importance to provide sufficient resources and to identify potential key preventive interventions. There are indications of an increased risk of various adverse health outcomes among children to mother with BN. A recent systematic review has compiled existing studies on maternal eating disorder and childhood development. Children to mothers with BN seem to have a higher degree of early developmental difficulties, including poorer motor, language, and social development, compared with children to mothers without eating disorder. Additionally, hyperactivity and peer difficulties are more common in children to bulimic mothers, as are anxiety and obsessive-compulsive symptoms (Martini et al. 2020). In a large population-based study, maternal BN was associated with an increased risk of autism spectrum disorder and attention-deficit/hyperactivity disorder (Mantel et al. 2022). Factors driving the association between maternal eating disorders and increased risk of offspring developmental impairment are presumably a complex interplay between genetic and environmental factors.

One study has investigated the impact of maternal BN on childhood respiratory morbidity and found that maternal BN is associated with an increased risk of early childhood wheezing. Additional studies on long-term consequences on childhood health are lacking, but warranted.

Management of Pregnant Women with Bulimia Nervosa

In similarity with AN, BN is associated with an increased risk of menstrual disturbances and multiple adverse pregnancy and perinatal outcomes. Therefore, the recommendations on management of pregnant women with BN are virtually analogous to the management of women with AN.

Among women with infertility planning to conceive with prevalent eating disorder, focusing on treatment of the eating disorder is essential due to the associated risks in pregnancy. Advice and education on the importance of an adequate weight and nutritional intake and well-being prior to attempting to conceive is recommended to increase the likelihood of conception and promote a healthy pregnancy (NICE 2020).

In many countries, a routine enquiry of ongoing and previous mental illness, including eating disorder, is recommended for all women enrolling in antenatal

maternity healthcare. It is important to acknowledge that women with eating disorder may be reluctant to share their ongoing or previous eating disorder to health professionals. The stigma surrounding eating disorders and feelings of shame are patient-related factors known to impede health seeking for eating disorders in general (Ali et al. 2017). Additionally, among health professionals in maternal healthcare, lacking of confidence, due to insufficient professional training, has been reported to hamper the identification of pregnant women with eating disorders (Bye et al. 2018). Keeping the many barriers for acknowledging pregnant women with eating disorders in mind, focus on a nonjudgmental and delicate enquiry when screening for eating disorders is important (Bye et al. 2018).

Women, who disclose an ongoing or previous eating disorder, should be regarded as a risk population during pregnancy and postpartum period and be offered intensified support throughout the pregnancy. An early pregnancy appointment with an obstetrician for assessment of the patient's physical and mental health is recommended. Depending on whether the eating disorder is ongoing or past, the co-occurrence of other psychiatric diseases, the severity of the disease, and the patient's individual need and wish, a tailored follow-up scheme should be developed. A low threshold for referral to specialized eating disorder unit (or perinatal specialist mental health service if not available) is preferable during the pregnancy and postnatal period. Referral to a curator or psychologist, specialized in management of eating disorders, is another alternative. In order to provide information on the importance of adequate nutrition and nutritional support and pregnancy-adjusted exercise during pregnancy, referral to nutritionist and physiotherapist should also be considered. Intensified frequency of antenatal visits to midwife with a focus on continuity of care in order to facilitate identification of altered patient well-being throughout pregnancy is preferable. In agreement with the patient, frequent weight measurements are recommended in conjunction with the antenatal visits. Underweight patients (BMI <18.5) and patients with insufficient weight gain or patients with weight and shape change preoccupation are alarming signs of relapsing or uncontrolled disease and hence reasons for concern. BN is not associated with fetal growth restriction, and extra fetal growth scan is indicated in pregnant women with BN as well, in particular among women with poor gestational weight gain. Clearly, women with severe eating disorder presentation during pregnancy should be managed by a multidisciplinary team involving specialized obstetric, internal medicine and psychiatric care.

In light of the increased risk of deteriorated eating disorder symptoms, disease relapse, depression, and anxiety and attachment difficulties postnatally, the intensified support should continue for up to 1 year postpartum (NICE 2020) (Fig. 2).

Applications to Other Eating Disorders

In this chapter we have reviewed the impact of bulimia nervosa (BN) on fertility, pregnancy, postpartum period, as well as neonatal and child health. There is a separate chapter reviewing the impact of anorexia nervosa (AN) on fertility,

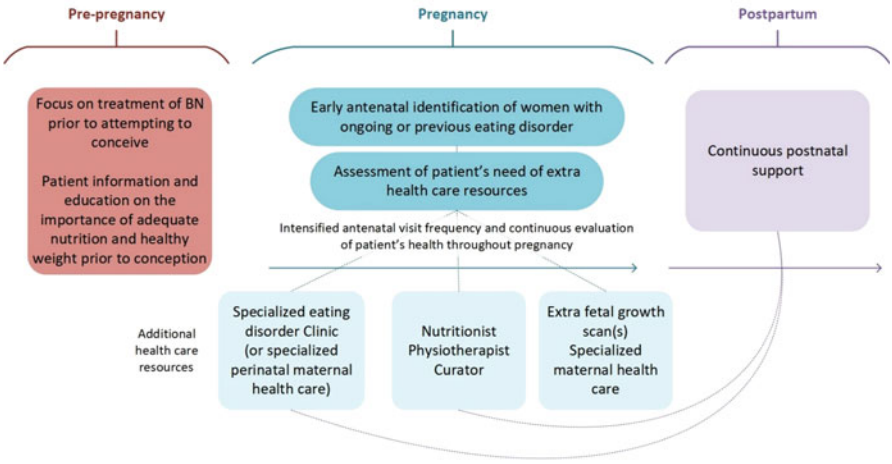


Fig. 2 Overview of clinical management of women with bulimia nervosa prior to pregnancy and during the pregnancy and postpartum period

pregnancy, postpartum, and child health. In brief, the prevalence of amenorrhea among women with BN is higher compared with the general population but lower compared to women with AN. Periods of starvation in BN could induce functional hypothalamic amenorrhea by similar mechanism as among women with AN, but BN is additionally associated with polycystic ovary syndrome (PCOS), which is characterized by oligo- or amenorrhea. Women with BN are at increased risk of several adverse pregnancy and perinatal outcomes, but not to the same extent as women with AN. Moreover, there is evidence of separate distinct neurocognitive phenotypes in AN versus BN, which is likely to partly explain some of the differences in childhood developmental outcomes. Hence, the information within this chapter can only partly be transferable to women with AN. Moreover, a majority of studies have focused on women with specific eating disorders such AN or BN, wherefore it is difficult to extrapolate results to women with unspecified eating disorders. There are however indications of similar rates of adverse pregnancy and perinatal outcomes among women with unspecified eating disorder as women with AN.

Key Facts

Key Facts of Amenorrhea in Bulimia Nervosa

Menstrual disturbances are common symptoms in women with bulimia nervosa and are usually caused by functional hypothalamic amenorrhea (FHA) or polycystic ovary syndrome (PCOS).

In FHA, stress and energy deficit induce an aberration in the hormonal regulation of the menstrual cycle, by interfering with the release of regulating hormones from the hypothalamus and pituitary, leading to amenorrhea and consequently infertility.

First-line treatment of FHA consists of treating underlying eating disorder and restoring the energy balance, which normalized the menstruation and restores fertility.

PCOS is characterized by hyperandrogenism, oligo- or anovulation, and polycystic ovarian morphology.

Key Facts of Pregnancy and Perinatal Outcomes in Women with Bulimia Nervosa

Women with bulimia nervosa might experience improved or deteriorated eating disorder symptoms throughout pregnancy.

Anemia and gestational diabetes are more common in pregnant women with bulimia nervosa compared with healthy pregnant women.

Pregnant women with bulimia nervosa are at moderately increased risk of preterm delivery, and their children more commonly have a small head circumference as compared to healthy women.

Key Facts of Management of Pregnant Women with Bulimia Nervosa

Among pregnant women, ongoing, recent, or previous bulimia nervosa should be identified and acknowledged in antenatal screening.

Given the association between bulimia nervosa and increased risk of adverse pregnancy, neonatal, postpartum, and child outcomes, pregnant women with bulimia nervosa should be considered a high-risk population.

Pregnant women with ongoing or previous bulimia nervosa should be offered additional support throughout pregnancy, including psychologist or psychiatrist contact, nutritional support and intensified follow-up, extra growth ultrasound in third trimester, and earlier postpartum follow-up.

Summary Points

- Menstrual disturbances are common symptoms in women with bulimia nervosa (BN) and commonly attributed to either functional hypothalamic amenorrhea (FHA) or polycystic ovary syndrome (PCOS).
- FHA and PCOS are diagnosed, and differentiated between, by careful examination, including endocrine evaluation.
- First-line treatment of FHA consists of restoring energy balance, leading to normalized menstruation and fertility.

- Some women with bulimia nervosa experience improvement of eating disorder symptoms during pregnancy, whereas others experience deterioration of eating disorder symptoms throughout the pregnancy.
- Pregnant women with bulimia nervosa are at increased risk of several pregnancy complications, including anemia, hyperemesis gravidarum, and gestational diabetes.
- Maternal bulimia nervosa is associated with adverse perinatal outcomes, including preterm delivery and low head circumference in their neonates.
- Depressive and anxiety symptoms are more common among women with bulimia nervosa in the postpartum period.
- Feeding difficulties are more common in children to mothers with bulimia nervosa.
- Children to mothers with bulimia nervosa are at increased risk of impaired neuropsychiatric and cognitive development and more likely to seek healthcare for childhood wheezing.
- Pregnant women with recent or previous bulimia nervosa should be recognized as a high-risk population in antenatal screening and offered additional appropriate healthcare resources.

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Part IV

Binge Eating Disorder

Long-Term Outcome of Inpatients and Outpatients with Bulimia Nervosa

47

Norbert Quadflieg

Contents

Introduction 942
The Studies 943
Remission from Bulimia Nervosa 943
Persistence of Bulimia Nervosa at Follow-Up 946
Cross-Over to Other Eating Disorders at Follow-Up 947
Chronicity of Eating Disorders 949
Aspects of Social Functioning at Follow-Up 950
Mortality 951
Outcome of Bulimia Nervosa in Males 952
Application to Other Eating Disorders 952
Mini-Dictionary of Terms 952
Key Facts of Bulimia Nervosa 953
Key Facts of Follow-Up 953
Key Facts of Mortality 953
Summary Points 954
References 954

Abstract

The long-term outcome of bulimia nervosa is highlighted from several perspectives. The percentage of patients not meeting criteria for bulimia nervosa at follow-up varied widely over studies with no recognizable temporal pattern. Relapse after remission was frequent. About 10 years after treatment, remission seems to get increasingly rare in bulimia nervosa. Poor outcome at follow-up was found in the long run in one third to one half of the patients treated for BN. Compared to the general population, all-cause mortality was elevated in bulimia nervosa increasing the risk of death for bulimia nervosa patients by 50%.

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Compared to anorexia nervosa, bulimia nervosa is associated with less mortality but is nevertheless a severe eating disorder. Judging from the rare studies on males with bulimia nervosa, there seems to be no larger differences in the outcome of bulimia nervosa between males and females.

Keywords

Anorexia nervosa · Binge eating · Binge eating disorder · Bulimia nervosa · Chronicity · Death · Diagnostic cross-over · Eating disorders · Eating disorder NOS · Mortality · Outcome · Recovery · Remission · Social functioning · Standardized mortality ratio

Abbreviations

AN	Anorexia nervosa
BED	Binge eating disorder
BN	Bulimia nervosa
DSM-5	*Diagnostic and Statistical Manual of Mental Disorders* (5th edition)
DSM-III	*Diagnostic and Statistical Manual of Mental Disorders* (3rd edition)
DSM-III-R	*Diagnostic and Statistical Manual of Mental Disorders* (3rd edition revised)
DSM-IV	*Diagnostic and Statistical Manual of Mental Disorders* (4th edition)
ED-NOS	Eating disorder not otherwise specified
SMR	Standardized mortality ratio

Introduction

Bulimia nervosa (BN) is an eating disorder which was introduced as a separate entity only some 40 years ago (Russell 1979). This limits the number of outcome studies, and some clarifications are in order to define the meaning of key terms for this chapter. Long-term outcome is meant to describe the status of a patient beyond the end of treatment. This may involve a time period as short as several months or as long as several decades. To reflect a real long-term outcome – and based on the studies available – this chapter includes studies with at least 5 years of follow-up.

Although findings are very limited for some areas, outcome in this chapter includes the status of the eating disorder at follow-up as well as some aspects of social functioning and, as the worst possible outcome, mortality. The spectrum of symptoms in BN includes both behavioral (binge eating and compensatory behavior) and psychological symptoms (e.g., focus on avoiding weight gain, body weight and shape as a central aspect of self-evaluation). As behavioral symptoms remit earlier than psychological symptoms (Clausen 2004), it is important to include both aspects in the definition of eating disorder outcome (Bardone-Cone et al. 2010; Richmond

et al. 2020). The best approach to reflect both aspects in the same outcome measure seems to be eating disorder diagnosis, and this is what is used in this review.

One outcome category not included in this review is partial remission. While improving on the severity of the eating disorder is important for the patient, their caregivers, and the therapists, this category is often not clearly defined in the literature. For example, some studies define the change from BN to eating disorder not otherwise specified (ED-NOS) as partial remission, while other studies with well-founded rationale (see Crow et al. 2009) include ED-NOS as a diagnosis of eating disorder.

Additionally, studies on inpatient and outpatient treatment are included without differentiating between these treatments in reporting outcome. The decision of treating BN patients as outpatients or inpatients depends heavily on the healthcare system of a specific country and does not necessarily reflect symptom severity.

The Studies

A total of 21 studies were included in this review. Table 1 gives an overview of the study characteristics. For several studies, more than one key publication is available, and this is shown in the table. Some studies reported outcome for more than one follow-up. Most studies focused on females, and some studies included females and mostly a rather small and unspecified number of males. Only one study reported on a larger number of males with BN.

One study used clinical charts to establish eating disorder diagnoses, while the other studies followed the criteria published in the *Diagnostic and Statistical Manual of Mental Disorders*, third (*DSM-III*; American Psychiatric Association 1980), third revised (*DSM-III-R*; American Psychiatric Association 1987), fourth (*DSM-IV*; American Psychiatric Association 1994), or fifth (*DSM-5*; American Psychiatric Association 2013) edition.

Remission from Bulimia Nervosa

A necessary requirement for recovery is achieving absence of illness symptoms. For eating disorders this is a requirement rarely achieved completely, as eating includes a broad spectrum of behaviors and attitudes towards food and eating. The intake of food is a behavior that cannot be ceased completely, so there is always the possibility for intervening disturbance. Consequently, remission from BN often includes some residual symptoms, an implication also applying to the outcome measure of eating disorder diagnosis. One major issue concerns the length of symptom-free interval to declare a patient recovered. While the authors of the large study from Boston (initiated by David Herzog; long-term outcome published by Eddy et al. 2017) recommended 6 months of absence of symptoms for the definition of recovery (De Young et al. 2020), shorter intervals are common, and many studies do not define the symptom-free interval at all.

Table 1 Studies on the long-term outcome of bulimia nervosa. This table lists all long-term outcome studies of bulimia nervosa included in this review. In these studies outcome was assessed after a minimum of 5 years after treatment. Several studies reported more than one follow-up with different time points. The diagnostic system refers to the *Diagnostic and Statistical Manual of Mental Disorders*, third (*DSM-III*), third revised (*DSM-III-R*), fourth (*DSM-IV*), and fifth (*DSM-5*) edition, published by the American Psychiatric Association in 1980, 1987, 1994, and 2013, respectively

Study	Diagnostic system	Treatment and gender	Sample size at follow-up living	Length of follow-up (years)
Abraham 1998 Abraham et al. 1983	*DSM-IV*	Outpatients Females	43	10–15
Ben-Tovim et al. 2001	*DSM-III-R*	Outpatients Females	84	5
Castellini et al. 2011	*DSM-IV*	Outpatients Males and females	99	6
Reiss and Johnson-Sabine 1995	*DSM-III*	Outpatients Females	32	6
Collings and King 1994	*DSM-III-R*		44	10
Herzog et al. 1999	*DSM-III-R/ DSM-IV*	Treatment-seeking females	110	7.5
Eddy et al. 2017			107	9
Eddy et al. 2017			107	22
Eielsen et al. 2021	*DSM-5*	Inpatients Females	25	5
Eielsen et al. 2021			25	17
Fairburn et al. 1995	*DSM-IV*	Outpatients Females	90	6
Fallon et al. 1991	*DSM-III-R*	Inpatients Females	46	2–9
Fichter and Quadflieg 2004 Fichter and Quadflieg 1997	*DSM-IV*	Inpatients Females	162	6
Fichter and Quadflieg 2004			162	12
Grilo et al. 2007	*DSM-IV*	In- and outpatients and treatment-seeking females	23	5
Hergenroeder et al. 2015	Clinical charts	Inpatients Males and females	29	7
Hsu and Sobkiewicz 1989 Hsu and Holder 1986	*DSM-III*	Outpatients Females	35	4–6
Keel et al. 1999, 2000	*DSM-IV*	Outpatients Females	173	11.5 (10–15)
McIntosh et al. 2011	*DSM-III-R*	Outpatients Females	109	5

(continued)

Table 1 (continued)

Study	Diagnostic system	Treatment and gender	Sample size at follow-up living	Length of follow-up (years)
Nakai et al. 2014	*DSM-III-R*	Outpatients Females	82	7
Norring and Sohlberg 1993	*DSM-III-R*	Outpatients Females	16	6
Quadflieg and Fichter 2019	*DSM-IV*	Inpatients Males and females	1241	11
Quadflieg and Fichter 2019 (subgroup)			147	21
Reas et al. 2000	*DSM-III*	Outpatients Females	44	9.3 (4–14)
Strobel et al. 2019	*DSM-IV*	Inpatients Males	59	7.5
Tseng et al. 2004	*DSM-IV*	In- or outpatients Males and females	45	5 (2–15)
Van Son et al. 2010	*DSM-IV*	Outpatients Males and females	63	5

Remission rates (absence of an eating disorder diagnosis at follow-up) varied widely from 20% to 77% (Table 2). One obvious assumption would be to find increasing remission rates with increasing length of follow-up. As Fig. 1 illustrates, however, this is not the case. The highest remission rates (above 70%) were reported for follow-up intervals of 5 (Ben-Tovim et al. 2001), 9 (Reas et al. 2000), and 10–15 (Abraham 1998) years, while the lowest remission rates (below 30%) were found 5 (Van Son et al. 2010) years, 7 (Hergenroeder et al. 2015), and 17 (Eielsen et al. 2021) years after treatment. Interestingly, one study found the identical remission rate of 68% at the 9- and 22-year follow-up in the same sample of treatment-seeking females (Eddy et al. 2017). Similarly, the remission rate was nearly identical at 6-year (67%) and 12-year (66%) follow-up in the same inpatient sample (Fichter and Quadflieg 2004). Actually, no temporal pattern of remission is identifiable at this time, but we may cautiously conclude that with increasing length of observation, improvement and remission are found more often in these patients (Herzog et al. 1999). However, concluding from a few studies, after about ten years, additional remission seems to get increasingly rare in BN.

Two studies covered very long follow-up intervals of more than two decades. In a subgroup from a large sample of inpatients, Quadflieg and Fichter (2019) found 42% recovered after 21 years, and Eddy et al. (2017) reported 68% recovered in their treatment-seeking sample after 22 years. Clearly, more very long-term studies are needed to explain this discrepancy.

A different approach to follow-up is observing remission not at the time of follow-up, but at any time point of the follow-up period. The Boston study reported recovery in 73% of treatment-seeking females at some time point of the 7.5-year follow-up interval. Over this time 35% relapsed into BN again after recovery (Herzog et al. 1999).

Table 2 Remission from eating disorder at follow-up (no eating disorder diagnosis at follow-up). This table lists all long-term outcome studies of bulimia nervosa included in this review which reported the number of patients who had no bulimia nervosa at follow-up

Study	Length of follow-up (years)	Recovered %
Abraham 1998 Abraham et al. 1983	10–15	74
Ben-Tovim et al. 2001	5	77
Castellini et al. 2011	6	50
Collings and King 1994	10	52
Eddy et al. 2017	9	68
Eddy et al. 2017	22	68
Eielsen et al. 2021	5	44
Eielsen et al. 2021	17	20
Fairburn et al. 1995	6	54
Fallon et al. 1991	2–9	39
Fichter and Quadflieg 2004 Fichter and Quadflieg 1997	6	67
Fichter and Quadflieg 2004	12	66
Hergenroeder et al. 2015	7	28
Hsu and Sobkiewicz 1989 Hsu and Holder 1986	4–6	60
Keel et al. 1999, 2000	11.5 (10–15)	42
McIntosh et al. 2011	5	65
Nakai et al. 2014	7	48
Norring and Sohlberg 1993	6	50
Quadflieg and Fichter 2019	11	38
Quadflieg and Fichter 2019 (subgroup)	21	42
Reas et al. 2000	9.3 (4–14)	73
Strobel et al. 2019	7.5	44
Tseng et al. 2004	5 (2–15)	38
van Son et al. 2010	5	29

Persistence of Bulimia Nervosa at Follow-Up

A certain proportion of patients treated for BN retained this diagnosis at follow-up. While it is generally unclear if this diagnosis was present throughout the entire follow-up period, or was present again at follow-up after periods without the diagnosis, both variants reflect a chronic state of BN. As with remission, rates of chronic BN varied widely between studies (Table 3). With one exception (Tseng et al. 2004), all studies reported less than a quarter of the patients having BN at follow-up. Again, as illustrated in Fig. 2, there is no evident temporal pattern of chronicity of BN. In the

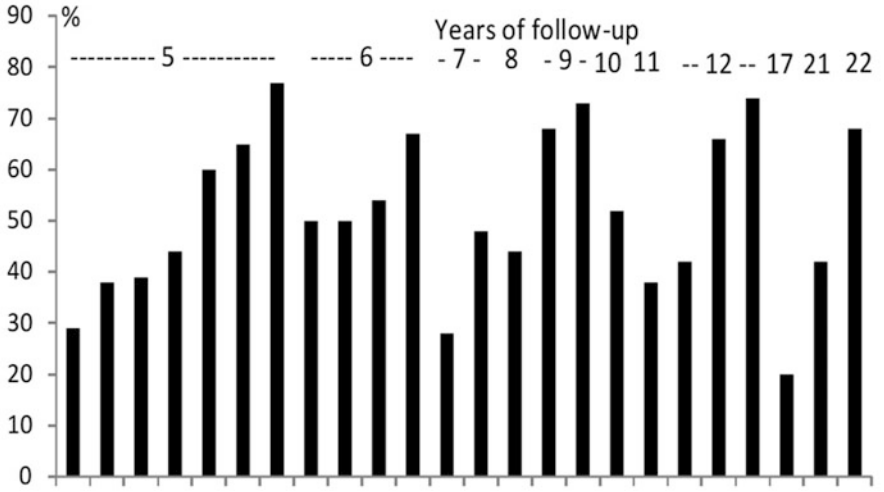


Fig. 1 Remission from eating disorder at follow-up. The percentage of patients remitted from bulimia nervosa and who had not switched to another eating disorder at follow-up is shown by the height of the bars. Bars are organized according to length of follow-up and within this category by the value of percentage. Each bar represents one study

study of Quadflieg and Fichter (2019), percentages of persistent BN were similar in the large total sample after 11 years (14%) and the smaller subsample after 21 years (12%).

Cross-Over to Other Eating Disorders at Follow-Up

While the broader category of eating disorders is fairly stable, there is a well-known instability of single-eating-disorder diagnoses with a frequent change between diagnoses (Milos et al. 2005). Only a small number of patients crossed from BN at treatment to anorexia nervosa (AN) at follow-up. Cross-over to AN was rare and observed in 0 to 4% of the follow-up samples (Table 4). The only exception was the outpatient sample of Castellini et al. (2011) with a somewhat higher rate of 9%. This study also reported a relatively high rate of cross-over to binge eating disorder (BED; 11%), and these numbers may reflect a special design feature of the study. Only a few other studies reported cross-over to BED with a maximum frequency of 2% in the female sample of Fichter and Quadflieg (2004) and the male sample of Strobel et al. (2019). Much more frequent was the cross-over to ED-NOS (Fig. 3) with rates as high as 38% in the very long-term subgroup of Quadflieg and Fichter (2019). However, these findings are not easy to interpret. Considering that all patients had a full BN at intake into the studies, cross-over to ED-NOS may well be attributed to an improvement of the eating disorder. On the other hand, ED-NOS includes several subtypes (American Psychiatric Association 1994) and is also a severe eating disorder (Crow et al. 2009), and this cross-over may simply reflect a change of symptoms.

Table 3 Persistence of bulimia nervosa at follow-up. This table lists all long-term outcome studies of bulimia nervosa included in this review which reported the number of patients who still had bulimia nervosa at follow-up

Study	Length of follow-up (years)	Persisting bulimia nervosa at follow-up %
Abraham 1998 Abraham et al. 1983	10–15	5
Ben-Tovim et al. 2001	5	8
Fairburn et al. 1995	6	19
Fichter and Quadflieg 2004 Fichter and Quadflieg 1997	6	22
Fichter and Quadflieg 2004	12	11
Hsu and Sobkiewicz 1989 Hsu and Holder 1986	4–6	17
Keel et al. 1999, 2000	11.5 (10–15)	11
Quadflieg and Fichter 2019	11	14
Quadflieg and Fichter 2019 (subgroup)	21	12
Strobel et al. 2019	7.5	17
Tseng et al. 2004	5 (2–15)	40
Van Son et al. 2010	5	6

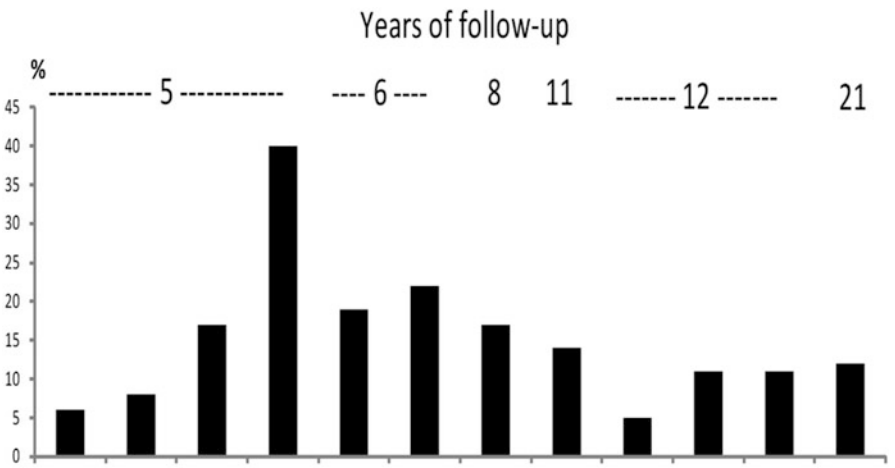


Fig. 2 Persistence of bulimia nervosa at follow-up. The percentage of patients who still or again had bulimia nervosa at follow-up is shown by the height of the bars. Bars are organized according to length of follow-up and within this category by the value of percentage. Each bar represents one study

Table 4 Cross-over from bulimia nervosa at treatment to other eating disorders at follow-up. This table lists all long-term outcome studies of bulimia nervosa included in this review which reported the number of patients who shifted from bulimia nervosa to another eating disorder at follow-up

Study	Length of follow-up (years)	Anorexia nervosa at follow-up %	Binge eating disorder at follow-up %	Eating disorder not otherwise specified at follow-up %
Abraham 1998 Abraham et al. 1983	10–15	0	./.	21
Ben-Tovim et al. 2001	5	1	./.	13
Castellini et al. 2011	6	9	11	./.
Fairburn et al. 1995	6	3	./.	23
Fichter and Quadflieg 2004 Fichter and Quadflieg 1997	6	4	1	1
Fichter and Quadflieg 2004	12	2	2	14
Hsu and Sobkiewicz 1989 Hsu and Holder 1986	4–6	3	./.	20
Keel et al. 1999, 2000	11.5 (10–15)	1	1	18
Quadflieg and Fichter 2019	11	3	1	35
Quadflieg and Fichter 2019 (subgroup)	21	1	1	38
Strobel et al. 2019	7.5	3	2	34
Tseng et al. 2004	5 (2–15)	2	./.	13
Van Son et al. 2010	5	0	./.	22

./. not reported separately and included in the eating disorder not otherwise specified category

Chronicity of Eating Disorders

Above we have taken a look at persisting BN and cross-over to other eating disorders. Considering the high interchangeability of eating disorder diagnoses, a more global look at diagnostic outcome is justifiable. Combining all eating disorder diagnoses in one category, chronicity of eating disorders is considerable. Percentages range from 22% (Ben-Tovim et al. 2001) to 56% (Strobel et al. 2019) with half of the studies below 32%. The other half of the studies reported about half of the samples

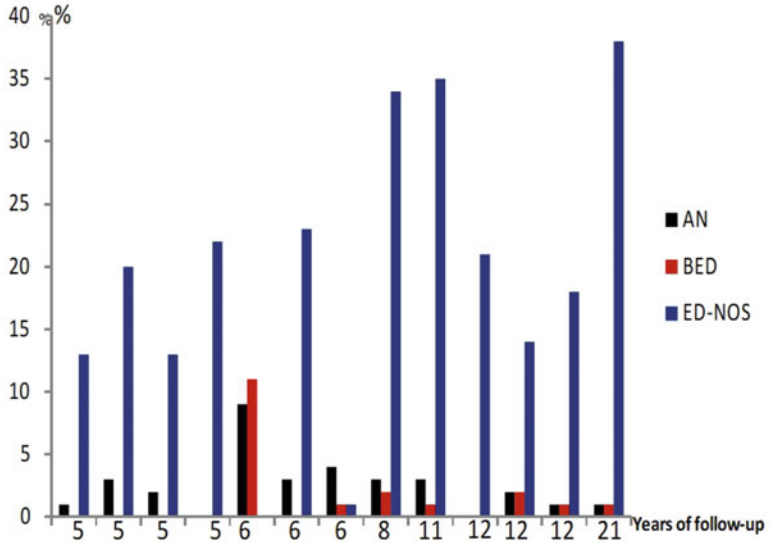


Fig. 3 Cross-over from bulimia nervosa at treatment to other eating disorders at follow-up. The percentage of patients who switched from bulimia nervosa at treatment to anorexia nervosa (black bars), binge eating disorder (red bars), or eating disorder not otherwise specified (blue bars) at follow-up is shown by the height of the bars. Each cluster of bars represents one study. The cluster of bars is organized according to length of follow-up. Missing bars in a cluster indicate either no such eating disorder was found at follow-up or not reported

with chronic eating disorder. So we may conclude that one third to one half of patients treated for BN will have a poor outcome of their eating disorder in the long run. Clearly there is a need for still more improved therapies of BN.

Aspects of Social Functioning at Follow-Up

Only very few studies reported on a limited number of indicators of social functioning at follow-up (Table 5). In the long run, more than half of the patients reported to have been married or cohabiting over the follow-up period or at follow-up. However, a considerable percentage also reported a divorce or separation over the follow-up period. Two studies reported the percentage of patients with children (58% and 39%), and two studies reported on employment of the patients at follow-up (49% and 100%). Using a questionnaire on social adjustment, patients reported improvement of social adjustment but still showed continuing impairment 10 years after treatment (Keel et al. 2000).

Table 5 Aspects of social functioning at follow-up. This table lists all long-term outcome studies of bulimia nervosa included in this review which reported on some characteristics of social functioning at follow-up

Study	Length of follow-up (years)	Married or cohabiting over follow-up period or at follow-up %	Separated or divorced over follow-up period or at follow-up %	Had children at follow-up %	Employed at follow-up %
Abraham 1998 Abraham et al. 1983	10–15	81	37	58	./.
Fairburn et al. 1995	6	75	./.	./.	49
Hsu and Sobkiewicz 1989 Hsu and Holder 1986	4–6	23	9	./.	100
Reas et al. 2000	9.3 (4–14)	57	./.	39	91

./. not reported

Mortality

Several studies mentioned the number of deaths at follow-up, allowing the calculation of the percentage of deceased patients in a sample. However, this crude mortality rate depends on sample size and will be inflated in small samples. A more precise assessment of mortality is the standardized mortality ratio (SMR) which compares the number of deaths in a sample with the expected number of deaths in the reference population of the same age and sex. Two long-term studies reported SMRs. In a mixed sample of mostly female and a small number of male inpatients, the SMR of 1.49 (95% confidence interval 1.10–1.97) was significantly elevated ($p < 0.05$), indicating a risk of death about one and a half times higher in BN than in the general population (Fichter and Quadflieg 2016). For a larger sample of 81 male inpatients, the SMR was 1.88 (95% confidence interval 0.86–3.58) and not significantly elevated (Quadflieg et al. 2019). These numbers include mortality from all causes. Causes of death directly attributable to BN are hard to define and not reported in the studies.

Outcome of Bulimia Nervosa in Males

There is only one study reporting long-term outcome in a larger sample of males (Strobel et al. 2019). Results regarding remission (Table 2), persistence (Table 3), and cross-over to other eating disorders (Table 4) are fairly within the range of studies of female patients, and we may conclude little difference between sexes from this scarce evidence. In an additional analysis of the inpatients from the mortality studies mentioned above, Fichter et al. (2021) compared the SMRs directly between males and females and found no significant difference in mortality between sexes.

Application to Other Eating Disorders

Long-term outcome studies similar to those described for BN exist for AN. Summarizing the results, AN is a still more severe eating disorder than BN, with lower remission rates and greatly higher mortality (SMR 5.35 ($p < 0.05$) in the study of Fichter and Quadflieg 2016; for males 5.91 ($p < 0.05$) in the study of Quadflieg et al. 2019). A number of patients with AN cross-over to BN at follow-up. Considering that a binge eating/purging type of AN is defined, a change between AN and BN may simply be a question of low versus normal weight. Additionally, ED-NOS of an anorectic type is defined as meeting criteria of AN with a body weight above the usual threshold of AN, but no maximum weight is given. This may contribute to higher cross-over rates from AN to ED-NOS.

For BED, comparable long-term outcome studies are less frequent. There are important differences to AN and BN. Compared to AN and BN, a much larger number of males seems to be affected by BED, and because of the exclusion of inappropriate compensatory behaviors after binge episodes, a better outcome could be hypothesized. Actually this is not the case, BED showing a similar outcome to BN. One exception is mortality which seems to be lower than in BN with a nonsignificant SMR for BED.

Mini-Dictionary of Terms

- **Chronicity:** Long enduring state of an illness with decreasing perspective of recovery or with an increase of necessary efforts to achieve improvement
- **Cross-over of diagnosis:** Transformation from one diagnosis to another, generally from the same spectrum of illness
- **Crude mortality rate:** Percentage of deceased individuals in a given sample or population
- **Follow-up:** Reassessment of a patient after treatment has ended for a certain time period
- **Inpatient treatment:** Treatment with the patient residing in a hospital for intensive treatment
- **Outcome:** The state of an illness or a functional characteristic at follow-up

- **Outpatient treatment:** Ambulatory treatment in the rooms of a therapist with the patient leaving after treatment session to return home
- **Relapse:** The reappearance of symptoms after recovery was achieved
- **Remission/recovery:** Being free from symptoms after an illness
- **Standardized mortality ratio:** The ratio of the number of observed deaths in a sample compared to the expected number of deaths in the reference population

Key Facts of Bulimia Nervosa

- Bulimia nervosa is a mental disorder with frequent binge eating episodes when more food than usually is consumed in a short time
- To avoid weight gain, measures are taken to remove the food before digestion (e.g., self-induced vomiting or use of laxatives)
- A low body weight and slim body shape are central to the self-evaluation of one's person
- Binge eating disorder is essentially bulimia nervosa without compensatory behavior
- The proportion of males is lower in bulimia nervosa than in binge eating disorder

Key Facts of Follow-Up

- In most studies follow-up is a cross-sectional assessment of the current state of the patient
- Retrospective assessment beyond the current state at follow-up depends heavily on the precision of the patient's memory and the careful exploration of the assessor
- Cross-sectional follow-ups reveal a picture at the time of assessment but not of the complete time period between end of treatment and follow-up
- Often patients received additional treatment during the follow-up period which is rarely reported in studies
- Only the follow-up status of patients who participated in follow-up can be reported
- It is not known if patients who did not participate in follow-up have a good or poor outcome
- There are a few long-term studies on bulimia nervosa in population samples, but it is not clear if these studies cover clinical cases requiring treatment

Key Facts of Mortality

- Mortality is more difficult to assess than one would expect
- Central registries of mortality allow a higher ascertainment rate of deceased patients

- Causes of death are rarely attributable directly to bulimia nervosa
- Computing the standardized mortality ratio requires a centralized death statistics of the population
- Death statistics yields the number of deaths from all causes, and only special causes of death are differentiated in these statistics
- The expected number of deaths in the general population includes also the patients with the illness of interest (here bulimia nervosa)

Summary Points

- In the long run, one third to one half of the patients treated for BN will have a poor eating disorder outcome
- Relapse after remission is frequent
- About 10 years after treatment, remission seems to get increasingly rare in bulimia nervosa
- The risk of death is elevated by 50% for bulimia nervosa patients, compared to the general population
- Bulimia nervosa is associated with less mortality than anorexia nervosa but is nevertheless a severe eating disorder
- Based on the current limited knowledge, no significant difference in the outcome of bulimia nervosa exists between males and females

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Parental Care and Binge-Eating Disorder

48

Federico Amianto and Benedetto Vitiello

Contents

Introduction 958
Psychopathological Aspects 959
Epidemiology 959
Attachment Liability in the Pathogenesis of BED 960
Parenting Style as a Measure of Early Attachment in Psychiatric Disorders 962
Parenting Correlates in Eating Disorders, BED, and Obesity 963
Parenting Influence on Personality Traits of Obese Participants With and Without BED 966
Evidences About Combined Maternal and Paternal Parenting Styles 968
No Specific Parental Style for BED Expression 969
Clinical Implications 970
Preventions Issues 972
Conclusion 972
Implications for Other Eating Disorders 973
Mini-Dictionary of Terms 974
Key Facts of Parental Care and Binge-Eating Disorder 974
Summary Points 974
References 975

Abstract

Binge-eating disorder (BED) has the highest prevalence among the EDs. Early attachment experiences are considered relevant cofactors for the development of BED and obesity later in life. A deficit attachment impairs the development of emotional control producing inability to cope with negative emotions in a framework of negative experiences. The inadequate coping mechanisms are strongly

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associated with BED and obesity. The risk for obesity is significantly increased by non-authoritative parenting styles in childhood. Physical and psychological abuses in childhood are strictly related to the development of obesity in adulthood. Parenting experience recalled by BED and non-BED obese participants is significantly different from that of healthy controls. The relationship between the obesity, distorted parenting in infancy, and psychopathology and personality traits of obese subjects can be considered as well established. The chapter goes on discussing specific researches linking parenting style to BED and obesity development. Clinical and prevention issues are discussed.

Keywords

Binge-eating disorder · BED · Obesity · Attachment · Parenting · Personality · Psychopathology · PBI · Care · Overprotection · Affectionless control · Prevention · Treatment

Abbreviations

AN	Anorexia nervosa
BED	Binge-eating disorder
BN	Bulimia nervosa
CBT	Cognitive-behavioral therapy
DALYs	Disability adjusted life years
DBT	Dialectical behavior therapy
DLPC	Dorsolateral prefrontal cortex
DSM 5	Diagnostic and Statistical Manual 5th edition
ED	Eating disorders
LNO	Light neglect obesity
Non-BED	Not affected with BED
PBI	Parental Bonding Instrument
SNO	Severe neglect obesity

Introduction

Binge-Eating Disorder (BED) is relatively common, with an estimated lifetime prevalence of about 1.53% in the general population, which is the highest rate among the EDs (Quian et al. 2021). Its prevalence is likely to increase along with the worldwide rising incidence of obesity and also in consideration of the greater attention that this disorder is receiving since the introduction of the diagnostic criteria into the DSM-5 (Amianto et al. 2015; Hudson et al. 2010; Trace et al. 2012).

BED has particular interest for primary care because of its link with obesity and with other medical and psychiatric comorbidities. In fact, BED is characterized by an excessive food intake without energy consumption compensation. This produces a rapid weight increase, and, in the subjects with a medium-long-term time of disease, it also produces the almost constant comorbidity with overweight or obesity. About

40–70% of people with BED who are overweight reach severe obesity conditions which make people with BED susceptible to the medical complications of being overweight (Kessler et al. 2013).

Psychopathological Aspects

Despite the fact that obese subjects with and without BED do not differ from each other in degree of overweight, binge eaters show considerable more concern about body weight and shape and also lower levels of self-reported physical appearance and global self-worth. In fact, BED is also associated with higher rates of psychopathology: among obese individuals, those with BED report greater eating psychopathology, psychiatric and medical disorders, social and occupational impairment, and low quality of life than those without BED (Herbozo et al. 2015). The relationship of BED with psychiatric symptoms like depression, anxiety, and substance abuse and the excessive concerns about food, body shape, and weight, along with increased body dissatisfaction and decreased self-esteem which affect people affected with BED, severely impair their well-being with consequences for their overall functioning (Grilo et al. 2013). This leads to reduced quality of life, increased health service utilization, and negative socioeconomic implications (Amianto et al. 2011a; Wang et al. 2011).

Other problematic features characterize BED patients. They often show relevant alexithymia and deficit in emotional identification and regulation (Carano et al. 2012; Compare et al. 2012). As a consequence (or not) of the difficulties in emotional management, they often carry high interpersonal problems (Blomquist et al. 2012; Sawaoka et al. 2012). Moreover, they often display rigid and poorly adaptive personality traits, so that the diagnosis of personality disorders is frequently present among the clinically referred population (Kessler et al. 2013; Schag et al. 2013). As it happens with other EDs, the comorbid diagnosis of a personality disorder is generally related to more severe psychopathology and worse prognosis (Amianto et al. 2011b; Carrard et al. 2012; Peterson et al. 2005), so that it has been proposed as a marker of major severity, rather than just an associated condition (Amianto et al. 2011b; Carrard et al. 2012; Peterson et al. 2005).

Epidemiology

The incidence of BED is the highest among EDs to such an extent that BED has been considered for a long time a disorder of adulthood. Instead, recent research suggests that the age of onset is lower than previously assumed (Kessler et al. 2013). In fact, it already occurs in childhood and adolescence with a slope in the curve of the age of onset between 15.5 and 27 years. Instead, the mean persistence of 4.3 years is lower with respect to that of BN (Kessler et al. 2013). As it concerns the long-term evolution, data show that BED tends to be a stable syndrome and that also the

binge-eating patterns display a relative stability (Peterson et al. 2012). Moreover, as a difference between AN and BN, the crossover rates with other EDs are significantly lower (Castellini et al. 2011).

Attachment Liability in the Pathogenesis of BED

Among the pathogenic factors which can contribute to the pathogenesis of eating disorders, attachment experiences have been claimed as a relevant component (Abbate-Daga et al. 2010; Kiesewetter et al. 2010; Tasca and Balfour 2014). Women affected with anorexia nervosa and bulimia nervosa often report high levels of separation anxiety in childhood and an insecure style of attachment in adulthood (Amianto et al. 2012; Fassino et al. 2009, 2010; Milan and Acker 2014). These experiences have been found to be related to the body dissatisfaction in ED subjects (Abbate-Daga et al. 2010).

A consistent body of research suggests a strong influence of family functioning on the development of obesity (Bahrami et al. 2013; Hernandez-Hons and Woolley 2012; Pinard et al. 2012). Many studies on family liability in the development of obesity support the addiction-model hypothesis of the pathogenesis of the binge eating. According to this model, the binge-eating behavior would reenact the pattern of unstable relationships, alternating merging and rejection, perceived in infancy by binge eaters (Cleveland et al. 2010). More specifically, early attachment experiences are considered relevant cofactors for the development of BED and obesity later in life (Abbate-Daga et al. 2010; Anderson and Keim 2016; Bahrami et al. 2013; Tasca and Balfour 2014). The attachment insecurity seems to predict the development of the key features of these disorders. Child and adult excessive food intake and obesity have been related to parental attachment insecurity (Anderson et al. 2012; Faber and Dubè 2015). A deficit attachment impairs the development of emotional control producing an individual's inability to cope with stress and negative emotions in a framework of internalized negative experiences. In fact, excessive food intake is conceptualized by many authors as an alternative coping mechanism to manage relational stress and related negative emotions (Faber et al. 2018; Kittel et al. 2015; Leehr et al. 2015). These inadequate coping mechanisms are strongly associated with the disordered eating behaviors which lead to obesity (Kittel et al. 2015; Leehr et al. 2015). Finally, some research underlined that attachment insecurity also represents a relevant prognostic factor for treatment of ED subjects, including the BED participants (Illing et al. 2010; Maxwell et al. 2014). In fact, treatments that address attachment insecurity are effective for decreasing binge eating in BED participants (Maxwell et al. 2014) (Tables 1 and 2).

Table 1 Parenting characteristics of BED and non-BED obese subjects[a]

	BED (a) $n = 357$ mean ± sd	Non-BED (b) $n = 453$ mn ± sd	HS (c) $n = 463$ mean ± sd	F	p	Post hoc	Effect size
PBI							
Maternal care	20.63 ± 9.94	22.25 ± 9.85	28.89 ± 7.68	97.87	0.000	c > b > a	0.134
Maternal overprotection	19.14 ± 8.83	18.61 ± 8.87	13.29 ± 7.99	62.20	0.000	a, b > c	0.089
Paternal care	18.92 ± 10.31	21.13 ± 10.34	25.76 ± 9.06	52.24	0.000	c > b > a	0.076
Paternal overprotection	17.93 ± 9.24	16.79 ± 9.29	9.65 ± 8.21	109.63	0.000	a, b > c	0.148

Note: n, number; sd, standard deviation; BED, participants with obesity with binge eating disorder; non-BED, participants with obesity without binge eating disorder; HS, healthy subjects; TCI, temperament and character inventory; PBI = Parental Bonding Instrument

[a]ANCOVA with age, number of binge episodes, BMI as covariates

Table extracted form Amianto et al., 2016

Table 2 Chi-square test of PBI parenting clusters among obese subjects' groups

	Neglectful n (%)	Affectionless control n (%)	Affectionate constraint n (%)	Optimal n (%)
Maternal parenting				
BED	47 (13.2)	202 (56.6)	49 (13.7)	59 (16.5)
Non-BED	56 (12.4)	236 (52.1)	81 (17.9)	80 (17.7)
HS	43 (9.3)	89 (19.2)	102 (22)	229 (49.5)
χ^2	3.54	149.16**	9.38*	149.68**
Paternal parenting				
BED	54 (15.1)	179 (50.1)	66 (18.5)	58 (16.2)
Non-BED	63 (13.9)	198 (43.7)	95 (21.0)	97 (21.4)
HS	83 (17.9)	63 (13.6)	80 (17.3)	237 (51.2)
χ^2	2.92	144.95**	2.10	144.52**

Note: n, number; BED, participants with obesity with binge-eating disorder; non-BED, participants with obesity without binge eating disorder; HS, healthy subjects
**$p < 0.000$; *$p < 0.01$
Table extracted form Amianto et al., 2021

Parenting Style as a Measure of Early Attachment in Psychiatric Disorders

In the context of the research on attachment liabilities on eating disorder outburst, many studies related the development of obesity to parenting styles. These researches evidenced that the risk of obesity was significantly increased by non-authoritative parenting styles in childhood. Instead more authoritative parenting styles seem to be protective against the development of obesity (Gartstein et al. 2018; Halliday et al. 2014; Kakinami et al. 2015; Sokol et al. 2017). On the other hand, it was also evidenced that physical and psychological abuses in childhood are strictly related to the development of obesity in adulthood, also from a neuropsychobiological point of view. In fact, familiar childhood traumas are effective in producing mental and emotional troubles related to maladaptive coping responses and, as an indirect consequence, to favor stress-induced metabolic disturbances which can be related to obesity development (Amianto et al. 2018; Ehlert 2013).

Some recent studies on parenting styles in ED subjects have been conducted using a traditional but still unsurpassed instrument, the Parental Bonding Instrument (PBI). The PBI represents a worldwide known validated instrument assessing parenting style during childhood and adolescence (until 16 years) through the child recollection of maternal and paternal relational attitudes. Parental attitudes are then classified into two dimensions: care and overprotection. The scores in these dimensions are considered in the high vs. low range based on a cutoff derived from the general population (Parker et al. 1979).

Many studies on parenting style conducted with PBI have demonstrated that low levels of parental care and high overprotection recalled in childhood are associated with acute and severe psychiatric symptoms in adulthood such as to depressive symptoms (Mannarini et al. 2018) and suicidal ideation (Goschin et al. 2013). Moreover, the same researches underline that the parenting style produced by the combination of low care and high overprotection from both parents was associated with schizotypy and anxiety (Giakoumaki et al. 2013), internalizing and externalizing symptoms (Mannarini et al. 2018), and high neuroticism (Takahashi et al. 2017).

Other studies on parenting influence on psychiatric disorders, including eating disorders, explored possible differential effects of maternal and paternal parenting styles on psychopathology development and expression. It is so that maternal overprotection has been associated with the expression of mood symptoms in adulthood, while, instead, paternal overprotection seems to be less correlated (Heider et al. 2006). Recent research on adolescents supports this previous evidence on adults. In fact, it is evident that a high maternal control is related to a higher risk for developing depressive, eating, anxiety, and behavioral disorders (Eun et al. 2018). On the other hand, it also suggests that high paternal care represents a strong resilience factor against the risk for social phobia, agoraphobia, and alcohol abuse/dependence (Eun et al. 2018) (Table 3).

Parenting Correlates in Eating Disorders, BED, and Obesity

The evidence from the research of Eun et al. (2018) that eating disorders are significantly associated with the perception of a low parental care and high overprotection in childhood is corroborated by a literature review including 24 studies applying the PBI to adult women (Tetley et al. 2014). Instead, specific research on parenting influences on the development of EDs produced less evidence concerning a well-differentiated role of maternal and paternal parenting attitudes in favoring eating psychopathology. A study in a large population of adult ED participants found that low maternal care seems to exert a direct effect on the development of body dissatisfaction (Grenon et al. 2016). Also the low paternal care seems to be influential on this psychopathological trait, but the influence is mainly mediated by attachment anxiety and media internalization (Grenon et al. 2016).

As it concerns obesity, previous studies have found that the personality abnormalities and the higher levels of psychopathology in subjects with obesity may be related to worse parenting recalled in adulthood (Amianto et al. 2012, 2016a, 2018, 2021). The research by Takahashi et al. (2017) evidenced that BED and non-BED recall lower maternal and paternal care and higher overprotection with respect to healthy participants, supporting a relevant role of attachment in the pathogenesis of their condition (Abbate-Daga et al. 2010; Anderson and Keim 2016; Bahrami et al. 2013; Tasca and Balfour 2014). Another study by Amianto et al. 2016a explored the characteristics of parenting style in a large sample of BED and non-BED obese participants who were searching for treatment at an eating disorder center and compared them with those of healthy controls (Masheb et al. 2011; Moroshko

Table 3 Odds ratio (OR) of different PBI maternal and paternal clusters

PBI subscales	BED/HS OR [95%CI]	Non-BED/HS OR [95%CI]	BED/Non-BED OR [95%CI]	BED + Non-BED/HS OR [95%CI]
Parent				
Maternal neglectful parenting	1.48 [0.95–2.30]	1.38 [0.90–2.10]	0.93 [0.61–1.40]	1.42 [0.98–2.07]
Maternal affectionless control	**5.48** [4.01–7.48]***	**4.57** [3.40–6.14]**	0.84 [0.63–1.10]	**4.95** [3.79–6.48]**
Maternal affectionate constraint	0.56 [0.39–0.81]	0.77 [0.56–1.07]	1.37 [0.93–2.01]	0.68 [0.51–0.90]
Maternal optimal parenting	0.21 [0.14–0.28]	0.22 [0.16–0.30]	1.08 [0.75–1.57]	0.21 [0.16–0.27]
Paternal neglectful parenting	0.82 [0.56–1.19]	0.74 [0.52–1.06]	0.91 [0.61–1.34]	0.77 [0.57–1.05]
Paternal affectionless control	**6.39** [4.56–8.94]***	**4.93** [3.56–6.82]**	0.77 [0.58–1.02]	**5.53** [4.10–7.46]***
Paternal affectionate constraint	1.09 [0.76–1.56]	1.27 [0.91–1.77]	1.17 [0.82–1.66]	1.19 [0.88–1.60]
Paternal optimal parenting	0.19 [0.13–0.26]	0.26 [0.19–0.35]	1.41 [0.98–2.01]	0.26 [0.17–0.29]

Note: PBI, Parental Bonding Instrument; OR, odds ratio; BED, participants with obesity with binge eating disorder; Non-BED, participants with obesity without binge eating disorder; HS, healthy subjects
In bold: *OR > 1.5; **:OR > 3; ***:OR > 4.5
Table extracted from Amianto et al., 2021

et al. 2011; Ruini and Fava 2012). According to previous literature, the parenting experience recalled by BED and non-BED obese participants was significantly different from that of healthy controls (Anderson et al. 2012; Faber and Dubè 2015). In particular, careless and overcontrolling parenting was described by obese participants as recurrent conditions, thus confirming that these parenting attitudes may represent possible risk factors for obesity development (Bahrami et al. 2013; Hernandez-Hons and Woolley 2012). Moreover, BED reported lower maternal and parental care than non-BED obese participants (Amianto et al. 2016a). This finding suggests that it is possible that particularly low levels of care may be specifically associated with BED, and it may explain the positive effects of attachment-based therapies in BED patients (Maxwell et al. 2014).

Nevertheless, the same study also performed a cluster analysis of the PBI characteristics which sharply distinguished the obese participants into two clusters (Amianto et al. 2016a). The larger one was characterized by fewer parenting patterns' distortions (i.e., intermediate care and overprotection) and was then defined the "light neglect obesity" cluster (LNO). The other one, including about one third of the whole sample, was characterized by severe neglectful and overcontrolling patterns (low care and high parental overcontrol) by both parents and was then defined as a "severe neglect obesity" cluster (SNO). The first cluster is poorly related to psychopathology and dysfunctional personality measures, while the second one shows more severe eating and general psychopathology and a personality profile characterized by more dysfunctional traits. The authors suggest that this cluster distribution implies that even the slight parenting distortions evidenced in the LNO can be related to the development of adult obesity and thus recommend a higher vigilance on parental attitudes (Anderson et al. 2012). In fact, also relatively mild parenting distortions may be related to the growing epidemic of obesity, which scientific literature does not justify with a growth of traumatic experiences within the family (Stevens et al. 2012). Moreover, they suggest that the more severe parenting distortions in the SNO are directly related to worse eating psychopathology in obese subjects with the only exception of the body dissatisfaction which is similar in both clusters.

The direct relationship between parenting and the development of obesity is supported also by the correlation pattern of parenting dimensions with personality traits, eating, and general psychopathology. In fact in the non-BED obese group, it is very extensive and interests all parenting dimensions (Amianto et al. 2016a). This definitely supports that also for both BED and non-BED obese participants, worse childhood parenting represents a relevant risk factor for eating and general psychopathology and also more dysfunctional personality traits.

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The relationship between the obesity and the distorted parenting in infancy and also between psychopathology and personality traits of obese subjects and their parenting features can be considered as well established (Amianto et al. 2012; Castellini et al. 2012; Müller et al. 2014; Schulz and Laessle 2010). Moreover, some literature also related the degree of attachment problems to the severity of psychopathology in BED (Caroleo et al. 2018; Otani et al. 2016). Nevertheless, it is less clear what is the role of parenting for the development of the binge-eating behavior and BED. In fact, despite the differences between BED and non-BED obese participants in personality and psychopathology features, no significant association between a specific parenting pattern and the development of BED has been established. Moreover, in the study by Amianto and coworkers (2016a) in BED subgroup, the relationship with participants' psychopathology is almost completely centered on the deficiency of maternal care, while a direct relationship between parenting and personality traits is not evident. It is thus suggested that obese participants with and without BED express different dynamics relating childhood parenting to the eating and general psychopathology and that these dynamics are direct for non-BED obese and indirect for BED participants (Kittel et al. 2015; Leehr et al. 2015). This supports that even if inadequate parenting is a relevant risk for obesity development (Anderson et al. 2012), it is not directly related to the development of overeating attitudes (Faber and Dubè 2015). This evidence is in accordance with the fact that while the diagnosis of BED was included into the DSM psychiatric disorders, obesity is not recognized as a psychiatric condition in itself (Amianto et al. 2015). This implies that BED is characterized by a complex pathogenesis in which concur numerous risk factors which mediate the influence of parenting features on psychopathology, as it happens in other eating disorders (Fassino et al. 2010). Obesity alone, instead, may represent a direct overcompensation of inadequate parenting patterns and of their deficits in emotional regulation as proposed by many authors (Faber et al. 2018; Kittel et al. 2015; Leehr et al. 2015).

Parenting Influence on Personality Traits of Obese Participants With and Without BED

The relationship between attachment and personality traits in obese participants is complex. According to literature, BED and non-BED obese participants display high harm avoidance, low reward dependence, persistence and self-directedness, and worse eating and general psychopathology than controls (Amianto et al. 2016a). BED participants also displayed higher harm avoidance, lower reward dependence, and self-directedness with respect to non-BED and healthy participants. These personality traits were coupled with a worse psychopathology profile of BED participants with respect to non-BED obese. Hence, BED shares with eating and other mental disorders a "core" personality profile (high harm avoidance and low self-directedness), and this is linked to both less caring parenting and greater psychopathology features (Fassino et al. 2013). Literature demonstrated that parenting attitudes are influent on the development of both traits (Oshino et al. 2007).

Moreover, a lower reward dependence has been related to maternal neglect in participants with obesity in a study by Amianto et al. (2016a). The relevance of these traits for psychological functioning is also supported by studies on healthy subjects which evidence that these personality traits mediate the influence of parental bonding on the perception of well-being (Murakoshi et al. 2020). It is thus possible, and should be explored in perspective studies to avoid the "effort after meaning" effect and to establish a causal connection, that personality traits mediate between attachment troubles and BED psychopathology.

According to the research available on the psychobiological model of personality (Cloninger et al. 1993), the severity of neglect and other parenting distortions directly influence the development of novelty seeking, harm avoidance, and self-directedness (Hintsa et al. 2007; Hwang et al. 2006; Keltikangas-Jarvinen and Salo 2009; Oshino et al. 2007).

The research conducted by Amianto and colleagues (2016a) shows the same correlation also in the obese population. It also evidences that the LNO group of obese adults is characterized by a low persistence. This result is in accordance with previous findings (Hwang et al. 2006; Sullivan et al. 2007) in the pediatric population, corroborating the hypothesis of an epigenetic influence of early parenting on the expression of this temperament trait. Instead, the SNO group, which is related to the most severe neglect, is characterized by low cooperativeness. Moreover, the study of Amianto et al. (2018) underlines that this trait displays lower levels in BED than non-BED participants. The low cooperativeness in obese participants, particularly in BED ones, is a common finding in the previous literature (Fassino et al. 2002; Sullivan et al. 2007), and it represents a severe risk factor for the therapeutic compliance, because it correlates with the expression of severe cluster B disorders (Cloninger et al. 1993). These evidences suggest a path in which severe neglect or abuses mediated cooperativeness may indirectly influence the outcomes of treatments for obesity. Future research is needed to confirm it.

One of the most surprising pieces of research by Amianto and colleagues (2016a) is that it displays an extensive correlation of parenting traits with personality and psychopathology in the LNO and control groups and a weaker and more limited one in the SNO cluster. In fact, in the less neglected participants belonging to the LNO group, maternal and paternal care are directly related with personality (Svrakic et al. 2002) and psychopathology features (Fassino et al. 2010). This pattern is different from that of control subjects in which both maternal care and overprotection are correlated with personality and psychopathology, suggesting that different parenting dynamics produce different effects in obese and non-obese subjects. Moreover, a novel finding from the study was that parenting features are poorly related to the personality or psychopathology traits in the SNO cluster. Instead, only in the SNO group, the BMI was related to paternal overprotection. This evidence suggests that the two obese clusters based on parenting are affected by dynamics connecting attachment to personality that are nonlinearly related to the severity of attachment troubles. A very high degree of neglect may be permissive for a stronger influence of the external environment on child development than it would be in a caring family (Cleveland et al. 2010). Hence, subjects growing in a severely neglectful family may

be heavily influenced by environmental factors (e.g., family distortions, traumas, sexual or physical abuses) that may distort personality development and foster psychopathology in a way that is relatively independent of parenting attitudes in itself. On the other hand, malfunctioning personality and psychopathology traits may also have produced more recollection biases in the SNO cluster as a consequence of an "effort after meaning" effect (Amianto et al. 2012). Definitively, the mechanisms linking early parenting experiences to the development of current personality and psychopathology are radically different between the LNO and SNO obese participants and may guide future research and help the personalization of therapeutic approaches (Ruini and Fava 2012).

What about the prevalence of the diagnosis of BED in the SNO and LNO parenting clusters? It was expected to have a higher prevalence of BED in the SNO cluster, since the subjects with BED display a greater level of psychopathology (Amianto et al. 2012; Castellini et al. 2012; Schulz and Laessle 2010). Instead, BED subjects are almost equally distributed among the two clusters. This unrelatedness of the BED diagnosis suggests that early parenting experiences measured with the PBI are not a specific risk factor for the development of BED. The paper thus suggests that other researches are needed to explore other risk factors, more specific for the BED pathogenesis, which possibly interact with the inadequate parenting to produce the complex and nonlinear pathogenesis which probably characterize the BED subgroup of obese subjects (Kiesewetter et al. 2010; Pinard et al. 2012; Schulz and Laessle 2010). The need for further research is also supported by the limitations of the study itself, which is cross-sectional and thus does not permit causal effects in the relationship between parenting style, personality, and psychopathology. Moreover, the sample was represented by treatment-seeking obese subjects; thus, its findings could not be generalized to all obese population but probably to those obese subjects with most severe psychopathology and worse personality trait functioning, possibly with a lesser differentiation with BED population. Moreover, also BED subjects may not be completely represented since some of them may be normal weight or may display lower levels of eating and general psychopathology.

Evidences About Combined Maternal and Paternal Parenting Styles

In the recent study by Amianto and coworkers (2021), the analysis of the parenting style combined between maternal and paternal influences was conducted in a large obese sample to better define the specific parenting mechanisms which may be influent on the development of obesity and BED. According to the expectations, the research outlined that the parenting style defined "affectionless control" (Parker 1989) is a relevant and specific risk factor for the development of obesity alone. The relevance of this finding descends by the evidence that neither parental neglect nor parental overcontrol alone was effective in increasing the risk for obesity (Amianto et al. 2016a). In fact, affectionless control is the combination of parenting attitudes of parents unresponsive to their child's needs for care and at the same time unable to

foster appropriate independence, hence producing an anxious attachment. Affectionless control has been suggested as a common pathogenic factor for different eating problems (e.g., anorexia or bulimia nervosa) which apparently do not share a common pathogenesis (Monteleone et al. 2019). Its relevance for the pathogenesis of obesity is also suggested by its correlations with higher neuroticism, with depressive symptoms, and with an altered expression of glucocorticoid receptor factors which may be considered specific for the weight increase (Avila et al. 2015; Preiss et al. 2013; Takahashi et al., 2017). Finally, affectionless control, even when expressed by only one parent, is so strongly associated with obesity, regardless of the presence of BED, that it may exert a very specific role in the pathogenesis of obesity, regardless of the presence of eating psychopathology (Amianto et al. 2016a, b; Faber et al. 2018).

Anxious attachment promoted by affectionless control impairs the development of positive working models and self-identity, both relevant to the pathogenesis of EDs (Tasca and Balfour 2014). Thus, obesity may derive from a failure, or at least a deficit, in the development of a coherent self, as suggested for the anorexia nervosa and other eating disorders (Amianto et al. 2016b). As suggested by Scalabrini and coworkers (Scalabrini et al. 2018), altered attachment patterns may impair the maturation of specific brain areas (mainly DLPC) pertaining to the midline structures which are implied in the perception of the sense of the self. In particular, among the functions of the self, self-awareness and self-regulation could be particularly relevant, for the dysregulated eating and problems in keeping a healthy body image. In fact, overeating may represent an attempt to fill a void due to the lack of self-boundaries, the food avoidance is an attempt to remark on them. The hypothesis of a common deficit represented by the fragility of self-boundaries which may be managed using different coping mechanisms in the two disorders with opposite weight effects may explain why obesity often precedes or follows anorexia nervosa (Murray et al. 2017).

There would be different pathogenic pathways from affectionless control to the disorders through the deficits of the self (Amianto et al. 2016b; Hymowitz et al. 2017). According to the double psychopathological pathway for eating disorders proposed by Arcelus et al. (2013), the first, connected to the sense of self-worth, would represent the basis for an extreme weight alteration, and it would be expressed in the anorexia nervosa or obesity. The second, connected with the sense of relational connectedness, would produce binge eating, thus leading to binge-purging anorexia nervosa, bulimia nervosa, and BED (Amianto et al. 2012).

No Specific Parental Style for BED Expression

The research on parenting styles by Amianto and coworkers (2021) did not find any specific association between a particular parenting and the expression of BED. The finding was unexpected since BED is the psychopathological condition most frequently associated with obesity; it is characterized by worse levels of attachment and involves a worse personality functioning and higher levels of psychological

suffering than obesity alone (Amianto et al. 2016a, 2018; Kessler et al. 2016). The fact that the affectionless control even being a relevant risk factor for obesity is not related to BED implies that it may only be influential on the unhealthy eating attitudes of subjects with obesity, without being related to specific BED psychopathology. Hence, since BED participants reported a particularly low care from both parents, their attachment problems may only be directly related to the development of their obesity and only indirectly involved in the pathogenesis of their BED.

Only the analysis of the combined parenting styles of the parental couple permitted some more specific association between parenting styles and BED (Amianto et al. 2021). In fact, the specific association of maternal neglectful parenting with paternal optimal parenting represented the highest relative risk for BED, while maternal affectionate constraint alone seems to display a protective effect. This evidence referred to the interactions of parenting styles within the parental couple is the more specific link between parenting style and BED pathogenesis. According to previous findings, it supports that BED, as it happens for other eating disorders, displays a complex pathogenesis more linked to the family dynamics than to the alteration of the parenting style of a parent alone (Fassino et al., 2009). On the other hand, when it is coupled with the evidence of the lower levels of maternal and paternal care in BED participants, it suggests that, consistent with previous literature, these complex dynamics are amplified and empowered by neglect to foster the pathogenesis of BED, similarly to what happens for other psychiatric conditions (Amianto et al., 2016a; Mannarini et al. 2018; Sokol et al. 2017).

Clinical Implications

The exploration of attachment, and in particular of parenting styles, among treatment-seeking obese participants permitted to identify specific distinctive features among BED and non-BED obese populations which can borrow relevant clinical implications.

As it concerns the relevance of the attachment dynamics for BED and non-BED population, the research findings may guide psychotherapeutic approaches in these disorders. In particular, they suggest the need for a particular attention paid by the therapists to the transfer and countertransfer reactions and to attachment relationship (Fassino et al. 2008). In fact, both the phase of engagement and that of dismissing from the therapeutic relationship may be particularly affected by attachment troubles of these subjects strictly related to early parenting experiences (Tereno et al. 2008).

The findings on parenting clusters identified two distinct groups of obese participants, which are independent from the diagnosis of BED. Mild neglectful parenting characterizes obese participants that, regardless of the BED diagnosis, are affected with moderate character immaturity, laziness, and low persistence. This suggests that this specific clinical group may need therapeutic projects with few drug treatments and limited psychiatric support due to their lower rates of psychopathology. Instead,

they could benefit from specific psychoeducation and psychological support, along with nutritional counseling, to balance their personality weaknesses. When psychotherapy could be indicated, CBT treatments may be recommended. In contrast, more severe neglect levels identify those subjects who need more medicalization due to their high psychopathology. These may include both antidepressants, useful to treat their mood disorders and to control binge eating, and also psychiatric drugs addressed to improve the treatment for personality disorders (e.g., atypical antipsychotics). Instead of a mere psychological support coupled with nutritional support, these subjects may deserve structured psychotherapy. Moreover, the psychotherapeutic approach in this subgroup should be personalized. Due to the higher personality disturbances, CBT treatments could be poorly applicable, while dialectical behavior therapy (DBT) or psychodynamic approaches addressed to personality disorders could be more effective (Amianto et al. 2012).

The differentiation of the clinical and psychological approaches between BED and non-BED obese subjects based on the findings on attachment features is less easy, since BED may not be related to a specific parenting style. Nevertheless, this absence of evidence based on attachment dynamics suggests building specific therapeutic protocols for each target symptom based on the diagnosis of obesity alone of the association with BED (Saltzman and Liechty 2016). In fact, obesity alone could be approached by psychological care protocols directly addressed to the psychodynamic consequences of the early troubled parenting and more specifically of affectionless control (e.g., the lack of self-care and self-compassion). Instead, those addressing the obese subjects affected with BED should prior take into account the personality troubles which may be considered mediators of the inadequate attachment on psychopathology (Amianto et al. 2015). Moreover, the treatment of obese subjects with BED should also consider their higher levels of psychopathology needing specific drug treatments. At this regard, some attempts have been made to address more specifically obese subjects affected with BED. The protocol described by Compare et al. (2013) as more effective on this disorder consists in a psychotherapy focused on the cognitive and interpersonal experiential perspectives of emotions, associated with dietetic assistance, drugs, psychoeducational interventions, and self-help activities.

In general terms, the research on attachment and parenting styles of BED and non-BED subjects permitted to conduct the pathogenesis of these disorders to a complex theoretical framework connecting the obesity symptoms to early attachment dynamics and their consequences for the development of the sense of the self, as for anorexia nervosa (Amianto et al. 2016b). This new theoretical framework may help clinicians and psychotherapists to modulate their interventions with a higher attention paid to attachment-related dynamics and the fragility of self-boundaries in these subjects. This may overcome the current difficulties (e.g., high dropout rate) and the low efficacy with respect to their medium- to long-term evolution of the psychological treatment for the obesity and BED as it was evidenced for anorexia nervosa (Amianto et al. 2019; Fassino et al. 2013).

Preventions Issues

Research underlines that dietary factors contribute worldwide to a large number of deaths and to a relevant loss of disability adjusted life years (DALYs) and also that the prevention of obesity and BED in particular is often conceived as a mere nutritional psychoeducation offered to children and less often to their families to prevent feeding distortions (The Lancet Public Health 2019). The present review suggests that more interventions targeted to improving parenting styles in childhood, in particular those focused on parenting neglect and on affectionless control, may be necessary to effectively prevent obesity and BED. According to a recent review, the improvement of the healthcare system in the USA accounts for a very low rate of improvement in population life expectancy; instead, the larger influences on population health derive from changes in habits and culture (Kaplan and Milstein 2019). Since parenting attitudes are a cultural factor more than a consequence of healthcare system functioning, moreover they are influenced by acculturation and thus may be modified by psychoeducation; the interventions directed toward their modulation display a high potential for improving the health of the population. It is for this reason that the prevention of the epidemics of obesity and BED should involve interventions which promote healthy parenting styles in addition to nutritional styles in the families at risk for development of obesity in their children (Chu et al. 2018). Primary prevention of obesity and BED through the changes of parenting styles in the general population should involve mass media and social communication. Also the healthcare systems (e.g., pediatricians or general practitioners) should be involved because it may represent a concrete support for the parents to be addressed to more empathic and less intrusive parenting attitudes toward their children since childhood (Atzil et al. 2011). Also the strategies for secondary and tertiary prevention of childhood and adult obesity and BED need to couple nutritional assistance to patients with psychoeducational and psychotherapeutic approaches addressed to affected subjects but also to their families when necessary (Arenaza et al. 2020).

In addition, according to the research of Amianto and coworkers (2021), the psychoeducational interventions may give a good chance for improvement even if they involve only one parent and if the parenting style of parents is not the optimal one. In fact, it has been evidenced that affectionless control represents a greater risk for obesity if both parents display it, while it is significantly lower if only one parent displays it. This means that the effects of affectionless control of one parent can be attenuated if the other has a different parenting style, although nonoptimal.

Conclusion

Notwithstanding their limitations, the reviewed studies provide the evidence for a strong association between a specific parenting style in childhood, i.e., the affectionless control, and the development of obesity in adulthood. Instead, even if BED displayed lower levels of care by both parents and higher overprotection with respect to non-BED obese participants, which are coupled with worse personality profile and

psychopathology features, no parenting style results as a specific risk factor for the development of this disorder. This seems to be a consequence of a more complex pathogenesis characterizing BED with respect to obesity alone, which probably involves traumas and life events which are not linearly related to parenting styles. Thus, as evidenced for other mental disorders, research suggests that parental neglect may represent the most relevant risk factor related to parenting for developing BED. In fact, parental neglect may help the development of inadequate personality traits and psychopathology under the pressure of environmental stressors, both within and outside the family.

Efforts to prevent child and adult obesity should take into account the existence of dysfunctional parental styles in childhood and their consequences for child and adult functioning, and the strategies which should be implemented to correct them. To take care of the parenting styles in infancy may elicit consistent cultural changes to adapt the parenting attitudes in the general population toward a greater attitude to respond to the needs of children. This may be particularly useful in view of the rapid evolution and greater complexity of current society. Future research should be addressed to explore the efficacy of these psychoeducational efforts (Morhosko et al., 2011).

Implications for Other Eating Disorders

Present research supports the importance of attachment dynamics for pathogenesis of eating and nutrition disorders and obesity, which at the present moment is not included in the DSM-5 ED chapter. Nevertheless, it suggests some specification in this regard. First, it supports that while the role of childhood attachment dynamics in favoring the outburst of obesity is direct and linear also in adulthood, the consequences of these dynamics are more difficult to be found in other eating disorders, as evidenced for BED (Amianto et al. 2021). In fact, even though some authors sustained the relevance of attachment dynamics for the outburst of eating disorders, they also suggested that this relationship is not linear, disorder-specific, and easy to be recognized with the studies of attachment in the adult population (Tasca and Balfour 2014). Recent theories concerning the outburst of anorexia nervosa, and eating disorders in general, suggested that the mediator for this relationship could be the deficitary development of the self in those subjects who received insufficient parental care (Amianto et al. 2016b). Future research concerning the role of parenting in the pathogenesis of EDs could benefit from a more objective assessment of the concept of the self which may be useful to underline the pathway by which defective attachment produces each eating disorder. Also the research connecting attachment dynamics with other concausal risk factors may help a better definition of the pathogenesis of each ED.

Second, the present research also suggests that childhood obesity may represent the early expression of attachment distortions, and the early recognition of overweight or obesity may help to recognize early risk factors of the development of a fragile self in adolescence. The assessment of any ED for future research should

consider and valorize the preexistence of childhood obesity and consider it as a specific indicator of dysfunctional attachment dynamics in this population. Future research may differentiate the risk factors implicated in the pathogenic pathways in those ED subjects with and without previous childhood obesity.

Mini-Dictionary of Terms

Parenting style = The ensemble of the attitudes that parents express managing the needs of their children.
PBI = Parental Bonding Instrument (PBI) is a worldwide known validated instrument assessing parenting style during childhood and adolescence.
Affectionless control = A parenting style characterized by low caring attitudes coupled with high overcontrol toward children activities, a major risk factor for obesity.
LNO obesity = Obese subjects that display low levels of childhood parenting neglect and lower psychopathology in adulthood.
SNO obesity = Obese subjects that display high levels of childhood parenting neglect and higher psychopathology in adulthood.

Key Facts of Parental Care and Binge-Eating Disorder

- Parental care alterations in childhood are strictly related to the development of obesity in adolescence and adulthood.
- Obese individuals with or without BED display parenting neglect with respect to controls.
- The severity of neglect is strictly related to more severe personality distortions and psychopathology expression.
- Recent research evidenced that childhood affectionless control is a specific risk factor for the development of obesity in adulthood.
- No specific parenting style is a predictor of BED.

Summary Points

- Binge-eating disorder (BED) has the highest prevalence among the EDs, and it is likely to increase.
- BED has particular interest for primary care because of its link with medical and psychiatric comorbidities.
- BED is associated with eating psychopathology, psychiatric and medical disorders, social and occupational impairment, and low quality of life.
- Early attachment experiences are relevant components of BED pathogenesis and of the other disordered eating behaviors which lead to obesity.

- Deficit attachment impairs the development of emotional control producing inability to cope with negative emotions in a framework of negative experiences.
- Non-authoritative parenting styles in childhood and physical and psychological abuses in childhood are strictly related to the development of obesity in adulthood.
- Personality abnormalities and the higher levels of psychopathology in subjects with obesity may be related to worse parenting.
- Parenting experience recalled by BED and non-BED obese participants is significantly different from healthy controls.
- The parenting style defined "affectionless control" is a relevant and specific risk factor for the development of obesity.
- The anxious attachment promoted by affectionless control impairs the development of positive working models and of self-identity.
- Obesity may derive from a failure in the development of a coherent self, as suggested for the anorexia nervosa.
- Obese participants express different relationships relating childhood parenting to psychopathology: direct for non-BED obese and indirect for BED.
- BED displays a complex pathogenesis possibly more linked to the family dynamics than to the alteration of the parenting style.

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DeltaFosB and Preclinical Binge Eating

49

Implications for Clinical Contextual Applications

Richard Quansah Amissah and Igor Timofeev

Contents

Introduction 983
ΔFosB and BE 984
ΔFosB: What, When, and How? 984
BE: What, When, and How? 987
Application to Other EDs 994
Mini-Dictionary of Terms 995
Key Facts of ΔFosB 996
Summary Points 996
References 996

Abstract

Binge eating (BE), an addictive behavior, can develop as a coping mechanism to mitigate the effects of a stressful event. It results in the expression of deltaFosB (ΔFosB), a protein involved in the initiation and maintenance of addictive behaviors, in the reward system. In humans, BE is characteristic of anorexia nervosa binge-purge subtype (AN-BP), bulimia nervosa (BN), binge eating disorder (BED), and other specified feeding or eating disorder (OSFED). Patients who binge display feelings of guilt, shame, and disgust following the binge. It was hypothesized that patients binge to reactivate a hypofunctioning reward system. However, following the binge, this system returns to its previous hypofunctioning state, suggesting that BE is associated with decreased reward system activity as demonstrated by several human and animal studies. Several treatment

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methods have been developed for BE; however, most are ineffective partly due to our poor understanding of the mechanisms underlying BE. As ΔFosB expression decreases neuronal excitability, it may underlie the decreased reward system activity observed in BE patients. These findings suggest that BE treatments that increase reward system activity may be an optimal treatment strategy. Moreover, most pharmacological treatments decrease dopamine release or dopamine receptor activity, which seems contradictory to the reward deficiency theory, which proposes that addictive behaviors are promoted by decreased dopamine release and receptor density, suggesting that treatments should rather stimulate dopamine release or increase dopamine signaling. Based on ΔFosB expression experimental results in bingeing animals, we suggest that treatments that block ΔFosB expression may be a promising new way to treat BED.

Keywords

Binge eating · DeltaFosB · Negative affect · Reward system · Inhibitory control · Treatment · Neuromodulation · Pharmacotherapy · Neuroimaging · Eating disorders

Abbreviations

AC	Adenylyl cyclase
AMPA	α-Amino-3-hydroxy-5-methyl-4-isoxazole propionic acid
AMPA-R	α-Amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor
AN-BP	Anorexia nervosa
BE	Binge eating
BED	Binge eating disorder
BOLD	Blood-oxygen-level-dependent
Ca^{2+}	Calcium
Ca^{2+} Ch	Calcium channel
CA1	Cornu ammonis 1
CAM	Calmodulin
CAMKII	Calcium/calmodulin-dependent protein kinase II
cAMP	Cyclic adenosine monophosphate
CBT	Cognitive behavioral therapy
Cdk5	Cyclin-dependent kinase 5
CREB	cAMP-response element binding protein
DA	Dopamine
Dopaminergic neuron	Dopamine-expressing neuron
DBS	Deep brain stimulation
DLPFC	Dorsolateral prefrontal cortex
DNA	Deoxyribonucleic acid
D1R	D1 dopamine receptor
D2R	D2 dopamine receptor

EDs	Eating disorders
EU	European Union
fMRI	Functional magnetic resonance imaging
GABAergic neuron	γ-Aminobutyric acid-expressing neuron
Glutamatergic neuron	Glutamate-expressing neuron
GluR2	Glutamate subunit 2
Gi/o	Gi/o protein-coupled receptor
Gs	Gs protein-coupled receptor
IEGs	Immediate early genes
K^+	Potassium
LDX	Lisdexamfetamine
MRI	Magnetic resonance imaging
MSNs	Medium spiny neurons
Na^+	Sodium
Acb	Nucleus accumbens
NK-κB	Nuclear factor kappa B
NMDA	N-methyl-D-aspartate
PET	Positron emission tomography
PFC	Prefrontal cortex
PKA	Protein kinase A
rTMS	Repetitive transcranial magnetic stimulation
tDCS	Transcranial direct current stimulation
USA	United States of America
VTA	Ventral tegmental area
ΔFosB	DeltaFosB

Introduction

In our day-to-day activities, humans are exposed to stimuli which could either result in positive or negative affect. Positive affect is associated with motivation and enthusiasm, while negative affect is associated with depression, anxiety, and fear (Watson et al. 1988). While positive affect is welcome, negative affect is not and usually forces individuals to develop coping mechanisms for them. These mechanisms may involve engagement in activities that help to mitigate the negative affect and could lead to maladaptive behaviors like drug and food addiction to mitigate the negative affect.

Drug addiction involves compulsively seeking and using drugs, accompanied by a feeling of loss of control. This is similar to what happens in patients who engage in binge eating (BE). DeltaFosB (ΔFosB) is a protein expressed in the brain, with highest degree of expression in the nucleus accumbens (Acb) and dorsal striatum, brain regions important for addiction (Nestler et al. 2001). It is responsible for the initiation and maintenance of addictive behaviors, and since BE is a form of addiction, the same protein may be implicated in its initiation and maintenance.

Due to the complexity of BE, several human and preclinical studies have been conducted to understand their underlying mechanisms. Knowing these mechanisms will help to develop effective treatments that target the etiology of the disorder and not just the symptoms. The main purpose of this chapter is to elucidate the involvement of ΔFosB in BE and to discuss possible treatments for BE, based on our knowledge of the role of ΔFosB in BE. Below, we will describe the main features of ΔFosB, how it is expressed, and its implication in eating behavior. We will also focus on eating disorders (EDs) that involve BE and are likely to be mediated by ΔFosB. We will compare results of imaging studies involving human patients with EDs with those in animal studies on EDs. We will further establish a relationship between these EDs and ΔFosB and subsequently discuss what the findings mean in the context of treatments for BE.

ΔFosB and BE

As animals interact with their environment, they are exposed to several stimuli. These stimuli are translated into signals within the brain through gene expression. Each time an animal is exposed to a stimulus, immediate early genes (IEGs) such as c-Fos, zinc finger protein, early growth response 1, and activity-regulated cytoskeleton-associated protein are expressed in the brain (Minatohara et al. 2016). These IEGs encode transcription factors that regulate gene expression. Unlike IEGs, which are transiently expressed and degrade immediately, ΔFosB is expressed following chronic stimulation, as shown in Fig. 1. It is a truncated *fosB* gene with a 37 kD isoform that is quite stable and was detected 1 month after last exposure to a stimulus (Nestler et al. 2001).

ΔFosB: What, When, and How?

ΔFosB is expressed following chronic stimulation with stress (Vialou et al. 2010), drugs (Perrotti et al. 2008), and palatable food (Wallace et al. 2008; Quansah

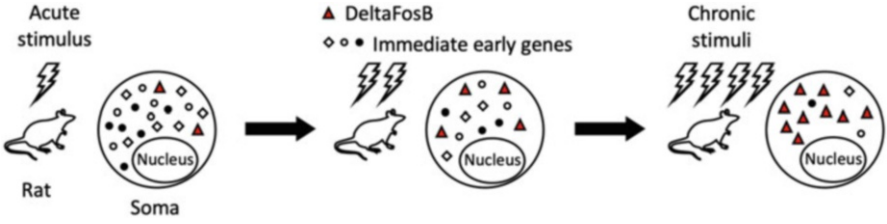


Fig. 1 ΔFosB expression in neurons following chronic stimuli. An acute stimulus results in the expression of immediate early genes and only a small amount of ΔFosB in neurons within the brain; however, as the stimulus progresses to chronic stimuli, immediate early genes degrade and ΔFosB expression increases

Table 1 ΔFosB expression in the brain using various stimuli

Article	Activity	Brain region
Perrotti et al. (2004)	Restraint stress	PFC, LC, VOC, PC, CP, Acb, LSP, BNST, DG, EP, MPA, GP, BLA, CeA, PAG, SG
Vialou et al. (2010)	Social defeat stress	Acb
Chen et al. (1997)	Electroconvulsive seizure	Cerebral cortex
Perrotti et al. (2008)	Cocaine, THC, morphine, ethanol	Acb, DS, PFC, Amyg, Hipp
Muñoz-Escobar et al. (2019)	Chocolate	PFC, Acb, BLA
Quansah Amissah et al. (2020)	Sucrose	PFC, Acb, VTA, LC, PVN, PBN
Wallace et al. (2008)	Sucrose, sex	Acb
Lobo et al. (2013)	THC, sucrose, morphine, cocaine, environmental enrichment, haloperidol	DS, Acb
Werme et al. (2002)	Wheel running	Acb
Sanna et al. (2019)	Sex	PFC, Acb, VTA
Cunningham et al. (2008)	Vagal nerve stimulation	NST, PVN, PBN, BNST, LC, CC, DRN

BLA, basolateral amygdala; LC, locus coeruleus; VOC, ventral orbital cortex; PC, piriform cortex; CP, caudate putamen; LSP, lateral septal nucleus; BNST, bed nucleus of the stria terminalis; DG, dentate gyrus; EP, endopiriform nucleus; MPA, medial preoptic area; GP, globus pallidus; CeA, central amygdala; PAG, periaqueductal gray; SG, superior geniculate; DS, dorsal striatum; Amyg, amygdala; Hipp, hippocampus; PVN, paraventricular nucleus of the hypothalamus; PBN, parabrachial nucleus; NST, nucleus of the solitary tract; CC, cingulate cortex; DRN, dorsal raphe nucleus

Amissah et al. 2020). Environmental enrichment (Lobo et al. 2013) and sexual activity (Sanna et al. 2019) also lead to ΔFosB expression. Other activities and stimuli which result in ΔFosB expression are listed in Table 1. Basically, chronic engagement in activities that are considered rewarding leads to ΔFosB expression. Even though most studies focus on ΔFosB expression in the Acb, it can also be expressed in the hippocampus, parabrachial nucleus, cingulate cortex, dorsal raphe nucleus, nucleus of the solitary tract, paraventricular nucleus of the hypothalamus, ventral bed nucleus of the stria terminalis, locus coeruleus, and ventral pallidum (Eagle et al. 2018; Cunningham et al. 2008). More importantly, it is expressed in reward processing regions, specifically the Acb, prefrontal cortex (PFC), and ventral tegmental area (VTA), in binge-like eating rats (Muñoz-Escobar et al. 2019; Quansah Amissah et al. 2020).

The stimulation of dopamine and glutamate receptors on Acb medium spiny neurons (MSNs) results in increased intracellular protein kinase activity which causes the activation of cAMP-response element binding protein (CREB) (Bito et al. 1996). The activated CREB is then phosphorylated, resulting in the expression of *fosB* and *c-fos* genes and a small amount of ΔFosB (Nestler et al. 2001). Persistent stimulation of receptors on MSNs leads to the downregulation of *c-fos* and *fosB* and the upregulation of ΔFosB (Renthal and Nestler 2009). As a transcription factor, ΔFosB regulates the transcription of other genes including nuclear factor kappa B (NK-κB), cyclin-dependent kinase 5 (Cdk5), α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA) glutamate subunit 2 (GluR2), Ca^{2+}/calmodulin-dependent protein kinase II (CAMKII), N-methyl-D-aspartate (NMDA) Z1, and glutamate decarboxylase (McClung and Nestler 2003).

What Is the Effect of ΔFosB Expression on Behavior?

Several studies have been conducted to elucidate the effects of ΔFosB expression on animal behavior, and these studies generally involved ΔFosB overexpression in the Acb of transgenic animal models. While this technique is not ideal, in that the protein is generally expressed at moderate levels within the brain, it has contributed significantly to our understanding of how ΔFosB mediates behavior. In drug abuse studies, ΔFosB overexpression in the rat Acb protects against the cocaine addiction phenotype by decreasing reinstatement of cocaine self-administration, promoting the extinction of cocaine seeking, and reducing cocaine self-administration (Zhang et al. 2014). ΔFosB overexpression also increases the sensitivity of transgenic rats to the rewarding effects of cocaine (Kelz et al. 1999). ΔFosB blockade in the Acb either promotes vulnerability or decreases resilience to social defeat in male mice (Vialou et al. 2010), while its overexpression in the rat Acb produces an antidepressant-like effect evaluated as decreased immobility time during the forced swim test. Regarding natural rewards, while the overexpression of ΔFosB in Acb dynorphin-producing MSNs increases wheel running, its overexpression in Acb enkephalin-producing MSNs has the opposite effect on wheel running (Werme et al. 2002). Rats overexpressing ΔFosB in the Acb shell increase their number of bar presses to obtain sucrose pellets (Zhang et al. 2014). Moreover, overexpressing ΔFosB in the Acb increases the number of nose pokes and lever presses of mice and rats, respectively, for a food reward (Olausson et al. 2006). These studies suggest that ΔFosB expression mediates motivational processes involved in the seeking and consumption of both drug and natural rewards, behaviors that are impaired during addiction.

What Is the Effect of ΔFosB on Neuronal Activity?

In the Acb, ΔFosB can regulate MSN synaptic properties by regulating the expression of the AMPA GluR2 receptor subunit gene (McClung and Nestler 2003). High ΔFosB expression causes an increase in the number of GluR2-containing AMPA receptors at the synapse. GluR2 regulates most of the biophysical properties of AMPA receptors (Isaac et al. 2007). AMPA receptors are tetramers, meaning they comprise of four subunits: GluR1, GluR2, GluR3, and GluR4, in different

combinations (Borges and Dingledine 1998). While the GluR1, GluR3, and GluR4 receptor subunits contain glutamine in the M2 membrane-associated hydrophobic domain at position 607, the GluR2 subunit contains arginine instead. The presence of arginine in the GluR2 receptor subunit introduces an additional positive charge at the receptor pore, which prevents the entry of Ca^{2+} (Isaac et al. 2007). By so doing, MSN neurons with GluR2-containing AMPA receptors show decreased firing rate and permeability to divalent cations like Ca^{2+} (Vialou et al. 2010). In hippocampal CA1 pyramidal neurons, ΔFosB overexpression causes a decrease in intrinsic membrane excitability, due to a reduction in hyperpolarization-activated depolarizing current, without an effect on the resting membrane potential or spike frequency adaptation (Eagle et al. 2018). The hyperpolarization-activated depolarizing current also reduces excitatory synaptic potentials at distal dendritic sites (Magee 1998). ΔFosB expression is therefore associated with decreased neuronal excitability. This is consistent with the assumption that ΔFosB expression likely signifies tolerance to chronic stimulation resulting in a decrease in neuron responsiveness to subsequent stimulation and the proposition that ΔFosB expression following chronic palatable food consumption in binge-like eating rats led to decreased activity in reward processing regions (PFC, Acb, and VTA) (Quansah Amissah et al. 2020; Nestler et al. 1999).

BE: What, When, and How?

BE is characterized by the consumption of large amounts of food in a discrete amount of time and loss of control during bingeing. BE involves the consumption of palatable foods (Allison and Timmerman 2007), and it is characteristic of multiple EDs such as anorexia nervosa binge-purge subtype (AN-BP), bulimia nervosa (BN), binge eating disorder (BED), and other specified feeding or eating disorder (OSFED) (American Psychiatric Association 2013).

The lifetime prevalence for AN is 0.6% (men, 0.3%; women, 0.9%), BN 1% (men 0.5%; women, 1.5%); and BED 3% (men, 2%; women, 3.5%) (Hudson et al. 2007). This shows that BN and BED are the most prevalent EDs and are more prevalent in females than males (Kessler et al. 2013). In the United States of America (USA), the economic cost of EDs for the 2018–2019 fiscal year was $64.7 billion (Streatfeild et al. 2021). The high prevalence of EDs and the associated cost suggest the need for studies to investigate the mechanisms that underlie EDs. Below, we will focus mainly on BN and BED which are the most prevalent EDs that involve BE.

Comorbidities associated with BE include depression and anxiety. Individuals who binge report feeling ashamed, anxious, guilty, and disgust following a binge (American Psychiatric Association 2013). Seventy-five percent of adults and 85% of adolescents who binge experience other comorbidities such as mood and substance use disorders, and even though majority of individuals who binge are obese, some have normal weights (Hudson et al. 2007). Individuals who binge also exhibit deficits in inhibitory control and mental inflexibility (Mobbs et al. 2011).

BE occurs in people of all ages, even though it typically occurs during adolescence (Hudson et al. 2007). BE is more commonly triggered by negative affect (Womble et al. 2001), including stress, and people who binge usually do so to decrease the negative effects of a stressful event (Hawkins and Clement 1984). BE is often associated with a sense of relief following the binge (Heatherton and Baumeister 1991); however, the experienced relief is short lasting, and individuals continue to binge (Deaver et al. 2003). The desire to avoid the aversive consequences because of abstinence from palatable foods has also been linked to relapse among BE individuals in recovery (Heatherton and Baumeister 1991).

What Do We Know from Human Studies?

In humans, the neurobiology of BE has been studied using imaging techniques. fMRI studies involving *monetary rewards* revealed decreased activity in the striatum, insula, and PFC of BED patients (Balodis et al. 2014; Balodis et al. 2013), while those that involved *food rewards* reported diminished insula, thalamus, and frontostriatal region activity during anticipation and consumption in BN patients (Bohon and Stice 2011; Skunde et al. 2016) and decreased activity in the insula and hippocampus in BED patients (Lyu and Jackson 2016). MRI studies have also revealed decreased gray matter volumes in the caudate nucleus and Acb in BN patients (Coutinho et al. 2015). Overall, these studies suggest that BE is associated with decreased activity in brain regions involved in reward processing and inhibitory control such as the PFC, striatum, and insula, supporting a hypothesis that individuals binge to reactivate a hypofunctioning reward system (Wang et al. 2001). A number of studies have also reported opposing results in similar regions in BE patients using neuroimaging techniques (Lee et al. 2017); however, the disparity in results could be due to differences in patient sexes and groups.

What Do We Know from Animal Studies?

Human neuroimaging studies provide information on major brain structures involved in BE, pointing to possible underlying mechanisms, but they do not tell us which types of neurons are implicated and how their manipulation will affect BE. These questions were investigated in animal models of BE using different approaches (see below).

Animal Models of BE

Even though several animal models of BE exist, none replicates all aspects of BE as defined in the DSM V; however, these models still provide useful information on BED. The main characteristic of BE is the consumption of larger than normal amounts of palatable food within a short period of time. To replicate this characteristic, rodents are given intermittent access to palatable food, like sucrose, chocolate, cookies, etc. (Calvez and Timofeeva 2016). Additional techniques include food restriction and some form of stress (Boggiano et al. 2007; Corwin et al. 1998). However, only intermittent access to palatable food was sufficient to induce binge-like eating in rats (Corwin et al. 1998). This technique may not be ideal because by definition BE is the consumption of food when not feeling physically hungry

(American Psychiatric Association 2013). Another approach that is employed to develop binge-like eating models is the use of stress since BE is usually triggered by some stressful event and BE patients usually binge to mitigate the effects of the stress (Boggiano et al. 2007; Calvez and Timofeeva 2016). Finally, people who binge report the feeling of a sense of loss of control during the binge. This loss of control is associated with compulsivity or loss of inhibitory control. In rodent models, this can be evaluated by assessing how much discomfort rodents are willing to endure to obtain a reward (palatable food). Indeed, the foot-shock maze test (Oswald et al. 2011) and the modified light/dark box test, tests that assess compulsivity, validate the similarity of this model with BED in humans (Quansah Amissah et al. 2020; Calvez and Timofeeva 2016).

Overview of the Reward System

The reward system mainly comprises of structures that make up the meso-corticolimbic dopamine system such as the VTA, PFC, and Acb (Kelley and Berridge 2002) (Fig. 2). The major types of neurons in the VTA, PFC, and Acb are dopaminergic, glutamatergic, and GABAergic (MSNs), respectively. The dopaminergic VTA projects to the Acb and PFC (Beier et al. 2015). In turn, PFC glutamatergic neurons target the VTA and Acb (Vertes 2004). The Acb GABAergic neurons target the VTA but not the PFC (Heimer et al. 1991) (Fig. 2). In the normal brain, reward consumption activates VTA dopaminergic neurons, which subsequently release dopamine in the PFC (Phillips et al. 2004) and Acb (van Zessen et al. 2012). PFC activity excites the Acb and VTA, leading to more dopamine release in the Acb (Murase et al. 1993). MSNs in the Acb target mainly GABAergic VTA neurons (Xia et al. 2011), resulting in the disinhibition of VTA dopaminergic neurons to further increase the dopamine release in the Acb. The optogenetic stimulation of VTA GABAergic neurons interrupts reward consumption (van Zessen et al. 2012), while VTA dopamine neuron stimulation leads to positive reinforcement

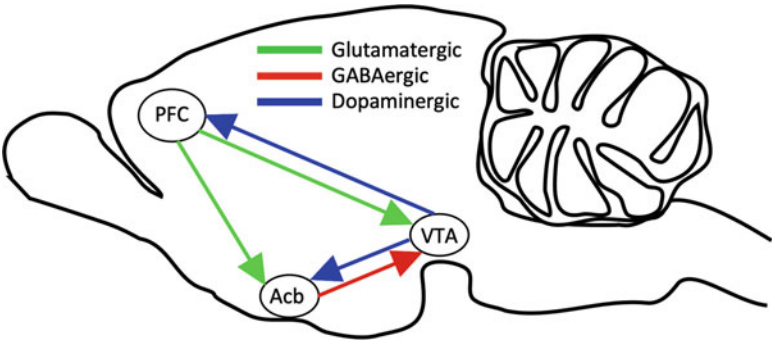


Fig. 2 Main projections from the key regions that form the mesocorticolimbic dopamine system. Neurons within the PFC, Acb, and VTA project to other regions within the reward system. PFC, prefrontal cortex; Acb, nucleus accumbens; VTA, ventral tegmental area. Red arrow, GABAergic neuron projection; green arrow, glutamatergic neuron project; blue arrow, dopaminergic neuron projection

(Kim et al. 2012). PFC activity increases following reward consumption (Horst and Laubach 2013), and inactivating the prelimbic part of the PFC results in a decrease in reward seeking (Sangha et al. 2014). During reward consumption, the activity of Acb MSNs decreases, while their stimulation attenuates consumption (Krause et al. 2010).

The neurons within the VTA, PFC, and Acb can be subclassified based on the types of receptors they express. Within these regions, neurons express receptors for a variety of neurotransmitters/modulators. Of particular importance, neurons that express D1 and D2 dopamine receptors can be found in the PFC and Acb (Simon et al. 2013). An increase in D2 dopamine receptor expression in the Acb increases motivation (Trifilieff et al. 2013). Compulsively eating obese rats have decreased D2 dopamine receptor expression in the striatum, while the knockdown of striatal D2 receptors resulted in the development of addiction-like reward deficits and the initiation of compulsive food seeking (Johnson and Kenny 2010).

Similarities Between Human and Animal Studies

BE involves the chronic stimulation of neurons through repeated palatable food consumption, which results in neuron desensitization (Moore et al. 2018), which may explain the decreased activity observed in the reward system of both patients and binge-like eating animals. Both human and preclinical studies seem to support the reward deficiency theory which suggests that addictive behaviors, including BE, are associated with hypofunctioning of the dopaminergic system reflected by decreased dopamine release and reduction in D2 dopamine receptor density (Blum et al. 2000). Obese individuals have lower D2 dopamine receptor densities in the striatum (Wang et al. 2001). Therefore, individuals who binge do so because of their hyposensitivity to dopamine, and they consume more food in order to experience its rewarding value. This supports the theory that people binge to reactivate a hypofunctioning reward system (Wang et al. 2001). In regions involved in inhibitory control like the PFC, decreased dopamine D2 receptor density was also associated with decreased activity, which may mediate the compulsive behavior associated with BE (Blum et al. 2014).

We propose that the desensitization or decreased activity of neurons that occurs during BE may be due to ΔFosB expression in the reward system (Fig. 3). We recently demonstrated that the number of ΔFosB-expressing neurons in the reward system of BE-prone (BEP) rats was significantly larger than that in BE-resistant (BER) rats (Fig. 4a, b, d, e, g, and h). The increase in the number of ΔFosB-expressing neurons in BEP rats was found in the mPFC, Acb, and VTA (Fig. 5a–c) (for details, see Quansah Amissah et al. (2020)). In a follow-up study, using an in vivo electrophysiological approach, we investigated reward system activity in a similar binge-like eating rat model. Local field potential, in particularly evoked potentials per lick, was lower in BEP rats as opposed to BER rats (Fig. 4c, f, i). These differences were significant in all investigated structures (Fig. 5d–f) and were mirror images of results obtained with ΔFosB expression. Unit recordings demonstrated that (a) the firing rate of neurons in the reward system in BEP rats was lower than that in BER rats, (b) sucrose consumption resulted in increased firing rate

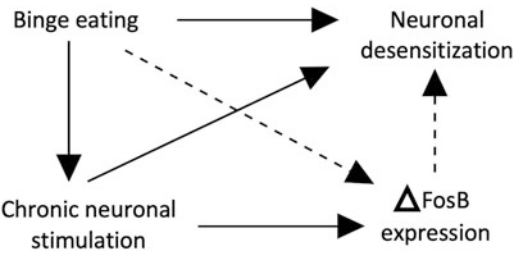


Fig. 3 Summary of possible relationship between BE, chronic stimulation, ΔFosB expression, and neuronal desensitization. BE causes chronic stimulation of reward system neurons, reward system desensitization, and ΔFosB expression suggesting that the desensitization observed in patients with BE may be due to ΔFosB expression in the reward system. Dashed arrow, possible mechanisms; solid arrow, known mechanisms

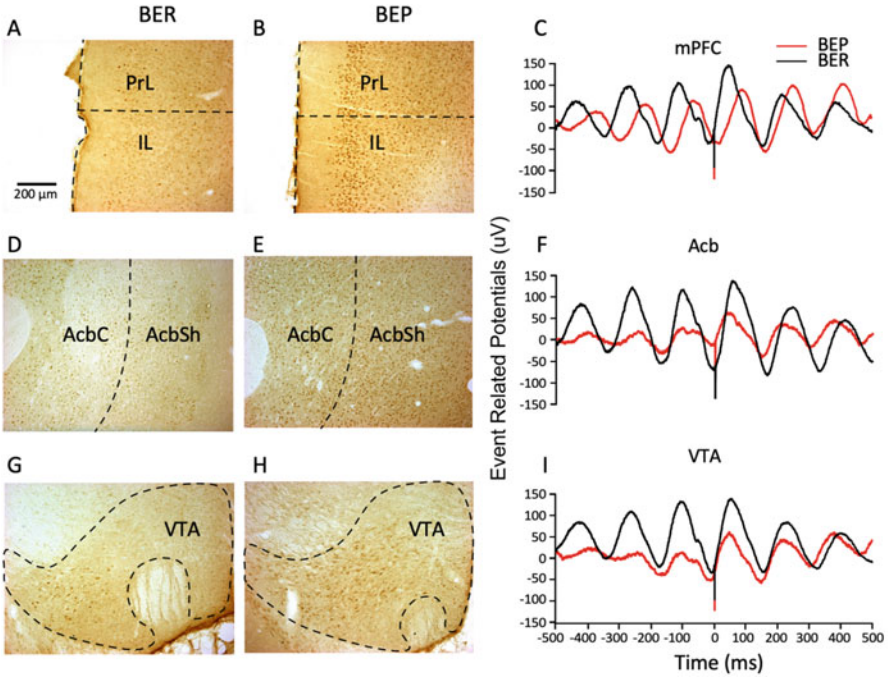


Fig. 4 ΔFosB expression in neurons in the reward system and the corresponding averaged event-related potentials (ERP) per lick in BEP and BER rats. **a** and **b**, ΔFosB expression in neurons in the prelimbic cortex (PrL) and infralimbic cortex (IL) of the medial prefrontal cortex (mPFC) in BEP and BER rats and the corresponding event-related potential centered on each lick in the mPFC (**c**). **d** and **e**, ΔFosB expression in neurons in the nucleus accumbens core (AcbC) and shell (AcbSh) in BEP and BER rats and the corresponding event-related potential centered on each lick in the nucleus accumbens (**f**). **g** and **h**, ΔFosB expression in neurons in the ventral tegmental area (VTA) in BEP and BER rats and the corresponding event-related potential centered on each lick in the ventral tegmental area (**i**). **a**, **b, d, e, g**, and **h** from Quansah Amissah et al. (2020). **c, f,** and **i** from Quansah Amissah et al. (2021)

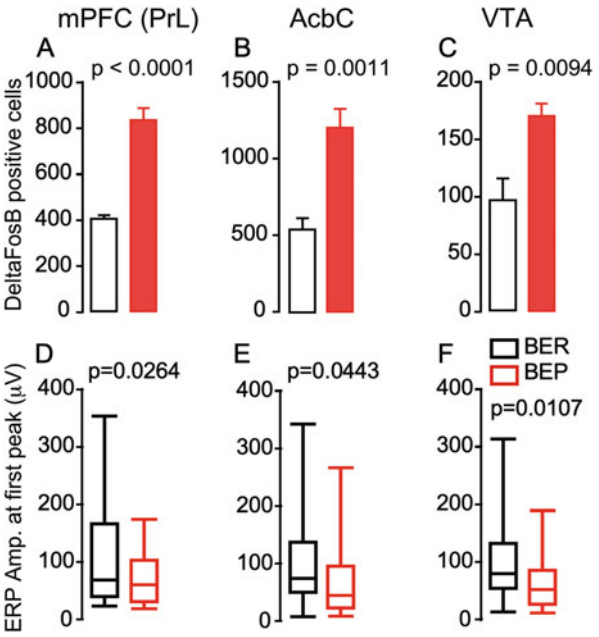


Fig. 5 Quantification of ΔFosB-expressing cells and the amplitude of the event-related potential in the reward systems of BEP and BER rats. (**a**–**c**) The number of ΔFosB-positive cells in the prelimbic cortex of the medial prefrontal cortex (prelimbic), the nucleus accumbens core, and the ventral tegmental area. (**d**–**f**) The event-related potential amplitude at the first peak just after each lick in BEP and BER rats for the medial prefrontal cortex, nucleus accumbens, and ventral tegmental area. (**a**–**c**) from Quansah Amissah et al. (2020), (**d**–**f**) from Quansah Amissah et al. (2021)

in both groups of rats, and (c) firing within 1 s before the beginning of palatable food consumption was significantly increased in BEP rats (Quansah Amissah et al. 2021). These studies are consistent with human fMRI studies that reported decreased reward system activity in BE patients. Thus, all available data point to the fact that patients binge to reactivate a hypofunctioning reward system.

Implications for Clinical Contextual Applications

Above, we described the neurobiology of BE. Based on known mechanisms, we propose below optimal treatments for BE.

For the prevention or treatment of BE, one needs to consider comorbid conditions such as stress, depression, or anxiety. Most common current treatments of BE include cognitive behavioral therapy (CBT), neuromodulation, pharmacotherapy, and, more recently, virtual reality. CBT is the best validated and frequently used treatment for BE, even though BE symptoms still remain in more than 60% of patients who undergo CBT (Slade et al. 2018; National Institute for Health and Care Excellence 2017). The use of virtual reality, which involves user interaction with and immersion in a simulated environment, often provides better results compared to CBT (Riva et al. 2021).

Pharmacological treatments for BE are used when patients do not respond to psychotherapy, patients are unwilling to undergo psychological or behavioral interventions, psychotherapy is unavailable, or there are other psychiatric comorbidities (McElroy 2017). Most pharmacological treatments aim to modulate the

dopaminergic system (Towell et al. 1988). Additionally, several animal studies have shown deficits in dopamine release and positive effects of dopamine receptor agonists on binge-like eating (Davis et al. 2009; Rada et al. 2010).

Lisdexamfetamine (LDX) is the only Food and Drug Administration-approved drug in the USA for treating moderate to severe BED (Heo and Duggan 2017). In humans, LDX reduces BE severity, BE days, and the associated compulsivity (McElroy et al. 2016). It works by blocking the reuptake of dopamine and noradrenaline (Heal et al. 2016). Unfortunately, LDX does not affect comorbidities of BE such as depression and anxiety, implying that it targets the main pathology of BE. Bromocriptine, a D2 dopamine receptor agonist, is another drug used for treating BE. In obese patients, it decreases body fat, body weight, and hyperglycemia (Meier et al. 1992). Another drug, KB220Z, an agent that stimulates dopamine release, has shown some success as a treatment for drug addiction. It is a homeostatic agent used to improve neurological deficits and the resistance of the nervous system to trauma, anxiety, stress, fatigue, and chemical imbalances (Chen et al. 2011). In heroin addicts, treatment with KB220Z significantly activated the caudate-accumbens dopaminergic pathway, alleviated withdrawal from antidepressant medication, and was considered a safer therapy for mild depression (Blum et al. 2012). This drug could have positive effects in the treatment of BE, a form of addiction.

A new pharmaceutical treatment for BE may be aiming to block the expression of ΔFosB in the brains of BE individuals to attenuate this addictive behavior. In animals, ΔFosB overexpression increases palatable food consumption (Wallace et al. 2008), suggesting that its downregulation or blockage might have the opposite effect in bingeing rats. In one study, ΔFosB expression in the orbitofrontal cortex was blocked through virally mediated expression of deltaJunD, a dominant negative antagonist of ΔFosB (Winstanley et al. 2007). ΔFosB expression can therefore be blocked; however, further studies on BE in animal models are needed before preclinical studies and further treatments in humans.

Neuromodulation is performed to modify the activity of specific neural circuits through the application of electric current with predetermined parameters in order to restore a functional state without damaging the brain tissue (Luan et al. 2014). Using this approach, action potentials can either be stimulated or blocked through invasive and noninvasive techniques (Luan et al. 2014). Invasive techniques for brain stimulation include intracranial and deep brain stimulation (DBS), while noninvasive techniques include transcranial magnetic stimulation (TMS), transcranial direct current stimulation (tDCS), transcranial alternate current stimulation (tACS), and more recently focused ultrasound stimulation (FUS).

Our results suggest that the PFC, Acb, and VTA are implicated in the generation of BED (Quansah Amissah et al. 2021; Quansah Amissah et al. 2020). Besides reward, the PFC is involved in several cognitive processes including cognitive control, attention, impulsive behavior, addiction, long-term declarative memory storage, etc. Therefore, the PFC is often targeted during neuromodulation in BE patients. Because comorbid conditions are different in different patients and the parameters of stimulation are different, the results of neuromodulation for ED are often contradictory. tDCS of the right or left DLPFC resulted in improvements in BE

symptoms among patients (Sreeraj et al. 2018). It has been known for a long period of time that intracortical anodal stimulation depolarizes neurons and increases firing (Purpura and McMurtry 1965). To achieve similar effects with tDCS, the needed current intensity has to be much higher than the established safety parameters. However, new stimulation parameters (intermittent stimulation) may result in better control of neuronal firing (Vöröslakos et al. 2018). Stimulation using such parameters have not been tested yet in BED.

In BED and BN patients, rTMS of the left dorsolateral prefrontal cortex (DLPFC) resulted in significant improvements in BE symptoms such as inhibitory control of impulsive behavior (Guillaume et al. 2018). Other studies reported no differences in symptoms following rTMS of the same region (Gay et al. 2016).

So far, DBS in BED patients has been rarely used. DBS of the bilateral lateral hypothalamus (Whiting et al. 2013) and Acb (Tronnier et al. 2018) improved bingeing and weight loss. In patients with cluster headaches, VTA DBS was attempted with some success, even though it resulted in side effects such as elevated blood pressure, tachycardia, and diplopia (Akram et al. 2016). In pigs, VTA DBS results in changes in blood-oxygen-level-dependent (BOLD) activity in the bilateral dorsolateral prefrontal cortex and ipsilateral posterior cingulate (Settell et al. 2017). VTA stimulation could therefore be applied in BE treatment; however, considering the associated adverse effects and the subsequent effects on other brain regions, it may be necessary to use this approach when other approaches fail.

Focused ultrasound stimulation is a new technique which can be used to noninvasively stimulate deep brain structures to control BED. So far, it has been used successfully in mice for peripheral stimulation in obesity-induced metabolic dysfunctions (Huerta et al. 2021). The use of this technique can be very promising for the stimulation of the Acb or VTA to increase neuronal firing which should reactivate the hypofunctioning reward system in affected patients.

To conclude, the control of BED can be achieved via either reduction of expression of ΔFosB, which, as secondary effect, will increase neuronal excitability in the PFC, Acb, and VTA, or by direct stimulation of these brain regions. Because the PFC, Acb, and VTA also control other brain functions, stimulation of these structures with current, magnetic field, or ultrasound can cause secondary effect. For the moment, secondary effects of activation due to reduction in ΔFosB expression cannot be excluded but are not known. Therefore, control of ΔFosB expression seems to be one of the most promising mechanisms in the control of BED.

Application to Other EDs

Similar to BN and BED, the etiology of AN, one of the three main EDs characterized by food restriction, severe emaciation, and distorted body image (Kaye et al. 2013), is poorly understood. Thus, the treatment is symptomatic (Rantala et al. 2019). There is no approved medication for AN (Bodell and Keel 2010), suggesting the need for

further research. Like BN and BED, the dopaminergic and serotonergic neurotransmitter systems are implicated in AN. In AN patients, increased 5-HT_{1A} serotonin receptor density and decreased 5-HT_{2A} serotonin receptor density have been reported in the PFC, leading to decreased activity (Carli et al. 2006; Bailer and Kaye 2010). PET studies in AN patients also revealed decreased extracellular levels of dopamine and increased D2/D3 receptor densities in the striatal regions (Frank et al. 2005). This suggests the need for new treatment methods, including pharmacotherapy and neuromodulation, which can increase activity in these regions by increasing serotonin and dopamine release or signaling, similar to treatments proposed for BED.

rTMS of the left DLPFC has been used in a number of studies involving AN patients resulting in significant improvements in AN symptoms (Choudhary and Roy 2017), but no improvement was found in similar treatments (Jaššová et al. 2018). An open-label, single-arm study also reported significant improvement in AN symptoms in seven patients following tDCS of the left DLPFC (Khedr et al. 2014). In terms of DBS, significant improvements in AN symptoms such as weight gain and obsession have been reported. In these studies, the regions targeted include the bilateral Acb (Wu et al. 2013) and the ventral striatum (McLaughlin et al. 2013).

Several pharmacological treatments that block dopamine and serotonin release and those that block serotonin reuptake have been attempted for AN with little to no improvements in symptoms (Ruggiero et al. 2001; Halmi et al. 1986), suggesting a need for alternative treatments. Mechanistic understanding of AN may reveal important insights into treatment strategies especially since AN is prevalent and associated with a high mortality rate (Harris and Barraclough 1998).

Mini-Dictionary of Terms

Comorbidity: Disorders or diseases that are present simultaneously as another disease or disorder of interest.

Compulsivity: Behaviors characterized by repetitive and persistent actions not related to a specific goal, even in the presence of adverse consequences.

Impulsivity: It involves rash decision-making without prior thought of the consequences of one's action to maximize pleasure.

Inhibitory control: The ability to inhibit a specific behavior in response to a stimulus to achieve a specific goal.

Medium spiny neurons: Neuron type that makes up the majority (about 90%) of neurons in the striatum.

Reward: A stimulus that is pleasurable, induces motivation to obtain it, and promotes learning of cues and behaviors to obtain it.

Key Facts of ΔFosB

- The ΔFosB protein is 101 amino acids shorter than the FosB protein.
- Upon initial expression, ΔFosB has a molecular weight of 33 kD; however, persistent stimulation results in the modification of the protein into its stable 37 kD isoform.
- All drugs of abuse lead to ΔFosB expression.
- ΔFosB modulates the growth of neurites and the function of neurons by regulating the expression and activity of the cyclin-dependent kinase 5 protein.
- ΔFosB is a molecular switch that sustains addiction.
- Chronic wheel running and alcohol consumption also leads to ΔFosB expression.

Summary Points

- BE is characteristic of EDs such as AN-BP subtype, BN, BED, and OSFED.
- BE involves the consumption of large amounts of palatable food which results in the chronic stimulation of neurons within the reward system.
- The chronic stimulation of reward system neurons results in the desensitization of the reward system which is observed as decreased activity in human patients who binge and in binge-like eating animal models, consistent with the hypothesis that people binge to reactivate a hypofunctioning reward system.
- The desensitization observed in the reward system of patients who binge may be due to the expression of ΔFosB in neurons in brain regions within the reward system.
- According to the reward deficiency theory, addictive behaviors, including BE, are characterized by decreased dopamine release and signaling in the reward system, and therefore techniques that promote dopamine release and signaling may be effective as treatments for BE.
- Due to the role played by ΔFosB in initiating and maintaining addictive behaviors, treatments that block its expression may be effective in BE patients.

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Characterization of Binge Eating Days in Daily Life

50

Julia Reichenberger, Ann-Kathrin Arend, and Jens Blechert

Contents

Introduction 1004
Binge Eating in Eating Disorders 1004
Measuring Binge Eating: State of the Art and Its Limitations 1004
Example of Studying Binge Eating through EMA 1006
Affect 1007
Dietary Restraint and Weight Loss Dieting 1009
Food Craving/Hunger and Urge to Binge 1010
Physical Appearance and Body Dissatisfaction 1010
Cognitive States: Expectancy and Executive Functioning 1011
External Context 1011
The Aftermath: Consequences of Binge Eating 1012
Future Directions in EMA Research on Binge Eating Prediction 1012
Interventions/Clinical Implications 1015
Application to Other Eating Disorders 1015
Mini Dictionary of Terms 1016
Key Facts of Emotional Eating 1016
Key Facts of Ecological Momentary Assessment 1016
Summary Points 1017
References 1017

Abstract

Binge eating refers to eating an unusual large amount of food coupled with experiencing a loss of control over eating. Although various methodologies have been used to assess binge eating and its momentary antecedents, ecological momentary assessment (EMA) has been most influential recently, as it examines these states in daily life and thus provides the most naturalistic data. EMA results showed that not only negative affect/stress, dieting, food craving/hunger but also

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cognitive states (e.g., executive functioning), physical appearance/body dissatisfaction, and external context precede binge eating in daily life. Reported consequences of binge eating are negative affect and compensatory behaviors. Apart from reviewing the existing literature on antecedents and consequences of binge eating in different populations, we discuss future directions for research and clinical implications.

Keywords

Binge eating · Ecological momentary assessment · Affect · Stress · Food craving · Dieting · Fasting · Intervention · Anorexia nervosa · Bulimia nervosa · Binge eating disorder · Smartphone · *eHealth*

Abbreviations

AN	Anorexia Nervosa
BED	Binge Eating Disorder
BN	Bulimia Nervosa
EMA	Ecological Momentary Assessment

Introduction

Binge Eating in Eating Disorders

Binge eating is defined as eating an unusual large amount of food in a certain time period while experiencing a loss of control over eating, that is, not being able to control what to eat and when to stop (American Psychiatric Association 2015). Such binge eating episodes are a diagnostic criteria of bulimia nervosa (BN), binge eating disorder (BED), and the binge-purge subtype of anorexia nervosa (AN). Reliably assessing binge eating seems crucial and identifying antecedents and consequences of such episodes seems important to tailor helpful interventions curbing binge eating.

Measuring Binge Eating: State of the Art and Its Limitations

Binge eating can be assessed with different methodologies. *Self-report questionnaires* represent the most economic method, for example, by asking about the frequency of binge eating episodes and its associated states and traits. Most questionnaires assess the two main features of objective binge eating separately: whether the amount of consumed food was larger than what another comparable individual would have eaten under the same circumstances and whether control over eating was lost. Yet, it might not be easy to estimate the amount of food so that also subjective binges during which an individual experiences a loss of control without having eaten an objectively large amount of food may be counted as objective binge eating

episodes. Thus, the frequency of objective binge eating may be overestimated. Moreover, in these one-time measurement questionnaires, time-varying as well as momentary and short-lived antecedents and consequences of binge eating are hard to capture and reliance on memory is high. To exemplify, the Eating Disorder Examination Questionnaire (EDE-Q) or the Eating Disorder Diagnostic Scale assesses eating disorder symptoms such as the frequency of binge eating episodes (see Peyser et al. 2020 for an overview). Individuals need to recall binge eating episodes over the last 28 days, which might be easier with only a few episodes occurring, however, more difficult with several episodes per week. Interestingly, a study showed that whereas the diagnostic interview revealed two groups of individuals with and without BED, the frequency of binge eating episodes in the following naturalistic assessment was similar between both groups (Le Grange et al. 2001). Thus, relying on the diagnostic interview only might have overlooked binge eating episodes and potentially resulted in inadequate diagnosis. Moreover, self-reports make retrospective attribution more likely (e.g., "I had a binge eating episode so I must have been sad before"). Similarly, there is an ongoing discussion, whether emotional eating can validly be assessed with self-reports or if they rather reflect mere attribution effects (so-called emotional about eating hypothesis; Bongers and Jansen 2016; Adriaanse et al. 2011).

Another possibility to assess binge eating more objectively is through *laboratory test meals* which allow greater degree of standardization and minimize recall biases. Binge eating episodes can reliably be assessed in the laboratory (Peyser et al. 2020) and experimental manipulation of antecedents is possible (e.g., eliciting negative affect for emotions through a sad movie). To illustrate, participants were randomized into one group viewing a sad movie and another group viewing a neutral movie for 45 min (Van Strien et al. 2012). Both groups were offered crisps and M&Ms while watching the movie. Participants were invited to eat whatever they liked and were instructed to eat at least one piece of snack without knowing that the amount of food they have eaten was being measured. Results showed that self-reported high emotional eaters ate more during the sad compared to the neutral movie, whereas low emotional eaters ate less. However, the approach of experimentally assessing antecedents of binge eating also suffers from several limitations: Because of the artificial setting in the laboratory, binge eating episodes lack ecological validity. Eating in the laboratory is restricted to certain food types the experimenter presents (i.e., mostly one or two types of foods), while natural binge eating may be highly person-specific (e.g., one person preferring cookies as binge foods, another one crisps). Further, individuals may feel discomfort during the experiment as binge eating is often accompanied by shame or guilt. As a result, individuals might present socially desirable behavior, avoid binge eating in the laboratory, and postpone it to later when being at home. Finally, there are several challenges with regard to conducting laboratory binge eating studies (e.g., costs and time for setting up the laboratory, test meals, etc.).

To overcome these limitations, assessing binge eating and its predictors in daily life presents a promising avenue. Ecological Momentary Assessment (EMA), or more broadly speaking Ambulatory Assessment, enables researchers to measure

behavior, emotions, or cognitions several times throughout the day as they unfold in their natural environment (Shiffman et al. 2008). Individuals are prompted on their smartphone several times a day to answer questions about their mood, context, location, among others ("signaled measures"), while at the same time reporting binge eating episodes whenever they occur (self-initiated, "event-based" measurement). Hence, EMA allows to naturally assess binge eating alongside its potential antecedents and consequences at a relatively high temporal resolution (order of a few hours). In the following paragraph, we will exemplify an EMA study assessing binge eating and its antecedents before summarizing the most influential predictors (i.e., affect, dieting, hunger/food craving, physical appearance-related aspects, cognitive constructs, and external context) as previously reported in EMA studies.

Example of Studying Binge Eating through EMA

In a recent study, we examined patients with an interview-diagnosed eating disorder with regard to binge eating and other eating disorder symptoms in their daily life. Participants installed a customized smartphone app and answered questions about their affect, stress, and eating behaviors six times a day at specific time points (i.e., signal-contingent sampling) for eight consecutive days (see Fig. 1). Binge eating was further assessed "event-contingent" so that whenever a binge eating episode occurred, participants self-initiated the smartphone app (exemplified by the red figure between the last two prompts) and answered questions about potential binge episodes (e.g., whether overeating, loss of control, and compensatory behavior occurred, as well as affect after the binge). Please note that sometimes participants forget to report the binge eating episode separately on an event, which might be due to the affective turmoil during and after the binge. Thus, an additional, retrospective measurement on the subsequent signal (e.g., at 9.30 pm in this example) was taken.

In this study, one patient diagnosed with BED reported a binge eating episode in the late afternoon. As you can see in Fig. 2, the participant reported negative affect and nearly no hunger on a scale from 0 (=not at all) to 100 (=very much) at the last prompt before the binge eating episode. At 3:37 pm, the participant completed an EMA *event* for the binge episode, reporting to be alone, having eaten ~700 calories in that binge and again being in a negative affective state directly after the binge.

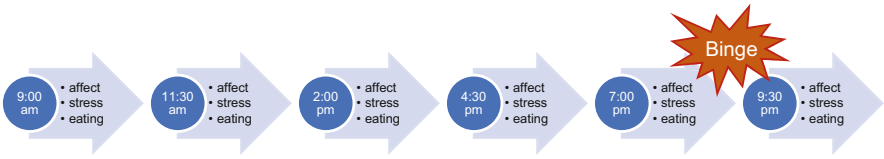


Fig. 1 Ecological Momentary Assessment sampling. Exemplified sampling scheme for one day of an EMA study

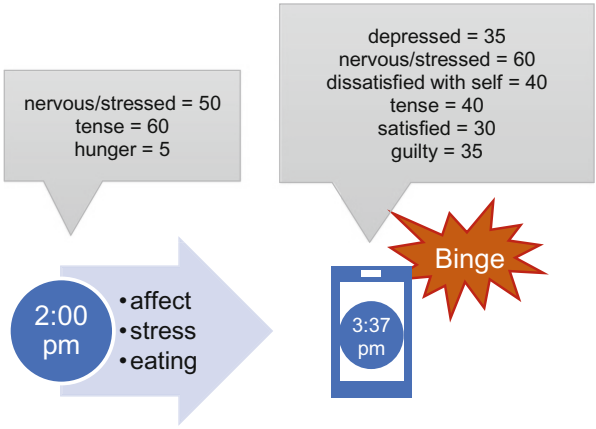


Fig. 2 Exemplified binge episode during Ecological Momentary Assessment. EMA sampling of a binge eating episode with information of the previous prompt (=antecedent) on the left and aspects after the binge (=consequences) on the right

Affect

Nibbling candy while studying for an exam, eating chocolate after a breakup – such additional food intake in response to negative affect (e.g., sadness, worry) is termed *emotional eating*. Emotional eating is relatively prevalent in the general population and thus not inherently pathological, but can gain clinical relevance when the additional food intake evolves into binge eating (i.e., eating large amounts, experiencing loss of control). Indeed, patients with eating disorders regularly attribute their binge eating episodes to negative affect (Alpers and Tuschen-Caffier 2001), and correspondingly, negative affect resembles the most widely reported antecedent of binge eating (Wolfe et al. 2009). According to the affect regulation model (Booth 1994), negative affect triggers binge eating which in turn alleviates negative affect by distraction or the use of comfort foods. Through principles of instrumental conditioning with negative reinforcement, binge eating will thus become more likely in the future.

General and Specific Negative and Positive Affect in Daily Life

A meta-analysis by Haedt-Matt and Keel (2011b) reviewed 36 previous naturalistic studies with a total of 968 patients with an eating disorder and demonstrated that greater negative affect preceded binge eating episodes in daily life. Since then, study activity has been increasing and also those newer studies have supported this positive relationship between negative emotions and binge eating across the eating disorder spectrum (Svaldi et al. 2019; Goldschmidt et al. 2012, 2014b; Ambwani et al. 2015; Engel et al. 2013; Lavender et al. 2016; Munsch et al. 2012; Smith et al. 2018; Stevenson et al. 2018; Keating et al. 2019; Schaefer et al. 2020; Berg et al. 2017; Chami et al. 2021; Wonderlich et al. 2022). Another study specified negative affect to emotions high on negative valence, arousal, and avoidance relation (e.g., nervous, distressed) preceding binge eating episodes (Becker et al. 2018).

Apart from general negative affect, certain emotions may play a particular role in emotional binge eating: Previous research highlighted the role of anger (Engel et al. 2007), fear, hostility, sadness, but especially guilt (Berg et al. 2015) in preceding binge eating episodes. Similarly, other research emphasized the role of stronger feelings of guilt (Schaefer et al. 2020) and shame (Goldschmidt et al. 2018) as important affective states prior to binge eating in daily life.

In contrast to greater negative affect, also lower *positive* affect has been found prior to binge eating episodes (e.g., Becker et al. 2018; Schaefer et al. 2020; Le Grange et al. 2001). However, evidence is more inconsistent with also nonsignificant associations being reported in individuals with obesity (Smith et al. 2018) and a reverse direction of association in associations in men, that is, higher positive affect prior to binge eating episodes (Mason et al. 2021a).

Stress

Strongly intertwined with negative affect, also higher stress predicted subsequent binge eating (Smith et al. 2021b). Another study showed that stress was higher before binge eating episodes and normal eating episodes in individuals with BED compared to a non-BED sample (Le Grange et al. 2001). However, stress might not be independently related to binge eating but through increases in negative affect: interpersonal stressors, daily hassles, and stress appraisal impacted subsequent binge eating through an increase in negative affect (Goldschmidt et al. 2014b). In the same vein, other research suggests that momentary stress might predict increases in binge eating through increase in negative affect (Srivastava et al. 2021a).

Affective Lability, Emotion Dysregulation, and Dissociation

Although affect "peaks" (e.g., high negative affect) seem pivotal in binge eating prediction, also affective *lability*, that is, fluctuations in emotional experiences may be interesting. Affective lability predicted binge eating episodes (Anestis et al. 2010; Kukk and Akkermann 2017). Such momentary fluctuations seem to be stronger predictors of binge eating episodes compared to retrospective self-reported affective lability (Anestis et al. 2010). Other studies found that emotion dysregulation seems important in daily binge eating (Keating et al. 2019; Kukk and Akkermann 2017). The dysfunctional emotion regulation strategy rumination, that is, repetitive thinking, predicted subsequent binge eating in individuals with BED, although no role of emotion regulation as moderator of the negative affect–binge eating relationship was found (i.e., stronger affect-bingeing relationship in those with dysfunctional emotion regulation) (Svaldi et al. 2019). This partially contrasts with findings showing that rumination actually mediated the association of negative affect with subsequent binge eating, that is, negative affect increased binge eating through its effect on rumination (Smith et al. 2021a). Relatedly, dissociation (i.e., a state in which a person disconnects from one's own feelings or thoughts) was elevated prior to binge eating episodes, independent of negative affect (Engelberg et al. 2007) and higher momentary dissociation even led to sharper increases of negative affect (Mason et al. 2017).

Dietary Restraint and Weight Loss Dieting

Besides affect, another group of theories explain binge eating through dieting and dietary restraint. According to the "dietary restraint theory," weight loss dieting or restrictive eating puts people at risk for binge eating (Polivy and Herman 1985). Dieting and withstanding omnipresent eating pleasures consume cognitive control resources; however, whenever dietary rules are broken, such dietary slips are interpreted as evidence for a lack of self-control. As a result, individuals may temporarily abandon their efforts to restrict eating behavior, binge eating resulting in binge eating. In the end, individuals end up in a vicious circle in which strict dietary restraint is repeatedly punctuated with episodes of binge eating (see Fig. 3). Hence, the importance of dietary restraint for binge eating is emphasized in several influential theoretical models of eating disorders (e.g., see Fairburn et al. 2003; Burton and Abbott 2017, 2019). In contrast to that, other research has emphasized that well-planned dietary restriction alongside consistent self-monitoring and realistic weight and eating goals can have positive health outcomes and does not necessarily increase the risk to binge eating (Schaumberg et al. 2016). The discussion on the advantages and disadvantages of dietary restraint is ongoing and EMA research is giving important insights.

In an EMA study in individuals with BN, higher caloric restriction on a given day increased the probability of binge eating on the same day as well as the next day (Zunker et al. 2011). Similarly, restraint has been noted as antecedent for binge eating in individuals with BED (Le Grange et al. 2001) or unselected individuals (Kukk and Akkermann 2017). Interestingly, individuals with AN experienced a higher risk of binge eating after fasting for 8 h; however, meal skipping was associated with a lower risk of same-day binge eating (De Young et al. 2014). However, other studies could not find a significant relationship between restrictive eating behavior and subsequent binge eating episodes in individuals with AN (Fitzsimmons-Craft et al. 2015) or BN (Engelberg et al. 2005) or same-day binge eating episodes in individuals with BN or BED (Chami et al. 2021). Other studies even found the reverse relationship in that a higher level of restraint was associated with lower risk of binge eating in individuals with obesity or binge eating pathology (Legenbauer et al. 2018; Pearson et al. 2018). However, please note that both of these studies assessed the *desire to* restrict or *thought about* restricting food intake

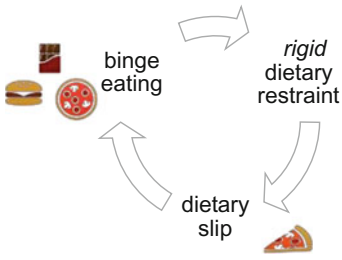


Fig. 3 Relationship between restraint and binge eating. Vicious circle of dietary restraint causing binge eating and vice versa

instead of actual restriction, potentially accounting for the reverse direction. Interestingly, the study of Engelberg et al. (2005) showed that higher restraint preceded stronger binge craving, suggesting that restraint might influence binge eating via higher urge to binge, with additional factors determining whether such cravings translate into actual binges.

Food Craving/Hunger and Urge to Binge

Within this pernicious cycle mentioned above, hunger and food craving may be important interfaces between dietary restraint and binge eating (Booth et al. 1990). While actual caloric restriction can trigger hunger and hunger can drive (homeostatic) overeating, problematic eating behaviors are probably more related to food craving. Food craving has been linked with snacking and with palatable, high-caloric food consumption in the context of self-reward or "comfort eating" (Hill 2007).

Indeed, in BED samples, craving sweets preceded binge eating (Greeno et al. 2000), and binge eating was more likely on days with higher food craving than on days with lower food craving (Chami et al. 2021). Regarding mechanisms, another study showed that higher food craving preceded binge eating but only in individuals whose appetitive network was activated in a laboratory food cue reactivity task (Wonderlich et al. 2017). There might also be an interplay between different factors: Food cravings that led to a binge eating episode were associated with higher tension, lower mood, and lower hunger than those food cravings that did not lead to a binge eating episode (Waters et al. 2001). As a related construct, desire to binge (i.e., binge craving) was higher before binge eating episodes but also normal eating episodes in daily life in individuals with BED compared to healthy individuals (Le Grange et al. 2001).

Interestingly, hunger alone does not seem to constitute an important precursor of binge eating: A meta-analysis showed that hunger was higher before regular eating episodes compared to binge eating episodes (Haedt-Matt and Keel 2011a). Similarly, also Goldschmidt et al. (2018) reported lower hunger prior to binge eating episodes relative to non-binge episodes.

Physical Appearance and Body Dissatisfaction

According to the spiral model of eating disorders, comparing one's actual self to an ideal-self results in a discrepancy that can triggering eating disordered behavior (Heatherton and Polivy 1992). Similarly, the transdiagnostic model of eating disorders (Fairburn et al. 2003) points to the core psychopathology of an overevaluation of shape and weight and their control. Thus, appearance, and especially body-related aspects, might also be of relevance when considering antecedents of binge eating.

Indeed, upward comparisons against subjectively more attractive individuals did increase the likelihood of binge eating in daily life (Drutschinin et al. 2018). Experience of a higher self-ideal discrepancy interacted with higher negative affect in predicting binge eating (Mason et al. 2021c). Other research found that

momentary body dissatisfaction predicted subsequent binge eating episodes (Srivastava et al. 2021b) or urges to binge eat (Fitzsimmons-Craft 2017). The impact of body dissatisfaction on binge eating in daily life may best be explained by a dual-pathway model in which body dissatisfaction influences negative affect on the one hand and dietary restraint on the other, which in turn lead to binge eating in daily life (Holmes et al. 2015). Moreover, in women with AN, stress associated with food, shape, or weight-related media exposure was associated with greater risk of subsequent binge eating (White et al. 2016). Similarly, state weight and shape concerns were related to concurrent and subsequent binge eating in daily life (Panza et al. 2021). Greater momentary appearance-related stress preceded binge eating in individuals with AN which might be mediated by momentary anxiety (Mason et al. 2018).

Cognitive States: Expectancy and Executive Functioning

Emotions, cognitions, and behavior are interconnected so that cognitive aspects might also play a role for binge eating (i.e., a behavior) to occur. Previous research showed that individuals with BED tend to selectively allocate their attention towards palatable food (i.e., attentional bias; e.g., Sperling et al. 2017) which might facilitate binge eating. When experiencing a strong urge to binge, inhibitory control could aid in withstanding that impulse. However, research demonstrated that individuals with binge eating as in BED have poorer executive functioning and thus less inhibitory control (e.g., Iceta et al. 2021; Prunell-Castañé et al. 2021).

Smith et al. (2020a) showed that apart from negative affect itself, a positive eating expectancy (i.e., believing that eating would actually improve one's mood) was associated with binge eating. Schaefer et al. (2021) replicated this finding and showed that such eating expectancies correlated with reductions in negative affect after binge eating (negative reinforcement). Additionally, executive functioning might interact with negative affect in their impact on daily binge eating: The relationship between negative affect and binge eating was stronger on days marked by reduced inhibitory control, at least in individuals with AN-BP or BN (Smith et al. 2020b). Additionally, Smith et al. (2020a) used ambulatory tasks to measure attentional biases towards food via the dot-probe task. The authors found that a higher momentary attentional bias towards palatable foods was related to an increased risk of subsequent binge eating.

External Context

Binge eating might need a specific external context in order to occur. As stated above, binge eating may be accompanied by feelings of shame or guilt or feeling disgusted with oneself so that being with others would be experienced as discomforting. In some individuals (especially with AN-BP or BN), binge eating may also be followed by subsequent compensatory behavior like vomiting so that a bathroom nearby may be important. Finally, binge eating requires an unusually large

amount of food available which might pose specific requirements to the environment (e.g., storage space).

Consistent with this context dependency, binge eating was found to be more likely when being alone and at home (Munsch et al. 2012; Greeno et al. 2000; Svaldi et al. 2019; Stein et al. 2007; Goldschmidt et al. 2018) than in other settings. In addition, binge eating was more likely in the early afternoon or evening hours (Stein et al. 2007; Smyth et al. 2009; Schreiber-Gregory et al. 2013), but additionally around 1 pm (Smyth et al. 2009), on weekdays compared to weekend days, and its average duration in daily life was reported to be 42 min (Schreiber-Gregory et al. 2013).

The Aftermath: Consequences of Binge Eating

According to theories of operant learning, binge eating would need to be followed by positive consequences in order to be self-reinforcing. However, a meta-analysis concluded that negative affect actually increased following a binge eating episode in daily life and decreased only after purging behavior in individuals with BN (Haedt-Matt and Keel 2011b). Yet, this research is inconsistent with other findings of a significant decrease in negative affect after binge eating in BED (Schaefer et al. 2020; Wonderlich et al. 2022), AN or BN (De Young et al. 2013; Lavender et al. 2016; Wonderlich et al. 2022), as well as with findings of decreased stress following a binge episode in BN (Fischer et al. 2017). Research also points to individual differences so that decreases in guilt following a binge eating episode are moderated by diagnosis (i.e., stronger decrease in BN compared to AN) and compensatory purging (i.e., more decreases in those who did not typically engage in self-induced vomiting than those who are)(De Young et al. 2013). Such affective responses to binge eating episodes may be a marker of treatment response, at least in BED (Mason et al. 2021b): Patients with greater net increases in positive affect after bingeing at baseline exhibited better treatment responses at the end of the treatment and follow-up.

With regard to compensatory behavior after a binge eating episode, research is mixed. Binge eating did neither predict subsequent fasting nor meal skipping in individuals with AN (De Young et al. 2014). Similarly, binge eating was associated with subsequent purging behavior in individuals with AN either in a negative direction, that is, binge eating reducing the likelihood of purging (Lavender et al. 2016), or a positive direction, that is, binge eating increasing the likelihood of purging (Goldschmidt et al. 2015).

Future Directions in EMA Research on Binge Eating Prediction

Methodological Considerations in the Affect–Binge Eating Relationship

Our review suggests that the most consistent precursor of binge eating is negative affect; however, the range of affective states is very broad. The affective

consequences of binge eating episodes are heterogeneous and thus the maintaining mechanism seems less clear. In this regard, several methodological aspects when assessing and analyzing the mutual relationship between affect and binge eating in daily life seem worth mentioning:

First, choosing an appropriate sampling frequency seems necessary to capture the highly dynamic process of an affect–binge eating relationship. Kockler et al. (2018) illustrated how emotional processes during binge eating change every 15 min across a 1.5 h time window; a dynamic which lower sampling frequency would have overlooked. Similarly, inconsistent results with regard to the post-binge affect ratings might be explained by sampling frequency (Berg et al. 2017): Average pre-binge ratings were assessed 2.5 h before the binge eating episode whereas post-binge ratings are on average closer in time to the binge eating episode (~20 min). The pre- and post-assessments are not equidistant and research suggests that negative affect might even further increase during the 2.5 h before the binge. As a result, previous findings might not ultimately be contradictory and negative affect might be reduced after a binge episode, but future research with a more fine-grained sampling frequency is needed. Second, the majority of studies assumed a linear relationship between negative affect and the probability to binge eating (i.e., the higher the negative affect, the more likely a binge). However, other research supports a threshold model in which the impact of affect on binge eating is nonlinear and dependent on whether a threshold value of negative affect is breached (Fuller-Tyszkiewicz et al. 2014). Hence, testing different modeling approaches when analyzing the affect–binge eating relationship might be worthwhile.

Moderators in the Relationship Between Antecedents and Binge Eating

Our review mostly covered the main effect of antecedents (states) on binge eating (see Fig. 4). However, there might also be several person-level (traits) characteristics like self-report data (e.g., emotional, restrained or external eating style, trait food craving, trait stress eating, impulsivity), sex, patient status (e.g., AN-BP, BN or BED), or body mass index that moderate the momentary relationships between an antecedent and binge eating (see Fig. 4). Research also points to the advantage of combining daily binge eating data with preceding laboratory assessments of impulsivity (Smith et al. 2019a) or assessments of altered responses to food cues in response to stress (Fischer et al. 2017; Wonderlich et al. 2018) as they might impact the affect–binge eating relationship in daily life. Hence, accounting for such aspects might further aid in disentangling the complex and partially inconsistent relationships between antecedents and binge eating in daily life.

Including Objective Assessment Measures

Most EMA studies reduce retrospective biases but still rely on self-report data. However, certain aspects might be complemented by objective measures by the use of mobile technology (Smith and Juarascio 2019; Smith et al. 2019b). To illustrate, negative affect or stress might be objectively assessed via physiological responses (e.g., heart rate or cortisol) or voice recordings (Grabowski et al. 2019). Similarly, objective measures of context might be measured through smartphone

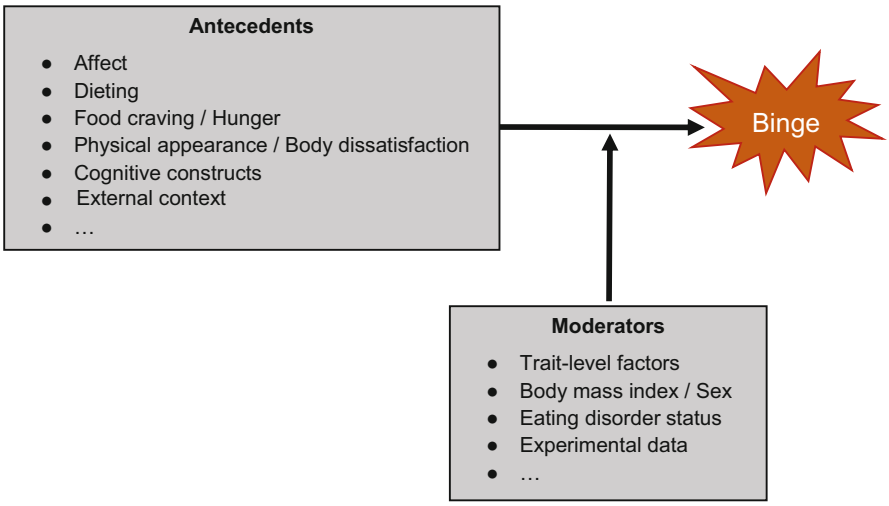


Fig. 4 Main effects and moderators on binge eating. Main effect of antecedents on binge eating in daily life and their moderation by several between-person moderators

sensors assessing GPS location or acoustic features of the environment (e.g., see Trull and Ebner-Priemer 2013 for an overview). Acquiring such information from sensors instead of asking individuals would be less burdensome on the one hand and would avoid interfering with one's natural routine while providing a high temporal resolution of context changes. Future EMA studies might profit from including such objective assessments and examining distinct and shared associations with subjective reports as antecedents of binge eating.

Individualized Approaches ("N of One Studies")

The EMA research reviewed above has linked a relatively broad range of factors with binge eating. Thus, binge eating predictions for a given individual are difficult to make based on the current, group-based research approach. Although indispensable for theory building and generalization, such nomothetic models (models derived from group data) perform poorly in predicting binge eating for a given individual (Adolf et al. 2014; Fisher et al. 2018). Negative emotions might accurately predict binge eating in some individuals, but fail to do so in others, for whom other antecedents (e.g., extensive fasting or dissociative states) are predictive. Thus, idiographic analyses and intervention approaches in the domain of binge eating research and treatment are on the rise (Smith and Juarascio 2019). The longitudinal time series data that come with EMA studies afford statistical modeling of individual relationships, for example, through multilevel modeling (e.g., Schwartz and Stone 1998). Further approaches like Network Models, Latent Class/Profile Analyses, and Latent Class Vector-Autoregression can be used to identify person-specific variable sets associated with binge eating within a single participant or identify clusters of

individuals with similar person-specific variables sets (Goldschmidt et al. 2014a; Müller et al. 2014; Pannicke et al. 2022).

Interventions/Clinical Implications

Knowledge on antecedents of binge eating is crucial for developing effective interventions to reduce binge eating. However, intervention approaches specifically aiming at reducing the relationship between an antecedent and binge eating by interventions being delivered in daily life are still rather scarce (e.g., Smith and Juarascio 2019). Yet, modern technology allows the use of ecological momentary interventions (EMIs), defined as interventions which are delivered in real time, for example, via smartphone app. Indeed, previous research has reported that EMIs might be effective in reducing binge eating (e.g., see Smith and Juarascio 2019; Anastasiadou et al. 2018; Ahmadiankalati et al. 2020 for overviews and further information). Based on the ideographic models mentioned above (person-specific networks), new kinds of individualized interventions in daily life can be applied. Taking these idiographic binge eating models to predict person specific high-risk times for binge eating episodes and send interventions via smartphone application right before these times is termed "Just-in-Time Adaptive Intervention" (JITAI; Juarascio et al. 2018). An intervention might be sent to the user when being in a specific state (e.g., negative affect, stress) and environmental context (e.g., alone at home) and at certain times (e.g., in the evening) to tackle binge eating.

Application to Other Eating Disorders

In this chapter, we reviewed studies that assessed antecedents (e.g., negative affect, dieting, food craving) of binge eating in daily life using ecological momentary assessment. Several eating disorders like bulimia nervosa, binge eating disorder, and the binge-purge subtype of anorexia nervosa are characterized by frequent binge eating episodes. However, binge eating episodes with lower frequency can also occur in individuals diagnosed with the restrictive subtype anorexia nervosa or in individuals with overweight and obesity. Antecedents and consequences should mainly be similar but potentially with a slightly different focus (e.g., dieting may be a more important predictor of binge eating in daily life in the restrictive subtype anorexia nervosa). Moreover, the momentary antecedents assessed in daily life have also been shown in laboratory and psychometric studies. In this regard, two meta-analyses examined the relationship between laboratory-elicited affect and eating behavior, however, with contradictory conclusions: Cardi et al. (2015) reported that negative affect was related to higher food intake, whereas Evers et al. (2018) could not find a significant relationship between negative affect and food intake. Note that both meta-analyses did not explicitly review binge eating behavior but food intake in general. Similarly, caloric deprivation (Agras and Telch 1998) or body-related aspects (Svaldi et al. 2009) have been shown in laboratory studies as

antecedents of binge eating or desire to binge, but again, results are mixed with other research finding no associations between these antecedents and binge eating assessed in a laboratory setting (e.g., Sysko et al. 2017; Hetherington et al. 2000). More consistently, previous research using self-reports underpin the antecedents mentioned in the chapter, especially affect, dieting, food craving, and body dissatisfaction (Vanderlinden et al. 2004; Wolfe et al. 2009).

Mini Dictionary of Terms

- **Binge eating**. Eating an unusual large amount of food without being able to control yourself.
- **Urge to binge**. A strong negative desire to binge eat that might evolve into an actual binge eating episode.
- **Ecological Momentary Assessment**. A method to study the natural behavior and environment of a person, mostly by the use of a smartphone app.
- **Emotional eating**. Experiencing food craving or eating in response to negative emotions.
- **Food craving**. Experiencing a strong desire to consume a specific food, especially high-caloric, high in fat or sugar.

Key Facts of Emotional Eating

- Nearly half of the individuals eat more in response to stress, half eat less.
- Individuals may change their eating behavior in response to negative but also positive emotions.
- Positive emotional eating may be a functional eating style associated with a lower body mass index.
- Healthy individuals and patients with an eating disorder differ on negative and positive emotional eating.
- Other consummatory behaviors like smoking or alcohol drinking could also be used as emotion regulation strategy.

Key Facts of Ecological Momentary Assessment

- The term Ecological Momentary Assessment (EMA) was coined in 1994 by Stone and Shiffman.
- EMA can be applied to a wide range of behaviors, experiences, and conditions.
- EMA sampling includes signal-, event-, and interval-contingent sampling.
- Reactivity (i.e., changing behavior in response to the assessment) and compliance should be considered.
- EMA may pose a burden to participants as they frequently have to answer questions during their daily routine.

Summary Points

- Binge eating can be examined using self-reports, experimental or naturalistic studies.
- Higher negative affect and stress are robust predictors for binge eating in daily life.
- Research on the importance of dietary restriction on binge eating in daily life is mixed.
- Whereas food craving and desire to binge seem important for subsequent binge eating, hunger seems not.
- Exposure to physical-appearance-related content and body dissatisfaction constitute antecedents of binge eating.
- Higher eating expectancy and lower executive functioning facilitates binge eating.
- Binge eating in daily life occurs mostly in the afternoon and evening when being alone at home.
- Future research on naturalistic binge eating should consider the sampling frequency of EMA data, between-person characteristics, and include objective assessment methods.
- Individualized approaches may aid in disentangling divergent findings and inform treatment approaches in the form of Just-in-Time-Adaptive-Interventions.

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Cancer and Binge Eating

51

Anna Dolgon-Krutolow and Tyler B. Mason

Contents

Introduction 1026
Behavioral Risk Factors for Cancer 1028
Associations with Binge Eating and Related Disorders 1031
Mental and Emotional Health, Binge Eating, and Cancer 1033
Conclusions and Future Directions 1035
Application to other Areas 1036
Mini-dictionary of Terms 1036
Key Facts 1037
Summary of Points 1037
References 1037

Abstract

Cancer and binge eating each place significant burden on individuals' mental and physical health, which ultimately impacts the healthcare and public health sectors. While there has been a high volume of research on cancer and binge eating separately, the possibility of a relationship between cancer and binge eating is an important, yet understudied, topic for scientific research and discussion. In the current chapter, similarities between cancer and binge eating are highlighted, including the overlap of major known risk factors and psychological correlates of cancer and binge eating. Many risk factors for cancer development, such as obesity, low physical activity, poor nutrition, and substance use, are also associated with binge eating and related disorders. Additionally, many of the psychological correlates of binge eating are commonly experienced by individuals with cancer – e.g., negative affect, emotion dysregulation, and impulsivity. From the cancer and binge-eating literatures, it is possible that there might be an association

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between cancer and binge eating, but the nature of the association is unclear. Future empirical research is needed to study the relationship between cancer and binge eating.

Keywords

Cancer · Binge eating · Binge-eating disorder · Eating disorders · Cancer risk · Psychology · Mental health

Introduction

Cancer currently stands as the second leading cause of death in the United States, and common comorbidities of the disease (e.g., obesity, poor nutrition, smoking, and alcohol use) often decrease survival rates even further (Rivera and Brawley 2019). Although the rate of cancer incidence has remained fairly stable since the 1990s, the peak of diagnoses has not yet fallen from the drastic increase in prevalence from 1974 to 1992 (Incidence 2021; National Cancer Institute 2021). High mortality rates related to cancer, as well as its noncommunicable nature, have made it a serious topic of discussion throughout the public health sector, especially because the risk of cancer development is multifaceted, spanning beyond just physical health (American Cancer Society 2021). In addition to its impact in the United States, cancer has been found to disproportionately impact low- and middle-income countries, which is associated with a deficit in the healthcare systems necessary for supporting the burden of the disease (American Cancer Society 2018). Consequently, low- and middle-income areas have less access to prevention at the primary level due to lack of educational tools and increased exposure to risk factors, at the secondary level through lack of diagnostic materials, and at the tertiary level through lack of access to treatment and rehabilitation (List and O'Connor 2020). Figure 1 displays some of the leading behavioral, environmental, and biomedical risk factors for cancer development.

Additionally, cancer is one of the most prevalent diseases that has continued to spread in developed countries despite advances in research and technology. Specifically, the most common cancers, such as lung, breast, and colon cancer, have been associated with workplace carcinogens that are common in developed regions (Viegas et al. 2017). Previous research has shown associations between cancer incidence and access to public healthcare, treatment quality, and both structural and social inequality (Rivera and Brawley 2019). With these factors in mind, cancer is something that adversely impacts public health through high mortality rates, expensive treatments, and increasing prevalence, whereas major risk factors for cancer heavily rely on public health interventions and preventions to rectify (Rivera and Brawley 2019; Viegas et al. 2017).

Cancer has a myriad of negative physical and mental health impacts. A few of the many common physical side effects of cancer include anemia, bleeding and bruising, osteoporosis, heart problems, and hypothyroidism (Knight Cancer Institute). In

Behavioral Risk Factors	Environmental Risk Factors	Biomedical Risk Factors
Obesity	Sunlight	Genetic Susceptibility
Nutrition & Diet	Radiation	Hormonal Factors in Females
Physical Activity	Occupational Exposure	
Substance Use	Pollution	
Cancer Screening Behaviors		

Fig. 1 Leading behavioral, environmental, and biomedical risk factors for cancer

addition to these symptoms, research has also found that cancer is negatively correlated with health-related quality of life as a result of decreased physical functioning, increased pain over the course of the disease, and lower overall health status of patients (Boini et al. 2004). Cancer patients are also more likely to be diagnosed with future comorbidities such as cardiovascular disease, hypertension, high blood pressure, and musculoskeletal problems (Ng et al. 2018). Additionally, individuals with cancer have higher rates of endocrine, nutritional, and metabolic diseases (Ng et al. 2018). These factors shed light on the decline in physical health status that is commonly associated with cancer.

Mental health of cancer patients is also an increasing topic of discussion, as previous studies have shown increased mental health disorders among cancer groups. Mood disorders are specifically prevalent among populations with cancer, and patients are prescribed antidepressants more often than non-cancer groups (Ng et al. 2018). The psychological impacts of cancer are thought to arise from stressors present in diagnosis, treatment, remission, and recurrence of the disease (Iwamitsu et al. 2005; Lloyd et al. 2019; Reece et al. 2013). Therefore, mental health is an issue that influences all stages of the disease development and treatment. Support for the various stressors that can arise throughout the course of cancer

often goes unaddressed and contributes to disproportionate negative mental health outcomes for individuals with cancer (Ferrell et al. 2003). In addition, stress-related psychological factors such as maladaptive coping mechanisms and negative emotional response have also been associated with higher cancer incidence (Mason and Smith 2021).

While cancer is clearly one of the most pressing public health issues currently, associations between cancer and binge eating and associated disorders, such as bulimia nervosa and binge-eating disorder, have rarely been studied (Mason and Smith 2021). Given lack of data on binge eating and cancer, the current chapter will highlight behavioral risk factors for cancer and how these overlap with binge eating as well as mental and emotional health in binge eating and cancer. Then, conclusions and future directions will be provided.

Behavioral Risk Factors for Cancer

Obesity. Obesity is an established risk factor for cancer development (De Pergola and Silvestris 2013), and obesity and weight problems are said to account for as high as 20% of cancer cases (Wolin et al. 2010). The extent of risk that is associated with obesity-related cancer has been shown to vary by race/ethnicity. Research has found that Black adults with obesity are more susceptible to cancer development than other racial groups (Renehan et al. 2008). Additionally, obesity has been attributed to approximately 20% of cancer deaths in women and 14% in men, suggesting some gender disparities related to obesity and cancer risk (Renehan et al. 2008). Specifically, women with obesity and breast cancer have poorer outcomes than counterparts without obesity, and inflammation caused by obesity is linked to shorter survival rates in breast cancer patients (Goodwin and Boyd 1990). However, equally increased risk of colon cancer has been related to greater adiposity among patients with obesity, suggesting gender disparities in obesity-related cancer may be dependent on cancer type (Willett 2000). Studies have also found various incidences of cancer patients with obesity receiving inadequate chemotherapy dosages based on their weight, decreasing positive treatment outcomes in populations with obesity (Griggs et al. 2005). Obesity can also weaken the immune system, which further relates obesity to negative cancer outcomes and increased rates of diagnosis among individuals with obesity (Moulin et al. 2008).

Nutrition and diet. Nutrition and diet quality have been linked to both the risk and prevention of cancer. Research has found that diet may account for up to 35% of cancer deaths alone (Doll and Peto 1981). Statistics from Doll and Peto (1981) do not account for the influence of diet and nutrition on cancer development, suggesting diet and nutrition may play an even more significant role in cancer development, incidence, and mortality combined. Certain dietary suggestions have been made by the American Cancer Society and World Cancer Research Fund, such as decreasing consumption of high calorie foods and beverages, to lower cancer risk (American Cancer Society 2018). Research has shown that following these guidelines can

decrease risk of developing cancer by between 10% and 61% (American Cancer Society 2018).

Specifically, high fruit and vegetable, fiber, and dairy product consumption are correlated with decreased cancer risk, and consumption of red meat, processed meat, and salt are positively correlated with greater cancer risk (Block et al. 1992; Latino-Martel et al. 2016; Steinmetz and Potter 1991). Additionally, a systematic review by Makarem et al. (2018) found elevated sugar intake was associated with anywhere from 23% to 200% higher cancer risk. Overall sugar intake as well as intake from added sugars, free sugars, sucrose, desserts, and sugary drinks was each related to higher cancer risk (Debras et al. 2020; Faruque et al. 2019). Consequently, sugar and saturated fat intake have been correlated with increased weight gain and obesity, which may provide an indirect mechanism through which saturated fat intake, sugar intake, and cancer are related (Beulen et al. 2018; Stanhope 2016).

Diet and nutrition have also been associated with increased risk and mortality of certain cancers. For example, fiber intake was inversely correlated to colorectal and colon cancer incidence, and doubling fiber intake led to a 40% reduction in colorectal cancer diagnosis (Bingham and Riboli 2004). Increased caloric intake has been found to increase risk of breast, colon, rectum, prostate, endometrium, kidney, cervix, ovary, thyroid, and gallbladder cancers (Albanes 1987). Further, colon cancer rates are correlated with increased consumption of animal fat and meat (Giovannucci et al. 1994), and higher saturated fat consumption is associated with higher risk for developing breast cancer by over twofold (Bingham and Riboli 2004).

In addition to nutrient consumption, malnutrition is also related to lack of cancer control, particularly in regions where food insecurity is abundant. In low-income areas, malnutrition is often associated with decreased access to cancer treatment and increased risk of cancer-related morbidity and mortality (Sala et al. 2004). Overall, data shows that diet is an important risk factor for cancer and that increased risk can develop from both overconsumption of specific foods and through malnutrition caused by underconsumption (Albanes 1987; Sala et al. 2004).

Physical activity. Physical activity is a significant protective factor against cancer development, and increased levels of physical activity are related to longer survival times for cancer patients (Wolin et al. 2010). Low levels of physical activity are often associated with obesity and weight gain, which can lead to increased cancer risk through obesity mechanisms (Wolin et al. 2010). Yet, physical activity has also been shown to reduce cancer risk irrespective of obesity status (Hardman 2001). For example, research found that physically active men with higher body mass index were less likely to develop cancer than their nonactive counterparts (Hardman 2001), suggesting physical activity on its own is correlated with lower risk.

Various cancers have been studied individually with regard to physical activity and its possible protective effects. Research has found particularly robust evidence for the protective effect of physical activity in colon cancer compared to other cancers (Hardman A. 2001; Thune and Furberg 2001). Further, physical activity reduced incidence of prostate cancer from 10% to 30% on average (Hardman A. 2001), and physical activity directly after breast cancer diagnosis was associated with reduced disease-related mortality (Holmes et al. 2005).

Multiple mechanisms have been suggested through which physical activity may lower cancer risk. The first is through reduced likelihood of obesity and weight gain, which have been discussed as major risk factors for cancer development (Wolin et al. 2010; Thune and Furberg 2001). Physical activity also improves the immune system, and research suggests that exercise increases natural killer cells, macrophages, and cytokines (Hardman 2001). Additionally, increased physical activity is associated with increased oxygen free radicals, which stimulate the secretion of enzymes that have been studied to help prevent cancer development on a cellular level (Hardman 2001).

Substance use. Substance use behavior can also influence one's risk of cancer development. In the United States, four percent of cancer deaths are attributed to alcohol consumption (Sauer et al. 2019), and, in Europe, approximately 10% of all cancer incidence is related to alcohol consumption (Roswall and Weiderpass 2015). Additionally, Khan et al. (2010) found that alcohol increased risk of breast cancer by 2% for each additional drink consumed per week. Gender may also affect these associations with research showing that men are at higher risk for alcohol-related cancer diagnoses (Roswall and Weiderpass 2015). This may partly be due to environmental factors that lead to increased rates of binge drinking and higher overall alcohol consumption rates in men (Peralta et al. 2010).

An arguably more serious risk factor for cancer development is cigarette smoking and use of tobacco. Studies found that cigarette smoking causes up to 90% of lung cancers in the United States, and cigar, cigarette, and secondhand smoke are all directly correlated with some of the deadliest cancers, such as lung and respiratory (Khan et al. 2010; Sauer et al. 2019). This is becoming increasingly more relevant in the United States where cigarette smoking accounts for 29% of all cancer deaths (Sauer et al. 2019). Additionally, advertisements by the tobacco industry are targeting younger generations (Josefson 1998), which is problematic, as research suggests those who quit smoking earlier in life see larger decreases in mortality from lung cancer (Khan et al. 2010). Although quitting early in life leads to lower mortality rates, smokers who quit at any life stage have been shown to live 10 years longer on average after cancer diagnosis (Sauer et al. 2019).

Cancer screening behaviors. Important protective factors for cancer have also been identified, and arguably one of the most significant is the use of cancer screening and overall screening behaviors. The National Cancer Institute 2021 discusses the importance of screening behavior in early cancer diagnosis and prevention, typically before symptom onset. Cancers that are identified in early stages, before symptoms appear, are much easier to treat and often lead to better patient outcomes. Screening behaviors can include physical examinations, lab tests, imaging, and genetic tests, which may identify cancer biomarkers and other signs of cancer.

Research regarding the effects of screening behaviors on cancer mortality and incidence has had mixed results. Studies showed that up to 50% of decrease in prevalence and mortality rates of colorectal cancer (which has one of the highest mortality rates) are attributed to increased screening (A.G. Zauber 2015). Mammography screening has been widely accepted as a successful preventive factor for breast

cancer and involves a simple, noninvasive physical examination (Miller et al. 2010). However, some evidence suggests that both low- and high-risk groups for cancer development have similar rates of screening, which may suggest that the method is less efficacious than previously believed (Song and Giovannucci 2016). But, it is possible that high-risk groups develop more serious types of cancer, and other modifiable risk factors may play a role in these statistics. Regardless, screening has begun to play a significant role in primary and secondary cancer prevention over the last 30 years. Rates of screening are largely dependent on knowledge of risk, screening attitudes, social norms, and fear of cancer development (Wardle et al. 2015).

Associations with Binge Eating and Related Disorders

Binge eating occurs across the lifespan in diverse groups of individuals and can range in frequency and severity. Binge-eating disorder (BED) is a specific type of eating disorder that is characterized by recurrent binge-eating episodes and represents a high frequency and severity form of binge eating (Hilbert 2019). It differs from other more commonly known eating disorders because no compensatory methods (such as purging, laxative use, or restriction of intake) are used after binge eating. BED has just recently been included as a recognized eating disorder in psychiatric classification systems (Hilbert 2019). Although there is almost no research directly examining associations between binge eating and BED with cancer risk and mortality, many behavioral risk factors and comorbidities of binge eating are also risk factors for cancer development and mortality (see Fig. 2).

For example, patients with BED have significantly increased rates of obesity (Dingemans et al. 2002; McCuen-Wurst et al. 2018; Smith et al. 1998). Specifically, McCuen-Wurst et al. (2018) reported that those with BED were at three to six times greater likelihood of obesity compared to those without BED. Childhood obesity and early onset of being overweight are also more significantly reported in patients with BED (Fairburn et al. 1998). It is suggested that BED may have a causal effect on obesity development, likely due to increased energy intake from recurrent binge-eating episodes (Dingemans et al. 2002). In addition, the prevalence of BED among individuals with obesity was found to increase proportional to degree of obesity (Dingemans et al. 2002). Higher prevalence of obesity in patients with BED suggests the possibility of increased cancer risk in these populations, as obesity is a significant risk factor for cancer.

In addition to obesity, BED is also related to poorer nutrition and dietary intake. Studies have found that individuals with BED are more likely to skip meals, engage in night eating, and consume high-fat diets, snack foods, and desserts (Dingemans et al. 2002; Kiziltan et al. 2005). Relatedly, a recent study showed that intake of sweet and fast foods was associated with elevated ratings of binge-eating symptoms in middle-aged men (Mason et al. 2021), and, in a separate study, pregnant women with BED had higher consumption rates of fat, monounsaturated fat, saturated fat, and total energy (Siega-Riz et al. 2008). This suggests that both men and women

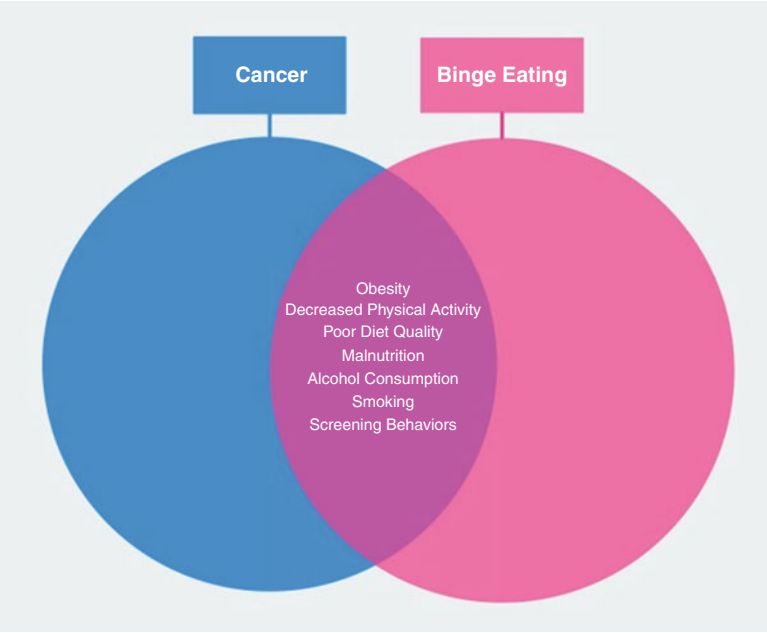


Fig. 2 Shared behavioral risk factors between cancer and binge eating

with binge eating are at an increased risk for poor diet, which could increase risk for cancer development.

Although little research has been done on the correlational or causational effects of BED and physical activity, trends have shown lower physical activity levels in those with BED (Galasso et al. 2020). In addition to lower physical activity, patients with BED are less physically fit than counterparts with obesity but without BED and are more likely to report musculoskeletal pain, which could be related to lack of consistent exercise (Vancampfort et al. 2014). Consequently, these individuals may be less likely to experience the protective effects of exercise on cancer outcomes. Research has also begun to consider physical activity as a possible mitigating factor for binge-eating episodes. For example, research showed adults reporting higher levels of physical activity had lower binge-eating symptoms compared to those with lower activity (Mason et al. 2021; Smith et al. 2020). Thus, lack of physical activity is a comorbidity of both BED and cancer, and increased physical activity may improve binge-eating symptoms and cancer outcomes.

Smoking and alcohol use are associated with binge eating, and similar mechanisms may operate in predicting the onset and maintenance of binge eating and substance use. For example, both alcohol consumption and binge eating are often used as maladaptive coping mechanisms and are strongly correlated with measures of maladaptive coping (Fitzsimmons and Bardone-Cone 2010; Metzger et al. 2017). A study by Munn-Chernoff et al. (2013) also found that addictive personality traits were common in both individuals who engage in binge eating and those with alcohol

problems. In addition, disordered eating behaviors among men are positively correlated with higher alcohol consumption (Berro et al. 2021), and substance use comorbidities are common in those with binge eating and associated eating disorders (Hudson et al. 2007; Munn-Chernoff et al. 2013). Further, a study on college students by Saules et al. (2009) found smokers to disproportionately engage in binge eating compared to those who had never smoked. Also, a separate study by Udo et al. (2016) noted increased metabolic abnormalities in individuals with binge eating who smoked, which suggests smoking in combination with binge eating may be correlated with poorer metabolic health than either alone. In relation to smoking cessation efficacy, smokers who engaged in binge eating had lower success rates with smoking cessation and more weight gain while trying to quit compared to smokers without binge eating (Marney et al. 2010; Udo et al. 2016). Therefore, higher rates of smoking among those with binge eating may increase cancer risk due to increased adverse health effects of smoking and poorer cessation rates.

Lastly, individuals with binge eating may be less likely to complete routine cancer screening and other preventive behaviors. A study on the utilization of healthcare among those with BED found lower rates of healthcare utilization after diagnosis (Watson et al. 2018). This may be due to a lack of awareness and knowledge of BED throughout the medical field and stigma that is associated with BED and obesity (Watson et al. 2018). While research has yet to examine associations between binge eating and cancer screening behaviors, Lawrence et al. (2015) found lower cancer screening rates in those with comorbid mental illnesses. Similarly, those with preexisting mental disorders were less likely to seek out healthcare and had lower rates of cancer treatment than those without preexisting mental disorders (Baillargeon et al. 2011). These studies highlight the importance of increasing access to healthcare and screening behaviors among those with binge eating to reduce cancer risk.

Mental and Emotional Health, Binge Eating, and Cancer

The mental and emotional consequences of cancer also may contribute to a relationship between cancer and binge eating, given the high overlap between binge eating and mental and emotional health (Hudson et al. 2007). Previous research has focused on all phases of cancer and their known impacts on mental and emotional health. For example, after cancer diagnosis, individuals have major increases in risk of anxiety, stress reaction/adjustment disorder, depression, and substance use (Lu et al. 2016). Cancer type and patient demographics also relate to the severity and type of mental health consequences experienced (Linden et al. 2012; Iwamitsu 2005). For example, female and youth cancer patients had the highest levels of anxiety and depression, while women with hematological cancer had the most severe emotional distress, cancer severity (such as advanced stages, poor prognosis, and invasive treatments), and increased risk of emotional distress. (Linden et al. 2012). Additionally, Iwamitsu et al. (2005) found strong relationships between adjustment to cancer and anxiety both before and after diagnosis. Breast cancer patients who suppressed negative

emotions and anxiety symptoms ended up with more emotional distress, and chronic anxiety significantly contributed to rates of psychological distress in these women. Additionally, emotional and mental health consequences have been studied in cancer treatment populations. For instance, of women undergoing chemotherapy for stage I–III breast cancer, one-third experienced moderate depression and over 15% experienced moderate to severe anxiety (Reece et al. 2013). Both radiation and chemotherapy treatments were also associated with decreased overall quality of life in children and adults (Bell et al. 2018).

The mental and emotional health of cancer patients both before and after diagnosis and treatment is strongly related to recovery rates and overall outcomes for these individuals (Ji et al. 2020; Lloyd et al. 2019; Cunningham et al. 2015; Baillargeon et al. 2011). For example, a cohort study by Cunningham et al. (2015) found cancer patients who had received recent psychiatric services had poorer survival rates of breast and colorectal cancer. The same study also noted a more general correlation with history of mental illness and lower cancer survival rates. The timeline of cancer survival also may play a role in the mental health status of those in remission, as long-term cancer survivors did not show any significant differences in terms of self-reported mental health status (Keating et al. 2005). Furthermore, the severity of cancer influences the mental health of patients, specifically those with colorectal cancer. Previous research has found increased risk for depressive, cognitive, anxiety, and overall mental health disorders in colorectal cancer survivors, with lower survival rates in those diagnosed with any mental illness (Lloyd et al. 2019). Additionally, cancer survivors used significantly more mental health services than the general population which suggests poorer mental health status among this group (Hewitt and Rowland 2002).

Poor mental and emotional health status (that is oftentimes associated with cancer diagnosis, treatment, and remission) is also a common risk factor for binge-eating development, course, and treatment (Dingemans et al. 2020; Goldschmidt et al. 2014; Mason and Smith 2021). Given this, cancer diagnosis may be associated with the development of binge eating; Fig. 3 outlines possible pathways by which cancer may lead to binge eating. Specifically, the pathways between cancer diagnosis and binge eating may be through poor mental and emotional health and maladaptive

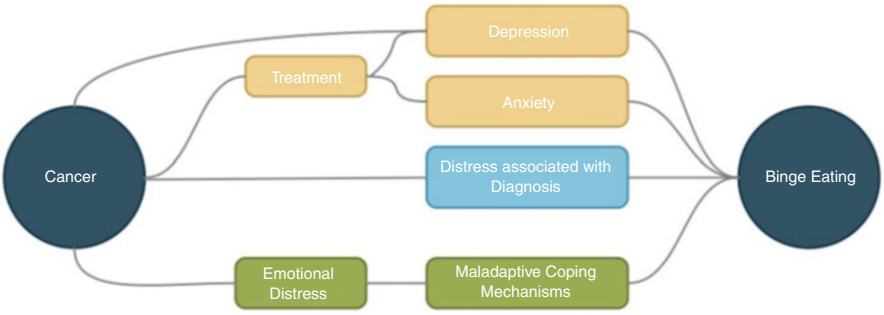


Fig. 3 Possible pathways from cancer diagnosis to binge eating

coping responses. Broadly, depression and anxiety rates are much higher in individuals with BED, and mood disorders are more common in individuals with BED and obesity compared to those with only obesity (Rosenbaum and White 2015; Sheehan and Herman 2015). Further, specific psychological characteristics associated with poor mental health, including low self-esteem, negative affect, emotional dysregulation, and maladaptive coping, are positively correlated with BED and binge eating risk (Sulkowski et al. 2011; Agüera et al. 2021). These characteristics also parallel many mental health problems that may emerge in cancer patients after diagnosis. Additionally, cancer diagnosis and treatment are often considered traumatic life events (depending on the severity, progression of disease, and cancer type), and previous research has reported trauma to be relevant for predicting onset of binge eating (Brewerton 2008; Timothy 2007).

Conclusions and Future Directions

Although little to no research exists on the direct relationship between cancer and binge eating or BED, studies on risk factors for cancer and binge eating individually suggest that there may be a relationship between cancer and binge eating. However, the nature of the relationship is unclear (e.g., whether this is a correlational, causational, bidirectional, or unidirectional relationship). As displayed in Fig. 4, there are likely bidirectional and complex relationships between cancer and binge eating. Nevertheless, obesity, poor nutrition, decreased physical activity, increased smoking and alcohol consumption, and lower utilization of screening behaviors share commonality for both cancer prevalence and mortality and binge eating. Additionally, similar mental and emotional health risks have been associated with both binge eating and cancer, suggesting that a combination of physical, environmental, mental, and emotional health factors contribute to this multifaceted relationship.

In conclusion, the lack of direct research on binge eating and cancer prevents any definite conclusions from being made about the nature of the relationship between

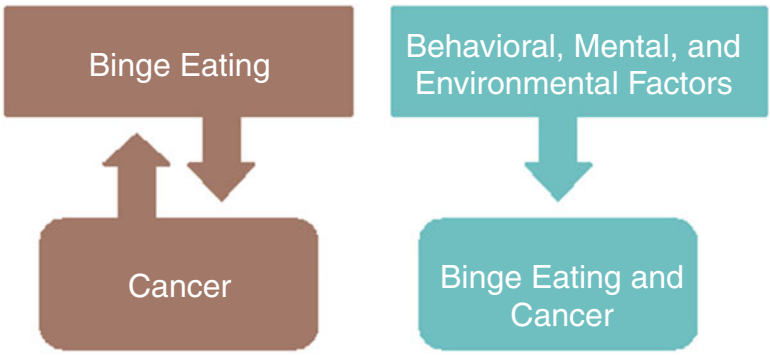


Fig. 4 Possible directional relationships between cancer and binge eating

the two. Shared risk factors may act as a pathway through which binge eating and cancer are related. This topic is becoming increasingly more relevant in the twenty-first century as cancer stands at the second largest cause of death in the United States, and binge eating and related disorders increasingly impact public health (National Cancer Institute 2021; Hudson et al. 2007). Cancer poses a serious risk to individual mortality, physical, and mental health in addition to its burden on global healthcare systems (Cunningham et al. 2015; Ferrell et al. 2003; Knight Cancer Institute 2020; Ng et al. 2018; Rivera and Brawley 2019; Viegas et al. 2017). Consequently, the recent inclusion of BED in psychiatric classification systems suggests that both prevalence and significance of the disorder are increasing, due to increased recognition and new diagnostic procedures (Kornstein 2017). As binge eating and BED continue to be researched, important future directions should include the study of the nature of the relationship between binge eating and cancer.

Application to other Areas

Food addiction, obesity, health and well-being, cancer mortality, public health, psychological outcomes for cancer patients, preventative interventions for cancer, and binge eating.

Mini-dictionary of Terms

- **Binge Eating Disorder (BED):** An eating disorder that is characterized by recurring binge eating episodes without compensatory behaviors and associated distress
- **Cancer:** A disease resulting from the uncontrolled division of abnormal cells that can lead to tumor growth and metastasis
- **Binge eating:** Consuming abnormally large quantities of food accompanied by a feeling of loss of control
- **Behavioral risk factors:** Behaviors that increase risk for disease or disorder and can be changed or prevented
- **Correlational effects:** Variables that are thought to be statistically related, such that changing of one variable will result in changes to another
- **Causational effects:** Change in a specific variable is directly responsible for the production of some change in another variable
- **Maladaptive coping mechanisms:** Unhealthy or ineffective methods used by an individual to reduce negative affect, such as stress or anxiety
- **Metabolic abnormalities:** Abnormal chemical reactions in the body that are responsible for disrupting metabolism
- **Modifiable risk factors:** Factors that may increase the risk of developing a disease or disorder that can be changed
- **Obesity:** A medical condition in which a person has excess body fat accumulation often defined as a body mass index greater than 30

- **Protective factors:** Factors that are associated with reduced risk for a negative outcome
- **Screening behaviors:** Use of preventative methods that help to screen an individual for risk or presence of specific diseases and disorders
- **Secondhand smoke:** Smoke that is inhaled involuntarily from being in close proximity to smokers
- **Substance use behavior:** Use of either drugs or alcohol that can lead to addiction or problematic use
- **Workplace carcinogens:** Substances found in the workplace that are known to be capable of causing cancer

Key Facts

- The relationship between cancer and binge eating is of increasing importance due to the significant prevalence of both in the twenty-first century.
- Clear overlap exists between behavioral risk factors and mental and emotional health correlates for both binge eating and cancer.
- More research is needed on the nature of the relationship between binge eating and cancer.

Summary of Points

- Binge eating and cancer are both increasing in prevalence in the twenty-first century, and both significantly impact individual and public health.
- Cancer and binge eating share similar behavioral risk factors such as obesity, nutrition status, physical activity, smoking and alcohol use, and utilization of healthcare.
- Cancer and binge eating also have similar mental and emotional health correlates such as anxiety, depression, emotion dysregulation, and maladaptive coping.
- Little research exists on the relationship between binge eating and cancer although evidence suggests a plausible association between the two.

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Fat Mass and Obesity-Related Gene (FTO) and Binge Eating Disorder in Adults and Adolescents

52

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Contents

Introduction 1044
FTO and Eating Disorders in Adults 1046
FTO and Binge Eating Disorder in Children and Adolescents 1050
Neural Studies in Homeostatic and Reward Circuits and FTO 1052
Limitations and Strengths 1056
Summary and Conclusions 1057
Mini-dictionary of Terms 1058
Key Facts of Binge Eating 1058
Summary Points 1058
References 1059

Abstract

The fat mass and obesity-related gene (FTO) is expressed in all body tissues regulating energy homeostasis, eating behavior, and appetite. More recently, studies have shown that FTO is associated with several eating disorders such as binge eating disorder (BED), bulimia nervosa, and anorexia nervosa, as well as several subclinical manifestations of disordered eating. Indeed, adults and adolescents with FTO alleles (e.g., rs993909, rs1558902, rs1421085) exhibited higher scores in BED scales and number of binge episodes and higher scores in

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emotional eating scales as well as the number of emotional eating episodes. Children and adolescents with FTO alleles reported higher scores in food enjoyment and food responsiveness compared to control groups. The results are supported by the neurological studies that showed higher activation in brain areas responsible for rewarding and motivation to eat in carriers of the FTO alleles. Taken together, the studies indicated a significant association between FTO variants and BED and eating behaviors/pathologies, which suggest that these genotypes likely contribute to the onset and/or maintenance of eating disorders.

Keywords

Binge eating disorder · Emotional eating · Bulimia nervosa · Anorexia nervosa · Eating behavior · Obesity-related gene · Energy intake · Food rewarding · Food enjoyment · Food responsiveness · Motivation to eat

Abbreviations

AN	Anorexia nervosa
BED	Binge eating disorder
BMI	Body mass index
BN	Bulimia nervosa
DSM-5	*Diagnostic and Statistical Manual of Mental Disorders, 5th edition*
FTO	Fat mass and obesity-related gene
TFEQ	Three-Factor Eating Questionnaire

Introduction

Eating disorders are psychiatric illnesses, characterized by abnormal or disturbed eating habits, with a higher incidence in adult women and female adolescents (Bhattacharya et al. 2020; Herpertz-Dahlmann 2015). One type of eating disorder, binge eating disorder (BED), is characterized by a large amount of food consumption in a short period of time, and it is not followed by compensatory behaviors (e.g., use of laxatives, prolonged periods of fasting, excessive exercise). It is commonly associated with rapid eating, eating to uncomfortable fullness, eating large amounts of calories even in absence of hunger, and feeling guilty or embarrassed after overeating. According to the *Diagnostic and Statistical Manual of Mental Disorders*, *5th edition* (DSM-5), these binge episodes should occur at least once a week for at least 3 months to be classified as BED. Previous evidence showed that about 8% of individuals with obesity present with BED, and this prevalence is even higher (20–30%) in individuals enrolled in weight loss treatments and in those waiting for bariatric surgery (48%) (Ágh et al. 2015; Bhattacharya et al. 2020; de Zwaan 2001; Vinai et al. 2015).

Another related eating disorder, bulimia nervosa, is defined by recurrent episodes of binge eating followed by some type of compensatory behavior. Those episodes

should occur at least once a week for a period of 3 months to be considered an eating disorder according to DSM-5. On the other hand, anorexia nervosa refers to the restriction of energy intake relative to the body requirements, resulting in a significantly low body weight in the context of age, sex, and development. Individuals with anorexia nervosa present intense fear of weight gain or becoming fat or engage in persistent behaviors that interfere with weight gain despite low body weight. Both, bulimia nervosa and anorexia nervosa, are accompanied by a fear of weight gain and/or becoming overweight and by an overvaluation of weight and shape.

In addition, eating disorders are associated with several pathologies and health consequences; among others, cardiac complications, decreased bone density, and gastrointestinal and endocrine disorders are the most common (Bhattacharya et al. 2020; Bulik et al. 2019). BED is associated with diabetes and metabolic syndrome, mainly due to its link with overweight/obesity, as well with addiction disorders (Grilo et al. 2013; Keski-Rahkonen and Mustelin 2016; Yip et al. 2011). However, anorexia nervosa carries the highest mortality rate among individuals with eating disorders, mainly due to medical complications from starvation or suicide (Smink et al. 2012; Winkler 2017). A recent study stated that 60% of the deaths in individuals with anorexia nervosa are accounted by sudden cardiac arrest and suicide (Westmoreland et al. 2016). The high prevalence and associated morbidity and mortality highlight the need for more research on the etiology of eating disorders to prevent its onset and/or the development.

Even though the etiology of eating disorders involves a complex combination of environmental, psychological, and biological factors, genetics has been considered one of the strongest components in the development of these conditions (Bulik et al. 2019; Davis 2015). For instance, one of the candidate genes is mapped in the obesity-related gene (FTO), which encodes for a 2-oxoglutarate-dependent nucleic acid demethylase (Gerken et al. 2007). Most of the studies on FTO genotypes have been carried out on rs9939609 variant (Castellini et al. 2017; Mehrdad et al. 2021; Melhorn et al. 2018; Müller et al. 2012; Palmeira et al. 2019; Rivas et al. 2018); however, studies including multiple variants can also be noted in the literature (Cameron et al. 2019; González et al. 2021; Jonassaint et al. 2011).

It is known that the FTO gene is expressed in all body tissues and also widely expressed in the hypothalamus, a brain region that regulates energy homeostasis, eating behavior, and appetite (Doaei et al. 2019; Gerken et al. 2007; Gholamalizadeh et al. 2018). Indeed, individuals with the FTO rs9939609 variant presented decreased fullness and hunger suppression (Mehrdad et al. 2021; Melhorn et al. 2018; Carvalho et al. 2018; Dougkas et al. 2013; Karra et al. 2013) as well as higher food craving frequency for high-energy food items and higher food reinforcement (Dang et al. 2018; Rivas et al. 2018). As such, the consumption of highly palatable food items among children and adults with the rs9939609 allele was found to be higher compared to control groups (Chuang et al. 2015; Tanofsky-Kraff et al. 2009). In addition, the FTO in multiple variants (rs9939609, rs1558902, rs861869) was associated with lower scores in cognitive restraint measured by the Three-Factor Eating Questionnaire (TFEQ) (Mehrdad et al. 2021; Kirac et al. 2016; Cornelis et al. 2014).

Some FTO variants, particularly the rs9939609 variant, foster greater appetite and food hedonics, drive to eat, and less control over food which may ultimately predispose to the development of eating disorders and/or subclinical eating pathologies. Accordingly, the present chapter synthesizes available literature on the association between the FTO variants and eating disorders, focusing mainly, but not only, on BED in the pediatric and adult population. This review also contributes evidence of the association between the FTO variants and emotional eating and other eating behaviors and pathologies that contribute to the onset and maintenance of eating disorders. Finally, neural studies in reward and inhibitory control circuits in individuals with FTO polymorphisms will be presented and discussed in order to provide neurobiological support to the eating behavior findings of the studies included in this chapter.

FTO and Eating Disorders in Adults

In the following section, we included the studies that investigated the association between FTO multiple variants and eating disorders. Also included in this section are results of studies that measured emotional eating in individuals associated with FTO and multiple different variants. Even though emotional eating is not classified as eating disorder, it is considered a pathological behavior defined as the tendency to eat in response to different emotions, and it is highly associated with the development of eating disorders and obesity (Fioravanti et al. 2014; Ricca et al. 2009).

Table 1 displays the studies including BED, bulimia nervosa, and anorexia nervosa and FTO polymorphisms in adults. Most of the studies that investigated the relationship between different FTO variants and eating disorders found significant associations between them. More specifically, adults with the rs9939609 (Castellini et al. 2017; Mehrdad et al. 2021) and rs1558902 (Cornelis 2014) alleles presented higher scores in BED scales and greater number of binge eating episodes (González et al. 2021; Cameron et al. 2019; Castellini et al. 2017; Cornelis et al. 2014). In fact, a multivariate analysis reported that individuals carrying the FTO rs9939609 allele present 2.72 higher score on a scale to estimate risk of eating disorders compared to individuals who did not present this genotype, indicating higher risk of developing eating disorders in these individuals (Mehrdad et al. 2021). Similarly, González et al. (2021) observed that individuals with FTO rs9302652/rs2388405/rs17818902 variants were almost two times (IC = 1.12–3.21) more likely to present with BED compared to the control group.

It should be noted, however, that some studies did not find associations between FTO variants and BED. Specifically in women living with obesity and BED, no significant differences in the frequencies of polymorphisms of the FTO gene were observed when compared to a control group without the eating disorder (Cameron et al. 2019; Palmeira et al. 2019). Even though both studies presented methodological strengths, the authors discussed that the low sample size that yielded limited statistical power could have contributed to the null associations. On the other hand, the number of binge eating episodes was found to be higher in the group with FTO

Table 1 FTO alleles and eating disorder studies in adults

Study	Sample size	Type of study	Variables	Main results
Abdella et al. (2019)	475 adults	Cross-sectional	FTO rs9939609 variant TFEQ, food craving	↑ Cognitive restraint associated with ↓ food craving in individuals <25 years FTO allele significantly affects the relationships between age, BMI, eating behaviors, and food cravings ↓ Emotional eating with age in the FTO allele + genotype group
Cameron et al. (2019)	178 women BED with obesity ($n = 73$) BED without obesity ($n = 55$) Normal weight without BED ($n = 50$)	Cross-sectional/ case control	FTO rs9939609, rs8050136, rs3751812, rs1421085, and rs1121980 variants BED score Body composition Attachment Styles Questionnaire (ASQ)	No differences in FTO alleles or body composition between groups FTO alleles ↑ binge frequency in the subgroup of individual with high ASQ relationships as secondary
Carvalho et al. (2018)	70 women living with obesity	Cohort	FTO rs9939609 variant Appetite, food preferences, body composition, hormones and inflammatory markers, BED score	↑ Insulin preprandial ↓ Ghrelin and IL6 ↑ Leptin in the postprandial period in the FTO allele + genotype FTO allele + genotype presented moderate BED ↑ Cholesterol consumption No differences in caloric intake between genotypes
Castellini et al. (2017)	369 participants Eating disorders ($n = 250$) Control group ($n = 119$)	Cross-sectional/ case control	FTO rs9939609 variants Emotional Eating and Identity Scale and eating disorders questionnaire, body composition	FTO allele more frequent among patients with eating disorders FTO allele was associated with BED behavior, ↑ emotional eating, ↑ eating disorder scores including AN and BN

(continued)

Table 1 (continued)

Study	Sample size	Type of study	Variables	Main results
Cornelis et al. (2014)	3852 participants	Cross-sectional	FTO rs1558902 variants Emotional eating, uncontrolled eating, BMI, TFEQ	FTO allele associated with ↑ uncontrolled eating and ↑ emotional eating ↑ BMI and ↓ cognitive restraint
González et al. (2021)	748 participants AN ($n = 233$) BED ($n = 119$) Control group ($n = 396$)	Cross-sectional/ case control	FTO rs7205987, rs9921255, rs6499662, rs7205987, rs1125338, rs2192872, rs708258, rs12599672, rs11076017, and rs9924877 variants Binge eating and AN, psychopathological symptoms, eating disorders Inventory Test	FTO alleles were associated with interoceptive awareness, bulimia, and maturity fears In patients with AN, FTO alleles were linked to anxiety, depression, and phobic anxiety
Jonassaint et al. (2011)	1762 participants AN ($n = 1085$) Control group ($n = 677$)	Cross-sectional/ case control	FTO rs7193144, rs8043757, rs3751812, rs11075990, rs9941349, rs17817964, and rs9930506 variants AN, BN scales, anxiety, harm avoidance, impulsivity, obsessionality, compulsivity	No associations between FTO alleles and eating disorder phenotypes or any related eating behavior pathology
Mehrdad et al. (2021)	197 participants	Cross-sectional/ case control	FTO rs9939609 variant, mental health, eating behaviors, eating disorders, emotional eating	FTO allele + genotype ↑ Risk poorer eating behavior ↑ Mental health disorders ↑ Emotional eating ↑ Eating disorders
Muller et al. (2012)	6095 participants AN ($n = 689$) BN ($n = 477$) Healthy non-population-based controls ($n = 978$) Population-based	Cross-sectional/ case control	FTO rs9939609 variant, BN and AN	Association between FTO allele and BN and AN compared to both control groups

(continued)

Table 1 (continued)

Study	Sample size	Type of study	Variables	Main results
	controls ($n = 3951$)			
Palmeira et al. (2019)	93 women BED ($n = 31$) Control group ($n = 62$)	Cross-sectional/ case control	FTO rs9939609 variant and BED	No significant associations were found between FTO alleles and BED

FTO, fat mass and obesity-associated gene; *BMI*, body mass index; *BED*, binge eating disorder; *BN*, bulimia nervosa; *AN*, anorexia nervosa; *TFEQ*, Three-Factor Eating Questionnaire

rs1421085 allele and BED who also presented high attachment avoidance as measured by the Attachment Styles Questionnaire Relationship (Cameron et al. 2019). In this particular study, FTO polymorphisms seemed to interact with attachment style to increase binge eating in women with obesity.

Along the same lines, FTO variants were also associated with higher scores in questionnaires assessing eating disorders such as bulimia nervosa and anorexia nervosa (González et al. 2021; Castellini et al. 2017; Müller et al. 2012). Indeed, those individuals were 12% and 18% more likely to present bulimia and anorexia nervosa, respectively, compared to a control group without the FTO rs9939609 allele (Müller et al. 2012). The association became more robust after adjustment for BMI and age in the participants with anorexia nervosa (OR = 1.67). Anorexia nervosa and other FTO variants (rs10521303, rs9924877, rs7203181, and rs12599672) were also linked to other personality dimensions and psychopathological traits such as anxiety, depression, phobic anxiety, interoceptive awareness, and maturity fears (González et al. 2021).

As was the case with BED, not all studies found significant associations in adults. Two studies included only women or adults that found no association between FTO alleles and bulimia nervosa (Jonassaint et al. 2011; Palmeira et al. 2019), anorexia nervosa, or any other psychological/psychopathological traits such as impulsivity, anxiety, harm avoidance, obsessionality, or compulsivity (Jonassaint et al. 2011). The authors stated that those results can be due to the small sample size (Jonassaint et al. 2011; Palmeira et al. 2019) and the number of comparisons conducted (Jonassaint et al. 2011), which compromised the power of the analyses.

Several studies have investigated FTO and subclinical forms of disordered eating in adults. Specifically, the FTO rs9939609 and rs1558902 variants have been shown to be associated with emotional eating scores, emotional eating episodes (Abdella et al. 2019; Castellini et al. 2017; Cornelis et al. 2014; Mehrdad et al. 2021), as well as increased severity of emotional eating (Castellini et al. 2017). A recent study indicated that individuals with FTO rs9939609 alleles presented 50% higher risk of presenting emotional eating episodes compared to participants who did not present

this genotype (Mehrdad et al. 2021). Noteworthy, emotional eating scores in individuals with this allele were found to decrease with age (Abdella et al. 2019).

Collectively, the studies included in Table 1 present strong evidence of the association between FTO variants and eating disorders and/or eating pathologies. We observed that four out of six studies indicated association between BED and FTO alleles, four out of four studies indicated association between FTO variants and emotional eating, and three out of four studies indicated association between anorexia nervosa and FTO genotype in the adult population. The FTO rs9939609 was the most common allele included in the studies. More precisely, BED and emotional eating were found to be highly associated with the FTO genotype in adults.

FTO and Binge Eating Disorder in Children and Adolescents

Table 2 lists the studies that included eating behavior and FTO polymorphisms in children and adolescents. The association between FTO rs1558902 and BED was only examined and observed in one study with children and adolescents (Micali et al. 2015). The other studies conducted in the younger population reported associations between the FTO rs9939609 and loss of control overeating, which is one of the main characteristics of binge eating (Tanofsky-Kraff et al. 2009; Emond et al. 2017; Velders et al. 2012), and scales of food responsiveness and food enjoyment (Emond et al. 2017; Tanofsky-Kraff et al. 2009; Velders et al. 2012), which might also predispose to binge eating episodes.

In the lone study that examined an association between BED and FTO rs1558902 in adolescents, Micali et al. (2015) observed that girls aged 14–16 years were slightly more likely to present an association between this genotype and BED compared to boys. Furthermore, at age 16 years, adolescents with the FTO rs1558902 allele were 28% more likely to have increased binge eating frequency.

Association between FTO rs9939609 variant and loss of control overeating, increased food responsiveness, and emotional eating frequency were also observed in other studies (Emond et al. 2017; Tanofsky-Kraff et al. 2009; Velders et al. 2012). Children and adolescents with one or two FTO alleles were nearly two times more likely to have a loss of control eating episodes and selected foods higher in fat at a buffet meal compared to those who did not present any FTO allele (Tanofsky-Kraff et al. 2009). Children with the FTO rs9939609 were more likely to present high scores of food enjoyment and in food responsiveness (Velders et al. 2012), similar to the results observed in preadolescents (Emond et al. 2017; Rivas et al. 2018). Those observations were found in children as young as 4 years of age (Velders et al. 2012), demonstrating the early effects of genetic factors in eating behaviors and the need for interventions and nutrition education at early ages in order to potentially prevent the onset of disordered eating and BED.

In summary, consistent association between FTO variants and eating behaviors/pathologies was reported in studies with children and adolescents. These results thus suggest that carriers may be genetically predisposed to the development of

Table 2 FTO alleles and eating disorders in children and adolescents

Study	Sample size	Type of study	Variables	Main results
Emond et al. (2017)	178 preadolescents 9–10 years	Cross-sectional	FTO rs9939609 variant, BMI, enjoyment of food, and food responsiveness	Association between FTO alleles and ↑ food enjoyment ↑ Food responsiveness
Mendoza et al. (2020)	99 adolescents with eating disorders AN ($n = 22$) BN ($n = 56$) BED ($n = 21$)	Cross-sectional/ case control	FTO rs9939609 variant, BED, AN, BN, circulating leptin	Circulating leptin levels higher in individuals with BED Association between FTO alleles and ↑ weight/leptin index and ↑ leptin levels in the BN group
Micali et al. (2015)	9912 participants Adolescents at age 14 years ($n = 5958$) and 16 years ($n = 4948$)	Cohort	FTO rs1558902 variant, BED, BMI, age, gender	Association between BED and FTO allele FTO allele ↑ risk of BED among girls compared to boys
Rivas et al. (2018)	258 children and adolescents (8–14 years)	Cross-sectional	FTO rs9939609 variant, TFEQ, food reinforcement, food responsiveness, emotional overeating, enjoyment of food	FTO allele and overweight subjects presented ↑ food reinforcement ↑ food responsiveness, ↑ emotional overeating, ↑ enjoyment of food
Tanofsky-Kraff et al. (2009)	289 youth aged 6–19 years	Cross-sectional/ case control	FTO rs9939609 variant, loss of control eating, energy intake, perceived fullness, palatability	Association between FTO alleles and BMI Children and adolescents with 1 or 2 FTO alleles report more frequent loss of control eating episodes and select foods higher in fat at a buffet meal Loss of control eating and more frequent selection of energy-dense, palatable foods No difference in fullness after a meal No differences in palatability
Velders et al. (2012)	1718 pre-schooled children aged 4 years	Cross-sectional	FTO rs9939609 variant, impulsivity, loss of control eating, food enjoyment, food	No relation between FTO allele and BMI FTO allele was associated with ↑ food

(continued)

Table 2 (continued)

Study	Sample size	Type of study	Variables	Main results
			responsiveness, and ADHD symptoms	responsiveness and ↑ food enjoyment Children with the FTO allele + were ↓ likely to have symptoms of ADHD and ↑ emotional control

FTO, fat mass and obesity-associated gene; *BMI*, body mass index; *BED*, binge eating disorder; *BN*, bulimia nervosa; *ADHD*, attention-deficit/hyperactivity disorder

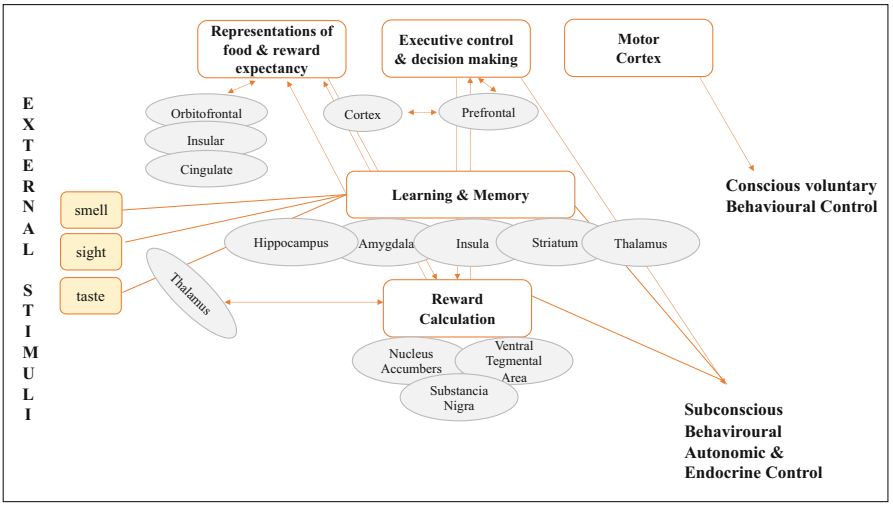


Fig. 1 Neural systems involved in reward, cognitive, and executive functions. (Adapted from Berthoud et al. (2011))

disordered eating. All studies that measured food enjoyment (three studies) and food responsiveness (three studies) observed associations with FTO alleles. These data also indicate possible mechanisms through which FTO variants operate to increase the likelihood of excess body weight in children and adolescents (Mendoza et al. 2020; Rivas et al. 2018; Tanofsky-Kraff et al. 2009).

Neural Studies in Homeostatic and Reward Circuits and FTO

An extensive number of studies have been carried out in an attempt to map the neural circuits of eating behavior in hopes of identifying potential brain regions associated with eating pathologies and unhealthy eating habits. Figure 1 displays the neural

systems involved in reward, cognitive, and executive functions that also are involved in the ingestive behavior.

In a nutshell, ingestive behavior consists of preparatory, consummatory, and post-consummatory phases (Berthoud 2002), and reward processing is carried out during the entire process (Berthoud et al. 2011; Berthoud and Zheng 2012; Epstein et al. 2011). In the preparatory phase, "executive control," "decision-making," and "reward expectancy" play an important role in the food choice and selection. Higher activation in the orbitofrontal, insular, and cingulate cortices represents a higher reward expectancy for a meal containing rewarding food items (Appelhans et al. 2011). During the consummatory phase, direct pleasure is derived mainly from gustatory and olfactory sensations, and the nucleus accumbens and the ventral tegmental area are activated according to the pleasantness of consuming those food items (Felsted et al. 2010; Rolls 2005). Higher activation in these regions portrays higher pleasantness during eating (Mccrickerd and Forde 2016). Finally, the post-consummatory phase is a general feeling of satisfaction of eating. Meals that demonstrated higher pleasantness enhance higher reinforcement power, and those items are more likely to be consumed in future meals (Epstein et al. 2003, 2011).

The "memory and learning" regions of the brain (e.g., amygdala, insula, striatum, and thalamus) mediate the entire process of food consumption, connecting with the rewarding evaluation during the consummatory and post-consummatory phase as well as with reward expectancy in the pre-consummatory phase (Mccrickerd and Forde 2016). Consumed items that presented in higher rewarding evaluation (during consummatory and post-consummatory phases) are more likely to activate the learning and memory regions and are more likely to be selected in future meals (Epstein et al. 2003, 2011; Mccrickerd and Forde 2016).

In the following section, we will present the results of studies on the FTO genotype and brain regions involved in "executive control," "decision-making," "reward expectancy," "learning and memory," and "reward calculation." Those results provide biological and neurological evidence of altered brain functions in individuals with the FTO variants that contributes to binge eating episodes and binge eating disorders in these individuals.

Table 3 displays the studies that assessed brain activity in areas associated with executive control, reward expectancy, learning and memory, and reward calculation in individuals with the FTO alleles. fMRI studies showed greater responsivity in brain areas responsible for reward expectancy such as the insula (Ndiaye et al. 2020; Olivo et al. 2016), as well in areas involved in the learning and memory circuits such as the amygdala (Melhorn et al. 2018), striata (Lancaster et al. 2018), nucleus accumbens (Dang et al. 2018; Lancaster et al. 2018; Melhorn et al. 2018; Olivo et al. 2016), and putamen (Karra et al. 2013) in individuals with FTO alleles when exposed to a palatable food image. Most part of the studies were carried out in the rs9939609 allele, and a single study included the rs1558902 allele (Ndiaye et al. 2020). The higher striatal activation was observed with food and monetary stimulus in young adults (Lancaster et al. 2018), indicating that the neurobiological response associated with FTO genotypes may not be food-specific and may confer an increased risk for multiple rewarding stimuli (i.e., smoking, alcohol, drugs of

Table 3 FTO alleles and neural studies

Study	Sample size	Type of study	Variables	Main results
Chuang et al. (2015)	697 participants	Cohort	FTO rs1421085 variant and impulsivity, food choices, aging	FTO allele + genotype: presented a dose-dependent increments in BMI during aging ↓ Medial prefrontal cortical function ↓ Brain function in regions intrinsic to impulse control and taste responsiveness ↑ Impulsivity ↑ Intake of fatty foods
Dang et al. (2018)	78 participants	Cross-sectional	FTO rs9939609 variant and food cravings, dopamine function	↓ Food craving with age except in individuals with FTO allele + genotype ↑ Lack of control overeating No difference in activity in the putamen and ventral striatum No association between FTO allele and dopamine receptor density in the striatum
Heni et al. (2016)	5166 participants	Cross-sectional	FTO rs8050136 variant and dopamine receptor density, insulin sensitivity	FTO allele + genotype ↑ Body fat and waist circumference ↓ Reduced peripheral insulin sensitivity ↓ Central insulin sensitivity in the caudate nucleus in individuals with the FTO allele + genotype ↓ D2 receptors
Karra et al. (2013)	359 participants	Cross-sectional	FTO rs9939609 variant and body composition, brain activity, ghrelin, PYY, leptin levels, visual analogue scale	FTO allele + genotype: ↑ BMI, body fat mass, and visceral fat area No differences in fasting appetite ↓ Suppression of hunger High-calorie food images ↑ appealing in the postprandial ↑ Activity of the hypothalamus, ventral tegmental area/substantia nigra, left globus pallidus, and left thalamus

(continued)

Table 3 (continued)

Study	Sample size	Type of study	Variables	Main results
Lancaster et al. (2018)	1055 participants	Cross-sectional	FTO alleles (not specified) and activation of the striatum during reward, BMI	FTO allele + genotype ↑ Response in reward-dependent striatal activation during monetary stimuli ↑ Appetitive stimuli (calorically high food images)
Melhorn et al. (2018)	114 participants	Cross-sectional	FTO rs9939609 variant and appetite measures, food cues, brain activity related to reward, insulin, ghrelin, GLP-1	FTO allele + genotype ↓ Fullness ↑ Energy intake Pre-meal ↑ Activation by "fattening" food images (compared with objects) in the medial orbital frontal cortex Post-meal ↑ Activation by fattening (compared with nonfattening) food cues in the ventral tegmental area/substantia nigra, amygdala, and ventral striatum
Ndiaye et al. (2020)	4236 participants	Cross-sectional	FTO rs1558902 variant and brain areas related to reward (insula and substantia nigra)	FTO allele + genotype ↑ Eating addiction and reward behaviors ↑ Expression in substantia nigra and insula
Olivo et al. (2016)	30 men	Cross-sectional	FTO rs9939609 variant and brain activity in areas related to reward	FTO allele + genotype ↑ Anxiety and punishment sensitivity ↑ Dopaminergic cortico-striatal circuit and areas involved in inhibitory control, decision-making, and salience attribution (the insular cortex, middle orbital gyrus, and inferior frontal gyrus) ↑ Anxiety scores and hypersensitivity to the hunger state

FTO, fat mass and obesity-associated gene; *BMI*, body mass index; *CHO*, carbohydrates; *PFC*, prospective food consumption

abuse, gambling, etc.). Only one study found no difference in the activation in the putamen and ventral striatum in seniors with FTO rs9939609 allele (Dang et al. 2018); however, the study included only 78 participants, which offers limited statistical power to detect associations. Alternatively, it is possible to argue as well that the seniors were able to develop non-food-related coping strategies over a lifetime to maintain healthier eating behavior, but future research is needed to verify why associations may differ based on age and maturity.

Studies observed that high-calorie food images compared to non-food-related images were more appealing for individuals with the FTO rs9939609 variant compared to individuals who did not present this genotype (Karra et al. 2013; Lancaster et al. 2018; Melhorn et al. 2018), whereas no genotype differences in appeal ratings for nonfattening food were observed in a different study (Melhorn et al. 2018). After a standard meal, individuals with this genotype exhibited higher activation in brain regions responsible for rewarding calculation (ventral tegmental area/substantia nigra) and brain regions involved in memory and learning process (amygdala and ventral striatum) when exposed to high energy density food items. Those results suggest that the energy density of the meals was more rewarding among individuals with the FTO rs9939609 (Karra et al. 2013; Melhorn et al. 2018) and rs1558902 (Ndiaye et al. 2020) variants.

Furthermore, other studies investigated the activity of brain areas involved in inhibitory control and decision-making and FTO variants (Chuang et al. 2015; Karra et al. 2013; Olivo et al. 2016). Indeed, previous evidence suggested the association between lower inhibitory control and higher impulsivity in individuals with BED and bulimia nervosa (Manwaring et al. 2011; Schag et al. 2013; Stojek and MacKillop 2017). For instance, Chuang et al. (2015) observed the FTO rs1421085 variant is associated with hyporesponsivity in the activity of medial prefrontal cortical function with aging, enhancing lower impulse control and impulse control toward food in these individuals. Similarly, other studies observed lower sensitivity in the medial orbital frontal cortex (Melhorn et al. 2018) and in the left putamen, a region implicated in regulating goal-directed behavior (Karra et al. 2013), and in the middle orbital gyrus and inferior frontal gyrus (Olivo et al. 2016) in individuals with the FTO rs9939609 variant. Indeed, those results were associated with lower scores in cognitive restraint measured by the TFEQ in these individuals (Olivo et al. 2016; Mehrdad et al. 2021), which also contributed to energy overconsumption in this population. Taken together, these results show that the FTO rs9939609 and rs1421085 variants play an important role in neural responsivity to food and reward cues in brain regions controlling energy homeostasis and reward and inhibitory control in adults.

Limitations and Strengths

It is important to acknowledge the limitations of this review. Firstly, we did not conduct a meta-analysis to quantify the association between FTO and eating disorders due to significant heterogeneity across studies, so the magnitude of

observed associations should be verified in future research. For the most part, the studies included in the chapter are cross-sectional; only two were cohort longitudinal studies. As such, causal links between FTO variants and eating disorders and/or eating pathologies cannot be determined, and more longitudinal studies with multiple follow-up evaluations are needed to better determine directionality. In addition, some of the studies presented small sizes that likely limited the statistical power to detect significant associations. Additionally, the criteria used to assess eating disorders were often different among the studies, which also might have contributed to the heterogeneity of the observed results. Additionally, very few studies have investigated whether carriers of these FTO variants display a different response to psychological or pharmacological treatment of eating disorders, an important area of future inquiry in this era of personalized medicine. Finally, more studies in children and adolescents are also necessary to better determine whether early nutritional education or psychoeducation can help attenuate the effects of FTO genotypes on the development of eating disorders.

Summary and Conclusions

Most of the results of the studies included in this review indicated associations between BED, emotional eating, and FTO alleles in adults. In the younger population, the association of FTO alleles and eating behaviors and/or pathologies that favors the development of BED was more common rather than an association with BED per se, but it is noteworthy that we observed only one study that investigated the association between FTO alleles and BED in children and adolescents. The studies that measured brain activity in individuals with this genotype collectively reported that the FTO variants are associated with neural circuits that normally modulate motivational changes to food reward, food cues, decision-making, and inhibitory control. As such, this provides some neurobiological evidence for a potential mechanism in which FTO genotypes may confer risk of disordered eating and diagnosable eating disorders, but future research using prospective longitudinal designs with multiple follow-up evaluations are needed to provide a clearer understanding of the potential neurobiological mechanisms.

Taken together, the results of studies reviewed in this chapter indicate that FTO variants are consistently associated with an increased risk of eating disorders such as BED, bulimia nervosa, and other eating pathologies, with supporting neurobiological evidence from neuroimaging studies in both adult and pediatric populations. This highlights that carriers of the FTO variants may be genetically predisposed to the development of eating disorders, information that is important for targeted prevention and treatment programs in the era of personalized medicine.

Mini-dictionary of Terms

- **Anorexia Nervosa**: eating disorder characterized by constant small amount of energy intake causing excessive weight loss. It is accompanied by the fear of gaining weight and body image disturbances.
- **Binge Eating**: eating disorder characterized by the consumption of large quantities of food in a short period of time and a sense of lack of control overeating.
- **Bulimia Nervosa**: eating disorder characterized by binge episodes followed by compensatory mechanisms (e.g., excessive exercise, purging, use of laxatives, etc.).
- **Emotional Eating**: tendency to eating in response to different emotions.
- **Food Craving**: is defined as a strong, irresistible, desire to consume specific type of food.
- **Food Enjoyment**: refers to the extent to which an individual finds pleasure in eating and desire to eat.
- **Food Responsiveness**: refers to the extent to which an individual indicates interest in and desires to spend time eating food.
- **Food Reward**: momentary value of a food item at the time of ingestion; usually high-calorie food items tend to be more rewarding.
- **Relative Reinforcing Value**: how hard the individual is prepared to work to gain access to food rather than a nonfood alternative.

Key Facts of Binge Eating

- It was considered an eating disorder only in 2013 in the "*Fifth Edition of the Diagnostic and Statistical Manual of Mental Disorders*."
- The global prevalence of BED was 0.9% in 2018, whereas women had a prevalence of 1.4% and men 0.4%.
- It is the most common eating disorder in the USA and in individuals with obesity.
- It impairs health-related quality of life, and it is associated with increased healthcare utilization and healthcare costs.
- The healthcare costs per patient with BED might range between $2372 and $3731 per year in the USA.

Summary Points

- FTO alleles are associated with BED scores and binge episodes mainly in adults.
- FTO alleles are associated with higher scores in emotional eating scales and the number of emotional eating episodes in adults and children.
- FTO alleles are associated with higher scores in food enjoyment and food responsiveness in children and adolescents.

- FTO alleles are associated with higher activation in brain areas responsible for rewarding and motivation to eat.
- FTO alleles are associated with lower inhibitory control.

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Neuroimaging in Binge Eating Disorder

53

Serkan Turan

Contents

Introduction 1064
Structural MRI Studies 1065
Functional MRI Studies 1065
Diffusion Tensor Imaging and Magnetoencephalography Studies 1076
PET-SPECT Studies 1079
Future Directions 1079
Mini-Dictionary of Terms 1080
Key Facts 1080
Summary Points 1080
References 1081

Abstract

Binge eating disorder (BED) is defined as recurrent and distressing episodes of excessive food intake despite psychological and physical consequences without the inappropriate compensatory weight loss behaviors characteristic of bulimia or anorexia nervosa. Neurobiological underpinnings associated with BED have been investigated; however, few structural and functional neuroimaging studies to date have described on the etiology, clinical features, and course of BED. The purpose of this chapter is to synthesize the recent literature on neuroimaging studies on the etiology, clinical features, and course of BED, which has been excluded from the category of "eating disorders not otherwise specified" in *DSM-V* and has specific diagnostic criteria. Neuroimaging studies provide evidence including altered function of prefrontal, insular, and orbitofrontal cortices and the striatum with altered reward sensitivity and food-related attentional biases. These unique neurobiological changes might be crucial in defining the overlapping neural features and directing targeted therapies of BED. To disrupt this vicious cycle, novel research-based studies examining the endogenous DA, NE, 5-HT, opiate, and

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other systems (e.g., glutamatergic) in the striatum and cortex of individuals with BED are necessary.

Keywords

Binge eating disorder · Neuroimaging · Eating disorders · Obesity · Magnetic resonance imaging

Introduction

Binge eating disorder (BED) is an eating disorder (ED) characterized by uncontrolled episodes of overeating in a short period of time. In May 2013, the American Psychiatric Association (APA) recognized BED as a distinct eating disorder in the *Diagnostic and Statistical Manual of Mental Disorders*, Fifth Edition (*DSM-V*) (APA 2013). One of the main features of BED is the distinguishing feature of bulimia nervosa (BN); the patient does not resort to compensatory behaviors and interventions such as forcing himself to vomit, using drugs that cause diarrhea, or using diuretic drugs.

In prevalence studies conducted in recent years, the lifetime and 1 year prevalence of BED according to *DSM-V* is estimated to be 0.85% and 0.44%, respectively. Eating behavior is a complex paradigm with or without conscious awareness, directed by internal or external stimuli. From a holistic perspective, it is recommended to consider environmental and individual factors and their interactions to understand the complexity of BED. Based on data from clinical functional imaging and cognitive studies, there is a growing consensus that several interconnected behavioral intermediate phenotypes are impaired in BED, including mindful bias toward food cues, impulsivity and cognitive inflexibility, persistent or compulsive behaviors, motivation, and reward processing.

Neuroimaging studies have contributed to understanding the etiopathogenesis of EDs; but there are some limitations of the studies in the literature: (1) difficulty in distinguishing whether the differences observed in the brains of individuals with EDs are the cause of the disease or whether they occur afterward with the effect of weight loss; (2) a high comorbidity frequency; (3) generalized sample (AN, BN, BED), not specified; (4) the wide age range of the sample groups, including adolescents and adults.

There is limited information in the literature about the neuroimaging findings that may play a role in the etiology of BED. The current literature focuses on functional changes when reviewed, so little is known about the putative changes as the structural data have not been extensively investigated. Studies on the biological processes that lead to the formation of BED suggest that dopamine, opioids, ghrelin, and serotonin have a role in the etiology. Changes in the reward-related regions of the brain, dopamine, acetylcholine, or opioid systems are said to increase binge eating episodes.

In this section, we aimed to review neuroimaging studies on the etiology, clinical features, and course of BED, which has been excluded from the category of "eating disorders not otherwise specified" in *DSM-V* and has specific diagnostic criteria.

Structural MRI Studies

Magnetic resonance imaging (MRI) is a medical imaging technique which used three dimensional pictures of anatomic structure. Recent developments in brain imaging techniques have also been reflected in the field of eating disorders. Although the number of studies is less than for other eating disorders (AN and BN), the results provide important steps to be taken in the detection of possible brain regions for a better understanding of the etiopathogenesis of BED. Computerized tomography (CT) and MRI studies, which provide information about structural abnormalities, report that BED patients have changes in brain regions particularly associated with reward and impulsivity. Structural MRI studies in binge eating disorder are summarized in Table 1. Schäfer and colleagues (2010) described gray matter volume (GMV) abnormalities in the anterior cingulate cortex (ACC) and medial orbital frontal cortex (OFC) which were implicated in decision-making in BED. In a recent study, Turan et al. (2021) acquired structural MRI which examined regional brain volumes in obese with or without BED. Greater GMVs were found in the right medial OFC and the left medial OFC compared to the non-BED obese. These findings might point to a behavioral mechanism in people with BED that is even more gratifying than regular hunger satiation.

In a study evaluating voxel-based morphology of brain volume, (1) the use and repetition of habit-based learning was observed more frequently in obese individuals with BED compared to obese individuals without BED, and (2) significant reductions in the left lateral OFC volumes were detected in individuals with BED (Voon et al. 2015). These findings are consistent with rodent and human imaging researches that have linked these areas to model-based goal-directed behavior. In a recent study, subcortical brain volumes and cortical thickness were measured in BED individuals by using MR brain scan imagings. Another aim of the researchers was to evaluate the relationship between these measures and the scores on dietary restraint, disinhibition, and hunger from the Three-Factor Eating Questionnaire (Abdo et al. 2020). According to the study's findings, higher scores in uncontrolled eating were associated with increases in GMV in the nucleus accumbens. The larger nucleus accumbens volume suggests that it may be associated with greater motivation for food and uninhibited binge eating behavior observed in the BED.

Functional MRI Studies

fMRI is an imaging method that allows to show the changes in cerebral blood supply dependent on blood oxygen level at rest or during function. These changes are called BOLD (blood oxygen level dependent), which provides a reliable measure of a local

Table 1 Summary of structural MRI studies in binge eating disorder

Study	Region	Study group	Study design	Demographics	Diagnostic criteria	Aims & findings	Conclusions
Schäfer et al. 2010	Germany	BED: $n = 17$ BN: $n = 14$ HC: $n = 19$	Cross-sectional, outpatient clinical sample	BED: 22.3 y (SD: 2.6) F: 100% BN: 26.4 y (SD: 6.4) F: 100% HC: 23.1 y (SD: 3.8) F: 100%	*DSM-IV-TR*	To investigate the GMVs of BN and BED. All patient groups were characterized by increased GMVs of the medial OFC compared to HCs	Greater volume of the medial OFC in BED was associated with decision-making, reward, and self-regulation processes
Voon et al. 2015	USA and UK	BED: $n = 20$ Obese: $n = 20$ HC: $n = 93$	Cross-sectional, community sample	BED: 43.95 y (SD: 9.47) F: 60% Obese: 44.70 y (SD: 10.12) F: 45% HC: 23.22 y (SD: 2.75) F: 42.4%	*DSM-IV-TR* The Research Diagnostic Criteria	To examine the premature responding in obese patients with and without BED. Significant reductions in left lateral OFC volumes were detected in individuals with BED	The role of these areas was associated with model-based goal-directed behavior

Abdo et al. 2020	USA	BE: $n = 54$ Non-BE: $n = 412$	Cross-sectional, community sample	BE: 48.7 y (SD: 18.6) F: 64.82% Non-BE: 47.0 y (SD: 19.4) F: 65.78%	Semi-structured diagnostic psychiatric interviews (EDE-Q and the TFEQ)	To evaluate the subcortical brain volumes and cortical thickness of BE and its associated eating behaviors by analyzing structural brain scans. Higher scores in uncontrolled eating were associated with increases in GMV in the nucleus accumbens	The larger nucleus accumbens volume suggests that it may be associated with greater motivation for food and uninhibited binge eating behavior observed in binge eaters.
Turan et al. 2021	Turkey	BED: $n = 26$ Obese: $n = 25$ HC: $n = 27$	Cross-sectional, outpatient sample	BED: 15.04 y (SD: 1.79) F: 68% Obese: 14.64 y (SD: 1.73) F: 68% HC: 14.59 y (SD: 1.39) F: 70.37%	*DSM-V*	To investigate the regional GMV abnormalities and appetite-regulating hormone levels (NPY and leptin) in obese patients either with or without BED compared to HCs. Left medial OFC volumes were greater in patients with a diagnosis of BED compared with other groups	Alterations of GMVs might point to a behavioral mechanism in people with BED that is even more gratifying than regular hunger satiation

Note: BED binge eating disorder, *BN* bulimia nervosa, *DSM Diagnostic and Statistical Manual of Mental Disorders*, *EDE-Q* Eating Disorder Examination Questionnaire, *F* female, *GMV* gray matter volume, *HC* healthy controls, *OFC* orbitofrontal cortex, *SD* standard deviation, *TFEQ* Three-Factor Eating Questionnaire, *UK* United Kingdom, *USA* United States of America, *y* years

increase in neural activity. Due to the heterogeneity throughout the design of the fMRI studies included, investigations differ according to the type of stimuli used during the test (decision-making and learning paradigms; food-related stimuli; body image-related stimuli). A number of functional connectivity alterations in patients with BED have been found in imaging studies that examined task-dependent brain activity. Functional MRI studies in BED are summarized in Table 2. Balodis and colleagues (2013a) examined brain activation in BED using a monetary incentive delay task and found diminished activity in several prefrontal and insular regions. The same researchers also examined the neurobiological underpinnings of reward processing by using a monetary incentive delay task during fMRI. After the treatment, the results of the study found that ventral striatal activity during a reward expectation was inversely related to binge eating deprivation (Balodis et al. 2014). However, another study in patients with BED, BN, and HC showed a significant difference in neural response to food cues but not monetary reward (Simon et al. 2016). In a neuroimaging study which investigated neural reward processing and binge eating in adolescent girls, the relationship between task-guided brain regions and attack intensities was evaluated from the Pittsburgh Girls Study – Emotions Substudy. Shared underpinnings between reward processing and EDs have also been described; greater vmPFC and caudate responses during reward receipt were concurrently associated with severity of binge eating episodes (Bodell et al. 2018).

A recent study conducted by Stopyra et al. (2019) demonstrated functional connectivity changes in dorsal ACC-somatosensory cortex coupling in BED. This network is essential for the self-referential and personally salient stimuli processing. Lee and friends (2017) used functional MRI while performing a Stroop Match-to-Sample task acquisition to investigate the differences in prefrontal cognitive control over disease-salient stimuli. Participants with BED showed increased ventral striatal activity in response to food images compared to healthy controls. The ventral striatum has a prominent role for processing salience of stimuli and reward-related cues. The researchers found that patients with BED had greater reward sensitivity but lack inhibitory control, indicating a loss of eating control.

Based on evidence that it may be associated with changes in reward processing, in a study published in 2021, clinicians evaluated that individuals with BED would exhibit lower ventral and dorsal frontostriatal rsFC involved in self-regulatory control and perform poorer performance on tasks assessing the tendency toward impulsivity and compulsivity in reward-seeking behaviors (Haynos et al. 2021). Researchers examined the correlations of resting state functional connectivity with frequency of binge eating days as indicative of symptom severity, and they also examined the relation between rsFC patterns and performance on neurocognitive paradigms that measure the tendency toward impulsive or compulsive drive for reward. Individuals with BED demonstrated a lower rsFC between the nucleus accumbens, a ventral striatum region involved in goal-oriented behavior; the left superior frontal gyrus (SFG), a frontal region involved with executive control; and the left posterior cingulate. They showed a lower rsFC between the ventral caudate and two clusters in the left SF. This ventral frontostriatal hypoconnectivity was significantly associated with a poorer performance on a reversal learning task as well

Table 2 Summary of functional MRI studies in binge eating disorder

Study	Region	Study group	Study design	Demographics	Diagnostic criteria	Aims & findings	Conclusions
Schienle et al. 2009	Germany	BED: $n = 17$ BN: $n = 14$ HC-NW: $n = 19$ HC-OW: $n = 17$	Cross-sectional, outpatient clinical sample	BED: 26.4 y (SD: 6.4) F: 100% BN: 23.1 y (SD: 3.8) F: 100% HC-NW: 22.3 y (SD: 2.6) F: 100% HC-OW: 25.0 y (SD: 4.7) F: 100%	*DSM-IV-TR*	To investigate the neural correlates of visually induced food reward and loathing in BED. The BED patients reported enhanced reward sensitivity characterized by increased OFC responses while viewing food pictures compared to HCs	Strong OFC recruitment together with the self-reported elevated reward responsiveness might be associated with increased reinforcement sensitivity in BED patients
Weygandt et al. 2012	Germany	BED: $n = 17$ BN: $n = 14$ HC-NW: $n = 19$ HC-OW: $n = 17$	Cross-sectional, outpatient clinical sample	BED: 26.4 y (SD: 6.4) F: 100% BN: 23.1 y (SD: 3.8) F: 100% HC-NW: 22.3 y (SD: 2.6) F: 100% HC-OW: 25.0 y (SD: 4.7) F: 100%	*DSM-IV-TR*	To evaluate the role of different visual food cues encoded in the brain and how this encoding differs between patients suffering from BED, BN, HC-NW, and HC-OW. BED patients decoding above chance in the ventral striatum show that it is central for the processing of the incentive value of reward-related cues	The best differential diagnostic separation between BED and BN patients was obtained in the left ventral striatum

(continued)

Table 2 (continued)

Study	Region	Study group	Study design	Demographics	Diagnostic criteria	Aims & findings	Conclusions
Balodis et al. 2013a	USA	BED: $n = 19$ Obese: $n = 19$ LC: $n = 19$	Cross-sectional, outpatient clinical sample	BED: 43.7 y (SD: 12.7) F: 73.68% Obese: 38.3 y (SD: 7.5) F: 52.63% LC: 34.8 y (SD: 10.7) F: 52.63%	*DSM-V*	To examine the brain activation in in BED using a monetary incentive delay task. Results show diminished activity in several prefrontal and insular regions	The GMV differences in BED support the idea of altered generalized reward processing
Balodis et al. 2013b	USA	BED: $n = 11$ Obese: $n = 13$ LC: $n = 11$	Cross-sectional, outpatient sample	BED: 47.6 y (SD: 12.7) F: 81.82% Obese: 35.4 y (SD: 9.3) F: 38.46% LC: 32.7 y (SD: 11.3) F: 45.46%	*DSM-V*	To investigate the neural correlates of cognitive control (involving conflict monitoring and response inhibition) in obese individuals with BED. Obese patients with BED have decreased activities in brain regions associated with inhibition control	BED patients' reduced capacity to engage impulse-control-related brain areas appears to be linked to food constraint
Balodis et al. 2014	USA	BED: $n = 19$	Cross-sectional, outpatient clinical sample	BED: 43.7 y (SD: 12.7) F: 73.68%	*DSM-V*	To evaluate the neurobiological underpinnings of reward processing by using a monetary incentive delay task during fMRI. The results of the study found that ventral striatal activity during a reward expectation was inversely related to binge eating deprivation	Specific brain regions underlying reward processing may represent important therapeutic targets in BED

Simon et al. 2016	Germany	BED: $n = 27$ HC: $n = 28$	Cross-sectional, outpatient clinical sample	BED: 38.26 y (SD: 13.75) HC: 38.0 y (SD: 10.85)	*DSM-V*	To investigate the expectation and receipt of food reward compared with monetary reward in patients with BED. In patients with BED, BN and HC showed significant difference in neural response to food cues but not monetary reward	An altered responsiveness of the reward network to food stimuli is associated with BED
Lee et al. 2017	South Korea	BED: $n = 12$ BN: $n = 13$ HC: $n = 14$	Cross-sectional, community sample	BED: 23.6 y (SD: 2.6) F: 100% BN: 23.7 y (SD: 2.2) F: 100% HC: 23.3 y (SD: 2.2) F: 100%	*DSM-V*	To investigate the differences in prefrontal cognitive control over disease-salient stimuli in BED. Participants with BED showed increased ventral striatal activity in response to food images compared to HCs	BED may be associated with greater reward sensitivity but lack inhibitory control, indicating a loss of eating control
Reiter et al. 2017	Germany	BED: $n = 22$ HC: $n = 22$	Cross-sectional, clinical sample	BED: 29.0 y (SD: 9.4) F: 72.73% HC: 27.8 y (SD: 4.54) F: 68.18%	*DSM-IV* and *DSM-V*	To investigate the impairment in flexible behavioral adaption of BED patients. BED was characterized by less aI/vlPFC activation during exploratory decisions	The decision-making in BED was characterized by enhanced switching between choices, indicating a bias toward exploratory decisions during behavioral adaptation in a dynamic environment
Stopyra et al. 2019	Germany	BED: $n = 27$ BN: $n = 29$ HC-NW:	Cross-sectional, outpatient clinical sample	BED: 38.39 y (SD: 13.06) BN: 27.45 y (SD: 10.55) HC-NW: 26.86 y (SD:	*DSM-IV*	To evaluate the three resting-state networks involving brain areas in BED. In BED patients demonstrated functional connectivity changes in dorsal	This network is essential for the self-referential and personally salient stimuli processing

(continued)

Table 2 (continued)

Study	Region	Study group	Study design	Demographics	Diagnostic criteria	Aims & findings	Conclusions
		$n = 30$ HC-OW: $n = 28$		6.59) HC-OW: 39.40 y (SD: 10.48)		ACC-somatosensory cortex coupling in BED	
Fleck et al. 2019	USA	BED: $n = 18$ HC: $n = 15$	Cross-sectional, clinical sample	BED: 37.2 y (SD: 9.9) F: 100% HC: 40.0 y (SD: 8.2) F: 100%	*DSM-V*	To investigate the effects of lisdexamfetamine treatment on ventral prefrontal cortex (vPFC) and striatal brain activation in BED. After 12 weeks of treatment, vmPFC subcortical activation levels were found to be predictive of response to treatment	Activation of the vmPFC and thalamus is correlated with a decrease in binge eating attacks and obsessive-compulsive symptoms
Martins et al. 2020	UK	BED: $n = 5$ BN: $n = 20$ HC: $n = 23$	Cross-sectional, clinical sample	BED/BN: 23.6 y (SD: 3.79) F: 100% HC: 25.58 y (SD: 6.31) F: 100%	*DSM-V*	To investigate the abnormalities in resting brain physiology in women with BN/BED. Findings showed significantly increased rCBF in the medial PFC, OFC, right insula, and ACC in women with BN/BED likely reflecting basal regional hypermetabolism and increased resting neural activity	The increased rCBF may be associated with continuous feelings of monitoring of binge-activating stimuli in the environment and body shape/weight self-judgment

Haynos et al. 2021	USA	BED: $n = 27$ HC: $n = 21$	Cross-sectional sample	BED: 23.6 y (SD: 2.6) F: 100% HC: 23.3 y (SD: 2.2) F: 100%	*DSM-V*	To investigate the functional organization of brain networks that mediate reward in BED. Individuals with BED would exhibit lower ventral and dorsal fronto-striatal rsFC involved in self-regulatory control and perform poorer performance on tasks assessing the tendency toward impulsivity and compulsivity in reward-seeking behaviors	Hypoconnectivity of striatal networks that modulate self-regulation and reward processing may promote the clinical phenomenology of BED

Note: *ACC* anterior cingulate cortex, *BED* binge eating disorder, *BN* bulimia nervosa, *DSM Diagnostic and Statistical Manual of Mental Disorders*, *F* female, *GMV* gray matter volume, *HC* healthy controls, *HC-NW* healthy controls normal weight, *HC-OW* healthy controls overweight, *LC* loss of control, *OFC* orbitofrontal cortex, *PFC* prefrontal cortex, *rCBF* regional cerebral blood flow, *SD* standard deviation, *UK* United Kingdom, *USA* United States of America, *y* years

as with frequency of binge eating. This dysconnectivity may be the drive of compulsive pattern of reward seeking among individuals with a higher weight and the reflection of compromised ability to shift away from a reward; individuals with BED showed a lower rsFC between the dorsal caudate and clusters distributed across the frontal regions (left SFG and left inferior frontal gyrus) and the temporal regions (left middle temporal gyrus and right superior temporal gyrus). This hypoconnectivity between the striatum and posterior and temporal regions suggests deficits in decision-making function. More widespread hypoconnectivity was present in the dorsal striatum which is especially implicated in habitual reward learning. This chapter suggests that the brain regions subserving cognitive and behavioral inhibition are less synchronized at rest in BED compared with individuals of a similar body weight without an eating disorder.

Ensemble coding findings were reported by Weygandt and colleagues, who investigated how different visual food cues are encoded in the brain and how this encoding differs between patients suffering from BED and BN, overweight controls, and normal weight controls (NWC). Subregions of the amygdala, the ventral striatum, and the ACC separated between food and non-food stimuli only in patients with eating disorders. This suggests that eating disordered patients exhibit a deviant motivational and attentional processing of visual food cues, which could trigger binge eating attacks. BED patients decoding above chance in the ventral striatum show that it is central for the processing of the incentive value of reward-related cues. Interestingly, striatal patterns and patterns in the ACC, characterized by stronger responses to food cues as compared to neutral stimuli, in BN patients and obese controls suggest that relative to BED patients, food cues are more attractive and attention grabbing for BN patients and obese subjects and exert a stronger impact to seek and consume food (Weygandt et al. 2012).

In another fMRI study, obese patients with BED have decreased activities in brain regions associated with inhibition control (right lateral and anterior medial orbital cortex, ventromedial prefrontal cortex, and inferior frontal gyrus) when compared to obese and normal subjects without BED (Balodis et al. 2013b). As a result, BED patients' reduced capacity to engage impulse-control-related brain areas appears to be linked to food constraint. The observed variations in brain correlates of inhibitory processing in BED compared to obese and lean comparison groups show that binge eating, an eating strategy used by obese people, has specific neurobiological contributions. In parallel with the results of this study, a food-cue stimuli presentation during fMRI by Schienle and colleagues (2009) describes changes in neural activity in the ACC and medial OFC against increased sensitivity to food reward in the BED group. These findings point to the ACC's possible role in binge eating behaviors, which might include negative emotionality. Strong OFC recruitment together with the self-reported elevated reward responsiveness might be associated with increased reinforcement sensitivity in BED patients.

A very elegant task by Fleck and colleagues (2019) show that the effect of lisdexamfetamine on emotional network can regulate BED's increased brain reaction to food imagery and reduce binge eating, indicating that the dopamine and noradrenaline systems are involved in binge eating pathophysiology. After 12 weeks of

treatment, vmPFC subcortical activation levels were found to be predictive of response to treatment. The findings suggest that activation of the vmPFC and thalamus is correlated with a decrease in binge eating attacks and obsessive-compulsive symptoms.

A fMRI study was conducted with one group of obese people with binge eating episodes given a placebo ($n = 21$) and the other group given an opioid receptor antagonist (GSK1521498) ($n = 21$). In the study, the participants' power to comprehend high-/low-calorie food images and their motivation to see these images were measured. The group receiving opioid receptor antagonists had, compared to placebo, (1) a decreased motivation to see images of high-calorie food but liked the images and (2) decreased activity of the right pallidum/putamen in response to images of high-calorie food (Cambridge et al. 2013). Although motivation and liking were associated prior to drug administration and in the placebo group, this relationship was lost following mu-opioid antagonism.

Although it is known that BED patients suffer from behavioral control deficits during recurrent binge eating episodes, identification and intervention methods for behavioral control skills continue to be investigated. On the behavioral level, Reiter and colleagues (2017) investigated neural correlates of model-free prediction errors (PEs) and flexible behavioral adaptation via PEs incorporating inference about unchosen options and expected these signals to be associated with BOLD activation in the vmPFC. The authors found impaired behavioral adaptation in a dynamic environment in BED as compared with healthy controls. The study found that the decision-making in BED was characterized by enhanced switching between choices, indicating a bias toward exploratory decisions during behavioral adaptation in a dynamic environment. In addition to this, BED was characterized by less aI/vlPFC activation during exploratory decisions. This finding supported that patients learn similar to controls but perform suboptimally owing to enhanced switching. They found reduced BOLD activation in the vmPFC of BED patients, which is one possible substrate for impaired goal-directed decision-making. vmPFC PE signatures incorporating inference on alternative options were positively associated with successful choices and negatively associated with switching behavior. Patients suffering from BED in this study did not exploit a relatively better option as consistently as controls but showed pronounced switching behavior which can be regarded as an impaired balance between exploratory and exploitative choice behavior. This disbalance was accompanied by fewer correct choices.

Another study addressed two questions (Martins et al. 2020): Do women with BN/BED, compared with HC, present alterations in resting brain perfusion? Can intranasal oxytocin restore or attenuate these resting alterations? A significant increase in regional cerebral blood flow (rCBF) was shown in the medial PFC, OFC, right insula, and ACC in women with BN/BED likely reflecting basal regional hypermetabolism and increased resting neural activity. This increased rCBF may be associated with continuous feelings of monitoring of binge-activating stimuli in the environment and body shape/weight self-judgment since the medial PFC and ACC are two key areas involved in self-monitoring and control regulation. Additionally the medial PFC, ACC, and right insula correlated positively with global scores on

the EDE-Q. Researchers also found decreased GMV in the right temporal lobe in BN/BED patients. This negative correlation is explained with two mechanisms: the first was that increased rCBF was the result of local functional plasticity in response to GMV loss in this region, and the second was that GMV loss occurred due to excitotoxicity as a result of increased rCBF caused by neural hyperactivity. The absence of functional and structural abnormalities in the ventral or dorsal striatum in this study explained by alterations may become evident by anticipation or valuation of hedonic stimuli (e.g., food).

Diffusion Tensor Imaging and Magnetoencephalography Studies

Diffusion tensor imaging (DTI) is a developed magnetic resonance imaging (MRI) technique that can be used to evaluate the structural integration of white matter (WM) tracts in the brain and to identify pathological changes at the microstructural level, such as axonal or myelin damage. In recent years, there have been studies using advanced imaging techniques such as DTI to determine that there are some disorders in the connection pathways such as association and commissural fibers that connect different lobes and hemispheres in the brains of patients diagnosed with eating disorders. Diffusion tensor imaging and magnetoencephalography studies in BED were summarized in Table 3. Estella et al. (2020) used DTI to investigate WM microstructure in women with BED and obesity, compared to normal weight control (NWC) and to women with obesity only (OBC). The hypothesis was that those with BED would show WM alterations in pathways involved in reward and inhibitory control circuitry (i.e., self-regulation), compared to other groups. The BED group compared to NWC showed greater axial diffusion (AD) in the forceps minor, superior and inferior longitudinal fasciculus, inferior fronto-occipital fasciculus, anterior thalamic radiation, and forceps major. Fractional anisotropy (FA) increases in the forceps minor in BED may also reflect self-regulation difficulties. BED group showed differences in pathways connecting fronto-limbic and parietal regions. To be specific, greater FA in the forceps minor which is involved in flexible cognitive responses and greater AD in the superior longitudinal fasciculus, cingulate gyrus, and corpus callosum compared to the OBC group were observed. This difference between OBC and BED groups may reflect a distinction independent of BMI. The increase in FA in the BED group appears to be consistent with the findings in the previous studies of BN, that is, increases in FA being associated with greater symptomatology (binge eating episodes) and less intact executive functions beyond the effects of BMI. The microstructural differences present in fronto-limbic regions suggested that BED may be associated with changes in reward-related structural organization. Briefly they all indicated altered microstructure organization in pathways involved in decision-making and reward appraisal in BED patients. Since they corrected for BMI, they suggested that WM changes specific to the BED group may be part of BED pathology. Based on the data, they propose that in BED, WM alterations in AD and FA in pathways connecting the fronto-limbic and

Table 3 Summary of diffusion tensor imaging, PET-SPECT, and magnetoencephalography studies in binge eating disorder

Reference	Region	Study objective	Population	Clinical assessment	Main assessment	Main results	Risk
Karhunen et al. 2000	Finland	BED: $n = 8$ Obese: $n = 11$ HC: $n = 12$	Cross-sectional, clinical sample	BED: 36.1 y (SD: 9.3) F: 100% Obese: 45.0 y (SD: 10.0) F: 100% HC: 39.8 y (SD: 9.7) F: 100%	*DSM-IV*	To investigate the cerebral responses of binge eating subjects elicited in response to exposure to food. rCBF increases in the left frontal and prefrontal cortices of patients with BED in response to food/body shape-related stimulus	The left hemisphere and its frontal and prefrontal regions could thus play a role in binge eating behavior
Kuikka et al. 2001	Finland	BED: $n = 11$ Obese: $n = 7$	Cross-sectional, clinical sample	BED: 39 y (SD: 9) F: 100% Obese: 41 y (SD: 9) F: 100%	*DSM-IV*	To investigate the serotonin transporter binding in obese binge eating women. BED patients have reduced serotonin transporter binding in the midbrain region compared to those without BED	Impaired 5-HT transporter binding in their midbrain may contribute to concurrent or sequential periods of binge eating and depression
Hege et al. 2015	Germany	BED: $n = 17$ Obese: $n = 17$	Cross-sectional, outpatient sample	BED: 41.88y (SD: 8.46) F: 100% Obese: 41.35 y (SD: 12.33) F: 100%	*DSM-IV*	To assess the neuronal correlates of increased impulsivity in BED during behavioral response inhibition. Results show a hypoactivity in the prefrontal control network and increased errors during inhibitory control	BED is associated with an attentional impulsiveness-related attenuation in response inhibition performance

(continued)

Table 3 (continued)

Joutsa et al. 2018	Finland	BED: $n = 7$ Obese: $n = 19$ HC: $n = 14$	Cross-sectional, clinical sample	BED: 49.4 y (SD: 5.1) F: 100% Obese: 41.8 y (SD: 10.3) F: 100% HC: 44.9 y (SD: 12.9) F: 100%	*DSM-V*	To compare MOR availability between morbidly obese and BED subjects. BED patients had widespread reduction in [11C] carfentanil binding compared to control subjects	MOR system dysfunction may be a shared pathophysiological feature in BED
Estella et al. 2020	Brazil	BED: $n = 17$ Obese: $n = 13$ HC: $n = 17$	Cross-sectional, clinical sample	BED: 33.82 y (SD: 7.2) F: 100% Obese: 38.03 y (SD: 9.7) F: 100% HC: 23.7 y (SD: 11.0) F: 100%	*DSM-V*	To assess the white matter microstructure in BED. The BED group (vs. HC) had greater axial diffusion in the forceps minor, anterior thalamic radiation, superior and inferior longitudinal fasciculus	The microstructural differences present in fronto-limbic regions suggested that BED may be associated with changes in reward-related structural organization

Note: *BED* binge eating disorder, *DSM Diagnostic and Statistical Manual of Mental Disorders*, *F* female, *HC* healthy controls, *MOR* mu-opioid receptor, *rCBF* regional cerebral blood flow, *SD* standard deviation, *y* years

temporal-parietal regions may be associated with repetitive difficulties during processes of eating-related decision.

Furthermore, findings from a magnetoencephalography study support that patients with BED show a hypoactivity in the prefrontal control network and increased errors during inhibitory control (Hege et al. 2015).

PET-SPECT Studies

Obtaining molecular and functional information about metabolism, tissue perfusion, structure of vessels, and cellular contents is very important in the diagnosis and treatment of psychiatric diseases such as eating disorders. In this context, single photon emission computed tomography (SPECT) and positron-emission tomography (PET) are used to investigate functional states such as explaining the molecular and biological interactions in the onset of the disease, monitoring treatment response, drug development, biodistribution, receptor interactions, and evaluation of target binding kinetics. SPECT and PET studies in BED are summarized in Table 3. In a SPECT study using [99m Tc] ethyl-cysteine-dimer, neural responses to neutral versus food cues were examined. rCBF increases in the left frontal and prefrontal cortices of patients with BED in response to food-/body shape-related stimulus (Karhunen et al. 2000). In this direction, in another study by Kuikka et al. (2001), 11 obese women with BED and 11 obese women without BED were examined for serotonin transporter binding by radioligand labeling method. It has been shown that obese women with BED have reduced serotonin transporter binding in the midbrain region compared to those without BED.

Morbid obesity and eating disorders are both associated with widespread alterations in brain mu-opioid receptor availability with regional differences. A recent study was conducted with radioligand [11C] carfentanil using PET on the availability of mu receptors in the brain and the relationship of these receptors with various behavioral phenotypes, especially in patients with BED and morbid obesity (Joutsa et al. 2018). They found that obesity with and without binge eating was associated with decreased mu-opioid receptor availability throughout the brain, and it may be a general neurobiological mechanism associated with disorders involving excessive food intake. Considering the PET and SPECT studies, there is a need for prospective studies examining the endogenous DA, NE, 5-HT, opiate, and other systems (e.g., glutamatergic) in the striatum and cortex of individuals with BED.

Future Directions

Given the prevalence of the disease and treatment outcomes for many individuals with BED, evidence-based treatments are only possible with a better understanding of the underlying mechanisms of the disease. Although the cost of designing neuroimaging research is high compared to other research, larger sample sizes and longitudinal study designs will add much more information to this field, thereby

increasing the generalizability and applicability of the results of these studies. There is an increasing need for therapeutic neuroimaging studies that evaluate mindfulness-based interventions, which have been increasing in recent years. Additionally, especially with the lack of data reproducibility in neuroimaging research, future studies will be well positioned to design and record preclinical experiments and to plan how neuroimaging data is carefully planned.

Mini-Dictionary of Terms

- **Neuroimaging:** The method is the use of various techniques to view the structure, function, or pharmacology of the nervous system, either directly or indirectly
- **Binge eating:** Eating much more food than normal in a short time in attacks and losing control in the meantime
- **Reward processing:** The hedonic pleasure derived from reward consumption and the motivational salience of a reward
- **Gray matter**: It is the region where neuron cell bodies are present and without myelin sheath
- **Inhibitory processing:** The capacity to exert control over one's mental processes and behaviors, to disregard an internal or external stimulus, and to take a different course of action

Key Facts

- Binge eating disorder (BED) is an eating disorder characterized by binge eating episodes not accompanied by compulsive behaviors
- Neuroimaging studies in BED mostly focus on the evaluation of functional structures
- Neuroimaging techniques suggest a causal relationship between altered reward sensitivity and food-related attentional biases in BED individuals
- The latest causal relationships have been established between regional gray matter volumes and eating disorder psychopathology
- Beyond health consequences, the effects of clinical presentations of BED have significant social and economic losses to individuals and society at large

Summary Points

- BED can be defined as impulsive/compulsive eating disorders with altered reward sensitivity and food-related attentional biases
- Structural MRI studies report that BED patients have changes in brain regions particularly associated with reward and impulsivity

- Functional connectivity alterations in patients with BED have been found in imaging studies that examined task-dependent brain activity
- In BED cases, increased regional cerebral blood flow response was detected in the left temporal and prefrontal region in response to stimuli
- The precise neurobiology of BED remains unclear, and ongoing, large-sample, and longitudinal researches are required

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Binge Eating

54

The Role of Bariatric Surgery

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Contents

Introduction 1084
Definitions and Indications of BMS 1087
BED 1090
Prevalence of BED in Bariatric Patients 1092
Instruments Used to Diagnose BED 1094
Psychological Aspects: Behavioral and Dietary Reorganization 1096
Mini-Dictionary of Terms 1098
Key Facts 1098
Summary Points 1099
References 1099

Abstract

Obesity is a complex multifactorial disorder that combines biological, psychological, and social aspects and requires a multidisciplinary approach for proper understanding, diagnosis, and treatment. Bariatric surgery, for some patients, is the most effective tool for obesity treatment and control; however, some patients do not achieve the desired weight or regain part of the lost weight. Even though it is an effective treatment for obesity and associated comorbidities, emotional and behavioral changes can damage lifestyle's recovery and adjustments to maintain the expected results with the surgical procedure. Among eating disorders (EDs), binge eating disorder (BED) and binge eating (BE) are those with the highest incidence among obese candidates for bariatric and metabolic surgery (BMS). Considering that changes in eating behavior can negatively influence weight loss, recognizing this condition becomes essential for early reintervention in order to guarantee the expected success to the patient after undergoing bariatric surgery.

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Keywords

Binge eating · Bariatric surgery · Obesity · Binge eating disorder · Weight regain

Abbreviations

ASMBS	American Society of Metabolic and Bariatric Surgery
BE	Binge eating
BED	Binge eating disorder
BES	Binge Eating Scale
BMI	Body mass index
BMS	Bariatric and metabolic surgery
CBT	Cognitive behavioral
DM2	Diabetes mellitus type 2
DMS-IV	Diagnostic and Statistical Manual of Mental Disorders, fourth edition
DSM-V	Diagnostic and Statistical Manual of Mental Disorders, fifth edition
ED	Eating disorder
EDE-BSV	Eating disorder examination questionnaire bariatric surgery version
EDE-Q	Eating disorder examination questionnaire
LOCE	Loss of control eating
QEWP-5	Questionnaire on Eating and Weight Patterns-5
RYGB	Roux-en-Y gastric bypass
SBBMS	Brazilian Society of Bariatric Surgery

Introduction

It is known that weight loss is a recurrent difficulty in the life of obese patients. Obtaining good results using the conventional treatments offered, such as the use of drugs, adoption of healthy eating habits, and the practice of physical activity, transforms the lives of these patients into a daily struggle. Thus, the demand for bariatric surgery has increased considerably and has demonstrated some success.

Bariatric surgery is becoming widely recognized and has become the most effective treatment for controlling severe obesity. Added to this, its results can bring about a decrease or remission in diabetes, a reduction in cardiovascular risk, improvement in sleep apnea and joint pain, and, consequently, an improvement in quality of life and a considerable reduction in the risk of mortality (World Health Organization (WHO) 2000; Al-Najim et al. 2018; Opozda et al. 2018). In view of this, bariatric surgery came to be called bariatric and metabolic surgery (BMS).

One of the important factors determining the success of the surgical procedure is the percentage of weight loss. Weight loss occurs drastically in the immediate postoperative period. This is due to the decrease in gastric capacity and the consequent reduction in nutrient absorption. Together, these factors provide quick satiety to the patient (Nikiforova et al. 2019). However, this rapid weight loss stabilizes on

average between 12 and 18 months after the surgery, which is the period known as the "honeymoon" in which the patient manages to lose as much weight as possible (Associação Brasileira Para o estudo da obesidade e da síndrome metabólica (ABESO) 2016; Fangueiro et al. 2021).

However, a proportion of patients may not achieve the expected weight loss or may experience significant weight regain over the next decade (Nasirzadeh et al. 2018). A Swedish study, carried out with obese individuals, showed that 10 years after surgery, 9% of patients lost less than 5% or maintained their baseline weight (Sjöström et al. 2015).

After this period, several determinants act in the maintenance and weight loss of the patient. These determinants are changes in eating habits, physical activity, hormonal or metabolic alterations, postoperative anatomical factors, and emotional and behavioral changes (Freire et al. 2020; Ribeiro et al. 2018). These factors can influence the recovery and the readjustment of the patient's lifestyle needed to maintain the results expected from the surgical procedure (Meany et al. 2014; Pinto-bastos et al. 2019). The effectiveness of surgical interventions considering weight loss alone can vary significantly between individuals; 20% to 30% of patients have insufficient weight loss or weight regain in the medium and long term after the surgical procedure (Bianciardi et al. 2021).

Thus, as the number of surgeries performed increases, the time elapsed since performing the procedure also increases, making postoperative clinical and psychological evaluations increasingly necessary. Parallel to this is the importance of verifying, from a psychosocial perspective, possible changes in symptoms as a result of weight loss.

Concern about the preoperative psychosocial status is one of the reasons why clinical practice requires that individuals seeking bariatric surgery undergo multidisciplinary assessments before surgery. This assessment is designed to identify potential psychiatric and behavioral contraindications to surgery (psychosis, untreated major depression, active substance abuse, or significant behavioral noncompliance). In addition, in the preoperative period, it is the role of the health professional to provide patients with information about the dietary and behavioral challenges they will face after surgery. During this multidisciplinary follow-up, patients will then be educated on the basic elements of the postoperative diet and the behaviors needed to achieve optimal postoperative results. This includes meals with small portions; chewing food thoroughly and slowly; avoiding foods high in carbohydrate, fat, sugar, and other poorly tolerated foods; increasing water intake; avoiding alcoholic beverages; and identifying and treating binge eating (BE) and/or snacking (Behary and Miras 2015).

The majority of patients undergoing bariatric surgery maintain adequate weight loss in the long-term follow-up. However, a subset of patients undergoing bariatric surgery experience less than expected weight loss, weight gain, or psychosocial distress after surgery. Some of these negative results are due to the manifestation of what is known as an eating disorder (ED).

BE episodes are included in the classification of EDs from the Diagnostic and Statistical Manual of Mental Disorders (DSM-V), organized by the American

Psychiatric Association (American Psychiatric Association 2013). These episodes are defined by eating more food in a short period of time than most people would consume under similar circumstances (Moshe et al. 2017). The episodes are marked by the feeling of lack of control and the feeling of guilt or shame, usually described by those whose eating behavior is defined as compulsive (Moraes and Almeida PE de M 2018).

These dietary pathologies can be predictors for weight regain, demonstrating the importance of their identification, through appropriate postoperative monitoring, so that it is possible to provide a timely referral for reassessment and counseling to mitigate weight regain (Sarwer et al. 2012). Therefore, better understanding of dietary psychopathology in the years following bariatric surgery, the times when they reappear, and their impact on weight regain can provide insights into the timing of postsurgical interventions (Nasirzadeh et al. 2018).

This disorder has significant impacts on the individual's organism and social life, as it acts directly on the quantity and quality of food consumed and on the absorption of nutrients. The literature recognizes as EDs the rumination disorder, pica, restrictive food intake disorder, anorexia nervosa, bulimia nervosa, and binge eating disorder (BED) (American Psychiatric Association 2013; Sena 2014; Chao et al. 2016).

Here, we are going to talk specifically about BED, which is one of the EDs that can directly influence the long-term weight loss success expected by the surgical procedure. The occurrence of a high prevalence of EDs in patients who are candidates for bariatric surgery is common. It is observed that this relationship occurs because BED is prevalent among obese individuals (Ivezaj et al. 2017a; Opolski et al. 2015; Sarwer et al. 2019; van Hout et al. 2005).

After bariatric surgery, the consumption of large amounts of food, which characterizes BE and which is necessary for a diagnosis as established by the Diagnostic and Statistical Manual of Mental Disorders, fifth edition (DSM-V), is often physically difficult or impossible. This is due to the anatomical and physiological alterations that are imposed by the surgery. Studies show that, eventually, some postbariatric patients can ingest an objectively large amount of food (Meany et al. 2014; Brode and Mitchell 2019). Even faced with the difficulty of eating large amounts of food, patients can develop new problematic eating behaviors related to BE. These new behaviors are manifested by the loss of control while eating (LOCE), the habit of snacking, subjective BE, or the consumption of small amounts of nutrient-rich foods, which circumvent the action mechanism of the surgery. It is noteworthy that the patients at a higher risk of developing new eating behaviors, especially LOCE, are usually the patients who met the criteria for BED before surgery (Freire et al. 2020; de Zwaan et al. 2010; Ivezaj et al. 2017b). Studies suggest that LOCE – characterized as the feeling of an inability to stop eating or control the amount of food consumed, regardless of the amount ingested – should be considered the main characteristic of BE (Andrea and Ana 2020; Goldschmidt 2017). Furthermore, the behavior of eating at night may also be present in some of the patients undergoing bariatric surgery. These eating pathologies can be enough for the patient to progress to postoperative weight recovery (Nasirzadeh et al. 2018).

The occurrence of BE as well as the other EDs mentioned above is not considered a contraindication for the performance of bariatric surgery. This is because in the first years after surgery, the period when the greatest weight loss occurs, the frequency of these eating behaviors is significantly reduced (Freire et al. 2020; Bianciardi et al. 2021). The literature to date indicates that bariatric surgery generally produces good results and a decline in dietary psychopathology in the first year after surgery; however, recurrence can occur at any time beyond this initial year, emphasizing the need for these conditions to be monitored, controlled, and handled by the multidisciplinary team (Nasirzadeh et al. 2018).

Definitions and Indications of BMS

BMS has evolved considerably since its origins in 1952. The first surgical technique applied was small bowel resection with subsequent anastomosis. Initially, the bariatric surgical procedure was performed without many controls, triggering high rates of surgical failure, morbidity, and mortality. Over the years, several surgical techniques have been tested. Some have proven to be beneficial, while others have been abandoned due to low weight loss, postsurgical complications, or the development of new safer and more effective procedures. With the advances in surgical techniques, as well as better monitoring of patients before and after surgery, improvements in long-term weight loss and a reduction in morbidity and mortality were observed. In 1967, the technique called Roux-en-Y gastric bypass (RYGB) was performed for the first time. The surgery was developed with the objective of exclusively treating obesity; however, throughout history, it has also gained great prominence for the control, improvement, or even remission of associated comorbidities. As it provides these benefits, it has since been denominated BMS (World Health Organization (WHO) 2000; Phillips and Shikora 2018; Buchwald 2014; Eldar et al. 2011).

Between 2011 and 2018, the number of bariatric surgeries performed by Brazilians grew by 84.73%, according to data from the Brazilian Society of Bariatric and Metabolic Surgery (SBBMS). This exponential increase placed Brazil in second position as the country that most performs this surgery in the world, just behind the United States. Despite these expressive data, however, there are many prerequisites to be met for the patient to become suitable for surgery.

The surgical procedure is indicated for adults up to 65 years of age with resistance to clinical treatment for at least 2 years and with a BMI > 40 Kg/m^2 regardless of the presence of comorbidities or BMI > 35 Kg/m^2 associated with comorbidities (Associação Brasileira Para o estudo da obesidade e da síndrome metabólica (ABESO) 2016). Adolescents aged 16 to 18 years can be operated on as long as there is pediatric follow-up by the multidisciplinary team and that they respect the consolidation of the epiphyses cartilage of the wrist. In Brazil, the most recent Resolution of the Federal Council of Medicine (2172/2017) expanded the indication of bariatric surgery for patients with diabetes mellitus type 2 between 30 and 70 years of age and BMI from 30 to 34.9 Kg/m^2, as long as the disease has not

been controlled with clinical treatment. Furthermore, it is necessary that the diagnosis has been defined for at least 10 years. Contraindications for bariatric surgery are Cushing's syndrome; dependence on alcohol or illicit drugs during surgery; severe uncontrolled psychiatric illness; moderate to severe dementia; a recent history of myocardial infarction, stroke, and cardiac stent; current cardiac ischemia or severe valve dysfunction; and the difficulty of understanding risks, benefits, expected results, treatment alternatives, and lifestyle changes required after the procedure (Associação Brasileira Para o estudo da obesidade e da síndrome metabólica (ABESO) 2016).

According to the American Society for Metabolic and Bariatric Surgery (ASMBS), a patient who is unable to achieve weight loss and maintain it for a period of time and who has a BMI $\geq$ 40 kg/m^2 or is more than 100 pounds overweight is eligible for bariatric surgery. Patients with a BMI $\geq$ 35 kg/m^2 and at least one or more obesity-related comorbidities, such as type 2 diabetes (DM2), hypertension, sleep apnea and other respiratory disorders, nonalcoholic fatty liver disease, osteoarthritis, lipid abnormalities, gastrointestinal disorders, or heart disease, are also eligible for BMS. In adolescents, the recommendation to perform BMS is for those with a BMI $\geq$ 35 kg/m^2 and who present the following comorbidities: DM2, moderate or severe sleep apnea, pseudotumor cerebri, or severe fatty liver disease. Those with a BMI $\geq$ 40 kg/m^2 and those with less severe comorbidities such as high blood pressure, high cholesterol, and mild or moderate sleep apnea are also qualified.

The surgeries are differentiated by the working mechanism. There are three basic procedures in BMS, which can be didactically divided and classified as restrictive procedures, malabsorptive procedures, or mixed procedures.

Restrictive procedures are those that reduce gastric capacity, leading the patient to consume less food and inducing a quick feeling of satiety. Among these procedures, there are those that are purely restrictive, those that do not stop the patient's hunger, and those that are restrictive and metabolic, such as *sleeve* gastrectomy, which, in addition to inducing early satiety, also reduce the degree of hunger (de Oliveira et al. 2019).

Malabsorptive procedures, currently in disuse, slightly alter the gastric capacity and drastically alter the absorption of nutrients. These are surgical techniques that cause a large intestinal diversion, reducing the time the food is in the intestinal transit and, consequently, also reducing its absorption capacity, which will lead to weight loss (Associação Brasileira Para o estudo da obesidade e da síndrome metabólica (ABESO) 2016).

Mixed procedures, considered the gold standard, are those that cause restriction in gastric capacity and a mild reduction in nutrient absorption capacity, such as the RYGB technique.

Currently, the laparoscopic approach is the most widely used method for performing BMS, with only a small percentage of all procedures performed in open access. The most commonly performed BMSs are the laparoscopic sleeve gastrectomy, also known as the *sleeve*, and the laparoscopic RYGB (Wolfe et al. 2016; Sociedade Brasileira de Cirurgia Bariátrica e Metabólica (SBBMS) 2017).

RYGB is characterized by the creation of a gastric reservoir (with a capacity of 40 to 50 ml) close to the small gastric curvature. The remainder of the stomach is excluded, including the entire fundus and the gastric antrum, the duodenum, and the initial portion of the jejunum. The reconstruction of the transit is carried out by forming a Roux-en-Y loop, with a length that varies from 75 to 150 cm. In addition, a silicone band can be placed a few centimeters above the gastrojejunal anastomosis to calibrate the passage of food. Thus, nutrients are shifted from the upper to the middle of the small intestine. As a consequence, there is a feeling of satiety more quickly and less absorption of nutrients due to the formation of the Y-shaped transit. This technique promotes weight loss equivalent to approximately 70% of the patient's total weight, which is greater than that found in techniques that are only restrictive, such as the *sleeve*, for example, as well as having a low mortality rate (0.5%). However, supplementation with vitamins and minerals, such as vitamin B12, is necessary, in addition to frequent monitoring of serum levels of vitamin D, calcium, and iron (Associação Brasileira Para o estudo da obesidade e da síndrome metabólica (ABESO) 2016).

Sleeve gastrectomy is an anatomically simple but irreversible operation in which 80% of the greater curvature of the stomach is excluded, leaving the anatomy of the small intestine unchanged. A probe is passed into the pylorus against the small curvature of the stomach, and a laparoscopic stapler positions a line of staples that follows the length of the probe to the angle of His. Although the process does not involve anastomosis, the length of the staple line puts the patient at risk for bleeding or fistula, particularly as it is a high-pressure chamber, which differs from RYGB. This surgical technique causes the stomach to reduce its storage capacity to 60–100 ml. Due to the removal of the bottom of the stomach, ghrelin levels decrease, consequently decreasing the feeling of hunger, thus characterizing the restrictive metabolic technique (Wolfe et al. 2016; Stein and Silverberg 2015).

The degree of weight loss that patients experience varies according to individual, the surgical technique applied, and the time elapsed since the surgical procedure. The SBBMS considers obesity recurrence when, in the long term, there is a recovery of 50% of the weight loss or 20% of the weight regained associated with the reappearance of comorbidities. The controlled relapse of obesity, on the other hand, is when the patient recovers, in the long term, between 20% and 50% of the weight loss (Buchwald et al. 2004; Berti et al. 2015; Bryant et al. 2020).

Throughout its history, BMS has undergone major advances related to patient safety and the development of more reliable and effective surgical techniques. However, $<1\%$ of patients eligible for bariatric surgery according to established criteria actually undergo the surgery. Some likely reasons for this include lack of health plan coverage and fear of long-term adverse events. Whatever the reason, these trends highlight the continuing need to not only care for a global population of patients who experience an increasing degree of mortality from a variety of causes but also to find a more efficient way to treat a greater percentage of patients and at the same time educate them about their fears around the stigma of BMS.

The challenge for metabolic and bariatric surgeons is to continue to foster a culture of safety, and for this to occur, high standards of effectiveness in carrying out

BMS must be maintained. Fortunately, given the need to evolve and advance surgical techniques targeting metabolic diseases and weight loss, BMS has a promising and exciting future. New procedures, technologies, devices, and interventions are under development while maintaining high standards of safety and effectiveness. These advances include the emergence of numerous technologies and devices that are currently undergoing extensive research. All of these devices offer the promise of significant weight loss with greater safety and simplicity compared to more conventional operating procedures. The future of BMS promises improved techniques and continued attention to patient safety, with new mechanisms of action that will result in less change in the gastrointestinal anatomy, which, in turn, will likely lead to better patient acceptance for surgery (Phillips and Shikora 2018).

BED

The BED is of particular interest due to its relationship with obesity and its medical and psychiatric comorbidities. BED has a high socioeconomic impact due to a higher risk of morbidity and mortality, as well as a reduction in quality of life, greater problems of social coexistence, and increased use of health services compared to people with the same BMI and who do not have the disorder (Dawes et al. 2016).

Although BED was first described in the 1950s by Stunkard, its elevation to diagnostic category only occurred in 1994, when it was included in Appendix B of the Diagnostic and Statistical Manual of Mental Disorders, fourth edition (DSM-IV) in the form of a disorder that needs further studies for better characterization. Thus, since then, there has been greater interest in research in this area, due to the need to discriminate obese individuals with BE from those without BE and bulimics. BED is thus included in the DSM-V as a new ED category.

BED is evidenced through its main characteristic: regular episodes of BE. Each episode of BE is characterized by the objective consumption of large amounts of food over a period of up to 2 h and accompanied by the subjective feeling of loss of control over the type of food ingested, as well as its quantity. If these episodes are recurrent, that is, they occur on average at least once a week for 3 months, the syndrome denominated BED is confirmed (American Psychiatric Association 2013; Sarwer et al. 2011).

In addition, the identification of BE is reinforced whenever the manifestation of suffering marked by compulsive attitudes toward eating is observed in the individual. Among these attitudes, it is necessary that at least three of the following characteristics are present: (World Health Organization (WHO) 2000) consuming the food excessively quickly, unusually when compared to people who do not have BED; (Al-Najim et al. 2018) ingesting an excessive amount of food to the point of causing gastric discomfort; (Opozda et al. 2018) ignoring the physical feeling of hunger and consuming large amounts of food; (Nikiforova et al. 2019) isolating oneself during food intake due to shame about how much one eats; and (Associação Brasileira Para o estudo da obesidade e da síndrome metabólica (ABESO) 2016) and feeling guilty, depressed, and disgusted with oneself. It is also observed that, unlike

other EDs, which also involve BE, BED differs, for example, from bulimia nervosa, by the absence of inappropriate compensatory behaviors for weight loss that routinely occur, such as induction of vomiting, strenuous physical exercise, or misuse of laxatives and/or diuretics (Sena 2014).

It is increasingly recognized that a small subset of patients are diagnosed with EDs after bariatric surgery (Brode and Mitchell 2019).

BE is usually evidenced in individuals who tend to have greater problems in their social life, who suffer a lack of affection, and who have low self-esteem, negative feelings related to body weight, and very restrictive diets, among many other causes that can be observed at the clinical follow-up.

Allied to this, we need to consider that binge episodes should be followed by a feeling of lack of control over the type of food eaten as well as its quantity. One of the signs of loss of control is the individual's inability to avoid eating or to know how to stop eating. Here, the individual's need to eat an excessive amount of food is observed, not considering the quality, appearance, or flavor of the food.

BED has an impulsive characteristic. Impulsivity refers to the lack of ability to inhibit automatic behavior (also known as response inhibition) and the tendency not to measure future consequences in favor of more immediate outcomes (known as delay discounting). These choices between preferences for immediate rewards in relation to future rewards will become evident when the professional indicates to the patient the choice of smaller immediate rewards. Furthermore, executive function, defined as an individual's ability to regulate attention and maintain goal-directed behavior, is believed to play a central role in impulsiveness. Lack of impulse control can reduce the ability to inhibit automatic behavior (e.g., excessive consumption of highly palatable snacks) and can increase preference for immediate rewards over long-term rewards (e.g., choosing highly palatable snacks over a healthier option). Thus, impulsivity can contribute to the excessive weight gain seen in extreme obesity and can impact the results of bariatric surgery (Sarwer et al. 2019).

It should be noted that we must consider the way in which this occurs, and thus it is necessary to analyze the moment when BE episodes occur. Do these episodes occur during special occasions, such as holiday festivities and social events with friends, or do they occur daily at everyday meals? These situations must be taken into account during clinical care as they will help the professional to delimit the existence of BE.

BE is of particular concern in bariatric populations due to the possible attenuation of weight loss. Studies suggest that postoperative disorders, and particularly postoperative BED and LOCE, may contribute to worse weight loss outcomes (Ivezaj et al. 2017b). Although BE episodes in bariatric surgery are alleviated by the anatomical and physiological alterations imposed by the surgery, restricting the amount of food consumed, over time many individuals are able to endorse or develop this behavior (Brode and Mitchell 2019; Smith et al. 2019). Thus, suboptimal weight loss and regain may result not only from an uninhibited diet but also because, over time, patients are able to consume greater amounts of food (Brode and Mitchell 2019).

In addition, patients can develop new problematic eating behaviors, such as loss of control while eating (LOCE), snacking, subjective BE, or consumption of small

amounts of nutrient-rich foods, which make up the mechanism of action of the surgery. The behavior of eating at night may also be present in some patients undergoing bariatric surgery. These dietary pathologies may be sufficient for postoperative weight recovery (Nasirzadeh et al. 2018). Successful weight loss has been associated with self-monitoring of weight-related behavior, which could be indicative of self-regulatory capacity. Since LOCE and BE are largely characterized by difficulties in self-regulation, the lack of self-monitoring may be related to postoperative LOCE.

BE and excessive food intake are two prevalent obesity-related characteristics that contribute to excessive calorie intake and weight gain. BE is characterized by the subjective experience of loss of control (LOCE) during eating, regardless of the actual amount of food consumed. Overeating is characterized by eating a large amount of food, regardless of LOCE. Therefore, LOCE and the ability to eat large amounts of food are two independent but interrelated constructs (Eldar et al. 2011).

Although the diagnosis of BED, specifically the criteria for an episode of BE, requires the consumption of an objectively large amount of food, evidence suggests that it is the characteristic of loss of control while eating that may be the most important characteristic (Lavendera et al. 2014).

Both BE and BED are more common among individuals with obesity compared to individuals with normal weight (Schag et al. 2016). In addition, previous research has documented that 43.4% of candidates for bariatric surgery report LOCE (Smith et al. 2019).

Although binge-eating episodes are often alleviated because surgery restricts the amount of food patients can eat, over time some may be able to consume larger amounts (Smith et al. 2019). Therefore, the importance of identifying eating behaviors through appropriate postoperative monitoring is clear, in order to mitigate weight regain.

Prevalence of BED in Bariatric Patients

Surgery is recognized as an effective treatment for severe obesity and associated comorbidities; however, there is enormous variability in weight loss outcomes after surgery. The weight change trajectories of bariatric patients start to diverge between 6 and 12 months after surgery, and different trajectories have an impact on the prevalence of comorbidities and the corresponding health costs (Cassin et al. 2020).

Studies estimate that 50% of patients who undergo the RGBY technique and 59% of those who undergo sleeve gastrectomy experience some degree of weight gain and approximately half of the patients who undergo RGBY regain more than 20% of the maximum initial weight loss (Ivezaj et al. 2017b).

BED is a relatively common disorder, with an estimated lifetime prevalence in the general population of around 1.4%. However, this estimate increases substantially among obese individuals, without marked differences between sexes.

Establishing a psychiatric diagnosis before bariatric surgery is a challenge. Although preoperative guidelines recommend that patients undergo a clinical

psychological evaluation prior to surgery, it is possible that some patients become more engaged during assessments, minimizing psychopathology symptoms. Thus, these patients present themselves in the most favorable way possible in order to obtain a positive recommendation for surgery from the professional (Dawes et al. 2016).

In obese individuals who are candidates for bariatric surgery, the prevalence of BED was estimated at 4.6% to 27.1% (Chao et al. 2016; Sarwer et al. 2019). Added to this is the presence of a diagnosis of depression (19%) at the time of surgery (Dawes et al. 2016). It is likely that the prevalence will increase, especially considering the increasing incidence of both obesity and EDs around the world and not because of the expansion of diagnostic criteria introduced in the DSM-V (Ivezaj et al. 2017b).

Although LOCE and BED initially decrease soon after surgery, a substantial proportion of patients report postoperative LOCE and BED, with studies showing wide variation in postoperative rates, from 0% to 46% (Fangueiro et al. 2021; Meany et al. 2014; Cella et al. 2019; Latner et al. 2004; Kalarchian et al. 2002). A recent study that carefully evaluated the presence of BED before surgery found no statistically significant difference in weight loss at the end of the first postoperative year between those who received the diagnosis before surgery and those who did not. However, by the 24th month after the surgical procedure, participants diagnosed without BED had lost 23.9% of their initial weight, compared with 18.6% for those with BED (Chao et al. 2016).

Possible contributions to this wide variation in the prevalence of LOCE and BED include the different types of surgery used, the type of instrument used for diagnosing EDs, and the length of postsurgical follow-up. Another possibility that justifies this wide variation in the prevalence of LOCE and BED is that individuals minimize problems related to eating before surgery, or even that, over time, individuals find it more difficult to adhere to the necessary postoperative dietary guidelines to maintain the expected results of the surgery and, as a result, experience a sense of loss of control over eating (Meany et al. 2014; van Hout et al. 2005; Eldar et al. 2011; Maggard et al. 2005; Branson et al. 2005).

Furthermore, in obesity, BE episodes are known to be difficult to assess because they are not as distinct as episodes of bulimia nervosa, which often end with some type of compensatory behavior, such as vomiting (Meany et al. 2014).

These data suggest how beneficial it would be to perform routine monitoring assessments of eating behavior well beyond the first year after surgery, as many individuals continue to report a feeling of long-term loss of control over their eating (Smith et al. 2019). This self-reported inability to control these impulses in the postoperative period is associated with less weight loss and greater emotional distress in the first postoperative years.

Data on the incidence of postoperative BED are scarce due to the lack of follow-up, screening, and standardization in the assessment of these comorbidities. Given this and the rapid increase in demand for bariatric surgery in the last decade, the need for better understanding of the outcomes in the postoperative period is evidenced.

Instruments Used to Diagnose BED

The guidelines recommend a multidisciplinary assessment of candidates for bariatric surgery to identify potential psychological factors that could compromise surgery outcomes. After performing the procedure, it is recommended that multidisciplinary follow-up takes place beyond the first year.

During the assessment and follow-up of the patient by the multidisciplinary team, BED assessment instruments can be used. The instruments are divided into three categories: (World Health Organization (WHO) 2000) clinical interviews, (Al-Najim et al. 2018) self-monitoring, and (Opozda et al. 2018) self-administered questionnaires. The set of these instruments helps the professional in tracking, monitoring, and diagnosing BED (American Psychiatric Association 2013).

A clinical interview is considered the gold standard for the diagnosis of BED. The lines of treatment include different types of therapy, such as cognitive behavioral (CBT), dialectical, and interpersonal behavior, in addition to the possibility of associating the use of drugs when necessary. The clinical interview is the essential element of the doctor-patient meeting and aims to identify/treat the disorder, get to know the individual, and establish a relationship of trust, respect, complicity, and bond with them and their family. However, this follow-up requires time, privacy, and, above all, patient compliance. If this does not occur, the success of the treatment will be compromised.

The self-monitoring instrument consists of diaries or food records completed by the patient and aims to describe in detail what was consumed; the time and place of meals; the feelings associated with these moments, such as guilt or anger; and compensatory behaviors associated with food. The advantage of food diaries is the fact that records are made at the time of consumption, so do not depend on the patient's memory. This instrument also identifies the types of foods and preparations consumed, measures current consumption, and provides less error when there is detailed guidance for completing the diary. As disadvantages, it is observed that the patient may not perform the recording correctly because they know they are being evaluated or because they are not motivated and committed to the treatment. In addition, it may be difficult to estimate quantities and servings as this requires time and knowledge of household food measurements (Fisberg et al. 2009).

Self-administered questionnaires used in clinical practice serve only as a screening tool for the diagnosis of BED. We can cite the self-administered EDE-Q questionnaire (self-administered version of the EDE interview), the Binge Eating Scale (BES), the Questionnaire on Eating and Weight Patterns-5 (QEWP-5), and the self-administered questionnaire in the bariatric surgery version (EDE – BSV).

The EDE-Q is a tool used to help diagnose EDs in general. It addresses several dietary and self-image issues, such as objective BE, subjective BE, and LOCE, and is applied through questionnaires and self-report criteria. This tool is composed of a global score of psychopathology of EDs, totaling 41 items, and its result is presented through four subscales: food restriction and concern with food, weight, and body shape (Taba et al. 2021).

The BES aims to assess behavioral, emotional, and cognitive parameters of individuals with obesity and is also validated for application in bariatric patients (Nasirzadeh et al. 2018). It consists of 16 items, each of which has three to four statements, totaling 62 statements. Each statement is worth from zero to three points, from the absence ("0") to the maximum severity ("3") of BE symptoms. The final score is the result of the sum of the points for each item. The result is divided into severe BE (score $\geq$ 27), moderate BE (score between 18 and 26), and no BE (score $\leq$ 17) (Freitas et al. 2001; Ribeiro et al. 2016; Järvholm et al. 2020).

The QEWP-5 is composed of 28 questions related to BE episodes, indicators of loss of dietary control, compensatory weight management methods, weight and diet history, degree of concern about weight and body, and basic demographics. The QEWP-5 was specifically developed to provide a diagnosis of BED according to the criteria of the DSM-IV, having been subsequently revised to fully meet the proposals established in the manual and named the QEWP-R. The questionnaire can be administered in an interview format, where it is read to the patient. It is indicated for screening BED in the general population and for distinguishing purgative BN from non-purgative BN. It can also be applied to patient samples; however, the diagnosis of BED as stated above must be confirmed by a clinical interview (De Moraes et al. 2020, 2021).

The EDE-BSV, in turn, was adapted and modified for bariatric surgery. It is a semi-structured clinical interview that has been adapted for bariatric patients and designed to assess the extent and severity of ED psychopathology, including LOCE, during the past 28 days. LOCE eating episodes are defined as the number of episodes with a feeling of loss of control that occurred during the previous month. The EDE-BSV captures four categories (or "subscales") of the EDE-Q, including dietary restriction, dissatisfaction with shape and body weight, and overvaluation of shape and body weight. These categories, however, were adapted in some ways in order to meet the specifications of the bariatric population. First, the items that made up the original restriction category, which is related to pathological behavior, were also extended to a new and revised restriction category in order to avoid the physical discomfort that can occur in patients undergoing BMS. Second, items relating to compensatory behaviors (such as vomiting, use of laxatives, and diuretics), which were labeled "purging," were also included as a category. Additionally, these items were classified into purging to prevent weight gain and purging to avoid physical discomfort. These items and categories were added because the motivation to avoid or alleviate physical discomfort after bariatric surgery could elucidate the endorsement of restrictive and compensatory behaviors (Globus et al. 2021; Lawson et al. 2020).

The relevance of using these questionnaires in preoperative patients requires in-depth observation, since in the postoperative stage the amount of food ingested is subjective. The limited gastric capacity imposed by the surgery masks the behavioral parameter and can compromise the answers to the questionnaires. Therefore, the assessment should be focused on loss of control, that is, on the sentimental and cognitive side of the compulsion, which will enable better identification of patients with BE in the postoperative period (Colquitt et al. 2014).

We cannot fail to consider that self-administered questionnaires, despite working as a screening method, also have some limitations. The data are self-reported which may, perhaps, alter/compromise the results obtained. It is also suggested that bariatric patients receive nutritional guidance before the time of surgery. Most patients go through a dietary re-education process aiming to achieve a more adequate diet, already expecting good results after the bariatric surgery. It is therefore necessary to raise the hypothesis that these patients may have been influenced beforehand when they received guidance on healthy eating habits, inducing them to opt for the "best answer" without actually leading to an internal change.

Psychological Aspects: Behavioral and Dietary Reorganization

The presentation of "traditional" BED with objectively large amounts of food is uncommon in the postoperative period due to the physical changes after bariatric surgery. However, loss of control while eating, regardless of size, occurs and is associated with psychological impairment, including greater psychopathology of the ED in the postoperative period. Preliminary findings suggest that adults with LOCE who present for treatment after bariatric surgery and who meet all criteria for BED except the ingesting an excessive amount of food criterion have a presentation similar to adults with "traditional" BED (with the size requirement) (Goldschmidt 2017; Gradaschi et al. 2019).

Secretive eating, which is characterized by the hidden consumption of food, occurs among adults with BED. This behavior is considered one of the indicators for LOCE, which in turn determines BE or BED. However, the frequency and clinical characteristics of this secretive eating among post-bariatric patients who experience LOCE ingestion remain unknown (Lydecker et al. 2019).

The treatment for BED, as well as for EDs in general, is influenced by its etiological history, consisting of a complex interaction between hereditary, psychological, and environmental factors, and should be taken into account in treatment planning (Brambilla et al. 2009).

Treatment options must be multidisciplinary and appropriate to deal with symptoms and comorbidities. One should also consider the high rates of treatment dropout and the low maintenance of the results achieved, which are typical of this disease (Ivezaj et al. 2017b).

The main objective of treatment with BED is to achieve abstinence from BE episodes. Weight loss will be a consequence and not the focus of the treatment. The increase and maintenance of motivation, education for a healthier diet and lifestyle, modification of dysfunctional thoughts and habits, the increase in insights and skills to deal with conflicts and negative emotions, the treatment of physical and psychiatric comorbidities, good relationship with food and the body, and relapse prevention should be considered as the main points.

It is essential to identify patients at risk of postoperative LOCE and to monitor their eating behaviors and the progress of weight loss. Patients identified with LOCE and psychological comorbidities can then benefit from a targeted intervention to

address both situations. However, these patients may need additional support to remain involved in treatment because there is evidence that patients with BED and LOCE may be less compliant with postoperative dietary recommendations and are less likely to attend postoperative appointments (Brode and Mitchell 2019; Andrea and Ana 2020).

Clinical interventions that make simultaneous use of CBT and medications for emotional and psychiatric problems were also linked to a lower probability of LOCE, helping to reduce the negative effects of EDs (Smith et al. 2019).

Monitoring food intake may be particularly relevant for self-regulation in this population and may help to prevent LOCE, as eating smaller portions more often is recommended after bariatric surgery. Eating more frequent meals and snacks can be a good indicator of better adherence to postsurgical guidelines and perhaps another marker of self-regulatory capacity.

It should also be considered that during meals some patients may have certain feelings, such as guilt or fear. In these cases, the act of eating should be practiced without judgment. Attention should be focused only on what food does to the body. When we judge what we are eating and the amount of it, more food will be needed to satisfy our cravings, which can result in overconsumption. Therefore, it is essential to work on the importance of eating for pleasure and with full attention, demystifying the beliefs that there are permitted or prohibited foods, healthy or unhealthy (Warren et al. 2017).

The practice of mindful eating reduces episodes of BE as it acts on impulsivity. Impulsiveness leads to greater food consumption and loss of control over feelings of hunger and satiety (Schag et al. 2016). Thus, it is important to ensure that the patient eats at regular times and avoids prolonged fasting. There are practices that reduce impulsiveness and that should be used to facilitate patient adherence to treatment, such as eating in quiet places; preparing the table for meals; avoiding stimuli such as TV, cell phones, and other media devices; breathing deeply before starting any meal; paying attention to the taste, odor, and appearance of the food; enjoying every moment of the meal; and using the cutlery every time you take the food to your mouth.

As postoperative eating behaviors are associated with weight loss and/or recovery, attention should be focused on the follow-up period. Considering the prospective value of eating in BE, BED, and LOCE, preventive or early detection attitudes seem to be sensitive strategies to help prevent worse outcomes.

Thus, given the stigma of bariatric surgery, along with the strict dietary guidelines recommended in the postoperative period, examining the secretive eating of individuals seeking treatment for EDs after bariatric surgery represents an opportunity to better understand the psychopathology of the ED.

The field of metabolic and bariatric surgery continues to evolve, and it is increasingly important to continuously develop research and studies aimed at understanding which characteristics and behaviors associated with outcomes are similar, both unsuccessful and successful, with a view to the high diversity and complexity of behaviors and the triggers that each patient presents.

Future studies on these issues may shed additional light on important procedures in preoperative assessments, such as the value of psychological assessment and

weight control. These studies also have great potential to improve patient selection, refine preoperative education and intervention algorithms, and develop action strategies to help patients who do not have an optimal outcome after the initial procedure.

Mini-Dictionary of Terms

- Bariatric surgery is becoming widely recognized and has become the most effective treatment for controlling severe obesity.
- However, a proportion of patients may not achieve the expected weight loss or may experience significant weight regain over the next decade.
- BED negatively influences long-term weight loss.
- How patients can develop new problematic eating behaviors related to binge eating (BE), even faced with the difficulty of eating large amounts of food.
- The occurrence of binge eating is not considered a contraindication for the performance of bariatric surgery.
- There are three basic procedures in BMS, which can be didactically divided and classified as restrictive procedures, malabsorptive procedures, or mixed procedures.
- BE is characterized by the objective consumption of large amounts of food over a period of up to 2 h and accompanied by the subjective feeling of loss of control over the type of food ingested, as well as its quantity.
- A substantial proportion of patients report postoperative LOCE and BED, despite the fact that both initially decrease soon after surgery.
- A clinical interview is considered the gold standard for the diagnosis of BED.
- Treatment options must be multidisciplinary and appropriate to deal with symptoms and comorbidities.
- Monitoring food intake may be particularly relevant for self-regulation in this population and may help to prevent LOCE, as eating smaller portions more often is recommended after bariatric surgery.
- The field of metabolic and bariatric surgery continues to evolve, and it is increasingly important to continuously develop research and studies aimed at understanding which characteristics and behaviors associated with outcomes are similar, both unsuccessful and successful, with a view to the high diversity and complexity of behaviors and the triggers that each patient presents.

Key Facts

- The benefits of bariatric surgery are significant for patients with severe obesity.
- It is widely accepted that bariatric surgery patients require lifetime follow-up to assess for weight loss, comorbidity changes, and nutritional deficiencies.
- The best established and most successful method for durable weight loss.
- Bariatric surgery has significant impact on many of the complications associated with obesity.
- Lifelong follow-up of patients is helpful to prevent weight regain and ensure they are meeting their goals.

Summary Points

- Bariatric surgery is becoming widely recognized and has become the most effective treatment for controlling severe obesity.
- BED negatively influences long-term weight loss.
- Even faced with the difficulty of eating large amounts of food, patients can develop new problematic eating behaviors related to binge eating.
- The identification of binge eating is reinforced whenever the manifestation of suffering marked by compulsive attitudes toward eating is observed in the individual.
- BED has an impulsive characteristic.
- Successful weight loss has been associated with self-monitoring of weight-related behavior, which could be indicative of self-regulatory capacity.
- Binge eating and excessive food intake are two prevalent obesity-related characteristics that contribute to excessive calorie intake and weight gain.
- Treatment options must be multidisciplinary and appropriate to deal with symptoms and comorbidities.

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Linking Sleep Deprivation and Binge Eating: Empirical Evidence and Underlying Mechanisms

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Silvia Cerolini

Contents

Introduction 1104
The Detrimental Effects of Sleep Deprivation 1105
Association Between Sleep Deprivation and Increased Food Intake and Impaired Dietary Behavior: Underlying Mechanisms 1105
Biological Pathway 1106
Cognitive and Neural Pathways 1106
Emotional and Behavioral Pathways 1108
Sleep Deprivation and Binge Eating: Still Little Evidence 1109
Chronic Sleep Deprivation and Binge Eating 1110
Poor Sleep Quantity and Quality in Night Eating Syndrome Are Associated with Binge Eating 1111
Novel Empirical Evidence Exploring Both Sleep Deprivation and Binge Eating 1112
Conclusions 1113
Applications to Other Eating Disorders 1114
Mini-Dictionary of Terms 1115
Key Facts of Sleep Deprivation and Binge Eating 1115
Summary Points 1115
References 1116

Abstract

Acute and chronic sleep deprivation have detrimental effect on physical and mental health and may affect eating behavior. Empirical findings demonstrated that sleep deprivation increases food intake and alters eating behavior through different potential pathways. These underlying mechanisms may be biological, cognitive, neural, emotional, and behavioral. Furthermore, cross-sectional evidence documented an association between sleep deprivation and disordered eating and binge eating. Similarly, some studies linked poor sleep due other comorbidities with binge eating. Additional novel experimental studies also

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support the link between sleep deprivation and binge eating. Despite these summarized findings, still little evidence is available to establish firm conclusions about the directionality of this link, and the need to further research is predominant.

Keywords

Poor sleep · Sleep deprivation · Eating behavior · Binge eating · Disordered eating · Sleep · Underlying mechanism · Eating disorder · Binge eating disorder · Chronic sleep deprivation · Acute sleep deprivation · Food intake

Abbreviations

BED	Binge eating disorder
BMI	Body mass index
ED	Eating disorder
IFG	Right inferior frontal gyrus
NES	Night eating syndrome
OSAs	Obstructive sleep apnea syndrome
vMPFC	Ventral medial prefrontal cortex

Introduction

In the last years, the interest in the link between sleep and eating behavior has grown exponentially, thus leading researchers to increase the production of studies and evidence supporting this association. A quick search on the main scientific databases (e.g., PubMed), inserting the keywords eating disorders OR eating behavior AND sleep, found 96 results between 2000 and 2010. From 2010 to 2020, the number of studies has tripled to 339. This number increases more when we insert the keyword "obesity" (i.e., 8431 results from 2000 to 2020). Indeed, the relationship between sleep and obesity has been largely investigated since an increase in obesity and a parallel decrease of sleep duration have been registered worldwide (World Health Organization 2021; Ford et al. 2015).

Despite the increased interest in these topics, few studies directly examined the link between poor sleep quantity or quality and eating disorders, especially binge eating disorder (BED). In part, evidence may be extrapolated from the cross-sectional and longitudinal studies linking poor sleep quantity or quality with eating disorders (e.g., Allison et al. 2016; Harvey et al. 2011) or obesity (e.g., Bacaro et al. 2020). Other evidence can be derived from the experimental studies testing the effect of sleep deprivation on eating behavior and food intake (e.g., Al Khatib et al. 2017). Similarly, other empirical evidence comes from studies examining the effect of poor sleep quantity or quality on emotion regulation and executive functions (e.g., Vriend et al. 2013; Ballesio et al. 2018, 2019; Cerolini et al. 2020), which are involved in

self-regulation of eating behavior (e.g., Ruscitti et al. 2016; Dohle et al. 2018). Consistently, different potential pathways underlying the relationship between poor sleep and changes in eating behavior have been hypothesized (e.g., biological, cognitive, emotional, and behavioral; Lundahl and Nelson 2015).

Considering this framework, the chapter aims to review the literature presenting possible indirect and direct evidence supporting the link between chronic and acute sleep deprivation and disordered eating behavior, especially binge eating. The potential pathways underlying this link will be analyzed and discussed.

The Detrimental Effects of Sleep Deprivation

Sleep deprivation can be defined as the condition of not having enough sleep, and it can be either chronic or acute. Chronic sleep deprivation may consist of persistent poor sleep quantity and/or quality. Inversely, acute sleep deprivation may be defined as not having adequate duration and/or quality of sleep for a short period of time, usually 1 or 2 days. The overall detrimental long-term effect of chronic sleep deprivation is clear enough: shortened sleep duration has been associated with increased risk of all-cause mortality (Liu et al. 2017). Similarly, poor sleep quantity and quality (i.e., chronic insomnia) have been associated with mortality risk (Parthasarathy et al. 2015). Negative long-term effects of chronic sleep deprivation resulted in an increased risk of many physical (i.e., cardiovascular diseases, Sofi et al. 2014) and mental diseases (i.e., depression, Baglioni et al. 2011). Meta-analytic evaluations of longitudinal data agreed in demonstrating the role of short sleep duration in increasing the risk of obesity among adults (Bacaro et al. 2020) and children (Fatima et al. 2015).

In parallel, the short-term effects of experimentally induced sleep deprivation (i.e., acute sleep deprivation) have been demonstrated by many studies, causing an increase in food intake (Al Khatib et al. 2017; Capers et al. 2015) and impairments in cognitive (e.g., de De Bruin et al. 2017; Lim and Dinges 2010) and emotional functioning (Killgore et al. 2008, 2017). Biological and neural changes implicated in increased dietary intake or altered eating behavior have also been reported in results of acute sleep deprivation (e.g., Van Cauter et al. 2008; Demos et al. 2017).

Association Between Sleep Deprivation and Increased Food Intake and Impaired Dietary Behavior: Underlying Mechanisms

The link between chronic and acute sleep deprivation and food intake seems quite complex. Hence, several underlying mechanisms may regulate this relationship. Different authors (e.g., Lundahl and Nelson 2015; Knutson et al. 2007) suggested that biological, cognitive, emotional, and behavioral factors may function as mediators or moderators of this relationship.

Biological Pathway

The potential underlying biological mechanism can be illustrated through the studies evaluating the association between sleep, circadian rhythmicity, hormones, and metabolism. Particularly, the levels of several hormones fluctuate according to the light and dark cycle, and their regulation is influenced by interactions between the effects of sleep and the circadian rhythms (Kim et al. 2015). Studies examining the impact of sleep disturbance and circadian disruption on hormonal and metabolic function are useful to understand if hormonal or metabolic imbalances may occur when the sleep cycle and intrinsic timing system are unsynchronized (Kim et al. 2015). The first evidence supporting the biological mechanism is the seminal studies of Spiegel et al. (2004) examining the effect of acute sleep deprivation on appetitive hormone disruption. They found a reduction in leptin level (i.e., the hormone that sends satiating signals to the appetite control centers in the hypothalamic region of the brain; Ahima et al. 2000) and an increase in ghrelin level (i.e., the hormone that sends signals from the stomach to the brain that triggers an increase in appetite; Van Der Lely et al. 2004). Later evidence supported this first finding in children (Hart et al. 2013) and adults (Chaput et al. 2007; Taheri et al. 2004). In 2007, in the article entitled "The metabolic consequences of sleep deprivation," Kristen Knutson argued that the relationship between sleep deprivation, weight gain, and increased risk of diabetes involves alterations in glucose metabolism, upregulation of appetite, and decreased energy expenditure. Overall, acute sleep deprivation has been demonstrated to have detrimental effects on appetite regulation, carbohydrate metabolism, and endocrine function (Van Cauter et al. 2008), as synthetized in Fig. 1.

Cognitive and Neural Pathways

Secondly, cognitive and neural mechanisms can underlie the association between sleep deprivation and eating behavior (as showed in Fig. 2). Executive functions can

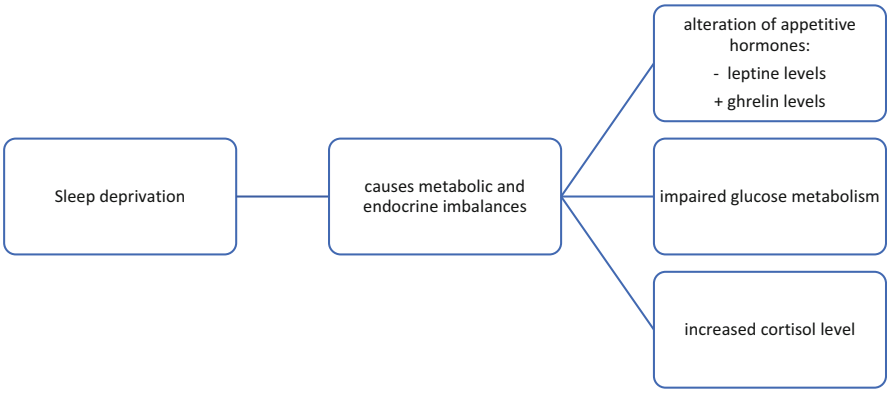


Fig. 1 Potential biological mechanisms implicated in the relationship between sleep deprivation and altered eating behavior

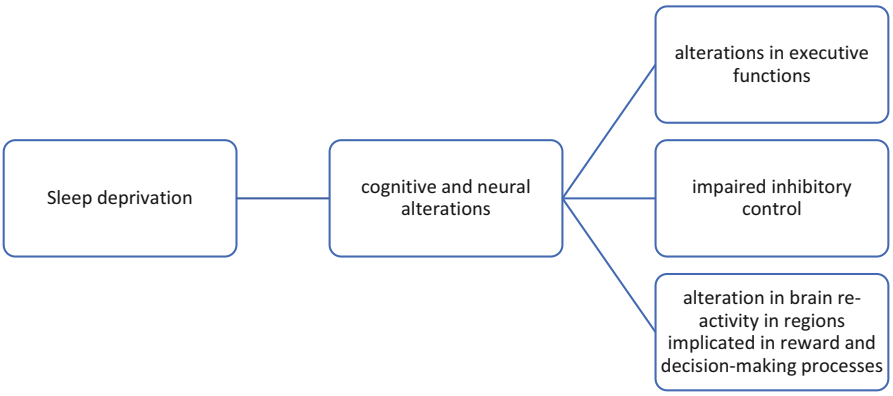


Fig. 2 Potential cognitive and neural mechanism underlying the relationship between sleep deprivation and altered eating behavior

be defined as cognitive processes involved in the control of basic psychological processes such as attention, memory, and emotion (Miyake et al. 2000) and include inhibitory capacities and switching attention processes (Diamond 2013). Impairments in executive functions, such as depletion of inhibitory abilities, have been measured after sleep deprivation (Couyoumdjian et al. 2010; Gorgoni et al. 2014). Poor executive control has been associated with higher caloric consumption and greater consumption of snacks and high-fat food (Rollins et al. 2010; Hall 2012). However, the directionality of the link between executive functions and eating self-regulation is still unclear (Egbert et al. 2019). Cedernaes et al. (2014) found that total sleep deprivation impaired cognitive control in response to food stimuli in healthy young men, increasing the impulsivity in response to food cues. Consistently, other authors found that sleep deprivation and sleepiness may impair executive and cognitive functioning, such as inhibitory control over food intake, motivation, and mood (Burke et al. 2015; Killgore et al. 2013). Also, neuroimaging evidence (Demos et al. 2017) indicates that sleep deprivation increases the reactivity to food stimuli in regions of reward processing (i.e., nucleus accumbens/putamen) and sensory/motor signaling (i.e., right paracentral lobule). These authors found that the whole brain showed greater food cue-responsivity after sleep deprivation in an inhibitory control region as the right inferior frontal gyrus (IFG) and the ventral medial prefrontal cortex (vMPFC), which has been implicated in reward coding and decision-making.

Similarly, Katsunuma et al. (2017) argued that unrecognized sleep loss (i.e., sleep debt accumulated in daily life) could promote brain hyper-reactivity to food cues compared to optimal sleep conditions. Consistently with these results, Benedict et al. (2012) found that acute sleep deprivation enhances the brain's response to hedonic food stimuli in normal-weight men (i.e., increased activation of the right anterior cingulate cortex in response to food images). Contrarily, some studies reported the opposite pattern of results, demonstrating that youths' poor sleep was associated with decreased brain reactivity to reward (Hasler et al. 2012; Holm et al. 2009). Lundahl and Nelson (2015) claimed that this effect of disrupted sleep pattern on

reward processing (increasing or decreasing reward sensitivity) might negatively affect eating behavior, resulting in greater reward-seeking behaviors given the high reinforcing value of the reward, or alternatively, leading to a compensatory increase in reward-seeking behavior. In fact, the positive association between reward sensitivity and food craving, overeating, and BMI has been previously reported (Davis et al. 2004, 2007; Franken and Muris 2005; Stice and Yokum 2016). Furthermore, a study including a sample of children by Nederkoorn et al. (2006) found that sensitivity to reward was greatest in children who engaged in binge eating compared to healthy controls.

Emotional and Behavioral Pathways

Lastly, emotional and behavioral mechanisms can underlie the relationship between sleep deprivation and eating behavior. The negative effects of acute and chronic sleep deprivation on emotional functioning are well documented, leading to increased negative emotions, emotional reactivity, and poorer emotion regulation skills (Killgore et al. 2008, 2017; Baglioni et al. 2010). A complex interplay has been suggested between sleep and emotion regulation, namely, sleep influencing emotion regulation and vice versa, through a bidirectional link (Cerolini et al. 2015; Fairholme and Manber 2015; Kahn et al. 2013). Daily emotions may affect sleep and sleep may affect emotions during the following day in a vicious cycle (Cerolini et al. 2016; Simor et al. 2015; Takano et al. 2014). This impairment in emotional functioning or sleep quantity or quality may, in turn, lead to an alteration of dietary behavior. Hence, the lack of emotion regulation is a key element of disordered eating behavior such as emotional eating and binge eating (Kukk and Akkermann 2017; Ruscitti et al. 2016; Cerolini et al. 2018). The use of dysfunctional strategies for regulating emotions is associated with increased food intake, especially comfort foods (Evers et al. 2010). More, the experimental induction of negative affect has been shown to cause greater food intake in laboratory settings, particularly among individuals with high levels of self-reported emotional eating (Wallis and Hetherington 2004). Likewise, negative affect has been identified as one of the main triggers precipitating binge eating (Leehr et al. 2015).

In parallel, chronic sleep deprivation and sleep disturbances have been associated with binge eating (Trace et al. 2012). Experimentally induced negative affect has been associated with increased food intake among women with high levels of emotional eating and reporting sleep deprivation (Dweck et al. 2014).

Taken together, all these findings indirectly support the hypothesis that sleep deprivation may increase food intake and trigger overeating through an emotional pathway.

Behavioral factors are also relevant in the association between sleep deprivation and increased eating behavior or binge eating. For example, a systematic review of the literature by Felső et al. (2017) found that sedentarism and unhealthy dietary patterns could be considered a mediator of the relationship between short sleep and childhood obesity. More, a reduction in energy expenditure after sleep deprivation

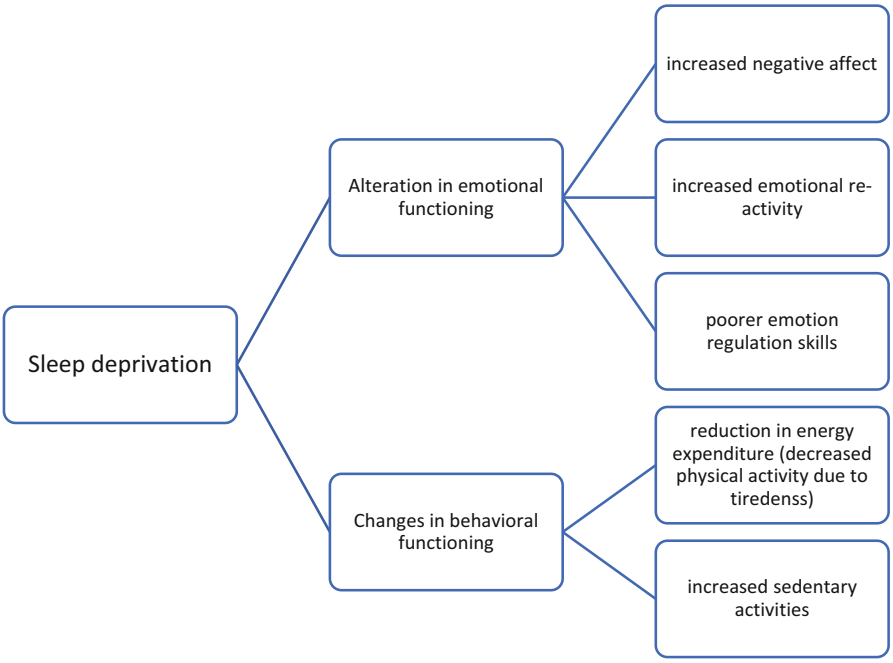


Fig. 3 Potential emotional and behavioral mechanisms underlying the relationship between sleep deprivation and altered eating behavior

could result from decreased physical activity due to tiredness (Dinges et al. 1997; Patel et al. 2006). This may lead to frequently engaging in modern sedentary activities (e.g., television viewing, video game playing, cognitive working, music listening), which promote overconsumption of food in our current obesogenic environment (Chaput et al. 2011) and binge eating (Burmeister and Carels 2014). Also, a recent study by Zhu et al. (2020), using a daily diary approach for seven consecutive days, found that between-person fatigue and poor sleep quality were predictors of uncontrolled eating, emotional eating, and snacking. Figure 3 synthetically shows the above explained mechanisms.

In conclusion, disordered eating behavior and binge eating can be associated with a previous condition of chronic sleep deprivation. Still, it can also be triggered by acute sleep deprivation through different mechanisms, such as biological, cognitive, neural, emotional, and behavioral (please see Fig. 4).

Sleep Deprivation and Binge Eating: Still Little Evidence

Despite the growing interest in the relationship between sleep deprivation and eating behavior, few studies still directly examined the link between sleep deprivation and binge eating. The larger body of studies in support of this link is that one including

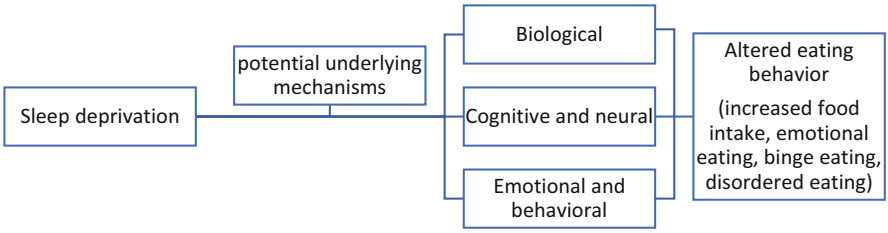


Fig. 4 Potential mechanisms underlying the relationship between sleep deprivation and altered eating behavior

the cross-sectional association between chronic sleep deprivation (e.g., insomnia) and eating disorders, including BED, bulimia nervosa, or subthreshold binge eating symptomatology (which will be briefly discussed in this section, but it will be deeply documented in ▶ Chap. 9, "Insomnia in Eating Disorders"). Other evidence derives from the studies linking binge eating and night eating syndrome, which may result in disrupted sleep patterns and poor sleep quantity and quality (similarly, also, in this case, some points will be mentioned, but the topic is deepened by the two chapters dedicated to night (nocturnal) eating syndrome). In addition, very few novel experimental studies directly investigated the impact of acute sleep deprivation on eating-related behavior in participants with binge eating symptomatology.

Chronic Sleep Deprivation and Binge Eating

Poor sleep quality and poor sleep quantity are highly prevalent among patients diagnosed with an eating disorder (ED, e.g., 50.3% reported by Kim et al. 2010), and chronic sleep deprivation may exacerbate the severity of ED symptoms (Kim et al. 2010; Lombardo et al. 2015). The relationship between poor sleep and ED symptomatology can be mediated by depression (Lombardo et al. 2015), which is known to be comorbid with both (e.g., Baglioni et al. 2011; Slane et al. 2010). A prospective study by Lombardo et al. (2015) including 271 ED patients found that:

1. Poor sleep at admission predicted worse ED symptomatology through the mediation of depression
2. Six-month chronic sleep deprivation predicted the severity of ED symptoms both directly and through the mediation of depression
3. Chronic sleep deprivation predicted worse clinical conditions after 6 months of treatment

Overall, the literature linking poor sleep (i.e., insomnia) and ED pathology is still understudied. Innovative research is necessary to understand this potential bidirectional association deeply and to identify the risks posed by dysregulated sleep on ED treatment outcomes and relapse rates (Christensen and Short 2021).

Focusing on binge eating symptomatology, some studies reported the presence of poor sleep quantity and quality (i.e., difficulties in the sleep onset latency; Vardar et al. 2004) in obese BED patients seeking treatment. Relatedly, a study by Trace et al. (2012), including 3790 women aged 20–47 years, documented the presence of current poor sleep quantity and quality and lifetime binge eating in 6.4% of the total sample, after controlling for obesity. The authors found that binge eating symptomatology was associated with self-reported poor sleep and sleep problems such as difficulties falling asleep, sleepiness during the daytime, and disturbed sleep. Additionally, a study by Quick and co-workers (2016) reported a cross-sectional association between poor sleep quantity and binge eating among 1252 US college students. These authors found that individuals sleeping less than 8 h per night had significantly more negative eating attitudes, poorer internal eating behavior regulation, and greater binge eating, compared to those sleeping for a longer duration, even after controlling for potential confounding variables. Additional evidence, including obese and normal-weight children with and without binge eating and objectively measured sleep, found that obese children with binge eating slept significantly worse than the other two groups (Tzischinsky et al. 2000). Furthermore, sleep disturbances such as obstructive sleep apnea syndrome (OSAs), which is known to be accompanied by chronic sleep deprivation (Cho et al. 2018) and obesity (Kuvat et al. 2020), has been found to be associated with binge eating and BED in a sample of 1099 obese patients candidate for bariatric surgery (Sockalingam et al. 2017).

These findings indirectly support the association between chronic sleep deprivation and binge eating. However, cross-sectional findings do not establish the directionality of this link, which remains an open debate.

Poor Sleep Quantity and Quality in Night Eating Syndrome Are Associated with Binge Eating

Overall, empirical evidence supported the association between poor sleep quantity and quality and night eating syndrome (NES, Lombardo and Cerolini 2022). In parallel, NES has been found to be often associated with eating disorders, especially BED. A study by McCuen-Wurst and co-workers (2018) documented that around 15–20% of patients with NES presented comorbid BED. Also, another study (Tu et al. 2019) found that NES was present in different subgroups of patients diagnosed with EDs. Specifically, NES was identified in 10.3% of patients with anorexia nervosa, 34.9% of patients with bulimia nervosa, and 51.7% of patients with BED. These authors reported that some clinical features might overlap among groups (i.e., depression, sleep quality, sleep medications use, and daytime dysfunction). However, other specific clinical features may clearly distinguish between diagnostic categories discussed elsewhere (i.e., see Lombardo and Cerolini 2022).

Considering the studies linking sleep deprivation and binge eating and the studies linking NES and binge eating is not clear yet if chronic sleep deprivation triggers binge eating behavior, or inversely, urge to binge eating and binge eating behavior impairs sleep, thus leading to chronic sleep deprivation.

Novel Empirical Evidence Exploring Both Sleep Deprivation and Binge Eating

Overall, very few studies have considered sleep deprivation and binge eating-related behaviors. As mentioned before, the link is mostly supported by studies investigating the cross-sectional association between chronic sleep deprivation and binge eating. Nevertheless, few experimental evidence analyzing the effect of acute sleep deprivation on binge eating behavior, or including sleep-deprived individuals with binge eating, are available. Preliminary results of studies addressing these points will be described below.

Particularly, a first quasi-experimental study by our research group at Sapienza University of Rome (Cerolini et al. 2018) evaluated the effect of acute sleep deprivation on food intake in participants reporting binge eating symptoms and depressive emotional eating. The procedure consisted of two lab sessions: one after a night of partial sleep deprivation (5 h of sleep allowed) and one after a habitual night of sleep. Two groups of participants took part in the study: one group of individuals reporting binge eating and one control group of participants denying any eating symptomatology. All participants slept at their homes and went the subsequent morning to the lab. A large breakfast buffet was served during both lab meetings, and researchers unobtrusively measured food intake. This novel preliminary study yielded inconsistent results: a single night of partial sleep deprivation increased the number of snacks and decreased the amount of fiber consumed during the day independently from binge eating symptomatology. The authors found an increase in daily food intake in people who habitually do not binge and do not eat in response to negative emotions, while individuals reporting this symptomatology seemed to be not affected by partial sleep deprivation in increasing food intake. Moreover, participants with depressive emotional eating consumed overall fewer Kcal and carbohydrates during breakfast and from snacks during the day, compared to individuals with low emotional eating. These findings may be explained in different ways: (a) since the binge eating group reported poorer sleep (i.e., more severe insomnia symptoms), the partial sleep deprivation induction (5 h) may have been insufficient to produce the expected results; (b) this group may skip breakfast more often than controls; (c) the procedure may have triggered restrictive and dieting goals, and social desirability may have intervened, especially in participants with eating symptomatology.

Additional findings are derived from a study using the same procedure but including participants with chronic sleep deprivation (i.e., chronic insomnia) and good sleepers (Lombardo et al. 2020), thus providing first evidence on the effect of chronic and acute sleep deprivation on eating behavior. Results revealed that only good sleepers increased food intake at breakfast at an increasing body mass index (BMI) level after sleep deprivation. At the same time, no effect was found on the amount of food consumed during the day. Moreover, participants with chronic insomnia consumed less food after both nights than good sleepers. Also, in this case, the potential explanations may be different. One of them may concern eating habits: this group may skip breakfast more often than good sleepers; therefore, daily

habits should be considered. Likewise, in the long run, people with insomnia may be less vulnerable to the effects of acute sleep deprivation on food intake. This suggests the need for studies especially addressing the long-term effects of sleep deprivation both with longitudinal and experimental designs. This study has the merit of being the first employing partial sleep deprivation in an ecologically translatable setting, as the free-living condition, and a food intake assessment in a laboratory setting, taking also into account chronic sleep deprivation.

Lastly, a similar procedure has been used in another study (Cerolini et al. 2020) evaluating the effect of partial sleep deprivation on executive functions, which, as explained before in this chapter, are involved in the self-regulation of eating behavior (e.g., Dohle et al. 2018). This study is the first to explore the impact of sleep deprivation on executive functions in participants reporting binge eating and healthy controls. The only exception is the study by Cedernaes et al. (2014), in which authors tested the effect of total sleep deprivation in healthy young men, registering an impairment in inhibitory control in response to food stimuli. In our study, instead, we found that partial sleep deprivation decreased inhibitory control in the binge eating group, thus preliminary supporting one of the potential cognitive mechanisms underlying the relationship between sleep deprivation and binge eating behavior. At the same time, we also measured more overall inhibitory control in the binge eating group compared to the healthy controls after the habitual night. This may suggest that usually, people reporting binge eating symptomatology show higher inhibitory control. Still, when sleep-deprived or triggered by emotional stimuli, they may decrease this cognitive control, thus leading to disinhibition and binge eating. Moreover, we did not find any effect of the sleep deprivation or the impact of the group on attentional switching, a measure of cognitive flexibility, though this result is in line with previous studies (Kittel et al. 2017; Manasse et al. 2015; Wardle-Pinkston et al. 2019). This preliminary study demonstrates that sleep deprivation may affect inhibitory control in participants reporting binge eating, highlighting their potential mediating role in influencing eating behavior.

In summary, the heterogeneity of these preliminary results does not allow to establish a firm conclusion about the effect of sleep deprivation on eating behavior. Future studies replicating and extending the procedure and taking into account different variables are needed to clarify these effects. Moreover, to better understand the directionality of this relationship, studies exploring the impact of sleep deprivation on eating behavior, specifically focusing on binge eating behavior, and, at the same time, investigating the role of eating behavior (i.e., binge eating) in affecting sleep, are warranted. Different population groups should be evaluated within this aim, including patients with other ED diagnoses or individuals with different BMI or eating habits.

Conclusions

This chapter aimed to review the literature's heterogeneity considering sleep deprivation and eating behavior, especially binge eating. Few studies directly examined this link, except for some cross-sectional studies, which do not allow to determine a

causal and, therefore, temporal relationship. The broader body of evidence is derived from experimental studies evaluating the effect of sleep deprivation on eating-related behaviors. However, studies assessing the impact of sleep deprivation on eating behavior in the clinical population with ED are still lacking. This is a big gap in the research literature since the role of poor sleep and disrupted sleep patterns in exacerbating ED symptomatology, predicting worse treatment response, and increased relapse rates and hindering recovery has been pointed out (Christensen and Short 2021; Lombardo et al. 2015). Moreover, to the best of my knowledge, until now, no studies have yet explored the potential bidirectionality of the link between sleep deprivation and eating behavior, especially binge eating, which would be a topic of great interest for both sleep and ED researchers and clinicians. If demonstrated, this bidirectionality should be taken into account both at the time of evaluation, diagnosis, and during the treatment process, since sleep and eating behavior may continuously interact. Clinicians should know and take into account the effect of chronic and acute sleep deprivation on eating behavior, and vice versa the effect of disordered eating, especially binge eating, on sleep patterns. Ideally, this may lead to an integration of the assessment, diagnostic, and treatment process in which sleep and eating behaviors are equally considered. This may include cognitive behavioral therapy programs for insomnia, the promotion of good sleep hygiene, and psycho-educational interventions in patients with EDs about the effects of sleep deprivation on dietary behavior, and also, about how changes in eating behavior may affect sleep.

Applications to Other Eating Disorders

In this chapter, studies examining the association between sleep deprivation and eating behavior have been reviewed. Particularly, the main focus has been the link between chronic and acute sleep deprivation and disordered eating, especially binge eating. Potential underlying mechanisms of this relationship have been hypothesized, presenting the literature in support of each pathway. Despite the lack of experimental and longitudinal studies directly supporting this association, the broader body of literature analyzed in this chapter provides indirect aid to this link. This includes studies linking chronic or acute sleep deprivation in patients with different eating disorders, not only presenting binge eating. Hence, understanding the association between poor sleep and eating behavior/disordered eating may be of strong interest for clinicians and researchers involved in the field of eating disorders. In fact, sleep and eating behavior are two fundamental processes which may bidirectionally interact. This can mean that they can influence each other both negatively and positively, and therefore they should be taken into account both at the time of evaluation, at diagnosis, and during the treatment process. Clinicians should know and take into account the effect of chronic and acute sleep deprivation on eating behavior, and vice versa the effect of disordered eating, especially binge eating, on sleep patterns. Ideally, this may lead to an integration of the assessment, diagnostic, and treatment process in which sleep and eating behaviors are equally

present. This may include cognitive behavioral therapy programs for insomnia, the promotion of good sleep hygiene, and psycho-educational interventions in patients with eating disorders about the effects of sleep deprivation on dietary behavior, and vice versa, how changes in eating behavior may affect sleep.

Mini-Dictionary of Terms

- **Acute sleep deprivation**. The condition of not having adequate duration and/or quality of sleep for a short period of time, usually 1 or 2 days.
- **Chronic sleep deprivation**. The condition of having persistent poor sleep quantity and/or quality.
- **Circadian rhythm**. The natural 24-h cycle that regulates physiological, behavioral, and molecular changes, according to the light and dark cycle.
- **Insomnia**. Clinical condition associated with habitual sleep deprivation and sleep fragmentation. It is the most prevalent sleep disorder involving difficulties in falling asleep or maintaining sleep accompanied by impaired daytime functioning, negative mood, and fatigue.
- **Sleep deprivation**. The condition of not having enough duration and/or quality of sleep.

Key Facts of Sleep Deprivation and Binge Eating

- Sleep deprivation is the condition of not having enough sleep, and it can be either chronic or acute.
- In the long-term, chronic sleep deprivation detrimentally impacts physical and mental health, increasing risk of obesity in adults and children.
- Experimentally induced sleep deprivation increases food intake and alters dietary behavior.
- Biological, cognitive, neural, emotional, and behavioral mechanisms may underline the relationship between sleep deprivation and eating behavior, especially binge eating.
- Cross-sectional and preliminary experimental studies examining the link between sleep deprivation and eating behavior and binge eating are available.

Summary Points

- Sleep deprivation affects eating-related behaviors. Chronic sleep deprivation has been proved to be associated with increased incidence of obesity, while acute sleep deprivation increases food intake and alters dietary behavior.
- Several potential underlying mechanisms might be involved: biological changes in hormones and metabolism, cognitive and emotional impairment, neural changes in brain reactivity, and behavioral factors as sedentary activities.

- Cross-sectional findings support the link between sleep deprivation and disordered eating, especially binge eating. However, a lack of experimental and longitudinal evidence examining this association is available.
- Novel preliminary findings including experimental procedures and participants reporting binge eating symptomatology yielded mixed results, thus preventing to establish causal relationships.
- Future studies analyzing the potential bidirectional link between sleep deprivation and eating behavior, such as binge eating, are highly desirable.

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The Criterion B Binge-Eating Symptoms

56

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Contents

Introduction 1122
The BED Diagnostic Criteria 1123
The Development of Criterion B in BED 1125
The Validity and Clinical Utility of the Criterion B Three-Symptom "Threshold" 1126
Research Supporting the Validity of Individual Criterion B Symptoms 1126
Eating more Rapidly during Binge Eating 1127
Eating to the Point of Having Physical Discomfort 1128
Eating Large Quantities in the Absence of Physical Hunger 1128
Eating Alone Due to Embarrassment about Binge Size 1129
Feeling Depressed, Disgusted, or Guilty Following Binge Eating 1130
Relevance of Criterion B Symptoms to Special Populations 1131
The Criterion B Symptoms in Non-pharmacological BED Treatment 1132
Summary 1133
Applications to Other Eating Disorders 1133
Mini-Dictionary of Terms 1134
Key Facts of the Criterion B Binge-Eating Symptoms 1135
Summary Points 1135
References 1135

Abstract

The Criterion B binge-eating symptoms are five symptoms that co-occur with binge-eating episodes. Three out of five Criterion B symptoms must be endorsed for an individual to be diagnosed with binge-eating disorder (BED) under the fifth edition of the *Diagnostic and Statistical Manual of Mental Disorders*. The first aim of the current chapter is to describe the development of the Criterion B binge-eating symptoms. The second aim of the current chapter is to review evidence supporting the validity and clinical utility of the Criterion B binge-eating symptoms. Specifically, some studies have been interested in determining if three is the

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appropriate number of these symptoms that should be required to fulfill this diagnostic criterion. Other studies provide information about the commonality of each Criterion B symptom, the validity of each Criterion B symptom, and each symptom's clinical utility. The third aim of this chapter is to describe how the Criterion B symptoms may be relevant for assessing BED in special populations (e.g., youth, men, different ethnic and/or racial identities, persons seeking bariatric surgery) and treating BED in general. Finally, we also discuss how the Criterion B symptoms may be relevant to understanding other eating-disorder diagnoses because binge-eating episodes occur across various eating disorders.

Keywords

Binge eating · Binge-eating disorder · Eating disorders · Diagnosis · Diagnostic criteria · DSM-5 · ICD-11 · Assessment · Treatment · Obesity

Abbreviations

AN-BP	Anorexia nervosa binge/purge subtype
BED	Binge-eating disorder
BMI	Body mass index
BN	Bulimia nervosa
CBT	Cognitive-behavioral therapy
DBT	Dialectical behavior therapy
DSM	*Diagnostic and Statistical Manual of Mental Disorders*
EDNOS	Eating disorder not otherwise specified
ICAT	Integrative Cognitive-Affective Therapy
ICD	International Classification of Diseases and Related Health Problems
LOC	Loss of control
MB-EAT	Mindfulness-Based Eating Awareness Training
OSFED	Other Specified Feeding or Eating Disorder

Introduction

Binge-eating disorder (BED) is an eating disorder associated with a significant detrimental impact on affected individuals' mental health, psychosocial functioning, and physical health. This impact leads to greater need for healthcare services and increased healthcare costs (Ágh et al. 2015). For example, in a nationally representative sample of US adults, individuals who met criteria for BED had greater functional impairment relative to individuals without BED in a variety of life domains, including professional, home, and social activities (Pawaskar et al. 2017). Other nationally representative research in US adults found that BED was significantly associated with numerous medical concerns (Udo and Grilo 2019). After controlling for other psychiatric diagnoses (any lifetime mood, anxiety, substance use, personality, conduct, or post-traumatic stress disorder), significant associations remained between BED and greater likelihood of high blood pressure and

diabetes (Udo and Grilo 2019). Given the impact of BED on individuals' physical and mental health, it is critical to accurately identify, assess, and effectively treat individuals with BED.

The accurate identification and assessment of psychiatric disorders is facilitated by valid diagnostic criteria. A diagnosis of BED requires binge-eating episodes that are distressing and occur at least once weekly on average. When using the fifth edition of the *Diagnostic and Statistical Manual of Mental* Disorders (DSM-5; American Psychiatric Association 2013) as a diagnostic guide, binge-eating episodes must also be associated with at least three additional specific symptoms. These specific binge-eating symptoms are the Criterion B symptoms, which we review in this chapter. First, we briefly detail the development of the Criterion B binge-eating symptoms from proposed research criteria into diagnostic criteria. Second, we review evidence supporting the validity and clinical utility of the Criterion B symptoms. Finally, we discuss these symptoms' relevance to special populations, BED treatment, and other eating-disorder diagnoses.

The BED Diagnostic Criteria

Diagnostic criteria for BED (see Table 1) are formally outlined in the DSM-5 (American Psychiatric Association 2013). BED is also included in the 11th published edition of the International Classification of Diseases and Related Health Problems (ICD-11; World Health Organization 2019). To receive a BED diagnosis in the DSM-5, an individual must repeatedly engage in objective binge-eating episodes. Objective binge-eating episodes in the DSM-5 have two main components: 1) feeling a loss of control (LOC; i.e., feeling like one must keep eating) and 2) eating an objectively greater amount than most people would in a similar setting and within a similar discrete timeframe (American Psychiatric Association 2013). Binge-eating episodes in the ICD-11 require only the presence of LOC (Berner et al. 2020). In other words, the amount of food consumed is irrelevant for defining binge-eating episodes according to the ICD-11. According to both the DSM-5 and ICD-11, individuals diagnosed with BED should experience binge-eating episodes at least once weekly for an extended period of time (see Table 1). Under both diagnostic systems, individuals diagnosed with BED should also report distress pertaining to their binge-eating episodes. Both diagnostic systems also require that other eating-disorder diagnoses be ruled out (see Fig. 1) because binge eating occurs in several different eating-disorder diagnoses. In the context of BED, binge-eating episodes are not accompanied by compensatory behaviors (e.g., restricting, excessive exercise, purging) as they are in bulimia nervosa (BN). Episodes are also not accompanied by significantly low body weight as they are in anorexia nervosa binge/purge subtype (AN-BP).

In addition to the difference in binge-size requirements between the DSM-5 and ICD-11 definitions of BED, there is one additional difference: in the DSM-5, binge-eating episodes in BED must be also associated with three or more specific binge-eating features. These features (the Criterion B symptoms) are 1) eating more rapidly

Table 1 DSM-5 (American Psychiatric Association 2013**) versus ICD-11** (World Health Organization 2019) Criteria for Diagnosing Binge-Eating Disorder. This table provides a paraphrased summary comparison of the BED criteria as outlined in the DSM-5 (American Psychiatric Association 2013) and the ICD-11 (World Health Organization 2019)

DSM-5	ICD-11
Criterion A: Binge-eating episodes are present. During these episodes, a person experiences a loss of control while eating an objectively large amount of food in a given timeframe	Binge-eating episodes are present. During these episodes, a person experiences a loss of control while eating in a given timeframe
Criterion B: At least three of the subsequently listed features accompany the binge-eating episodes: Eating more rapidly during binge eating, eating to the point of having physical discomfort, eating large quantities in the absence of physical hunger, eating alone due to embarrassment about binge size, and feeling depressed, disgusted, or guilty following binge eating	A person eats a greater quantity *or* in a different manner while binge eating. Episodes may commonly be associated with emotions generally perceived as uncomfortable and/or negative (e.g., disgust, guilt)
Criterion C: Binge eating is associated with significant distress	Binge eating is either associated with substantial distress or causes substantial impairment in a person's functioning
Criterion D: Binge-eating episodes are at least as frequent as once per week for a 3-month period	Binge eating is recurrent (i.e., at least once a week) over the course of "several" months
Criterion E: The person does not engage in compensatory behaviors. If such behaviors were present, a diagnosis of bulimia nervosa would be more appropriate. The person also does not have medically low bodyweight. If low bodyweight was present, a diagnosis of anorexia nervosa would be more appropriate	Compensatory behaviors are not paired with binge-eating episodes like in bulimia nervosa

during binge eating, 2) eating to the point of having physical discomfort, 3) eating large quantities in the absence of physical hunger, 4) eating alone due to embarrassment about binge size, and 5) feeling depressed, disgusted, or guilty following binge eating (American Psychiatric Association 2013). These five "features" constitute the Criterion B binge-eating symptoms. The ICD-11 BED definition does not specifically require the presence of Criterion B symptoms. However, the ICD-11 does reference additional possible characteristics of binge eating such as negative emotions (e.g., disgust, guilt) and eating "differently than usual" (World Health Organization 2019). Overall, reference to these additional binge-eating features in both diagnostic systems suggests that Criterion B symptoms may provide important additive information when assessing BED.

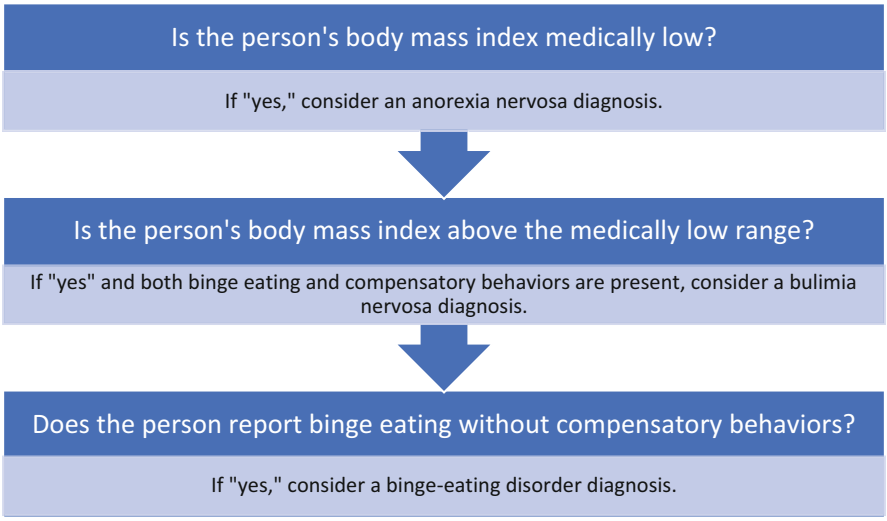


Fig. 1 Hallmark symptom consideration for eating-disorder diagnoses. This figure displays the core symptoms that distinguish the three specific eating-disorder diagnoses in the DSM-5 and ICD-11 from one another. If full criteria (e.g., any necessary frequency criteria and/or other core features, such as the Criterion B symptoms, beyond the hallmark symptom for each diagnosis) for the otherwise most appropriate diagnosis are not met, an "other specified" or "unspecified" diagnosis should be considered. Although Criterion B binge-eating symptoms may be present across diagnoses that include binge eating, they are only considered diagnostically when assigning a diagnosis of binge-eating disorder

The Development of Criterion B in BED

When BED was first studied for consideration as a potential eating-disorder diagnosis, the Criterion B symptoms were included as part of the provisional BED diagnostic criteria for research purposes. The Criterion B symptoms were originally referred to as "associated features" that co-occurred with the LOC that individuals experience during a binge-eating episode (Spitzer et al. 1992). As a result of preliminary research and input from experts, BED was provisionally designated an Eating Disorder Not Otherwise Specified (EDNOS) in the DSM-IV (American Psychiatric Association 1994; Mond 2013). BED was formally added to the eating-disorder diagnostic category in the DSM-5, eliminating its previous status as a "provisional diagnosis needing additional research" (Mond 2013). To reduce the use of non-specific eating-disorder diagnostic codes in the International Classification of Diseases and Related Health (ICD), BED was also included in the 11th version of the ICD (ICD-11; World Health Organization 2019) in 2019 (Claudino et al. 2019).

According to both the DSM-IV and the DSM-5, a person must endorse a minimum of three of the five Criterion B symptoms for a diagnosis of BED to be

appropriately made. There may be instances when someone endorses fewer than three of the Criterion B symptoms, yet has binge eating that is not associated with compensatory behaviors or low weight. In such instances, a clinician may instead diagnose the person with an "Other Specified Feeding or Eating Disorder" (OSFED, the DSM-5 equivalent of EDNOS). Thus, the three-symptom Criterion B threshold can make an important diagnostic difference. As a result, some studies have focused on determining whether the three-symptom "threshold" is the appropriate threshold to accurately identify individuals with fully diagnosable BED.

The Validity and Clinical Utility of the Criterion B Three-Symptom "Threshold"

Since the publication of the DSM-5, research has examined the validity and clinical utility of the three-symptom threshold for diagnosing BED (e.g., White and Grilo 2011; Klein et al. 2016; Vannucci et al. 2013). White and Grilo (2011) used a community sample of individuals diagnosed with BED, BN, or no eating disorder. They tested whether the number of Criterion B symptoms (i.e., endorsing anywhere from one through five symptoms) affected the ability to distinguish individuals with binge eating from those without. Results suggested that three symptoms were the appropriate number of symptoms for "correctly" diagnosing clinically significant binge eating characteristic of either BED or BN. Klein et al. (2016) studied a sample of university students in which nearly 75% of the sample met full criteria for DSM-5 BED. Klein et al. (2016) found that endorsing three Criterion B symptoms best distinguished university students who endorsed an item measuring distress about their binge eating from those who did not. Mustelin et al. (2017) employed a population registry-based study in Finland to examine factors associated with Criterion B symptoms in general community members. The number of Criterion B symptoms a person endorsed was significantly positively associated with both distress and body mass index (BMI). In contrast, Vannucci et al. (2013) found that college-aged women who met the three-symptom Criterion B threshold did not differ on eating disorder-related impairment from those who endorsed only one or two symptoms. In summary, the majority of evidence suggests that the three-symptom threshold does an adequate job in distinguishing individuals with binge eating-related distress from those without such distress.

Research Supporting the Validity of Individual Criterion B Symptoms

Research on the characteristics associated with binge-eating episodes provides information about the individual validity of each Criterion B symptom. For example, laboratory-based studies and ecological momentary assessment studies provide information about experiences prior to, during, and/or after binge eating. Some research tested the prevalence of each symptom to determine whether a given

symptom is uncommon or, alternatively, very common. Inferences about each symptom's relationship to eating-disorder severity may also be made from some research. Research pertaining to the validity and clinical utility of each individual Criterion B symptom is reviewed in the following sections.

Eating more Rapidly during Binge Eating

Research studies suggest that during binge-eating episodes, individuals with BED consume around 2000 calories within approximately 42 min (Forbush and Hunt 2014; Mourilhe et al. 2021). However, based on the available empirical evidence, it is unclear whether eating more rapidly during binge-eating episodes is a reliable characteristic of binge-eating behavior (White and Grilo 2011). Early research on the BED criteria found that eating more rapidly than usual showed the lowest reliability of the five Criterion B symptoms (Brody et al. 1994). Authors suggested that the low reliability may be because individuals with BED *typically* eat rapidly. Therefore, eating rapidly during a binge-eating episode may not be an experience unique to binge eating (Brody et al. 1994). More generally, increased eating rate is associated with having a BMI in the obese range, suggesting that this criterion may simply reflect weight status (Guss et al. 1994; Ohkuma et al. 2015).

One objective method for measuring rate of intake during binge-eating episodes includes laboratory feeding paradigms. During laboratory feeding studies, individuals are instructed to simulate both binge eating and normal eating in a "buffet style" setting where a range of foods are provided. Food intake is measured by weighing food before and after the meal. In some studies, food is placed on a scale that is concealed underneath a fake panel in the table. This facilitates covert weighing of food throughout the meal. Average eating rate is calculated by dividing total energy intake by meal duration. Change in the rate of intake (acceleration or deceleration) is calculated by measuring intake every few seconds during the meal. Some laboratory feeding studies showed that individuals with BN displayed a faster average eating rate when instructed to binge eat compared to when instructed to eat normally (Hadigan et al. 1989; LaChaussee et al. 1992). Additionally, the difference in average eating rate between binge-eating episodes and normal meals was greater among individuals with BN compared to controls (Hadigan et al. 1989; LaChaussee et al. 1992). However, these findings are not consistently found for binge-eating episodes among individuals with BED (Goldfein et al. 1993; Guss et al. 1994). Two studies found that, when instructed to binge eat, individuals with BED ate at a *slower* average rate and over a longer duration compared to non-BED controls (Guss et al. 1994; Goldfein et al. 1993).

In summary, research lacks strong support for the idea that individuals with BED eat relatively more rapidly during binge-eating episodes. However, there is some evidence that eating more rapidly does occur in the binge-eating episodes of individuals with BN. Therefore, eating more rapidly during binge eating may not be a consistently valid symptom of binge-eating episodes in BED but may have relevance for assessing binge eating in other eating disorders.

Eating to the Point of Having Physical Discomfort

During binge eating, people with BED may consume food to a point of fullness that is associated with physical discomfort. This uncomfortable fullness has been positively associated with binge-eating episode frequency (Richson et al. 2020). One survey of university students (the majority of which had BED) suggested that uncomfortable fullness associated with binge eating is commonly reported (Klein et al. 2016). Studies measuring gastric capacity among individuals with BED may also provide validity evidence. Studies have reported that individuals with BED have greater gastric capacity, which may impact the experience of satiety and fullness after a fixed-sized meal (Geliebter et al. 2004). One study measured gastric capacity using ratings of abdominal discomfort with increasing stomach pressure. Specifically, participants swallowed a gastric balloon which was subsequently filled with water. As the balloon was filled, participants rated their discomfort level until reaching maximum tolerance. Findings indicated that individuals with BED tolerated more discomfort than did a group of non-BED controls who had a BMI within the overweight category (Geliebter et al. 2004). Another study used a two-step water-load test to examine differences in gastric signals between individuals with BN or BED and BMI-matched healthy controls. Results showed that individuals with BN or BED drank more water to reach satiation, which was closer to their self-rated maximum fullness level than BMI-matched healthy controls (van Dyck et al. 2021).

Together, results suggest that individuals with BED may have greater gastric capacity that may delay the development of satiety during a meal and increase the likelihood of eating large amounts of food. Without normal satiation, individuals with BED may have trouble terminating intake until reaching a point of physical discomfort. Eating until one is uncomfortably full may, therefore, be a symptom of a larger deficit in satiety and fullness among individuals with BED. However, it remains unclear whether larger gastric capacity precedes or is a consequence of BED. Overall, eating until one experiences physical discomfort (i.e., uncomfortable fullness) appears to be a valid characteristic of binge-eating episodes (and possibly also eating style more generally) in individuals with BED.

Eating Large Quantities in the Absence of Physical Hunger

Certain models of binge eating suggest that binge eating may serve as a maladaptive form of affect regulation, whereby individuals engage in binge eating to cope with, weaken, or distract from negative emotionality (Haedt-Matt and Keel 2011a). From this perspective, binge-eating episodes may be triggered by negative affect rather than physiological cues (e.g., hunger) that otherwise normally regulate eating. Indeed, research suggests that affect may be more likely to trigger binge eating than hunger cues (Haedt-Matt and Keel 2011b). Eating when one is not physically hungry may also contribute to the sense of LOC experienced during binge-eating episodes because of the absence of an obvious physiological reason for eating.

Another factor that may contribute to the symptom of eating large quantities despite a lack of physical hunger is hedonic hunger, which is defined as a motivation to eat tasty or palatable foods in the absence of physiological hunger (Lowe and Butryn 2007). Individuals with high levels of hedonic hunger may consume palatable food for enjoyment rather than for satiation/energy needs. Pleasure-driven consumption may, in turn, increase risk for overeating and excess weight gain. Initial studies showed that hedonic hunger was associated with the development or worsening of LOC over eating, which represents a defining feature of binge eating (Witt and Lowe 2014; Lowe et al. 2016). Increased motivation to consume rewarding foods and hedonic processes may lead to increased craving for food, which may contribute to initiation of binge eating (Fedoroff et al. 2003). Recent research also suggests that the symptom of eating large quantities in the absence of physical hunger is positively associated with binge-eating episode frequency (Richson et al. 2020). In sum, binge eating in BED may be triggered by both affective and hedonic processes, both of which may motivate eating behavior outside of physical hunger. Overall, the Criterion B characteristic of eating large quantities of food regardless of physically "feeling" hunger appears to be an important, valid characteristic of binge-eating behavior.

Eating Alone Due to Embarrassment about Binge Size

Individuals often have binge-eating episodes when they are alone (Latner and Clyne 2008; Svaldi et al. 2019). Eating alone during binge-eating episodes is more common among individuals with objectively large binge-eating episodes relative to individuals with smaller LOC eating episodes (Palavras et al. 2013). Therefore, eating alone may be a particularly valid characteristic of binge-eating episodes in DSM-5-defined BED. Research that has measured binge-eating episodes and the emotions associated with binge eating in real time (i.e., ecological momentary assessment research) has found that shame prior to binge-eating episodes is associated with binge eating alone (Goldschmidt et al. 2018). This finding suggests that shame subsequently leads to eating alone. However, the wording of this symptom assumes that individuals eat alone *because* they are specifically embarrassed about the quantity of food they are eating, rather than because they are experiencing shame or embarrassment, in general.

Research has shown that eating in secret is indicative of greater eating-disorder psychopathology among individuals with BED (Lydecker and Grilo 2019). Similarly, the.

"eating alone" Criterion B symptom was associated with greater impairment among individuals with any eating disorder that included binge-eating episodes (i.e., binge-spectrum eating disorders; Richson et al. 2020). Finally, eating alone due to embarrassment was the least frequently endorsed Criterion B symptom in several studies of individuals with binge-spectrum eating disorders (White and Grilo 2011; Klein et al. 2016; Richson et al. 2020). These studies also suggested that the "eating alone" symptom was indicative of greater binge-eating severity

(Richson et al. 2020) and distress about binge eating (Klein et al. 2016). Taken together, eating alone due to embarrassment about binge size may be a less common Criterion B symptom, but one that is still important to assess because it may be indicative of greater severity. Therefore, binge eating alone that is facilitated by embarrassment may be a clinically useful symptom for both assessing BED and for BED treatment planning.

Feeling Depressed, Disgusted, or Guilty Following Binge Eating

Research on negative emotions after binge-eating episodes is mixed (Berg et al. 2015). More specifically, some research suggests that binge eating is effective at subsequently reducing negative affect (Berg et al. 2015); this research is consistent with the affect regulation model of binge eating. In contrast, other research suggests that negative affect persists or even increases after binge eating (Haedt-Matt and Keel 2011a). The latter research is consistent with the Criterion B symptom of "feeling depressed, disgusted, or guilty following binge eating."

Several studies on the Criterion B symptoms specifically found that the symptom of depressed mood, disgust, or guilt following binge eating is commonly endorsed (White and Grilo 2011; Klein et al. 2016; Richson et al. 2020). Because of its high prevalence, the endorsement of negative affect following binge eating may not be a particularly useful indicator of impairment levels or level of binge-eating psychopathology (Richson et al. 2020). The commonality of post-binge negative affect may also be inconsistent with the affect regulation model of binge eating. In other words, the commonality of feeling depressed, disgusted, or guilty following binge eating suggests that binge eating is *not* effective at reducing negative emotional experiences like the affect regulation model suggests. However, the common presence of negative affect following binge eating does support the overall validity of the "feeling depressed, disgusted, or guilty following binge eating" symptom.

The separate requirement within the BED diagnosis that binge eating be experienced as distressing may explain the high prevalence of this Criterion B symptom, as depressed mood or guilt may be experienced as distress (see Table 1). Indeed, one study found that this Criterion B symptom had the strongest association with distress about binge eating (Klein et al. 2016). This symptom may be a useful binge-eating screening item due to its absence being an accurate identifier of non-binge-eating controls in one study (White and Grilo 2011). Overall, results suggest that "feeling disgusted/depressed/guilty afterward" is a valid, common characteristic of binge eating. However, as a result, it may be difficult to make inferences about BED severity or associated impairment solely from the endorsement of feeling depressed, disgusted, or guilty following binge eating.

Relevance of Criterion B Symptoms to Special Populations

In addition to adults, BED can occur in children and adolescents. Due to developmental differences between children/adolescents and adults, some researchers have posited that the BED diagnostic criteria (including the Criterion B symptoms) may need to be adjusted for children and young adolescents (Tanofsky-Kraff et al. 2008; Marcus and Kalarchian 2003). For example, it may be difficult for children to eat alone because caregivers may monitor eating or due to school-settings in which children are required to eat with peers. Additionally, LOC during eating may be more important for diagnosing BED in children/adolescents than the amount of food eaten during the LOC eating episodes (Morgan et al. 2002; Tanofsky-Kraff et al. 2004; Tanofsky-Kraff et al. 2005; Goldschmidt et al. 2008). Thus, eating to the point of uncomfortable fullness may be a symptom that is less applicable in younger populations; however, this possibility has not been explicitly tested in research to our knowledge. Overall, relative to adults, little is known about how the Criterion B symptoms may apply to the experiences of children/adolescents with binge eating.

Though much of what is known about the Criterion B symptoms comes from adult samples, there are also special adult populations in which less is known about these symptoms (e.g., individuals who identify as men, individuals with minoritized racial and/or ethnic identities). One study that compared women and men found that the majority of binge-eating symptoms examined (including variations of the Criterion B symptoms) were more common among women than men (Mustelin et al. 2017). Men and women also may exhibit differences in terms of which Criterion B symptoms are most commonly endorsed (White and Grilo 2011). Certain symptoms may also be more or less relevant to the experience of binge eating among persons from different ethnic and/or racial backgrounds. For example, one study noted that the experience of embarrassment associated with overeating may be particularly helpful for assessing binge eating in girls and young women from Native American backgrounds (Striegel-Moore et al. 2011). Another study found that various binge-eating symptoms were relatively less common among participants who identified as African American (Franko et al. 2007). More research is needed to clarify the validity of the Criterion B symptoms across a fuller, more inclusive spectrum of adult populations. Addressing existing gaps in knowledge about the Criterion B symptoms in minoritized populations is particularly important given that binge eating may occur at elevated rates in certain minoritized populations (e.g., Perez et al. 2016).

Another population in which it is important to assess BED (and the Criterion B symptoms) is individuals who have undergone bariatric surgery. Bariatric surgery refers to a range of surgical procedures (e.g., gastric bypass) that are intended to facilitate weight loss and prevent serious weight-related medical complications in individuals with obesity (Wolfe et al. 2016). Research suggests that BED is one of the most common mental health disorders among individuals seeking and undergoing bariatric surgery (Dawes et al. 2016; Kalarchian et al. 2007). Although a substantial number of bariatric surgery candidates may endorse binge eating or are diagnosed with BED prior to bariatric surgery, evidence largely suggests that BED

diagnosis prior to bariatric surgery does not reliably predict long-term weight-loss outcomes (Kops et al. 2021). However, the development or re-emergence of BED or binge-eating symptoms following surgery may interfere with weight loss and increase post-operative complications such as uncomfortable gastrointestinal symptoms (Conceição et al. 2017; Sarwer et al. 2008; Smith et al. 2019). Thus, it may be important to understand the extent to which the Criterion B binge-eating symptoms represent the eating experiences of individuals following bariatric surgery. Additionally, binge-eating behavior may present differently among individuals who have undergone bariatric surgery. Specifically, because of restricted gastric capacity resulting from bariatric surgery, the consumption of large amounts of food may not be feasible. However, individuals may experience distress related to LOC over eating and Criterion B symptoms following surgery, which may increase risk for weight regain or poor weight loss outcomes following surgery (Meany et al. 2014). For example, rapid eating may be associated with eating that is emotionally driven in bariatric populations (Canterini et al. 2018). Emotionally driven eating could, in turn, lead to poorer surgical outcomes (e.g., weight regain). Among individuals who have had bariatric surgery, the presence of several Criterion B symptoms in addition to LOC eating may also be associated with greater distress and poorer weight loss outcomes relative to individuals who only endorse LOC eating (Ivezaj et al. 2018). In summary, assessing and treating Criterion B symptoms in bariatric populations may hold clinical utility for ensuring positive surgical outcomes.

The Criterion B Symptoms in Non-pharmacological BED Treatment

BED is commonly treated using Enhanced Cognitive Behavior Therapy, an adaptation of traditional cognitive-behavioral therapy for eating disorders (CBT-E; Fairburn 2008). Individuals participating in CBT-E log their food intake (including recording binge-eating episodes) as well as any thoughts or notable circumstances surrounding food intake. As a result, it may become clear that certain Criterion B symptoms are commonly associated with a client's binge-eating episodes. For example, food logging may reveal that an individual only experiences binge-eating episodes when they are alone. Therapy may then focus on identifying ways the client could remove themselves from an environment where being alone leads to binge eating (e.g., by going on a walk or for a drive) or identifying alternative activities to do when alone. CBT-E's focus on increasing regular eating may reduce the occurrence of other Criterion B symptoms such as eating rapidly and eating to physical discomfort because regular eating increases structure in a person's pattern of eating and gradually facilitates the return of accurate hunger/fullness cues (Fairburn 2008). Behavioral weight loss interventions also emphasize structured eating (Grilo 2017), thus potentially leading to a similar effect on binge-eating symptoms.

Rapid eating and physical discomfort resulting from binge eating may also be similarly targeted in the emphasis on meal planning within Integrative Cognitive-Affective Therapy (ICAT; Wonderlich et al. 2010). Even more directly than CBT-E,

Integrative Cognitive-Affective Therapy (ICAT) emphasizes identifying specific situations and emotions that are associated with binge eating. Thus, awareness of both binge-eating triggers (especially emotional triggers) and emotional consequences is increased through ICAT. As a result, ICAT could be particularly effective at reducing the presence of negative affect-related Criterion B symptoms. However, to our knowledge, this possibility has not been directly examined through research.

BED treatments that focus on mindfulness, including Dialectical Behavior Therapy (DBT) for binge eating (Telch et al. 2001) and Mindfulness-Based Eating Awareness Training (MB-EAT; Kristeller and Wolever 2010), may also reduce certain Criterion B symptoms. A core focus of both DBT and MB-EAT is mindfulness skills, which may be useful for individuals with BED who experience binge-eating episodes despite not feeling hungry or have trouble stopping a binge-eating episode despite nearing a point of uncomfortable fullness. Mindfulness skills could raise a person's awareness to these bodily cues before or during binge eating. Similarly, another DBT focus is emotion regulation. These skills encourage noticing thoughts, emotions, and behaviors that may be unhelpful or distorted so one can then behaviorally respond in a healthier way. Such emotion regulation skills may target Criterion B symptoms that are associated with negative emotional experiences, such as feeling depressed, disgusted, or guilty following binge eating.

Summary

The Criterion B symptoms originated from research on potential characteristics associated with binge-eating episodes. Although the Criterion B symptoms may be experienced by anyone who presents with binge eating, the Criterion B symptoms are only part of the diagnostic criteria in DSM-5 BED (although the ICD-11 BED diagnosis alludes to similar binge-eating symptoms). The Criterion B symptoms vary in terms of their validity and clinical utility. More research is needed on the validity of the Criterion B symptoms in special populations across ages, persons of different weight status, and persons of different identities. Finally, the Criterion B symptoms have relevance across BED treatment modalities.

Applications to Other Eating Disorders

Binge eating is a transdiagnostic symptom that is present across several DSM-5 eating disorders, including AN-BP, BN, and certain presentations of OSFED. Criterion B symptoms are included only in the DSM-5 diagnosis of BED. However, it is possible that persons with other eating disorders also experience Criterion B symptoms during binge-eating episodes. The extent to which Criterion B symptoms could predict eating-disorder severity or impairment has not been explored extensively in different eating-disorder diagnostic groups. In clinical settings, understanding what behaviors, cognitions, and emotions are present during binge eating, regardless of diagnosis, could be important in informing case conceptualizations and treatment

plans. For example, knowing that a client has binge-eating episodes despite a lack of physical hunger may point to the importance of identifying and addressing non-physiological binge-eating triggers. Similarly, knowing that a client tends to binge eat alone may lead to treatment goals of trying to eat meals with others. Therefore, the Criterion B binge-eating symptoms may have the potential to inform severity, impairment, case conceptualization, and treatment plans in AN-BP, BN, and certain forms of OSFED. Future research could explore the extent to which the Criterion B binge-eating symptoms apply to subjective binge-eating episodes, in which an individual feels out of control when eating a small or normal amount of food. Subjective binge eating is present in DSM-5 OSFED diagnoses such as purging disorder. Individuals who experience subjective binge eating often report similar levels of distress pertaining to this behavior as individuals who experience objective binge eating (Li et al. 2019). Therefore, Criterion B symptoms may also apply to the experience of subjective binge eating across diagnostic boundaries.

Mini-Dictionary of Terms

- **Binge-eating disorder.** An eating disorder in which individuals have a normal or greater body mass index and have one main eating-disorder behavioral symptom: binge-eating episodes during which one feels out of control over their eating.
- **Bulimia nervosa.** An eating disorder characterized by normal or greater body mass index, as well as both binge-eating episodes and compensatory behaviors (e.g., restricting/fasting, laxative use, diuretic use, self-induced vomiting, exercising very hard).
- **Criterion B binge-eating symptoms.** The Criterion B symptoms are five symptoms that may be associated with binge-eating episodes and are part of the DSM-5 diagnostic criteria for binge-eating disorder.
- **DSM-5.** The DSM-5 is a manual of psychiatric diagnoses (such as eating disorders, anxiety disorders, etc.) used in the United States that specifies the different symptoms/characteristics a person should have in order to be given a certain diagnosis.
- **ICD-11.** The ICD-11 is an internationally used diagnostic system (i.e., for medical diagnoses, psychiatric diagnoses, etc.) that describes the criteria for various diagnoses.
- **Other Specified Feeding or Eating Disorder.** This DSM-5 eating-disorder diagnosis may be given to characterize a set of clinically significant eating-disorder symptoms that do not fit with a specific diagnosis of binge-eating disorder, bulimia nervosa, or anorexia nervosa.
- **Validity.** Validity is a psychometric term broadly referring to how well a construct (e.g., binge-eating psychopathology) is measured or represented by something (e.g., a symptom set, a questionnaire) intended to assess/represent that construct.

Key Facts of the Criterion B Binge-Eating Symptoms

- The Criterion B symptoms are five symptoms or characteristics that may be associated with binge-eating episodes.
- Endorsement of at least three out of the five Criterion B symptoms is required to meet the DSM-5 criteria for a diagnosis of BED, but not the ICD-11 criteria for BED.
- The five Criterion B symptoms vary in terms of how common they are and in terms of how much they are associated with other factors relevant to BED assessment (e.g., distress, severity).
- The Criterion B symptoms are often relevant to BED treatment targets.
- Because binge eating occurs in additional eating-disorder diagnoses beyond BED, the Criterion B symptoms also likely apply to the experiences of people with other eating disorders.

Summary Points

- In the DSM-5, BED is characterized by binge-eating episodes, distress about binge eating, and various other symptoms that are associated with the binge-eating episodes known as the Criterion B symptoms.
- The Criterion B symptoms are not formally a part of the ICD-11 BED diagnostic criteria but are referenced as possible characteristics of binge-eating episodes.
- BED is a relatively new eating-disorder diagnosis; as a result, its diagnostic criteria (including the Criterion B binge-eating symptoms) continue to be studied.
- Research supports the three-symptom Criterion B threshold in the DSM-5.
- Certain Criterion B symptoms appear to be more common than others, whereas other symptoms may be less common but more strongly associated with clinical characteristics like greater severity and impairment.
- The Criterion B symptoms may need to be adjusted to meet the unique needs of children/adolescents.
- The Criterion B symptoms should be assessed regardless of BED status in bariatric populations.
- The Criterion B symptoms are often relevant to various treatments that aim to reduce the frequency of binge-eating episodes and normalize eating patterns.
- Future research may wish to study the Criterion B symptoms across other eating-disorder diagnoses that include subjective binge-eating episodes.

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Part V

Other Specified and Unspecified Feeding or Eating Disorders

Cognitive-Behavioral Therapy and Purging Disorder

57

Zaida Agüera, Isabel Baenas-Soto, and Fernando Fernández-Aranda

Contents

Introduction 1145
Defining Purging Disorder 1145
Etiopathogenesis and Risk Factors 1145
Clinical and Personality Features 1146
Medical Complications for Purging Behaviors 1148
Treatment Approaches 1150
Medical and Pharmacological Approach 1150
Cognitive-Behavioral Therapy 1150

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CBT Outcome for Purging Disorder 1151
Applications to Other Eating Disorders 1152
Mini-Dictionary of Terms 1152
Key Facts of Purging Disorder 1153
Summary Points 1153
References 1154

Abstract

Purging disorder is an eating disorder subtype characterized by purging behaviors to control weight (i.e., self-induced vomiting or misuse of laxatives, diuretics, and/or other medications). It was recognized for the first time in the DSM-5 (2013) within the other specified feeding or eating disorder category. The lifetime prevalence of purging disorder is comparable to both anorexia nervosa and bulimia nervosa, placing it as a significant eating disorder phenotype. Purging disorder is symptomatologically similar to bulimia nervosa, except for the absence of binge eating episodes. However, despite the common features with other eating disorders, purging disorder appears as a clinically significant and potentially distinctive disorder. Therefore, the present chapter reviews and discusses the clinical and distinctiveness features of this disorder, as well as the treatments of first choice (i.e., cognitive-behavioral therapy). This chapter also highlights that studies on PD treatment outcomes are currently limited, available results are inconsistent, and evidence-based treatments are lacking.

Keywords

Cognitive-behavioral therapy · Eating disorders · Medical complications · Other specified feeding or eating disorder · Purging disorder

Abbreviations

AN	Anorexia nervosa
BED	Binge eating disorder
BMI	Body mass index
BN	Bulimia nervosa
CBT	Cognitive-behavioral therapy
CBT-E	Enhanced cognitive-behavioral therapy
CCK	Cholecystokinin
DSM-5	*Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition*
ED	Eating disorder
GLP-1	Glucagon-like peptide type 1
OSFED	Other specified feeding or eating disorder
PD	Purging disorder
PYY	Peptide YY
RCT	Randomized controlled trial

Introduction

Defining Purging Disorder

Purging disorder (PD) is an eating disorder (ED) subtype included for the first time within the other specified feeding or eating disorder (OSFED) category in the *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* (DSM-5) (American Psychiatric Association 2013). However, before the formal recognition of PD as a diagnostic subtype, some previous studies already attempted to describe the characteristics of clinical conditions consistent with PD (Keel et al. 2005), often as a category of subthreshold bulimia nervosa (BN). According to the DSM-5, PD is symptomatically characterized by recurrent purging behaviors to control weight or shape similar to BN (i.e., self-induced vomiting or misuse of laxatives, diuretics, or other medications), but in the absence of binge eating episodes. In addition, PD requires a body mass index (BMI) greater than 18.5 kg/m^2, which differentiates it from anorexia nervosa (AN) purging subtype (American Psychiatric Association 2013). In fact, PD appears to lie in the middle of the weight spectrum, with AN at the lower and binge eating disorder (BED) at the higher end of this continuum.

PD is considered the ED diagnostic subtype most similar to BN, given the shared psychopathology and personality traits (Krug et al. 2021) and the overlap in purging behaviors as core symptoms (American Psychiatric Association 2013; Riesco et al. 2018). However, while individuals with PD may or may not report a subjective loss of control overeating, it differs from BN in the endocrine and psychological factors linked to binge eating episodes (e.g., hunger, intense feelings of satiation after meals, and ability to control food intake) (Murray and Anderson 2015; Dossat et al. 2015). This growing evidence that PD is a clinical diagnostic entity per se has also been supported by a recent study that has identified different clusters within the PD category with differential symptomatological and severity characteristics (Krug et al. 2020).

Literature has yielded lifetime prevalence rates of PD ranging from 1.1% to 5.3% for women in community samples (Tasca et al. 2012; Murray and Anderson 2015; Hammerle et al. 2016). Specifically, in clinical settings, prevalence of PD reaches rates of 3–18% in inpatient units (Dalle Grave and Calugi 2007) and up to 24% in outpatient settings (Binford and le Grange 2005). However, since these prevalence rates were published before the DSM-5, it is not clear whether they have captured the real prevalence of PD based on the DSM-5 criteria (Stice et al. 2013). To our knowledge, no studies of prevalence for men with PD are reported so far. However, a study on high school samples shows a significantly higher prevalence of PD in females compared to males (Haedt and Keel 2010).

Etiopathogenesis and Risk Factors

PD sometimes remains unrecognized, but its clinical significance needs to be highlighted (Lydecker et al. 2018). In comparison with other EDs, PD usually presents with a later age of onset (Stice et al. 2009; Smith et al. 2017; Riesco et al.

2018). In fact, PD most typically first onsets in early adulthood, at approximately 20 years of age (Murray and Anderson 2015), and it is uncommon before the age of 18 years (Stice et al. 2009).

As with other EDs, the heterogeneous etiopathogenesis of PD includes multiple interacting factors, such as biological, developmental, psychological, and sociocultural aspects.

Biological factors: (a) Genetic factors and familiar influence (Munn-Chernoff et al. 2015; Hübel et al. 2018); (b) endocrine factors related to appetite regulation (e.g., peptide YY (PYY), cholecystokinin (CCK), glucagon-like peptide type 1 (GLP-1), leptin, amylin, insulin, ghrelin) (Steiger and Bruce 2007; Jimerson et al. 2010; Dossat et al. 2015; Keel et al. 2018; Keel 2019; Maske et al. 2020); and (c) other endocrine systems (e.g., serotonin dysregulation, neurotrophins, dopamine, the hypothalamic-pituitary-adrenal axis, opioids, estrogen, etc.) (Steiger and Bruce 2007).

Psychological factors: Certain psychological factors have been frequently associated with the development and maintenance of PD, as in the case of other EDs, such as specific personality traits (i.e., low self-directedness and high sensation seeking, harm avoidance, and perfectionism), high levels of somatization, emotional distress and negative affect, body dissatisfaction, and eating and weight concerns (Haedt-Matt and Keel 2015; Smith et al. 2017).

Developmental and sociocultural factors: Higher premorbid BMI, parent-perceived childhood overweight, family modeling of dieting or weight concerns, perceived family pressure to lose weight or be thin, and the influence of the ideal of beauty based on thinness, mass media influence, peer pressure regarding body-related criticisms, body dissatisfaction, and frequent dieting are associated with the onset of PD (Stice 2001; Haines et al. 2008; Neumark-Sztainer et al. 2010; Allen et al. 2015; Keel 2019). Family environmental variables, such as childhood trauma or abuse, have also been identified as risk factors for purging behaviors (Steiger and Bruce 2007).

The risk factors above described are common with other EDs. Furthermore, in PD, both behavioral (e.g., purging behaviors) and cognitive symptoms (e.g., fear of gaining weight or becoming fat) tend to emerge simultaneously (Stice et al. 2021). Thus, it is very important to identify the duration and onset of these symptoms to know whether the PD symptoms are primary/secondary to another diagnosis, such as BN, and the crossover ED diagnosis (Fig. 1).

Clinical and Personality Features

Common with other EDs, PD is associated with significant functional impairment, severity, chronicity, medical complications, suicidality, and mortality (Stice et al. 2013; Koch et al. 2014; Forney et al. 2016, 2021; Smith et al. 2017). As noted above, purging behaviors to control weight, fear of weight gain, and overvaluation of body shape are the core symptoms (behavioral and cognitive) of this disorder. Similar to BN, PD exhibits significantly greater drive for thinness, dietary restraint, and body

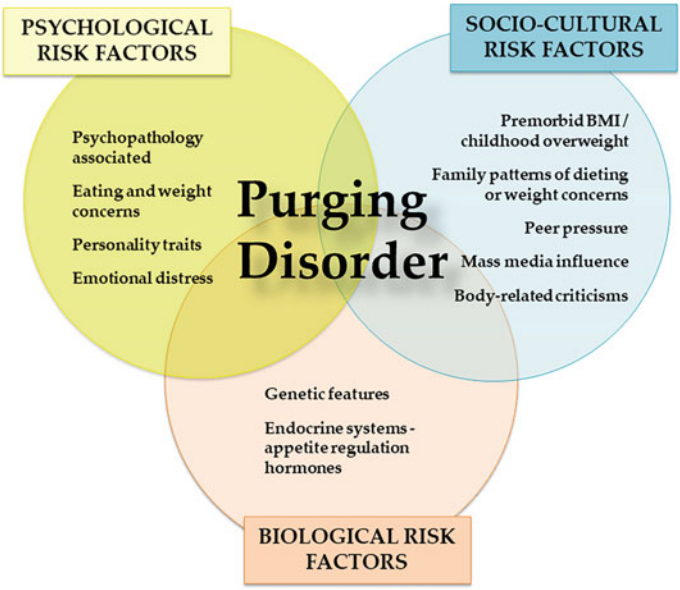


Fig. 1 Risk factors of purging disorder. The etiopathogenesis of purging disorder includes interacting biological, psychological, and sociocultural aspects

dissatisfaction (Keel et al. 2011). It is also well documented that approximately 30% of individuals with PD feel a loss of control eating, even when they intake small amounts of food (i.e., "subjective binge eating") (Goldschmidt et al. 2016; Smith et al. 2017), leading to an increased desire to purge (Keel 2019). Despite common features with BN, PD has been associated with significantly lower eating disinhibition and different subjective and physiological responses to food than BN (Keel et al. 2005, 2007).

Premorbid overweight conditions have also been associated with the development of PD (Keel 2019), while the current BMI of patients with PD could be linked to ED severity, in terms of using more extreme weight control methods (Krug et al. 2020). Diagnostic crossover between BN, BED, and PD appears rare in adult groups (Fairburn et al. 2000; Keel et al. 2005), but it is more frequent for BED and PD than for BN in the adolescence (Stice et al. 2013).

Individuals with PD report an impaired quality of life in the physical, psychological, and social domains (Forney et al. 2021). They also exhibit high levels of general psychopathology and emotional distress (Keel et al. 2008; Krug et al. 2021), similar to BN and AN (Tasca et al. 2012). Notably, PD shows elevated mortality and suicide rates (Koch et al. 2013, 2014), as well as frequent comorbidity with psychiatric disorders such as anxiety disorders, depression, compulsive behaviors (such as skin-picking, non-suicidal self-injury, hair-pulling, and compulsive exercise), impulsive behaviors (such as aggression, alcohol use, and drug use), and some personality disorders (i.e., obsessive-compulsive, borderline, and avoidant personality disorder)

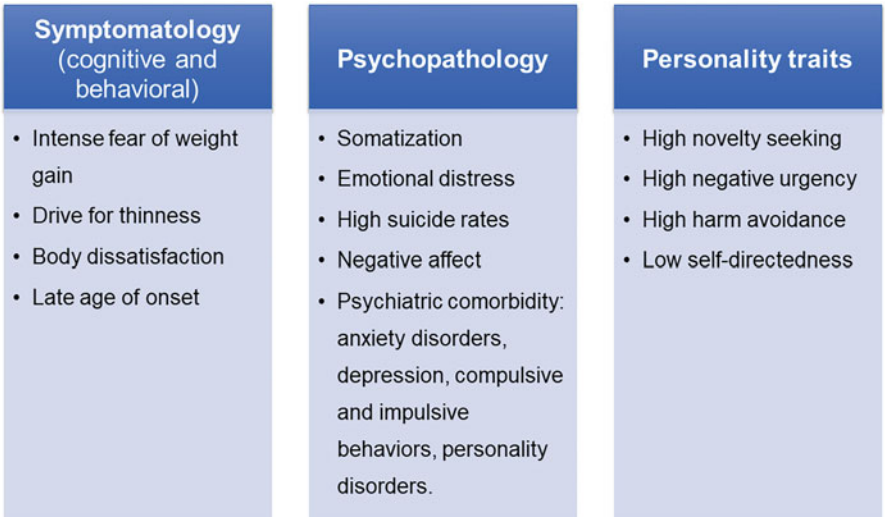


Fig. 2 Clinical profile of purging disorder. This figure shows the main eating-related, psychopathological, and personality features of purging disorder

(Keel 2007; Keel et al. 2008; Smith et al. 2017; Balasundaram and Santhanam 2022). In comparison with BN, PD has been associated with lower levels of lifetime mood disorders, but higher rates of current anxiety disorders (Keel et al. 2008). However, in both EDs, purging behavior would act similarly as a regulator of negative affect (Haedt-Matt and Keel 2015; Smith et al. 2017).

Regarding personality traits, individuals with PD usually present dysfunctional personality traits, characterized by both high novelty seeking/negative urgency and harm avoidance, and low self-directedness (Davis et al. 2020). However, compared to BN or BED, PD reports lower prevalence of impulse control disorders and lower levels of impulsivity, as well as higher levels of self-esteem (Keel et al. 2011; Smith et al. 2017; Davis et al. 2020). Furthermore, although BN and PD share clinical features, some mechanisms underlying these characteristics might be different. For example, while purging behaviors in PD are associated with anxiety-related traits, in BN, however, they are linked to more impulsive traits (Brown et al. 2011) (Fig. 2).

Medical Complications for Purging Behaviors

Purging behaviors present in PD contribute to aggravating and/or triggering medical complications at different levels, but the individual premorbid somatic conditions in each case must be considered (Forney et al. 2016). Many of these medical disturbances are shared by different ED (e.g., AN, BN), especially those derived from vomiting or misuse of laxatives/diuretics. In this line, medical problems across body systems include metabolic and electrolyte disturbances (e.g., dehydration, hypokalemia), gastrointestinal affection (e.g., inflammation, functional dysregulation, bleeding, intestinal obstruction),

musculoskeletal and bone consequences (e.g., skeletal muscle weakness, rhabdomyolysis, osteomalacia, bone fracture), and cardiovascular damage (e.g., heart muscle affection, tachycardia, hypotension), among others (Smith et al. 2017; Keel 2019; Balasundaram and Santhanam 2022). Specifically, vomiting is associated with oral and dental damage (e.g., erosions, ulcers, bleeding), gland problems (e.g., parotid sialadenosis), blood affection (e.g., facial purpura, subconjunctival hemorrhages), and gastrointestinal mucosal irritation and reflux. Typically, Russell's sign (characterized by lesions on the hands in the context of skin scraping against teeth) has been described among patients with self-induced vomiting. On the other hand, the abuse of purging products (i.e., laxatives) is linked to interference with insulin secretion and acute hepatic failure, altered bowel habit, seizures, and renal disturbances (e.g., inflammation, calcium deposits). Interestingly, some of the described complications are closely associated with the electrolyte imbalance (i.e., hypokalemia) derived from purging behaviors, such as prolonged QT intervals in patients with self-induced vomiting or a characteristic arrhythmia called "torsade de pointes" in the cases of laxative abuse. Regarding the presence of the different purging behaviors among patients with PD, the study by Krug et al. (2020) differentiated three clinical clusters: Cluster 1 (only self-induced vomiting), Cluster 2 (self-induced vomiting and laxative use), and Cluster 3 (all the methods). In this vein, the latest cluster was associated with a more severe clinical profile, and this may lead to greater medical complications (Fig. 3).

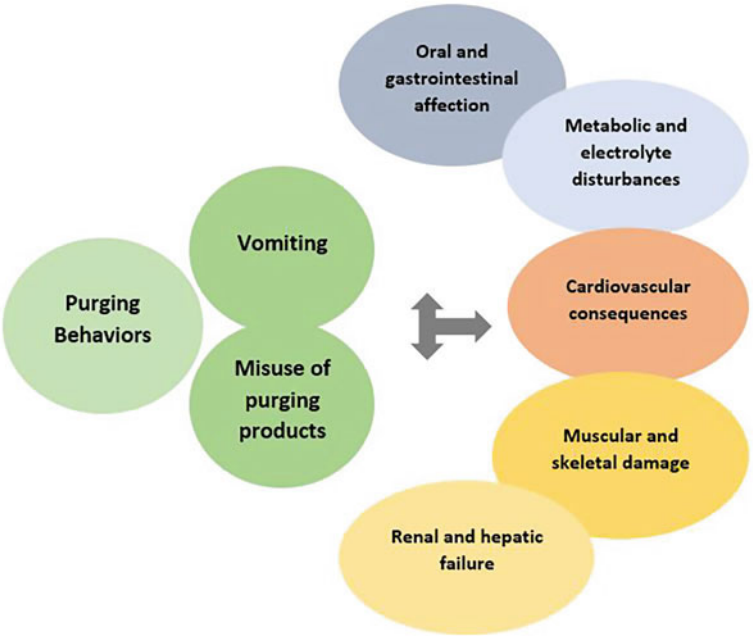


Fig. 3 Medical complications. Medical complications in purging disorder affect different body systems and are mostly related to purging behaviors

Treatment Approaches

The management of PD is similar to that for BN. The treatment strategies should address cognitive and behavioral symptoms, comorbid psychopathology, and psychosocial aspects, as well as the acute and chronic medical complications arising from purging behaviors (Forney et al. 2016; Balasundaram and Santhanam 2022). However, a major limitation in the literature is that no controlled trials (RCTs) have examined specific treatment protocols for PD so far, and usually those ED subtypes have been excluded from RCTs (Murray and Anderson 2015).

Medical and Pharmacological Approach

Considering the medical complications cited above, the medical examination of individuals with PD should include a complete metabolic panel, a blood count, and a comprehensive body examination including the teeth to prevent serious complications (Forney et al. 2016).

Medications like antidepressants, antipsychotics, or mood stabilizers may help treat coexisting psychiatric illnesses such as anxiety or depression. Fluoxetine is the only FDA-approved drug used for the treatment of BN and BED although its use has not been approved for PD.

Cognitive-Behavioral Therapy

Cognitive-behavioral therapy (CBT) and the enhanced version of CBT (CBT-E) are the first-line treatments for adults with ED. CBT is the most empirically supported treatment for ED, including PD. The CBT-E, according to Fairburn's manual (Fairburn 2008), is an evidence-based treatment that emphasizes the core of ED-related psychopathology, such as overvaluation of body weight and shape, body image distortion, or unhealthy weight control measures. It also includes modules to address other factors that may be maintaining the ED, such as interpersonal functioning, low core self-esteem, or clinical perfectionism. Patients with PD may benefit from the CBT-E mood intolerance module. This module provides strategies for accepting the sensation of fullness and related anxiety. Exposure and response prevention techniques may also be helpful in avoiding purging after eating. These approaches can help individuals with PD learn to reinterpret bodily sensations and satiety cues as a natural part of the digestive process. In the last sessions, relapse prevention is addressed. In addition, growing evidence suggests the convenience of focusing on targets aimed at learning emotional regulation skills from the first sessions of CBT (MacDonald et al. 2017b; MacDonald and Trottier 2019). Additionally, psychoeducational and motivational aspects may need to be considered in the management of PD, in order to facilitate both early detection and intervention to diminish the duration of the disorder (Fernández-Aranda et al. 2021) (Table 1).

Table 1 Evidence-based treatment targets for purging disorder

Evidence-based treatment targets for purging disorder	
Cognitive-behavioral therapy (CBT) *(as first-line treatment approach)*	Eating disorder-related psychopathology
	Interpersonal functioning
	Low self-esteem and clinical perfectionism
	Emotional regulation skills
	Teaching strategies for accepting the sensation of satiety and related anxiety
	Exposure and response prevention techniques for avoiding purging after eating
Additional therapy goals	Enhancing motivation
	Psychoeducation
Medical management	Blood test and complete metabolic examination
	Dental examination
	Complete body examination
Pharmacological treatment	Antidepressants[a], antipsychotics, or mood stabilizers for comorbid psychiatric illnesses

[a]Fluoxetine has been approved for bulimia nervosa, but not yet for purging disorder

CBT Outcome for Purging Disorder

Little is known about the treatment outcome of PD. The literature in this topic is still scarce and controversial. Moreover, recent research reports inconsistent remission rates in this clinical population, ranging from 45% (Ekeroth et al. 2013; Riesco et al. 2018) to 95% (Stice et al. 2013). Reported recurrence rates range from 5% to 6% (Stice et al. 2009, 2013). This relapse rate is lower for PD than for other EDs, suggesting that the maintenance processes of purging behaviors may be weaker in this disorder (Stice et al. 2013). Long-term follow-up studies show that at 10 years of follow-up, 30% meet criteria for full recovery (Forney et al. 2021).

Likewise, the few studies comparing treatment outcomes with other EDs also reveal conflicting results, due to heterogeneous samples. While some studies find similar remission rates with other OSFED types or with full ED syndromes (Keel et al. 2005; Tasca et al. 2012; Ekeroth et al. 2013; Riesco et al. 2018), others find a better prognosis of PD compared to AN (Smith et al. 2017). In this vein, specific personality traits such as higher harm avoidance, persistence, and self-directedness have been associated with greater remission rates after a CBT treatment (Riesco et al. 2018). Likewise, it has been shown that training in emotion regulation strategies from the first CBT sessions can be beneficial for patients, with even better outcomes at 6-month follow-up after treatment (MacDonald et al. 2017b; MacDonald and Trottier 2019). In addition, CBT intervention with emotional regulation techniques appears to be associated with a more rapid response to treatment compared to motivational interviewing (MacDonald et al. 2017a).

Regarding treatment adherence, PD shows high dropout rates, even higher than those of other EDs. It has been suggested that PDs are less motivated and have less

illness perception than full syndromes. Specifically, in these patients, the risk of dropping out therapy has been associated with a personality profile characterized by lower scores on harm avoidance, reward dependence, and self-directedness (Riesco et al. 2018).

Applications to Other Eating Disorders

In this chapter, we have reviewed purging disorder (PD) and its treatment outcome following cognitive-behavioral therapy (CBT). First, the need to study PD as a diagnostic entity and not just as a phenotype within other specified feeding or eating disorder (OSFED) has been highlighted. This review has revealed that PD presents distinctive and no less severe features than other DSM-5 full syndromes such as anorexia nervosa (AN), bulimia nervosa (BN), or binge eating disorder (BED). In this vein, these findings could be extrapolated to reinforce the interest in further examining other subtypes of OSFED such as atypical AN, subthreshold BN, subthreshold BED, or night eating syndrome, mainly the latter. Identifying the intrinsic characteristics, the clinical significance, and the distinctiveness of the diagnostic phenotypes, beyond considering them as subthreshold subtypes, justifies the intervention. In addition, it is important to identify significant differences in severity between different EDs, full or partial syndromes, to warrant appropriate treatments. Controlled trials examining specific treatment protocols are also needed, not only for PD but also for other less studied specified and non-specified ED diagnostic subtypes. In conclusion, understanding the functional nature of purging behaviors in PD and other clinical features of other less studied ED may improve their characterization in future diagnostic systems, as well as their prevention and intervention modalities.

Mini-Dictionary of Terms

- ***Other specified feeding or eating disorders (OSFED)***. A diagnostic category that encompasses those individuals who do not meet the full diagnostic criteria for anorexia nervosa, bulimia nervosa, or binge eating disorder but who have a significant eating disorder
- ***Purging behaviors.*** Compensatory behaviors to control weight and shape including self-induced vomiting or misuse of laxatives, diuretics, and/or other medications.
- ***Purging disorder.*** An eating disorder subtype characterized by purging behaviors, included in the OSFED diagnostic category
- ***Cognitive-behavioral therapy***. A treatment approach designed to recognize and address dysfunctional thoughts, emotions, and behavioral patterns
- ***Adherence.*** The degree of agreement in complying with the medical/therapeutic recommendations given by the healthcare professional

- ***Remission.*** The absence of symptoms for a sustained period (full remission). Partial remission means a substantial symptomatic improvement but with residual symptoms
- ***Dropout.*** Treatment discontinuation before the completion of a predetermined treatment program

Key Facts of Purging Disorder

Purging disorder is an eating disorder more prevalent among females with lifetime prevalence rates between 1% and 5% and up to 24% in clinical population.

Although purging disorder shares clinical features with other eating disorders, such as bulimia nervosa, its clinical significance and distinctiveness have been proven.

Medical complications in purging disorder affect different body systems, mostly shared with other eating disorders and associated with purging behaviors.

Cognitive-behavioral therapy (CBT) has been described as the first-line treatment in eating disorders, including purging disorder.

Results related to treatment outcomes to CBT in purging disorder are scarce and inconsistent. However, emotion regulation and exposure and response prevention strategies might be key therapeutic target in the treatment of this disorder.

Higher dropout rates have been described in purging disorder compared to other eating disorders, which has been associated with specific personality traits.

Summary Points

- Purging disorder is a clinically significant and distinctive disorder
- Purging disorder lifetime prevalence rates range from 1.1% to 5.3% among general population and up to 24% in clinical settings
- Medical disturbances in purging disorder are mostly shared by different eating disorders, especially those derived from self-induced vomiting or the abuse of purging products
- Like bulimia nervosa, cognitive-behavioral therapy is the first-choice treatment for adults with purging disorder
- Although results related to treatment outcome of purging disorder are scarce and inconsistent, cognitive-behavioral therapy intervention with emotional regulation and exposure and response prevention techniques seems to be associated with positive treatment outcomes
- High dropout rates among patients with purging disorder may be associated with some personality traits (i.e., low scores on harm avoidance, reward dependence, and self-directedness) and with limited motivational aspects

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Purging Disorder

58

Impact on Diet and Nutritional Status

Sarrah I. Ali, Sophie R. Abber, and Pamela K. Keel

Contents

Introduction 1158
Definition of Purging Disorder 1158
Prevalence and Age of Onset 1159
Biological Correlates 1160
Summary 1161
Effects of Dietary Restraint 1161
What Is Dietary Restraint? 1161
Micronutrient Deficiencies Associated with Dietary Restraint 1162
Macronutrient Deficiencies Associated with Dietary Restraint 1163
Effects of Purging 1163
Nutritional Consequences of Self-Induced Vomiting 1163
Nutritional Consequences of Laxative Misuse 1164
Nutritional Consequences of Diuretic Misuse 1165
Role of the Dietitian 1165
Conclusion 1168
Applications to Other Eating Disorders 1168
Mini-Dictionary of Terms 1169
Key Facts of Purging Disorder 1169
Summary Points 1169
References 1170

Abstract

Purging disorder is an eating disorder characterized by recurrent purging behaviors in the *absence* of objectively large binge-eating episodes in individuals who are not underweight. These purging behaviors are used to forcefully evacuate matter from the body to influence shape or weight and include self-induced vomiting and laxative, enema, diuretic, and medication misuse. Although purging is the central feature of the disorder, the illness is also characterized by high levels

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of dietary restraint, whereby individuals limit the overall amount of food they eat, purposely go long periods of time without eating, and/or exclude foods from their diet as a means of influencing shape or weight. This chapter reviews the serious nutritional consequences associated with dietary restraint, self-induced vomiting, laxative misuse, and diuretic misuse and outlines the important role that dietitians may play in the treatment of purging disorder.

Keywords

Purging disorder · Diet · Nutrition · Dietary restraint · Vomiting · Laxatives · Diuretics · Macronutrients · Micronutrients · Vitamins · Carbohydrates · Fat · Protein · Vitamins · Minerals

Abbreviations

BMI	Body mass index
CCK	Cholecystokinin
GLP-1	Glucagon-like peptide 1
OSFED	Other specified feeding or eating disorder
PYY	Peptide tyrosine tyrosine

Introduction

Definition of Purging Disorder

Purging disorder is an eating disorder characterized by recurrent purging behaviors in the *absence* of objectively large binge-eating episodes in individuals who are not underweight. These purging behaviors are used to forcefully evacuate matter from the body as a means of influencing shape or weight and include self-induced vomiting and laxative, enema, diuretic, and medication misuse. Within the fifth edition of the *Diagnostic and Statistical Manual of Mental Disorders*, purging disorder is a specified condition included under the other specified feeding or eating disorder (OSFED) category (American Psychiatric Association 2013).

Purging disorder may be confused with other eating disorders such as anorexia nervosa and bulimia nervosa. Though there are some overlapping features between purging disorder and each of these disorders, respectively, it is a distinct condition (see Fig. 1). Purging disorder differs from bulimia nervosa in three ways. First, objectively large binge-eating episodes are a central feature of bulimia nervosa and do not occur in purging disorder. Second, although purging may occur in bulimia nervosa, it is not required. Individuals with bulimia nervosa may compensate for binge eating through fasting or excessive exercise. Neither of these constitute purging behaviors. Third, individuals with purging disorder may experience a loss of control over their eating, but this is not required for a diagnosis of the disorder, whereas loss of control is a required aspect of binge eating in bulimia nervosa. Purging disorder differs from anorexia nervosa in several ways. First, medically low

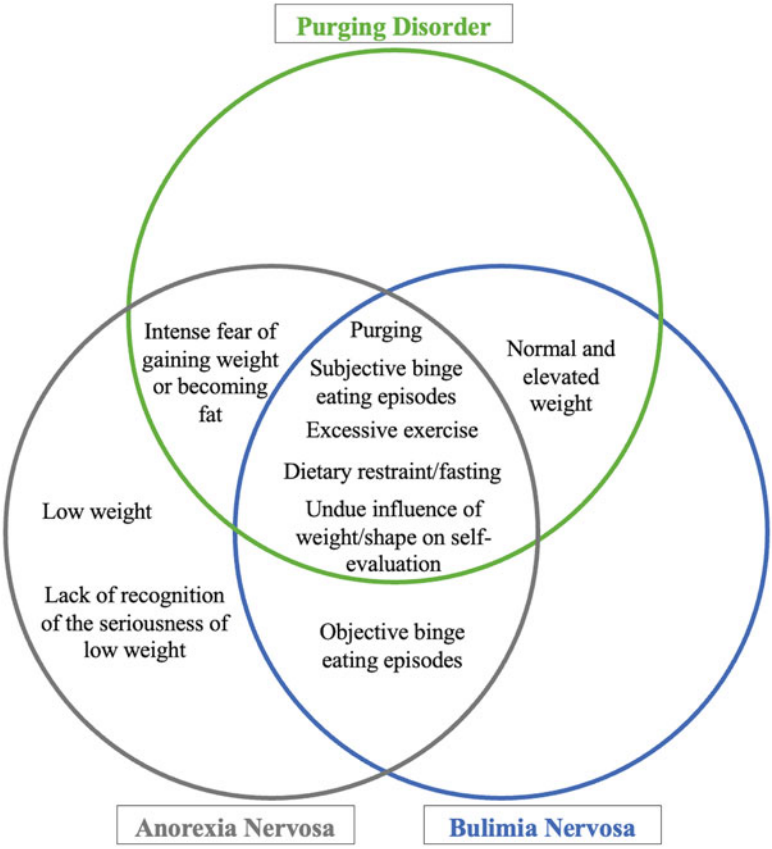


Fig. 1 Features of purging disorder, bulimia nervosa, and anorexia nervosa. This figure shows the overlapping and distinct features of bulimia nervosa, anorexia nervosa, and purging disorder

weight is a central feature of anorexia nervosa and is absent in those with purging disorder. In addition, although individuals with anorexia nervosa may engage in purging, this is not required for a diagnosis. Further, individuals with anorexia nervosa may engage in objectively large binge-eating episodes, and these do not occur in those with purging disorder for whom purging occurs after normal or small amounts of food.

Prevalence and Age of Onset

Studies examining the lifetime prevalence of purging disorder have reported estimates ranging from 1.1% in adult women (Favaro et al. 2003) to 6.2% in adolescent girls (Glazer et al. 2019). These differences may reflect secular changes that have been found for bulimia nervosa (Hudson et al. 2007; Kendler et al. 1991) and may

suggest that the disorder is becoming increasingly common in more recent birth cohorts. Alternatively, differences in assessment method or retrospective recall of conditions may account for this range (Moffitt et al. 2010). The prevalence of purging disorder does appear to be greater in adolescent girls and women than in adolescent boys and men (Mitchison et al. 2020; Keel 2020); however, it is important to note that purging disorder does occur in males. Finally, compared to bulimia nervosa and anorexia nervosa, purging disorder appears to have a later age of onset (Smith et al. 2017), with one study indicating peak age of onset between 18 and 20 years (Stice et al. 2009).

Biological Correlates

Despite purging and dietary restraint, individuals with purging disorder are not underweight. Recent findings suggest that this may reflect elevated premorbid body mass index (BMI). Specifically, Yilmaz et al. (2019) found that children who went on to develop purging disorder later in their lives had significantly higher BMIs by age 6 for boys and age 5 for girls, compared to children who did not go on to develop an eating disorder. Notably, this difference in BMIs between groups continued over time.

Although purging and dietary restraint do not produce a medically low weight in purging disorder, they may produce weight loss and maintenance of a weight below premorbid body weight (i.e., weight may be *suppressed*). Weight suppression is defined as the difference between one's highest prior adult weight and their current weight (Lowe 1993), and it has been shown to predict future onset of purging disorder (Stice et al. 2020). Weight suppression has also been identified as a predictor of illness maintenance in bulimic syndromes, including purging disorder (Keel and Heatherton 2010; Bodell et al. 2017). This association is mediated by heightened drive for thinness (Bodell et al. 2017).

Research has revealed several differences in biological responses to food among groups of women with purging disorder, women with bulimia nervosa, and women without eating pathology (Keel et al. 2007, 2018; Jimerson et al. 2010; Dossat et al. 2015). Compared to women without eating disorders, both the purging disorder and bulimia nervosa group have demonstrated elevated levels of ghrelin (Keel et al. 2018), a hormone which triggers hunger, and lower levels of leptin (Jimerson et al. 2010), a hormone that modulates energy balance in the body. These findings may reflect consequences of elevated dietary restraint and evidence of weight suppression in both groups and contribute to an increased drive to eat and feeling that eating is out of control.

In response to a standardized meal, women with bulimia nervosa have demonstrated significantly lower cholecystokinin (CCK) and glucagon-like peptide 1 (GLP-1) responses, hormones that signal the brain to stop eating a meal (Keel et al. 2018), compared to healthy women and women with purging disorder. This finding may contribute to excessive food intake in bulimia nervosa compared to

purging disorder and healthy eating. Finally, in response to a standardized meal, women with purging disorder demonstrated significantly greater increases in a hormone called peptide tyrosine tyrosine (PYY) compared to the other groups. This hormone signals the brain to delay onset of a subsequent meal, and the differences in this hormone predicted the differences in gastrointestinal distress across groups (Keel et al. 2018). Intact CCK and GLP-1 satiation signals combined with *excessive* PYY responses could help to explain why individuals with purging disorder do not consume an excessive quantity of food but feel as if they have eaten too much (Keel et al. 2018).

Summary

Purging disorder is an eating disorder that shares features with both bulimia nervosa and anorexia nervosa but represents a distinct constellation of symptoms. Similar to other disorders of eating, purging disorder is most commonly observed in women and girls, but it can affect men and boys. Unique biological correlates may account for purging in the absence of objectively large binge episodes among individuals who maintain a minimally healthy body weight. The remainder of this chapter will discuss the serious negative impact purging disorder can have on diet and nutritional status, specifically outlining how levels of nutrients (i.e., carbohydrates, fat, protein, water, vitamins, and minerals) may be altered by this disorder. Additionally, the important role that dietitians may play in the treatment of purging disorder will be outlined.

Effects of Dietary Restraint

What Is Dietary Restraint?

Dietary restraint includes behaviors such as limiting the overall amount of food one eats, purposely going long periods of time without eating (i.e., fasting), and excluding certain foods from one's diet as a means of influencing shape or weight. Individuals with purging disorder report dietary restraint at a level equal to or exceeding the levels of dietary restraint observed in other eating disorders. A review of purging disorder through meta-analysis revealed that individuals with purging disorder endorsed significantly greater dietary restraint compared to individuals with anorexia nervosa and binge-eating disorder and did not differ significantly from those with bulimia nervosa (Smith et al. 2017). Given differences in body mass index observed across eating disorders, self-reported differences between purging disorder and anorexia nervosa may not represent differences in actual food intake, particularly if those with anorexia nervosa underreport their symptoms. Despite this, it is clear that purging disorder involves elevated dietary restraint, which has negative consequences for nutritional status.

Micronutrient Deficiencies Associated with Dietary Restraint

Studies of micronutrient deficiencies in eating disorders characterized by food restriction elucidate potential nutritional consequences in purging disorder (see Table 1 for a summary of the vitamin deficiencies potentially associated with dietary restraint and purging). Specific micronutrient deficiencies linked to dietary restraint in eating disorders include calcium, iron, folic acid, vitamin A, vitamin B12, vitamin C, thiamine, vitamin D (Díaz-Marsá et al. 2017), vitamin B6 (Rock and Vasantharajan 1995), vitamin E, copper, and zinc (Humphries et al. 1989; Ross 2007; see Table 2 for a summary of the mineral deficiencies potentially associated with dietary restraint and purging). Each of these micronutrient deficiencies can have

Table 1 Potential vitamin deficiencies associated with purging disorder

	Dietary restraint	Self-induced vomiting	Laxative misuse	Diuretic misuse
A	X		X	
B1 (thiamine)	X	X		X
B6	X			X
B9 (folic acid)	X		X	X
B12	X			
C	X			X
D	X	X	X	
E	X		X	X
K		X	X	

This table summarizes vitamin deficiencies associated with dietary restraint, vomiting, laxative use, and diuretic use generally and thus represents possible vitamin deficiencies associated with purging disorder

Table 2 Potential mineral deficiencies associated with purging disorder

	Dietary restraint	Self-induced vomiting	Laxative misuse	Diuretic misuse
Calcium	X	X	X	X
Copper	X			
Iron	X		X	
Magnesium		X		X
Manganese		X		
Phosphorus			X	
Potassium		X	X	X
Sodium		X	X	X
Zinc	X	X		X

This table summarizes mineral deficiencies associated with dietary restraint, vomiting, laxative use, and diuretic use generally and thus represents possible mineral deficiencies associated with purging disorder

different adverse effects. For example, a short-term B12 deficiency may cause fatigue, and a thiamine deficiency may exacerbate psychiatric symptoms, including depression and anxiety (Setnick 2010; Hart 2016). Individuals with purging disorder endorse elevated depression and anxiety (Keel et al. 2008), and micronutrient deficiencies should be considered as a potential underlying factor. As such, it is important for medical professionals to monitor potential micronutrient deficiencies in patients with purging disorder and consider nutritional supplements to address them.

Macronutrient Deficiencies Associated with Dietary Restraint

In addition to micronutrient deficiencies, individuals with eating disorders characterized by dietary restraint may also experience deficiencies in macronutrients (Reiter and Graves 2010) which include carbohydrates, fat, protein, and water. Carbohydrates are an important source of energy (Herrin and Larkin 2013), and insufficient carbohydrate consumption can have negative consequences such as muscle breakdown (Hart 2016). Insufficient fat consumption can lead to problems such as impaired growth and problems with reproduction (Jones and Rideout 2014; Hart 2016). Finally, protein deficiency can impair growth and contribute to problems with immune function (Wu 2009; Hart 2016). As with micronutrient deficiencies, it is important for medical professionals caring for individuals with purging disorder to monitor and treat potential macronutrient deficiencies.

Effects of Purging

Purging behaviors include self-induced vomiting, laxative/enema misuse, diuretic misuse, and medication misuse for the purposes of weight control. While each method of purging may be associated with a unique set of nutritional consequences, all methods can produce dehydration. Importantly, some individuals who engage in purging use multiple methods (Haedt et al. 2006), which may compound adverse effects on nutritional status. The following section will focus on the nutritional effects of self-induced vomiting, laxative misuse, and diuretic misuse.

Nutritional Consequences of Self-Induced Vomiting

Self-induced vomiting is the most commonly used method to evacuate matter from the body in purging disorder (Keel 2020; Forney et al. 2014). Self-induced vomiting is performed by stimulating the back of the throat to induce gagging, which causes the abdominal walls to contract and expel stomach contents such as food, fluids, and stomach acid. Over time, some individuals may gain the ability to vomit without physically stimulating the back of the throat (Mehler 2011). When an individual consumes food and then engages in self-induced vomiting, some of the food is

expelled from the stomach and thus never reaches the small intestine where the majority of nutrients are absorbed. Therefore, frequent self-induced vomiting contributes to nutrient deficiencies.

Both low potassium and low sodium have been directly linked to self-induced vomiting in individuals with eating disorders (Forney et al. 2016; Rock and Curran-Celentano 1996). Repeatedly engaging in self-induced vomiting causes the kidneys to eliminate potassium from the blood, which can result in hypokalemia (low potassium; Keel 2020). Self-induced vomiting also produces dehydration, which causes the kidneys to eliminate sodium, potentially resulting in hyponatremia (low sodium; Keel 2020). A retrospective chart analysis found that individuals with bulimia nervosa had significantly lower magnesium, manganese, zinc, calcium, potassium, ferritin, and vitamin D compared to individuals without eating disorders (Barron et al. 2017). Although these deficiencies cannot be solely attributed to self-induced vomiting (i.e., they could be a result of dietary restraint and/or other methods of purging), they do indicate *potential* nutritional consequences of self-induced vomiting which may be relevant to purging disorder.

Research on the effects of frequent vomiting in other conditions may generalize to effects of frequent self-induced vomiting. For example, frequent vomiting in the context of hyperemesis gravidarum (a disorder characterized by severe, persistent vomiting during pregnancy) has been linked with thiamine and vitamin K deficiencies (London et al. 2017). Severe, frequent vomiting in hyperemesis gravidarum and cyclic vomiting syndrome is associated with electrolyte imbalances, particularly hypokalemia (Lacy et al. 2018).

Nutritional Consequences of Laxative Misuse

Laxatives are used to eliminate stool from the body. There are several types of laxatives: bulk-forming, osmotic, lubricant, stool softeners, and stimulant. Bulk-forming laxatives (e.g., psyllium, methylcellulose) are fiber-based and work by absorbing additional liquid into the intestines in order to form a softer and bulkier stool. Osmotic laxatives (e.g., milk of magnesia, magnesium citrate) also increase fluid in the intestine to soften the stool. Lubricant laxatives (e.g., mineral oil) lubricate the stool allowing it to pass more easily through the intestines. Stool softeners (e.g., Colace) increase the amount of water in the stool. Finally, stimulant laxatives (e.g., senna, bisacodyl, castor oil) stimulate muscle contractions to move stool through the intestines more quickly. Bulk-forming laxatives and stool softeners work over the course of 1–3 days, while osmotic laxatives, lubricant laxatives, and stimulant laxatives typically produce a bowel movement within hours.

Stimulant laxatives are the most frequently misused among individuals with eating disorders (Roerig et al. 2010). Misusing stimulant and osmotic laxatives can result in the malabsorption of nutrients (Bo-Linn et al. 1983), by speeding passage of nutrients through the intestine too quickly for proper absorption. Fat-soluble vitamin deficiencies are a common result of laxative misuse (Anderson et al. 1997; Baker and Sandle 1996). Laxative misuse has also been linked with dehydration and low levels

Table 3 Potential nutrient deficiencies linked to laxative type

Laxative type	Potential deficiency
Bisacodyl (stimulant laxative)	Potassium
Magnesium hydroxide (osmotic laxative)	Iron Phosphate Folic acid
Mineral oil (lubricant laxative)	Beta-carotene Calcium Phosphorus Potassium Vitamin A Vitamin K Vitamin D Vitamin E

This table provides examples of specific nutrient deficiencies that have been linked to different types of laxatives

of potassium and sodium given that a significant amount of fluid and minerals are lost through diarrhea. Laxatives generally have been linked with specific nutrient deficiencies depending on the type used (see Table 3 for examples of potential nutrient deficiencies associated with specific laxative types; Moss 2007). These include deficiencies in iron, phosphate, folic acid, beta-carotene, calcium, phosphorus, vitamin A, vitamin K, vitamin D, and vitamin E (Moss 2007).

Nutritional Consequences of Diuretic Misuse

Diuretics increase urination to reduce water weight. Individuals with purging disorder may abuse prescription diuretic medications meant to treat high blood pressure (e.g., thiazides, furosemide), or they may use other agents that have diuretic effects (e.g., dandelion, caffeine). As with self-induced vomiting and laxative misuse, frequent diuretic misuse may lead to dehydration and electrolyte imbalances, particularly with regard to sodium, potassium, and calcium (Keel 2020). Diuretic misuse also often leads to deficiencies in magnesium, zinc, vitamin B1, vitamin B6, vitamin C, vitamin E, and folic acid (Moss 2007).

Role of the Dietitian

Dietitians can play an important role in treating purging disorder, similar to their role in the treatment of other eating disorders (Reiter and Graves 2010; Jeffrey and Heruc 2020; Heruc et al. 2020a; see Table 4 for a summary of their role). The scope of a dietitian's practice includes but is not limited to providing education on the importance of nutrition for overall well-being, correcting false beliefs about nutrition and weight, aiding in meal planning and the development of treatment goals, and treating nutritional deficiencies through use of nutritional supplements (Reiter and Graves

Table 4 Summary of the role of the dietitian

Key role of the dietitian
Recognize possible signs and symptoms of eating pathology
Recommend referrals to other clinicians and specialists (e.g., primary care physicians, psychologists, psychiatrists)
Debunk weight loss myths and fad diets
Recommend dietary supplements
Aid in meal planning
Aid in the development of treatment goals
Provide general nutrition education

This table summarizes the important role dietitians can play in the treatment of purging disorder

2010; Ozier and Henry 2011; Herrin and Larkin 2013). It is recommended that dietitians participate as a part of a larger, multidisciplinary team (Ozier and Henry 2011; Thomas 2000), rather than attempting to treat eating disorders alone. Their support may be most beneficial for patients with nutritional complications, for those at high risk of refeeding syndrome, and for those with comorbid conditions that may impact nutritional recommendations (e.g., diabetes, food allergies, inflammatory bowel disease; Heruc et al. 2020b).

Peebles et al. (2017) developed and tested an inpatient nutrition rehabilitation protocol that may be of interest to dietitians treating children or adolescents with eating disorders as part of a multidisciplinary team in an inpatient setting. This protocol provides details on how to determine developmentally appropriate clinical goal weights as well as calorie intake goals to promote weight restoration. Of note, clinical goal weights are based on the examination of the patient's premorbid historical growth curves (where the aim is to return to their premorbid growth trajectory), and it takes into consideration the patient's current pubertal stage, their cognitions, and their growth potential (Peebles et al. 2017).

In their book *Nutrition Counseling in the Treatment of Eating Disorders*, Herrin and Larkin (2013) emphasize the importance of nutrition counselors educating patients about "biologically appropriate weight," meaning a genetically predetermined bodyweight that is comfortably and easily maintained when not engaging in disordered eating behaviors (Herrin and Larkin 2013). According to Herrin and Larkin, a biologically appropriate weight is also consistent with premorbid weight. Herrin and Larkin recommend explaining to patients what biologically appropriate weight is and potential signs that a biologically appropriate weight has been achieved. These signs include no longer experiencing disordered eating behaviors, regular menses for biological females and normal testosterone levels for biological males, sufficient energy, and adequately consuming food in response to feelings of hunger and feelings of fullness (Herrin and Larkin 2013). The authors also provide more specific potential indicators of biologically appropriate weight that can be discussed with patients. These include a weight that is at least 10 to 20 pounds heavier than one's weight at high school graduation, a BMI between 20 kg/m^2 and 30 kg/m^2 for female adults, a BMI between 25 kg/m^2 and 35 kg/m^2 for male adults, and for children/adolescents, a weight between the 25th and 85th

percentile that is also consistent with their growth curve (Herrin and Larkin 2013). Although potentially challenging, helping individuals come to accept that there is a wide range of weights that can be considered biologically appropriate and that their own biologically appropriate weight may be higher than their current weight (or a weight that is promoted by one's family or culture) can be an important part of eating disorder treatment.

Dietitians may be the first healthcare professional consulted by an individual with purging disorder, making it important that they recognize possible signs and symptoms of eating disorders (Reiter and Graves 2010; Herrin and Larkin 2013). Because purging disorder can occur in any individual regardless of sex, gender, age, race, or ethnicity, universal screening for eating disorders is recommended. Dietitians should routinely assess for eating disorders in patients who have recently gained or lost a significant amount of weight, have significant concerns about body shape or weight, are adhering to restrictive diets (whether self-imposed or due to medical conditions like celiac disease or irritable bowel syndrome), report gastrointestinal symptoms, or participate in activities that are sensitive to weight or require meeting a specific weight criterion (e.g., dancers, figure skaters, wrestlers; Heruc et al. 2020a). In cases where a dietitian suspects an untreated eating disorder, they may begin by recommending referral to a primary care physician for bloodwork, including a work-up of electrolytes, manganese, phosphate, ferritin, vitamin B12, vitamin D, cholesterol, complete blood count, red cell folate, magnesium, and zinc (Barron et al. 2017). Dietitians may use lab results to inform recommendations for low-risk supplements to offset abnormalities caused or exacerbated by dietary restraint or purging, such as phosphate and B12 supplements (Barron et al. 2017).

When dietitians are the first healthcare contact, they should also refer patients for psychotherapy for their purging disorder. While providing therapy is outside the scope of a dietitian's practice, it is important for them to have a working knowledge of principles of evidence-based eating disorder treatment such as the importance of regular eating and psychoeducation surrounding the (lack of) efficacy of purging for weight control. This may require continuing education, as care of patients with eating disorders may not be adequately addressed in standard dietetic training (Heruc et al. 2020a). Dietitians should secure mutual release of information permission to coordinate the care they provide with others on a patient's treatment team, including but not limited to the primary care physician, psychotherapist, and, as relevant, psychiatrist, through regular team-based communication. Frequent communication among members of the treatment team is critical to a successful outcome.

Even after nutrient deficiencies are corrected, continued nutrition counseling may be required to address changing nutritional needs (Setnick 2010). The Australia & New Zealand Academy for Eating Disorders published extensive practice and training standards for dietitians providing eating disorder treatment to help clarify their role (Heruc et al. 2020a). These practice and treatment standards include detailed information for dietitians on how to properly screen for eating disorders; their professional responsibilities (e.g., engaging in clinical supervision); how to assess, diagnose, and treat nutritional issues; as well as how to monitor and evaluate progress made throughout intervention (Heruc et al. 2020a).

Conclusion

Purging disorder is an eating disorder characterized by recurrent purging behaviors to influence shape or weight in the *absence* of objectively large binge-eating episodes in individuals who are not underweight. Although purging is the central feature of the disorder, it is also characterized by high levels of dietary restraint. Both purging and dietary restraint have severe consequences for nutritional status that a dietitian should address as part of a multidisciplinary treatment team. When a dietitian suspects that a patient may have an undiagnosed eating disorder, an important first step may be recommending referral to a primary care physician for bloodwork, following guidelines for the medical management of eating disorders (Academy for Eating Disorders 2021). In addition to recommending low-risk supplements to offset deficiencies, dieticians have an important role to play in refuting myths about weight management, discouraging use of fad diets, and meal planning. Recently practice and training standards have been developed to clarify these important responsibilities in the care of patients with eating disorders.

Applications to Other Eating Disorders

In this chapter, the impact of purging disorder on diet and nutritional status and the role of the dietitian in treating purging disorder were reviewed. Information presented on the nutritional consequences of dietary restraint (i.e., micronutrient deficiencies, macronutrient deficiencies, and their associated effects) are applicable to eating disorders characterized by dietary restraint. Other eating disorders that involve dietary restraint include anorexia nervosa, bulimia nervosa, and other types of OSFED (e.g., atypical anorexia nervosa, bulimia nervosa of low frequency and/or limited duration). Information presented on the nutritional consequences of purging (e.g., micronutrient deficiencies, macronutrient deficiencies, electrolyte imbalances, dehydration, etc.) through self-induced vomiting, laxative misuse, and diuretic misuse is applicable to other eating disorders characterized by purging behaviors. Other eating disorders characterized by purging behaviors include bulimia nervosa, anorexia nervosa binge/purge subtype, and other types of OSFED (e.g., bulimia nervosa of low frequency and/or limited duration).

Information presented on dietitians' roles in treating purging disorder is applicable to all eating disorders. Indeed, helping to correct nutritional deficiencies, educating patients on the importance of nutrition for overall health and well-being, identifying and correcting false beliefs about nutrition, and meal planning are key aspects of the treatment of any eating disorder within the context of nutrition counselling.

Mini-Dictionary of Terms

- ***Macronutrients***. *Fat, protein, carbohydrates, and water.*
- ***Micronutrients***. *Vitamins and minerals.*
- ***Nutrients***. *Substances found in food and water that are essential for proper human development and functioning.*
- ***Other specified feeding or eating disorder***. *A specified condition in the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders that encompasses clinically significant eating pathology that does not meet criteria for full-threshold anorexia nervosa, bulimia nervosa, or binge-eating disorder.*
- ***Purging***. *A behavior used to influence shape and/or weight that forcefully evacuates matter from the body.*

Key Facts of Purging Disorder

- Purging disorder was first officially recognized and defined as an other specified feeding or eating disorder in the 5th edition of the *Diagnostic and Statistical Manual of Mental Disorders* in 2013.
- Although individuals with purging disorder do not have binge-eating episodes, they may experience a loss of control while eating small or normal amounts of food. This is called a *subjective* binge-eating episode.
- While purging disorder appears to disproportionately affect women and girls, it also affects men and boys.
- Elevated pre-illness body mass index and weight suppression predict future onset of purging disorder.
- Individuals with purging disorder report elevated levels of depression and anxiety, which may be exacerbated by nutritional deficits (e.g., thiamine deficiency).

Summary Points

- Purging disorder is characterized by recurrent purging behaviors in the absence of binge-eating episodes in individuals who are not underweight.
- Purging behaviors include self-induced vomiting and laxative, enema, diuretic, and medication misuse.
- Individuals with purging disorder often engage in dietary restraint, whereby they limit the overall amount of food they eat, purposely go long periods of time without eating, and/or exclude foods from their diet as a means of influencing shape or weight.
- Dietary restraint and purging are associated with nutritional abnormalities, including macronutrient and micronutrient deficiencies.
- Dietitians can help to treat nutritional abnormalities associated with purging disorder as part of a multidisciplinary team.

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Purging Disorder

59

Diagnostic Considerations, Mechanisms, and Treatment Implications

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Contents

Introduction 1175
Purging Disorder Defined 1176
Prevalence of Purging Disorder 1177
Impact of Purging Disorder 1177
Differences between PD and Other Eating Disorders 1178
Potential Mechanisms 1180
  Overvaluation of Body Shape and Weight 1180
  Hunger and Satiety 1181
  Emotion Dysregulation 1181
  Impulsivity 1182
Treatment Considerations 1183
Conclusion 1184
Applications to Other Eating Disorders 1185
Mini-Dictionary of Terms 1186
Key Facts of Purging Disorder 1187
Summary Points 1188
References 1188

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Abstract

Purging disorder (PD) is a potentially debilitating eating disorder that is characterized by recurrent purging behaviors including self-induced vomiting or misuse of laxatives, diuretics, or other medications to influence shape or weight in the absence of objective binge eating. Evidence is mixed as to whether PD is more, less, or equally severe relative to other eating disorders that involve purging. Some researchers have questioned whether PD should be considered a unique diagnosis at all given the mixed evidence on the specificity of PD compared to other eating disorders. Yet, PD is common with lifetime prevalence rates ranging from 4 to 6%, and up to 7% of patients who present for treatment for an eating disorder having a diagnosis of PD. PD is also associated with a number of medical and psychiatric issues. Both psychological (emotion regulation, body dissatisfaction, trait anxiety, and cognitive restraint) and biological (satiety) factors have been identified as potential mechanisms in the development and maintenance of PD. In comparison to bulimia nervosa (BN) in which purging is used specifically to compensate for food eaten during an objective binge episode, in PD, purging may represent a persistent weight control strategy. Little has been written about whether or how treatment should differ for PD based on this functional distinction. Specific treatments for PD have not been developed and compared to existing evidence-based treatments making it difficult to know if treatment outcomes could be optimized by prioritizing the specific mechanisms (e.g., cognitive restraint, trait anxiety, satiety) that drive purging in PD.

Keywords

Purging disorder · Eating disorders · Bulimia nervosa · Laxatives · Diuretics · Self-induced vomiting · OSFED · Noncompensatory purging

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Abbreviations

AN	Anorexia nervosa
AN-BP	Anorexia nervosa, binge eating/purging subtype
AN-R	Anorexia nervosa, restricting subtype
BED	Binge eating disorder
BMI	Body mass index (kg/m^2)
BN	Bulimia nervosa
BN-P	Bulimia nervosa, purging subtype
DSM	*Diagnostic and Statistical Manual of Mental Disorders*
OSFED	Other Specified Feeding and Eating Disorder
PD	Purging disorder

Introduction

Purging disorder (PD) is a potentially debilitating eating disorder that is characterized by recurrent purging behaviors to influence shape or weight in the absence of objective binge eating (*American Psychiatric Association* [*APA*] 2013). Purging behaviors include self-induced vomiting, or misuse of laxatives, diuretics, or other medications (e.g., herbal supplements, thyroid medications, appetite suppressants, etc.). Up to 7% of patients who present for treatment for an eating disorder have a diagnosis of PD (Tasca et al. 2012; Vo et al. 2017). Differential diagnosis between PD and other eating disorders that involve purging behaviors, including anorexia nervosa (AN), binge eating/purging subtype (AN-BP), and bulimia nervosa (BN), can be challenging due to overlap in symptoms. Mixed evidence as to the specificity of PD on topographical (purging type and frequency), developmental (age of onset, course of illness), and treatment (prognosis, treatment outcomes) indicators has led some researchers to question whether it should be considered a separate diagnosis from BN at all. Little is known about whether or how treatment should differ for PD based on the core mechanisms implicated in its development and maintenance. Like other eating disorders, both emotion regulation and drive for thinness have been implicated as core mechanisms. However, differences from other eating disorders have been found in psychological (impulsivity, trait anxiety, cognitive restraint) and biological (hunger and satiety) mechanisms. This chapter will review key diagnostic differences between PD and the other eating disorders. Given the topographical similarities, special consideration will be given to differential diagnosis between PD and the other eating disorders that may involve purging behaviors, namely, AN-BP and BN. Next, the chapter will review potential mechanisms that are thought to contribute to its development and maintenance. Finally, considerations for treating PD will be highlighted. Before addressing these clinical questions, the chapter will begin by briefly defining PD and then describing the scope of PD's impact including prevalence, medical comorbidities, and psychosocial impairment.

Purging Disorder Defined

Traditionally, research on eating disorders focused on the diagnoses of AN and BN. However, over the last two decades there has been increasing recognition that a broader range of eating disorders exists. PD was added to the *Diagnostic and Statistical Manual fifth Edition* (APA 2013) as a subclass of the Other Specified Feeding and Eating Disorder (OSFED) diagnostic classification. The OSFED category captures symptom presentations that are characteristic of an eating disorder but do not meet the full criteria for a full-threshold eating disorder. For instance, symptoms that are limited in duration (e.g., symptoms occurring for less than 3 months), low frequency (e.g., binge eating or purging occurring less than once a week), or atypical in presentation (e.g., significant weight loss with a body mass index within the normal range) are generally subsumed under the OSFED designation.

PD is typically defined as recurrent purging behaviors in the form of self-induced vomiting, or misuse of laxatives, diuretics, or other medications for the purpose of influencing shape or weight, and in the absence of binge eating (APA 2013). PD shares many common features with other eating disorders. Thus, differential diagnosis between PD and other eating disorders that involve purging can be particularly challenging. Since the construct of PD was first introduced, the definition has evolved to better differentiate it from other eating disorders. Early on, some advocated for the inclusion of non-purging weight control behaviors such as fasting and compulsive exercise (Favaro et al. 2003; Keel et al. 2005; Machado et al. 2007). However, the current consensus favors the narrower inclusion criteria of recurrent purging in the form of self-induced vomiting or misuse of laxatives, diuretics, or other medications occurring at least once a week in order to prevent an overly heterogeneous diagnostic category (Glazer et al. 2019; Haedt and Keel 2010; Keel 2019).

Currently, a diagnosis of PD requires that the individual not be "underweight" (differentiating it from AN), not engage in binge episodes (differentiating it from BN), and engage in body image disturbance (APA 2013; Keel and Striegel-Moore 2009; Keel 2019). However, the *DSM-5* criteria provide little guidance as to how to define "underweight" or whether the binge must be "objectively large." Unlike BN, in which purging primarily functions to compensate for objective binge eating, in PD, purging is noncompensatory, meaning it occurs after eating small or normal-sized quantities of food. Individuals with PD often experience subjective binge episodes, in which they experience a loss of control during eating episodes that are not objectively large in quantity. This has led some researchers to argue for the inclusion of loss of control as a clinically significant feature of PD that should be included in its definition (Forney et al. 2014). Differences from other eating disorders may also exist with regard to the typical method of purging used. Some evidence suggests that compared to individuals with BN, individuals with PD are more likely to use laxatives rather than vomiting as their primary method of purging (Wade 2007), although not all studies have found a difference in methods (Binford and le Grange 2005).

Prevalence of Purging Disorder

In comparison to other eating disorders, PD is relatively common. Lifetime prevalence rates of PD in population-based surveys range from 3.8% to 6.2%, which is between two to three times higher than AN (1.3%) or BN (0.75%; Glazer et al. 2019; Keel 2019; Munn-Chernoff et al. 2015). Whereas the prevalence of PD is similar in treatment seeking and population-based samples (4.5–6.7%; Tasca et al. 2012; Vo et al. 2017), AN or BN have been shown to outnumber PD by as much as 17 to 1 in inpatient treatment settings, and 6 to 1 in outpatient treatment settings (Nakai et al. 2018). As will be discussed later in this chapter, these discrepancies in prevalence rates may be due to differences in severity, such that PD may be less likely to require intervention than AN or BN. At the same time, PD can be associated with dangerous physical and psychological consequences and can be chronic and difficult to treat. This raises the question of whether PD is less likely to be detected due to the absence of objectively impairing characteristics (e.g., low weight, binge eating) that may be more likely to draw clinical attention. In contrast, because purging behaviors are typically done in secret and may be easier to conceal, they may go unnoticed unless they occur frequently enough to cause significant functional impairment or medical instability, making them all the more dangerous.

In terms of demographic characteristics, similar to AN and BN, PD is more prevalent among women and girls than boys and men (Haedt and Keel 2010; Mitchison et al. 2020), and is particularly common among adolescents and young adults. However, the peak prevalence of PD extends across a wider age range (ages 16–27 years) than AN (ages 16–18) or BN (ages 19–22; Glazer et al. 2019). PD also has a later peak age of onset (18–20 years), and shorter illness duration than either AN or BN (Smith et al. 2017). PD is associated with higher premorbid BMI as early as age five (Yilmaz et al. 2019), and PD is associated with a higher BMI than AN but a lower BMI than BN (Krug et al. 2021). Together, these demographic characteristics paint a picture of PD as more common but potentially less enduring than AN or BN.

Impact of Purging Disorder

Research widely supports conceptualizing PD as a clinically significant disorder marked by impairments in eating and a number of other life domains (see Keel and Striegel-Moore 2009 for a review). Specifically, individuals with PD may experience serious medical complications and greater social, physical, psychological, familial, and educational impairment compared to those without an eating disorder (Forney et al. 2021; Haedt and Keel 2010; Krug et al. 2020). They are more likely to have been diagnosed with a comorbid psychiatric disorder (e.g., depression, anxiety, personality, substance use, or impulse control disorder) and report greater emotional distress and suicidality than those without an eating disorder (Allen et al. 2013; Smith et al. 2017). Because of these complications, PD is associated with increased risk of mortality, particularly in those with severe illness that requires inpatient treatment (Koch et al. 2013).

In terms of medical risk, the serious and life-threatening medical complications of purging behaviors are well-documented (see Forney et al. 2016 for a review). Self-induced vomiting is associated with a host of medical problems including dental complications (gum recession and tooth erosion, pain, and lesions), gastric reflux, heartburn, and irritable bowel syndrome all caused by excess stomach acid. Dehydration from self-induced vomiting and laxative or diuretic misuse also causes imbalances in key electrolytes like sodium, chloride, and potassium, which can result in kidney failure, arrhythmias, and, ultimately, cardiac arrest. Leaching of key nutrients can also cause muscular-skeletal complications like softening of the bones, muscle weakness, and muscle tenderness. Additionally, laxative misuse can result in impaired colon motility, bowel dysfunction, chronic diarrhea, constipation, and pelvic floor dysfunction. Due to these and other severe medical risks, it is critical that patients should be educated on the warning signs of such medical complications and instructed to follow up with a medical professional immediately. Because medical issues can progress quickly, close and regular medical monitoring is critical for patients with PD.

Differences between PD and Other Eating Disorders

While the available evidence widely supports the utility of classifying PD as a clinically significant eating disorder syndrome, the data are decidedly less clear on where it falls on the spectrum of severity in comparison to other eating disorders characterized by purging behaviors. Studies that have examined comparisons between PD, AN-BP, and BN on a range of eating and non-eating related outcomes have varied widely, with some studies finding PD to be less severe on a range of indicators (purging frequency, ED psychopathology, illness course, treatment outcomes) than either AN-BP or BN and others finding it to be equivalent or more severe than one or both (see Smith et al. 2017 for a review). This variability may be due to differences in sample (adolescent vs. adult), setting (treatment-seeking vs. community), and definitions of PD that are used. Indeed, clinical characteristics of PD (e.g., treatment response, BMI, ED psychopathology) have been shown to vary based on a number of severity indicators with more frequent purging and purging via self-induced vomiting (vs. other methods) showing worse outcomes (Krug et al. 2021). In an effort to make sense of these conflicting findings, Smith et al. (2017) conducted a meta-analysis comparing PD with other eating disorders. Results suggested that despite having similar duration of illness, PD may have a later age of onset, less pervasive course, and better treatment outcomes compared to AN-BP. At the same time, those with PD had more frequent purging behaviors and higher dietary restraint compared to AN-BP. Compared to BN, individuals with PD had higher remission rates over the natural course of the illness, along with lower eating disorder psychopathology, less frequent purging, and lower body dissatisfaction (Smith et al. 2017). Several studies have also found PD to be associated with lower rates of mood disorders and suicidality than either AN-BP (Koch et al. 2013) or BN (Keel et al. 2008; Roberto et al. 2010). In contrast, other studies suggest that

comorbid mood and anxiety disorders, substance use, suicidality, and psychosocial impairment are equivalent to or greater than that seen in either AN-BP (Tasca et al. 2012) or BN (Krug et al. 2021; Wade 2007). Meta-analytically, individuals with PD appear to have higher rates of substance use and equivalent levels of depression, anxiety, and suicidality compared to individuals with AN, but lower levels of depression, and equivalent levels of suicidality, anxiety, and substance use as individuals with BN (Smith et al. 2017).

Together this evidence suggests that PD is less severe than AN-BP on most severity indicators except purging frequency and dietary restraint. This is likely attributable to the negative impact of low weight associated with AN-BP, but the greater prominence of purging as a persistent weight control strategy in PD. Likewise, PD appears to be topographically similar and less or equally severe as BN on most, if not all, indicators, which has led a number of researchers to question whether PD should be conceptualized as a distinct disorder from BN (e.g., Ekeroth et al. 2013). Data on diagnostic crossover further support this argument, with diagnostic crossover rates up to 51% for BN to PD and 24% for AN-BP to PD (Eddy et al. 2010; Glazer et al. 2019). In contrast, low crossover in the opposite direction may point to the persistence of PD (Ekeroth et al. 2013; Koch et al. 2013). Indeed, PD has been shown to have diagnostic stability over a mean follow-up period of 10.2 years, with similar long-term prognoses as AN and BN (Forney et al. 2021). These findings have led researchers to highlight that at least some transitions into PD represent partial remission from another eating disorder rather than a "true" diagnostic crossover (Eddy et al. 2010; Ekeroth et al. 2013; Koch et al. 2013).

Clearly the research on where PD stands within the spectrum of eating disorders is mixed at best and in need of further empirical attention. There are several reasons why this might be the case. First, variability in how PD has been defined across studies has likely muddied the comparisons that can be made, and inconsistencies across studies should be contextualized in light of these different definitions. Second, severity is a broad construct that has been operationalized by a variety of indicators including frequency of ED behaviors, other ED psychopathology (e.g., dietary restraint, restriction, body dissatisfaction, etc.), age of onset, length of illness, and treatment outcomes (e.g., remission, drop out, loss of diagnostic status). The multitude of indicators makes clear comparisons across eating disorders challenging, particularly given that within each disorder individuals can vary greatly on these metrics. Third, and related to this point, one consistent theme that appears to emerge from the extant literature so far is that, despite efforts to reduce diagnostic heterogeneity, PD remains a broad diagnostic category that captures a wide range of severity. In this way, community samples may paint a much less severe picture of PD than samples in which patients are purging at a frequency that warrants inpatient treatment. As an example, some data suggest that in an inpatient setting, PD has a significantly higher mortality rate than BN (but not AN; Koch et al. 2013; Koch et al. 2014). However, because few existing studies have examined mortality rates, it is not clear if this finding is limited to PD in its most severe form, or extends to all presentations of the disorder. As such, overarching statements about the relative

severity of PD compared to other eating disorders characterized by purging may be less meaningful than an assessment of severity within the disorder itself.

Potential Mechanisms

A number of researchers have advocated for retaining PD as an independent diagnosis based on the fact that PD shows unique associations with certain clinical characteristics thought to drive engagement in ED behaviors. Specifically, purging in the context of AN-BP or BN is typically a method of compensating for binge eating, and is often driven by emotion regulation, negative affect, and impulsivity. In contrast, while PD does show associations with emotion regulation, as will be reviewed below, evidence suggests that purging in PD is more likely than AN-BP or BN to be used as a pervasive weight control strategy that is also motivated by anxiety and a drive for thinness. We review the evidence for each of these potential mechanisms in relation to PD below.

Overvaluation of Body Shape and Weight

Body dissatisfaction is a known transdiagnostic risk factor of eating disorders. A core tenet of the transdiagnostic cognitive behavioral theory of eating disorders (Cooper and Fairburn 2011; Fairburn et al. 2003) is that overvaluation of body shape and/or weight drives the use of eating disorder behaviors, specifically restriction, in order to control body shape and weight. For individuals who engage in bingeing and purging, bingeing is a consequence of restriction, and purging follows to compensate for the excessive food intake, which, in turn, further fuels overvaluation of shape and weight. In this way, the presence of binge eating maintains the eating disorder cycle in AN-BP and BN by promoting overvaluation of shape and weight and dietary restriction and restraint (Fairburn et al. 2003; Tabri et al. 2015). In support of this point, research has shown that presentations of PD which include subjective binge eating episodes are associated with significantly greater body dissatisfaction and negative affect as compared to when subjective binge eating is not present (Smith et al. 2017). Consequently, binge eating may be a particularly distressing symptom for individuals with AN-BP and BN given its close association with weight gain. In the absence of binge episodes, purging may be experienced as less naturally reinforcing, which shortens the course of the illness (Smith et al. 2017).

As noted, individuals with PD tend to have histories of higher childhood weight and may use purging to control eating due to longstanding dissatisfaction with their bodies. In support of this, a prospective examination of unique risk factors for different eating disorders found that PD was predicted by both body dissatisfaction and more frequent dieting compared to AN (which was predicted by negative affect and low BMI), and compared to BN (which was predicted by body dissatisfaction and overeating) (Stice et al. 2017). Thus, although body dissatisfaction increases risk

for most eating disorders, overeating was a specific risk factor for BN, whereas dieting uniquely predicted PD.

Hunger and Satiety

Biological evidence supports the notion that PD may represent a pervasive weight control strategy that differs from the impulsively driven compensatory purging that occurs in BN. Specifically, PD has been associated with similar degrees of cognitive restraint but lower degrees of hunger, food preoccupation, and fear of losing control over eating compared to BN (Keel et al. 2005; Wade 2007). This suggests that both disorders are marked by strict dietary rules, but that in PD, the use of purging is less motivated by the hunger and preoccupation with food that appear to motivate binge eating. These findings have been replicated in experimental studies that have shown that in individuals with PD, satiety-related hormones are significantly higher compared to individuals with BN, and on par with healthy controls (Dossat et al. 2015; Keel et al. 2018). In these studies, women with BN ate significantly more in an ad libitum meal test to reach the same level of fullness as women with PD, and both groups reported significant increases in gastrointestinal distress (nausea, stomach ache, and desire to vomit). Moreover, only individuals with PD showed elevations in the postprandial gut satiety peptide, PYY, which signals to the brain to delay the start of the next meal after eating has ended. Together, these findings support the idea that individuals with BN, but not PD, experience increased hunger and decreased satiety, which might contribute to the loss of control seen in binge eating, followed by purging to compensate (Keel et al. 2018). In contrast, in PD the combination of intact satiation (i.e., fullness) and excessive satiety (i.e., desire to delay eating after last meal) may promote the urge to vomit after consumption of normal amounts of food.

Emotion Dysregulation

There is a large body of literature indicating that eating disorder behaviors in general (Stice 2002), and purging behaviors in particular, function as behavioral strategies to cope with negative emotions (Keel et al. 2005; Keel et al. 2008; Wade 2007). In such cases, purging behaviors typically represent one of multiple forms of maladaptive coping that are used to manage or modulate negative emotions, along with other eating disorder behaviors, self-injury (e.g., cutting, burning, scratching, hair pulling), substance use, and/or risky sexual behaviors. Indeed, substantial research links purging symptoms to difficulties with emotion regulation. A more comprehensive review of this work in relation to BN and PD is covered in another chapter in this volume (▶ Chap. 41, "Emotion Regulation in Bulimia Nervosa and Purging Disorder"). Briefly, certain components of emotion regulation (e.g., negative emotionality, poor emotional awareness, and nonconstructive coping with negative emotions) may interact with body dissatisfaction to explain purging in the absence of binge eating. Extensive research demonstrates that negative affect may be a

particularly salient risk factor for binge eating and purging behaviors, with ecological momentary assessment data showing that in individuals with BN, negative affect is most elevated immediately before purging, decreases after purging, and then subsequently increases again (Haedt-Matt and Keel 2011). This pattern has also been found after purging in the absence of objective binge (Smyth et al. 2007) or subjective loss of control eating (Engel et al. 2013), as well as in individuals with PD (Haedt-Matt and Keel 2015). Such findings highlight the affect regulatory function of purging. Adding to this picture, a lack of positive affect has been shown to predict purging and to decrease more slowly when purging occurs compared to when it does not (Haedt-Matt and Keel 2015). Together, these findings demonstrate the negatively reinforcing function of purging in the context of PD through the combined effects of reducing negative affect and preventing decreases in positive affect.

Impulsivity

Impulsivity is a broad construct that has been examined widely with regard to different eating disorders. BN has been shown to be more highly associated with impulsivity compared to PD, which is thought to contribute to the compensatory nature of purging in BN (Fink et al. 2009). Specifically, lower scores on facets of impulsivity such as disinhibition (Roberto et al. 2010) and negative urgency (i.e., the tendency to act rashly when distressed; Davis et al. 2020) have been shown to differentiate BN from PD. Subjective binge eating in the context of PD also appears to be associated with higher levels of impulsivity and anxiety compared to individuals with PD who do not engage in subjective binge eating (Brown et al. 2011). Facets of impulsivity may also interact with overvaluation of shape and weight to predict noncompensatory purging, explaining some of the inconsistencies in the literature on the role of body dissatisfaction and related constructs in PD.

Some evidence suggests that behavioral inhibition – a facet of impulsivity marked by the tendency to withdraw from harmful situations (broadly, the opposite of negative urgency) – moderates the relationship between overvaluation of shape and weight and noncompensatory purging. Specifically, in one study, overvaluation of weight and shape had a stronger positive association with noncompensatory purging at higher (compared to lower) levels of behavioral inhibition. In contrast, when overvaluation of weight and shape was lower, behavioral inhibition appeared to protect against engagement in noncompensatory purging (Liebman et al. 2019). In combination with the weaker association with negative urgency, this finding suggests that noncompensatory purging in the context of PD may be associated with a temperamental disposition to avoid, rather than react to harmful or anxiety-provoking stimuli. In the context of high overvaluation of shape and weight, individuals with PD may evaluate purging behaviors as less harmful than the risk of gaining weight, leading to reliance on this behavior as a weight control strategy. In contrast, when shape and weight is not a primary concern, behavioral inhibition may actually dissuade individuals from engaging in this harmful weight control strategy. This is in line with research showing that PD is particularly associated with trait

anxiety (Brown et al. 2011). Other research has documented that harm avoidance is negatively associated with treatment drop out and positively associated with full or partial remission from PD (Riesco et al. 2018). These findings suggest that that recognition of the dangers of purging may be an important motivational factor for treatment of PD, particularly when overvaluation of shape and weight is high.

Treatment Considerations

Few treatment studies have examined treatment outcomes for PD specifically, and to date, no randomized controlled trials of PD treatment have been conducted (Keel 2019). In one case series of 57 patients with PD, dropout was high (37%) and full remission by the end of treatment was low (21%; Riesco et al. 2018). This data is preliminary and needs to be replicated in randomized controlled trials before conclusive statements about treatment outcomes for PD can be made. However, while not a treatment study, at least one longitudinal study of 563 non-treatment-seeking adolescents with PD showed a similarly persistent course of PD (31%) after one or more years of follow-up (Glazer et al. 2019). Clearly, for some individuals PD can be persistent and, as reviewed above, associated with a range of psychosocial complications that can cause serious long-term impairment. Current evidence-based eating disorder treatments such as CBT-E (Fairburn et al. 2008) are effective options for eating disorders, but have not been examined for PD specifically. Thus, it is not yet known if certain adaptations may be necessary to optimize treatment gains for this disorder. Below we highlight a few key clinical recommendations that clinicians should consider when working with someone with PD.

As noted earlier, in the absence of binge episodes, patients may be less motivated to change their purging behaviors due to the greater perceived benefits of being able to control their weight. Indeed, individuals with PD tend to report lower motivation to change their symptoms, and have a greater likelihood of treatment drop out than those with full spectrum eating disorders (Riesco et al. 2018). One potential explanation for this is that they may experience less severe physical consequences of their eating disorder, and therefore may be less motivated to stop the behaviors and continue in treatment. Indeed, an early study found that PD was associated with less distress related to the eating disorder, but equivalent impairment compared to BN, suggesting that despite the impairment it causes, individuals may not experience PD as problematic (Keel et al. 2008). This may be particularly the case for less severe presentations of the disorder where physical symptoms and impairment are not motivating enough to outweigh the perceived benefits of the behavior. Moreover, even for more severe presentations, individuals may view purging as an acceptable and controllable strategy to manage weight, akin to exercise, fasting, or other dieting behaviors. Thus, recognition of the dangers of purging may be an important motivational factor for treatment of PD, particularly when overvaluation of shape and weight is high. Clinicians should educate patients on the multitude of physical and psychological risks associated with purging, as well as the fallacy that purging is an

effective and controllable dieting strategy to help them re-evaluate their cost-benefit analysis of this behavior.

Second, the research summarized in this chapter highlights an important point regarding the function of purging behaviors in the context of PD. Namely, while purging in both BN and PD serves an emotion regulatory function, in BN, purging is more commonly used as an impulsive strategy to make up for excess food intake, whereas at least for some individuals, the function of purging in PD is a persistent and controlled strategy to maintain weight. In both cases individuals may use purging to cope with distress associated with emotion regulation difficulties. However, the disorders may differ in how purging is used to manage this distress (impulsively in BN vs. planfully and persistently in PD). Although CBT-E (Fairburn et al. 2008) is designed to be transdiagnostic, it is possible, (and to date untested) whether certain modifications may be necessary to address the unique cycle of ED thoughts and behaviors that characterizes PD. For instance, while restriction may still be a primary target, treatment may also need to prioritize targeting subjective binges through education about the difference between a binge and a normal-sized eating episode. Further, treatment of PD with CBT-E may require addressing dietary restraint early in treatment to identify food rules that trigger purging episodes and identifying food and body related beliefs that fuel overvaluation of shape and weight. Finally, in recognition of the fact that the precipitants for purging are multi-determined, patients with PD may benefit from a "purging analysis" earlier in treatment to help them identify the multitude of triggers (e.g., physiological symptoms, perceived loss of control, breaking a dietary rule, emotion dysregulation) for purging.

Third, treatment should also acknowledge the unique physiological processes that underlie PD and predispose individuals to experience nausea, stomach ache, and a desire to vomit after eating normal amounts of food (Keel 2019). Components of existing evidence-based treatments like CBT-E target these symptoms through psychoeducation on fullness as a barrier to regular eating and a trigger for non-compensatory purging (Fairburn et al. 2008). However, for some patients for whom behavioral inhibition and overvaluation of shape and weight is high, psychoeducation may not be enough. In such cases, the most effective treatment may incorporate exposure exercises to build patients' tolerance for these gastrointestinal symptoms after meals, in order to ultimately reduce them. However, such clinical techniques have yet to be examined in treatment studies.

Conclusion

Purging disorder is a debilitating eating disorder that affects a sizable minority of the population and carries with it significant physical and psychological consequences. Research on PD has grown considerably over the last two decades with the extant literature largely supporting that PD is a clinically significant disorder. However,

more research is needed to better understand how PD differs from other eating disorders including if it should be considered as categorically distinct, or is better represented as a subtype of eating disorders marked by purging. Currently, the extant literature on PD is mixed at best, which may be in part because it has relied on inconsistent and shifting definitions of the PD construct. Therefore, more research is also needed to clarify and standardize the diagnostic criteria for PD in order to ensure comparability across studies. Finally, treatment studies are needed to understand how PD responds to existing interventions for eating disorders and whether modifications are needed. Existing research points to the hypothesis that treatment outcomes could be optimized if motivation, dieting mindset, and physiological symptoms associated with eating are prioritized, although this also has yet to be tested directly. Addressing these questions could significantly enhance treatment effectiveness for this disorder.

Applications to Other Eating Disorders

Purging disorder (PD) shares many clinical features with other eating disorders. Anorexia nervosa (binge eating/purging subtype; AN-BP) and bulimia nervosa (BN) share the same features of purging with PD but are separate, standalone diagnoses in the *DSM-5* (APA 2013). PD is currently classified under the Other Specified Feeding and Eating Disorder (OSFED) diagnostic category along with other eating disorders that include purging behaviors, such as BN of low frequency and/or limited duration. Even within the OSFED category, the frequency and exact type of purging required for a diagnosis of PD compared to other eating disorders characterized by purging are not clearly described in the *DSM-5*, making accurate diagnosis challenging. On top of this, diagnostic crossover is common from full-threshold eating disorders to PD, suggesting that eating disorders may be better understood as a continuum of severity rather than discrete categories. Continued research using a standard definition is needed to help differentiate between PD and other eating disorders.

PD appears to respond to leading evidence-based treatments for eating disorders; however, there may still be opportunities for adaptation to optimize treatment response. First, high diagnostic crossover between eating disorders, and particularly from full-threshold eating disorders to PD, means that ongoing assessment of symptoms is critical to ensure that treatment prioritizes the most current symptom profile. Given the similarities of PD with other eating disorders, existing evidence and knowledge can be leveraged as a starting point in understanding and treating PD. For example, adaptations to enhanced Cognitive Behavioral Therapy for eating disorders (CBT-E; Fairburn 2008) may include addressing subjective binges by reframing the perception of an eating episode as a binge, rather than conducting a "binge analysis" or identifying and managing the precipitants for binges as would be the goal for BN or AN-BP.

Mini-Dictionary of Terms

Anorexia nervosa (AN): An eating disorder characterized in the *DSM-5* (APA 2013) by restriction of food intake resulting in significantly low weight (based on age, sex, etc.), intense fears of weight gain or behaviors that interfere with weight gain, and undue influence of weight and shape on self-evaluation or disturbance in how one perceives one's weight or shape.

AN includes two subtypes: 1) **Restricting type (AN-R)**, which refers to AN without recurring binge eating or purging in the last 3 months, and 2) **Binge eating/purging type (AN-BP)**, which refers to AN with recurring binge eating *or* purging in the last 3 months (i.e., self-induced vomiting or misuse of laxatives, diuretics, or enemas).

Binge eating disorder (BED): An eating disorder characterized in the *DSM-5* (APA 2013) by objectively large binge eating episodes occurring at least once per week for 3 months. Other potential features of a binge include eating faster than usual, eating until uncomfortably full, eating when not hungry, eating alone due to embarrassment, and feeling guilty afterwards. No recurring inappropriate compensatory behaviors (e.g., purging) are present for BED.

Bulimia nervosa: An eating disorder characterized in the *DSM-5* (APA 2013) by objectively large binge eating episodes *and* recurring compensatory behaviors to prevent weight gain (e.g., self-induced vomiting; misuse of laxatives, diuretics, or other medications; fasting; or excessive exercise). *Both* binge eating and compensatory behaviors must occur at least once a week in the last 3 months. There must also be undue influence of weight and shape on self-evaluation.

Some authors (e.g., Koch et al. 2013) further specify a **BN purging subtype (BN-P)**, which is not described in the *DSM-5*. This refers to BN in which the compensatory behaviors refer to purging behaviors and *not* fasting or excessive exercise.

Objective binge eating: A discrete eating episode (e.g., within 2 hours) in which the amount of food eaten is much larger than what most people would eat in similar circumstances, and importantly there is a loss of control (e.g., feeling like one cannot stop eating).

Other Specified Feeding and Eating Disorder (OSFED): An eating disorder characterized in the *DSM-5* (APA 2013) by clinically significant or distressing eating disorder symptoms that do *not* meet full criteria for another eating disorder. Examples include purging disorder (see below), atypical anorexia nervosa, and bulimia nervosa of low frequency or duration.

Purging disorder (PD): A type of eating disorder classified under OSFED in the *DSM-5* (APA 2013) in which recurring purging behaviors (e.g., self-induced vomiting or misuse of laxatives, diuretics, or other medications) are used to influence weight or shape. Binge eating is absent.

Outside of the official *DSM-5* description, researchers have more narrowly described PD as purging in the form of self-induced vomiting or misuse of medications (as described above), at the *exclusion* of fasting and excessive exercise, with

these behaviors occurring at least once a week (e.g., Glazer et al. 2019; Haedt and Keel 2010).

Subjective binge eating: Similar to an objective binge eating episode, there is a loss of control in eating, but the amount of food is not larger or is only minimally larger than what most people would eat in similar circumstances (e.g., a regularly sized meal or snack).

Key Facts of Purging Disorder

1. PD is a subclass of Other Specified Feeding or Eating Disorder (OSFED) in the *DSM-5*.
2. PD involves purging behaviors (e.g., self-induced vomiting or misuse of laxatives, diuretics, or other medications) in the absence of binge eating.
3. Unlike BN, in which purging primarily functions to compensate for objective binge eating, purging in the context of PD is non-compensatory, meaning it occurs after eating small or normal-sized quantities of food.
4. Individuals with PD often experience subjective binge episodes, in which they experience a loss of control during eating episodes that are not objectively large in quantity.
5. Exact definitions of PD, including severity, have evolved over time which may partly explain inconsistent findings in the literature.
6. Lifetime prevalence rates of PD in population-based studies range from 4% to 6% (Glazer et al. 2019; Keel 2019; Munn-Chernoff et al. 2015).
7. Current rates of PD range from 5% to 7% in treatment seeking samples (Tasca et al. 2012; Vo et al. 2017).
8. The peak age of onset of PD is later, and duration of illness is shorter (Smith et al. 2017) than AN or BN.
9. PD is associated with a number of medical (e.g., dental complications, electrolyte imbalances, and potentially fatal organ issues; Forney et al. 2016) and psychiatric issues such as depression and anxiety (Allen et al. 2013; Smith et al. 2017).
10. PD appears to be less severe than AN-BP on most severity indicators (e.g., comorbid mood disorders and suicidality; Koch et al. 2013), except purging frequency and dietary restraint (Smith et al. 2017).
11. PD appears to be less or equally severe as BN on most severity indicators (e.g., comorbid mood and anxiety disorders, suicidality, substance use; Keel et al. 2008; Krug et al. 2021; Roberto et al. 2010; Smith et al. 2017; Wade 2007).
12. Diagnostic crossover from BN to PD (up to 51%) and from AN-BP to PD (up to 24%) is high (Eddy et al. 2010; Glazer et al. 2019), whereas the reverse is not (3–5%; Ekeroth et al. 2013; Keel et al. 2005; Koch et al. 2013).
13. Purging in PD appears to represent more of a pervasive weight control strategy that is motivated by anxiety and a drive for thinness, whereas purging in the context of AN-BP or BN is more typically a method of compensating for binge eating, and is often driven by negative affect and impulsivity.

Summary Points

1. PD is a common and debilitating form of eating disorder, and research is mixed in terms of whether or not it is more, less, or similar in severity compared to other eating disorders with purging behaviors, such as AN and BN.
2. Mechanisms of action relevant to PD include emotion regulation, body dissatisfaction, trait anxiety, and cognitive restraint and satiety.
3. More research is needed that uses consistent definitions of PD to better differentiate it from other eating disorders.
4. More research examining treatment outcomes specifically for PD is needed to inform the development and tailoring of optimal treatments for PD.
5. Potential treatment adaptations for PD include addressing motivation for eliminating purging, providing psychoeducation on the psychological and physical consequences of purging, and addressing physical symptoms that may precipitate purging.

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Body Weights and Mass and Links with Nighttime Eating

60

Cigdem Koroglu and Leslie J. Baier

Contents

Introduction 1192
Circadian Rhythm of Food Intake and Changes in Nighttime Eating 1193
Delayed Timing in NE and Its Consequences 1195
Hormone Profiles in NE 1195
Assessment of NE 1196
Effects of NE on Weight Management and Diabetes Management 1197
NE and BMI 1197
NE and Diabetes 1197
Etiology of Nighttime Eating and Links to BMI 1198
Psychological Factors 1198
Genetic Components 1198
Hypocretin Receptors and NE 1199
Applications to Other Eating Disorders 1200
Mini-Dictionary of Terms 1200
Key Facts of Night Eating Syndrome 1201
Summary Points 1201
References 1202

Abstract

Night eating syndrome is an eating disorder with the core features of evening hyperphagia and nocturnal eating. It is considered as a dysfunction of circadian rhythm which results in a dissociation between daily sleep and food intake rhythms. Out-of-phase eating can have adverse effects on the metabolism, such as increased risk of obesity and metabolic syndrome. Many studies have had outcomes supporting this view, presenting associations of nighttime eating with higher BMI, whereas other studies failed to find any association. This chapter provides an overview of the circadian rhythm of food intake and changes in

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nighttime eating and details the effects of nighttime eating on body weight and disease management in individuals with diabetes. Studies on the genetic basis of nighttime eating and the proposed mechanisms underlying this disorder are also discussed.

Keywords

Nighttime eating · Night eating syndrome · Out-of-phase eating · Food intake · Body mass index · Obesity · Circadian rhythm · Sleep · Single nucleotide polymorphism · Hypocretin receptors · HCRTR1

Abbreviations

AN	Anorexia nervosa
BED	Binge eating disorder
BMI	Body mass index
ED	Eating disorder
HCRTR1	Hypocretin receptor 1
NE	Nighttime eating
NEQ	Night Eating Questionnaire
NES	Night eating syndrome
NPY	Neuropeptide Y
SCN	Suprachiasmatic nuclei
SNP	Single nucleotide polymorphism
T1D	Type 1 diabetes
T2D	Type 2 diabetes

Introduction

Food intake and energy expenditure are the two main determinants of body weight and adiposity, the latter often measured as body mass index (BMI) (Piaggi 2019). Eating disorders (EDs) may lead to changes in body weight and BMI since they dramatically affect food intake. In fact, BMI is an important criterion for differential diagnosis of ED types. For example, bulimia nervosa may be ruled out if the patient's BMI is below a specified threshold, and instead anorexia nervosa (AN) with binge/purge subtype might be considered as the appropriate diagnosis (Treasure et al. 2020). Similarly, binge eating disorder (BED) is characterized by obesity due to the recurrent episodes of excessive food intake (Monteleone and Maj 2008). Another ED that has been gaining increased attention due to its contribution to BMI is night eating syndrome (NES).

NES was first described in 1955 by Albert Stunkard as an eating pattern seen in people with obesity. The disorder manifested with nocturnal hyperphagia, insomnia, and morning anorexia. Nocturnal hyperphagia, the main feature of NES, was defined as consuming at least 25% of total daily calories during the evening and night hours (Stunkard et al. 1955). Since this original description of NES, the criteria for

nocturnal hyperphagia, insomnia, and morning anorexia have been modified in various literature (Striegel-Moore et al. 2006), the major change being the inclusion of nocturnal periods of waking from the sleep to eat into the definition of nocturnal hyperphagia by Birketvedt et al. (1999). In 2008, an international research meeting was held to establish consensus criteria for NES (Allison et al. 2010). The newly proposed criteria retained nocturnal hyperphagia as the core feature of NES and redefined it as >25% of daily caloric intake occurring after the evening meal, which might be accompanied or replaced by regular nocturnal awakenings (≥2 per week) for food intake. Sleep disturbances and morning anorexia are listed as possible features along with the other symptoms like depressed mood and a strong urge to eat before sleep onset (Allison et al. 2010). The proposed diagnostic checklist also included criteria for differential diagnosis: awareness of nocturnal eating episodes to distinguish NES from sleep-related eating disorder, not having another medical or psychiatric disorder as a primary diagnosis, and maintenance of nocturnal eating for over 3 months.

The prevalence of NES is estimated to be 1.5% in the general population (Vander Wal 2012) but is reported to be much higher in different study cohorts for obesity. In a study of bariatric surgery candidates by Allison et al. (2006), and a study of patients with obesity by Gluck et al. (2001), 9% and 14%, respectively, of the participants met the criteria for NES. However, most studies do not characterize individuals for NES, but instead only consider the core feature of NES, namely, the nighttime eating (NE) habit. Studies on NE showed an even higher prevalence (14%–36%) for this eating pattern among people with obesity (Adami et al. 2002; Cerú-Björk et al. 2001; Gluck et al. 2008), suggesting that NE might be causative for obesity. In support of a causative role for obesity, NE behavior as part of NES or as an isolated phenotype has been shown to predict weight gain (Gluck et al. 2008). This correlation is not surprising given the previous findings from out-of-phase eating and sleep restriction experiments. Out-of-phase food intake resulted in obesity in mice (Arble et al. 2009), while sleep restriction has been shown to increase food intake (Spaeth et al. 2013). It is important that the daily rhythms of food intake and sleep should be in harmony to maintain healthy weight.

Circadian Rhythm of Food Intake and Changes in Nighttime Eating

Food intake is regulated by homeostatic processes and circadian rhythm in the body. Homeostatic regulation of food intake is under control of two opposing pathways: orexigenic and anorexigenic pathways. These pathways involve the actions of anorexigenic and orexigenic agents such as leptin, ghrelin, insulin, neuropeptide Y (NPY), and α-MSH, as well as anorexigenic and orexigenic neuronal populations residing in the hypothalamus (Huvenne and Dubern 2014). Anorexigenic pathways act after meals by increasing satiety. The adipocyte-derived hormone leptin binds to the leptin receptors in the hypothalamus and activates POMC-expressing neurons while inhibiting NPY expressing neurons. POMC is cleaved into α-MSH peptides,

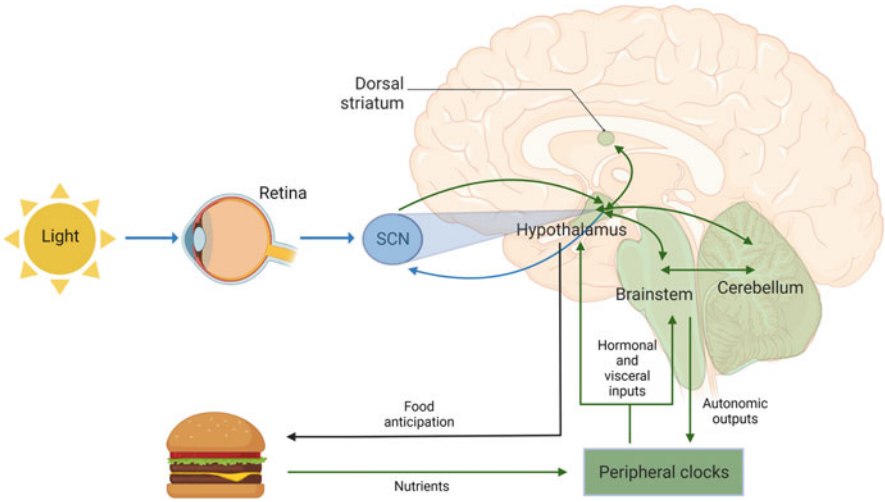


Fig. 1 Circadian control of feeding by the master and the secondary clocks. Circadian clock systems and their interaction with each other and the environmental cues. The master clock and its entrainment pathway are shown in blue. The secondary clocks and their entrainment pathways are shown in green. Circadian rhythmicity enabled by the master and food clocks enables the organism to predict food availability and engage in food anticipatory behavior. SCN = suprachiasmatic nuclei. Created with BioRender.com

which can bind to MC4R and MC3R. This interaction results in a suppression of food intake (Zegers et al. 2012). Orexigenic pathways are predominant in the fasted state, during which ghrelin is released from the gastric cells and activates the NPY and Agouti-related peptide expressing neurons in the hypothalamus (Nakazato et al. 2001).

In addition to hormonal regulation, circadian rhythm is one of the main systems in the regulation of food intake. Circadian rhythm is the internal process of organisms that predict the day-night cycle to regulate physiological functions accordingly. Circadian rhythmicity is enabled by endogenous clocks including a master clock located in the suprachiasmatic nuclei (SCN) of the hypothalamus and several secondary clocks in the brain and peripheral organs (Challet 2019) (Fig. 1). The master clock is synchronized by light; however, when light is absent, the master clock sustains itself and generates ~24 h cycles (Froy 2011). The secondary clock system in the brain and periphery can be reset by other environmental and physiological clues (Fig. 1). The secondary circadian system involved in food intake is referred as the food clock, and it can be readjusted by the timing of food intake via a feedback mechanism. The food clock together with the master clock sets daily windows for food intake that mostly occur during the daily active phase of an animal. Within these feeding windows, animals present behavioral anticipation for the food (Challet 2019). Secretion of many hormones involved in metabolism oscillate in sync with feeding windows, showing peak levels during anticipated feeding or fasting phases (Challet 2015).

Delayed Timing in NE and Its Consequences

The sleep-wake cycles of people with NES are typically undisturbed despite regular nocturnal awakenings (O'Reardon et al. 2004). However, their circadian rhythm of food intake is delayed. These observations suggested a dissociation of the circadian clocks of sleep and food intake (O'Reardon et al. 2004). Delayed timing of eating seen in NES and NE may reset the secondary circadian clocks, since these can be entrained by meal timing. However, the master clock in the SCN cannot be reset by habitual late eating because it is synchronized only by light (Challet 2019). Therefore, out-of-phase eating results in desynchronization of circadian clocks. For example, meal anticipation triggers an increase in plasma cortisol levels, yet a major cortisol peak always occurs early in the morning regardless of eating or skipping breakfast (Bogdan et al. 2001). Out-of-phase eating, such as Muslims practice during Ramadan, results in a totally different pattern of cortisol oscillation rather than a simple delay (Bogdan et al. 2001).

As a result of the complex interactions between circadian clocks and metabolic hormones, out-of-phase eating can have adverse effects on metabolism (Challet 2019), such as increased adiposity or metabolic syndrome (Allison et al. 2014). It has been shown that night shift workers have a higher prevalence of obesity, type 2 diabetes, and cardiovascular disease (Akerstedt and Wright Jr 2009). Circadian disruptions in shift work give rise to decreased insulin sensitivity and increased blood pressure (Scheer et al. 2009). Similarly, NE behavior results in a change in neuroendocrine profiles leading to weight gain (Birketvedt et al. 1999; Gluck et al. 2008).

Hormone Profiles in NE

Many hormones involved in metabolism exhibit circadian oscillation, and their rhythms and plasma levels change in NES. In a study of neuroendocrine profiling in NES, daily phases of ghrelin were similar between NES cases and controls, but the nocturnal levels were significantly lower in NES cases (Allison et al. 2005). The same study reported that leptin, melatonin, and cortisol did not show a significant difference between NES and control groups; however, an earlier study reported lower nocturnal plasma levels for leptin and melatonin and higher plasma levels for cortisol throughout the day (Birketvedt et al. 1999). Based on their findings, Allison et al. (2005) concluded that the differences in plasma hormone levels between NES and control groups were likely to be the result of the altered timing of food intake rather than the cause. A 2009 study (Goel et al. 2009) focused more on the pattern of circadian rhythms of the hormones rather than plasma concentrations. They found that people with NES have 1–3 h phase delays for circadian rhythms of leptin and insulin and about 5 h phase advance for ghrelin. These studies showed that the general pattern of daily peaks and lows was similar for both NES and control groups with a variation on the timing and the amplitude of the plasma level peaks, suggesting that the circadian disruption is not as prominent as more drastic changes

in eating patterns such as fasting during Ramadan. Although neuroendocrine characteristics have been reported only for people with NES, as opposed to people with NE habit with or without the additional phenotypes of NES, similar circadian changes may be predicted for NE phenotypes in general based on our current knowledge on the relation of meal timing and circadian rhythms.

Assessment of NE

As mentioned above, NE is characterized by the consumption of at least 25% of daily caloric intake after dinner and/or at least two episodes of nocturnal eating per week. However, in the absence of nocturnal eating episodes, it can be difficult to be certain of the NE phenotype because different cultures/societies eat dinner at different times in the evening. Allison et al. have proposed that dinner be defined as the first meal occurring between 5 pm and 8 pm (Allison et al. 2010), and subsequent food ingestions are regarded as calories consumed after dinner. However, in many parts of the Mediterranean, Asia, and South America, the standard dinner time is well after 8 pm, the most well-known examples being Spain and India. Therefore, nocturnal eating seems to be more reliable factor in characterization of NE. The time frame for nocturnal ingestion is usually taken as the 6–8 h period starting after 10 pm or 11 pm ((Gluck et al. 2008; O'Reardon et al. 2006).

The Night Eating Questionnaire (NEQ) is a widely used tool to assess the presence and the severity of NE. The original 9-item NEQ was later expanded to include 14 questions about daily food intake and sleeping pattern (Allison et al. 2008; Gluck et al. 2001; Marshall et al. 2004), and modified versions of NEQ have been developed to be used in children (Lundgren et al. 2012) or to include additional phenotypical assessments related to NES (Innamorati et al. 2018). In outpatient study settings, diary data logged by the participants frequently accompanies NEQ for NE assessment. Participants keep daily logs about their food intake as well as sleep and mood (Birketvedt et al. 1999; Lundgren et al. 2008; O'Reardon et al. 2004). In addition to diaries, some studies include the use of motion sensors to keep track of an individual's nightly awakenings (Birketvedt et al. 1999; O'Reardon et al. 2004).

After the first description of NES (Stunkard et al. 1955), NE and NES have rarely been assessed in inpatient settings, where phenotyping can be done with more accuracy (Allison et al. 2005; Birketvedt et al. 1999; Gluck et al. 2008). One exception is a study by Gluck et al. (2008), which utilized computerized vending machines (Venti et al. 2009) in an inpatient setting to allow for ad libitum access to food 24 h per day. The vending machine recorded both the time of use and the quantity of food selected such that nocturnal ingestions could be precisely recorded, enabling a robust phenotyping within the study group.

Effects of NE on Weight Management and Diabetes Management

NE and BMI

Numerous studies have examined whether there is a relationship between NE and BMI. Many studies have reported a positive correlation (de Zwaan et al. 2014; Gluck et al. 2008; Kucukgoncu et al. 2014; Morse et al. 2006); however, other studies have found no association between NE and BMI (Cerú-Björk et al. 2001; Friedman et al. 2006; Melo et al. 2018; Runfola et al. 2014). The main limitation for most of these studies is that the phenotyping depends on questionnaires for NE and self-reported height and weight values for BMI; therefore, there could be differences due to accuracy of the data. In addition, most of these studies are cross-sectional and compare the BMI of NE and non-NE groups at the time of recruitment; therefore, these cross-sectional data cannot be used to predict weight gain over time. The study by Gluck et al. (2008) was one of the few studies that did include follow-up data on weight measurements, and this study concluded that NE is related to weight gain. Nevertheless, this study was listed in a review (Gallant et al. 2012) among those with negative findings for BMI and NE relation because the baseline BMI values did not differ between NE and non-NE groups.

Several theories have been proposed to explain the discrepancy in findings of a relationship between NE and BMI. For example, Gallant et al. proposed that the genetic background of a person and/or population could affect the relationship between NE and BMI (Gallant et al. 2012). Another theory has been that weight gain is gradual and cannot be easily observed in cross-sectional studies of young adults (Bruzas and Allison 2019). Supporting this view, Meule et al. (2014a) showed that NE was positively associated with BMI specifically in a sample of middle age to older adults (ages 31–60). Given that the mean ages of individuals differ greatly among studies examining NE and BMI, age could be an important moderator on this relationship. Yet another explanation for the lack of association between NE and BMI in some studies could be differences in compensatory behaviors. For example, some people with NE could participate in excessive exercising and/or calorie restriction during the day (Bruzas and Allison 2019; Lundgren et al. 2008; Runfola et al. 2014). Runfola et al. (2014) found that university students with NES were significantly more likely to have histories of being underweight due to past AN. Therefore, the relationship between NE and BMI may be complex, and although the few studies with BMI follow-up data report gradual weight gain in individuals with NE (Andersen et al. 2004; Gluck et al. 2008), more studies with follow-up data are needed to fully understand the long-term effects of NE.

NE and Diabetes

EDs have been suggested to affect individuals with either type 1 diabetes (T1D) or type 2 diabetes (T2D). Among people with T2D, the more prevalent form of diabetes, around 40% of people have an ED. NES and BED are the two most

common forms of EDs seen in T2D populations (García-Mayor and García-Soidán 2017). A study of NE in relation to T2D found that 7% of participants with T2D met the diagnostic criteria for NES, a prevalence higher than the general population (Hood et al. 2014). Similar to what has been reported among individuals with T2D, NE was observed in about 8.5% of people with T1D (Morse et al. 2006).

NE behavior has also been proposed to increase difficulty in diabetes management (Hood et al. 2014; Vander Wal 2012). Poor dietary habits among individuals with NE, such as breakfast skipping, may be one cause of poor glycemic control (Hood et al. 2014). Since NE is a prevalent comorbidity in diabetes and has adverse effects on the disease management, it must be assessed in patients with T1D and T2D along with the other types of EDs.

Etiology of Nighttime Eating and Links to BMI

Psychological Factors

The original study that describes NES suggested that this disordered pattern of eating was a response to stress (Stunkard et al. 1955). In fact, the NES cases presented in that study suffered from traumatic life events and periods of high stress and anxiety, which coincide with the reoccurrences of NES symptoms. Later studies showed that emotional triggers are associated with NE. Emotional regulation was suggested to be a moderator of the NE and BMI relationship (Meule et al. 2014b). Data from questionnaires indicate that high levels of emotional eating are associated with NE severity and BMI (Meule et al. 2014b). NE has also been found to associate with stress, anxiety, and depression (Borges et al. 2017). Techniques that reduce stress and anxiety were found to be helpful in managing NE, indicating that these psychological factors have a role in NE (Pawlow et al. 2003). Depressed mood and major depressive disorder are highly comorbid with NE (Vander Wal 2012). Although it is not clear that depression, anxiety, and stress have a causative role in NE, the presence of any of these mental conditions is more common among individuals with NE (Bruzas and Allison 2019).

Genetic Components

Familial aggregation has been shown for NES indicating that genetic factors contribute to this ED (Lundgren et al. 2006). However, to date, very few genetic studies have been conducted for NE. Since NE can be conceptualized as a disorder of circadian rhythm of food intake, the circadian clock genes (Rijo-Ferreira and Takahashi 2019) have been the most studied candidate genes for NE. Liu et al. (2014) studied the *PER1* gene which is a member of the period gene family and one of the main clock genes. *PER1* is expressed in the SCN, and in studies of mice, a mutation in this gene caused a change in peak time of food intake.

Although findings from animal models can help to establish a set of candidate genes to search for variations underlying the heritability of NE, genetic studies of NE in humans are very limited. One study in humans analyzed the *VGF* gene as a candidate based on a database search (Sabbagh et al. 2016). However, conducting a genome-wide association study for NE, which is the standard method for identifying genetic variants that contribute to a polygenic trait, is challenging because no large cohorts of individuals clinically characterized for NE currently exist. In contrast to NE, common types of EDs, such as AN, do not have these sample size limitations, and genome-wide association studies have been performed on thousands of individuals characterized for AN (Wang et al. 2011).

A small study by Köroğlu et al. (2020) is the only genetic study, to our knowledge, that utilized data from humans who were clinically characterized for NE. Rather than conduct a genome-wide association study which lacked power in their small sample of cases and controls, this study assumed a correlation between NE and BMI and therefore only considered a preselected set of variants that have been shown to significantly associate with BMI in large cohorts from the Genetic Investigation of Anthropometric Traits (GIANT) and UK Biobank databases (Yengo et al. 2018). Among these BMI-associated variants, Koroglu et al. determined that variation in *HCRTR1* also associated with NE in their sample of inpatients characterized for NE. *HCRTR1* encodes hypocretin (also known as orexin), whose physiology (detailed below) gives credibility to the association results. However, future genome-wide studies with large, well-powered sample sizes could uncover the role of additional genes that contribute to NE and NES.

Hypocretin Receptors and NE

The hypocretin (also known as orexin) system can be regarded as the junction of the sleep and feeding regulation mechanisms. It has been considered as one of the secondary circadian clocks regulating food intake. Hypocretin 1 and 2 peptides are encoded by *HCRT* in the hypothalamus. *HCRT* is a clock-controlled gene, and its expression varies during the day (Challet 2019). Hypocretin neuropeptides are endogenous ligands for two G-protein-coupled receptors, hypocretin receptor 1 encoded by *HCRTR1* gene and hypocretin receptor 2 encoded by *HCRTR2* gene (Sakurai 2007). Hypocretin-producing neurons originating from the hypothalamus innervate the entire brain and regulate sleep and stimulate feeding.

The different types of hypocretins and their distinct receptors are thought to have unique physiological roles (Marcus et al. 2001). Mutations in *HCRT* and *HCRTR2* cause narcolepsy (Hungs and Mignot 2001; Lin et al. 1999; Peyron et al. 2000), whereas no mutation in *HCRTR1* was found in human narcolepsy cases, and Hcrtr1 knockout mice, unlike Hcrtr2 knockout mice, did not present disturbed wakefulness and rapid-eye movement sleep patterns (Sakurai 2007). The involvement of *HCRTR1* in feeding is better supported than its role in sleep. Intraperitoneal injection of hypocretin receptor 1 antagonist reduced feeding in rats, revealing the important role of Hcrtr1 in mediating food intake (Haynes et al. 2000). It has also been found

that Hcrtr1, but not Hcrtr2, is upregulated in response to fasting (Lopez et al. 2000). These studies reveal the important functions of hypocretins and their receptors in feeding and sleep regulation and indicate the divergence in functions between the receptors, which makes them intriguing candidates for increased risk of NE.

Applications to Other Eating Disorders

In this chapter we have reviewed neuroendocrine changes due to NE and the adverse effects of this habit on weight management and diabetes and discussed the genetic and environmental factors that might contribute to the development of NE. We also described the characteristics of NES, an ED with NE as the main feature, which is included in the *Diagnostic and Statistical Manual of Mental Disorders*.

Although NES was previously considered as a disorder similar to BED (Napolitano et al. 2001), according to the current view, diagnosis of any other ED excludes NES (Cleator et al. 2012). Therefore, NES cannot be comorbid with another ED. On the other hand, NE is reported to be common in individuals with a diagnosis of other EDs (Lundgren et al. 2011). This indicates an overlap in causes, including genetic factors. Therefore, a genetic susceptibility locus identified for NES could be a candidate locus for another ED and vice versa.

Identification of genes and/or genetic variants that contribute to ED could help in understanding the underlying physiology and lead to improved therapies and or drug targets. A major challenge for these genetic studies is the lack of large datasets of robustly phenotyped individuals for the less common EDs. Until large samples are collected for the uncommon EDs to allow for adequately powered genome-wide association studies, hypothesis-based studies must be conducted. For example, if a particular eating phenotype is consistently associated with a higher or lower BMI or another anthropometric trait, genetic data from current large biobanks could be used in conjunction with the genotyping results from the limited sample of that ED. This strategy, employed by Köroğlu et al. (2020) who restricted their analysis of genetic determinants for NE to only variants known to affect BMI, uncovered a compelling candidate for NE. Knowledge of risk variants that are unique to a specific ED could aid in the diagnosis. In addition, merging information on metabolic pathways affected by genetic risk factors with knowledge of environmental influences may ultimately lead to better treatment of EDs.

Mini-Dictionary of Terms

- ***Anorexia***. *Markedly reduced appetite or complete aversion to food*
- ***Bariatric surgery***. *Variety of procedures performed on the stomach or intestines to induce weight loss in people with obesity*
- ***Body mass index***. *A measurement derived from the weight of a person in kilograms divided by the square of their height in meters. It is expressed in units of* kg/m^2*, and it is the most used value to determine adiposity*

- ***Circadian rhythm***. *The internal process of the organisms that predicts the day-night cycle and regulates the physiological functions*
- ***Genome-wide association study***. *In this method, the genomes in a sample set including phenotypically different individuals are scanned using genetic markers, and the differences in the allele frequencies of those genetic markers are used in statistical tests to identify associations of genotypes and phenotypes*
- ***Hyperphagia***. *Abnormally increased appetite and excessive hunger*
- ***Narcolepsy***. *A neurological disorder characterized by a disorganization of sleep and wakefulness. Patients with narcolepsy have disturbed sleep during the night and chronically sleepy during the day. They tend to prematurely enter rapid-eye-movement sleep phase*

Key Facts of Night Eating Syndrome

The main diagnostic criterion is the presence of nighttime eating, which is defined as intake of >25% of daily calories after the evening meal and/or the occurrence of regular nocturnal awakenings (≥2 per week) for food intake.

The patients are aware of and recall their nocturnal eating episodes.

To be diagnosed with night eating syndrome, at least three of the following five symptoms must be present: morning anorexia, strong urge to eat after dinner and before sleep, having sleep onset or sleep maintenance problems at least four nights per week, believing that one must eat to initiate or return to sleep, and depressed mood that worsens in the evening.

At least 3 months of nighttime eating must have been maintained to consider night eating syndrome diagnosis.

Night eating syndrome diagnosis is considered only if the disordered pattern of eating is not secondary to substance abuse or another psychiatric disorder.

The prevalence of night eating syndrome is about 1.5% in the general population.

Treatment options include medications such as selective serotonin reuptake inhibitors and nonmedical interventions, mainly cognitive behavioral therapy.

Summary Points

- *Food intake is regulated by homeostatic processes and circadian rhythm in the body*
- *Nighttime eating is a disruption in circadian rhythm with a dissociation between eating and sleeping rhythms*
- *Out-of-phase eating seen in nighttime eating results in a change in neuroendocrine profiles*
- *Many studies showed that nighttime eating is associated with a higher BMI, and studies with follow-up weight measurements reported gradual weight gain in people with nighttime eating*

- *Nighttime eating is also associated with poor glycemic control and poor dietary habits in patients with type 2 diabetes*
- *Assessment of nighttime eating commonly includes questionnaires and food diaries*
- *Familial aggregation indicates genetic factors for nighttime eating, and the genetic background could be one of the major contributors to the NE and BMI relationship*
- *Circadian clock genes and others involved in sleep and feeding regulation such as hypocretin peptides and their receptors have been highlighted as candidate genes for nighttime eating*
- *A genetic susceptibility locus identified for night eating syndrome can be a candidate locus for another eating disorder because of the overlap of symptoms*

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Night Eating Syndrome and Network Analysis of Features

61

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Contents

Introduction 1209
Night Eating Syndrome 1209
History of Night Eating Syndrome 1209
Development of the Research Diagnostic Criteria 1211
Prevalence and Comorbidities 1212
Etiology and Medical Model Conceptualization 1212
Network Theory of Psychopathology 1213
Weaknesses of the Medical Model 1213
Network Theory 1213
Advantages of Network Theory 1215
Modeling the Network Approach to Psychopathology: Network Analysis 1215
Network Structure 1216
Network Properties 1217
Accuracy and Stability 1218
Network Approach to Psychopathology in Eating Disorders 1218
Outline of Emerging Research 1218
Network Approach to Psychopathology in NES 1219
Clinical Implications 1223
Future Directions in Network Analysis of NES 1224
Network Comparisons 1224
Temporal Network Analysis Models 1225
Refine Intervention Targets 1226
Applications to Other Eating Disorders 1226
Mini-Dictionary of Terms 1227

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Key Facts of Night Eating Syndrome and Network Analysis of Features 1227
Key Facts of Night Eating Syndrome 1227
Summary Points 1228
References 1228

Abstract

Night eating syndrome (NES) is an eating disorder (ED) characterized by a disrupted circadian rhythm that results in aberrant sleep, mood, and eating behaviors. The core features of NES include evening hyperphagia (i.e., consumption of $\geq$25% of total daily calories after the evening meal) and/or nocturnal ingestions of food after awakening from sleep. The conceptualization of NES has been informed by the medical model paradigm of disease, which assumes the presence of a distinct, underlying mechanism that causes symptoms. Utilizing this paradigm presents challenges for research and practice related to NES, as the causal mechanisms of NES are relatively unknown and conceptualization of NES has varied considerably over the past few decades. In response to the limitations of the medical model paradigm, recent work on EDs has focused on reconceptualizing ED psychopathology using the network approach to psychopathology. This approach focuses on identifying (a) functional, causal interactions among symptoms and (b) symptoms most important to specific disorders. This chapter provides an exploration on the conceptualization of NES when examined through this network approach. First, this chapter examines the history of NES conceptualization through a medical model lens. Next, it offers an overview of network analysis, emphasizing the methodology used to model the network approach to psychopathology. Findings from recent work on NES using network analysis are also presented. Finally, research and clinical implications from this study will be provided, as well as future directions for network analysis of NES.

Keywords

Night eating syndrome · Network analysis · Eating disorders · Network approach to psychopathology · Medical model paradigm of disease · Psychopathology · Eating disorder treatment · Conceptualization of eating disorders · Core features of night eating syndrome · Symptoms

Abbreviations

BMI	Body mass index
DSM-5	*Diagnostic and Statistical Manual of Mental Disorders*, 5th edition
ED	Eating disorder
EDNOS	Eating disorder not otherwise specified
FGL	Fused graphical lasso
GLASSO	Graphical least absolute shrinkage and selection operator
NES	Night eating syndrome
OSFED	Other specified feeding and eating disorder

Introduction

Night eating syndrome (NES) is an eating disorder (ED) characterized by a disrupted circadian rhythm that results in aberrant sleep, mood, and eating behaviors (Muscatello et al. 2021). Indeed, individuals with NES experience a delay in their circadian pattern of food intake, which manifests as the two core features of NES: (a) evening hyperphagia (i.e., consumption of $\geq$25% of total daily calories after the evening meal) and/or (b) nocturnal ingestions of food after awakening from sleep (Allison et al. 2010). These individuals must also demonstrate awareness of their eating (i.e., they must be awake while eating), experience possible morning anorexia and/or concomitant mood or sleep disturbances, and exhibit distress or impairment for at least 3 months (Allison et al. 2010).

Historically, conceptualization of NES has been guided by the medical model paradigm of disease, which assumes the presence of a distinct, underlying mechanism that causes symptom presentation. Therefore, researchers have focused on identifying the exact causal mechanism from which NES symptoms manifest. However, despite advances in understanding the etiology of NES since it was first described in the literature, the underlying causal mechanism is still relatively unknown. In addition, NES criteria have varied considerably over the past few decades, which has contributed to significant challenges in research and clinical examinations of this disorder (Vander Wal 2012).

As an alternative to the medical model approach, recent work on other EDs has focused on reconceptualizing ED psychopathology using the network approach to psychopathology (Levinson et al. 2018b). Whereas the medical model paradigm emphasizes casual mechanisms from underlying factors, the network approach to psychopathology focuses on identifying (a) functional, causal interactions *among* symptoms and (b) symptoms most important to specific disorders (Borsboom and Cramer 2013). The network approach to psychopathology gained popularity in the past decade, with growing number of studies focusing on ED psychopathology and treatment (Monteleone and Cascino 2021).

This chapter aims to deliver insight on the conceptualization and unique features of NES when examined through this network approach. First, this chapter examines the history of NES conceptualization through a medical model lens. Next, it offers an overview of network analysis, emphasizing the methodology used to model the network approach to psychopathology. Findings from recent work on NES using network analysis are also presented. Finally, research and clinical implications from this study will be provided, as well as future directions for network analysis of NES.

Night Eating Syndrome

History of Night Eating Syndrome

NES was first identified in 1955 as a cluster of nonnormative eating behaviors that would arise during periods of stress (Stunkard et al. 1955). Such behaviors included morning anorexia (i.e., lack of morning hunger or eating behavior in the morning),

evening hyperphagia, and sleep-onset insomnia (i.e., difficulty getting to sleep more than 50% of the time; Stunkard et al. 1955). Since then, the conceptualization and diagnostic criteria of NES have evolved considerably (Striegel-Moore et al. 2006a). Although iterations of NES criteria retained some form of the three original symptoms, amendments to these symptoms – particularly with regard to evening hyperphagia – have led to definitional inconsistencies across studies.

Following the proposal of the original NES symptoms in 1955, the first revision to NES criteria occurred in 1996 to better operationalize the symptoms. Subsequently, NES was defined as absence of appetite for breakfast, consumption of 50% or more of total daily calories after 7:00 p.m., and difficulty with sleep onset or maintenance (Stunkard et al. 1996). However, as interest and recognition of NES emerged, researchers often amended or operationalized these symptoms differently. For example, studies have specifically operationalized morning anorexia in terms of food quantity or consumption cutoff times (i.e., "skipping breakfast" or "delay of eating for several hours after awakening"; Geliebter 2002; Gluck et al. 2001; Rand et al. 1997). The definition of evening hyperphagia was interpreted by Rand et al. (1997) simply as "excessive evening eating," with a proposal to exclude the specified percentage of daily caloric intake (50%) after the evening meal due to claims that persons with obesity were inaccurate at reporting caloric intake. Studies that have retained a percentage-based specification of evening caloric intake have ranged considerably (e.g., >25%, >50%), along with the operationalization of "evening" (e.g., after evening meal, after evening meal but before bed, after 6:00 pm–after 8:00 pm; Striegel-Moore et al. 2006a). Lastly, several studies failed to define sleep disturbance beyond "insomnia," and there exist wide ranges of frequencies for number of sleep disturbances (i.e., three times/week, four times/week, more than half the time, or nightly; Striegel-Moore et al. 2006a).

Additional NES symptoms were also proposed as research in NES continued to grow. Rand et al. (1997) suggested that symptoms should include delay of eating after awakening for several hours and "evening tension and/or feeling upset" (an early allusion toward negative mood, which would be added later). Spaggiari et al. (1994) examined NES through the lens of a sleep disorder, proposing criteria that were more focused on symptoms that occurred during sleep, including (a) a drive to eat upon awakening in the night, (b) the inability to return to sleep without eating, (c) becoming fully awake during nocturnal eating episodes and full recall of such episodes in the morning, (d) and a quick return to sleep after eating. Nocturnal ingestions of food after awakening from sleep were again referenced in 1999, as was worsening of mood in the evening (Greeno et al. 1995; Birketvedt et al. 1999; Vinai et al. 2008).

The variation in operationalized diagnostic criteria for NES has presented a significant challenge in research and clinical examinations of this disorder (Vander Wal 2012). For example, studies reviewing prevalence and epidemiology of NES will often cite the inconsistent diagnostic criteria as possible reasons for high variability in prevalence rates across different populations (Muscatello et al. 2021). In addition, the *Diagnostic and Statistical Manual of Mental Disorders*, including its most recent edition (DSM-5; American Psychiatric Association [APA] 2013), has

not recognized NES as a separate diagnosis, likely due in part to these varying definitions (Striegel-Moore et al. 2006a). Currently, NES is subsumed under the "eating disorder not otherwise specified" (EDNOS) or "other specified feeding and eating disorder" (OSFED) categories, with little specification. Criteria for NES in the OSFED category do not include any mention of morning anorexia and conceptualize evening hyperphagia and nocturnal ingestion as "[r]ecurrent episodes of night eating, as manifested by eating after awakening from sleep, or by excessive food consumption after the evening meal. There is awareness and recall of the eating" (APA 2013, p. 354). With such little specification, accurate identification and diagnosis of NES and its distinction from other EDs under OSFED remains a challenge for clinicians.

Development of the Research Diagnostic Criteria

To provide a standardized definition for NES, the First Night Eating Symposium was held in Minneapolis in 2008, and from this, Allison and colleagues proposed a set of specific research diagnostic criteria, presented in Table 1 (Allison et al. 2010). Within these criteria, evening hyperphagia, defined as consumption of at least 25% of daily caloric intake after the evening meal; nocturnal ingestion of food, defined as evening awakenings with ingestions at least twice a week; or both must be present for a diagnosis of NES (Criterion A), along with awareness of these eating episodes (Criterion B), at least three of five additional symptoms (Criterion C), and associated distress or impairment in functioning (Criterion D) lasting for at least 3 months (Criterion E).

Table 1 Research diagnostic criteria for night eating syndrome (NES)

Criterion	Definition
A	The daily pattern of eating demonstrates a significantly increased intake in the evening and/or nighttime, as manifested by one or both of the following: 1. At least 25% of food intake is consumed after the evening meal 2. At least two episodes of nocturnal eating per week
B	Awareness and recall of evening and nocturnal eating episodes are present
C	The clinical picture is characterized by at least three of the following features: 1. Lack of desire to eat in the morning and/or breakfast is omitted on four or more mornings per week 2. Presence of a strong urge to eat between dinner and sleep onset and/or during the night 3. Sleep onset and/or sleep maintenance insomnia are present four or more nights per week 4. Presence of a belief that one must eat in order to initiate or return to sleep 5. Mood is frequently depressed and/or mood worsens in the evening
D	The disorder is associated with significant distress and/or impairment in functioning
E	The disordered pattern of eating has been maintained for at least 3 months
F	The disorder is not secondary to substance abuse or dependence, medical disorder, medication, or another psychiatric disorder

Prevalence and Comorbidities

Estimates of prevalence rates for NES are quite varied due to inconsistent criteria and exclusion from DSM. Nonetheless, current estimates include ranges between 0.5% and 1.5% in the general population (Rand et al. 1997; Striegel-Moore et al. 2005), 5.7% in university students (Nolan and Geliebter 2012), 12.3–22.4% in psychiatric outpatient populations (Saraçlı et al. 2015), 6–16% among those patients visiting obesity clinics (Cerú-Björk et al. 2001; Gluck et al. 2001; McCuen-Wurst et al. 2018), and up to 55% in patients undergoing bariatric surgery for obesity (de Zwaan et al. 2015). There are little differences in rates of NES between gender, age, and ethnicity (Aronoff et al. 2001; Striegel-Moore et al. 2006b; Colles et al. 2007). Individuals with NES also show high comorbidity with major depressive disorder (Küçükgöncü and Beştepe 2014), substance use disorder (Lundgren et al. 2006; Küçükgöncü and Beştepe 2014), sleep-wake disorders (Lundgren et al. 2011; Hood et al. 2014), and other EDs (Colles et al. 2007; Allison et al. 2007; Vander Wal 2012; Tu et al. 2019).

NES has shared close ties with overweight/obesity since its inception, as the syndrome was first identified through the clinical observation of individuals with obesity and was thought to be a behavioral expression of this weight status (Stunkard et al. 1955; Gluck et al. 2017). Prevalence rates for NES are higher in populations with obesity (6–16%; Küçükgöncü et al. 2015), and individuals with obesity in psychiatric outpatient settings are five times more likely to meet criteria for NES compared to individuals without obesity (Lundgren et al. 2006). Despite this relationship between obesity and NES, however, extant research has suggested that not all individuals with NES are persons with overweight/obesity (Birketvedt et al. 1999; Striegel-Moore et al. 2006b; de Zwaan et al. 2006; Lundgren et al. 2008). In addition, Vander Wal (2012) noted that obesity may be associated with NES, but the directionality of this relationship is not known, and symptoms of NES may balance out the likelihood of potential weight gain (i.e., morning anorexia compensating for evening hyperphagia and nocturnal ingestion of food).

Etiology and Medical Model Conceptualization

As is the case with many disorders, the evolution of NES conceptualization and etiology have been heavily influenced by the medical model paradigm of disease. This paradigm (Lilienfeld and Treadway 2016) posits that mental health disorders are causal entities that result in myriad dysfunctional symptoms (Borsboom and Cramer 2013). In other words, the medical model proposes that psychiatric disorders have underlying causes that (1) lead to the expression of certain symptoms and (2) explain the co-occurrence of certain symptoms in related clusters. For NES, the proposed core mechanism is a circadian rhythm shift, and several causes have been suggested, including genetic (Root et al. 2010), biobehavioral (Stunkard et al. 2006; Lundgren et al. 2013; Pollack and Lundgren 2014), neuroendocrine (Birketvedt et al. 1999, 2014), and psychosocial (Allison et al. 2007; Takeda et al. 2004; Vander Wal

2012; Sevincer et al. 2016; He et al. 2018) factors. Despite these proposals, the cause of NES is still relatively unknown (Lundgren et al. 2012b), but current conceptualizations suggest that NES has an underlying common cause, and research to date has been focused on identifying causal mechanisms of NES.

Network Theory of Psychopathology

Weaknesses of the Medical Model

One of the major weaknesses of the medical model paradigm when applied to conceptualizing psychiatric disorders is the reliance on a latent variable theory. This theory proposes that unseen factors give rise to observable phenomenon. This concept is applied to psychiatry insomuch that mental health disorders are thought to precipitate dysfunctional mental health symptoms. For example, major depression is posited as the manifestation of specific observable symptoms (e.g., depressed mood, loss of interest, fatigue, difficulty concentrating, etc.) that are caused by an underlying unobserved factor, much like how an infection would give rise to a fever, headache, and respiratory symptoms (Borsboom and Cramer 2013). While these symptoms are distinct (i.e., seen as separate symptoms), they are causally homogeneous, and the removal of the underlying factor (i.e., depression, the infection) will result in symptom alleviation. Furthermore, in the medical model, symptoms are distinct from the underlying condition (i.e., medical conditions can occur asymptomatically).

When applying the medical model to psychopathology, it seems reasonable to suggest that a psychiatric disorder like depression should (a) have an underlying cause that is independent from the symptoms, and (b) this underlying cause should give rise to all related depressive symptoms (Borsboom and Cramer 2013). Therefore, such a theory asserts that an individual could have depression without any symptoms. It is highly unlikely that this scenario exists, and it remains unlikely that any future measurement techniques will be developed to detect disorders independent of their symptoms. Indeed, the medical model of disease as the cause of symptoms does not appear to hold true with psychiatric disorders, and the relationship between symptoms and disorders needs to be conceptualized differently (Borsboom and Cramer 2013).

Network Theory

Network theory presents an alternative approach to this conceptualization. It suggests that symptoms are not the result of an underlying latent cause, but that psychiatric disorders result from a functional, causal interaction among symptoms (i.e., symptoms cause each other; Borsboom and Cramer 2013; Borsboom 2017). This interaction is conceptualized as connections between, and dynamic relationships among, a network of symptoms. This has been referred to as the "network

approach to psychopathology" (Borsboom 2017). Indeed, interest in the network approach to psychopathology has grown considerably since Borsboom and Cramers' (2013) seminal article (Contreras et al. 2019; Robinaugh et al. 2020), with Robinaugh et al. (2020) identifying 363 articles on this topic across myriad psychiatric disorders.

Figure 1 illustrates this approach through a visual representation of a proposed network structure. The external field represents circumstances from outside the network that have direct influences on symptoms (i.e., adverse life events). These circumstances can "activate" symptoms within the network, which may activate neighboring symptoms, leading to the presentation of psychiatric disorders (Borsboom and Cramer 2013). Some symptoms may be more strongly connected to others, or clustered closely with others, and these symptoms are likely to impact each other to a greater degree. Indeed, such connections can lead to symptoms becoming self-sustaining and the disorder persisting even with the removal of the original influence (see Fig. 2; Borsboom 2017).

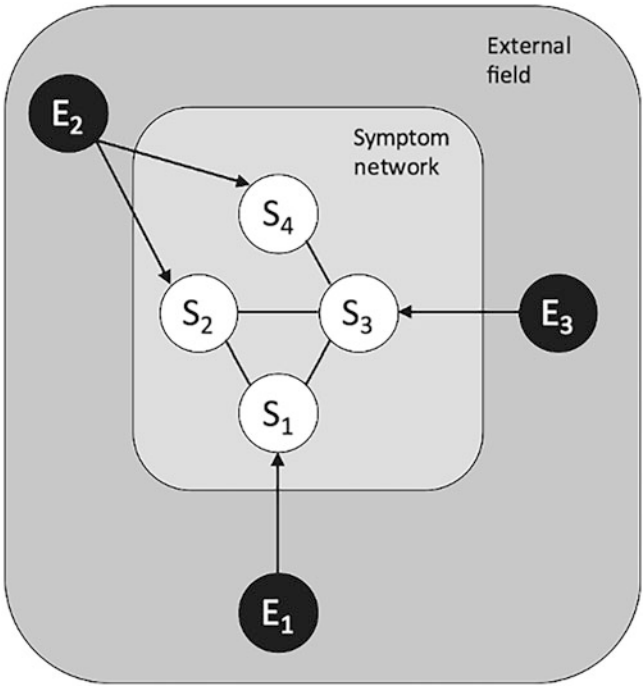


Fig. 1 A symptom network of four symptoms. Symptoms that have a tendency to activate each other are connected by a line (e.g., S_1–S_2). Symptoms can also indirectly activate each other (e.g., S_1–S_4) through a shared symptom (e.g., S_3). External factors (e.g., adverse life events) exist in the external field and can directly affect one or more symptoms. *S* symptom, *E* external factor. (From Borsboom (2017) with permission)

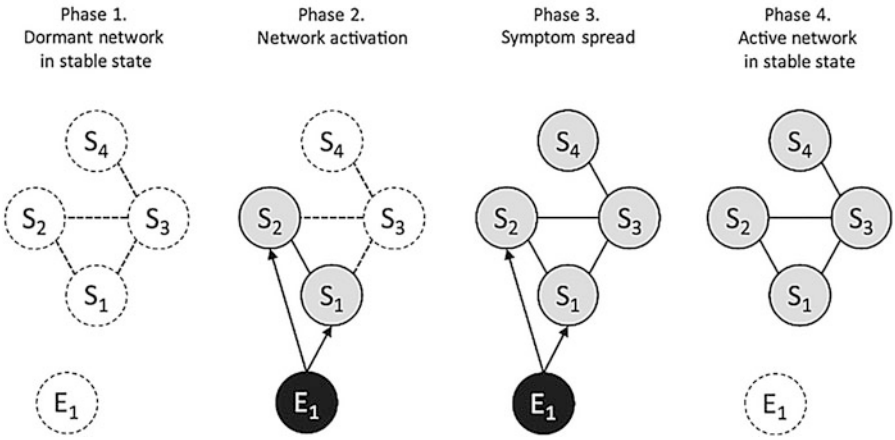


Fig. 2 The development of psychiatric disorders according to network theory. Phase 1 represents a dormant network. An external event occurs that triggers the activation of select symptoms (phase 2), which spreads to connected symptoms (phase 3). If the network is strongly connected, the network may become self-sustaining after the external event is removed (phase 4). *S* symptom, *E* external factor. (From Borsboom (2017) with permission)

Advantages of Network Theory

Network theory presents several advantages over latent variable theory. Chief among these advantages is that network theory more closely models how clinicians instinctively conceptualize, diagnose, and treat psychopathology (Borsboom 2017). For example, in contemporary cognitive-behavioral models of psychopathology, there is an emphasis on how patterns of thoughts, behaviors, and emotions might be self-reinforcing within a triangular system. Thus, cognitive-behavioral therapists employ techniques to elucidate how these patterns are functionally linked together and how they may perpetuate a disorder (DuBois et al. 2017). Interventions are then chosen based on this interaction of symptoms, rather than identifying and addressing an underlying cause (Borsboom 2017). Therefore, an examination of a disorder through network theory appears to best match this approach, whereby a clinician conceptualizes a network that identifies which symptoms are present and which interactions are sustaining each other. As a result, a clinician would ideally identify the most important or most influential symptoms – based on how that symptom maintains or activates other symptoms – as a target for treatment.

Modeling the Network Approach to Psychopathology: Network Analysis

Networks can be both graphically and quantitatively modeled using network analysis (Borsboom and Cramer 2013; Epskamp et al. 2018a). This method is a

data-driven approach used to determine the network structure of a particular disorder. Techniques for network analysis have been derived from methodology used on social networks (Otte and Rousseau 2002) and neural networks (de Haan et al. 2009). A brief primer on the basic concepts of network analysis as applied to the network approach to psychopathology is presented below.

Network Structure

Within a given network, symptoms are represented as *nodes*, and the connection between symptoms is referred to as an *edge.* These edges can either represent the presence of a correlation (unweighted) or can be used to indicate both the presence and the magnitude of the correlation (weighted). In a weighted network, the size of an edge denotes the strength of the correlation (thicker lines indicate stronger correlations and vice versa), and the color reflects the sign of the correlation. In addition, edges can also be used to determine the directionality of relationships between symptoms, with directed models using arrows on the edges to represent the direction of the association (i.e., symptom A predicting symptom B in the order toward the arrow's end, suggesting possible causation) and undirected models using lines with no arrows (i.e., indicating a relationship but not modeling directionality or possible bidirectionality).

Approaches to Modeling Network Structure

There exist various approaches to modeling network structure using cross-sectional data that assess relationships between symptoms at one point in time, often using self-report questionnaires or structured clinical interviews (McNally 2021). These approaches include *association*, *concentration*, *relative importance*, and *Bayesian networks* and differ on their use of undirected versus directed models and whether their edges represent zero-order correlations or partial correlations (Borsboom and Cramer 2013). As concentration networks are more commonly used in psychopathology research, this approach will be explored in depth, and readers are encouraged to review McNally (2016, 2021) for more information on the other approaches.

Concentration networks utilize a matrix of partial correlations as a means to determine direct or indirect relationships (Borsboom and Cramer 2013). These networks are also known as Gaussian graphical models (Lauritzen 1996) and are part of a more general class of models called pairwise Markov random fields (Epskamp and Fried 2018). As partial correlations are correlations between nodes that remain after all other nodes are controlled for, this approach may assist in determining the causal structure of a network. Data used to model these networks are typically continuous, but there exist options to model binary (Ising model; van Borkulo et al. 2014) and mixed continuous and categorical (mixed graphical model; Haslbeck and Waldorp 2020) data. These networks, however, are vulnerable to sampling error, which may result in artificially inflated or spurious edge estimates (Epskamp and Fried 2018).

One strategy to solve the issue of many small and potentially spurious correlations is the use of regularization, which sets a penalty on network estimation based on model complexity (Epskamp and Fried 2018). The graphical least absolute shrinkage and selection operator technique (GLASSO; Friedman et al. 2008) is one such regularization method. This reduces the overall number of edges by fixing a penalty on small values, shrinking them to zero, and dropping them from the model. This leads to the estimation of a sparse model with relatively few (i.e., presumably true) edges. Such parsimonious models are considered more interpretable (Epskamp et al. 2018a). Recent studies, however, have called into question the use of GLASSO, as this technique was originally developed for networks where the number of nodes exceeded the number of cases, which is unusual in psychopathology networks (Williams et al. 2019; Williams and Rast 2020). These studies suggest through simulations that GLASSO could eliminate true edges in the effort to estimate a sparse model. They suggest instead using confidence intervals to determine nonzero edges (Williams and Rast 2020).

Network Properties

Centrality

Network analysis can also be used to identify the core symptoms that are most important to maintaining the structure of the network (Borsboom and Cramer 2013). By adapting methodology from social network analysis (McNally 2021), these core symptoms are identified by assessing centrality indices, which work by determining the relative influence of specific nodes within the network. While centrality indices identify nodes that are of the greatest importance to the overall network structure (i.e., they can be considered the driving or maintaining force in the network provided certain conditions are met), these nodes *do not* have to represent hallmark symptoms of a disorder (i.e., depressed mood in major depressive disorder; McNally 2016; Borsboom 2017).

Indeed, there are several indices used to determine centrality, all of which differ slightly in their approach, but they all represent how interconnected a specific symptom is to other symptoms within the network. Such indices include *degree*, *betweenness*, *closeness*, *strength*, and *expected influence*. As *strength* and *expected influence* are the most widely used indices in psychopathology networks (as well as the most stable indices; Epskamp et al. 2012), readers are encouraged to see McNally (2021) for more information on the other three.

Strength centrality is measured by the sum of the absolute value of the edge weights between a particular node and all other nodes directly connected to it and represents how strong the direct connections are between that node and all other in the network. This is a useful index because it is likely that activation of symptoms with high strength centrality will trigger the activation of other symptoms (McNally 2016). This represents an accurate measure of relative importance if all edges in a network are positive; however, the accuracy of this index can become distorted by the increasing presence of negative edges (McNally 2021). *Expected influence*

centrality arose as a response to this limitation and takes the sign of the edge weights into account, thus providing a more accurate measure of centrality as the number of negative edges in a network increases, or one identical to strength if the network only contains positive edges (Robinaugh et al. 2016).

In order to state accurately that a node is more central than other nodes in a network, a high centrality value on a specific node should be statistically significantly different from centrality values on most, if not all, other nodes in the network (Fried 2016, 2018). This is assessed via bootstrapped difference tests (Epskamp et al. 2018a). To date, there are no established rules for how many significant differences between nodes are sufficient to consider a node highly central, and some studies have stated that a highly central node is meaningfully interpretable if its centrality indices are significantly different from at least half of the other nodes (Forrest et al. 2019; Beauchamp et al. 2021).

Accuracy and Stability

After estimating the network structure based on one of the above approaches and analyzing the network structure with regard to its parameters (i.e., presenting a graphical representation to reveal relationship density between nodes, assessing node centrality, determining clustering of nodes into communities), the next step is to evaluate the accuracy and stability of these network parameters before a thorough interpretation of the network can be made. As networks are based on sample data and given the relatively small sample sizes used in some psychopathology research (Hevey 2018), network analysis can be susceptible to sampling variation as network complexity increases (Epskamp et al. 2018a). Thus, researchers using network analysis are encouraged to follow three steps to assess for accuracy (i.e., how prone the network is to sample variation) and stability (i.e., how similar the network interpretation remains with fewer observations): (1) use bootstrapped confidence intervals to assess the accuracy of the estimated edge weights, (2) assess the stability of centrality indices that are estimated on subsets of the data, and (3) explore significant differences between edge weights and centrality indices using bootstrapped difference tests (Epskamp et al. 2018a). These steps, in addition to methods that determine if differences in network parameters between samples are genuine (Jones et al. 2021), have been used to address concerns regarding the replicability of findings in network analysis (McNally 2021). Readers are suggested to review Epskamp et al. (2018a) for a tutorial on these procedures.

Network Approach to Psychopathology in Eating Disorders

Outline of Emerging Research

The application of network analysis in psychopathology research has extended to EDs within recent years. Indeed, network analysis has been used in over two dozen studies to estimate network models among individuals with anorexia nervosa,

bulimia nervosa, binge eating disorder, and OSFED (Monteleone and Cascino 2021). Although researchers have continued to advocate for efforts to reconceptualize EDs from the network approach to psychopathology (Smith et al. 2018; Levinson et al. 2018b), recent work has also been done to derive other clinical applications from this approach, namely, the prediction of treatment outcomes in EDs (Smith et al. 2019; Vanzhula et al. 2019; Hilbert et al. 2020; Elliott et al. 2020; Brown et al. 2020; Monteleone et al. 2021). Despite this growing literature, however, only one study has been done that has specifically examined this approach with relation to NES (Beauchamp et al. 2021).

Network Approach to Psychopathology in NES

Beauchamp et al. (2021) examined the psychopathology network of NES in a community sample of individuals diagnosed with NES recruited over 5 years. One hundred and forty-four participants were included in the study, participants were between 20 and 85 years of age ($M_{age} = 43.97$, $SD = 12.14$), and the majority were female (67.6%), were White (60.1%), and had a body mass index (BMI) score that put them in the obese range (56.1%). NES diagnoses, based on the research diagnostic criteria (Allison et al. 2010), were confirmed using the Night Eating Syndrome History and Inventory (Lundgren et al. 2012a), and participants also completed the Night Eating Questionnaire (Allison et al. 2008) and the Eating Disorder Examination (Fairburn et al. 2008). To further capture behavioral symptoms associated with NES (i.e., morning anorexia, nocturnal awakenings, nocturnal ingestions of food, and evening hyperphagia), participants completed 10-day, 24-h food and sleep diaries. In addition, participants were asked about non-NES-specific symptoms (i.e., symptoms that have been associated with NES but are not part of the diagnostic criteria) to broaden the potential plausible causal network of symptoms. Based on the proposed etiology and maintenance of NES in the literature thus far, this included depressed mood, circadian rhythm patterns, sleep quality and daytime sleepiness, and perceived stress. Symptoms were assessed via the Beck Depression Inventory-II (Beck et al. 1996), Morningness-Eveningness Questionnaire (Horne and Östberg 1976), Pittsburgh Sleep Quality Index (Buysse et al. 1989), Epworth Sleepiness Scale (Johns 1991), and Perceived Stress Scale-10 (Cohen and Williamson 1988), respectively. After the removal of one symptom that was found to be capturing a similar construct of another (i.e., number of awakenings removed, as this was captured by the number of nocturnal ingestions which inherently suggests nocturnal awakenings), there were 17 symptoms included in network estimation.

Results from this study found that the psychopathology network of NES was sparsely connected (i.e., relatively few connections between symptoms; see Fig. 3), though the estimates of symptom centrality were stable. Surprisingly, neither evening hyperphagia nor nocturnal ingestions of food were found to be central symptoms in the network, which are necessary symptoms for a diagnosis of NES to be made as per the research diagnostic criteria. Instead, depressed mood, poor sleep quality, and a strong urge to eat during the night (all represented by Criterion C in the

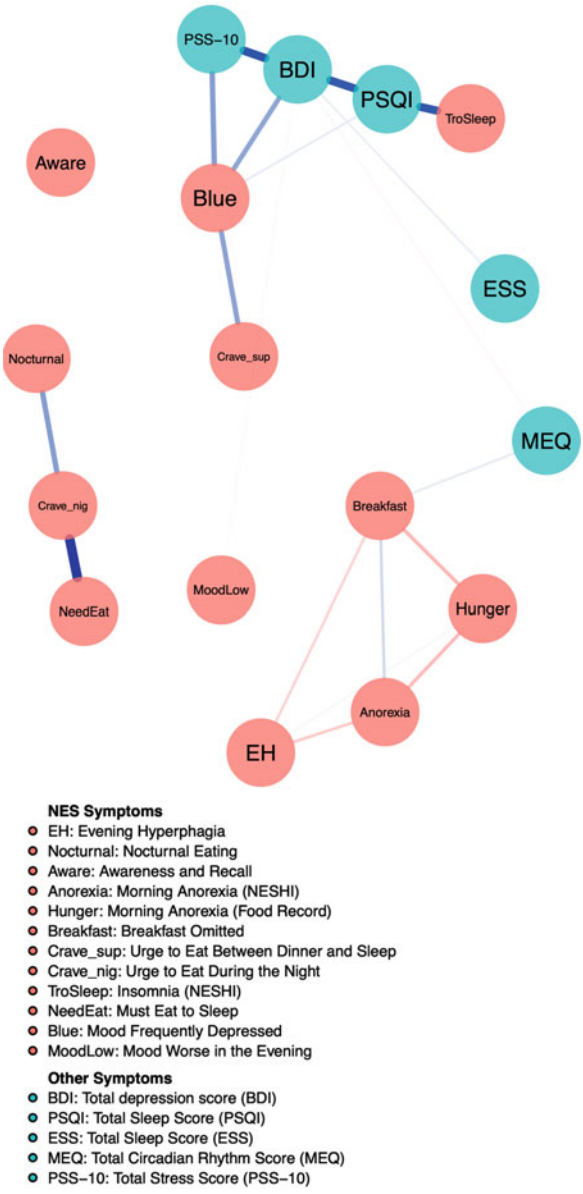


Fig. 3 The psychopathology network of NES. Blue and red lines indicate positive and negative associations, respectively, and line thickness indicates strength (e.g., thicker line equals stronger association). (From Beauchamp et al. (2021) with permission)

research diagnostic criteria) were found to be the most central symptoms (i.e., symptoms with the greatest importance to the network; see Fig. 4) and statistically more central than most other symptoms in the network (see Fig. 5).

The authors stated in their conclusions that these results call into question the conceptualization of NES as presented by the research diagnostic criteria,

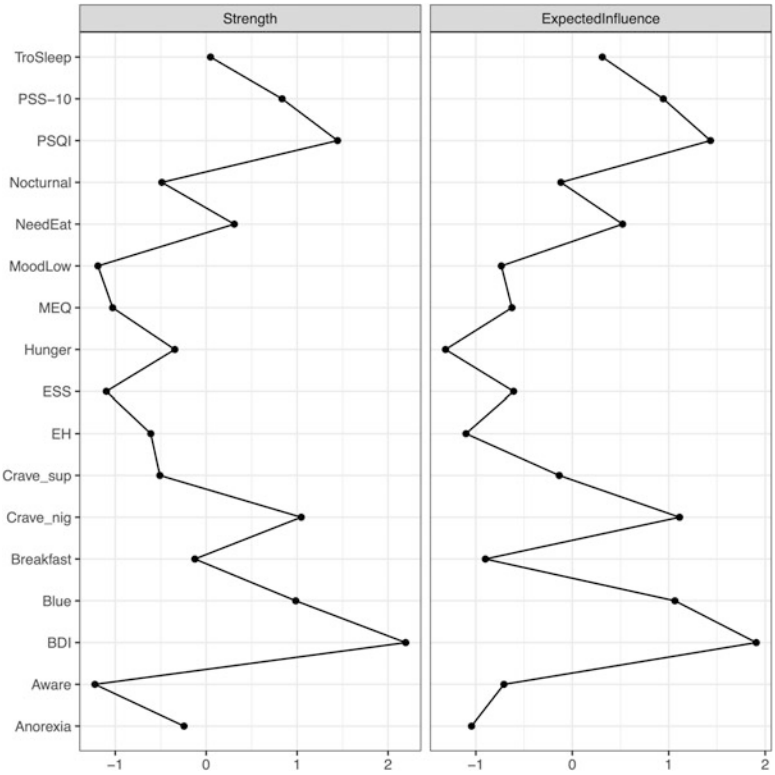


Fig. 4 Centrality plot for the psychopathology network of NES. Plot is standardized on z-scores ($M = 0$, $SD = 1$) and higher numbers mean greater centrality. (From Beauchamp et al. (2021) with permission)

particularly that both evening hyperphagia and nocturnal ingestion of food – both symptoms in Criterion A and considered defining features of NES – were not the most central symptoms. Other researchers of network theory, however, have emphasized that central symptoms do not have to be hallmark symptoms of a disorder and are instead conceptualized as having greater importance (i.e., driving or maintaining forces in a network; Borsboom 2017; McNally 2021). Beauchamp et al. (2021) claimed that perhaps evening hyperphagia and nocturnal ingestion of food are not the most important symptoms, but are instead resulting behaviors in a symptom chain that begin with depressed mood and urge to eat during the night, respectively.

In examining the connections between symptoms in the NES network model to determine this potential symptom chain, Beauchamp et al. (2021) found that depressed mood was directly associated with disturbances in sleep, stress, circadian rhythm patterns, and the urge to eat between dinner and sleep, with no other direct connections to remaining NES symptoms. Of course, this would mean that if depressed mood was indeed the most central symptom, it appeared that increases in depressed mood would correlate with poorer sleep quality (which was also the

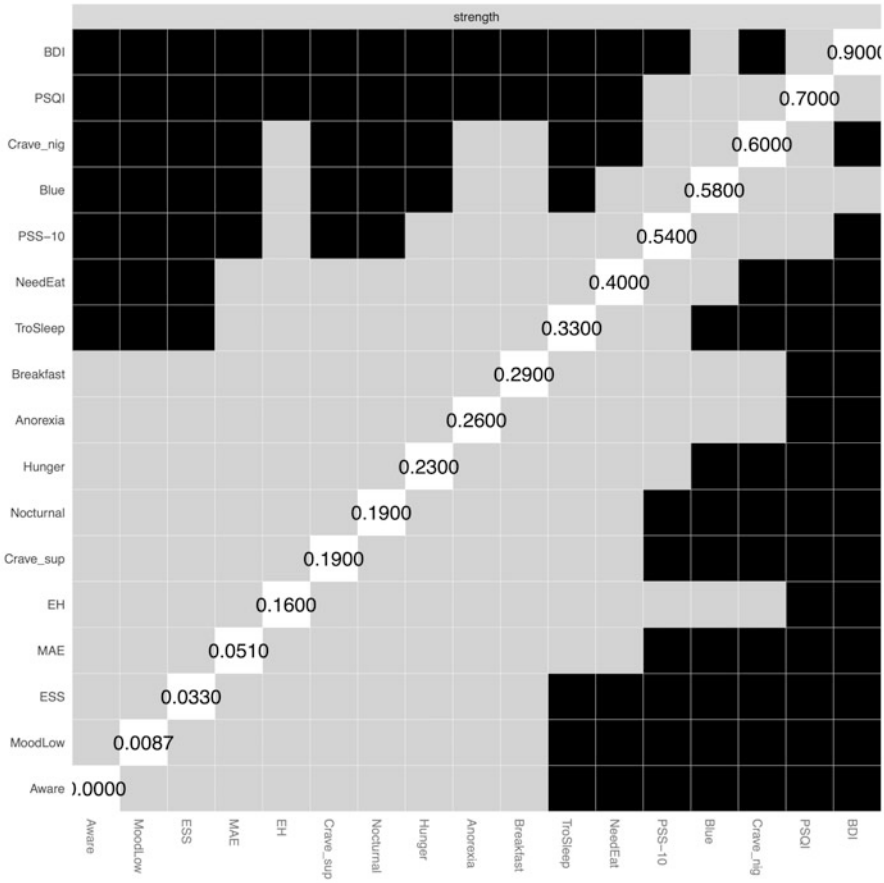


Fig. 5 Bootstrapped strength difference results. Values on the diagonal indicate unstandardized strength centrality values for the corresponding symptom. Black boxes represent significant differences in strength between symptoms, and gray boxes represent nonsignificant differences. (From Beauchamp et al. (2021) with permission)

second most central symptom), increased stress, a preferred evening circadian pattern, and increased urges to eat between dinner and sleep. Indeed, this connection eventually leads to evening hyperphagia. In addition, urge to eat during the night (the third most central symptom) was directly associated with the need to eat in order to sleep and nocturnal eating (i.e., nocturnal ingestion of food). Therefore, it is likely that two symptom chains exist, whether alone or concurrently, and are ordered such that (a) an individual may feel that they have an urge to eat during the night which makes returning to sleep virtually impossible, and so they engage in nocturnal ingestions of food, and/or (b) a combination of depressed mood and poor sleep, along with an urge to eat between dinner and sleep, cascades through additional symptoms and eventually results in evening hyperphagia. The authors caution that

the directionality and temporal ordering of these associations are unclear due to the cross-sectional nature of the data and that these results need to be confirmed with longitudinal studies.

Clinical Implications

The conceptualization of NES through the lens of network theory presents several advantages from a clinical standpoint. Beauchamp et al. (2021) indicated that the three central symptoms (i.e., depressed mood, poor sleep quality, and urge to eat during the night) can be considered primary intervention targets, as treating these symptoms may lead to disruptions in the symptom chain that maintain NES. Indeed, researchers exploring EDs with network analysis postulate that interventions that target highly central symptoms may also greatly impact other symptoms in the network (Levinson et al. 2018b). In addition, changes to the most central symptoms seen in psychopathology networks have been strongly associated with changes in overall symptom severity compared to changes in less central symptoms (Robinaugh et al. 2016). Researchers have cautioned, however, that it is also possible that central symptoms may arise as the consequence of other symptoms, or a bidirectional relationship may occur and central symptoms may be both a cause and consequence (Levinson et al. 2018b; McNally 2021). In addition, it is questionable if current psychological treatments could target a specific symptom without simultaneously impacting adjacent symptoms in the network (McNally 2021). Nevertheless, extant literature supports targeting highly central symptoms as a means to provide treatment (Levinson et al. 2018b) or predict treatment outcomes (Hilbert et al. 2020; Elliott et al. 2020; Brown et al. 2020).

An additional domain of conceptual and clinical utility explored by Beauchamp et al. (2021) was NES symptom heterogeneity as determined by network structure and density. The authors stated that, under current research diagnostic criteria, only three of five symptoms in Criterion C are necessary for a diagnosis of NES. This is consistent with several other DSM-5 diagnoses (e.g., major depressive disorder requiring five or more symptoms from a list of nine), and such heterogeneity is considered another limitation of the medical model paradigm (van Borkulo et al. 2015). As network structure is concerned with the clustering and/or ordering of symptoms (i.e., "where" the symptoms are in the network) and network density is connections between symptoms (i.e., "how" symptoms are connected, how sparse or densely connected is the overall network, and how strong is each individual connection), how might the activation of one symptom (and its connection with core and distal symptoms) lead to differences in presentation and levels of clinical impairment/distress in an individual with NES? In addition, are certain clusters of symptoms more likely than others to sustain NES or might influence prognosis or recovery? Beauchamp et al. (2021) recommended comparisons of different network models between samples (i.e., the network comparison test; van Borkulo et al. 2022). Indeed, such a technique has been used to suggest that (a) network density, as well as certain clusters of symptoms, can predict response to treatment (van Borkulo et al.

2015; Smith et al. 2019) and (b) network density, but not network structure, is different (i.e., stronger) when comparing clinical versus nonclinical samples (Vanzhula et al. 2019). Therefore, clinical assessments and treatments may wish to target select clusters of symptoms, as well as focus on ways to weaken symptom connections as whole. In addition, network comparisons may be especially useful when evaluating samples of individuals that meet clinical versus subclinical thresholds of NES, particularly with symptoms that require specific occurrence rates (i.e., episodes of nocturnal ingestions of food per week).

Future Directions in Network Analysis of NES

This chapter provided a brief overview of NES, an ED presently characterized by a disrupted circadian rhythm resulting in a shifted pattern of food intake in individuals with concomitant alterations in sleep, mood, and eating behaviors. Research to date has conceptualized NES through a medical model paradigm of disease, which suggests that symptoms of NES are the result of an underlying common cause, though this causal mechanism remains poorly understood, and the functional relationships between symptoms are relatively unknown. In addition, the numerous variations in diagnostic criteria for NES have presented a significant challenge in accurately conceptualizing this disorder from a research and clinical perspective. Beauchamp et al. (2021) presented an alternative approach to conceptualization of NES by examining the core symptoms using the network approach to psychopathology. Results from this study suggested that depressed mood, poor sleep quality, and a strong urge to eat during the night after the initiation of sleep were found to be the core symptoms of NES, rather than evening hyperphagia and nocturnal ingestion of food, the key symptoms presented by Allison et al. (2010). Lastly, research and clinical implications of these results were presented. Of course, results from this one study have propagated numerous research questions, and the emergence of network analysis as a technique in the field of psychopathology over the past decade has resulted in several novel methods to allow such further exploration into the psychopathology network of NES. Thus, this chapter closes with a discussion on future directions for network analysis of NES.

Network Comparisons

First, among one of the next steps in further exploring the conceptualization of NES using the network approach to psychopathology is to include a larger, more diverse sample. However, it might also be of great benefit to examine group differences with a somewhat different network analysis technique. Recently, Costantini et al. (2019) outlined a new method for estimating and analyzing psychopathology networks, particularly when estimating networks between different groups (e.g., clinical versus nonclinical samples, males versus females, etc.), called the *fused graphical lasso* (FGL) method. These researchers state that estimating a single network that includes

all groups will fail to illustrate inter-group differences, but also that estimating a separate network for each group would fail to capture inter-group similarities. In addition, they report that differences observed are likely to arise as much from sampling fluctuations as from true differences. This FGL method more accurately estimates different networks for each group by including group similarities as they occur among the different groups. This technique has also been used in other ED network analysis literature to compare diagnosis and age differences between networks (Schlegl et al. 2021).

In addition to making comparisons between demographic variables, it would be important to explore differences in weight status among individuals with NES. As stated above, NES can occur in individuals with and without overweight/obesity. While some studies have found no differences in symptomatology between these two groups, others have found (a) higher incidences of nocturnal awakenings and food consumption, (b) that populations with NES who were persons without overweight/obesity were younger, and (c) that NES symptoms preceded obesity. Indeed, it is unknown if network structure and/or density differs between individuals with and without overweight/obesity. Also, it is possible that BMI does not represent the appropriate cutoff that differentiates such network differences between those with and without overweight/obesity. These classifications are based on a BMI cutoff of 25 kg/m^2. Future studies can explore this by identifying where networks differ on a BMI continuum through the use of model-based recursive partitioning. This technique uses decision trees to detect optimal splits on selected variables by assessing parameter instability and is seen as similar to a moderation analysis (e.g., examining how parameters differ based on subgroups; Jones et al. 2020). This technique could more accurately explore exactly where network differences are on a continuum of BMI, rather than by cutoff.

Temporal Network Analysis Models

Second, future studies should also include longitudinal analyses of individuals with NES via temporal time-series networks. Network analysis models developed from cross-sectional data are limited in their ability to model within-subject variance or to account for changes across time. Newer methods that can assess for intraindividual differences have been developed to capture this within-subject variation and more accurately how symptoms maintain disorders at both group and individual levels (Fisher et al. 2017; Epskamp et al. 2018b). These temporal group-level models (i.e., multilevel vector autoregression models) can assess for intraindividual differences across time, between-subjects similarity, and differences between the within- and between-subjects networks. This would require large amounts of frequent longitudinal datapoints, and such methods have been used in prior ED network analysis research by adopting ecological momentary assessment (Levinson et al. 2018a) or perceived causal relations (Klintwall et al. 2021) techniques. Notably, Levinson and colleagues (Levinson et al. 2018a) claim that better understanding how symptoms maintain themselves at both group and individual levels will lead to

(1) the development of novel, personalized treatments and (2) explaining the large amounts of heterogeneity among EDs.

Refine Intervention Targets

Lastly, newer literature on network theory has called into question the usefulness of identifying central symptoms as effective treatment targets, particularly among models using cross-sectional data (Henry et al. 2021; Lunansky et al. 2021). These researchers have argued that symptom centrality is based on structure/density of the network, but do not account for network *dynamics* (i.e., how symptoms influence one another; Lunansky et al. 2021). While they do not rule out the usefulness of temporal time-series networks, these authors suggest using concepts from *control theory* (a discipline from the field of mathematics that deals with controlling dynamic systems; Henry et al. 2021) to facilitate the selection of intervention targets. Indeed, such an approach can not only identify the best symptom (or set of symptoms) to target for intervention, but can estimate how effective the intervention might be on affecting other symptoms in the network (Henry et al. 2021). Conversely, this technique can also estimate which symptom would have the most profound effect on activating other symptoms (i.e., which symptom, after being influenced by an external event, would set off the cascade of symptoms leading to the presentation of a disorder; Lunansky et al. 2021). In light of these potential findings, the utilization of such an approach in a sample of individuals with NES should be prioritized.

Applications to Other Eating Disorders

This chapter reviewed the application of the network approach to psychopathology on NES to explore the core features and symptom relationships in an NES network. This approach has already been used to estimate network models among other EDs, particularly to explore the reconceptualization of ED psychopathology, to predict treatment outcomes, and to develop novel, personalized treatments. However, the NES network is unique among other ED networks in that it included symptoms that are related to, but not specific to, ED behavior (e.g., mood, circadian rhythm, sleep, and stress). Indeed, few other ED networks include such nonspecific symptoms (Monteleone and Cascino 2021), and including a broader range of these symptoms in network estimation may help refine ED conceptualization, explore symptom connections between EDs and comorbid disorders, and capture central symptoms more accurately. In addition, given the high rates of heterogeneity in ED symptom presentation and response to treatment, researchers have suggested including more general psychopathology symptoms, as well as external field factors, to help explain interindividual differences in treatment response (Levinson et al. 2018a; Monteleone and Cascino 2021). While these clinical applications have yet to be explored with an NES network, efforts to conceptualize NES with the network approach to

psychopathology have found that NES-specific symptoms (i.e., evening hyperphagia and nocturnal ingestion of food) were not of great importance to the network. Rather, non-NES-specific symptoms (e.g., depressed mood, poor sleep quality) were found among the most central symptoms in the network.

Mini-Dictionary of Terms

- **Centrality.** A relative measure of a node's overall importance (i.e., influence) within a network.
- **Concentration networks.** Networks that are estimated using partial correlations. Edges between nodes can be interpreted as relationships that exist when the effects of all other nodes are accounted for.
- **Network approach to psychopathology.** An approach to conceptualizing psychiatric disorders that focuses on how a network of causal interactions among symptoms influences the development and maintenance of the disorder.
- **Night eating syndrome (NES).** An eating disorder currently characterized by a delayed circadian pattern of eating that results in increased consumption of food after the evening meal and/or eating during the night after awakening from sleep. Individuals with NES may also experience reduced eating behavior during the morning, as well as changes in sleep and mood.
- **Strength and expected influence.** Two widely used centrality indices that determine how strongly a node is directly connected with all other nodes in a network. Expected influence accounts for the valence of a connection and is more accurate than strength when networks have negative edges.

Key Facts of Night Eating Syndrome and Network Analysis of Features

Key Facts of Night Eating Syndrome

Night eating syndrome (NES) was first identified in 1955 by Stunkard and colleagues as a cluster of nonnormative eating behaviors that came during periods of stress in individuals with obesity.

Prevalence rates for NES are about 1.5% for the general population and are higher in populations with obesity (6–16%; up to 55% in patients undergoing bariatric surgery for obesity), but not all individuals with NES are persons with overweight/obesity.

NES has not been recognized as a separate diagnosis in the *Diagnostic and Statistical Manual of Mental Disorders* and is subsumed under the "other specified feeding and eating disorder" category.

Specified diagnostic criteria were proposed in 2010 by Allison and colleagues to provide as standardized definition of NES for clinical and research purposes.

Core features of NES include the consumption of ≥25% of total daily calories after the evening meal (i.e., evening hyperphagia) and/or nocturnal ingestions of food after awakening from sleep.

When conceptualized with the network approach to psychopathology, these core features are not the most important symptoms in the NES network model.

Depressed mood, poor sleep quality, and a strong urge to eat during the night after the initiation of sleep were considered the most important symptoms.

According to the network approach to psychopathology, these symptoms may cause evening hyperphagia and nocturnal ingestions of food and should be considered primary intervention targets.

Summary Points

- Night eating syndrome (NES) is an eating disorder characterized by the consumption of ≥25% of total daily calories after the evening meal (i.e., evening hyperphagia) and/or nocturnal ingestions of food after awakening from sleep.
- Conceptualizations of NES have been based on the medical model paradigm of disease, which assumes an underlying mechanism that causes symptoms.
- Other eating disorders have been reconceptualized using the network approach to psychopathology, which assumes a functional, causal network of symptoms.
- Network analysis can be used to model the network approach to psychopathology and can assess for symptoms that are most important or influential to the network.
- Evening hyperphagia and nocturnal ingestions are not the most important symptoms in an NES model; rather depressed mood, poor sleep quality, and a strong urge to eat during the night are considered most important.
- These three important symptoms may be the cause of evening hyperphagia and nocturnal ingestions and should be considered primary intervention targets.
- Beyond more accurately conceptualizing NES, network analysis can also be used to examine group differences (i.e., gender, weight status), understand how symptoms maintain themselves, and facilitate the selection of intervention targets.

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Avoidant/Restrictive Food Intake Disorder in Children

62

Yaara Shimshoni and Eli R. Lebowitz

Contents

Introduction 1236
ARFID in Children 1237
Characteristics 1237
Prevalence of ARFID 1238
Impact of ARFID 1239
Differential Diagnosis 1240
Etiology 1241
Assessment of ARFID 1242
Treatment of ARFID 1243
Summary 1251
Mini-Dictionary of Terms 1251
Summary Points 1253
References 1254

Abstract

Avoidant/restrictive food intake disorder (ARFID) is characterized by dietary restrictions that are not based on weight or shape concerns but that result in marked interference in feeding, growth, or psychosocial functioning (American Psychiatric Association, Diagnostic and statistical manual of mental disorders, 5th edn. American Psychiatric Publishing, Arlington, 2013; Eddy et al., Int J Eat Disord 52(4):361–366. https://doi.org/10.1002/eat.23042, 2019). ARFID was introduced as a diagnostic category in the 5th edition of the DSM in 2013, and research into ARFID remains limited and provides only partial understanding of the different aspects of the problem such as its prevalence, characteristics and driving factors, assessment, and treatment. The aim of this chapter is to summarize and discuss this knowledge with a focus on childhood ARFID.

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Keywords

Avoidant/restrictive food eating disorder · Assessment · Children · Prevalence · Clinical presentation · Treatment · Etiology · Differential diagnosis

Introduction

Avoidant/restrictive food intake disorder (ARFID) was introduced in the 5th edition of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM) in 2013 as an expansion of the DSM-4 diagnosis of feeding and eating disorder of infancy and early childhood (American Psychiatric Association 2013). This change allowed for individuals – children and adults – with significant food selectivity who previously did not meet diagnostic criteria for feeding and eating disorder of infancy and early childhood to receive recognition in the DSM. The main changes were the removal of restrictions on the age of onset (which was previously before age 6 years) and on weight (which previously had to be low). A similar diagnosis of ARFID has been recently included in the newest version of the International Classification of Diseases (ICD-11), which is the World Health Organization's comprehensive classification system for all diseases and health problems (Claudino et al. 2019). The inclusion of ARFID in the ICD-11 indicates that this eating problem is gaining universal recognition.

Individuals with ARFID limit the variety or quantity of foods they eat to the extent that these limitations are associated with marked interference in feeding, growth, or psychosocial functioning (American Psychiatric Association 2013). While many young children, especially between the ages of 2 and 5, exhibit picky eating which is usually not severe and tends to resolve over time (Taylor et al. 2015), ARFID is different. To meet a diagnosis of ARFID, the restricted eating must persist and lead to meaningful interference in at least one of the following ways: (a) weight loss or failure to gain weight; (b) nutritional deficiency; (c) dependence on nutritional supplements or enteral feeding (e.g., tube feeding); or (d) psychosocial impairment such as difficulty with friends, at school, in the family domain or experiencing personal feelings of distress (DSM-5, criteria A1–A4). There are also several exclusion criteria. First, the restricted eating cannot be driven by fear of gaining weight or by distorted body image. If this is the case, a different eating disorder such as anorexia nervosa or bulimia nervosa might be considered. Additionally, the restricted eating cannot be due to lack of available foods or cultural norms. It is possible for ARFID to co-occur with other psychiatric or medical conditions, although to qualify for an ARFID diagnosis in addition to other conditions, the eating problem must meet criterion A and be severe enough to require specific clinical attention, beyond what would be expected for the co-occurring problem (DSM-5 criteria B–D).

Although seemingly clear, the operationalization of these diagnostic criteria has ambiguities, potentially contributing to inconsistent findings on various aspects of ARFID, including assessment, prevalence, correlates, course, and treatment, all of

which impede our understanding of this problem. For example, one recently published study sought to examine the degree to which different operationalizations of the diagnostic criterion A for ARFID contributed to differences in the frequency of individuals who were eligible for an ARFID diagnosis (Harshman et al. 2021). These researchers identified 19 different potential operational definitions and determined how many individuals in a sample of 80 individuals enrolled in an avoidant/restrictive eating study (children, adolescents, and young adults) would meet for ARFID using each of the definitions. They found considerable differences in ARFID diagnosis eligibility depending on the operational definition utilized. Using the strictest definition, 50.0% ($n = 40$) of participants met criteria for ARFID, while the application of the most lenient definition led to nearly double that number, resulting in 97.5% ($n = 78$) meeting criteria for ARFID. For an in-depth account of the challenges relating to the diagnosis and operationalization of the ARFID diagnostic criteria, see a summary by the Radcliffe ARFID Workgroup, a cohort of international experts in the field of feeding and eating disorders (Eddy et al. 2019), and a systematic review of diagnostic validity in ARFID (Strand et al. 2019).

Although there are many aspects of ARFID that are not well understood, since its official introduction in 2013, research into this eating disorder has been rapidly expanding. This chapter aims to provide a summary of current evidence-based understanding of ARFID – its characteristics, impact, etiology, assessment, and available treatments. Of note, although ARFID can be diagnosed throughout the lifespan, the vast majority of publications to date focus on ARFID in children and adolescents (Strand et al. 2019). For this reason, this chapter will focus on findings relating to ARFID in this population.

ARFID in Children

Characteristics

Current research into the clinical characteristics of ARFID highlights its heterogeneity. For example, some children with ARFID are underweight, while others maintain average and even above-average weight, often due to supplements intake, tube feeding, or consuming mostly energy-dense processed foods. Some have a long-lasting history of difficulty with food intake, often dating back to infancy, while others may have started only recently to restrict their intake, perhaps following a choking incident or severe stomach bug. Some have additional medical or mental problems that impact their eating, such as gastrointestinal problems, oral-sensory motor problems, autism spectrum disorder (ASD), or anxiety, while others do not. For some, the ARFID manifests in significant nutritional deficiency (e.g., low levels of minerals like iron, zinc, and magnesium and vitamins A, C, and D), while for others most ARFID-related impairment occurs in the psychosocial domain (e.g., interfering with the ability to function well with friends and family members and at school).

The DSM provides examples of factors that may be driving the restriction in eating: (a) apparent limited interest in eating or poor appetite; (b) selectivity of foods based on their sensory properties such as smell, texture, color, and temperature; and (c) fear of aversive consequences from eating such as choking, vomiting, or gastrointestinal pain (American Psychiatric Association 2013). The validity of these three distinct presentations has been examined and is gaining support (Norris et al. 2018; Zickgraf et al. 2019a). Based on these phenomenological distinctions, Thomas et al. (2017c) proposed a three-dimensional model of the neurobiology of ARFID, rooting these phenomenological distinctions in neurobiological abnormalities in sensory perception, homeostatic appetite, and negative valence systems (for further elaboration see below under "Etiology").

It is important to note that these three presentations are not mutually exclusive, and it is not rare to encounter children whose symptoms fit more than one of these presentations. For example, one paper reported on the case of an 11-year-old boy who showed features of all three ARFID presentations. This child presented with a lifelong history of sensory sensitivity, apparent limited interest in food, and phobia of vomiting, all resulting in him restricting his diet to a single food item (yogurt) for more than 5 years (Dolman et al. 2021). Additionally, Zickgraf et al. (2019a) identified a fourth subgroup of patients who exhibited both poor appetite and selective eating. This group had the longest history of growth faltering and was least likely to present with acute weight loss. Further, the DSM recognizes that there could be additional factors driving the restricted eating, though these are not yet well described. For example, one study of children and adolescents referred to a hospital-based pediatric eating disorder service and diagnosed with ARFID ($N = 102$, ages 8–18 years) identified age, weight, and duration of illness as factors influencing the presentation of ARIFD. In this sample, adolescents (ages 12–18 years) presented with higher rates of depression compared with children (ages 8–11 years); those with chronic ARFID symptoms ($\geq$12 months) presented with significantly lower weight than those with acute symptoms ($<$12 months); and those with acute symptoms endorsed significantly higher suicidal ideation and/or self-harm (Duncombe Lowe et al. 2019). The heterogeneity in ARFID presentation, suggesting distinct etiological and maintenance factors for different restrictive eating patterns, has led to calls for the development of interventions that consider variability in clinical symptoms, demographic characteristics, and appropriate levels of care (Eddy et al. 2019; Zickgraf et al. 2019a).

Prevalence of ARFID

There is a paucity of epidemiological research on ARFID, and prevalence estimates have ranged widely, in both clinical and community samples (Bourne et al. 2020). This could be attributed, in part, to the lack of clear and agreed-upon operationalized definitions of the diagnostic criteria in the DSM, forcing researchers and clinicians to rely on clinical judgment (Harshman et al. 2021).

In community samples, reports of ARFID prevalence range between 0.3% and 3.2%. An Australian population-based study of adolescents and adults ages 15 years and older ($N = 5737$) reported a 3-month point prevalence of 0.3% assessed both in 2013 and in 2014 (Hay et al. 2017). The estimated prevalence of other specific eating disorders was higher in comparison (0.4% and 0.5% for anorexia nervosa, 1.1% and 1.2% for bulimia nervosa). These rates were lower than the estimated prevalence of 3.2% for the heterogeneous group of other specified feeding or eating disorders (OSFED), which includes problems such as atypical anorexia nervosa (anorexia with weight loss that remains within or above the normal range) and atypical bulimia nervosa (subthreshold bulimia with low frequency of binge eating and inappropriate compensatory behaviors). In another self-report community-based study in Switzerland, ARFID was reported in 3.2% of children and adolescents ($N = 1444$; ages 8–13 years; Kurz et al. 2015). Both studies reported similar rates of ARFID in males and females.

Reports of ARFID prevalence in clinical samples of patients in children and adolescent tertiary care centers mostly range between 5% and 14% (Fisher et al. 2014; Norris et al. 2014), with the highest prevalence (22.5%) found in a pediatric partial hospitalization program (PHP) for eating disorders (Nicely et al. 2014). In a sample of 2231 consecutive referrals to pediatric gastrointestinal clinics (ages 8–18 years), the reported prevalence was 1.5% (Eddy et al. 2015). Most reports rely on retrospective chart reviews, documenting encounters from before ARFID was formally and clearly defined in the DSM.

Impact of ARFID

There is little research exploring the outcomes of ARFID, most of which focuses on medical monitoring of the more severe and low-weight ARFID patients admitted to inpatient care (Bourne et al. 2020). Available research suggests serious potential medical and mental sequelae of ARFID. When ARFID is characterized by weight loss or failure to gain weight, this could lead to trouble concentrating, sleep disturbances, and feeling weak, tired, or irritable. It is important to note that children are expected to continuously gain weight. Therefore, for children, maintaining the same weight over extended periods of time is considered weight loss and poses a serious problem (Bryant-Waugh and Higgins 2020). Another possible consequence of restricting food intake is nutritional deficiencies. These commonly include minerals such as iron, calcium, and zinc and vitamins A, C, and D. Deficiencies in these micronutrients can seriously compromise a child's health, leading to problems like anemia, poor bone health, eye and skin problems, and scurvy (Taylor and Emmett 2019).

In some cases, when the child is persistently losing weight and failing to meet energy and/or nutritional needs, it could be deemed medically necessary to introduce tube feeding (also known as nasogastric/gastrostomy feeding tubes). This usually leads to a meaningful improvement in the child's intake and weight and to short-term relief in the concern about the child's health. In the longer term however, tube

feeding may interfere with the body's natural tendency to regulate hunger, and the child may become dependent on the tube feeding and less motivated to eat independently. The insertion of the tube may also restrict the child to the home, leading to disengagement from normal life. For these reasons, it is recommended that when a tube is placed, this step is accompanied with a plan indicating when and how to remove it and encourage independent eating (Dovey et al. 2018).

For some children with ARFID, the main area of impact is in the psychosocial domain, impairing both the child's and the family's functioning. For example, ARFID can impact the child's ability to take part in daily social events such as eating at school or at a restaurant and going to play dates or birthday parties, negatively impacting their relationships with peers and family. ARFID can also have a detrimental impact on the family as a whole. Parents often describe experiencing distress, anxiety, frustration, and conflict between family members at mealtimes. Many parents accommodate the ARFID to alleviate the child's distress and make it easier for the child to eat in the short term (e.g., by providing the child only with their preferred foods). This accommodation, though well-intentioned, usually leads over time to maintenance of the ARFID symptoms and related impairment (Shimshoni et al. 2020; Zickgraf et al. 2019b).

Differential Diagnosis

Arriving at a diagnosis of ARFID involves ruling out other conditions that may better explain the restricted eating. Some examples are gastrointestinal conditions, oral-motor functioning, anxiety, and depression. It is also important to distinguish ARFID from other eating disorders such as anorexia nervosa, bulimia nervosa, and binge eating disorder. A central difference between ARFID and these other eating disorders is that in ARFID, the restriction of food intake is not driven by concerns about weight or shape and the individual with ARFID will not experience extreme anxiety relating to gaining weight (Izquierdo et al. 2019).

Among these eating disorders, anorexia nervosa stands out as a particularly relevant differential diagnosis, especially in children 8 years old and above (Bryant-Waugh and Higgins 2020). While there are some similarities between anorexia nervosa and ARFID, such as restricted food intake, negative impact on family members and relationships, and possibly weight loss or lack of motivation for change, there are also striking and important differences. Aside from the absence of underlying concerns about weight or shape or behaviors intended to promote weight loss in ARFID, studies comparing children with ARFID to those with anorexia nervosa found that children with ARFID were younger and a greater proportion were male (Nicely et al. 2014; Ornstein et al. 2017). Additionally, in ARFID the problematic eating typically dates back to early childhood, whereas in anorexia eating behavior was often normative before the development of the problem (Fisher et al. 2014). Although patients with ARFID and anorexia nervosa both restrict the foods they eat, those with ARFID often prefer energy-dense, high-fat, and high-sugar

foods (e.g., processed foods), whereas those with anorexia usually eat low-calorie, low-fat, and low-sugar foods, such as vegetables (Harshman et al. 2019).

Another difference between ARFID and other eating disorders relates to common co-occurring problems. While both ARFID and other eating disorders frequently co-occur with elevated levels of anxiety and depression (Thomas et al. 2018), some studies report higher rates of co-occurring anxiety disorders in ARFID compared with anorexia and bulimia (Fisher et al. 2014). One retrospective chart review reported generalized anxiety disorder in 50% of adolescents with ARFID ($N = 34$; Norris et al. 2014). Autism spectrum disorder also commonly co-occurs with ARFID, with estimates ranging between 3% and 13% of cases (Cooney et al. 2018; Lucarelli et al. 2017; Nicely et al. 2014). Additional conditions strongly associated with ARFID include oppositional defiant disorder (ODD), obsessive-compulsive disorder (OCD), attention-deficit/hyperactivity disorder (ADHD), gastrointestinal symptoms, and other medical conditions (Bryant-Waugh and Higgins 2020; Eddy et al. 2015; Fisher et al. 2014). Compared with other eating disorders, ARFID was found more weakly associated with mood disorders (Nicely et al. 2014).

Etiology

Why some children develop ARFID, and others do not, is not well understood. In line with the widely accepted biopsychosocial model for understanding heath and illness (Engel 1977), it is probable that several types of factors – biological, psychological, and environmental – and the interactions between them, contribute to the development of this problem (Brigham et al. 2018). Though applicable to most disorders, this complexity is underscored in the case of ARFID, a problem that is heterogeneous and that appears in high frequency alongside other mental and medical conditions, increasing the likelihood that ARFID is caused by the interplay between several different factors (Bryant-Waugh and Higgins 2020; Thomas et al. 2017c).

Some possible environmental contributors to the etiology of ARFID include familial and cultural beliefs and attitudes relating to food and family meal environment and food-related interactions (Satter 1999), as well as maternal food intake during pregnancy and breastfeeding (Mennella et al. 2001). For reviews of environmental factors impacting child eating preferences, see Savage et al. (2007) and Taylor and Emmett (2019). Other contributing factors may include mood, temperament, and arousal levels (Bryant-Waugh and Higgins 2020). Specific attention has recently been given to the role of disgust in the etiology of ARFID, though research is indicated to further understand and support this role (Menzel et al. 2019). Co-occurring problems may also influence the development of ARFID. For example, food allergies or celiac may lead some children to increase their overall food restrictions and avoidance, and autism spectrum disorder, often characterized by heightened sensory sensitivity, might increase sensitivity to smells and sounds associated with food and eating (Thomas and Eddy 2019). Twin studies provide

some indication that genetic factors might also play a role in taste preference (Cooke et al. 2007), though research into this question is scarce in the context of ARFID.

One etiological model that is gaining support is the three-dimensional model of the neurobiology of ARFID, which roots the phenomenological differences in ARFID in neurobiological abnormalities (Thomas et al. 2017c). According to this model, ARFID presenting with lack of interest in food might be associated with differences in activation of appetite-regulating centers in the brain, ARFID presenting with selective eating based on sensory characteristics might be associated with oversensitivity in taste perception, and ARFID characterized by fear of aversive consequences might be associated with hyperactivation of the fear processing brain circuitry. Since children can present with more than one of these three presentations, each individual's severity ratings across these three domains can be quantified and plotted on the three-dimensional model to create a unique ARFID profile.

Assessment of ARFID

Several measures are available for evaluating ARFID, including self-report screening instruments and clinician-administered diagnostic interviews. Screening instruments can indicate the need for further assessment and are not sufficient for establishing a diagnosis. Screening instruments for ARFID include the Eating Disorders in Youth-Questionnaire (EDY-Q; Kurz et al. 2015), intended to detect early-onset disordered eating in children ages 8–13; the ARFID Brief Screener (ARFID-BS; Dinkler et al. 2022), intended for parents of children ages 4–7; and the Nine Item ARFID Screen (NIAS; Zickgraf and Ellis 2018), which is the only screening instrument for adults/parents. A recent study validated the three subscales of the NIAS ("picky eating," "appetite," and "fear") and established recommended cutoff points for each subscale (Burton Murray et al. 2021). Because the NIAS was not able to distinguish ARFID from other eating disorders, the authors recommended using the NIAS as a screening measure for ARFID in combination with other screening measures for eating disorders, such as the Eating Disorder Examination-Questionnaire (EDE-Q; Fairburn and Beglin 2008).

Diagnostic interviews for ARFID include the Pica, ARFID, Rumination Disorder Interview (PARDI; Bryant-Waugh et al. 2019), the Eating Disorder Assessment for DSM-5 (EDA-5; Sysko et al. 2015), and the ARFID module of the Eating Disorder Examination (EDE-ARFID; Schmidt et al. 2019), which are all semi-structured interviews, and the Structured Clinical Interview for DSM-5 Disorders (SCID-5; Chen et al. 2019). For a comprehensive description of available assessment measures for ARFID and their psychometric properties, see Dinkler and Bryant-Waugh (2021).

In addition to determining whether a child meets diagnostic criteria for ARFID, clinical assessment should include a focus on the degree and domains of psychosocial impairment associated with the symptoms. It is also recommended that medical and nutritional assessments be completed by a medical health professional. In complicated ARFID cases, multidisciplinary input may be needed to assess

additional problems, such as gastrointestinal problems, autoimmune diseases, and oral sensorimotor concerns (Bryant-Waugh 2019; Eddy et al. 2019).

Treatment of ARFID

As ARFID was introduced to the DSM only in 2013, there is little research documenting treatment outcomes, and to date there are no well-established psychosocial treatments for ARFID (Bourne et al. 2020; Eddy et al. 2019). Aside from three small-scale pilot randomized controlled trials (RCTs) and three pilot open trials, treatment approaches have been presented through case reports, case series, and retrospective chart reviews. Studies have examined family-based treatment, child-centered cognitive-behavioral therapy, or parent-based interventions, with variability in intended age and setting. Table 1 summarizes psychosocial interventions for childhood ARFID.

Family-Based Treatment

Family-based treatment (FBT) is one of the most documented treatments adapted for childhood ARFID (FBT-ARFID; Lock 2021). FBT for ARFID is usually carried out in an outpatient setting and empowers parents as the primary agents managing behavioral change. This manualized treatment focuses on promoting increased volume of food intake (as in FBT for anorexia nervosa) and on increasing the variety of foods eaten, and applications of this treatment to each of the three common ARFID presentations have been described (Lock et al. 2019b). A pilot RCT in children aged 5–12 years compared FBT-ARFID ($n = 16$) to treatment as usual (TAU; $n = 12$). Participants in the TAU group were free to seek the treatments of their choice, not including FBT-ARFID. Results showed improvement in weight and ARFID symptom severity for children in the FBT-ARFID condition compared with children in the TAU group. Parents in the FBT-ARFID group showed significant changes in parental self-efficacy, and these changes were associated with improved clinical outcomes. These findings led the authors to highlight the importance of parental factors as one potential mechanism of therapeutic change. FBT for ARFID has been applied in combination with other approaches in both outpatient settings and as part of more intensive treatments. For example, one case study of a 9-year-old girl described the combination of FBT with the Unified Protocol for Transdiagnostic Treatment of Emotional Disorders in Children (UP-C; Eckhardt et al. 2019) in an outpatient setting, and in a PHP for children with acute ARFID onset and low body weight, aspects of FBT have been incorporated in a broad family-centered treatment program therapy (Ornstein et al. 2017). Spettigue et al. (2018) reported on a case series ($N = 6$, ages 10–14 years) applying FBT for ARFID in combination with medication in an inpatient and outpatient setting.

Cognitive-Behavioral Approaches

Another promising approach to treating childhood ARFID is cognitive-behavioral therapy (CBT). Most documented adaptations of CBT to ARFID have been

Table 1 Psychosocial interventions for childhood ARFID

Approach	Intervention	Setting	Key intervention components	Who is involved in treatment	Treatment duration and age	Empirical support
Family-based	Family-based treatment for ARFID (FBT-ARFID) (Lock et al. 2019a, b; Norris et al. 2016; Rosania and Lock 2020)	Outpatient	Externalizing, agnosticism, parent-led behavioral changes, focus is on changing eating behavior rather than family process/ dynamics	Child, parents, and siblings (optional)	Up to 22 sessions over 6 moths Ages 5–12 years	Pilot RCT with treatment as usual as comparator ($N = 28$) Case reports
	FBT adapted for ARFID + medication (Spettigue et al. 2018; Naviaux 2019)	Inpatient and outpatient	Medical monitoring, psychoeducation and support for parents, parent-led behavioral changes, relaxation techniques, medication and CBT for comorbid anxiety	Child and parents	4–6 months Ages 10–14 years	Case series ($N = 6$) Case report
	FBT + Unified Protocol for Transdiagnostic Treatment of Emotional Disorders in Children (UP-C) (Eckhardt et al. 2019; Burton et al. 2021)	Outpatient	Collaborative weighing, family engagement, externalizing, parent-led behavioral changes, cognitive restructuring, exposures, behavioral activation, mindfulness (Eckhardt et al. 2019; Burton et al. 2021)	Child and parents	24–29 sessions over 8–11 months Ages 6–11	Case reports

			And additional ASD specific techniques (Burton et al. 2021)			
Cognitive-behavioral	Cognitive-behavioral therapy for ARFID (CBT-AR) (Thomas et al. 2017a; Thomas et al. 2020)	Outpatient	Psychoeducation, monitoring of food intake, establishing regular eating routines, increasing volume of preferred foods or variety of foods, in vivo and interoceptive exposure	Individual or family-supported format depending on the patient's age	20 to 30 sessions Age 11 Ages 10–17 years Treatment intended for ages 10 years and up	Case report (Thomas et al. 2017a) Pilot open trial ($N = 20$) (Thomas et al. 2020)
	Broad CBT approach (Bryant 2013)	Outpatient	Self-monitoring, behavioral experiments, cognitive restructuring, breathing, relaxation	Child and parents	Length of treatment not specified Age 13	Case report
	Cognitive and behavioral treatment (Fischer et al. 2015)	Outpatient	Gradually increasing feeding demands and reinforcing consumption, cognitive restructuring breathing, relaxation, guided imagery	Child and parents	11 sessions Age 16	Case report
	Feeling and Body Investigators-ARFID Division (FBI-ARFID) (Zucker et al. 2019)	Outpatient	Interoceptive and exteroceptive inhibitory learning, exposure to aversive sensations, acceptance	Child and parents	11–15 sessions Age 4 Treatment intended for ages 4–10 years	Case report
	Exposure-based CBT integrating inhibitory	Partial hospitalization	Exposure, behavioral experiments, cognitive	Individual, parent and	4-week intensive day treatment (6–8 hours per day) followed by	Case series ($N = 11$)

(continued)

Table 1 (continued)

Approach	Intervention	Setting	Key intervention components	Who is involved in treatment	Treatment duration and age	Empirical support
	learning principles (Dumont et al. 2019)	program followed by outpatient treatment	restructuring, relaxation	child, and group sessions	4-week low-intensity outpatient treatment Ages 10–18 years	
	Family-centered cognitive-behavioral treatment (Ornstein et al. 2017; Bryson et al. 2018; Lane et al. 2020)	Partial hospitalization program Children with acute onset, low body weight	Meal planning, exposure and response prevention, cognitive restructuring, hierarchical reintroduction of foods in program and at home, contingency management, medication when needed	Child and parent and/or other family members	5 days per week for 8.5 hours per day including 2-hour school component for an average of 7 weeks Ages 7–17 years	Retrospective chart reviews ($N = 130$, $n = 32$ with ARFID (Ornstein et al. 2017); $N = 81$ [17])
Parent-based	Behavioral parent-only group treatment (Picky Eaters Clinic) (Dahlsgaard and Bodie 2019)	Outpatient	Psychoeducation, improving mealtime hygiene, parent-facilitated exposures, habituation, differential reinforcement, contingency management	Parents	7 group sessions. Each group included parents of 2–4 children	Pilot open trial ($N = 21$)
	Parent-based treatment (SPACE-ARFID) (Shimshoni et al. 2020;	Outpatient	Psychoeducation, promoting change in parent behavior: systematic reduction of	Parents	12–16 sessions Ages 6–14 12 weekly sessions Age 7	Pilot open trial ($N = 15$) (Shimshoni et al. 2020) Case report

	Shimshoni and Lebowitz 2020)		food-related stress and family accommodation, increasing supportive responses			(Shimshoni and Lebowitz 2020)
	Behavioral parent-training intervention (Murphy and Zlomke 2016)	Outpatient	Psychoeducation, in vivo parent coaching, parent modeling, differential reinforcement, gradual exposure, contingency management	Child and parents	18 sessions over 6 months Age 6	Case report
	Behavioral parent-training intervention through teleconsultation (Bloomfield et al. 2019)	Outpatient	Contingency management	Parents	Age 8	Case report
Hospital-based feeding programs	Integrated eating aversion treatment (iEAT) (Sharp et al. 2016)	Partial hospitalization program for children with chronic food refusal and dependence on enteral feeding or oral nutritional formula supplementation	Reinforcement, escape extinction, formulized meal structure	Child and parents	5 consecutive days with 14, 40-minute meals Ages 13–72 months	Pilot RCT with wait list as comparator ($N = 20$)
	Nutritional rehabilitation program (Strandjord et al. 2015)	Inpatient	Meal planning, nasogastric tube and nutritional	Child	5–13 days Ages 5–25 years	Retrospective chart review ($N = 318$, $n = 41$ with ARFID)

(continued)

Table 1 (continued)

Approach	Intervention	Setting	Key intervention components	Who is involved in treatment	Treatment duration and age	Empirical support
			supplements when needed			
	CHOP inpatient nutritional rehabilitation protocol (Peebles et al. 2017)	Inpatient	Rest, electrolyte monitoring, gradual increases in nutrition and weight gain, nasogastric tube and nutritional suppliants when needed, as well as psychotherapeutic support and nutritional education	Child, parents as part of treatment team	3–40 days Ages 5–23 years	Retrospective chart review ($N = 215$, $n = 9$ with ARFID)
	Nutritional rehabilitation + pharmacotherapy augmentation (Sharp et al. 2017)	PHP	D-cycloserine (DCS), escape extinction, reinforcement procedures	Child and parents	5 days Ages 20–58 months	Double-blind pilot RCT with placebo as comparator (N = 15)
	Multimodal approach (Dolman et al. 2021)	Inpatient	Multimodal approach combining elements from FBT, CBT, and pharmacotherapy (sertraline and olanzapine)	Child and parents	7 weeks Age 11 years	Case study

Note: ARFID, avoidant/restrictive food intake disorder; FBT, family-based treatment; CBT, cognitive-behavioral therapy; RCT, randomized controlled trial; SPACE, Supportive Parenting for Anxious Childhood Emotions; CHOP, Children's Hospital of Philadelphia

presented thus far through case examples, case series, and retrospective chart reviews (Bryant 2013; Dumont et al. 2019; Fischer et al. 2015; Ornstein et al. 2017; Thomas et al. 2017a) and have been applied in outpatient settings (e.g., Thomas et al. 2017a) as well as integrated in PHPs (e.g., Dumont et al. 2019). These interventions commonly include cognitive restructuring, systematic exposures to increased volume and/or variety of foods, self-monitoring, and relaxation techniques. One open trial examined the application of a manualized cognitive-behavioral treatment for ARFID (CBT-AR) in 20 participants (ages 10–17 years) in an outpatient setting (Thomas et al. 2020; Thomas and Eddy 2019). At posttreatment the authors reported significant reductions in ARFID severity scores, incorporation of new foods (mean = 16.7; SD = 12.1), and significant weight gains for participants in the underweight subgroup. Additionally, 70% of patients no longer met criteria for ARFID. Two retrospective chart reviews reported on the integration of CBT in an intensive family-centered treatment in a PHP ($N = 32$, 81, ages 7–17) and showed posttreatment gains in weight and reductions in eating disorder and anxiety symptoms as well as an increase in the number of foods patients were willing to eat (Lane et al. 2020; Ornstein et al. 2017).

One paper described an application of the Feeling and Body Investigators-ARFID Division (FBI-ARFID) for a 4-year-old girl with ARFID (Zucker et al. 2019). This exposure-based interoceptive treatment focused on exploring and experiencing aversive sensations rather than terminating them, in an acceptance-based framework.

Parent-Based Treatments

Another area of increasing focus examines parent-based interventions in outpatient settings. One pilot open trial examined acceptability, feasibility, treatment satisfaction, and preliminary efficacy of SPACE-ARFID (Supportive Parenting for Anxious Childhood Emotions adapted for ARFID; Shimshoni et al. 2020). The foundation for this adaptation of SPACE, an evidence-based treatment for child anxiety and OCD (Lebowitz et al. 2019), rests on commonly observed shared features between childhood anxiety and ARFID. These include elevated levels of anxiety and avoidance behaviors and the presence of family accommodation (Brigham et al. 2018; Eddy et al. 2019; Norris et al. 2014; Zickgraf et al. 2019b). Family accommodation refers to the ways in which parents and other family members change their own behavior to help their relative with a psychiatric illness avoid or alleviate distress related to the illness. Although family accommodation is usually well-intentioned, it is associated with greater symptom severity and functional impairment (Lebowitz et al. 2016; Shimshoni et al. 2019). SPACE-ARFID is a manualized parent-based treatment aimed at increasing food-related flexibility by helping parents to systematically reduce food-related stress and family accommodation and to increase supportive responses to the child's distress (Shimshoni and Lebowitz 2020). Results of this pilot study ($N = 15$, ages 6–14 years) showed significant reductions in ARFID symptom severity, ARFID-related impairment, and family accommodation and increases in food-related flexibility.

Another pilot open trial examined the acceptability, feasibility, and initial outcomes of a parent-only outpatient group behavioral treatment for childhood ARFID

(Picky Eaters Clinic; $N = 21$, ages 4–11 years). In this study, seven groups of parents (two to four families per group) participated in seven sessions focused on teaching parents to facilitate daily in-home exposures, differential reinforcement, contingency management procedures, and elements of parent management training. Results showed significant reductions in picky eating symptoms after treatment, and gains were maintained at 3-month follow-up (Dahlsgaard and Bodie 2019).

Other accounts of treatments with high parental involvement include a case of a 6-year-old girl who received a behavioral parent-training intervention which was successful in increasing her food intake variety (Murphy and Zlomke 2016) and the case of an 8-year-old boy who increased intake volume of non-preferred foods during a behavioral parent-training intervention delivered via teleconsultation (Bloomfield et al. 2019).

Hospital-Based Feeding Programs

Hospital-based feeding programs usually involve a multidisciplinary team and are of greater intensity compared with outpatient interventions. One prospective pilot RCT compared an intensive multidisciplinary behavioral feeding therapy to a waitlist condition in a 5-day PHP for young children with chronic food refusal and dependence on enteral feeding or oral nutritional formula supplementation ($N = 20$, ages 13–72 months; Sharp et al. 2016). Compared with the waitlist condition, children receiving therapy consumed more food and had fewer mealtime disruptions. Inpatient programs have also described the use of nasogastric tube feeding as part of feeding programs through retrospective chart reviews (Peebles et al. 2017; Strandjord et al. 2015) and case reports (Pitt and Middleman 2018; Schermbrucker et al. 2017). The benefits and negative effects of such procedures remain a contested issue in the field (Dovey et al. 2018).

Pharmacotherapy

In PHPs and inpatient settings, the use of pharmacotherapy (e.g., olanzapine, fluoxetine, mirtazapine, and cyproheptadine) for ARFID has also been examined in addition to other treatment modalities and reported mainly through retrospective chart reviews and case series (e.g., Brewerton and D'Agostino 2017; Gray et al. 2018; Spettigue et al. 2018). A single small-scale double-blind RCT for very young children with ARFID ($N = 15$, ages 20–58 months) compared intensive extinction-based feeding intervention and D-cycloserine (DCS) to the same intensive feeding intervention and placebo (Sharp et al. 2017). Compared with the placebo group, children DCS group showed increased food acceptance and decreased problem behavior during meals. To date, there are no established guidelines for the use of pharmacological treatments for ARFID, though it has been recommended that they be used in addition to other treating approaches and not as a first-line treatment intervention (Bryant-Waugh 2019; Naviaux 2019).

Summary

This chapter reviews findings contributing to the current understanding of ARFID in children and adolescents. Although research demonstrates that ARFID has specific characteristics and clinical profiles distinguishing it from other problems, there are many aspects of this eating disorder that are not yet well understood. For example, ARFID is currently conceptualized as a highly heterogeneous problem, yet little is understood about the nature of this heterogeneity. The DSM offers three examples of forces driving the restricted eating, though it is likely that there are additional drivers that have not yet been explored, such as cognitive inflexibility or a need for control (Bourne et al. 2020). Other questions that are only partially answered by available research include: What is the prevalence of ARFID? What is the impact of ARFID? What is the optimal treatment strategy for ARFID? Accurate epidemiological data are needed and can shed light on the prevalence of ARFID and assist in further characterizing the disorder in terms of age of onset and prevalence of specific ARFID presentations. Systematic research focusing on broader areas impacted by the ARFID, such as implications in the psychosocial domain, will allow for a more comprehensive understanding of the consequences of having ARFID including for those who do not require weight restoration in inpatient settings. And relating to the question of which treatments are best for treating ARFID, large-scale RCTs are urgently required to establish the efficacy of available treatment approaches.

As the field moves forward in studying and treating children with ARFID, it is likely that advances in each of the ARFID-related areas will advance the understanding of other areas. For example, a better understanding of the forces driving restricted eating will help to develop more effective treatment approaches and accurate assessment tools. More accurate and agreed-upon assessment tools will, in turn, provide more precise accounts of the prevalence of ARFID and will enable clinicians and researchers to better distinguish it from other problems and to determine criteria for remission.

Mini-Dictionary of Terms

Anorexia nervosa: an eating disorder characterized by intentional and extreme weight loss driven by concerns about body weight or shape.

Autism spectrum disorder (ASD): a range of neurodevelopmental disorders characterized by difficulties with social interaction and communication and by restricted and repetitive behavior.

Biopsychosocial model: a model that examines the interactions between biology, psychology, and socio-environmental factors to better understand a wide range of health-related conditions and issues.

Binge eating disorder: an eating disorder characterized by uncontrollably eating unusually large amounts of food in a relatively short time. Binge eating is different from bulimia nervosa in that it is not accompanied by behaviors aimed at neutralizing the food intake, such as vomiting, taking laxatives, or excessive exercise.

Bulimia nervosa: an eating disorder characterized by uncontrollably eating usually large amounts of food in a relatively short time, accompanied by behaviors aimed at neutralizing the food intake, such as vomiting, taking laxatives, or excessive exercise.

Cognitive-behavioral therapy (CBT): a type of psychological treatment that focuses on a person's thoughts, feelings, and behaviors which are understood to underlie or maintain the problem. CBT is a short-term and well-established treatment found effective in treating many different mental conditions.

Differential diagnosis: the process a clinician will go through in differentiating between two or more possible conditions characterized by similar signs or symptoms, in an effort to determine which diagnosis is most accurate.

DSM: *Diagnostic and Statistical Manual of Mental Disorders*. It is the mental health problems classification system of the American Psychiatric Association. The current edition of the DSM is the DSM-5.

Enteral feeding: the intake of food through the gastrointestinal tract. This includes the esophagus, stomach, and intestines. Mostly though, in the context of feeding/eating disorders, enteral feeding is used to describe tube feeding.

Epidemiological research: research that investigates the factors that determine the presence or absence of diseases and disorders in the population. Epidemiological research helps to understand how many people have a disease or disorder, if those numbers are changing, and how the disorder affects our society and our economy.

Family accommodation: describes the changes that family members make to their own behavior to help their relative with a psychiatric illness avoid or alleviate distress related to the illness. Although family accommodation is usually well-intentioned, it is associated with greater symptom severity and functional impairment.

Feeding and eating disorder of infancy and early childhood: an eating disorder characterized by failing to eat enough food to maintain weight and grow as expected. Applicable when the difficulties started before age 6 years. This eating disorder appeared in the DSM-4 (the 4th edition of the DSM) and was replaced in the DSM-5 with the introduction of ARFID.

ICD: International Classification of Diseases. It is the World Health Organization's comprehensive classification system for all mental and physical diseases and health problems. The current edition of the ICD is ICD-11.

Nasogastric tube: a plastic tube that is inserted through the nose, past the throat, and down into the stomach. Nasogastric tubes (also known as NG tubes) are often used to facilitate caloric intake when individuals are malnourished and cannot eat independently.

Macronutrients: types of foods needed in large amounts to maintain the body's system and structures. These include fat, carbohydrates, and protein.

Micronutrients: essential elements of our diet that are generally required in small amounts. These include numerous vitamins (such as vitamins A, C, and D) and dietary minerals (such as iron, zinc, and calcium).

Other specified feeding or eating disorders (OSFED): a diagnostic category in the DSM-5, referring to feeding and eating disorders that do not meet diagnostic criteria

for anorexia nervosa, bulimia nervosa, binge eating disorder, ARFID, pica, or rumination disorder. OSFED include atypical anorexia nervosa, atypical bulimia nervosa, and binge eating disorder of low frequency and/or limited duration.

Randomized controlled trial (RCT): a form of scientific experiment used to control for factors not under direct experimental control by randomly assigning participants to different research conditions. RCTs are often used in clinical research to study the efficacy of different treatments and are generally considered high-quality research.

Tertiary care: medical care that is highly specialized involving advanced and complex procedures and treatments.

Summary Points

- ARFID stands for avoidant/restrictive food intake disorder. Individuals with ARFID limit the variety or quantity of foods they eat to the extent that these limitations are associated with marked interference in feeding, growth, or psychosocial functioning.
- Because ARFID was introduced fairly recently, in the 5th edition of the DSM in 2013, there are scarce data on various aspects of ARFID such as assessment, prevalence, correlates, impact, and treatment.
- ARFID is understood to be a highly heterogeneous problem. Emerging evidence supports three distinct, but not mutually exclusive, presentations of ARFID: ARFID driven by lack of interest in eating/food, ARFID driven by sensory sensitivity, and ARFID driven by concerns relating to possible consequences of eating specific foods. It is also hypothesized that there are other driving factors not yet systematically explored.
- ARFID seems to be as prevalent as other eating disorders, and there are serious potential medical and mental implications of having ARFID. These include trouble concentrating, sleep disturbances, feeling tired and irritable, nutritional deficiencies leading to problems like anemia, poor bone health, eye and skin problems, and psychosocial impairment impacting friendships, family relationships, and academic performance.
- ARFID commonly co-occurs with other problems such as gastrointestinal conditions, oral-motor functioning, anxiety, autism spectrum disorders, oppositional defiant disorder, obsessive-compulsive disorder, and attention-deficit/hyperactivity disorder.
- There are several available assessment tools for ARFID including self-report screening measures as well as clinician-administered interviews for establishing a diagnosis of ARFID.
- To date, there are no well-established treatments for childhood ARFID. There is preliminary support for the application of family-based therapy (FBT), cognitive-behavioral therapy (CBT), and parent-based approaches. There is also some support for the use of pharmacotherapy, usually alongside psychosocial therapy.

- Despite research efforts into ARFID, current understanding of this eating disorder is limited. Rigorous research is needed to improve the understanding of the phenomenology, driving forces, assessment, and effective treatments.

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The Brain in Prader-Willi Syndrome

63

Kenichi Yamada

Contents

Introduction: Hyperphagia in Prader-Willi Syndrome 1263
PWS and Behavioral Phenotypes 1264
PWS Overview 1264
Diagnostic Criteria and Neurological Features 1264
Behavioral Characteristics 1264
Major Hypothetic Focuses on Brain Developmental Pathophysiology 1265
Hypothalamic Dysfunction with Altered HPA Axis 1265
Gene-Behavior Relationship: "Behavioral Phenotype" Concept 1265
Schaaf-Yang Syndrome 1266
BP1-BP2 Microdeletion Syndrome 1266
Neurochemical Alterations 1267
5-Hydroxytryptamine and Gamma Amino Butyric Acid 1267
Oxytocin and Vasopressin 1267
Ghrelin 1267
Neuroanatomical and Microstructural Structures of the Brain in PWS 1268
Hypothalamus and Pituitary Gland 1268
Brain Stem and the Midbrain 1268
Cerebellum 1268
Cerebrum 1270
Evidence on Altered Brain Structural and Functional Connectivity 1270
Structural Connectivity 1270
Functional Connectivity 1272
Electrophysiological Studies 1272
Functional Imaging Studies 1272
Future Avenues for Research 1274
Molecular, Cellular, and Pharmacological Approaches Combined with Advanced Imaging Technology 1274

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Neuromodulation 1274
Multidisciplinary Approach Toward Longitudinal Analysis of the Brain and Behavior ... 1275
Suggested Areas to Be Included in the Chapters as Background 1276
Applications to Other Eating Disorders 1276
Mini Dictionary of Terms 1278
Key Facts of Genetic Imprinting in PWS 1279
Key Facts of Nutrition in PWS 1279
Key Facts of Behavioral Phenotypes in Genetic Syndromes 1280
Summary Points 1280
References 1280

Abstract

Prader-Willi syndrome (PWS), a congenital genetic disorder, has received attention due to its features, including hyperphagic behavior with a unique genetic background. While clinical research on this syndrome has focused on the management of the endocrinological and metabolic manifestations, there is growing evidence for the involvement of the brain in the pathogenesis of developmental and behavioral characteristics. Furthermore, researchers have investigated the genetic influence on molecular and cellular processes related to behavior using mouse models. On the other hand, modern advanced magnetic resonance imaging, three-dimensional high-resolution structural imaging, diffusion imaging, and resting-state functional imaging have revealed structural and functional alterations in the brains of individuals with PWS, supported by updated optimization and statistical methods. This chapter discusses research on the brain in PWS and addresses its contribution to hyperphagia, which leads to obesity, as well as the neural mechanisms that may underlie the behavioral phenotypes of this syndrome.

Keywords

Autism · Arginine-vasopressin · Behavior · Brain · Cerebellum · Development · Diffusion · Hyperphagia · Hypothalamus · MRI · Pituitary · Prader-Willi syndrome · Resting state · T1-weighted image

Abbreviations

5-HT	5-hydroxytryptamine
AT	Adipose tissue
AVP	Arginine-vasopressin
cDN	Cerebellar dentate nucleus
DTI	Diffusion tensor imaging
ERP	Event-related potential
GABA	Gamma amino butyric acid
IPWSO	International Prader-Willi Syndrome Organization
MRI	Magnetic resonance imaging
MRS	Magnetic resonance spectroscopy
OXT	Oxytocin

PET	Positron emission tomography
PWS	Prader-Willi syndrome
snoRNA	Small nucleolar RNA
SPECT	Single-photon emission computed tomography
TD	typically developing
UPD	Uniparental disomy

Introduction: Hyperphagia in Prader-Willi Syndrome

Prader-Willi syndrome (PWS) is a relatively rare genetic syndrome characterized by complex multisystem involvement, spanning from endocrinological to neurodevelopmental and psychiatric domains. Excessive eating (hyperphagia) is a prominent behavioral feature of PWS, which may lead to obesity. However, individuals with PWS may face several difficulties and clinical challenges owing to the wide variety of features of this condition. The multifaceted, continuous, and extensive efforts coordinated by international collaborations (International PWS organisation: IPWSO. https://ipwso.org/) are dedicated to expanding knowledge, experience, and best practices in both the scientific and caregiver communities. The recognition of PWS not only as a mere eating disorder but also as a model to investigate the relationship between brain and behavior could lead to a better understanding and treatment of eating disorders. Herein, I will review PWS from the viewpoint of brain pathophysiology as a unique form of neurodevelopmental disorder, whose behavioral and developmental characteristics presumably originate, at least partially, in the brain.

The details of the various aspects of this disease are extensive and beyond the scope of this chapter. This chapter focuses on addressing issues regarding several original or replicated findings that make a significant contribution to the understanding of PWS (Table 1).

Table 1 Clinical findings prompting genetic testing for Prader-Willi, Schaaf-Yang, and associated syndromes

Age	Clinical findings
From birth to 2 years of age	Marked hypotonia with feeding difficulty, typically requiring tube feeding
2–6 years	Hypotonia with poor suck Global developmental delay
6–12 years	History of hypotonia with poor suck Global developmental delay Excessive eating with central obesity (if diet is not managed properly)
From 13 years to adulthood	Intellectual disability (usually mild to moderate) Excessive eating with central obesity (if caloric intake is uncontrolled) Short stature Hypothalamic hypogonadism Characteristic behavioral problems

(Modified with permission from Cassidy et al. 2012)

PWS and Behavioral Phenotypes

PWS Overview

PWS was first described by Prader, Labhart, and Willi in 1956, and subsequent observations have further revealed its endocrinological and neurodevelopmental features (Prader and Labhart 1956). In 1981, the results of a genetic analysis revealed its genetic background as originating from the 15q11–13 region (Ledbetter et al. 1981). Furthermore, genetic imprinting, a unique mechanism, has paved the path for classifying a subtype of PWS, namely, deletion type or uniparental disomy (UPD) (Nicholls et al. 1989). Moreover, growing evidence has revealed differences in the severity of behavioral disturbance, obesity, and susceptibility to psychosis between these subtypes (Aman et al. 2018). Interested readers are invited to read an excellent review on this topic (Cassidy et al. 2012).

Diagnostic Criteria and Neurological Features

Currently, PWS is diagnosed based on multiple criteria including physical features, endocrinological abnormalities, and genetic testing (Holm et al. 1993; Goldstone et al. 2008). Following an initial review of systems and comorbidity screening, clinicians apply a multidisciplinary approach that involves the management of complications and growth hormone supplementation. A multidisciplinary approach has been explored and pointed out as the best practice for PWS by the IPWSO.

The following neurological abnormalities are additional essential features of PWS: severe hypotonia requiring respiratory support or tube feeding in the postnatal period in neonates, global developmental delay from infancy, intellectual disability from preschool, and hypersomnia from school age to adulthood (Cassidy et al. 2012).

Behavioral Characteristics

Hyperphagia and Complex Behavioural Phenotypes

Hyperphagia is a salient and life-threatening behavioral feature that characterizes PWS. PWS patients experience hunger or lack of fullness continuously, which is likely to cause lifelong stress not only in the patients but also their families and caregivers. It typically increases the risk of multiple complications, such as obesity, diabetes, and cardiovascular and respiratory problems. The patients are assessed using the hyperphagia questionnaire, a robust and efficient tool that can measure in vivo food-seeking behavior (Dykens et al. 2007). The management consists of the following dimensions: dietary consultation, behavioral intervention, and severe complications. Moreover, bariatric surgery is also often performed in patients with PWS.

On the other hand, a constellation of behavioral features has been identified and replicated in different studies as an important aspect that may affect health management and reduce the patient's quality of life. Recently, a collaborative team of international experts established a constellation comprised of the following core behavioral features as a consensus for future clinical trials: hyperphagia, temper outbursts, anxiety, obsessive-compulsive behaviors, rigidity, and social cognition (Schwartz et al. 2021). Moreover, other relatively common features include skin picking, hypersomnia, lying, confabulation, and theft, despite being secondary to impulse control disorder or psychological defenses (Curfs 1992; Steinhausen et al. 2004).

Psychiatric Disturbances and Genetic Susceptibility

Researchers have reported high rates of psychiatric manifestations, depression, psychotic episodes, and obsessive-compulsive disorder, which are likely to occur in adolescents to young adults with PWS (Dykens and Shah 2003; Soni et al. 2007; Sinnema et al. 2011; Krefft et al. 2014). Higher rates of psychiatric manifestations in UPD indicate the difference in susceptibility to psychiatric disorders (Whittington and Holland 2018). In contrast, a recent questionnaire-based study demonstrated that while aberrant behaviors decline from a young adult age in the deletion type, food-related behaviors persist, despite aging and growth (Ogata et al. 2018). Future research should determine the specific clinical course, including dementia, in the elderly.

Major Hypothetic Focuses on Brain Developmental Pathophysiology

Hypothalamic Dysfunction with Altered HPA Axis

The hypothalamic dysfunction hypothesis has been long postulated by physicians and researchers in endocrinology. Convergent evidence indicates that the clinical and endocrinological features are best explained by a dysfunction in the hypothalamus, namely, primary (central) homeostatic dysregulation, hypersomnia, altered body temperature, and pituitary hypofunction, which lead to hypothyroidism and hypogonadism. These alterations have also been demonstrated at the molecular and cellular levels, thus providing possible clues for future therapeutic interventions (Swaab 1997; Bochukova 2021).

Gene-Behavior Relationship: "Behavioral Phenotype" Concept

Figure 1 depicts all recognizable genes in and near 15q11–13. Several genes in this region have been delineated, including *MAGEL2* (Luck et al. 2016; Tacer and Potts 2017; Chen et al. 2020), *Snord116* (Lassi et al. 2016; Qi et al. 2017; Polex-Wolf et al.

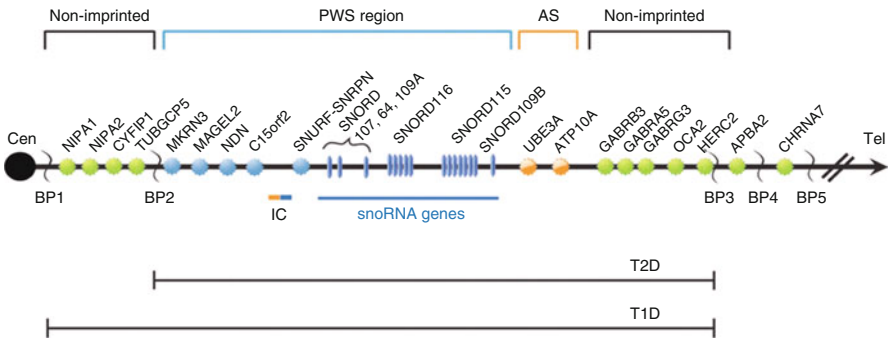


Fig. 1 Summary of the genetic map of chromosomal region 15q11.2-q13. The Prader-Willi syndrome region (shown in blue) has five copy genes that encode each polypeptide and a family of six snoRNA genes, both of which are expressed in a paternal-only manner. The Angelman syndrome region has two copy genes with preferential maternal-only expression, which is limited to certain tissue-specific regions. The jagged vertical lines denote common deletion breakpoints (BP). There are more copies of the *SNORD116* and *SNORD115* genes than are shown, and the map was not drawn to scale precisely. (Taken with permission from Cassidy et al. 2012)

2018), and *NDN* (Necdin) (Zanella et al. 2008; Wu et al. 2020; Yoshikawa 2021). Thus, some researchers have proposed the "behavioral phenotype" in molecular psychiatry as an endophenotype concept determined or constrained by a set of gene series.

Furthermore, genotype-phenotype investigations have successfully delineated various novel syndromes as follows:

Schaaf-Yang Syndrome

A newly proposed clinical form of genetic disorder caused by truncating pathogenic variants in the gene *MAGEL2* located at 15q11-15q13, the Prader-Willi critical region (Schaaf et al. 2013). This syndrome exhibits clinical overlap with PWS in the early stages of life but becomes gradually distinct toward childhood and adolescence, specifically in intellectual disability, language, and motor development (McCarthy et al. 2018).

BP1-BP2 Microdeletion Syndrome

An emerging cytogenetic condition with 15q11.2 Break point (BP)1-BP2 microdeletion (Burnside-Butler susceptibility locus). It is typically confirmed through genetic testing or chromosomal microarray analysis because of behavioral, cognitive, and/or psychiatric problems (Butler 2017). Four non-imprinted genes have been observed in this genomic region. They play a role in a wide spectrum of neurodevelopment and function (Rafi and Butler 2020).

Neurochemical Alterations

While researchers have investigated a wide range of neurochemical alterations that potentially contribute to behavioral characteristics in terms of core elements, PWS-specific and convergent evidence remain limited. It may arise from difficulties associated with a relatively small number of studies and conflicting findings in the same system with different methods. PWS mouse models have been rapidly developed in recent years, and the rapid progress in this research area may provide clues for drug discovery for the better management of hyperphagia and behavior. Due to limited space, I have shown here the major findings on each neurochemical substrate and refer interested readers to an excellent review for a detailed explanation.

5-Hydroxytryptamine and Gamma Amino Butyric Acid

Investigations in mouse models have detected 5-hydroxytryptamine (5-HT or serotonin) alterations in the brain of individuals with 15q11–13 gene deletion (Garfield et al. 2016; Davies et al. 2019). In addition, gamma amino butyric acid (GABA) has been implicated the pathophysiology since its concentration in plasma is changed in these patients (Ebert 1997), together with the fact that the genes encoding three $GABA_A$ receptor subunits are found within the PWS critical region.

Oxytocin and Vasopressin

Oxytocin (OXT) is another candidate that has been postulated as a relevant peptide. An initial neuropathological finding indicated marked reduction in the number of OXT-expressing neurons in PWS (Swaab 1997). Accordingly, a number of clinical trials of OXT supplementation have been performed via nasal spray. Those studies have shown that OXT is well tolerated in individuals with PWS and improves feeding and social skills (Einfeld et al. 2014; Tauber et al. 2017; Miller et al. 2017).

While arginine-vasopressin (AVP) has been less studied, attenuation of the polypeptide 7B2, prohormone convertase PC2, and AVP have been found in the hypothalamus of some individuals with PWS, indicating a processing defect, which may also explain to some extent the combination of behaviors in PWS (Gabreëls et al. 1998).

Ghrelin

Molecular, cellular, and hormonal research has been conducted to determine the causes of obesity and mental illness in PWS. Ghrelin is a gut peptide that exerts a broad spectrum of physiological responses, including appetite stimulation, lipid accumulation via regulating mechanisms in the hypothalamus, increase in gastric motility, regulation of glucose metabolism, and brown fat thermogenesis (Wevrick 2020).

It also modulates stress, anxiety, taste sensation, reward-seeking behaviors, and circadian rhythm (Tauber et al. 2019). The higher-order functions based on these neuroanatomical substrates are discussed in the next section.

Neuroanatomical and Microstructural Structures of the Brain in PWS

Hypothalamus and Pituitary Gland

While the neuropathological alteration is indeed the first objective evidence supporting the hypothesis as the hypothalamic origin of pathophysiology in PWS (Swaab 1997) (Fig. 2a), the pituitary structure is reportedly smaller with altered tissue microstructures, compared with those in PWS (Miller et al. 1996, 2008; Iughetti et al. 2008; van Nieuwpoort et al. 2011). A recent T_1-weighted magnetic resonance imaging (MRI) study demonstrated a correlation between pituitary image contrast and behavioral characteristics, such as autistic, hyperphagia, and obsessive features indexed by questionnaire scores, compared with those in typically developing (TD) controls (Yamada et al. 2021b) (Fig. 3a), which is highly consistent with the neurochemical findings (Gabreëls et al. 1998). Autoimmune or inflammatory processes speculated in recent reports warrant direct visualization (Grugni et al. 2018).

Brain Stem and the Midbrain

Neuropathological alterations have been described in midbrain and brainstem structures, indicating homeostatic and respiratory dysfunctions (Hayashi et al. 2011) (Fig. 2b). However, structural and volumetric alterations that exist in these structures, as well as the limbic structure, remain unclear; therefore, MRI studies are performed more actively.

Cerebellum

The cerebellum has also received some attention from the viewpoint of behavioral learning and cognition. While reduced volume and hypoplasia of the cerebellum have been reported (Titomanlio et al. 2006; Miller et al. 2009), an advanced MRI study using voxel-based morphometry demonstrated that the posterior part of the cerebellum, as well as total cerebellar volume, is smaller in individuals with PWS than in TD controls (Fig. 3b). Moreover, the altered lobular volume ratios (per total volume) were found to be negatively correlated with hyperphagic and autistic characteristics, and positively correlated with obsessive behavior. In contrast, the cerebellar dentate nuclei volume is larger in individuals with PWS and inversely associated with the intellectual quotient (Yamada et al. 2020b) (Fig. 4). These

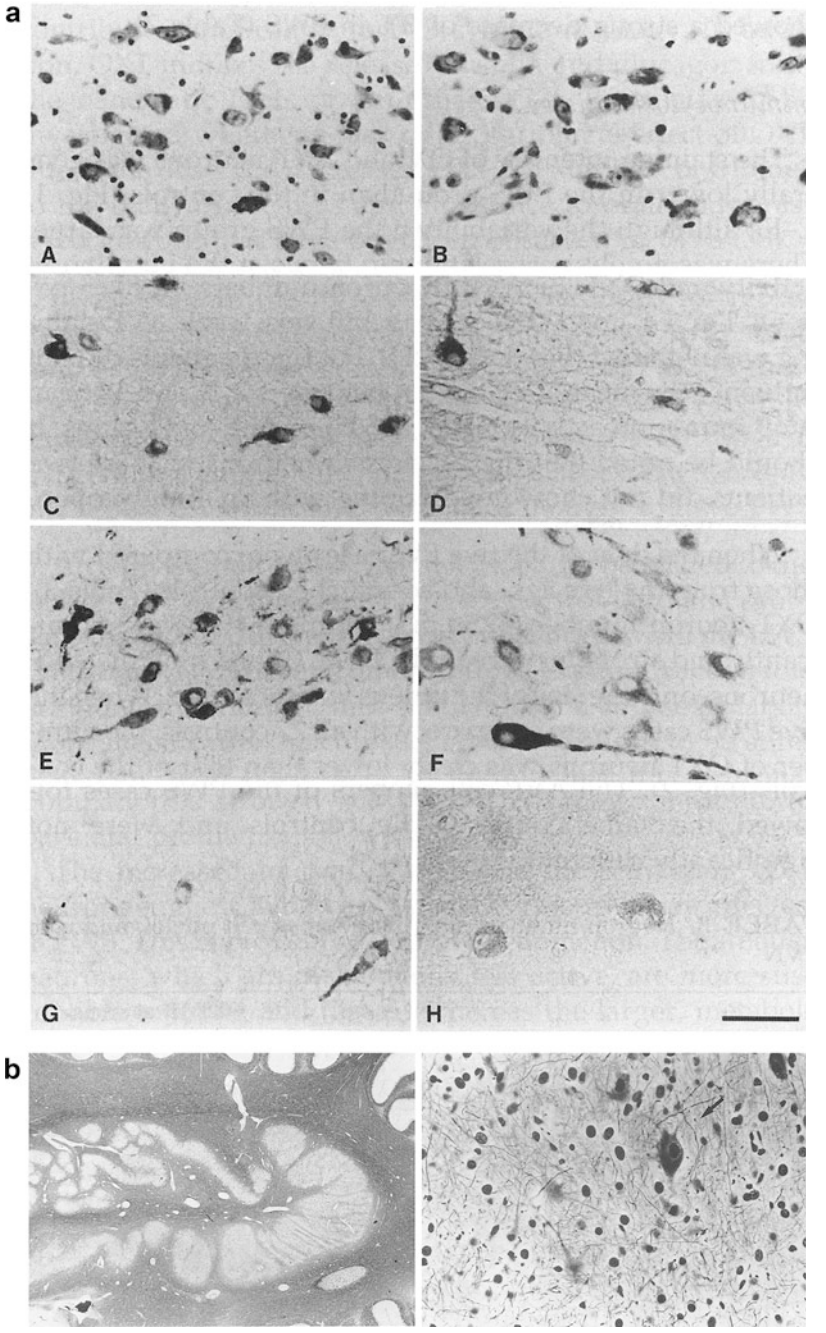


Fig. 2 The neuropathology of the hypothalamus and cerebellum in the brain of individuals with Prader-Willi syndrome. Neuropathological findings in the postmortem brain of individuals with Prader-Willi syndrome (PWS). (**a**) Reduced cell densities with lower immunocytochemical

findings strongly indicate that the cerebellum partially contributes to the behavioral and cognitive characteristics in PWS.

Cerebrum

The major characteristics of cerebral structures in individuals with PWS are as follows: (1) globally and locally reduced cerebral volume together with enlarged ventricles and Sylvian fissure (Miller et al. 2007a, b; Ogura et al. 2011; Honea et al. 2012; Xu et al. 2017; Manning et al. 2018; Yamada et al. 2022); (2) premature aging-related alteration (Manning et al. 2018; Azor et al. 2019), and (3) altered gyrification in the cerebral cortex (Lukoshe et al. 2014). Brain-predicted age difference scores derived from MRI-based machine learning have been found to be higher in the brain of individuals with PWS, thus indicating premature aging (Manning et al. 2018; Azor et al. 2019). This contrasts with a previous hypothesis on arrested brain development (Lukoshe et al. 2013). The details of increasing evidence are summarized in an excellent review (Manning and Holland 2015).

Evidence on Altered Brain Structural and Functional Connectivity

The human brain works as a unit; simultaneously, each part of the brain has a specific contribution, which is known as functional localization. A recent approach, namely, the Research Domain Criteria, seems to be convenient for brain research in PWS because it enables the decomposition of complex functional connections in a domain-specific and systematic manner (Salles et al. 2020).

Structural Connectivity

Structural connectivity was first investigated by diffusion tensor MRI in 2006 (Yamada et al. 2006). Altered white matter microstructure has been identified in multiple representative brain regions in individuals with PWS, including the frontoparietal area, callosal connection, and internal capsule. These are depicted

Fig. 2 (continued) staining intensities were identified. A comparison of the staining of thionine, oxytocin (OXT), and arginine-vasopressin (AVP) of controls (A, C, E) and PWS patients (B, D, F) showed lower staining in PWS patients, while an intense or weak OXT with only negligible AVP staining were observed in two PWS patients. (**b**) Disturbed undulating structures, resembling partial micropolygyria of the cerebral cortex in the cerebellar dentate nucleus in a case of PWS. Kluever-Bartera stain. (**c**) Grumose degeneration in the dentate nucleus. Dendrites were swollen, and a small amount of argyrophilic granular structures was detected. The arrow indicates a neuron showing a grumose-like alteration. Bodian stain. (Taken with permission from (**a**) Swaab et al. 1995, and (**b**, **c**) Hayashi et al. 1992)

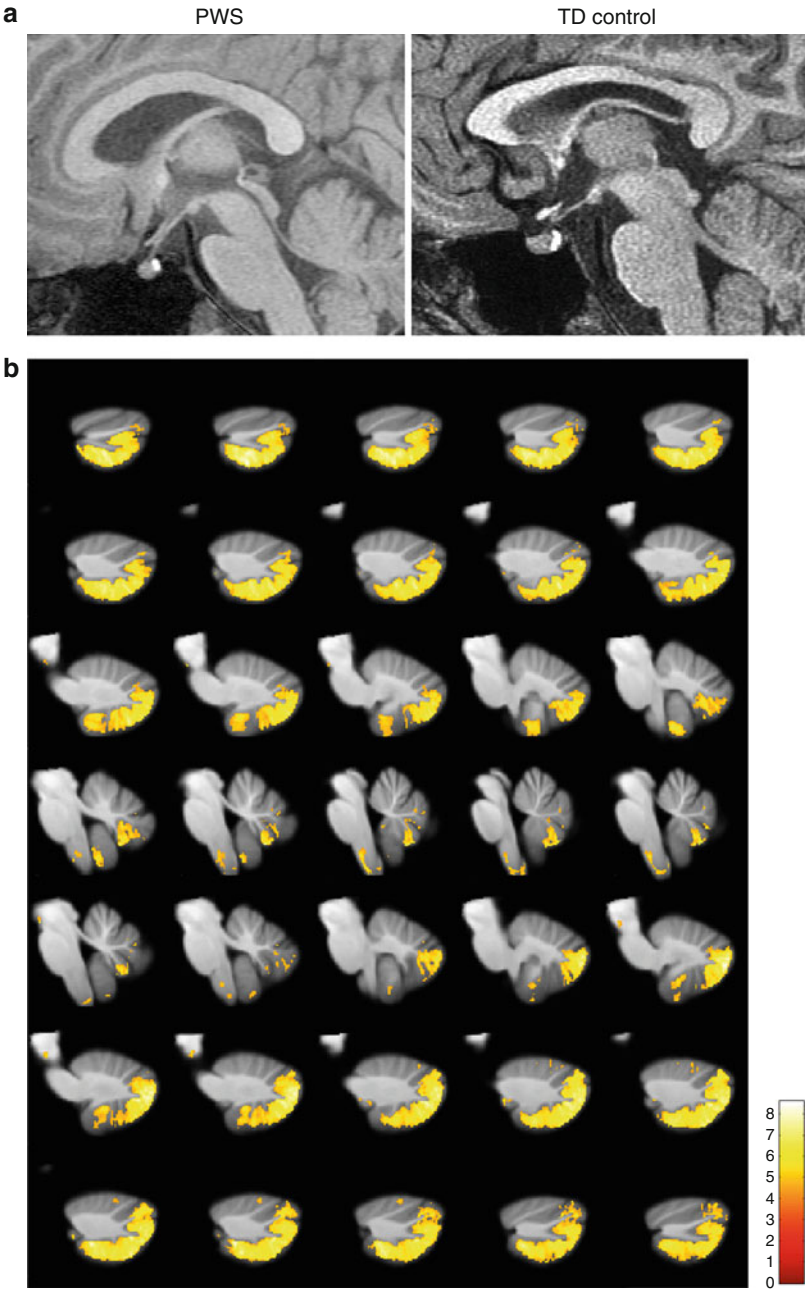


Fig. 3 Magnetic resonance imaging findings of subcortical structures in individuals with Prader-Willi syndrome. (**a**) Representative focused pituitary gland structural T_1 contrast magnetic resonance images (T_1 MRI) showing the anterior and posterior part of the pituitary gland from an adult individual with Prader-Willi syndrome (PWS) and an adult individual with typical

by altered indices suggesting modified brain maturation and connectivity, consistent with clinical features (Lukoshe et al. 2017; Xu et al. 2017; Rice et al. 2017).

Functional Connectivity

Furthermore, multimodal in vivo investigations have been performed to assess functional connectivity alterations of the brain in PWS.

Electrophysiological Studies

The neurophysiological basis for differences in cognitive properties was revealed by event-related potentials (ERP), together with electroencephalogram abnormalities in parietal-temporal brain areas, thereby indicating epileptic susceptibility in PWS. Differences in ERP responses have been reported between individuals with UPD and TD controls, indicating atypical face versus object processes. This might be associated with altered processing, attention and recognition of faces and their expressions (Brandt and Rosén 1998; Stauder et al. 2002, 2005; Halit et al. 2008; Priano et al. 2009; Key et al. 2013; Key and Dykens 2017).

Functional Imaging Studies

Single-photon emission computerized tomography (Ogura et al. 2013; Krishnadas et al. 2018) and position emission tomography studies (Sang et al. 2006; Dimitropoulos and Schultz 2008; Mantoulan et al. 2011; Reinhardt et al. 2016) have revealed altered distributions of cerebral blood volume and metabolic profiles, respectively. MR spectroscopy (MRS) studies have found reduced concentrations of gamma-aminobutyric acid, an inhibitory neurotransmitter, in specific brain regions of individuals with PWS (Hashimoto et al. 1998; Rice et al. 2016). In the future, challenging studies using MRS and manganese-enhanced MRI may reveal metabolic clues in the hypothalamus, albeit in a mouse model of PWS.

Currently, the highest spatial resolution with second-order time resolution can be achieved using functional MR imaging. This technique has been continuously applied to analyze brain connectivity from task-related to resting-state conditions. Food picture visual cues, oral glucose consumption cues, and simple motor task-related alterations have been detected as deactivation in the frontal area, parietal area,

Fig. 3 (continued) development (TD control). (**b**) Cerebellar structure displaying a significantly altered area in yellow color in individuals with Prader-Willi syndrome compared with typically developing controls. Statistical t-maps of volumetric data overlaid onto the infratentorial template as a T_1 MRI. Vertical color bars: t values. Significant level: $P < 0.05$. (Modified with permission from Yamada et al. 2020a, 2021b)

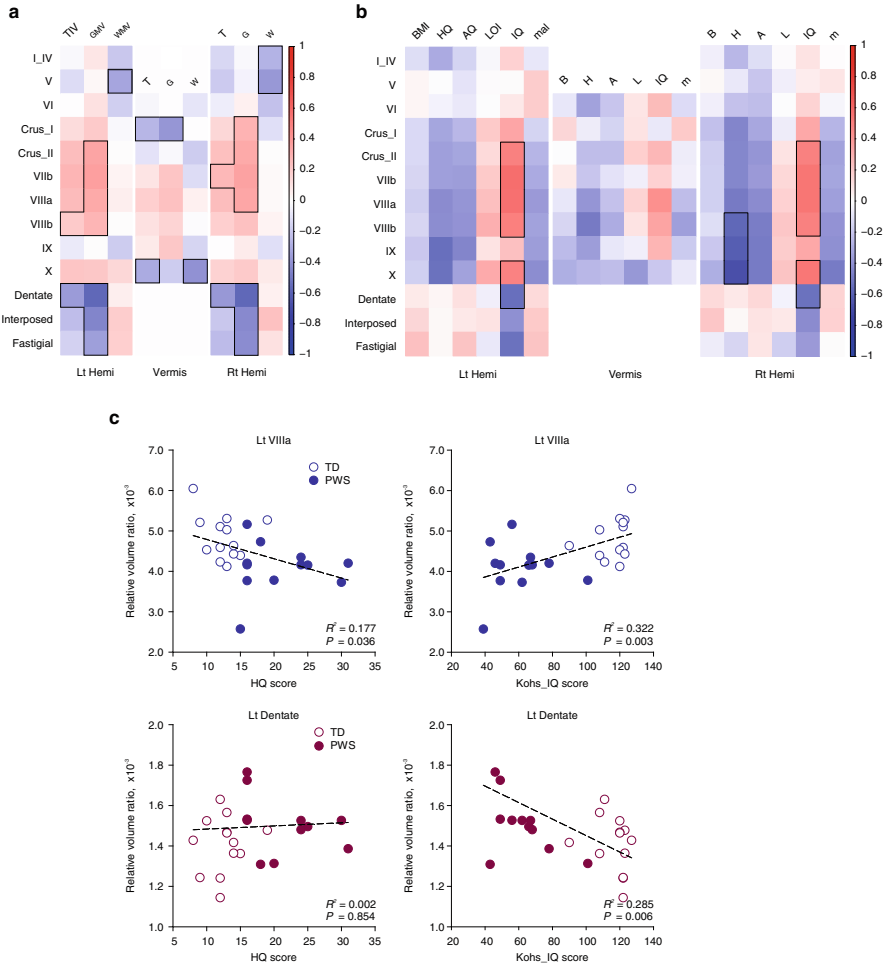


Fig. 4 (**a**) Multiple correlation analysis between regional cerebellar volumes and whole brain volumetric values in individuals with PWS and TD controls. (**b**) Multiple correlation analysis between regional volumes and clinical behavioral variables in individuals with PWS and TD controls. Color indicates correlation coefficients between the global volume-corrected volume of a lobule or deep cerebellar nucleus and the behavioral variable indicated above the column. Vertical color bar indicates positive and negative values by red and blue color, respectively. Bolded margins: $p < 0.05$ (error discovery rate corrected). (**c**) Scatter plots for lobules where significant differences are detected. Horizontal and vertical axes represent the total scores of behavioral assessment scales and global-corrected lobular volumes, respectively. Lt, left; Rt, right; Hemi, hemisphere; BMI (B), body mass index; HQ (H), hyperphagia questionnaire; AQ (A), autism spectrum quotient; LOI, Leyton obsessional inventory; IQ, intelligence quotient from Kohs block test; mal (m), maladaptive behavior score derived from the Vineland Adaptive Behavior Scale, second edition

and cerebellum, respectively, compared with TD individuals (Shapira 2005; Miller et al. 2007c; Holsen et al. 2009, 2012; Klabunde et al. 2015; Blanco-Hinojo et al. 2019).

Moreover, resting state analysis has enabled the visualization of intrinsic functional connectivity without a task as a hypothetical load (Zhang et al. 2013, 2015; Yamada et al. 2021a). Increasing evidence has revealed enhanced and reduced functional connectivity in a series of convergent brain regions, such as the hippocampus, amygdala, cerebellum, frontal, temporal, and parietal lobe. This has also been detected in frontal areas, particularly the dorsolateral and medial prefrontal cortices, anterior cingulate cortex, and orbitofrontal cortex, which have been reported to be functionally aberrant in task-based studies. These findings suggest that the widespread dysfunction in cortical and subcortical areas, which may be involved in the reciprocal control of motivational drive and inhibitory integration of the characteristic behavior in PWS.

In summary, growing evidence has suggested that, in PWS, altered brain connectivity exists between a wide range of brain regions spanning from lower-order structures and the cerebellum to the cerebral cortex and white matter. An altered topography with enhanced or diminished patterns is substantially consistent with the behavioral features observed in individuals with PWS. While these "hub nodes" share feeding, reward, and homeostatic regulations that are closely involved in hyperphagia, circuits reflecting the characteristics of PWS are yet to be discovered (Fig. 5).

Future Avenues for Research

Molecular, Cellular, and Pharmacological Approaches Combined with Advanced Imaging Technology

Researchers have recently introduced an integrated multiscale approach using noninvasive methods to bridge the pathophysiology from the molecular and cellular scale to visualization. A continuous approach to define mental and behavioral disorders in genetically determined neurodevelopmental disorders can provide a comparative perspective of the cortex pathophysiology in PWS (Holland et al. 2019). Considering an example using relative T_1 shortening in the cerebral cortex that suggests a glial function of aquaporins (Suzuki et al. 2017), these approaches might be informative and applicable in PWS for evaluating interventional effects in clinical trials (e.g., carbetocin, diazoxide choline-controlled release tablets, oxytocin, and cannabidivarin, a naturally occurring homolog of the phytocannabinoid cannabidiol). Moreover, an attempt to establish a system using induced pluripotent stem cells is currently in progress to reproduce the hypothalamus and its functional alteration in PWS (Soeda et al. 2019).

Neuromodulation

Neuromodulation is a novel and alternative approach that allows to regulate the neural connectivity in a noninvasive manner (Poje et al. 2021). Owing to the theory of vagal nerve stimulation and prior clinical application for epilepsy, vagal nerve

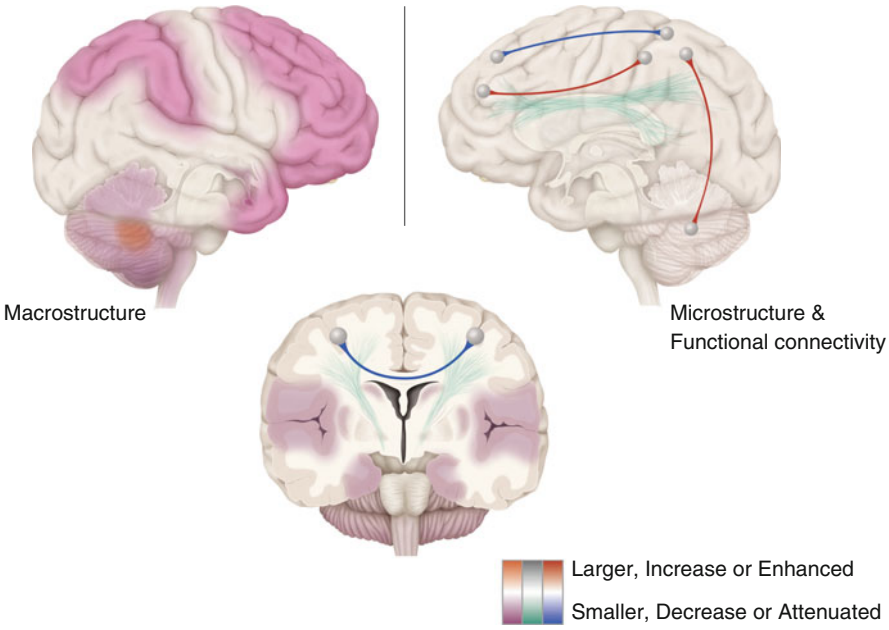


Fig. 5 Graphical summary of brain characteristics in Prader-Willi syndrome. All findings of brain characteristics in individuals with PWS, derived from magnetic resonance imaging studies until now, are graphically summarized. Upper left: macrostructural alteration detected in PWS compared with typically developing controls. Upper right: microstructural and functional connectivity alteration detected in PWS. Lower middle: coronal view showing both macrostructural, microstructural, and functional connectivity alterations detected in the slice containing basal ganglia and amygdala structures. The color bar indicates volume increase (yellow) or decrease (purple), neural fiber integrity increase (yellow) or decrease (green), and enhanced (red) or attenuated (blue) connectivity

stimulation trials in individuals with PWS have shown promising effects in reducing aggressive behavior (Manning et al. 2016). In the future, it is expected that the neuromodulations will be developed in conjunction with transcranial magnetic stimulation, which is both noninvasive and ethically acceptable.

Multidisciplinary Approach Toward Longitudinal Analysis of the Brain and Behavior

A safe, effective, and sustainable approach based on the core principles requires multidisciplinary collaboration (Cobo et al. 2021). Our behavioral choices are considered to be determined by both the biological background and environmental factors. Even if complex economic behavior patterns are constructed from finite, genetically controlled modules of behavior (Stacher Hörndli et al. 2019), environmental factors need to be taken into account carefully in PWS. Preferably, longitudinal analysis from pre- or early nutritional stage to the late stage will have a

significant potential to reveal unique developmental and behavioral trajectories. Advanced neuroimaging using a better preparation without sedation and integrated support will provide a better understanding of the functional and developmental alterations in the brain of individuals with PWS (Yamada et al. 2020a) (Fig. 6).

Suggested Areas to Be Included in the Chapters as Background

Guideline areas:

- Genetic syndrome and behavioral phenotype
- Behavioral characteristics (e.g., autism, obsessive-compulsive disorder)
- Brain function and localization
- Neurotransmitters
- Advanced neuroimaging
- Nutritional factors
- Life stages, such as neonatal period, childhood, adolescence, adulthood, and old age
- Occurrence of these disorders worldwide or in a single country
- Interventions that address the behavioral and developmental aspects
- The role of the parents, family, caregivers, and professionals

Applications to Other Eating Disorders

Cerebellar Contribution to Eating Disorders

In this chapter, we reviewed studies that focused on the cerebellum, in conjunction with other eating disorders leading to obesity. Of interest was the reduced volume of cerebellar structures observed in non-syndromic obesity (Miller et al. 2009), which has implications for other eating disorders in patients with behavior-related obesity. Hitherto, detailed volumetric and morphometric analyses have not yet been performed for other eating disorders because of the lack of specific detailed methods of analysis. We found that substructures of cerebellum contribute to the social and cognitive domain in individuals with PWS (Yamada et al. 2020b). Given the cerebellar alterations in other eating disorders, such as simple morbid obesity, frontotemporal dementia, and anorexia nervosa, the affected pathways might alter hypothalamic functionality.

Neurodevelopmental and Psychiatric Comorbidities in Eating Disorders

Altered or characteristic eating behaviors can be observed in a wide range of neurodevelopmental disorders and psychiatric conditions. While autism spectrum disorder patients may show a limited and obsessive selection of specific food or ingredients, a depressive state makes the patients eager to consume palatable and sweet food, eventually leading to reduced food intake. PWS includes a constellation of multiple neurodevelopmental and behavioral domains; however, it might help in

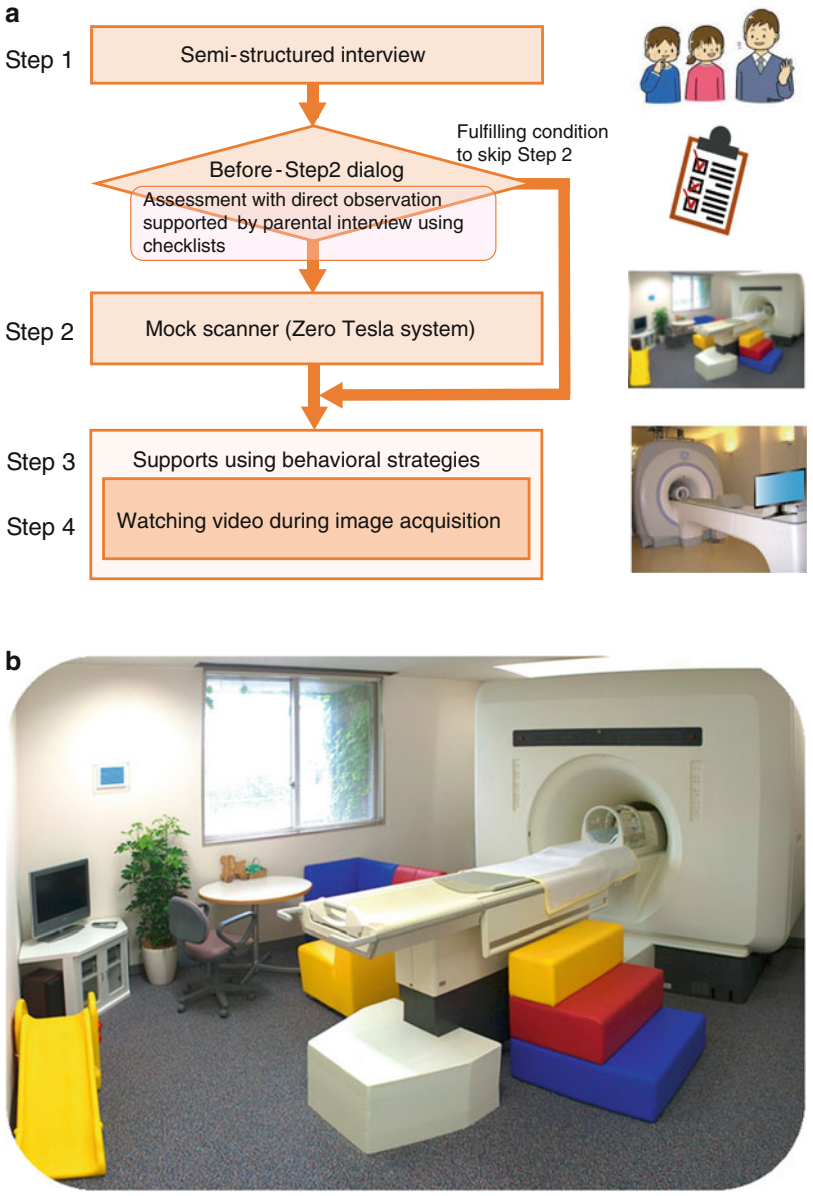


Fig. 6 Simulation protocol for the preparation of magnetic resonance imaging studies for individuals with behavioral and developmental characteristics. (**a**) Flow chart of the simulation protocol. Whether participants met the readiness status for the actual imaging is determined by the participant's responses on the checklist, along with their parents' consensual responses. The behavioral strategies shown in this figure represent the structured verbal or visual explanation of the imaging process, verbal incentives, and countdown of the remaining time in the real scanner. (**b**) "Zero-tesla" preparation system (mock scanner). (Modified with permission from Yamada et al. 2020)

understanding the possible contribution of each domain to other forms of eating disorders and vice versa.

Neuroendocrinological and Musculoskeletal Assessments and Interventions in Eating Disorders

While the multiple interaction of endocrinological abnormalities in PWS makes its pathogenesis complex, such a unique feature has a significant potential to open a new window for alternative approaches to eating disorders. Growth hormone supplementation in PWS has shown alterations of body mass composition and risks of complications associated with obesity, along with increasing body height and constitution in PWS (Pellikaan et al. 2021). In contrast, a recent report using body MRI showed that an altered adipose tissue (AT) composition: a decreased ratio of visceral/subcutaneous AT, in youth with PWS suggests an improved metabolic profile, and elevated ratios of AT to skeletal muscle may be a sign of a sarcopenic obesity-like phenotype (Orsso et al. 2017).

Mini Dictionary of Terms

- **Diffusion tensor imaging (DTI):** An advanced noninvasive imaging technology using MRI to visualize the diffusivity of free water molecules within the brain. Skewed diffusivity in the direction indicates the brain microstructure.
- **Magnetic resonance spectroscopy (MRS):** MRI is used to assess various neurochemical substrates within the brain, such as glutamate, N-acetyl aspartate, choline-containing compound, myoinositol, and GABA.
- **Cerebellar dentate nucleus (cDN):** A nucleus (a cluster of neurons in the central nervous system) in the cerebellum, which behaves like the "gateway" of output from information processed in the cerebellar hemisphere.
- **MAGEL2:** MAGE family member L2. A protein-coding gene that causes a form of clinical feature with autism spectrum disorder. The loss of function can contribute to the clinical aspects observed in PWS and Schaaf-Yang syndrome.
- **Small nucleolar RNAs (snoRNAs):** A class of noncoding RNAs involved in various physiological and pathological cellular processes. Mutations or the aberrant expression of SNORD115 and 116 are reportedly involved in the regulation of alternative splicing.
- **Single-photon emission computed tomography (SPECT):** Imaging modality that requires a radioactive agent to assess cerebral blood flow.
- **Positron emission tomography (PET):** Imaging technique based on positron emission used for the detection of tumors, metabolic alterations, and associated functional alterations.
- **Event-Related Potential (ERP):** Electrophysiological analysis used to detect altered gradients of electric potential associated with cognitive events.
- **Connectivity:** A pattern of neuroanatomical links ("anatomical connectivity") of statistically significant dependencies ("functional connectivity") or possible causal interactions ("effective connectivity") between distinct units within the

brain. The units usually correspond to individual neurons, neuronal populations, or anatomically localized brain regions.

- **Genetic imprinting:** People inherit two copies of their genes, one from each parent. Usually, both copies of each gene are active, or "turned on" in cells. However, in some cases, only one of the two copies gets normally turned on. The active or "turned on" copy depends on the parent of origin: while some genes are normally active only when inherited from the father, others are active only when inherited from the mother. This phenomenon is known as genomic imprinting.
- **Uniparental disomy (UPD):** A form of genetic situation, in which two copies of a chromosome are inherited from one parent, instead of one from each. Both UPD and imprinting mutations have been detected in DNA methylation studies.

Key Facts of Genetic Imprinting in PWS

- Genetic imprinting is a mechanism in which uniparental genetic information gets translated and reflected as a phenotype.
- In PWS, the 15q11–13 region inherited from the mother is translated, while that of paternal origin results in a different phenotype, namely, Angelman syndrome.
- While paternal deletion and maternal UPD account for approximately 65–75% and 20–30%, respectively, imprinting defect accounts for 1–3% of individuals with PWS.
- About half of individuals with imprinting defect have inherited it from an unaffected father with the imprinting center deletion on his maternal inherited chromosome 15, while the other half are de novo deletions on the paternally derived chromosome 15.
- DNA sequence changes are not found in these epimutations; therefore, the imprinting defect is thought to be due to random errors during spermatogenesis in the father or in early embryogenesis.
- For parents with PWS, genetic counselling may be required to understand the mechanism of the disease.

Key Facts of Nutrition in PWS

- Nutritional management is crucial for the health care of individuals with PWS.
- Individuals with PWS typically progress through seven discrete nutritional phases (Miller et al. 2011), namely, phases 0, 1a, 1b, 2a, 2b, 3, and 4.
- While phase 1a is characterized by hypotonia with feeding difficulty and decreased appetite in months 0–9, patients in phase 3 show hyperphagia and rarely reach satiety.
- Phase 3 is believed to be caused by a lack of satiety due to hypothalamic abnormalities, a topic that has not been fully investigated.
- Research and clinical practice have suggested that an increase in physical activity with a well-balanced and nutritionally dense diet can improve weight control in adolescents with PWS.

Key Facts of Behavioral Phenotypes in Genetic Syndromes

- Each genetic syndrome is likely to exhibit unique behavioral and developmental characteristics.
- In the fields of clinical genetics, molecular psychiatry, and behavioral pediatrics, such characteristics are referred to as behavioral phenotype.
- Some well-known examples are self-mutilation in Lesch–Nyhan syndrome, sleep disturbance, aggressive behavior in Smith–Magenis syndrome, and outgoing, engaging personalities with possible attention-deficit and anxiety disorders in Williams syndrome.
- It is important to mention that such characteristics are not fixed by the genetic background but can be reduced or enhanced depending on the environment of the patient.
- Effective collaboration with clinical geneticists, experts in dysmorphology medicine, developmental and behavioral neurologists, and psychiatrists in neurodevelopmental disorders is appreciated in clinical settings.

Summary Points

- Prader-Willi syndrome (PWS) is a congenital genetic syndrome that has received attention as a clinical condition characterized by hyperphagic behavior.
- The brain plays a role in the pathogenesis of the developmental and behavioral characteristics of PWS.
- While the genetic contribution to behavior has been investigated using mouse models, the structural and functional aspects of the brain have been revealed by advanced magnetic resonance imaging.
- Reduced volumes have been observed in the brain stem, pituitary, posterior cerebellum, amygdala, and frontoparietal cortices of individuals with PWS, along with altered integrity in the frontoparietal white matter structure.
- Altered functional connectivity has been detected in frontoparietal and parietocerebellar connections as attenuated and enhanced passages, respectively.
- An integrated multiscale approach with noninvasive methods is warranted to bridge the pathophysiology from the molecular and cellular scale to visualization.

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Behavioral Phenotype of Patients with Prader-Willi Syndrome

64

Maja Krefft and Maria Libura

Contents

Introduction 1288
Behavioral Phenotype in Patients with PWS across Lifespan 1289
Prenatal Period 1289
Neonatal and Infancy Period 1290
Early Childhood Period 1290
Teenage and Adolescent Period 1292
Adulthood 1293
Distinctive Features of the PWS Behavioral Phenotype 1294
PWS Phenotype and Intellectual Disability 1294
Self-Injurious Behavior 1296
Nutritional Stages 1296
The Relationship Between the Genotype and Phenotype of PWS 1297
Interventions Targeting Challenging Behaviors in PWS Patients 1298
Impact of Pharmacotherapy on PWS Patients' Behavior 1299
Application to Other Eating Disorders 1300
Mini-Dictionary of Terms 1300
Key Facts 1301
Summary Points 1301
References 1302

Abstract

Prader-Willi (PWS) syndrome is a genetically determined, complex, neurodevelopmental disorder characterized by a specific behavioral phenotype. The condition is best known as a syndromic cause of hyperphagia, resulting in early onset

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morbid obesity and consequent premature death, if the condition is not diagnosed early and managed properly. It is also characterized by a plethora of other developmental, cognitive, behavioral, and mental health challenges. The purpose of this chapter is to provide an overview of the changing behavioral phenotype of PWS across lifespan and discuss its distinctive features, current understanding, and available interventions.

Keywords

Prader-Willi syndrome · Self-injurious behavior · Behavioral phenotype · Obsessive-compulsive disorder · Hyperphagia · Obesity · Anxiety · Nutrition · Genotype-phenotype correlations · Food security

Abbreviations

ADD	Attention-deficit disorder
ADHD	Attention-deficit hyperactivity disorder
ASD	Autism spectrum disorder
GH	Growth hormone
IQ	Intelligence quotient
mUPD	Maternal uniparental disomy
OCD	Obsessive-compulsive disorder
PWS	Prader-Willi syndrome

Introduction

Prader-Willi syndrome (PWS) is characterized by a specific developmental trajectory and a corresponding behavioral phenotype, understood as a pattern of distinctive behaviors consistently exhibited by people diagnosed with the syndrome (Holland et al. 2003). Typical behavioral profile of patients with PWS encompasses symptoms resulting from hyperphagia, mild intellectual disability, obsessive-compulsive traits, as well as deficits in social functioning. Studies so far have failed to identify a specific age range at which the mental health of PWS patients would significantly deteriorate (Lo et al. 2015). Although there is variation between individuals in terms of clinical picture, i.e., symptom manifestations and their onset and severity (Bellis et al. 2022), the eating disorder is nearly universally present (Holland et al. 2003). Therefore, the behavioral phenotype should be considered as an increased likelihood of certain behaviors in patients with this syndrome (Hodapp et al. 1990) (Table 1). Behavioral features are so significant in PWS phenotype that they have been included in the diagnostic criteria from early on (cf. Holm et al 1993, Table 1) . The following chapter will detail the specific character of behavioral phenotypes across subsequent developmental stages in patients with PWS. It will also include a discussion of most challenging behaviors and their current understanding and impact on functioning.

Table 1 Diagnostic criteria for PWS (behavioral or related features are marked in bold) (Holm et al. 1993)

Major criteria	*Minor criteria*	*Supplemental criteria*
Muscular hypotension/weak suckling reflex	**Poor fetal movements in the third trimester of pregnancy, infantile lethargy, weak cry in infancy**	**High pain threshold**
Eating difficulties/poor weight gain	**Behavior disorders (at least 5): tantrums, obsessive-compulsive behavior, stubbornness, arguments, tendency to manipulate, perseverate**	Decreased vomiting
Excessive and rapid weight gain (12 months of age–6 years of age)	Sleep disturbance/night apnea	Thermoregulation disorders
Features of dysmorphia (at least 3): dolichocephaly, narrow two-sided dimension, amygdala-shaped eyelid gaps, small mouth with a narrow red upper lip, downward corners of the mouth	Low growth, hypopigmentation of skin and hair	Scoliosis and/or kyphosis
Hypogonadism	Small hands and/or feet in relation to body height	Premature pubarche symptoms
Psychomotor development delay/ difficulties at school	Narrow hands with straight ulnar border	Osteoporosis
Excessive appetite/obsessive craving/lack of satiety	Vision defects (myopia, astigmatism, strabismus)	**Exceptional puzzle solving skills**
A characteristic genetic defect	Thick, sticky saliva drying in the corners of the mouth	Normal neuromuscular test results
	Speech defects/nasal speech	
	Skin picking/self-harm	

Behavioral Phenotype in Patients with PWS across Lifespan

Prenatal Period

In an article published in 2020, Srebnik et al. proposed a prenatal phenotype of patients with PWS. It was based on a study of 101 pregnancies, in which the fetuses were later diagnosed with PWS. The study consisted of, inter alia, questionnaires and retrospective interviews with the mothers, comparing the pregnancy with a child, later diagnosed with PWS, against pregnancy with healthy offspring at the closest age. Data obtained from prenatal sonographic examinations was also included. The authors of the study were able to distinguish a number of symptoms the co-occurrence of which at the end of the second or the beginning of the third trimester

should raise concerns and prompt the methylation test for PWS. Among various traits observed in ultrasound scans, a significant diagnostic value was shown by a decreased abdominal circumference, especially when coinciding with polyhydramnios or a considerably decreased fetal movements (Srebnik et al. 2020). Other retrospective studies showed similar characteristics of fetuses with PWS among patients in China (Yang et al. 2020), the USA (Singh et al. 2018), Great Britain (Whittington et al. 2008), and France (Bar et al. 2017), also indicating nonspecific symptoms such as abnormal alignment of hands and feet, lack of vertical fetal movement (non-vertex presentation), and increased frequency of needing assistance during birth or caesarean (Bigi et al. 2008; Cassidy et al. 2012). Researchers involved in studies on prenatal PWS diagnoses point to the importance of implementing proper approach for further patient prognosis, as well as its ethical implications (Goldstone et al. 2008).

Neonatal and Infancy Period

A specific behavioral phenotype is also manifested in the subsequent stage of life of PWS patients – in neonatal and infancy development. Studies by Ge et al. done on a group of 102 Chinese infants recognized a pattern of motor behaviors presenting in over 90% of subjects, consisting of central hypotonia (96.1%), lack of sucking reflex, difficulties in feeding (93,1%), and weak crying (100%), irrespective of the syndrome's etiology. These symptoms showed to be highly indicative for the syndrome, along with the underdevelopment of genitals (Ge et al. 2019). Infants affected by PWS are described as permanently sleepy and having difficulty waking up for feeding. Immediately after birth, they show a decreased or lacking sucking reflex, they may require supplemental feeding via nasogastric tube, and they show a lowered appetite. Increased sleepiness is a characteristic trait in PWS patients, often continuing through their lifespan (Haig and Wharton 2003). Slower motor development results in delayed milestones (taking twice as long as indicated by norms, e.g., walking at 24 months), including those related to speech development (Cassidy et al. 2012).

Early Childhood Period

The onset of uncontrollable appetite is a crucial moment in the life of a patient with PWS. Studies show its occurrence between ages 4, 5, and 8 (Cassidy et al. 2012). Significant differences are shown in the course of this process, with a rapid onset or a gradual development of nonselective eating habits. Children start consequently finishing their meals and then actively seeking and even stealing food, and they tend to eat voraciously and don't experience the feeling of satiety (Haig and Wharton 2003). Studies show that hyperphagia increases with age, which results in a wider range of food-seeking behaviors among older patients (Dykens et al. 2007). The behavioral phenotype connected with the change of appetite also consists of a food-

related obsession and preoccupation with meals. Aberrant behaviors linked to food also include stealing and lying for the purposes of getting more food, eating nonedible items such as pet food, searching for food in trash, stealing money to buy food, or running away to get it (Cassidy et al. 2012; Butler et al. 2019).

Study of food-related behaviors among PWS patients, done by Holland et al. (2003) Lindgren et al. (2000) showed an indicative curve in food consumption in this patient population. A decelerating curve constitutes a typical eating pattern, where the appetite is high at the beginning of the meal, when the patient feels hungry, after which it decreases as the feeling of satiety rises. PWS patients exhibit a non-decelerating curve, indicating a lack of the feeling of satiety. At the same time, it's accompanied by a slower pace of eating at the beginning and overall, than is shown by healthy or obese children. This appears to imply that the abnormality of satiety has a greater impact than uncontrollable hunger on these patients (Lindgren et al. 2000).

Beyond the disrupted behaviors directly connected with hyperphagia and lack of satiety, other specific features of behavioral phenotype of PWS patients have been identified, present even from early childhood and found in 70–90% of patients. This phenotype consists of stubbornness, temper outbursts, mood swings, manipulative and compulsive-like controlling behaviors, as well as difficulty with interrupting or switching activities and actions once they had begun (Cassidy et al. 2012). Compulsive-like behaviors, such as repetitive questioning, stereotypical speech, hoarding behaviors, or symmetrical stacking, are considered as specific developmental delays and appear around age of 2. At this time, their intensity isn't largely deviated from the norm among the general population of children, but lasts longer in PWS patients and may persist even until adulthood suggesting their different role and distinct developmental trajectories involved in their occurrence (Dimitropoulos et al. 2001; Holland et al. 2003). Another aberrant behavior, beginning in childhood, is self-harm, especially skin picking. In the study by Dimitropoulos et al., as many as 40% of children with PWS, aged 4–5, exhibited these behaviors, a third of whom did so even until they started to bleed. Higher pain threshold that is characteristic for PWS patients minimizes negative consequences of self-harm and contributes to this behavior (Holland et al. 2019). This problem increases with the age of the patients and, without proper treatment, may even result in death in the course of the infection (Dimitropoulos et al. 2001; Bellis et al. 2022). The period of increased appetite often coincides with the appearance of temper outbursts. However, the relationship between these two behaviors isn't clear. As they appear later with age than among healthy children, and their aggravation is clinically relevant, a different developmental etiology in PWS patient group should be assumed. Temper outbursts often occur in the response to rejection, interruption of repeated activities, or a request to change activity before it's complete. They tend to be accompanied by verbal aggression, and sometimes physical violence, and may induce subsequent feelings of guilt and regret (Holland et al. 2019). Additionally, temper outbursts may also be a consequence of communication disorders, resulting from delayed speech development, which is also frequent in PWS patients, or as a response to dietary restrictions by caregivers (Dimitropoulos et al. 2001). Aggression, observed during childhood,

manifests by hitting others, while in teenage years tends to have a verbal form. The most frequent psychiatric diagnosis is oppositional defiant disorder, irrespective of genetic subtype (Lo et al. 2015; Feighan et al. 2020).

As children with PWS start school, intellectual disabilities become more and more evident. Although the average IQ values are 60–70 in PWS patients, and even 40% of them have borderline or low intellectual norm, this does not translate into the daily functioning of patients and their academic achievements (Cassidy et al. 2012).

Early childhood is also a period in which the features of autism spectrum disorder (ASD) features begin to appear (Descheemaeker et al. 2006). They are most pronounced in a range of behaviors such as insistence on sameness, attachment to routine, and schematic behaviors (Wigren and Hansen 2005). Research indicates deficits in the theory of mind in patients with PWS, meaning the lack of ability to recognize their own and other people's mental states. Greater intensity of aberrant behaviour is observed in patients with both ASD and PWS diagnosis than in individuals with ASD only (Lo et al. 2013). Autism spectrum symptoms are often accompanied by attention-deficit disorder (ADD) or attention-deficit hyperactivity disorder (ADHD) symptoms along with behavioral disorders (Wigren and Hansen 2005). These symptoms often worsen with age, but tend to partially resolve in adulthood (Cassidy et al. 2012).

Teenage and Adolescent Period

Self-injurious behaviors are widespread in teenage PWS patients, and according to the results of the study by Feighan et al. apart from skin picking, the most common include teeth grinding, body hitting, and self-biting and are most severe in adolescence (Feighan et al. 2020). Aggressive behavior also reaches its peak between the ages of 4 and 18. And among them, the most common are hitting, pushing, pulling others, and verbal aggression. The study also showed a high intensity of anxiety symptoms in patients with PWS in adolescence, with subsequent development of mood disorders. Patients are also often diagnosed with disruptive behavior disorders (DBD), which in some studies were associated with a higher frequency of OCD and skin picking. It is estimated, depending on a study, that 50% to almost 90% of PWS adolescent patients have at least one psychiatric diagnosis (Shriki-Tal et al. 2017; Feighan et al. 2020).

The first episodes of psychotic disorders also occur in adolescence, affecting up to 20–60% of patients with PWS, more often with maternal uniparental disomy (mUPD) etiology. Vogels et al. distinguished a subtype of psychotic disorders in PWS with early age and acute onset, variable course, and the need for hospitalization. The onset of psychotic disorders is often preceded by a prodromal phase in which the patient is affected by stress-related risk factors. Behaviors accompanying psychotic episodes are often strange, characterized by excessive activation or drop in energy, agitation, disturbances in the circadian rhythm, or changes in appetite. Psychotic disorders can often go undiagnosed because abnormal behaviors are attributed to the PWS (Vogels et al. 2004; Cassidy et al. 2012).

Apathy and inactivity, which accompany PWS patients practically from the prenatal period, in the teenage period, and in adulthood, present themselves with spending free time on solitary activities, such as puzzle-solving, idling, and computer gaming (Holland et al. 2019).

The study by Wigren et al. revealed an interesting phenomenon where the insistence on sameness was present in 50% of the studied patients and, despite the teenage age, remained at the level characteristic for children with PWS of preschool age. In previous studies, this symptom, along with skin picking, was classified as part of obsessive-compulsive disorder (OCD) alongside anxiety disorders, which was not replicated by Wigren's study. Skin picking was associated with mood swings, without a clear pattern of repetitive behavior (Wigren and Hansen 2005).

Adulthood

Accounts of behavioral characteristic trajectory in adulthood of PWS patients are somewhat heterogeneous. While some authors attest attenuation of challenging behavioral patterns, others report contradicting results. Elisabeth Dykens and colleagues developed the Hyperphagia Questionnaire, a tool enabling the assessment of food-seeking behaviors in patients with PWS (Dykens et al. 2007). Studies conducted with this tool showed persistence of maladaptive and hyperphagia-related behaviors in older adults with PWS, although their severity was lower than in younger groups. This may be related to the levels of hormones and neuropeptides as they decline with age, but the patients who reach late adulthood also tend to have better symptom control. Additionally, this tool contributed to the in-depth research on the correlation between hyperphagia and maladaptive and emotional problems in PWS patients, e.g., internalizing symptoms such as anxiety and depression (Dykens et al. 2007). On the other hand, population studies conducted on a group of PWS patients by Holland et al. showed an increase in the severity of eating disorders with age, which was associated with decreased parental control in adulthood, diagnosis of the syndrome at a later stage in life, and lack of adequate guidance on nutrition and food intake monitoring at the time of diagnosis (Holland et al. 2003). There is evidence, albeit limited, that in adulthood behavioral symptom severity may abate in some individuals. Dykens compared maladaptive and compulsive behaviors in 45 older adults with PWS (30–50 years) to children, adolescents, and young adults with the same condition, concluding that young adults had the highest risk for behavioral problems, while in older adults, it was significantly less pronounced (Dykens 2004). These results were not replicated by a Dutch study that found no diminishment of behavioral problems in older adults with PWS (Sinnema et al. 2011). The study also points to differences between genetic subtypes in adulthood, with more behavioral problems attested in PWS adults with mUPD compared with deletion.

A systematic review of the literature, published by Tarsimi et al. in 2021, covering 33 articles, revealed the behavioral profile of adult PWS patients as characterized by temper tantrums, autism spectrum, and compulsive behaviors. Mood disorders occurred

in 10–20% of patients and were often accompanied by psychotic symptoms. It should be emphasized that psychiatric disorders occurring in PWS do not always completely fit into the diagnostic criteria, which may lead to diagnostic overshadowing, despite a significant impact on the functioning of the patient and the life of their family; standardized diagnostic methods for this group are required (Tarsimi et al. 2021).

When discussing the behavior of PWS patients, their contribution to the increased mortality should be addressed. Behaviors related to seeking and stealing food, hasty secretive eating, and the lack of a feeling of satiety may result in choking, also due to gastrointestinal dysmotility, gastrointestinal perforation with necrosis, or intoxication. These behaviors are directly related to hyperphagia, regardless of obesity (Butler et al. 2019; Bellis et al. 2022).

The impact of the COVID-19 pandemic deserves its own, separate place in this chapter. According to the research of Wieting et al., it especially negatively affected the well-being and functioning of PWS patients. Lockdown contributed to the exacerbation of anxiety symptoms and behavioral disorders with increased temper tantrums and compulsions, as well as skin picking and behaviors related to food searching. Caregivers of patients reported anxiety about the pandemic situation among their charges, as well as worry about their own health. In addition, studies have shown a particular severity of the described symptoms among patients living at home with relatives, which implies the need for increased support for them during this difficult time (Wieting et al. 2021b). Distinctive features of PWS behavioural phenotype discussed in this section are summarized in Table 2.

Distinctive Features of the PWS Behavioral Phenotype

PWS Phenotype and Intellectual Disability

Three factors determining the behavioral phenotype of PWS patients were distinguished in contrast with a learning disability control group, for which four factors were established (Holland et al. 2003). The PWS factor analysis revealed the following clusters:

1. Eating and associated behaviors, such as lying and theft, limited mainly to food seeking and in some patients to home environment
2. Personality characterized by obsessive behaviors, outbursts of anger, and repetitive and aggressive behavior due to neurodevelopmental delay
3. Emotions, such as mood swings, skin picking, and argumentativeness associated with feeling low, especially when access to food was limited by caregivers

The authors proposed that eating behaviors form a separate constellation of characteristics in PWS, distinguishable from obsessive-compulsive traits. This may indicate a syndrome- specific pathophysiological mechanism related to lack of satiety behind this factor. On the other hand, obsessive and aggressive behavior appears to share a common etiology with developmental delays rather than food-

Table 2 Behavioral phenotype of PWS patients in consecutive life stages

Prenatal period	Neonatal and infancy period	Childhood	Adolescence	Adulthood
Decreased fetal movements	Central hypotonia	Change in appetite with subsequent hyperphagia and lack of satiety	Insistence on sameness	Persistence of food-related behaviors
Abnormal alignment of hand and feet	Lack of sucking reflex	Obsession and preoccupation with food	Mood swings	Maladaptive and emotional problems
Non-vertex presentation	Weak crying	Stealing, lying, wynning away to get more food	Auto-aggressive behaviors: skin picking, teeth grinding, body hitting	Explosive behaviors
	Excessive sleepiness	Eating nonedible items	Aggression toward others: pushing, pulling, verbal aggression	Compulsive behaviors
	Lowered appetite	Stubbornness, temper outbursts, mood swings	Anxiety symptoms	Increased mortality
	Delayed milestones	Manipulative behaviors	Mood disorders	
		Compulsive-like behaviors: repetitive questioning, hoarding	Disruptive behavior disorders	
		Difficulties with interrupting or switching activities	Psychotic disorders	
		Self-harm: skin picking, self-biting		
		Temper outbursts		
		Aggressive behaviors both verbal and physical		
		Autism spectrum features		

related issues, although these factors tend to be confounded in everyday functioning. Furthermore, the obsessive-compulsive behaviors and temper tantrums attested in PWS resemble typical obsessive behaviors found in children, and their rate does not change over time. Moreover, as the researchers propose, some patients seem able to move beyond this developmental stage and develop better coping skills, which lends further support to their link with arrested development. Self-injurious behavior in PWS, on the other hand, such as skin picking, and argumentativeness, seems to be connected with low mood, constituting a separate cluster (Holland et al. 2003).

Self-Injurious Behavior

Self-injurious behavior in PWS deserves a separate note, as this characteristic – even though commonly featured in PWS descriptions – is often underappreciated by the patient environment outside of the family context, which may lead to delayed intervention. For instance, what is known as skin picking is in fact a serious and challenging mental and behavioral issue characteristic of PWS, which in extreme cases may result in serious bodily harm and potentially life-threatening infections (Miller and Angulo 2014). Patients with this syndrome were found to be significantly more likely to engage in skin picking than age- and gender-matched controls with Down syndrome and nonspecific intellectual disability (Dykens and Kasari 1997). In a structured review of literature, Holland and Whittington report very high prevalence of skin picking in PWS, with attested rates ranging from 55% to nearly 100% depending on sampling method and chosen criteria, while the rate of self-injurious behaviors in persons with intellectual disability is estimated at 4.9% (Cooper et al. 2009; Whittington and Holland 2020). In PWS skin picking may take severe forms, leading to open wounds and ensuing complications. The high pain threshold in PWS means that what starts as a reaction to stress and anxiety may soon turn to repetitive behavior, which is difficult to uproot. Picking most often starts in areas where a person experiences discomfort, such as itching due to insect bites, and is more common when no other stimuli that would attract the patient's attention are present (Whittington and Holland 2020). In many cases, skin picking is accompanied by other forms of body-focused repetitive behavior, such as hair, nail, and teeth pulling, head banging, or rectal picking (Symons et al. 1999). Such behaviors are often addressed by environmental and behavioral interventions, but in more severe forms may require pharmacological treatment (Hustyi et al. 2013; Miller and Angulo 2014).

Nutritional Stages

PWS is best known as a syndromic cause of hyperphagia, resulting in early onset morbid obesity and consequent premature death if the condition is not diagnosed early and managed properly. The exact mechanism behind the development of hyperphagia in PWS remains unknown, yet there is a growing understanding of its natural course. In early literature on the syndrome, two nutritional stages were described: Stage 1 characterized by poor feeding and often associated with failure to thrive in infancy, followed by Stage 2, with the onset of hyperphagia and subsequent development of obesity (Gunay-Aygun et al. 2001). Miller and her team demonstrated that the development of hyperphagia and food-related behaviors is far more complex, encompassing seven nutritional phases: five main phases and subphases in phases 1 and 2 (Miller et al. 2011). According to this model, the initial stage Phase 0 in utero should be singled out, which is characterized by decreased fetal movements and retarded growth. Phase 1 is marked by infantile hypotonia, without obesity, or excessive appetite present. In subphase 1a, feeding difficulties

prevail, which may result in failure to thrive (ages birth—15 months). The next subphase 1b is one where a steady growth and weight increase at a normal rate occur (median age of onset: 9 months). In phase 2, weight gain begins, despite lack of increase in consumed calories and initially without a clear change in appetite in subphase 2a (median age of onset: 2.08 years). In subphase 2b, increased interest in food becomes manifest (median age of onset: 4.5 years), while phase 3 is associated with hyperphagia, insatiable appetite, and food seeking (median age of onset: 8 years). Phase 4 was attested in some adults, who apparently gained the ability to feel full following phase 3. This more complex model has implications for both research into pathomechanisms responsible for eating disorders in PWS and family counseling on obesity prevention in this syndrome (Miller et al. 2011).

The Relationship Between the Genotype and Phenotype of PWS

Previously mentioned studies by Dykens et al. with the Hyperphagia Questionnaire, in their preliminary results, showed no differences in hyperphagia in patients with different etiology of the syndrome (deletion or mUPD) (Dykens et al. 2007). Studies show higher verbal intelligence scores and less maladaptive behaviors in mUPD patients (Goldstone et al. 2008). However, mood swings, skin picking, and stubbornness, depending on the study, present either equally frequently regardless of the etiology of the syndrome or more commonly in patients with deletion (Boer et al. 2002; Holland et al. 2003; Wigren and Hansen 2005). Moreover, the severity of compulsions didn't show differences based on etiology (Lo et al. 2013, 2015). The major difference is in the development of psychotic disorders. Research indicates that this risk is significantly higher in patients with mUPD etiology (Boer et al. 2002). In this group, also bipolar disorder and cycloid psychosis are present with greater frequency (Butler et al. 2019). In addition, in an assessment of the prevalence of pervasive developmental disorders by Descheemaeker et al. in a group of PWS patients, mUPD was pointed as an additional risk factor for the development of autism spectrum symptoms (Descheemaeker et al. 2006).

Distinction in symptoms between deletion and uniparental disomy may result from the differences in the ways that loss of imprinted genes affects the neurodevelopment of the brain: haploid deficiency of genes not imprinted in deletion, or excess function of imprinted genes in disomy (Descheemaeker et al. 2006). Manzardo et al. shared an interesting conclusion from their research on genetic subtypes of PWS and neuropsychiatric diagnoses. It was suggested that all PWS subtypes presented a qualitatively similar phenotype, and the differences that did present may be due to the severity of the course of mental disorders, not the diagnosis itself. Differences in the intensity of disturbed, auto-aggressive, or compulsive behaviors and adaptation skills occurred in both types of deletion, with a lighter course and better academic performance presenting when the loss of a part of the chromosome was smaller (Manzardo et al. 2018).

Interventions Targeting Challenging Behaviors in PWS Patients

The basis for the treatment of PWS patients, which contributes to the reduction of disturbed and maladaptive behaviors, maintaining their good health and lowering mortality, is the provision of a food-secure environment (Bellis et al. 2022). Food insecurity contributes to the growth of anxiety and makes people obsessed with looking for food and food sources (Butler et al. 2019). This should be done respectfully of the rights of PWS patients to the highest possible degree of independence, choice, and autonomy while simultaneously strictly controlling the amount of meals and expenses (Goldstone et al. 2008). The patient should be informed of mealtimes, menus, and portions. Knowing the schedule of the day and interweaving activities that are desired (associated with less activity) and those that are not desired, but necessary (such as therapeutic interactions and physiotherapy), allows for the reduction of anticipatory anxiety and undesirable behaviors related to task-shifting (Butler et al. 2019). The most effective measures in improving functioning of PWS patients are summarised in (Table 3), following Dykens et al. 2007 and Goldstone et al. 2008.

Multifaceted therapeutic intervention should be started as soon as possible, preferably soon after birth (Goldstone et al. 2008; Feighan et al. 2020). Apart from maintaining daily routines aimed at regulating the consumption of meals, physical activity, and improving metabolism, it is important to introduce early intervention and then ongoing educational and psychological support. Speech and communication therapy are critical for lifelong functioning of individuals with PWS, as is provision of appropriate support structures, in education and vocational training. Communication with the PWS patient, as well as commands given, should be simple and literal. The patient should have time to process and absorb information, while the educational path should be flexibly adjusted to specific needs, ensuring the possibility of inclusion in the peer group for the purpose of socialization (Goldstone et al. 2008; Lo et al. 2015; Feighan et al. 2020). Such an approach helps reduce levels of anxiety and irritation, and thus manage challenging behaviors. Additionally, due to the deficits in theory of mind mentioned previously, people in the patient's environment should be encouraged to set more realistic expectations concerning exhibition of empathy and overall social-cognitive functioning (Lo et al. 2013). Providing

Table 3 Effective behavioral interventions

The most effective measures in improving functioning of PWS patients (Dykens et al. 2007; Goldstone et al. 2008)
Supervision and control of meals throughout lifetime
Restricted access to food (locked refrigerators, pantries)
Regular physical activity
A reduced calorie diet adapted to hypotension and slow metabolism
Behavioral therapy
Growth hormone supplementation
Psychological and behavioral counseling for families and caregivers

support and psychological counseling for the patient's family or caregivers is also an important element of successful intervention. Studies show that the burden on families and caregivers increases with the severity of hyperphagia as well as with the age of the patient, and severity of behavioral symptoms. Thus, the burden of the disease tends to increase over time (Kayadjanian et al. 2021). The literature emphasizes the negative impact of PWS on the quality of life and burden on both the patient and their family (Meade et al. 2021).

Impact of Pharmacotherapy on PWS Patients' Behavior

Any discussion of phenotypes and behavioral disorders in PWS patients should also take applied pharmacotherapy into account. While no pharmaceuticals improving the global functioning, dedicated to PWS, were found, psychopharmacotherapy allows to alleviate behavioral disturbances, even though it has a negative impact on the somatic burden of patients. On the other hand, drugs used in the pharmacotherapeutic treatments of somatic disorders in the syndrome may cause behavioral side effects (Butler et al. 2019). At the same time, behavioral disturbances related to eating, such as excessive water intake, may, along with undesirable effects of drugs, lead to electrolyte disturbances and be a potential threat to health and life (Butler et al. 2019). The use of psychopharmacotherapy in PWS patients should start with lower than standard doses and take into account the greater susceptibility to side effects in this group of patients (Goldstone et al. 2008).

Meta-analysis published in 2015 identified topiramate as a promising drug in the management of self-harm as well as of impulsive and aggressive behaviors. Among the antipsychotic drugs, the group of atypical neuroleptics is indicated as helpful in management of maladaptive behaviors. Risperidone has been shown to be effective in mUPD-related psychotic disorders. It should be remembered that neuroleptic drugs have well-documented side effects related to increased appetite and weight gain, which in the case of PWS patients requires strict medical control (Bonnot et al. 2016).

Furthermore, drugs from the group of antidepressants may also be found useful in the case of comorbid symptoms of OCD or mood disorders in patients with PWS (Bonnot et al. 2016). In recent studies of Deest el al., special attention was given to sertraline, a drug from the group of serotonin reuptake inhibitors, which significantly decreased the frequency of temper outbursts in 13 out of 14 patients, after 6 months of therapy (Deest et al. 2021).

The use of drugs to improve PWS patient's activation, such as serotonin reuptake inhibitors, aripiprazole, or modafinil, may, as a side effect, exacerbate behavioral disturbances related to agitation, mood lability, or even induced psychosis (Butler et al. 2019).

Supplementation of growth hormone (GH), from infancy through adulthood, proves to have a significant role in improving body composition and metabolism, but also to reduce challenging behaviors and improve cognitive functions (Cassidy et al. 2012). GH also contributes to the improvement of the quality of life, which may translate into reduction of mood disorders in this group of patients (Goldstone et al. 2008).

Hypogonadism found in the syndrome also often requires hormonal supplementation, which translates into an improved well-being and functioning of patients, but at the same time, it may carry the risk of exacerbating the behavioral disorders that occur in even every third patient, especially when they are burdened with mood instability or tendency toward aggression (Goldstone et al. 2008; Pellikaan et al. 2021). This should be taken into consideration especially for male patients in whom hormone replacement therapy may induce inappropriate or even aggressive sexual behavior (Crinò et al. 2003).

Given the high prevalence of skin picking among PWS patients, *N*-acetylcysteine supplementation has been gaining high interest as an effective therapeutic option. Despite initially promising results, the latest study showed only limited usefulness and effectiveness, especially in patients presenting with solitary rectal picking, or in combination with pharmacotherapy with neuroleptic drugs (Wieting et al. 2021a). Additionally, a randomized, double-blind, placebo-controlled study on the effect of probiotic supplementation showed no statistically significant improvement in psychological measurements related to development screening, aberrant behavior, and social and repetitive behaviors, among others. However, a significant statistical change was demonstrated on the Clinical Global Impression, leaving an open path for further research on this topic (Kong et al. 2021).

Application to Other Eating Disorders

As the best known cause of syndromic obesity, Prader-Willi syndrome may provide insights into the mechanisms of obesity and appetite control as well as energy expenditure. It serves as a model for research on disruption in hypothalamic pathways, hyperphagia, and the role of hormones in regulating food intake.

Mini-Dictionary of Terms

- Hyperphagia refers to abnormally increased appetite and urge to consume food, frequently associated with hypothalamic dysfunction.
- Food security is a form of behavioral intervention aimed at removing the temptation to search for edible items outside of mealtimes in persons with PWS. The term was coined by Drs Forster and Gourash. https://pittsburghpartnership.com/handouts/Food%20Security%20Basic.pdf.
- Behavioral phenotype of the genetic syndrome is a pattern of motor, cognitive, language, and social impairments that are consistently associated with its natural course.
- Genotype-phenotype correlation is a relationship between expression of alleles or variants in a particular gene or genetic location and subsequent disease presentation in a person.

- Self-injurious behavior refers to an act of physical aggression toward oneself, intended to (among others) express tension, stress, and anger but also to draw attention.

Key Facts

- Prader-Willi syndrome is a rare genetic condition resulting from loss of function of critical region genes on the long arm of paternally derived chromosome 15.
- Complex neuroendocrine disorder leads to morbid obesity in PWS if untreated.
- The condition is associated with a tendency to self-injury worsened by a high pain threshold.
- Intellectual disability is common in PWS, yet it cannot fully explain the observed behavioral phenotype.

Summary Points

- Prader-Willi syndrome is a complex neurodevelopmental disorder characterized by a specific behavioral phenotype.
- PWS is best known as a syndromic cause of hyperphagia, resulting in early onset morbid obesity and consequent premature death if the condition is not diagnosed early and managed properly.
- Self-injurious behavior is a highly common serious and challenging mental and behavioral issue characteristic of PWS, which in extreme cases may result in serious bodily harm and potentially life-threatening infections.
- Not all symptoms of the behavioral profile will always be present, and not all of them are due to the hyperphagia characteristic for the syndrome.
- Behavioral disorders may result both from the lack of control over food consumption by PWS patients and their frustration caused by overcontrol. Anxiety disorders also play a large part in the occurrence of behavioral disorders (Dimitropoulos et al. 2001).
- The understanding of the behavioral profile of PWS and its implications is crucial for the implementation of early therapeutic interventions which translates into improved patient prognosis and improvement in the quality of life for them and their family.
- Psychoeducation and knowledge of the behavioral profile are important for the families and caregivers of patients as they reduce their burden and improve their quality of life (Goldstone et al. 2008).
- With improved diagnosis, knowledge dissemination among families and access to growth hormone therapy tratment, behavioral disorders now come to the fore as challenging aspects of PWS management.

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Body Dysmorphic Disorder: Links with Eating Disorders and Gender-Related Factors

65

Amy Malcolm

Contents

Introduction to Body Dysmorphic Disorder 1306
Prevalence, Onset, and Course 1307
Core Symptoms 1307
Insight 1308
Comorbidities 1308
Functional Impairment 1309
Gender Differences in BDD 1309
Muscle Dysmorphia (MD): A Subtype of BDD 1310
Characteristics of MD 1310
Gender Differences Associated with MD 1312
Relationships Between BDD and Eating Disorders 1312
Differential Diagnosis: Distinguishing BDD from Eating Disorders 1313
Comorbidity of BDD and Eating Disorders 1314
Clinical Characteristics Common to BDD and EDs 1315
Considering Comorbid BDD and EDs in Treatment 1318
Conclusions 1319
Applications to Other Eating Disorders 1320
Mini-dictionary of Terms 1321
Key Facts of Body Dysmorphic Disorder: Links with Eating Disorders and Gender-Related Factors 1321
Summary Points 1322
References 1323

Abstract

Body dysmorphic disorder (BDD) is a mental disorder characterized by a distressing and impairing preoccupation with perceived defects in physical appearance. The disorder shares many clinical similarities with eating disorders (EDs) that involve a core component of disturbed body image, most notably

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anorexia nervosa and bulimia nervosa. In particular, the muscle dysmorphia subtype of BDD has close parallels with anorexia nervosa, though is characterized by a drive toward muscularity rather than toward thinness. Due to similarities between the disorders and the reality that BDD can involve concerns with body fat or weight, differentiating BDD from an ED can sometimes be challenging. In addition, BDD and EDs often co-occur; thus, clinicians must routinely screen for BDD among ED patients. Treatments tailored to symptoms of BDD as well as EDs must be used in instances of comorbid BDD and EDs, as treatment responses differ between the disorders.

Keywords

Body dysmorphic disorder · Muscle dysmorphia · Body image · Body dissatisfaction · Dysmorphophobia, Gender · Comorbidity · Anorexia nervosa · Bulimia nervosa · Dysmorphic concern · Appearance preoccupation · Steroids

Abbreviations

AN	Anorexia nervosa
BDD	Body dysmorphic disorder
BN	Bulimia nervosa
CBT	Cognitive behavioral therapy
ED(s)	Eating disorder(s)
MD	Muscle dysmorphia

Introduction to Body Dysmorphic Disorder

Body dysmorphic disorder (BDD) is a mental disorder that is characterized by a preoccupation with one or more perceived defects in physical appearance, which are either very slight or imperceptible to an objective observer (American Psychiatric Association 2013). This preoccupation is further accompanied by repetitive behaviors or mental acts in response to the appearance concerns at some time during the course of the disorder (American Psychiatric Association 2013). Lastly, the diagnosis of BDD cannot be made when the preoccupation is better explained by concerns of body fat or weight in a person whose symptoms meet criteria for an eating disorder (ED) (American Psychiatric Association 2013). This criterion is intended to help clinicians distinguish BDD from an ED and prevent misdiagnosis. Finally, the muscle dysmorphia (MD) specifier is applied to a diagnosis of BDD when the individual is primarily "preoccupied with the idea that his or her body build is too small or insufficiently muscular" (American Psychiatric Association 2013).

While written descriptions of BDD (historically called *dysmorphophobia*, meaning "fear of ugliness") have existed for more than a century, the disorder has received relatively little research and clinical attention (Veale and Neziroglu 2010). However, recent research has begun to demonstrate that BDD has many commonalities with EDs, especially anorexia nervosa (AN) (Phillipou et al. 2019). In addition, there has

been strong discussion about whether the MD subtype of BDD should be considered a standalone ED (Murray et al. 2010). In this chapter, a detailed overview of BDD and MD is provided, accompanied by commentary on associated gender-related factors, and followed by discussion of overlaps and differences between BDD (and MD) and EDs.

Prevalence, Onset, and Course

BDD is common, with large studies estimating a point-prevalence of 1.7–2.4% for BDD in general adolescent and adult populations (Buhlmann et al. 2010; Koran et al. 2008; Rief et al. 2006; Schneider et al. 2017b). While the average age at onset is 16 to 18 years, data suggests that most cases of BDD develop before 18, with early onset being associated with an increased likelihood of lifetime AN or bulimia nervosa (BN) (Bjornsson et al. 2013; Phillips et al. 2005b). BDD typically develops slowly over time, and generally follows a chronic and continuous illness course once established (Phillips et al. 2005b).

Core Symptoms

Appearance preoccupations in BDD may encompass any bodily feature. However, the most common areas of preoccupation are the skin, nose, mouth or teeth, face/facial features, or hair. The specific size, shape, color, texture, or symmetry, or relative proportions of these features, often forms the focus of concern (e.g., facial skin is "too red") (Malcolm et al. 2021). Concerns with other areas, such as body build, breast/chest, hands, genitals, legs, abdominal area, or buttocks, are also common (Malcolm et al. 2021). Furthermore, concerns might also relate to generalized feelings of "ugliness" or "abnormality," or concerns of insufficient masculinity or femininity in appearance (Veale and Neziroglu 2010; Malcolm et al. 2021). Most individuals with BDD will have concerns about multiple bodily areas (5–7, on average), which may change to other areas over time (Phillips et al. 2005b). Typically, thoughts of appearance concerns are present for 3 to 8 h per day (Phillips et al. 1998). Such thoughts about appearance are extremely distressing and difficult to ignore (Kollei and Martin 2014).

Appearance concerns in BDD typically elicit strong urges to engage in excessive, repetitive, time-consuming, or unusual behaviors or mental acts, that are performed with the goal of examining, hiding, or "improving" the area of appearance concern (see Table 1). People with BDD spend one to eight hours per day engaging in behavioral symptoms (Phillips et al. 2005b). While attempts to alter appearance by seeking cosmetic procedures is common, receiving such procedures typically results in a worsening of BDD symptoms or simply leads to a transferral of appearance concerns to a new body area (Veale 2000).

Table 1 Common behaviors associated with body dysmorphic disorder

Behaviors	Examples
Appearance checking	Viewing self in mirrors or other reflective surfaces (e.g., windows, polished cutlery, etc.) Frequent reflection checks, or prolonged gazing Touching or feeling body areas, measuring body areas Taking photographs of the self
Appearance camouflaging	With makeup, hairstyles, accessories (e.g., hat) With body positioning (e.g., hunching, keeping hand over face, controlling facial expressions) With clothing; may also spend extended amount of time changing/choosing clothes
Comparing appearance	Comparing to others, film and media or social media, or to own past appearance (e.g., old photos of self)
Excessive or repetitive appearance routines	Grooming (e.g., washing, hair styling, hair removal) Skin care or beauty treatment routines Meticulous or repeated makeup application
Reassurance seeking	Repeatedly asking others for reassurances about appearance Asking on the Internet for feedback on appearance photos
Attempts to alter appearance	Use of makeup, beauty products, skincare or haircare products Dieting or excessive exercise regimes Seeking cosmetic, dermatological, aesthetic dental, or plastic surgery procedures to change appearance Skin picking with intent to "improve" texture Idiosyncratic methods, which may be diverse or illogical (e.g., chewing gum all day to "tighten jaw muscles")
Information gathering	Obsessive researching of possible appearance-enhancing products, treatments, or procedures
Distraction techniques	E.g., choosing a colorful or bizarre hairstyle to "distract" from nose concerns

Insight

Illness insight in BDD encompasses the degree to which a person can recognize their appearance concern as being excessive or inaccurate and psychological in origin (rather than reflecting a physical reality). Approximately 72% individuals with BDD have poor or absent insight, and commonly endorse delusions of reference (e.g., "that other people are noticing or are disgusted by my appearance") (Phillips et al. 2012).

Comorbidities

Comorbidity is common in BDD, with a majority of individuals having at least one comorbid diagnosis over the lifetime (90%) or concurrently with BDD (81%) (Gunstad and Phillips 2003). Major depression is the most common concurrent comorbidity (e.g., 53% to 87%), followed by social anxiety disorder (31% to

34%), obsessive-compulsive disorder (25%), other anxiety disorders (7% to 16%), EDs (4% to 9.5%), and substance or alcohol use disorders (up to 13%) (Gunstad and Phillips 2003; Phillips et al. 2005b, 2007; Ruffolo et al. 2006; Frare et al. 2004).

Functional Impairment

BDD is, on average, associated with severe functional impairment and poor quality of life across numerous domains (Didie et al. 2007; Phillips et al. 2005a). In particular, BDD involves a high degree of interpersonal impairment, such as experiencing relationship conflicts, social isolation, or becoming housebound (Didie et al. 2007, 2012; Phillips et al. 1998). Moreover, hospitalization, suicidal ideation, and suicide attempts are markedly high in BDD, with some estimates suggesting a rate of completed suicide that is higher than that of major depression, bipolar disorder, or AN (Phillips 2017).

Gender Differences in BDD

Data suggests that BDD impacts men and women in roughly equal proportions and that overall, there are more similarities than differences among men and women with BDD (Buhlmann et al. 2010). Similarities include the average severity of BDD symptoms, average age at onset, and severity of associated depression, stress, anxiety, and social anxiety symptoms (Malcolm et al. 2021). In addition, studies which have examined gender differences in body areas of concern among individuals with BDD have typically found more similarities than differences (Malcolm et al. 2021; Perugi et al. 1997; Phillips and Diaz 1997; Phillips et al. 2006). In particular, concerns with skin and facial features are highly common across both genders. However, these studies have typically found that men tended to be more concerned than women about their genitals (e.g., penis size), their body build (feeling inadequately muscular, or that build is "too small"), and their hair with regard to thinning or balding. Conversely, women were more likely than men to have concerns about their body weight or shape, legs (e.g., calves and/or thighs), stomach, buttocks or hips, and breasts (Malcolm et al. 2021; Perugi et al. 1997; Phillips and Diaz 1997; Phillips et al. 2006). These gender differences seem to coincide with common areas of nonclinical body dissatisfaction among men and women in the general population (Phillips et al. 2006). Though illness insight has not been well-compared between men and women with BDD, one recent study has indicated that women may have slightly poorer insight than men on average (Malcolm et al. 2021).

Men and women with BDD generally show similar patterns of behavioral symptoms in response to appearance concerns, including in the types of behaviors (e.g., mirror checking) and the severity of symptomatic behaviors (Malcolm et al. 2021; Perugi et al. 1997; Phillips and Diaz 1997; Phillips et al. 2006). However, some studies have reported that camouflaging behaviors are more common among women than men with BDD, including use of cosmetics (likely explained by social norms

encouraging cosmetic use among women only), clothing selection, and positioning of the hands to cover areas of concern (Phillips et al. 2006; Malcolm et al. 2021). Although one study also reported more frequent mirror checking by women than by men (Perugi et al. 1997), others have not replicated this finding (Malcolm et al. 2021; Phillips and Diaz 1997; Phillips et al. 2006). Finally, there has not been any comprehensive investigation of BDD among gender-diverse populations, an important research area that requires further attention.

Muscle Dysmorphia (MD): A Subtype of BDD

The DSM-5 describes MD as a specific presentation of BDD that is primarily characterized by a preoccupation with the idea that one's body build is too small or insufficiently muscular (American Psychiatric Association 2013). The condition was initially conceptualized as a form of "reverse anorexia" (or "bigorexia") when it was first identified among male bodybuilders (Pope Jr et al. 1993). This is because, in contrast to individuals with AN who perceive themselves as "fat" despite being of low weight or emaciated, individuals with MD perceive themselves as "small," "puny," or "weak" despite being very large and muscular.

Although no further diagnostic criteria for MD (beyond the criteria for BDD) are included in the DSM-5, Pope et al.' (1997) initial research into the condition produced detailed operational diagnostic criteria for MD that is commonly used by researchers and clinicians today. These criteria require preoccupation with the idea that one's body is inadequately muscular and lean, which may involve characteristically related behaviors of excessive weight lifting and excessive dietary attention, and which meet at least two of the four following conditions: (i) the individual compulsively prioritizes the maintenance of workouts and dietary schedules over important social, occupational, or recreational activities, (ii) the individual avoids situations where the body is exposed or endures such situations with marked distress, (ii) the preoccupation causes clinically significant distress or functional impairment, or (iv) the individual pursues workouts, dietary practices, or use of performance-enhancing substances despite knowledge of associated physical and mental health risks. Finally, the preoccupation with body size or muscularity must not be better explained by fear of weight gain or fatness (as in AN), or by preoccupation with other aspects of appearance (as in other forms of BDD). Among individuals who are diagnosed with BDD, approximately 9.3% meet Pope's criteria for MD (Pope et al. 1997).

Characteristics of MD

Behaviorally, MD is characterized by a pattern of excessive weight training, undertaken with the goal of muscular growth. Individuals with MD often adhere to a rigid training routine which may be maintained through injury or to the extent that social or occupational functioning is impacted, else extreme anxiety may arise if a workout

is missed (Cunningham et al. 2017). Clinically significant symptoms of MD are commonly identified among competitive bodybuilders (e.g., 84%) and recreational weight lifters (Pope et al. 1997). Individuals with MD seem be attracted to these activities due to their goals of increased muscularity, but it remains unclear whether engagement in such activities may also be a risk factor for MD development.

MD typically involves many behavioral symptoms that are common in BDD more broadly, including mirror checking, touching, feeling, or measuring body areas, and use of camouflage behaviors such as wearing loose-fitting clothing. Avoidance behaviors, such as selecting "quiet" hours to attend public exercise facilities or avoiding situations where the body may be exposed (e.g., change-rooms or public bathing/swimming), are also highly common. Relative to more "typical" presentations of BDD, MD is similar in the severity of preoccupations, number of non-muscularity appearance concerns, degree of interference caused by symptom-related behaviors, and a poor degree of insight into symptoms (Pope et al. 2005). However, men with MD may be more likely than men with "typical" BDD to have attempted suicide, have poorer quality of life, and have a higher frequency of substance use disorder and steroid abuse (Pope et al. 2005).

MD typically involves excessive attention to diet within the context of supporting muscle development. Individuals often follow strict diet regimens characterized by extreme protein intake, frequent and/or strictly scheduled food intake, eating beyond fullness, excess use of protein supplements or other nutritional supplements, or liquification of food to make extreme caloric intake easier (e.g., blending/pureeing food), all intended to fuel the growth of trained muscles (Cunningham et al. 2017; Griffiths et al. 2013). Individuals with MD may also make use of "bulk and cut" diets, a two-phase diet popular among competitive bodybuilders but which has little scientific backing (Lenzi et al. 2021; Griffiths et al. 2013; Lavender et al. 2017). The "bulking" phase lasts several weeks to months and involves excess protein and carbohydrate intake, undertaken with the belief that a hypercaloric intake will maximize muscle growth from weight training (Lenzi et al. 2021). However, "bulking" typically leads to increased adiposity due to extreme caloric surplus. As increased adiposity can obscure muscular definition and thus cause dissatisfaction with muscularity, the "cutting" phase is then employed to reduce body fat and enhance muscular definition. "Cutting" involves restricting nonprotein food intake (e.g., carbohydrates) to stimulate fat loss, and may include attempts to maintain a caloric deficit for weeks or months. However, protein intake is typically maintained at an above-average level during this time (Lenzi et al. 2021). The "cutting" phase can result in a loss of lean tissue as well as adiposity, which may cause muscle dissatisfaction and prompt users to begin the "bulk and cut" cycle anew (Lavender et al. 2017).

MD and Steroid Abuse

MD also involves a strong association with anabolic-androgenic steroid abuse. Studies have reported as much as 50% to 100% of participants with MD have used steroids (Lavender et al. 2017). Conversely, steroid use is less common among weight lifters who do not exhibit MD symptoms (e.g., 7%). Data suggests

that the onset of MD symptoms typically precede use of anabolic-androgenic steroids (Olivardia et al. 2000), consistent with the proposal anabolic-androgenic steroid abuse is an attempt to "improve" preexisting body image concerns related to insufficient muscularity (Rohman 2009). Accordingly, data suggests that weight lifters with high MD symptoms are significantly more likely than those with lower MD symptoms to have used anabolic-androgenic steroids excessively (e.g., for 6 to 150 months in total over the lifetime) (Kanayama et al. 2006). However, use of steroids may also perpetuate MD symptoms, as once used, an individual typically gains a level of muscularity that is not naturally achievable. When steroid use is ceased, there is a loss of muscularity as the body returns to a natural state, which could further exacerbate body dissatisfaction and muscle preoccupation (Olivardia et al. 2000).

Gender Differences Associated with MD

Research and discussion of MD has typically been focused on males, yet there is data to suggest that women are also impacted by MD. In a convenience sample of 1150 American military personnel, muscle dysmorphia was identified in approximately 12.7% of men and 4.2% of women (Campagna and Bowsher 2016). Further, a recent study of Australian adolescents reported MD prevalence rates of 2.2% for males and 1.4% for females (Mitchison et al. 2021). In that study, adolescent boys with MD were found to be significantly more likely than girls with MD to have "severe" preoccupation, and to have a weight lifting regime that significantly interfered with their life (Mitchison et al. 2021). However, it is currently unclear whether there are other substantial differences in MD symptomatology between men and women with MD, as most studies to date have recruited male participants only. Recently, sociocultural ideals regarding the female body appear to be moving more toward lean, toned physiques, emphasizing visible muscularity rather than thinness alone (Bozsik et al. 2018; Wagner et al. 2020). As such, the study of MD among women is likely an important yet currently neglected research area.

Relationships Between BDD and Eating Disorders

In the current DSM-5 (American Psychiatric Association 2013) and upcoming draft of ICD-11 (World Health Organization 2019), BDD is currently classified as belonging to the obsessive-compulsive and related disorders family. This classification has been highly controversial, as research to evaluate whether BDD is best situated in this category or alongside other conditions, such as anxiety disorders or EDs, is lacking (Malcolm et al. 2018). In particular, there has been limited research examining relationships between BDD and EDs characterized by body image concern, such as AN (Phillipou et al. 2019). Recent proposals have argued that BDD, AN, and BN should be reclassified together in a new category of "body image disorders," due to the many similarities among these conditions (Phillipou et al. 2016, 2017). In yet

another perspective, it has been argued that MD should be considered a standalone disorder (as opposed to a subtype of BDD), which should be positioned within the EDs family (Murray and Touyz 2013). Regardless of classification debates, there is substantial evidence to show that BDD (including MD) shares many features with AN, which warrant careful attention when screening for or treating comorbid presentations.

Differential Diagnosis: Distinguishing BDD from Eating Disorders

Diagnosis of BDD according to the DSM-5 criteria requires that "the appearance preoccupation must not be better accounted for by concerns with body fat or weight in an individual whose symptoms meet criteria for an ED" (American Psychiatric Association 2013). This criterion ensures that individuals who meet criteria for an ED are not incorrectly diagnosed with BDD instead. However, overlaps between BDD and certain EDs, particularly AN and BN, necessitate very careful exploration of symptoms to ensure that appropriate diagnoses are made. For instance, a person who is primarily concerned with body fat or weight, but who does not meet criteria for any ED, might yet meet criteria for BDD. Diagnoses of both BDD and an ED may be appropriate when there is evidence of both clinically significant concerns with body fat or weight that are associated with disordered eating behaviors and clinically significant preoccupation with perceived defects in other aspects of appearance that are not related to body fat or weight. As such, clinicians who suspect either BDD or an ED must carefully screen for symptoms of both disorders. Moreover, it is important for clinicians to carefully probe for appearance concerns across the entire body when screening for either BDD or an ED. It is very common for individuals with BDD to keep some or all of their appearance concerns secret due to shame or fear of being seen as vain (Veale et al. 2015). As such, failure to ask about broader appearance concerns may result in a missed BDD diagnosis. Box 1 illustrates an example of comorbid eating pathology and BDD concerns.

Box 1 An Example Case of Comorbid Atypical AN and BDD

Sarah is a 29-year-old woman who describes feeling overwhelmed with thoughts that she is "too big," and "ugly," describing concerns with her skin texture and "deep, cut-like" eye wrinkles. On physical examination, Sarah's skin appears healthy, there are only very fine lines around her eyes (normal for her age), and her weight is in a healthy range for her height (BMI = 23). Sarah reports running for 2 h each day to lose weight and eats no more than 800 calories per day. She weighs herself daily and will exercise twice if she feels she exceeded her calorie limit. When asked about her skin and eyes, Sarah describes repeatedly checking her looks in the mirror or touching up her makeup, which has made her for work on several occasions.

(continued)

Box 1 (continued)
She refuses to leave the house without heavy makeup and spends large amounts of money on various skincare and anti-wrinkle creams. At work, she has trouble concentrating on tasks as her thoughts continually return to worries about her body weight and appearance. Sarah describes being unable to make eye contact with customers, as she "can't bear to have them see how fat and ugly [she] is." Sarah avoids social events as she fears that others will reject or humiliate her for her weight and appearance "flaws."

In the example of Box 1, Sarah is likely to meet criteria for both BDD and atypical AN. She shows fears of weight gain and feelings of shame over her body weight and uses severe caloric restriction and excessive exercise to control her weight. Conversely, Sarah's preoccupations with her skin and eyes are likely to be symptoms of BDD. Of note, her concerns about eye wrinkles seemed excessive, as very fine eye wrinkles are not out of the ordinary for an adult woman. Concerns about her weight, skin, and eyes seem to equally preoccupy Sarah for hours each day, feed problematic behaviors (e.g., dietary restriction, excessive exercise, mirror scrutinizing, costly product use, compulsive makeup use), and cause significant avoidance and functional impairments both at work and in her social life.

Comorbidity of BDD and Eating Disorders

EDs commonly co-occur with BDD. For instance, in a large study of 200 individuals with BDD recruited from the community, it was reported that 32.5% of participants had a lifetime ED diagnosis, with 9% reporting AN, 6.5% reporting BN, 5.5% reporting binge ED, and 17.5% reporting an ED not otherwise specified (Ruffolo et al. 2006). Moreover, 9.5% of participants in this study met current criteria for both BDD and an ED. Of note, it was also reported that the majority of participants with a history of ED developed BDD symptoms before the onset of ED symptoms (63.1%), while 16.9% developed both BDD and an ED within the same year (Ruffolo et al. 2006). Regarding MD, it has been reported that up to 29% of men with MD have a history of an ED (Murray et al. 2010). In another study of weight lifters with MD, it was reported that approximately 13% of men and 47% of women had a history of either AN or BN (Pope et al. 1997).

Studies which have screened for BDD among ED patients also report high rates of comorbidity. In an investigation of 158 patients with mixed EDs, 45% screened positive for BDD (Dingemans et al. 2012). Similarly, rates of BDD among individuals with AN have been reported between 9.8% to 39% (Kollei et al. 2013; Grant et al. 2002; Cerea et al. 2018). However, in one study of inpatients with AN, Grant et al. (2002) found that none of the AN patients who screened positive for BDD during the study had been previously diagnosed with the disorder. These data

suggest that the comorbidity of BDD and EDs may be grossly underestimated due to the underdiagnosis of BDD in routine clinical settings (Veale et al. 2016).

Clinical Characteristics Common to BDD and EDs

Differentiating core clinical characteristics of BDD from those associated with an ED can be challenging. Most prominently, BDD shares with AN and BN severe disturbances in body image and dissatisfaction, intrusive negative thoughts about appearance, and an overvaluation of appearance in judgments of self-worth (Hrabosky et al. 2009; Hartmann et al. 2013; Beilharz et al. 2019; Rosen and Ramirez 1998). Often, BDD can be differentiated from an ED on the basis of appearance concerns, as data suggests that individuals with BDD are significantly more likely than those with AN to have concerns centered on facial features, skin, or hair, while those with AN are more likely to be concerned by body areas closely linked to weight concerns (e.g., hips, thighs, stomach, waist) in addition to overall weight (Toh et al. 2020). However, up to 29% of individuals with BDD report experiencing significant weight or shape concerns that are not associated with significant eating pathology (Kittler et al. 2007). Manifestations of BDD can further include concerns related to the shape, feel, or texture of body areas in body areas such as the stomach, thighs or buttocks, arms, or wrists, (e.g., "flabby," "too big," "cellulite-covered") which may seem to mirror concerns linked to body shape or weight among individuals with EDs.

On the other hand, a large proportion of individuals with AN or BN also report non-weight-related appearance concerns, such as concerns with their skin, breasts, teeth, nose, other facial features, or hair, that do not necessarily meet criteria for BDD (Gupta and Johnson 2000; Rosen et al. 1995). However, it is important to differentiate between dysmorphic concerns (i.e., which are objectively imperceptible or very slight) and concerns related to objective, observable changes in appearance that may stem from starvation among ED patients, such as increased hair growth (lanugo), dental lesions, or skin and hair changes (Beilharz et al. 2019).

In sum, clinicians must carefully inquire about appearance concerns across the whole body when suspecting any form of body image disturbance, whether it is BDD or an ED. Any identified areas of concern should then be examined to determine whether the concern has a clearly discernible physical basis, or whether it perhaps may represent a dysmorphic concern (i.e., the concern is imperceptible or very slight, or is within normal variation). Patients should then be asked about the degree of preoccupation and distress associated with each identified concern to aid in determining an appropriate diagnosis.

Both BDD and AN also share patterns of ritualistic, repetitive, or excessive body-focused behaviors. These include mirror checking and self-scrutinizing behaviors (e.g., measuring and weighing oneself), mentally comparing self to others, dieting, and excessive exercise (Grant and Phillips 2004). Both conditions also involve behaviors aimed at "improving" the perceived problem with physical appearance, such as altering weight or shape in AN through eating and exercise behaviors, or

altering the appearance of specific body or facial features in BDD with product use, grooming, exercise, or cosmetic procedures (Phillips 2017). In addition, both BDD and AN involve similar safety behaviors, such as choosing camouflaging clothing and avoiding places, activities, or social situations that exacerbate self-consciousness about appearance (Grant and Phillips 2004). However, individuals with BDD may engage in increased checking and appearance manipulation behaviors relative to individuals with AN (Kollei et al. 2012), and may be more avoidant of social situations (Rosen and Ramirez 1998).

Thus, investigation as to what behavioral reactions arise in response to identified appearance concerns may further aid in distinguishing symptoms of BDD from those of an ED. As noted previously, presence of clinically significant disordered eating behaviors and/or related compensatory behaviors, such as vomiting or use of laxatives, is not characteristic of BDD (American Psychiatric Association 2013). Finally, research suggests that individuals with comorbid BDD and AN may demonstrate more severe illness outcomes than those with AN alone, but not necessarily any more severe than those with BDD alone (Grant et al. 2002). These outcomes include significantly poorer psychosocial functioning, increased likelihood of psychiatric hospitalization, and triple the rate of suicide attempts among those with comorbid BDD and AN as compared to those with AN only (Grant et al. 2002).

Associated Features Common to BDD and AN

Both BDD and AN demonstrate a similar mean age of onset, in a range of approximately 16 to 18 years, though both conditions are also frequently associated with early onset during childhood (Hartmann et al. 2013). Both conditions also tend to exhibit a chronic illness course when left untreated (Hartmann et al. 2013). While both conditions also appear to involve poor insight into the nature of appearance concerns, data suggests that insight may be worse among those with BDD (Phillipou et al. 2019). BDD may also involve a higher risk of suicidal ideation and suicide attempts as compared to AN (Hartmann et al. 2013). Other clinical features that are common among both BDD and AN include perfectionism, tendency to worry, low self-esteem, and negative interpretive biases for ambiguous situations (Hartmann et al. 2013; Phillipou et al. 2019).

Cognitively, both BDD and AN have been associated with poor global visual processing (Lang et al. 2021), and poor performances on tests of executive functioning (Hartmann et al. 2013). Both conditions also show poor recognition of emotional expressions and tendencies to misinterpret emotional expressions as angry (Hartmann et al. 2013). Furthermore, direct neuroimaging comparisons of BDD and AN have demonstrated broadly similar abnormalities, as well as nuanced differences, in the function and structure of brain regions involved in visual processing (Phillipou et al. 2019; Moody et al. 2021). Potentially, abnormalities in visual processing systems may underpin the shared experience of extreme body image distortion that is common to BDD and AN.

Overlaps Between MD and AN

Data suggests that MD and AN involve a similar degree of body image disturbance, abnormal eating behaviors, and engagement in compulsive exercise, but with opposing characterizations (Murray et al. 2012). Individuals with MD demonstrate a significantly increased "drive for muscularity" than do individuals with AN (i.e., reflecting wishes to be larger and bulkier, and associated dietary and exercise behaviors). Conversely, individuals with AN are more concerned with thinness and demonstrate significantly greater dietary restriction and eating concerns than do individuals with MD (Murray et al. 2012). Accordingly, compulsive exercise is considered to be the primary feature of MD, with eating disturbances conceptualized a secondary feature (Pope et al. 1997). However, further research is needed to better understand the nature of eating behaviors in MD, as in both MD and EDs such as AN and BN, non-adherence to planned dietary practices often causes feelings of guilt or anxiety and triggers compensatory behaviors such as additional exercise (Murray et al. 2010).

Overlaps of BDD and EDs: Gender-Related Factors

Across BDD and EDs, gender-related factors seem to play a role in some aspects of illness presentation. EDs such as AN or BN predominately affect women, with estimates suggesting that men represent approximately 25% to 33% of AN or BN cases (Murray et al. 2017). Conversely, just over half of individuals with BDD are women (Buhlmann et al. 2010). However, it seems that men are substantially more likely than women to be affected by MD (Pope Jr et al. 1993). Regarding BDD, there are some subtle differences between men and women in common body areas of concern, which tend to align with normative masculine and feminine gender ideals that are prevalent in Western society (Malcolm et al. 2021; Phillips et al. 2006). In addition, MD has been conceptualized as involving an extreme valuation of the stereotypical masculine ideal, thus feeding a drive for increased muscularity (Lavender et al. 2017). Accordingly, men with MD have been found to show higher adherence to traditional masculinity norms than do men with BDD, such as endorsing the use of violence to solve problems (Blashill et al. 2020). Conversely, it has been argued that adherence to feminine ideals is more closely related to a drive for thinness, which characterizes EDs (Murray et al. 2017). For instance, Murray et al. (2013) reported significantly greater adherence to masculine norms among men with MD as compared to men with AN and gym-using male controls, while men with AN demonstrated significantly greater adherence to feminine norms than men with MD or gym-using men.

Further research in BDD and EDs is also needed among individuals who are transgender or who have nonbinary gender identities, as these groups may also have differing experiences of dysmorphic concern or ED pathology. For instance, transgender people who are not receiving gender-affirming hormone therapy have been found to have increased body dissatisfaction and ED symptoms as compared to those receiving hormone therapy (Jones et al. 2018).

Considering Comorbid BDD and EDs in Treatment

While BDD and AN have a number of similarities, treatments for the disorders have some differences. Treatment for BDD typically involves cognitive behavioral therapy (CBT) tailored for BDD and/or high-dose serotonin reuptake inhibitor (SSRI) medications. CBT for BDD is comprised of psychoeducation, cognitive restructuring, exposure and response prevention, relapse prevention training, and often, perceptual retraining (Wilhelm et al. 2013). Perceptual retraining involves practicing skills in viewing one's reflection objectively and learning how to adaptively use mirrors (i.e., at an appropriate distance and only for brief, purposeful periods). Motivational interviewing techniques are often utilized throughout treatment, especially for individuals with poorer insight (Wilhelm et al. 2013). Where appropriate, additional specialized strategies may be used to address MD, weight/shape concerns, or persistent cosmetic surgery seeking (Wilhelm et al. 2013). For MD, there is a focus on increasing awareness of factors that drive the desire to change body weight or shape, restructuring underlying beliefs or biases, increasing acceptance of the "realistic" or "natural" body, and reducing compulsive dietary and exercise behaviors (Wilhelm et al. 2013). Where relevant, psychoeducation about the health risks associated with steroids is provided, and patients are supported to reduce steroid use.

Other formulations of CBT for BDD emphasize use of mindfulness techniques and emotion-focused approaches, including self-compassion-based skills development and use of imagery rescripting (i.e., restructuring narratives and imagery of painful memories associated with dysmorphic concerns to redefine their meaning) (Veale and Neziroglu 2010). Current data suggests that approximately 40% to 80% of patients show a significant response (e.g., 30% decrease in symptom severity at posttreatment) to CBT for BDD, yet a high degree of specialized training in BDD-specific skills seems most closely tied to improved patient outcomes (Harrison et al. 2016; Wilhelm et al. 2019). In addition, SSRI medications administered at high doses and for extended periods seem beneficial for approximately 53% to 83% of patients (Phillips 2017).

Treatments for EDs often entail different approaches and outcomes. For instance, AN treatments often include ED-specialized family-based therapy, pharmacological interventions (e.g., antipsychotic medications), CBT enhanced for EDs (CBT-E), and ED-specialized inpatient or outpatient programs which may involve refeeding or heavily nutritional-focused components (Murray et al. 2019). In general, interventions for AN are often highly targeted toward weight gain and creating change in eating behaviors, which are essential for the prevention of medical risks related to starvation (Murray et al. 2019). These treatments are efficacious in promoting weight gain in the short term, but demonstrate very little efficacy in promoting long-term weight maintenance or recovery from psychological symptoms of AN (Murray et al. 2019). Further, in contrast to interventions for BDD, data suggests little to no benefit from commonly used pharmacological interventions in AN (e.g., SSRIs, antipsychotic medications), and mixed or moderate benefits from CBT-E or family therapy

(Linardon et al. 2017b). Thus, treatment for an ED with comorbid BDD must include targeted treatments for both disorders.

Role of Dysmorphic Concerns in Comorbid BDD and EDs

Findings suggest that increasingly severe dysmorphic concern is significantly associated with greater severity of eating concerns and shape and weight concerns among individuals with AN (Beilharz et al. 2019). Similarly, disturbances in body image and body dissatisfaction have been found to be consistent predictors of improvement or relapse in AN posttreatment (Murray et al. 2019). Thus, the presence of extreme dysmorphic concern associated with comorbid BDD will likely require intensive focus. Interventions developed specifically to address dysmorphic concern in BDD could be especially useful in these contexts (e.g., imagery rescripting, perceptual "mirror use" retraining, exposure-based approaches, and compassion-based approaches). In addition, clinicians must be attentive to shifts in dysmorphic concerns during treatment for persons with a comorbid ED and BDD. Among individuals with BDD, it is common for appearance concerns to move to other body areas, either spontaneously or after some form of physical change in an area of concern, such as following cosmetic procedure (Veale et al. 1996). Theoretically, physical changes associated with weight restoration during recovery from an ED may also prompt shifting appearance concerns in an individual with comorbid BDD. Thus, clinicians should regularly assess for new or changed appearance concerns among individuals with comorbid BDD.

Future Treatment Research Directions for Comorbid BDD and AN

Research into potential treatments for BDD and AN appear to demonstrate some overlaps, and converged treatments for these disorders may be especially effective in cases of comorbid illness. For instance, emergent research directions that may be beneficial for both disorders include visually focused cognitive remediation therapy, acceptance and commitment therapy-based approaches, or other "third wave" psychotherapies such as dialectical behavior therapy (Beilharz et al. 2017; Hartmann et al. 2013; Linardon et al. 2017a). In addition, comprehensive compassion-focused therapy has separately been proposed as a potentially beneficial treatment for each disorder (Veale and Gilbert 2014; Goss and Allan 2014). In the context of BDD or AN, compassion-focused therapy addresses body image concerns with a focus on shame, self-criticism, and self-hostility while building capacity for self-compassion, distress tolerance, and regulation of affiliative attachment-based emotions (Veale and Gilbert 2014). However, further research is needed to test the efficacy of these treatments in BDD and EDs.

Conclusions

BDD is a severe mental illness that involves many similarities to AN, especially in the severity of body image disturbance, core clinical features, and associated cognitive and neurobiological features. These overlaps may create challenges in

differentiating between BDD and AN, especially when BDD involves weight or shape concerns. However, careful investigation of specific appearance concerns and related behavioral symptoms will help differentiate between the disorders. The MD subtype of BDD further shows particularly strong links with AN in terms of disturbed eating patterns and excessive exercise behaviors, though with an opposing drive toward muscle gain and bulkiness. Across these conditions, gender-related influences seem to intersect with presentations of MD and EDs, though BDD appears more similar than different among men and women. Finally, given that BDD is highly likely to co-occur with AN or BN, it is essential that clinicians screen for BDD in any instance of a potential ED. This is extremely important as BDD symptoms are unlikely to be identified without direct questioning, and the presence of comorbid BDD is associated with significantly more severe psychosocial consequences for individuals with AN. Further, it is important that disorder-specific treatments are jointly utilized for comorbid BDD and EDs, as these disorders often respond to different treatment interventions. However, further research is needed to determine the most helpful course of action treating individuals with comorbid BDD and ED diagnoses, as outcomes for this group of patients are not well reported on.

Applications to Other Eating Disorders

This chapter has reviewed associations between body dysmorphic disorder (BDD) and EDs which involve similarly severe body image disturbance, most notably AN and BN. However, a number of other EDs do not involve any evidence of body image disturbance, and thus may be unlikely to have any strong links with BDD (e.g., pica, rumination disorder, avoidant/restrictive food intake disorder). It has been argued that these aforementioned conditions represent "true" feeding and EDs, whereas AN and BN are, at the core, body image disorders which manifest through problematic eating (Phillipou et al. 2017). This proposal provides a compelling explanation for the numerous close similarities between BDD (including MD) and AN, including overlaps in clinical, cognitive, and neurobiological features (Hartmann et al. 2013; Lavender et al. 2017).

One area of further research interest may be whether BDD has elevated associations with the proposed ED of orthorexia nervosa. Both BDD and orthorexia nervosa are conceptualized to involve obsessive-compulsive characteristics (Malcolm et al. 2018; Brytek-Matera 2012). Theoretically, preoccupation with a "healthy" diet in orthorexia nervosa could coincide with body image concerns related to having a "healthy" appearance in BDD, such as appearing highly fit and toned. Similarly, excessive attention toward the precise nutritional value of food or supplements (e.g., macro- or micronutrient properties) is a common feature of muscle dysmorphia (Lavender et al. 2017), and one which could overlap with orthorexic tendencies. Overall, further research is needed to better understand relationships between BDD, MD, and the EDs. Data comparing BDD and AN is still limited, and there is scant research to evaluate potential links between BDD and other EDs.

Mini-dictionary of Terms

- **Body dysmorphic disorder (BDD)**. A psychological disorder involving a distressing and impairing preoccupation with a perceived defect in physical appearance, which is not observable or appears slight to objective observers.
- **Dysmorphic concern**. Preoccupation with a distorted perception of appearance that is generally not consistent with objective observations (i.e., is imperceptible, or appears very slight, or is within normal variation), and which involves subjectively experienced anomalies in self-perception.
- **Illness insight**. Describes the degree to which a person can recognize disorder-relevant beliefs as being excessive or inaccurate. In BDD, insight relates to beliefs about perceived defects in appearance. In AN, insight relates to beliefs about the body being larger, heavier, or fatter than objective assessments indicate.
- **Muscle dysmorphia (MD)**. A specific presentation of body dysmorphic disorder that is primarily characterized by a preoccupation with the idea that one's own body is not sufficiently muscular. This concern is accompanied by excessive weight training behaviors and excessive attention to a protein-rich diet.

Key Facts of Body Dysmorphic Disorder: Links with Eating Disorders and Gender-Related Factors

- BDD was first named "dysmorphophobia" by the Italian psychiatrist Enrico Morselli in 1891, based on his observations of 78 patients. These patients exhibited persistent, intrusive, and severely distressing fears and beliefs that they had become (or may become) physically deformed, and each spent many hours obsessively checking their appearance. Morselli initially conceptualized BDD as a phobic (anxiety)-based condition involving obsessive and paranoid-delusional qualities.
- Data indicates that BDD is most prevalent among younger adults, with point-prevalence rates up to 4.4% among those aged 18 to 35 years (Koran et al. 2008). Approximately two-thirds of individuals experience BDD onset before age 18. This earlier onset has been associated with increased rates of suicidal behavior and ideation, and greater comorbidity (Bjornsson et al. 2013). Subclinical BDD symptoms often develop around age 12, and rates of subclinical BDD symptoms are estimated to be as high as 3.4% among children aged between 12 and 18 (Schneider et al. 2017a).
- BDD is highly prevalent in cosmetic and plastic surgery settings, with estimates suggesting a weighted prevalence of 5% to 20% in patients in cosmetic dentistry, dermatology, general cosmetic surgery, and rhinoplasty surgery settings. Individuals with BDD are attracted to these settings by hopes that a physical procedure might "fix" their perceived defect in appearance (Veale et al. 2016). However, cosmetic procedures are typically contraindicated for BDD due to poor psychological outcomes (Veale 2000).

- Reports from across the world suggest that BDD is not bound to any one culture, and generally shows similar prevalence rates, sex distribution, and profile of clinical characteristics across nations. However, data suggests that there may be some global differences in terms of specific appearance concerns which may coincide with differences in specific cultural values related to attractiveness. For instance, MD seems more prevalent in Western rather than Eastern cultures. This may be due to a long history of muscularity being closely tied to masculinity in Western cultures, but less so in Eastern cultures (Phillips 2017).
- The high rate of anabolic-androgenic steroid use among individuals with MD represents a significant physical health concern. Steroid use leads to suppression of the gonadal axis, which may result in infertility and changes in physical sex characteristics of both men and women (Anawalt 2019). Use of steroids has also been linked to an increased risk of a variety of cardiovascular consequences, such as atherosclerosis, arrhythmia, and dyslipidemia. In addition, individuals may exhibit increased aggression and impulsivity during active use, while withdrawal may exacerbate symptoms of depression and anxiety.

Summary Points

- Body dysmorphic disorder (BDD) is a mental disorder characterized by a distressing and impairing preoccupation with perceived defects in physical appearance.
- The muscle dysmorphia (MD) subtype of BDD is characterized by preoccupation with concerns of insufficient muscularity, excessive weight training, and excess attention to a protein-rich diet.
- While BDD equally affects men and women, with more similarities than differences in illness presentation, the MD subtype of BDD seems to predominately affect men.
- BDD and MD involve significant overlaps with AN and BN in key clinical characteristics, including having significant body image disturbance.
- BDD can often be differentiated from an ED on the basis of specific body image concerns and types of behaviors that are performed in response to these concerns.
- BDD and MD commonly co-occur with EDs, but are likely underdiagnosed in clinical settings.
- Clinicians must be careful to screen for BDD at any time a patient is being investigated or treated for an ED.
- Treatments for BDD differ from those commonly used to treat EDs; interventions specifically targeting BDD symptoms should be used conjointly with ED interventions in the case of comorbid BDD.

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Orthorexic Eating and Addictions: Links with Substance Use, Behavioral Addictions, and Research Gaps

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Contents

Introduction 1328
Definition and Clinical Aspects 1328
From the Healthy Interest in Diet to the Unhealthy Obsession with Diet 1329
Epidemiology, Risk Factors, and Clinical Relevance 1330
The Current Debate About the Behavior's Pathological Relevance 1330
Differential Diagnosis and Differentiation from Other Diseases 1331
Orthorexia Nervosa and Obsessive-Compulsive Symptoms 1331
Orthorexic Eating Within the Eating Disorder Spectrum 1332
Orthorexia Nervosa and Addictive Behaviors 1332
Comorbidity Between Orthorexia Nervosa and Substance-Related Addictions 1339
Empirical Evidence for a Link Between Orthorexia Nervosa and Substance (Ab)Use ... 1340
Comorbidity Between Orthorexia Nervosa and Behavioral Addictions 1340
Conclusion 1344
Open Questions and Future Directions 1345
Application to Other Eating Disorders 1345
Mini-Dictionary of Terms 1346
Key Facts of Orthorexia Nervosa Within the Debate of Categorization as New Mental Disorder 1347
Summary Points 1347
References 1348

Abstract

Orthorexia nervosa is described as an obsessive fixation on healthy eating in order to maintain and optimize health. The progressive rigidity of self-imposed dietary rules in orthorexia nervosa may resemble the maladaptive cycle of substance abuse. Phenomenological similarities are high time investment and cognitive and

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behavioral preoccupation. Nevertheless, the obvious negative health consequences of substance use disorders are contrary to the aim of orthorexic eating behavior. Moreover, Orthorexia nervosa does not allow the identification of specific foods or food groups which might serve as addictive substances. Based on current evidence, there is no link between Orthorexia nervosa and substance use or abuse. Behavioral addictions, defined as compulsive and excessive non-substance-related behaviors, have also been examined in relation to orthorexia nervosa. Addictive and compulsive exercising was moderately and positively related to orthorexia nervosa. Evidence of a link with food addiction and internet addiction is still too sparse to allow conclusions. Filling research gaps related to addictions and orthorexia nervosa could help to better understand the etiology of orthorexia nervosa and, thus, assess its distinctiveness from established psychiatric disorders.

Keywords

Orthorexia nervosa · Orthorexic eating · Substance use disorder · Substance abuse · Addiction · Dependence · Behavioral addiction · Exercise · Social media · Food addiction

Abbreviations

AN	Anorexia nervosa
ARFID	Avoidant/restrictive food intake disorder
DSM-5	*Diagnostic and Statistical Manual of Mental Disorders*, 5th edition
ED	Eating disorders
ICD-11	*International Statistical Classification of Diseases and Related Health Problems*, 11th edition
OCD	Obsessive-compulsive disorders
OrNe	Orthorexia nervosa
SES	Socioeconomic status

Introduction

Definition and Clinical Aspects

Health and fitness are key determinants of health and performance. A holistic understanding of health, however, is also becoming a central component of the most diverse lifestyles in our society – causing health to have an elevated source of meaning and health-promoting behaviors being passionately carried out (Crawford 1980). The question arises whether extreme forms of healthy lifestyle have pathological relevance when living healthy becomes a harmful obsession. In this context, the phenomenon *orthorexia nervosa* (OrNe) has received medial interest and is scientifically studied (Håman et al. 2015). This term was coined in 1997 by the American doctor Steven Bratman and composed of the Greek words "*ὀρθός* (orthós)" for right and "*ὄρεξις* (órexis)" for appetite; OrNe describes an obsessive fixation on a diet perceived as healthy and correct (Bratman 1997). Since early case studies describing this new

pathological way of eating, scientific interest has continuously increased. Still, OrNe is not formally recognized as a mental disorder. In 2018, an association of international researchers – the OrNe Task Force – has agreed on three primary diagnostic criteria described in Table 1 (Cena et al. 2019).

From the Healthy Interest in Diet to the Unhealthy Obsession with Diet

In more detail, obsessive preoccupation with healthy eating refers to the amount of time spend for planning, obtaining, preparing, and/or eating one's food. On the other hand, it contains self-imposed rigid and inflexible rules which may be strictly controlled. Thereby, the definition of "healthful eating" might be in accordance with official recommendations, such as those from the World Health Organization (WHO 2000), but may also be incompatible with them. So, the perception of healthy eating may be based on individually varying dietary theories. For example, healthy food is often considered as pure, clean, organic, right, correct, natural, and safe, whereas unhealthy food is often referred to as processed, with added ingredients, prepared, treated, toxic, and contaminated. Those affected consider this to be harmful for their own health (Cena et al. 2019). It might also include any other definition of "healthy" or "unhealthy" according to the individual's superior ideas about foods or to dietary trends (Ferreira and Coimbra 2021) and cultures (Gramaglia et al. 2019). It is proposed that when individuals with OrNe are confronted with food which they consider unhealthy, they tend to suffer from emotional distress and fear of impaired health and disease. In addition, feelings of guilt when violating self-imposed dietary rules cause exaggerated fears and compensatory behaviors (Hayatbini et al. 2021). Dietary restrictions increase over time and food selectivity can contribute to cause nutritional deficiencies, such as anemia, extreme weight loss, global or selective malnutrition, and damage to health. Orthorexia nervosa may lead to symptoms that can also occur in the case of other severe illnesses which are associated with malnutrition, e.g., osteopenia, anemia, hyponatremia, and metabolic acidosis (Koven and Abry 2015).

As orthorexic eating behavior is accompanied by a high amount of cognitive preoccupation and time devoted to diet and nutrition, problems concerning attention and concentration may arise. Relatedly, individuals with OrNe miss time or activities in their personal, vocational, and/or academic lives. This may also result in social isolation and modification of social relationships. Overall, OrNe includes emotional (e.g., feeling guilty after having eating food considered to be unhealthy), cognitive (e.g., problems concerning attention and concentration), and/or social (e.g., social

Table 1 Primary diagnostic criteria of OrNe. (According to Cena et al. (2019))

1	Obsessional or pathological preoccupation with healthy nutrition
2	Emotional consequences (e.g., distress, anxiety) of non-adherence to self-imposed nutritional rules
3	Psychosocial impairments in relevant areas of life as well as malnutrition and weight loss

exclusion) consequences, which impose a negative effect on the individuals' educational, work, or social life (Cena et al. 2019). Despite these consequences on health, relationships, social life, and quality of life, the observance of rigid food rules is maintained in OrNe.

As further criteria, some authors recommend the presence of positive effects from following self-defined healthy eating (Dunn and Bratman 2016) or overvalued ideas about body- and health-related effects of specific foods or food groups (e.g., Barthels et al. 2015). Furthermore, it is discussed whether orthorexic eating behavior might be characterized by a moral or spiritual component leading to a feeling of ethical superiority over the lifestyle and eating habits of others which becomes part of their belief system and identity (Cena et al. 2019).

Epidemiology, Risk Factors, and Clinical Relevance

Reviews estimated that the prevalence of at least some orthorexic behaviors range from 6 to 89% (Dunn and Bratman 2016; McComb and Mills 2019). It is likely that these high numbers can be attributed to psychometrically poor diagnostic tools and their inability to differentiate healthy eating from pathologically obsessive healthy eating. Sound methods suggest rates between 3 and 7% in western countries, numbers that drop below 1% when clinical suffering is also considered (Dunn et al. 2017; Luck-Sikorski et al. 2019). Women seem to be slightly more affected than men although gender as a risk factor remains unclear to date (Strahler 2019). Further proposed risk factors are younger age and higher socioeconomic status (SES). In regard to age, findings are mixed what might be attributed to the methodological heterogeneity (tools, sample) of studies. While some studies suggest younger age to be a risk factor for developing OrNe (McComb and Mills 2019), current research hardly allows a conclusion because usually rather young samples are examined. From theory, it seems comprehensible that higher SES is linked to orthorexic eating. People with a higher level of education are more likely to have the financial resources to purchase high-quality food and are assumed to have easy access to knowledge about certain diets and nutrition (Pollard and Booth 2019). Research, however, has produced inconsistent findings so far. Currently, the samples examined are still very limited (e.g., recruitment primarily in the academic setting), and there is a high demand for more cross-SES and cross-cultural research. For further proposed risk factors, the reader is referred to recent narrative and systematic reviews (McComb and Mills 2019; Strahler and Stark 2019). Notably, proposed criteria reflect on this by adding that the behavior is not better explained by lack of available food or by associated culturally sanctioned practice.

The Current Debate About the Behavior's Pathological Relevance

Although orthorexic eating behavior may negatively affect the health status and quality of life, there is no consensus whether OrNe is of pathological relevance or

not. Present research on negative consequences mainly stems from a few case studies or from studies with poor diagnostic tools and should therefore be considered with caution (Strahler and Stark 2020). While there are possibly harmful consequences of this behavior (e.g., depressive symptoms, fear of negative evaluation, and exhaustion), it remains unclear whether those may be considered as pathological, i.e., whether they lead to individual suffering and significant impairments, and whether these consequences exceed the influence of other also present disorders. For example, OrNe was found to be associated with lower well-being as well as life satisfaction, but this effect was better explained by symptoms of pathological eating (Strahler et al. 2018; Zickgraf et al. 2019). Taking existing literature into account, the clinical relevance of OrNe still remains unclear and needs to be investigated further. In sum, OrNe should be described as a mental health problem associated with distress, impairment, and reduced well-being (Strahler and Stark 2020).

Differential Diagnosis and Differentiation from Other Diseases

To date, orthorexia nervosa has neither been included in the *International Statistical Classification of Diseases and Related Health Problems* (11th ed., ICD-11; World Health Organization 2018) nor the *Diagnostic and Statistical Manual of Mental Disorders* (5th ed., DSM-5; American Psychiatric Association 2013). As the diagnostic validity of OrNe is still uncertain, various disorder categories may be considered for the classification of OrNe on the one hand and for its distinguishability on the other hand. In this regard, two disorder categories are discussed in particular: *eating disorders* (ED) and *obsessive-compulsive disorders* (OCD). Both as well as OrNe seem to share common features such as perfectionism, anxiety, and cognitive rigidity (Koven and Abry 2015).

Orthorexia Nervosa and Obsessive-Compulsive Symptoms

Due to the high amount of cognitive and behavioral occupation, specific similarities with the obsessive-compulsive disorders can be found. In OrNe, thoughts are assumed to revolve around food and health in an intrusive manner. Furthermore, concerns regarding contamination or impurity may occur, while highly ritualized food preparation methods may consume a high amount of time (Bratman and Knight 2000; Koven and Abry 2015). Hence, OrNe might be conceived as an OCD whose obsessive thoughts and actions focus exclusively on food and nutrition. While symptoms of OCDs are experienced as ego-dystonic, those of OrNe are assumed to be ego-syntonic (Strahler and Stark 2020). Overall, the associations between OrNe and OCD are small to moderate and, moreover, insignificant when controlling for symptoms of EDs (Zickgraf et al. 2019; Bartel et al. 2020). Therefore, the placement of OrNe within the spectrum of EDs is favored in literature (Brytek-Matera et al. 2017; Meule and Voderholzer 2021).

Orthorexic Eating Within the Eating Disorder Spectrum

Several similarities with *anorexia nervosa* (AN) can be found. Both share the high need for control, exhibit goal-driven eating behaviors, and follow self-imposed strict dietary rules. When violating said rules, negative cognitive, emotional, and/or behavioral consequences occur, e.g., feelings of guilt and shame, or establishing even more rigid dietary rules. In contrast to AN, those affected primarily refer to the quality of foods instead of quantity. Despite possibly occurring with the rigid diet, weight loss is currently not assumed to be a leading motive for orthorexic eating behaviors. As a significant low body weight and body image disturbances are core features of AN, the lack of weight or shape concerns was suggested to crucially differentiate OrNe from AN (Cena et al. 2019). Current evidence, however, tend to contradict this conceptual assumption (Bartel et al. 2020; Meule and Voderholzer 2021). Since it does not involve body image disturbances as a formal diagnostic criterion, the *avoidant/restrictive food intake disorder* (ARFID) was additionally proposed as a conceptually proximate ED (Moroze et al. 2015). The restriction of diet in ARFID may be exhibited due to various reasons such as sensory characteristics of food or anticipated aversive consequences following food intake, e.g., choking sensations or abdominal pain (American Psychiatric Association 2013). The latter merely refers to immediate or short-term consequences, while orthorexic eating behaviors rather revolve about long-term consequences for the status of health (Zickgraf et al. 2019). Overall, the distinction of OrNe from the EDs remains unclear.

Not only EDs and OCDs are discussed in the context of OrNe. Anxiety disorders are also considered due to possibly similar underlying psychopathological mechanisms. For example, associations with illness anxiety were found, suggesting that OrNe might serve as an inappropriate compensatory behavior (Barthels et al. 2021). Interestingly, this may argue for OrNe as another eating disorder, since anxiety disorders were also found to precede the onset of eating disorders (Swinbourne and Touyz 2007). Moreover, it was also surmised that OrNe shares many features with (behavioral) addictions. This will be explained in more detail in the following section.

Orthorexia Nervosa and Addictive Behaviors

To summarize the existing body of work and identify gaps in knowledge, the following sections are based on a systematic literature search in three main databases, MEDLINE, PsycINFO, and Web of Science. Search terms included ((orthorexia nervosa) or orthorexic) and (addict* or (substance abuse) or (substance use) or compulsive or excessive or alcohol or smoking or (drug abuse) or (medical abuse) or gambling or gaming or (internet disorder) or (behavioral addiction)). As this is a narrative review, there was no predetermined research question and there is no detailed documentation of the search process. We have summarized and synthesized the findings below and in Table 2.

Table 2 Summary of study characteristics included in the narrative review

Authors	Country	Sample	Total sample age (M ± SD)	OrNe measure used (cutoff[a])	Addiction measure used (cutoff)	Main findings[b]
Substance use						
Aksoydan and Camci (2009)	Turkey	44 opera singers (54.5% f) 28 ballet dancers (71.4% f) 22 symphony orchestra (50.0% f)	38.8 ± 10.7 26.8 ± 5.0 30.0 ± 11.2	ORTO-15	Smoking (yes, no) Alcohol (yes, no)	No sig. lower ORTO-15 (=higher OrNe) in nonsmokers ($n = 52$) and non-alcohol consumers ($n = 55$)
Almeida et al. (2018)	Portugal	193 gym members (58.5% f)	32.8 ± 11.6	ORTO-15 (≤35)	Alcohol (yes, no) Tobacco (yes, no) Drugs (yes, no)	No sig. differences between OrNe cases ($n = 100$) and non-cases ($n = 93$) in alcohol consumption, tobacco use, and drug use
Erkin and Göl (2019)	Turkey	118 yoga practitioners (92.4% f)	f: 30.0 ± 9.4 m: 36.3 ± 3.8	ORTO-11	Smoking (yes, no)	No sig. differences between nonsmokers and smokers ($n = 12$) in ORTO-11
Fidan et al. (2010)	Turkey	787 medical students (40.9% f)	21.3 ± 2.1	ORTO-11	Current smoker (yes, no) Cigarettes per day (<1 pack, 1 pack, 1–2 packs, >2 packs)	Lower ORTO-11 (=higher OrNe) in smokers The more packs the lower ORTO-11
Hyrnik et al. (2016)	Poland	1899 high school students (52.5% f)	17.3 ± 1.0	ORTO-15 (≤40, ≤35, ≤33)	Smoking status (yes, no) Alcohol (never, occasionally, 1–5 x/month, 1–5 x/wk, >5	Higher risk for cutoff ≤40 (but not 35 or 33) when nonsmoking (odds ratio = 1.44)

(continued)

Table 2 (continued)

Authors	Country	Sample	Total sample age (M ± SD)	OrNe measure used (cutoff[a])	Addiction measure used (cutoff)	Main findings[b]
					x/wk) Drugs (never, occasionally, 1–5 x/month, 1–5 x/wk, >5 x/wk)	ORTO-15 sig. related to nonsmoking (direction not shown) Alcohol and drugs not reported
Karakus et al. (2017)	Turkey	208 nutrition and dietetics students (86% f)	?	ORTO-11	Smoking (never smoked, quit smoking, current smoker) Alcohol (yes, no)	No sig. differences between nonsmokers ($n = 181$) and smokers in ORTO-11 No sig. differences between alcohol nonconsumers ($n = 170$) and consumers in ORTO-11
Łucka et al. (2019a); Łucka et al. 2019b)	Poland	864 junior secondary, senior secondary, and university students (69% f)	f: 20.2 ± 3.3 m: 18.93 ± 3.67	ORTO-15 (≤35)	Smoking status (earlier, current, never) Alcohol (never, 1–3 x/month, 1–2 x/wk, more often) Drugs (never, few times in my life, 1–3 x/month, 1–2 x/wk, more often) Psychoactive substances used by relatives (none, alcohol, cigarettes, drugs)	No sig. difference between OrNe cases ($n = 240$) and non-cases in alcohol, smoking, drugs, and substance use of relatives
Oberle et al. (2021)	United States of America	847 adults (82% f)	21.72 ± 6.74	ONI	Alcohol (x drinks/wk) Smoking (yes, no)	Sig. correlation with alcohol ($r = -0.09$) No sig. differences between smokers ($n = 212$) and nonsmokers in ONI

Parra-Fernández et al. (2018)	Spain	454 students (65.0% f)	Median: 20 (19–22)	ORTO-11-ES (≤25)	Smoking (yes, no)	Sig. differences (direction not reported) between smokers ($n = 92$) and nonsmokers in ORTO-11-ES No sig. difference in OrNe prevalence between smokers (18%) and nonsmokers (12%)
Plichta and Jezewska-Zychowicz (2020)	Poland	1120 students (70.4% f)	18–35, categorical 93.3% ≤25	ORTO-15 (≤35)	Food frequency questionnaire (FFQ-6)	Alcohol consumption categories equally distributed among OrNe cases ($n = 317$) and non-cases
Roncero et al. (2017)	Spain	Sample 2: 242 adults (63.2% f)	24.9 ± 7.1	ORTO-15 ORTO-11	Smoking (yes, no) Alcohol (yes, no)	Lower ORTO-11 (= lower OrNe) in consumers of alcohol than in nonconsumers ($d = 0.29$) No sig. effects for ORTO-15 and smoking in ORTO-11
Vaccari et al. (2021)	Italy	328 adults of a clinical sample (56.7% f)	36.5 ± 13.8	ORTO-15	Smoking (no, <10 cigarettes, 10–20 cigarettes, >20 cigarettes) Alcohol (yes, everyday or almost everyday, sometimes (maximum 1–2 x/wk), never or almost never)	No sig. difference between OrNe cases ($n = 195$) and non-cases in smoking and alcohol consumption
Varga et al. (2014)	Hungary	810 students (89.4% f)	32.4 ± 10.4	ORTO-11-Hu	Smoking status (current, former, never) Alcohol (never, rarely, monthly, weekly, several times per wk, daily)	No sig. differences between smoking statuses in ORTO-11-Hu Sig. lower ORTO-11-Hu (=higher OrNe) with less alcohol consumption
Yılmaz et al. (2020)		63 patients with OCD (63.5% f)	34.7 ± 10.5	ORTO-11	Smoking (details missing) Alcohol (details missing)	No sig. correlations

(continued)

Table 2 (continued)

Authors	Country	Sample	Total sample age (M ± SD)	OrNe measure used (cutoff[a])	Addiction measure used (cutoff)	Main findings[b]
Substance abuse						
Oberle et al. (2022)	United States of America	471 adults (86% f)	19.98 ± 3.56	ONI	Alcohol (yes, no) Smoking status (yes, no) Drugs (yes, no) Alcohol (5-p scale *never* to *4+ x/wk*) Smoking (5-p scale *0–5 cigarettes* to *30+ cigarettes/d*) Drugs (5-p scale *not at all* to *>20x/12 mo*) CDS AUDIT UNCOPE	No sig. differences between users and nonusers (alcohol, smoke, drugs) No sig. correlation with smoking, alcohol, marijuana, illicit stimulant, opiate, or hallucinogen drugs Sig. correlation with illicit depressant drugs ($r = 0.12$) No sig. correlation with CDS, AUDIT, and UNCOPE
Strahler et al. (2018)	Germany	713 adults (79.8% f)	29.4 ± 11.2	DOS (≥30)	Fagerström current smoker (yes, no) AUDIT drug use (yes, no)	Addiction measures did not predict DOS No sig. differences between OrNe cases ($n = 27$) and non-cases in number of smokers, degree of dependence to tobacco smoking, AUDIT, current drug use
Behavioral addictions						
Exercise addiction						
Freire et al. (2020)	Brazil	60 exercise practitioners (63.3% f)	26.6 ± 7.8	ORTO-15	SDE	No sign. correlation ($r = -0.14$)

Kiss-Leizer and Rigo (2019)	Hungary	739 adults with interest in sport and diet (79.2% f)	29.7 ± 10.2	ORTO-11-Hu (low risk ≥35, medium risk 30–34, high risk ≤29)	Guilt if skipping training (5-p scale *always* to *never*)	Guilt: low risk < medium risk < high risk
Oberle et al. (2018)	United States of America (ethnically diverse, 38% white)	Sample 1: 228 psychology students (89.5% f)	20.3 ± 1.9	EHQ	EAI CET subscales rule-driven behavior and exercise rigidity	Sig. correlation with EAI ($r = 0.37$), CET rule-driven behavior ($r = 0.41$), CET exercise rigidity ($r = 0.42$)
Oberle et al. (2021)	United States of America	847 adults (82% f)	21.7 ± 6.7	ONI	CET subscales rule-driven behavior and exercise rigidity	Sig. correlation with CET exercise rigidity ($r = 0.37$), CET rule-driven ($r = 0.59$)
Strahler et al. (2021)	Germany	672 adults (75.5% f)	27.7 ± 11.1	DOS	EAI	Gender-specific sig. correlations ($r_f = 0.337$, $r_m = 0.500$
Rudolph (2018)	Germany	1008 fitness club members (44.5% f)	29.4 ± 11.6	DOS	EAI	Sig. correlation ($r = 0.421$)
White et al. (2020)	United States	103 male students	19.8 ± 1.7	ORTO-7	EDS	Sig. correlation ($r = 0.519$)
Food addiction						
Grammatikopoulou et al. (2018)	Greece	176 undergraduate students (79.6% f)	21.7 ± 1.9	BOT (≥4)	mYFAS	No sig. difference between OrNe cases ($n = 120$) and non-cases in mYFAS

(continued)

Table 2 (continued)

Authors	Country	Sample	Total sample age (M ± SD)	OrNe measure used (cutoff[a])	Addiction measure used (cutoff)	Main findings[b]
Social media addiction						
Yılmazel (2021)	Turkey	969 medical and nursing students using social media (63.9% f)	21.4 ± 3.2	ORTO-15 (≤40)	Social Media Addiction Scale	Higher risk for cutoff ORTO-15 ≤ 40 when high/very high addicted (odds ratio = 1.37)

Abbreviations: M, mean; SD, standard deviation; OrNe, orthorexia nervosa; ORTO-15/11/11Hu/8/R, questionnaire for the assessment of orthorexia nervosa and its versions; EHQ, Eating Habits Questionnaire; DOS; Düsseldorf Orthorexia Scale; BOT; Bratman Orthorexia Test; ONI, Orthorexia Nervosa Inventory; SDE, Scale of Dedication to Exercise; EDS, Exercise Dependence Scale; EAI, Exercise Addiction Inventory; CET, Compulsive Exercise Test; AUDIT, Alcohol Use Disorders Identification Test; Fagerström, the Fagerström Test for Nicotine Dependence; CDS, Cigarette Dependence Scale; UNCOPE, brief screen for DSM–5 substance use disorders; mYFAS, modified Yale Food Addiction Scale;?, not reported; f, females; wk., week; h, hours; x, times; r, correlation; sig., significant

[a]Cutoff only shown if of relevance for analyses

[b]Reports refer to findings and analyses from primary study

Comorbidity Between Orthorexia Nervosa and Substance-Related Addictions

The obsessivity, marked rigidity, and overcontrol with which individuals with orthorexic tendencies pursue their dietary behaviors despite profound negative consequences are similar to a maladaptive cycle seen in individuals with addictions. Addictive disorders were originally inextricably linked to the use of psychotropic substances. Those are defined as naturally occurring, synthetically produced, or chemically prepared substances that affect the central nervous system resulting in the alteration of perception, cognition, emotion, and behavior as well as the increase of the subjective psychical and physical well-being (American Psychiatric Association 2013). Discussing OrNe as a possible addiction, the question arises on what substance those affected are addicted to? Since the diets, which individuals with orthorexic eating behaviors follow and perceive as healthy, and the beliefs regarding the overestimated effects of foods vary, no specific foods or substances seem to be intertwined with OrNe (Bratman and Knight 2000; Barthels et al. 2015). Hence, there is no substance of abuse in OrNe; rather, some individuals may report emotional reward from the absence of the intake of unhealthy foods (Singh 2014). Individuals with OrNe seem to be "addicted" to the sensation of controlling their health and diet. Thus, excessive control over food intake, self-control in particular, may somehow become reinforcing. This is in stark contrast to substance-related addiction where indulgence of psychotropic substances culminates in high-risk consumption, and a loss of control over the usage may occur. The substance may be used more frequently, in larger quantities, or for longer durations than intended, thus interfering with areas of social or occupational activities and leading to conflicts. Moreover, a substantial time investment may be required to obtain the substance, intoxication, or recovery from said intoxication (American Psychiatric Association 2013). To some extent, the aspect of substance abuse seems applicable to OrNe. Since orthorexic eating behavior is characterized by high cognitive and behavioral occupation, the time invested in meal planning and preparation may lead to impairments in other areas of life. In addition, individuals affected by OrNe may refuse dinner invitations or have conflicts with friends or family because of a sense of moral superiority (Cena et al. 2019). Thus, similar to substance abuse, there is a loss of control over the preoccupation with healthy eating. While attempts to reduce or control usage of psychotropic substances fail, consumption is continued in order to achieve the state of intoxication – despite its negative consequences such as interpersonal conflicts or decrease of mental and physical health. Hence, a *substance use disorder* is considered present when a maladaptive pattern of substance use leads to clinically significant distress or impairment in social, occupational, or other important areas of functioning. Furthermore, *physical addiction* is given in a substance use disorder when tolerance has developed, i.e., an elevated dose is required to achieve the same extent of intoxication, or withdrawal symptoms occur (American Psychiatric Association 2013). Indeed, the diets of individuals affected by OrNe are assumed to get more rigid over time (Bratman and Knight 2000; Barthels et al. 2015). However, there is no study investigating the time course of said dietary

restriction, to date. Overall, the characteristics of OrNe and substance use disorders do not appear to coincide sufficiently to classify OrNe as the latter. Empirical evidence regarding this hypothesis is sparse, and comorbidity between orthorexic behaviors and substance abuse is currently unknown.

Empirical Evidence for a Link Between Orthorexia Nervosa and Substance (Ab)Use

Our literature search revealed only a few reports on legal (and illegal) substance use mostly suggesting similar orthorexic behaviors between smokers and nonsmokers (12 studies) and no relation to alcohol consumption (8 studies). For more study details, the reader is referred to Table 2. For smoking, two further studies reported significant differences, one showing a higher prevalence of orthorexic behaviors (Hyrnik et al. 2016) and one showing a lower prevalence in nonsmokers (Fidan et al. 2010). Two additional reports indicated higher orthorexic behaviors to be related to less alcohol consumption (Varga et al. 2014; Roncero et al. 2017). Furthermore, (illicit) drug use has been examined in four studies producing mainly null findings. The only significant result was a positive but small correlation with illicit depressant drug use ($r = 0.12$). Substance abuse and substance-related addictions have been examined in only two cross-sectional studies. There was no relation with the Fagerström Test for Nicotine Dependence or the Cigarette Dependence Scale, the Alcohol Use Disorders Identification Test, and the brief screen for DSM-5 substance use disorders (Strahler et al. 2018; Oberle et al. 2022).

Considering the characteristics of OrNe, i.e., consuming only foods of highest nutritional quality, makes alcohol, tobacco, medication, or illegal drug use very unlikely in these individuals. Previous null findings are therefore rather unsurprising. Importantly, due to the instruments used, most previous research only allows a limited conclusion on actual orthorexic behavior, which goes beyond the interest in healthy eating. In addition, investigated samples, i.e., students, young adults, and patients of limited age ranges, do not permit generalization.

Comorbidity Between Orthorexia Nervosa and Behavioral Addictions

Somewhat more appropriate than substance-related disorders seem to be the comparison of orthorexic behaviors with the so-called behavioral addictions. In the case of behavioral addictions, a behavior is exhibited excessively and is experienced as "out of control." In analogy to substance use disorders, six components of behavioral addictions can be described as follows: *Salience* refers to the elevated importance the behavior has for the individual. Thus, a high amount of emotional, cognitive, and behavioral preoccupation is involved leading to symptoms such as craving or social isolation. Negative emotional or physical consequences are experienced when the behavior is discontinued or reduced (i.e., *withdrawal*). In contrast, positive changes in mood are the consequences to the additive behavior which may be used as a

coping strategy in emotion regulation (i.e., *mood modification*). Furthermore, *tolerance* develops as the desired effects can solely be achieved by exhibiting more of the behavior. Hence, *conflicts* with others (e.g., friends and family), with other activities (e.g., occupation and education), or with the individuals themselves (intrapsychic conflicts) arise. Despite possible insight to the negative consequences, attempts to reduce the behavior fail or *relapses* to initial problematic quantity or intensity of behavior occur (Griffiths 2005). But not every behavior seems to have the potential to lead to an addiction. So far, evidence for gambling and computer gaming has been sufficient for both to be considered in international classification systems (DSM-5, ICD-11). In addition, other potentially addictive behaviors are currently discussed to be of pathological relevance, e.g., excessive and compulsive exercising or internet use (Griffiths 2005).

Phenomenological Overlap of Orthorexia Nervosa and Behavioral Addictions

Orthorexia nervosa has also been considered as a possible behavioral addiction (Strahler and Stark 2019). While some symptoms of orthorexic eating seem to be compatible with the components of behavioral addictions as healthy eating occupies the highest priority in daily life, there is neither evidence for tolerance nor withdrawal symptoms to date. Withdrawal symptoms in substance-related addictions are rather severe and may comprise physical (e.g., sweating, flushes, nausea, vomiting) as well as psychological symptoms (e.g., depression, anxiety, hallucinations). There are no such reports for orthorexia nervosa so far. Tolerance is theoretically assumed, i.e., increasingly rigid eating, but has not yet been studied. Nevertheless, orthorexic tendencies have been studied in relation to exercise addiction, food addiction, and social media addiction.

The Link Between Orthorexia Nervosa and Exercise (Addiction)

A balanced diet and physical activity are two essential lifestyle factors for maintaining physical and mental health and well-being. Just as for the quality of the diet, regular exercise can become an obsession, and the pursuit of health and fitness can become the focus of one's life. Due to the high importance of health and fitness for people with orthorexia nervosa, it was assumed that this behavior is also associated with increased physical activity and exercise behaviors. For example, studies in at-risk populations show that people who are active in sports, such as gym members, sports students, or yoga practitioners, should be considered as a risk group for developing orthorexic eating behaviors (Eriksson et al. 2008; Rudolph 2018). Correlative studies of individuals from the general population or students paint a rather inconsistent picture with some studies finding exercise and sports activity associated with orthorexia nervosa and others finding no associations. A recent meta-analysis summarized data from 21 studies and quantified the relationship between physical activity behaviors and orthorexic tendencies as $r = 0.09$ to $r = 0.19$ (Strahler et al. 2022). Regular exercise can also evolve from a healthy habit to an excessive, limitless, repetitive addiction to physical activity. In terms of clinical classification, exercise addiction (alternatively also compulsive exercise) should be

classified as a non-substance-related behavioral addiction (Hausenblas and Downs 2002; Griffiths 2005; Colledge et al. 2020). Comorbidity between orthorexic eating and addictive exercise behaviors has been examined in seven studies thus far (summarized in Table 2). Findings predominantly indicate moderate correlations between $r = 0.34$ and $r = 0.59$ (Rudolph 2018; Oberle et al. 2021; Strahler et al. 2021), and only one study found no correlation (Freire et al. 2020). The meta-analysis mentioned above puts the mean effect at $r = 0.29$ (Strahler et al. 2022). There is initial evidence for gender-specific correlations with higher scores in men as compared to women (Strahler et al. 2021) suggesting separate pathological mechanisms among genders. Research on factors contributing to this difference does not exist yet. Theoretical assumptions range from differences in health beliefs (Courtenay et al. 2002) to personality (Strahler et al. 2021), body image (Brytek-Matera et al. 2015; Brytek-Matera et al. 2017), and coping (Matud 2004). Overall, OrNe and exercise addiction appear as overlapping conditions with idiosyncratic clinical hallmarks. Another clinical syndrome that co-occurs with exercise addiction is disordered eating. More precisely, the presence of an eating disorder increases the risk for a comorbid exercise addiction by 3.71 times according to a recent meta-analysis (Trott et al. 2021). Hence, eating pathology seems to be linked with addictive exercising. Additionally, addictive behaviors might co-occur (Sussman 2017).

The Link Between Orthorexia Nervosa and Food Addiction

Hauck et al. (2020) investigated to what extent compulsive exercising and food addiction correlate within an athlete sample. In fact, both behavioral addictions were positively associated. According to the authors, it is questionable, however, whether highly processed and energy providing foods may be used to fuel one's body for the excessive amounts of exercise and optimize performances or whether they were overconsumed due to their addictive potential. It is controversially discussed whether food itself may be addictive at all (Fletcher and Kenny 2018). Bingeing might be equated with excessive consumption under loss of control triggered by craving or confrontation with a food stimulus. Therefore, specific food groups, e.g., highly processed foods or foods high in sugar and fat, seem to potentially be addictive "substances." A neurotransmitter system under suspicion to mediate the addictiveness of both food and psychotropic substances is the dopaminergic system. There are a few findings indicating alterations in the mesolimbic dopaminergic systems altering the reward value of food intake. For example, an association between reduced dopamine receptor density and obesity has been found in some (Wang et al. 2001) but not all studies (Ziauddeen and Fletcher 2013). Next to the assumptions of underlying neuronal processes, some researchers emphasize the proximity of high caloric or processed foods and substances, hence favoring the classification of food addiction as a substance use disorder. In fact, one particular macro food group is suspected of triggering addiction-like craving. *Carbohydrate craving* was established as a construct defined by an overwhelming desire to consume carbohydrate foods in order to increase one's negative mood as a form of self-medication (Wurtman 1990). It has been hypothesized that this effect for

carbohydrate foods occurs due to increased serotonin levels and synthesis that result from heightened tryptophan (Wurtman and Wurtman 1995). Currently, however, this hypothesis must be strongly doubted. A recent meta-analysis of the carbohydrate consumption-mood relationship showed no positive effect on any mood measure at any time after their consumption (Mantantzis et al. 2019). Rather, carbohydrate insertion was associated with higher fatigue and less alertness. Others argue that no specific molecule or substance of food groups clearly identifies as addictive and food addiction is thus to be regarded as behavioral addiction. Third, the validity and added value of the food addiction concept over already established eating disorders is questioned (Ziauddeen et al. 2012). Overall, the ongoing debate does not seem to lead to the inclusion of the concept of food addiction in the international classification systems anytime soon (Meule 2019). In regard to commonalities between food addiction and OrNe, there is only one report in Greek undergraduate students revealing no difference between OrNe cases and non-cases in terms of food addiction (Grammatikopoulou et al. 2018). Food groups discussed in regard to food addiction are predominantly of high fat and sugar. Reducing their consumption is commonly recommended (WHO 2000) which makes a ban more likely in the context of orthorexic eating behaviors. Nevertheless, the beliefs and assumptions about which foods are beneficial and detrimental to health are very subjective in OrNe. Not only scientifically based sources of information are used for this purpose, but others as well, such as social media (Bratman and Knight 2000; Håman et al. 2015).

The Link Between Orthorexia Nervosa and Social Media Addiction

Some authors argue that orthorexia is not a disorder with pathological value but a lifestyle phenomenon (Håman et al. 2015). In the context of this debate, it has been suggested that social media contributes to an unhealthy fixation with health. Whereas the influence of problematic internet use on eating disorders, such as bulimia nervosa and anorexia nervosa, as well as food preoccupation, is already known (Padín et al. 2021), there is little evidence regarding the effect on orthorexic tendencies. In terms of social media use, two previous studies linked more frequent Instagram use with greater level of orthorexic eating (Turner and Lefevre 2017; Lanitis and Raspin 2020). An effect is not found or at a much lower level found for other social media channels, such as Facebook, Twitter, Pinterest, Google+, Tumblr, and LinkedIn. Initial considerations regarding causal mechanisms about the general relation between problematic internet use and orthorexic tendencies proposed an effect called "echo-chamber" (Turner and Lefevre 2017). This effect describes the tendency of people to assess their mindset and worldview as more common than it really is. This is assumed to happen due to selective usage habits, i.e., predominantly consuming contents that support one's own assumptions. In this regard, one study employed a thematic analysis to examine individuals' understanding of the possible links between social media use and eating patterns (Lanitis and Raspin 2020). Qualitative analyses indicated "The Importance of Belonging," "Health as Art," and "Craving" as the three main themes suggesting an appeal of healthy eating practices which could generate an overestimation of orthorexic behaviors (Brytek-

Matera et al. 2015). Furthermore, there are considerations about questionable advices cutting out various food groups. These advices can lead to unbalanced nutrition and even promote the development of an eating disorder (Turner and Lefevre 2017). Using social networks in a nonfunctional way, that is, excessively, experiencing lack of control, and with negative consequences, has parallels with other internet-related behavioral addictions and substance-related disorders. Like OrNe, *social media addiction* has not yet been accepted as a separate diagnosis in the clinical classification systems (Andreassen 2015). Taking the lack of diagnostic certainty into account, global estimates report prevalences of problematic social media use ranging from 8.6% to 41.9% (Guedes et al. 2016). Studies highlight predisposing factors including depression, anxiety, attention deficit hyperactivity disorder, parallel substance abuse, social deficits, feelings of loneliness, lower self-esteem, and also increased stress vulnerability (Clayton et al. 2013; Moreau et al. 2015; Wegmann and Brand 2019). This parallels findings in OrNe. Research on the association between OrNe and social media addiction is sparse with, to our knowledge, only one study on this topic. Yılmazel (2021) found that orthorexic tendencies occur more frequently in nurses and doctors with high or very high social media addiction. To date, there are many theories but a lack of empirical evidence for an association between social media addiction and orthorexic tendencies.

Conclusion

Addictions or substance use disorders are commonly understood as self- and health-harming behaviors. Hence, the missing association of OrNe, in which the optimization of health is aimed through dietary behavior, with substance use and abuse is not surprising. On the conceptual level, known commonalities of OrNe with substance abuse consist in the modulation of anxiety and dysphoric mood as motivational background for obsessive healthy eating and addictive behaviors, respectively (American Psychiatric Association 2013; Koven and Abry 2015; Cena et al. 2019). Whereas the nonconsumption of substances leads to physical and psychological withdrawal symptoms (American Psychiatric Association 2013), the intake of "unhealthy" or forbidden foods is followed by in some way similar negative emotions such as guilt in OrNe (Cena et al. 2019). In contrast, there are no specific "substances" or food groups of interest in OrNe; rather, the control over the subjectively healthy diet itself seems to be addictive even if said diet is inappropriate and malnourishing. Usually, no awareness of the impairment due to orthorexic behaviors arises (Bratman and Knight 2000), while individuals affected by substance use disorders acknowledge the desire to stop substance use and suffer from relapses when impairment becomes noticeable (Raftery et al. 2020). Possibly, but currently unexplored, OrNe is also associated with insight, depending on symptom severity. Moreover, different cultural consequences of performing the behavior occur as maintaining a healthy diet is usually socially accepted and reinforced. In contrast, addictions are particularly stigmatized even compared to other mental disorders (Barry et al. 2014).

Open Questions and Future Directions

But there are still many open questions, the answers to which will contribute to a deeper understanding of the onset and development of orthorexic eating behaviors. For example, are factors that initiate the onset of orthorexic eating distinct from factors that maintain the behavior once started to eat only selected foods (Walsh and Devlin 1998)? Furthermore, the neurobiological mechanisms involved are unknown. Weight loss produced alterations in the neuronal reward system enhancing the reward of weight loss and starvation (Kaye 2008; Keating et al. 2012). Similar effects may contribute to OrNe. Since the reward system is further crucially involved in substance use (MacNicol 2017), this may resemble effects by OrNe and substance abuse. Overall, it is difficult to understand similarities between OrNe and addictions without grater knowledge of the complex etiology and pathogenesis that characterize OrNe. This also applies to the behavioral addictions discussed here in the chapter. While some neurobiological mechanisms are suspected to play a role in exercise addiction and food addiction, their contribution is still unclear and controversial (Hausenblas and Downs 2002; Fletcher and Kenny 2018; McComb and Mills 2019). Nevertheless, OrNe appears to be moderately associated with exercise addiction suggesting the possibility of shared or related underlying mechanisms (Strahler et al. 2022). The evidence on food and internet addiction is too limited to allow any conclusion, but negligible associations currently appear likely (Grammatikopoulou et al. 2018; Yılmazel 2021). In terms of substance-related and behavioral addiction, OrNe is similar in the excessive levels of cognitive, behavioral, and emotional preoccupation. However, there are crucial features of addictions, such as tolerance, lacking empirical evidence in orthorexic eating behaviors. Despite many unanswered questions, the compilation of findings in this chapter makes a close link to addictions unlikely. Rather, OrNe's closeness to the eating disorders suggest its classification within this category (Bartel et al. 2020). Practically, a deeper understanding regarding the etiology of OrNe is not only needed to indicate its clinical relevance and justification as a disorder on its own right but is also necessary to identify appropriate therapy methods and strategies. Nowadays, it is therefore recommended that therapy may be based on the guidelines for eating disorders rather than those for addictions.

Application to Other Eating Disorders

In this chapter, we have systematically reviewed current evidence about the link between orthorexia nervosa and addictive behaviors. Orthorexia nervosa is not included in current psychiatric classification systems, but above all, a closeness to eating disorders is considered most likely (Bartel et al. 2020). Hence, this chapter's question was also based on the assumption from the field of eating disorders, according to which the known eating disorders are also related to substance abuse. For the known eating disorders, a relation with, e.g., smoking has been reported as a strategy to control weight and appetite (Devoe et al. 2021). However, the harmful

consequences of such substances would contrast with the motives for pursuing orthorexic eating behaviors. The goal of maintaining and optimizing long-term health instead of weight loss makes an association seem unlikely.

Based on the present literature review, there was no link between OrNe and substance use and abuse. Behavioral addictions, defined as compulsive and excessive non-substance-related behaviors, have only rarely been studied so far. The most likely conclusion to be drawn here is a link with compulsive and excessive exercise behavior and sports. This corresponds to the known comorbidity of additive exercising and eating disorders. Research on other additive behaviors (food addiction, internet addiction) does not permit any conclusions.

One of the most important research questions, beyond this behaviors' pathological relevance, at present is the establishment of ON as an independent disorder category and thus differentiation from established disorders. The few studies that look at anorectic and orthorexic eating behavior in the course of therapy could also offer an auspicious approach in differentiating eating disorder and orthorexic symptomatology. Such studies demonstrate that while there is improvement of anorexic symptoms, orthorexic eating increases throughout therapy (Segura-Garcia et al. 2015; Barthels et al. 2017). This has been interpreted in terms of orthorexic eating to be a compensatory weight regulation strategy in patients with AN. Clinicians should be aware of orthorexic behaviors as compensatory behaviors in individuals with eating disorders and should consider screening for OrNe. In addition, possible links with social media use provide another relevant aspect not only in understanding risk factors but also in establishing prevention and intervention strategies. Overall, pathological eating behaviors are public health concerns that need to be understood in a multidimensional model of risk factors and determinants, i.e., genetic vulnerability, biological needs, cognitive-affective motives, psychosocial demands, and environmental factors.

Mini-Dictionary of Terms

- **Behavioral addictions.** Defined as a compulsion to engage in rewarding, non-substance-related behavior despite negative consequences and with the presence of functional impairment. The most recent version of the International Classification of Diseases (ICD-11) considers gambling disorder and gaming disorder. A number of other behavioral addictions are proposed, including buying-shopping disorder, pornography use disorder, and social networks use disorder.
- **Carbohydrate craving.** An overwhelming desire to eat carbohydrate foods as a self-medication to increase one's mood.
- **Exercise addiction.** Also exercise dependence or pathological exercising. Excessive volumes and feelings of lost control with exercising and sports, exercise is priority in life and is continued despite injuries and impairments in other important areas of life.

- **Obsessive-compulsive symptoms/disorder (OCD).** A group of symptoms characterized by recurrent unwanted thought (= obsessions) and/or repetitive behaviors that a person feels the urge to do repeat over and over (= compulsions). OCD is an anxiety disorder.
- **Orthorexia nervosa.** The obsessive fixation on healthy eating. Self-imposed rigid dietary rules aim at optimizing and maintaining health.
- **Psychotropic substances.** Substances whose intake alters the perception, cognition, emotion, and behavior as well as increases acute physical and psychological well-being of the consumer. Different psychotropic substances lead to specific states of intoxication.
- **Substance use disorder.** A mental disorder in which the maladaptive pattern of substance use leads to clinically significant distress or impairment in social, occupational, or other important areas of functioning.

Key Facts of Orthorexia Nervosa Within the Debate of Categorization as New Mental Disorder

- Orthorexia nervosa is a newly proposed harmful eating behavior where the individual is obsessed with the quality of diet and restricts his/her diet.
- Orthorexia nervosa can lead to severe weight loss, malnutrition, emotional distress, and impairments in daily functioning.
- Orthorexia nervosa shares features with known eating disorders (e.g., need for control, anxiety, perfectionism, overvalued ideas concerning diet) but is also different (e.g., focus on quality vs. quantity of diet, less consumption of legal drugs).
- Addictive exercise is usually linked to an eating disorder. Similar associations are seen for orthorexia nervosa.
- So far, it is unclear whether orthorexia nervosa is an illness adversely affecting a person or how much it differs from known disorders.
- Current therapeutic approaches resemble those used in the treatment of eating disorders.

Summary Points

- Orthorexia nervosa and substance use disorders seem to share phenomenological commonalities leading to maladaptive cycles: modulation of anxiety and dysphoric mood, high time investment, and cognitive and behavioral preoccupation.
- Since orthorexic eating behaviors are aimed at optimizing health, the consumption of psychotropic substances seems unlikely in orthorexia nervosa.
- The systematic literature search found no evidence for an unequivocal link between orthorexic eating behaviors and substance use or abuse to date.

- Orthorexia nervosa has been suspected to be a behavioral addiction, but its placement within the eating disorder spectrum seems more appropriate.
- Orthorexia nervosa is moderately and positively related to exercise addiction.
- There are research gaps regarding the link of orthorexia nervosa with other behavioral addictions such as food and internet addiction.

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Linking Orthorexia and Obsessive-Compulsive Symptoms

67

Lut Tamam and Hamdi Yılmaz

Contents

Introduction 1354
Symptoms of Orthorexia Nervosa 1355
Negative Effects of Orthorexia on Health and Functionality 1356
Prevalence of Orthorexia Nervosa 1357
Diagnostic Criteria of Orthorexia Nervosa 1358
Definition of Obsessive-Compulsive Disorder and Its Relationship with Eating Disorders ... 1361
Association of Orthorexia Nervosa with Obsessive-Compulsive Disorder 1364
Obsessive-Compulsive Disorder-Related Cognitive Features of Orthorexia Nervosa 1365
Association of Orthorexia Nervosa with Eating Disorders 1365
Association of Orthorexia Nervosa with Anorexia Nervosa and Bulimia Nervosa 1365
Distinguishing Features of Orthorexia Nervosa from Anorexia Nervosa and Bulimia Nervosa 1366
Association of Orthorexia Nervosa with Avoidant-Restrictive Food Intake Disorder 1367
Association of Orthorexia Nervosa with Other Mental Disorders 1368
Association of Orthorexia Nervosa with Obsessive-Compulsive Personality Disorder ... 1368
Association of Orthorexia Nervosa with Somatoform Disorders 1368
Association of Orthorexia Nervosa with Psychotic Disorders 1369
Unique Features of Orthorexia Nervosa 1369
Orthorexia Nervosa and Healthy Living Behaviors 1370
Orthorexia Nervosa and Exercise 1370
Orthorexia Nervosa and Social Media 1370
Smoking and Alcohol Use 1371
Vegetarian Diet 1371
Is Orthorexia Nervosa a Separate Mental Disorder? 1371
Treatment and Management 1372
Conclusion 1374
Applications to Other Eating Disorders 1374

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Key Facts of Orthorexia Nervosa with Obsessive-Compulsive Symptoms 1375
Summary Points 1375
References 1375

Abstract

Orthorexia nervosa is a phenomenon defined as a pathological focus on healthy eating. It is assumed that it shares some common features and possibly overlaps with other mental disorders, especially eating disorders and obsessive-compulsive disorder. Research on orthorexia nervosa has been increasing recently. In this section, the definition of orthorexia nervosa, its clinical and sociodemographic characteristics, and its relationship with other mental disorders, especially obsessive-compulsive disorder, are evaluated.

Keywords

Orthorexia nervosa · Obsessive-compulsive disorder · ED · Ritual · Exercise · Healthy eating

Abbreviations

AN	Anorexia nervosa
ARFID	Avoidant-restrictive food intake disorder
BN	Bulimia nervosa
DSM	*Diagnostic and Statistical Manual of Mental Disorders*
EDs	Eating disorders
OCD	Obsessive-compulsive disorder
OCPD	Obsessive-compulsive personality disorder
ON	Orthorexia nervosa

Introduction

The nature of the relationship between diet and health has long been debated. In recent years, awareness of healthy eating has increased markedly and has become one of the primary concerns of developed and developing societies (Brytek-Matera et al. 2017).

Currently, the World Health Organization recommends reducing sugar, fat, and salt intake, eating plenty of fruits and vegetables, and frequently exercising to lead a healthy life (Norum 2005). The craving for healthy food is not a disorder in itself. However, among some people, interest in healthy eating can turn into obsessive symptoms. The concept of orthorexia nervosa (ON) was first defined by Bratman in 1997 to express the pathological focus on consuming healthy foods and was later elaborated in a book written by Bratman (Bratman and Knight 2000). As a word, "Ortho" means "true, real, complete, valid." The word "Orexis" means "hunger, appetite." Bratman coined the term ON to describe pathological fixation associated

with the consumption of appropriate, healthy food. Bratman, in his book *Health Food Junkies*, defines diets as a disease that people do to feel more attentive and clean (Bratman and Knight 2000). ON was first defined as a "maniacal obsession in pursuit of healthy foods" by Donini et al. (2004). This chapter has given credibility to this case and term used to define ON, implying that ON is a concept worthy of scientific research. In the following years, the term ON has spread all over the world, and the number of studies on ON has increased.

Researchers debated whether ON should be incorporated into DSM-5 (*Diagnostic and Statistical Manual of Mental Disorders* Fifth Edition). However, a conjoint expert consensus could not be reached. As a result, it has not been included in the DSM-5 (2013) due to the absence of necessary and vigorous practical data for proper diagnosis. However, some researchers have established some criteria from their clinical experience (Barthels et al. 2015a; Moroze et al. 2015; Setnick 2013).

Symptoms of Orthorexia Nervosa

ON is defined as a pathological obsession with healthy eating and nutrition. It is characterized by a restrictive diet, marked eating patterns, and intense evasion of foods alleged to be unhealthy or impure. ON's focus is on achieving optimum health through strict dietary control (Lucka et al. 2019). Orthorexic individuals who are concerned about the choice of food regarding its purity, origin, whether it contains artificial ingredients or preservatives, etc. become hugely selective about it (Catalina Zamora et al. 2005). They obsessively avoid foods high in artificial colors, genetically modified components, preservatives, flavors, unhealthy salt, fats, or sugar. Since they want their food to be highly pure and free of additives, they can consume many foods raw. The preparation phase, preparation of kitchen utensils and other utensils, is also part of the obsessive ritual (Bartrina 2007). Orthorexic individuals show obsessive thoughts about food while performing tasks such as rituals for stacking and weighing or measuring food products and planning meals (Lucka et al. 2019). Over time, they develop their own unique food rules and eventually fall into a strict diet regimen. Excessive focus on foods and health can lead to the emergence of particularly complex eating patterns that take an unusually long time to execute (e.g., beliefs that one type of food should be taken after a certain amount of time for optimal digestion) (Koven and Abry 2015). This obsession can increase obsessive food-related anxiety, leading to disruptions in social relationships and emotional problems.

The change in daily behavior in orthorexic individuals has been defined in four stages (Mathieu 2005). In the first stage, people have excessive thoughts about their food that day and the following days. In the next stage, excessive control and criticism of food products occur. In the third stage, efforts are made to prepare meals following the principles of healthy eating. In the fourth stage, a feeling of success or failure is experienced according to the outcome of previous stages. In ON,

while the person's primary purpose is to improve health or lose weight, over time, diet becomes the most central part of their life (Catalina Zamora et al. 2005).

When orthorexic individuals feel they are violating a personal food rule by consuming wrong or unhealthy foods, they suffer under morbid thought and psychological torture, punishing themselves with stricter dietary restrictions. Some may think that sticking to a proper diet will help them achieve a sense of perfection by feeling better, pure, or clean (Chaki et al. 2013). This behavior pattern affects a person's quality of life over time and plays a restrictive role. Finally, the controlled diet they apply to change their lives becomes something that controls their whole life (Getz 2009).

Negative Effects of Orthorexia on Health and Functionality

Compulsive obsessions with certain types of food present in ON influence the physiological health of those affected and have significant psychosocial consequences. Orthorexic individuals often spend an excessive amount of time researching their food concerns. They may exhibit behaviors such as long-term research on food and health on the Internet; buying and reading excessive amounts of food, health, and nutrition books; and almost constantly reviewing food labels while shopping at the grocery store (OCD Center of LA 2011). So much so that the quality of the food they consume may become more critical than personal values, interpersonal and social relationships, and career plans (Bağcı Bosi et al. 2007).

Bratman noted that orthorexic individuals tend to maintain their diet based on a theory (e.g., macrobiotic diets or diets created for a particular blood type). When diet becomes more restrictive and complex, it will severely affect the person (Bratman and Knight 2000). The strict diet dependency in ON can lead to the removal of many essential nutrients from the diet and various nutrient and mineral deficiencies that may harm the health of individuals and ultimately reduce their quality of life (Bağcı Bosi et al. 2007). Depending on the individual's beliefs about healthy eating, the resulting diet may follow a vegetarian, gluten-free, or any other diet type (Bratman 2017). Extreme cases of ON may choose to starve rather than eat foods they consider tainted, unsanitary, and unhealthy (Bratman and Knight 2000).

Orthorexic individuals dislike letting go of control when it comes to food. They also follow strict, self-imposed rules that determine which and how the combination of foods can be eaten at certain times of the day (Varga et al. 2013). Such rigid eating habits can make it challenging to participate in social activities that revolve around food, such as dinner parties or dining out. This perspective can influence one's interpretations of others. It may cause different evaluations of people who do not have the same food habits as themselves. Orthorexic individuals do not share the same eating habits as other people and carry certain foods wherever they go. For this reason, social isolation may be inevitable in these individuals over time (Bratman and Knight 2000).

An intense feeling of guilt may occur in orthorexic individuals, sometimes when they think they have failed to maintain their rigid eating habits. Over time, food

choices can become very limited in both variety and calories. These choices may endanger the health of the individual (Costa et al. 2017). Various health problems can be seen after dietary restriction, ranging from nutrient deficiencies to osteopenia, hyponatremia, metabolic acidosis, reduced testosterone levels, and heart rate, as in severe anorexia nervosa (AN) cases (Moroze et al. 2015).

One of the most worrisome situations associated with ON is when children inherit orthorexic tendencies similar to their parents. Children who observe their parents' obsession with certain types of food might imitate this behavior. Sometimes, parents harshly limit their children's sugar intake or feed their children only with organic food. These restrictions may raise fears in children's minds that some foods are "bad and dangerous" and that eating these foods can cause damage to them (Getz 2009). Several case studies reported children with orthorexic parents who developed metabolic problems due to orthorexic feeding behavior (Hunter and Crudo 2018).

Prevalence of Orthorexia Nervosa

In the general population, AN has a lifetime prevalence rate of 0.5–0.9%, and for bulimia nervosa (BN), this rate is approximately 1.5% (Favaro et al. 2003; Hudson et al. 2007). Since ON is still not accepted as a separate psychiatric diagnosis and there are currently no specific widely accepted diagnostic criteria, we do not know its frequency with certainty. Prevalence rates vary widely based on the scales used and the sample. Most of the studies were conducted using the ORTO-15 scale, and prevalence rates in these studies ranged from 6.9% to 75.2% (Donini et al. 2004; Haddad et al. 2019). The prevalence of ON reaches 90.6% in some groups (Turner and Lefevre 2017). Previous studies primarily evaluated the prevalence of ON in high-risk groups. Kinzl et al. (2006) evaluated ON in dietitians using the Bratman orthorexia test and found the level of orthorexic tendency to be 34.9% and showed that 12.8% of the sample had a higher risk of developing ON. Bağcı Bosi et al. (2007) determined a 45.5% ON trend in Turkey in his study with the ORTO-15 scale. In a study with ORTO-15 scale, Aksoydan and Camci (2009) reported ON prevalence rate as 56.4% among performance artists, 81.8% among opera singers, 32.1% among ballet dancers, and 36.4% among symphony orchestra musicians. Fidan et al. (2010) calculated the ON risk rate in medical students as 43.6% with the ORTO-11 scale. Ramacciotti et al. (2011) found the prevalence rate of ON to be 57.6% in the general population with the ORTO-15 scale. This figure, which is much higher than the prevalence of other EDs, might be because of the inability of the ORTO-15 scale to differentiate healthy eating from orthorexic behaviors (Fig. 1) (Table 1).

Later, many scales evaluating ON were developed, and prevalence rates were examined. In studies conducted with the Düsseldorf Orthorexia Scale in a healthy population, consistent results were observed between 2.5% and 6.9% in Germany (Barthels et al. 2015a; Depa et al. 2017; Luck-Sikorski et al. 2019; Rudolph et al.

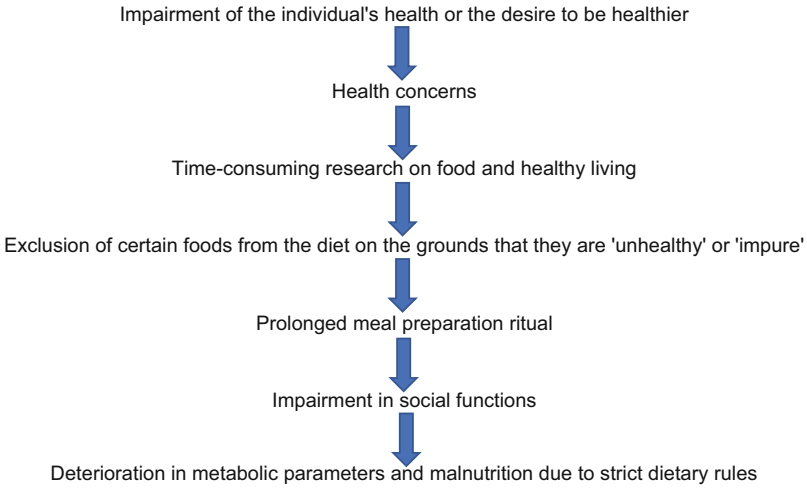


Fig. 1 Pathways to orthorexia

2017; Strahler et al. 2018) and as 8% in the UK (Chard et al. 2019). In another study with the Orthorexia Nervosa Inventory, the prevalence was found to be 4.5% (Oberle et al. 2021).

Orthorexic tendencies might be more common in some specific groups. The literature reports a higher prevalence of ON in specific groups, such as professional artists and ashtanga yoga practitioners (Herranz-Valera et al. 2014). The risk of ON might be higher in physicians, medical students, and dietitians (Herranz-Valera et al. 2014; Segura-Garcia et al. 2012). Besides, regular sports individuals have a higher orthorexic tendency (Bağcı Bosi et al. 2007). In many studies, ON symptomatology was higher among vegetarians and vegans than omnivorous individuals (Brytek-Matera et al. 2019; Brytek-Matera 2021). In addition, there are no consistent results on the relationship between ON and age, sex, level of education, and BMI (body mass index), suggesting the presence of cultural influences on orthorexia (Arusoğlu et al. 2008; Varga et al. 2013).

Diagnostic Criteria of Orthorexia Nervosa

ON does not yet have a widely accepted clinical definition and diagnostic criteria. However, some researchers have suggested possible valid diagnostic criteria for ON (Barthels et al. 2015b; Dunn and Bratman 2016; Moroze et al. 2015; Setnick 2013).

Studies that propose diagnostic criteria for ON include the following standard criteria: (a) obsessive thoughts, preoccupation with healthy eating, and strictly following a restrictive diet (which is believed to be healthy) while strongly evading foods thought to be unhealthy; (b) feelings of high emotional distress accompanying feelings of guilt, shame, and/or anxiety when restrictive dietary guidelines are

Table 1 Prevalence rates of orthorexia nervosa among healthy sample

Study				Material			Result
Source	Sample	Year	Country	Sample size	Gender rates (f/m)	Measure	Prevalence
Donini et al.	General population sample	2004	Italy	404	41.9/58.1	ORTO-15	%6.9
Kinzl et al.	Female dieticians	2006	Germany	283	100	Bratman orthorexia test	Orthorexia nervosa, %12.8; orthorexic behavior, %34.9
Arusoğlu et al.	Volunteers of Hacettepe University	2008	Turkey	944	578/416	ORTO-11	Tool adaptation (no data)
Aksoydan and Camci	Performance artists, opera singers, ballet dancers, and symphony orchestra musicians	2009	Turkey	94	55/39	ORTO-15	Total: %56.4 Opera singers: %81.8 Ballet dancers: %32.1 Symphony orchestra musicians: %36.4
Fidan et al.	Medical students	2010	Turkey	878	359/464	ORTO-11	Cutoff points for ORTO-11: 27 %36.9
Barthels	Users of social networks	2014	Germany	1307	904/393	DOS	%3.13
Brytek-Matera et al.	University students	2015a	Poland	327	283/44	Polish version of ORTO-15	%65.1
Strahler et al.	General population	2018	Germany	713	569/144	DOS	%3.8
Lucka et al.	School-age youth and young adults	2019	Poland	864	599/265	ORTO-15	Cutoff 40 point: %76.7 Cutoff 35 point: %27.8
Oberle et al.	University students and social media users	2020	USA	847	692/125	ONI	%4.5

Abbreviation: *ON, orthorexia nervosa; DOS, Dusseldorf Orthorexia Scale; ONI, Orthorexia Nervosa Inventory*

violated; (c) physical disorders in which nutritional deficiencies can result in substantial weight loss, malnutrition, and complications of physical health; and (d) psychosocial disorders related to social, occupational, and academic functioning that may result from other diagnoses (Dunn and Bratman 2016; Moroze et al. 2015; Setnick 2013).

According to Dunn and Bratman (2016), diagnostic criteria for ON should be as follows in Tables 2, 3, and 4).

Table 2 Diagnostic criteria for orthorexia nervosa according to Dunn and Bratman (2016)

A. Presence of excessive mental preoccupation with healthy eating, a diet theory, or a set of beliefs whose details may vary individual to individual; overstated emotional distress associated with food choices considered unhealthy; and weight loss, which might occur as a result of dietary choices (this should not be the primary goal):
1. Compulsive behavior and preoccupation with positive and restrictive eating patterns that the individual believes best promote health
2. Violation of the dietary instructions that the individual imposes on himself leads to exaggerated illness fear, a sense of contamination, and negative physical sensations, along with feelings of anxiety and embarrassment
3. Restrictions on nutrition that a person imposes on himself increase over time. Such restriction may involve eliminating all nutrition groups and increasingly frequent "cleanses" (partial fasts) that are considered cleansing/detox. There is no desire to lose weight, but this often leads to weight loss
B. Compulsive behavior and preoccupation is defined as a clinical disorder with one of the following:
1. Malnutrition, severe weight loss, and/or other medical complications resulting from a restrictive diet
2. Disruption of social, academic, or professional functioning due to beliefs and behaviors related to healthy eating
3. Evaluation of positive body image, self-esteem, identity, and/or satisfaction with compliance with self-determined "healthy" eating behavior

Table 3 Common and distinguishing features of orthorexia nervosa and OCD

Orthorexia nervosa	Common features	OCD
Symptoms associated with healthy eating	Intrusive thoughts (e.g., preparing food) and repetitive behaviors	Nonspecific obsessions and compulsions that may be unrelated to food
Egosyntonic intrusive thoughts and repetitive behaviors	Excessive time spent on thoughts and behaviors (e.g., on food selection and preparation)	Obsessions and compulsions that are often perceived as egodystonic
The main motivation is for pure and healthy nutrition	Impairment in social functioning	
	Perfectionism	
	Need to exert control	
	High anxiety levels	

Abbreviation: *OCD, obsessive-compulsive disorder*

Table 4 Common and distinguishing features of orthorexia nervosa and eating disorders

Orthorexia nervosa	Common features	Eating disorders
No fear of weight loss	Excessive worry about food and eating	Fear of gaining weight
Focus on the quality of the food	Life and behaviors are arranged to serve special eating habits	Focus of quantity of food
Clear, rationalized rules about eating	Impairment in social functioning	Secret rules about eating
No disturbances in body image	Malnutrition and weight loss	Disturbances in body image
No gender differences	Egosyntonic intrusive thoughts and repetitive behaviors	Female>male
	Perfectionism	
	Cognitive rigidity	
	High anxiety levels	

Definition of Obsessive-Compulsive Disorder and Its Relationship with Eating Disorders

Obsessive-compulsive disorder (OCD) is characterized by time-consuming, usually chronic, and sometimes episodic course, accompanied by obsessions and compulsions (Rasmussen and Tsuang 1986). OCD is usually comorbid with other psychiatric disorders such as depression, anxiety disorders, EDs, OCPD (obsessive-compulsive personality disorder), and suicidal thoughts (Costa and Hardan-Khalil 2019). OCD is a common psychiatric disorder like phobias, major depressive disorder, and substance use (El-Sayegh et al. 2003). The lifetime prevalence rate of OCD is 2.3%, and a 12-month prevalence is 1.2% (Ruscio et al. 2010). The lifetime prevalence of OCD comorbid with EDs was 13.9%, and the current prevalence rate was 8.7%. In fact, cases diagnosed with ED are at 8.9 times more lifetime risk for OCD than healthy controls (Drakes et al. 2021). The lifetime prevalence of comorbid AN among OCD cases ranges from 3 to 17%, and the current prevalence rate ranges between 0% and 2.4% (du Toit et al. 2001; LaSalle et al. 2004; Pinto et al. 2006). The prevalence of comorbid BN among OCD has not been studied extensively as AN, but lifetime prevalence rates range from 3.1% to 10%, and reported current prevalence rates are between 1% and 3.5% (Altman and Shankman 2009).

Murphy et al. (2004) found that cases with comorbid OCD and EDs have higher cerebral glucose metabolism, preventing them from effectively completing tasks requiring the prefrontal cortex and caudate nucleus work. They reported similar neurophysiological functioning in OCD and orthorexia. Available data suggest that EDs, including ON, and OCD may share some common underlying features (Table 5).

Table 5 The relationship of orthorexia with obsessive-compulsive symptoms and eating attitude in clinical samples

Study				Material		Relationship with ON	
Source	Patient group	Year	Country	Sample size	Tool	OC symptomatology	ED
Poyraz et al.	OCD, panic disorder, and generalized anxiety disorder	2015	Turkey	OCD: 49 PD: 44 GAD: 37	ORTO-11	Checking and dressing/grooming compulsions. There was significant difference between OC symptom severity and orthorexia nervosa. There was no significant difference between patient groups in the mean scores of orthorexia symptom severity	Orthorexic tendencies were found to increase as impaired eating attitudes increased in patient groups
Segura-Garcia et al.	ED	2015	Italy	32 (AN, 18; BN, 14)	ORTO-15	Longitudinal study. OC symptom severity was higher in eating disorder patients than the control group. After 3 years of follow-up, OC symptoms regressed despite an increase in orthorexic tendencies	Eating disorder patients were followed for 3 years, and a significant increase in orthorexic tendencies was found after treatment
Barthels et al.	OCD and ED	2017a	Germany	OCD: 30 ED: 40	DOS	The prevalence of orthorexia in OCD patients was similar to the healthy control group	The prevalence of orthorexia was found to be higher in the patient group with ED compared to the patient group with OCD

Yılmaz et al.	OCD	2020	Turkey	63	ORTO-11	Current order symmetry obsessions. There was no significant difference between OC symptom severity and orthorexia nervosa	Orthorexic tendencies were found to increase as impaired eating attitudes increased in patients with OCD
Vaccari et al.	OCD and anxiety-depressive spectrum disorder	2021	Italy	OCD: 50 Anxiety-depressive spectrum disorder: 42	ORTO-15	There was no significant difference between patient groups in the mean scores of orthorexia symptom severity	It was found to be associated with a restrictive dietary regime
Barthels et al.	Somatoform disorders	2021	Germany	31	DOS	Not evaluated	The patients displayed higher levels of orthorexic eating behavior than the control group

Abbreviation: ON, orthorexia nervosa; OCD, obsessive-compulsive disorder; DOS, Dusseldorf Orthorexia Scale; EDs, eating disorders; AN, anorexia nervosa; BN, bulimia nervosa; GAD, generalized anxiety disorder; PD, panic disorder; OC, obsessive-compulsive

Association of Orthorexia Nervosa with Obsessive-Compulsive Disorder

ON shares some common features with other psychiatric disorders such as OCD, AN, OCPD, illness anxiety disorder, somatic symptom disorder, and psychotic disorders (Koven and Abry 2015). Obsessive-compulsive tendencies are one of the most valuable and reliable features of ON. The previous studies consistently show that as obsessive-compulsive tendencies increase, orthorexic symptoms also increase. This trend is independent of the relationship of obsession and compulsion content with food (Poyraz et al. 2015; Roncero et al. 2017; Segura-Garcia et al. 2015).

Nevertheless, Moroze et al. (2015) suggested that obsession may be the root of ON. They stated that there might be a continuum between obsessive preoccupation with health and the distress caused by obsessive thoughts and beliefs about healthy eating. Koven and Abry (2015) reported that a potential relationship between ON symptoms and OCD might be considered if repetitive and ritualistic behaviors focus primarily on eating. The symptomatology of ON may be present when a person with an obsessive-compulsive tendency tends to ritually check their nutritional knowledge and increasingly has repetitive thoughts about attaining a better diet (Costa and Hardan-Khalil 2019).

ON was defined by the Los Angeles OCD Center (2011) as a hybrid of ED and OCD. Like OCD, ON is characterized by obsessive thoughts (thoughts about certain foods that are dangerously unhealthy) and compulsive behaviors (in this case, avoiding food, doing more research) to minimize the anxiety caused by these obsessive thoughts.

Similar to individuals with OCD, repetitive, intrusive thoughts about food and health, excessive worry, order symmetry, contamination and cleanliness obsessions at inappropriate times, as well as dressing, following ritualized and rule-based patterns, arranging food, washing, and controlling compulsions can be seen (Hayles et al. 2017; Yılmaz et al. 2020). Obsession with food intake is the most prominent behavioral association between ON and OCD (Costa et al. 2017). Also, as in individuals with OCD, the frequency of ON in men and women is similar (McComb and Mills 2019) (Table 6).

Table 6 Some magical thoughts about diet and eating

If we don't clean our body somehow, harmful toxins remain inside
It's good for a person to detoxify their body once in a while
An incorrect diet causes food to rot in the body
The idea that red foods raise hemoglobin is probably valid
Since 70% of our body is water, we should have a diet that is approximately 70% water
Vegetarian food is spoilt if it has been in contact with meat
Animal blood contaminates food

Obsessive-Compulsive Disorder-Related Cognitive Features of Orthorexia Nervosa

Orthorexic individuals have cognitive characteristics similar to individuals diagnosed with AN and OCD. In particular, themes of anxiety, perfectionism, impairment in external observation, and cognitive rigidity are common features of ON, EDs, and OCD. Like patients with OCD, orthorexic individuals devote most of their time to firm rules and overwork, and therefore, a decline in social functions may occur over time. In orthorexic individuals, meal preparation can take much time and may involve ritualistic features such as preparing food to represent compulsive behaviors, whether wood or ceramic materials are used. Similarly, a feature of OCD is the thought that if rituals are not completed, catastrophic consequences will occur in proportion to the perceived threat (Altman and Shankman 2009). This feature can also appear in orthorexic people because they might be uncomfortable when they think they are not following healthy eating instructions adequately. Like patients with OCD, orthorexic cases have restricted time for other activities because adherence to an inflexible eating style affects regular agendas (Dunn and Bratman 2016).

In contrast, patients with OCD exhibit obsessions and compulsions that are not limited to eating or food and generally have egodystonic features (Koven and Abry 2015). DSM-5 (2013) stated that the symptoms should not be better explained by the ritualized eating behavior observed in EDs to diagnose OCD. However, although a relationship was found between orthorexic symptoms and obsessive-compulsive tendencies in many studies among the general population, there was no significant increase in orthorexic symptoms in any of the studies conducted with OCD groups (Poyraz et al. 2015; Vaccari et al. 2021; Yılmaz et al. 2020).

Association of Orthorexia Nervosa with Eating Disorders

Association of Orthorexia Nervosa with Anorexia Nervosa and Bulimia Nervosa

There is some symptomatic overlap between ON and EDs, such as AN and BN. Catalina Zamora et al. (2005) emphasize that in orthorexic individuals, there are obsessive-compulsive mechanisms (rigidity, perfectionism, need to control one's life overeating), phobic mechanisms (intense anxiety about certain foods and avoidance of these foods), and hypochondriac mechanisms with personality traits similar to restrictive anorexia. In both orthorexic and anorectic individuals, lack of pleasure and control over one's life shifts to food when it comes to eating. Eating-related behavior dominates one's life, and one is overly concerned about it. They regulate their behavior and life to serve their particular eating habits. They face weight changes and malnutrition. Both orthorexic and anorectic individuals are achievement-oriented. They interpret sticking to their diet as a sign of self-discipline

and noncompliance as a failure of self-control. Obsessive-compulsive symptoms in ED and orthorexic individuals are egosyntonic and often do not accept functional disorders associated with their disease (Varga et al. 2013). It has been shown in many studies that as the worsening in eating attitude increases, orthorexic symptoms increase (Arusoğlu et al. 2008, Poyraz et al. 2015, Yılmaz et al. 2020).

However, orthorexic individuals focus on food quality, display unrealistic beliefs about food, and exhibit behaviors and desires to maximize health, while anorexic individuals focus on food quantity, and by the time, body image deteriorates and weakens (Brytek-Matera et al. 2015a). However, some authors state that fixation on food quality and type can also be seen in AN because these patients may follow specific strict dietetic instructions (Kummer et al. 2008; Misra et al. 2006). Therefore, adherence to the type of food might not be an essential criterion for ON. In addition, severe weight loss and malnutrition can occur in ON due to selective eating, which may follow a similar course to AN (Brytek-Matera 2012). On the other hand, while AN cases are prone to hide their anorexic behavior, orthorexic individuals are characteristically pleased with their lifestyle and eating choices and often do not hesitate to show it because of their sense of moral superiority (Koven and Abry 2015). In ON, individuals are reported to be motivated by the necessity to accomplish a sense of personal perfection or pureness, in contrast to AN, in which primary motivation is weight loss (Bratman and Knight 2000). However, some studies have suggested that motivation to achieve perfection is also the case for AN (Lilenfeld et al. 2006; Shafran et al. 2002).

Distinguishing Features of Orthorexia Nervosa from Anorexia Nervosa and Bulimia Nervosa

Unlike other EDs, ON is not associated with the desire to be thin. The underlying urge appears to be the desire to follow an excellent, healthy, or untainted diet. For example, organic vegetables and fruits might be considered safe foods for both anorexic and orthorexic individuals because they are viewed as healthy and low-calorie foods. However, frozen diet meals often seem acceptable for anorexic individuals but not for cases with orthorexic tendencies. Conversely, while pressed canola oil is an acceptable food for orthorexic individuals, it is seen as an unacceptable food for anorexic individuals who are afraid of gaining weight when they eat it due to its fat content (Getz 2009). In addition, ON differs from AN concerning BMI and gender variables. According to DSM-5 (2013), AN cases have low body weight. AN is more common in women than men, with a ratio of 9:1. On the contrary, symptoms of ON are not negatively correlated with BMI, and there are no differences in prevalence with regard to gender (Mccomb and Mills 2019).

Some studies indicate that ON and AN should be considered as disorders at various levels in the continuum of the same psychopathological dimension (Segura-Garcia et al. 2015). It has been proposed that ON symptoms are common among ED patients after treatment. These shared symptoms may be defined as the

transformation of ED, an undesirable side effect of psychotherapy, or the intellectualization of symptoms evolving into a socially acceptable behavior (Segura-Garcia et al. 2015). Another problem with the relationship between ON and EDs is that they occur together or in succession over time. ON may occur before the onset of ED or may manifest during remission and recovery.

On the other hand, ED experts in the UK argue that ON is not currently defined as ED because patients initially do not have low self-esteem, but can lead to eating disorders over time as dieting becomes more challenging (Mac Evilly 2001). Eating habits observed during the course of ON can lead to EDs as they become more restrictive and compulsive. One study suggested that ON is a risk factor for developing an ED, and it should be considered an initial stage rather than a separate disorder (Mac Evilly 2001). Other studies indicate that ON may be a comorbid disorder or a coping strategy to deal with an ED (Brytek-Matera et al. 2015b; Barthels et al. 2017b; Segura-Garcia et al. 2015). According to this view, focusing on healthy foods and reducing reliance on calorie intake may paradoxically lead to increased food variety and reduced risk of weight loss. Although patients continue to be meticulous when choosing their food, they begin to eat more calories which may be the first step toward recovery in EDs.

Association of Orthorexia Nervosa with Avoidant-Restrictive Food Intake Disorder

Several studies classified ON as an avoidant-restricted food intake disorder (ARFID) (Moroze et al. 2015, Brytek-Matera et al. 2015b). Both ARFID and ON may be associated with weight loss, malnutrition, and impairment in psychosocial functioning. Some findings common to both ARFID and ON may include increased stress at mealtimes, avoidance or feeling nervous when eating with relatives or friends, inability to maintain relationships due to conflicts about eating habits, and impairments in psychosocial functioning. The ED features in ARFID do not occur during AN or BN, and similar to ON, there is no evidence of body image disturbance or weight anxiety. Like ON, there is no difference in gender prevalence of ARFID, and common comorbidities are anxiety disorders and OCD (APA 2013).

These findings partially support the claim that ON might be a subtype of ARFID. However, clinical definitions of ARFID suggest that this disease develops in infancy or early childhood, usually after a traumatic experience with eating. Besides, ON appears to be more influenced by cultural health models learned in early adulthood. ARFID is characterized by avoidance of certain types of food (based on shapes, colors) and fear of the consequences of eating (Kreipe and Palomaki 2012). However, in ARFID, anxiety associated with eating may be the consequence of a traumatic experience (e.g., drowning) or an aversive experience (e.g., regular vomiting) rather than a result of the focus on improving health seen in ON (Bryant-Waugh and Kreipe 2012). The aforementioned risk factors of ARFID are not comprehensive; therefore, the possibility that the addition of food quality-related

factors or concerns about health loss encountered in ON to future updates of ARFID should not be disregarded.

Association of Orthorexia Nervosa with Other Mental Disorders

Association of Orthorexia Nervosa with Obsessive-Compulsive Personality Disorder

ON shares some features that overlap with other diagnostic categories, including OCPD. OCPD is a personality disorder manifested by fear and behavioral inhibition. It has prominent similarities with ON like perfectionism, rigid thinking, excessive commitment, extreme morality, and preoccupation with details and perceived rules (Koven and Abry 2015). No studies have examined association rates between OCPD and ON to date, but comorbidity between OCPD and OCD and between OCPD and ED has been comprehensively studied. Studies have shown that OCPD symptoms are closely related to EDs, especially AN, and noticeably predict the development of pathological eating habits (Anderluh et al. 2003; Lilenfeld et al. 2008).

Perfectionism, a feature of OCPD, has been accused in the psychopathology of AN and BN (Bardone-Cone et al. 2007). Perfectionism also plays a role in the course of developing and maintaining EDs (Bardone-Cone et al. 2007; Barnes and Caltabiano 2017). The previous studies suggest that cases with ON are also characterized by perfectionism and that perfectionism is a potential risk factor for ON (Koven and Abry 2015; Mathieu 2005; McComb and Mills 2019). The individuals with ON aim to have a perfect diet and to follow strict dietary instructions. Thus, it seems reasonable to think they have perfectionist character traits. Adherence to eating instructions was found to mediate the relationship between perfectionism and EDs (Brown et al. 2012).

Association of Orthorexia Nervosa with Somatoform Disorders

The symptoms of ON may also be similar to the health anxiety seen in somatoform disorders. In somatic symptom disorder, patients experience one or more chronic somatic symptoms which can or cannot be explained by medical evaluations, about which they are disproportionately preoccupied or fearful, leading to recurrent use of conventional and sometimes unconventional healthcare services. In illness anxiety disorder, individuals may experience bodily sensations and are extremely worried about the likelihood of an undiagnosed illness, often spending disproportionate time and energy on health problems. Either way, preoccupation with illness can lead to a secondary preoccupation with food and diet to deal with real or perceived illness. The individual may get into a compensatory dietetic program upon dissatisfaction with the conventional medical institutions or on specific advice from healthcare professionals to manage the disease with diet. Although there are few studies investigating the link between somatoform disorders and ON, it is known that health

anxiety is positively associated with food preoccupation, and there is evidence that health anxiety leads to significant problems in eating patterns (Koven and Abry 2015; Quick et al. 2012). However, longitudinal studies are warranted to further investigate whether health anxiety and somatic symptoms are risk factors for orthorexic eating behavior.

Association of Orthorexia Nervosa with Psychotic Disorders

Although there are no robust empirical data on this subject, ON is likely to indicate more severe psychopathology such as psychotic disorders. It is estimated that comorbidity of schizophrenia and eating disorders is generally low. However, the large number of anecdotal cases reporting the development of AN before the first psychotic episode has led to theories stating that the obsessive features of anorexia have the potential to evolve into more precise delusions over time. These theories also claim that nutritional deficiencies from food restriction might trigger psychosis. As ON is a relatively novel concept, prospective studies are needed to decide to what extent ON increases the likelihood of developing schizophrenia, delusional disorder, and related disorders. However, one of the most distinctive features of ON is control over food, which is considered as an attempt to possibly neutralize the loss of internal control experienced in the prodromal phase of schizophrenia (Møller and Husby 2000). In addition, some researchers thought disordered eating might act as a defense mechanism against psychosis (Hugo and Lacey 1998). At the theoretical level, the most related feature of ON with psychotic spectrum is magical thoughts about food, erroneous beliefs based on instinctive laws of contagion (i.e., real or imagined contact with objects continues to influence each other over time or space) (Aarnio and Lindeman 2004; Lindeman et al. 2000). Regardless of their origins (cultural or religious), magical beliefs about food are a medical concern as they can lead to severe nutritional deficiencies through the exclusion and rejection of food. Koven and Abry (2015) stated that independent of its content, high magical thinking is a commonly seen symptom of schizotypal personality disorder and might be a good indicator for possible psychosis.

Unique Features of Orthorexia Nervosa

While ON has some commonalities with OCD, EDs, and many other mental illnesses, some emergent symptoms are unique and equivocal to ON. Prominent among the specific symptoms of ON is an extreme obsession with regaining health or getting healthier. People with this disorder are unaware or may not accept the idea that this healthy diet may not be as beneficial for their health as they think. Another unique symptom of ON is that orthorexics are not obsessed with being thin or losing weight. Finally, as Bratman (2000) defines, the notion of being more accurate and superior to other individuals is a symptom not associated with other EDs or OCD.

Orthorexia Nervosa and Healthy Living Behaviors

Orthorexia Nervosa and Exercise

In the description of ON, the focus is mostly on eating habits, while other aspects of a healthy lifestyle indicative of ON have not been stated. For example, regular sports activities indisputably play an essential role in maintaining a healthy life, weight management, improving heart function, lowering cholesterol levels, and lowering stress and depression levels. However, its extreme forms may sometimes be associated with EDs (Bratland-Sanda et al. 2010; Ströhle, 2009). Considering that thoughts and behaviors in ON stem from the desire to be in excellent physical health, a commitment to healthy eating may also lead individuals to cover exercise activity as part of a more broad healthy lifestyle. More frequent and moderate physical activity may reveal motivation to pursue a healthy lifestyle. However, it is still possible to consider exercise as a part of the symptom cluster of ON (Kiss-Leizer et al. 2019).

Obsessive thought content of ON may be related to sport activities along with healthy eating (Kiss-Leizer et al. 2019). Indeed, higher levels of sport and physical activity are observed among ON symptomatology, which can also transform into exercise dependence to follow a compulsively rigid exercise regimen even during physical illness, injury, or other problems (Malmborg et al. 2017; Segura-García et al. 2012; Varga et al. 2014). Excessive preoccupation with standards, duties, and instructions and need to follow a firm order contribute to the development of both ON and exercise addiction (Strahler and Stark 2019). Interestingly, however, it was revealed that orthorexic people's motivation to exercise was to manage stress, rejuvenate, and increase positive impact by using exercise as a tool to improve physical health and avoid illness and improve their psychological health (Oberle et al. 2018). However, the association between ON and exercise is very complex and longitudinal studies are needed.

Orthorexia Nervosa and Social Media

Several mental health issues are closely related to Instagram and social media use. For example, higher levels of depression, EDs, and related behaviors are seen in young adults compulsively using social media (Carrotte et al. 2015; Lin et al. 2016). Without any scientific evidence, individuals are encouraged to eliminate several food groups from their diets on social media, potentially leading to an unbalanced diet and nutritional problems. In addition, this condition can aggravate psychological complications related to recommended food and, in some cases, lead to EDs such as AN or ON (Turner and Lefevre 2017).

The researchers note that Instagram use can result in ON as Instagram allows users to follow mostly food accounts based on their selections. Such selective exposure may make users believe healthy eating is more normative than it is and feel the need to conform to eating habits promoted on Instagram (Turner and Lefevre 2017). Instagram

users can use different diets (such as Paleo, vegan diet) to meet their compulsive control needs over original eating habits (Santarossa et al. 2019b).

Research suggests that ED groups create an environment where they connect and support each other through social media. Attitudes and behaviors of individuals with an unhealthy diet can be endorsed and promoted on social networks and eating-related websites. Such attitudes may lead individuals to develop EDs (Borzekowski et al. 2010). Social networking sites provide an almost limitless source for social comparison. Research indicates that especially young and female social media users compare their bodies with the bodies of celebrities and athletes and give them inspiration for a slim and ideal body (Santarossa et al. 2019a; Tiggemann and Zaccardo, 2015). However, studies on the relationship between ON and social media use are still in infancy, and more research is needed in the future.

Smoking and Alcohol Use

The obsession with wellness will likely require avoiding smoking and alcohol and including nutritional supplements and other complementary medicine ingredients into the diet. Studies supporting this hypothesis show that ON symptoms are observed more frequently in people who use nutritional supplements, do not smoke, and drink alcohol (Hyrnik et al. 2016; Varga et al. 2014). However, several other studies did not find any relationship between smoking and orthorexic symptoms (Aksoydan and Camci 2009; Fidan et al. 2010). In conclusion, studies to date did not report conclusive findings of a relationship between smoking and alcohol and ON.

Vegetarian Diet

The majority of studies show that vegetarians have more orthorexic behavior than those following an omnivorous regime (Brytek-Matera 2021; Brytek-Matera et al. 2019). Elimination of large micro- and macronutrients from a vegetarian diet may cause an increased risk of developing orthorexic behavior (Bratman and Knight 2000). A vegetarian diet is also another acceptable way to cover up disordered eating behaviors in public (Barnett et al. 2016). However, we should conduct more longitudinal studies to find out the role of a vegetarian diet in the development of ON.

Is Orthorexia Nervosa a Separate Mental Disorder?

Many people, especially in developed countries, have increased awareness of healthy nutrition, which becomes their primary focus. The increasing incidence of obesity has led to a significant increase in cardiovascular diseases, diabetes, hypertension, osteoarthritis, cancer, and many other health problems, mainly due to a

sedentary lifestyle. Therefore, concerned people start to be selective about the quality, quantity, and type of food they consume as a key to stay fit and healthy. But there is a subtle difference between being selective about food consumed and developing an obsession with a diet to be healthier. The development of such obsessions about the amount or type of food often leads to abnormal eating patterns and, in some cases, to psychological EDs (Chaki et al. 2013).

Orthorexic tendencies can be mentioned when a person restricts himself to a specific diet regimen with an obsessive urge to eat healthy (Getz 2009). In general, ON may come to mind when this condition is long-lasting, and this behavior has serious adverse effects on the person's quality of life (Bratman and Knight 2000).

With the growing media attention to ON, researchers have investigated the validity of ON as a unique disorder. Many have chosen to define ON as a variant of anxiety disorders or EDs (Mathieu 2005). Nevertheless, Bratman has proposed ON to be categorized as a specific ED. Bratman stated that ON and current EDs share many common features, but ON also has several important differences from other EDs (Bratman and Knight 2000).

The diagnostic classification of ON is currently unknown. However, Robins and Guze's (1970) seminal article suggests several steps for a mental disorder to reach diagnostic validity. The first step is the clinical definition currently available for ON. The second step is laboratory studies in which chemical, physiological, anatomical, and radiological findings are included, and psychological tests can be evaluated in this context. There is no generally accepted psychometric scale for ON and more research is needed on this topic. In addition, the neurobiological and neurophysiological basis of orthorexic eating has not been searched thoroughly, and like many other mental disorders, there is no specific laboratory test for diagnosing ON. The third step is differential diagnosis to prove the distinctiveness of a newly proposed diagnostic category and exclusion of other disorders. There has been an overlap between ON, EDs, and OCD in previous studies (Mccomb and Mills 2019). However, mental disorders could often exist together (Kessler 1994). Therefore, the simultaneous comorbidity of different disorders does not eliminate their distinctiveness. Thus to exclude other disorders, the person's distress should be proved to be caused by ON, not another mental disorder. The fourth and fifth steps, respectively, include follow-up and family studies, none of which were performed for ON. In summary, caution is advised when extending the diagnosis to ON based on the available evidence.

Discussions continue in the literature to decide whether ON, for which there are no formal diagnostic criteria yet, should be considered a separate disorder, a variant of another ED, an OCD-related disorder, or just an impaired eating habit (Brytek-Matera 2012; Ryman et al. 2019).

Treatment and Management

Although there are some recommendations for ON treatment, no studies have been conducted to date on treatment efficacy, other than case studies. The question regarding the classification of ON (a separate syndrome or a manifestation of another

disorder group) remains unresolved. However, the best intervention requires a multidisciplinary team approach that should include physicians, psychotherapists, and dietitians (Bartrina 2007; Koven and Abry 2015). A combination of drug therapy, psychoeducation, and cognitive-behavioral therapy could be implemented in outpatient settings with close monitoring (Mathieu 2005). In cases of significant malnutrition and weight loss, inpatient treatment may be required (Moroze et al. 2015).

During treatment, the individual is encouraged to eat a healthy diet. Orthorexic individuals may believe that giving up orthorexic eating behavior is the same as eating a bad diet. The goal is not to help the individual learn that all foods are healthy. Indeed, there are also foods that can harm health, especially if eaten in excess. The main purpose is to help the individual have a more balanced perspective toward food and learn to eat healthily and with pleasure. In other words, the goal is not to teach the individual to consume potato chips or sodas but to enable them to eat by choice rather than fear.

Regarding psychotropic drugs, selective serotonin reuptake inhibitors are reported to be beneficial for ON (Mathieu 2005), which also show some efficacy for both AN and OCD (Simpson et al. 2013). In one study, olanzapine was successfully used to reduce the obsessive nature of thoughts about magic food, and mirtazapine was successfully used in another case study followed up with a diagnosis of ON with comorbid depression (Moroze et al. 2015; Lopes et al. 2020). However, it should be noted that patients with ON may reject psychotropic drugs as they may be viewed as unnatural substances.

In psychotherapy, individualized interventions should be used by targeting the symptoms that are evident to the patient. Goals should focus on what patients eat, how they shop, and how they feel about the food they prepare and consume. Exposure and response prevention, together with habit reversal training, may be the most successful approach for treating the obsessive and compulsive aspects of ON (Koven and Abry 2015). Apart from that, providing psychoeducation about valid, current dietary science can help discourage orthorexic individuals from false beliefs about food.

According to LA OCD Center (2012), some parts of exposure and response prevention, which is the primary behavioral component of ON therapy, may be as follows:

- Gradually adding more types of food to the individual's diet, comprising healthy foods that she formerly deemed improper
- Reducing and eventually eliminating time spent investigating food
- Reducing and eventually eliminating the time spent arguing the health impact of food
- Return to everyday social life, including eating with others

Attention should be paid to refeeding syndrome, which is caused by disturbances in fluid and electrolyte balance. This syndrome occurs when nutrition is quickly reinstated after the body has adapted to hunger and malnutrition in patients who were

treated as inpatients due to significant weight loss and malnutrition. Refeeding syndrome can progress with sudden cardiac death and seizures and can be fatal. Other symptoms in this syndrome are hypertension, dyspnea, fatigue, weakness, confusion, and arrhythmias. Symptoms typically appear within 4 days of resumption of food intake. The first clinical manifestation of refeeding syndrome is low phosphate level (refeeding hypophosphatemia). Clinicians should be familiar with the signs and symptoms of fatal refeeding syndrome (Zickgraf 2020).

Conclusion

ON is an important and growing problem that needs serious consideration. While ON is not yet officially recognized as a disorder, failure to properly identify and treat the condition will cause serious problems for many people who suffer from these symptoms. However, making the patient aware of the extreme and distorted nature of their thoughts and behaviors regarding food purity may respond well to treatment with cognitive behavioral therapy.

Applications to Other Eating Disorders

In this section, ON symptoms are defined, and the relationship of ON with OCD and other mental disorders is discussed. ON is a unique phenomenon with distinct features. The obsessive-compulsive mechanisms underlying ON are interesting. Obsessive-compulsive mechanisms have been shown in other EDs, especially in AN and BN. However, it is interesting how critical obsessive mechanisms are under ARFID, which draws attention with some similar aspects to ON. It has been reported that ON can be seen together with other EDs. It is intriguing what the initiating factor is, which mechanisms sustain the process, what are the treatment options in comorbid conditions, or whether ON is a step in the recovery process. Although research on ON has increased, studies on the neurobiological aspects of ON are limited. In the future, revealing the neurobiological basis of ON and showing whether it is associated with OCD and EDs may help to illuminate the place of ON in classification systems. Conducting family and genetic studies related to ON may contribute to elucidating its relationship with other EDs. The prevalence of ON was evaluated in different populations with diverse rating scales and showed inconsistent results. ON prevalence rates seem inconsistent when considering other EDs with more balanced prevalence rates. When standardized assessment tools are developed for ON, prevalence rates of ON can be determined consistently, and the prevalence rates can be compared with other EDs. Consequently, more research conducted with a similar methodology on ON will define the diversity and changes in different cultures and populations.

Key Facts of Orthorexia Nervosa with Obsessive-Compulsive Symptoms

- Orthorexia nervosa is not currently included in the DSM-5. However, research continues to determine its place in diagnosis and classification systems.
- The main goal of orthorexia nervosa is to reach optimum health with a healthy and pure diet.
- Obsessive-compulsive symptoms are present in many eating disorders, including ON.
- It was found that as the severity of obsessive-compulsive symptoms increased, orthorexic symptoms also increased.
- The most prominent behavioral association between orthorexia nervosa and OCD is obsessions about food intake.

Summary Points

- Orthorexia nervosa is associated with impairment in social, occupational, and academic functioning and physical ailments due to nutrient deficiencies.
- Orthorexia nervosa shares some behavioral and cognitive features with OCD and EDs.
- Some important common features of orthorexia nervosa and OCD are perfectionism, impaired external observation, high anxiety levels, and deterioration in social functions.
- Some overlapping points of orthorexia nervosa with eating disorders are lack of enjoyment of eating, shifting control over life to food, weight changes, and facing malnutrition.
- The distinguishing features of orthorexia nervosa are that the main motivation for eating is a sense of perfection and purity, and they see themselves as superior to other people.

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Cardiac Vagal Imbalance and Emotional Eating

68

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Contents

Introduction 1382
Emotional Eating and Body Mass Index (BMI) 1383
Emotional Eating and Food Image Stimuli 1385
Emotional Eating and Food Craving 1385
Emotional Eating and Loss of Control Eating 1386
Emotional Eating and Hunger Inhibitory Control 1387
Neural Basis of Emotional Eating 1388
Emotional Eating and HRV 1391
Applications to Other Areas 1392
Mini Dictionary of Terms 1392
Summary Points 1393
References 1393

Abstract

Emotional eating is a maladaptive generalized behavior to regulate emotions as a momentary solution, and it is characterized by excessive food intake during states of emotional excitement or stress. The heart rate variability (HRV) as an

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evaluative parameter of emotional regulation indicates that the decrease of the vagal tone in the HRV is positively related to deficient self-regulation that might be associated with dysfunctional styles such as emotional eating. The explanatory emotional eating theory sustains this physiological mechanism by suggesting the sympathetic nervous system's activation and the existence of physiological incompatibilities between the action of eating and the presence of negative emotions which, instead of inhibiting the intake, boosts it. Nevertheless, evidence on the relation between the HRV and emotional eating demonstrates a predominance of the vagal response against the lower food stimulus under stress conditions.

Keywords

Emotional eating · Heart rate variability · Cardiac autonomic imbalance

Introduction

Emotional eating is characterized by an excessive food intake in states of emotional excitement or stress (Evers et al. 2010; Ouwens et al. 2003; Torres and Nowson 2007). This eating style is conceived as a maladaptive generalized behavior that operates as a momentary response to the regulation of emotions; however, it usually leads to different health problems such as weight gain, obesity, and behavioral eating disorders (Frayn and Knäuper 2018; van Strien et al. 2013). From a physiological point of view, emotional eating has been described as a surprising behavior considering that negative emotions are expected to induce states similar to satiety since they activate the autonomic nervous system (ANS) and appetite-suppressing hormone release. This is the proposal of Kaplan and Kaplan's psychosomatic hypothesis (1957) which poses that a normal response toward emotional excitement or stress is loss of appetite. Schachter (1968) sustained the same when explaining that negative emotions induce an increase in appetite-suppressing hormones such as catecholamine. Notwithstanding, some people tend to overeat when facing stress conditions or discomfort (Ouwens et al. 2003), contrary to the signals of the organism. Among the explanatory hypotheses of this phenomenon, there are proposals of psychological nature that suggest that food intake induced by uncomfortable emotions derives from a confusion between internal excitement states and hunger, probably due to neglected signals from the organism in early learning experiences during early childhood (Bruch 1964). In this same line, van Strien (2000) claims that among the predictors of emotional eating would be the lack of interoceptive awareness or complications in the identification and recognition of the internal signals of the organism, in this case, hunger or satiety and being able to overeat in front of a certain state of excitement. Another proposal comes from Heatherton and Baumeister (1991), who states the escape theory in which food and eating would be the mechanisms used to escape or divert attention during a negative self-evaluation redirecting it toward more pleasurable stimuli or experiences as the ones that come

from eating. Besides, a different approach to emotional eating has been described as an inhibited behavior that occurs under dietary restrictions. Polivy and Herman say that dietary restriction sustained over time is translated as exaggerated responsiveness toward external cues such as food characteristics and limited responsiveness toward the external signals of the organism. That is, when intake is permanently under cognitive control (rather than physiological) and is restricted, the sensitivity to the internal cues of hunger and satiety is reduced, resulting in disinhibition and overeating in situations where cognitive control is hampered (Herman and Polivy 1980). Emotional activation, such as stress or negative mood states, would act as inhibitors or disruptors of the restriction. This disinhibition not only occurs when facing dysphoric emotions but also as a response to sensory cues from palatable foods and alcohol consumption or in situations where self-regulatory abilities are reduced with high-stress moments, for instance (Ouwens et al. 2003).

There are parameters of physiological nature that function as emotional dysregulation predictors when anticipating maladaptive eating behavior. In this sense, heart rate variability (HRV) is positioned as one of the noninvasive and highly useful measures in clinical research, which allows the analysis of the changes that occur in the balance of the ANS, which facilitates information about certain abnormal physiological conditions (Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology 1996). HRV assessment has been conceived as the beat-to-beat rate variation within the heart rate, measured through the R-R intervals of the electrocardiogram over 24 h (Billman et al. 2015). Two indicators of the frequency domain emerge from this analysis: high-frequency power (HF) as an indicator of vagal activity and low-frequency power (LF) as a marker of sympathetic activity. However, LF has gained controversial appreciation since it has also been considered a parameter that includes sympathetic and vagal influence (Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology 1996; Reyes del Paso et al. 2013). In general terms, sympathetic activation has been associated with an increase in the LF and a decrease in HRV (Reyes del Paso et al. 2013). This reduction in HRV has been reported in several abnormalities in stress-related emotional regulation (Rodas et al. 2008). According to this, the presence of a link between eating behavior disorders and the presence of cardiac dysautonomia has been proposed (Jelinek et al. 2018; Mazurak et al. 2011), with a connection between this biological maladjustment and the emotional disturbance that leads to food intake. Thus, the diagnostic capacity of HRV allows us to understand the emotional dysregulations of behaviors concerning the decreased ability to regulate cardiac function, which leads to emotional eating (Moore 2018).

Emotional Eating and Body Mass Index (BMI)

A relationship between BMI, depression, and emotional eating has been found and is the last one that acts as a mediator which, at the same time, is related to future body weight gain. Likewise, people with dietary difficulties normally present a higher BMI and are more likely to acquire emotional eating disorders (Lazarevich et al.

2016). In this regard, the dysregulation of emotions exerts an indirect effect on BMI through emotional eating. Therefore, higher levels of emotional dysregulation might be associated with higher levels of emotional eating, which is also associated with higher levels of BMI (Jones et al. 2019). These results are consistent with different studies that suggest that emotional eating is tightly related to emotional dysregulation (Gianini et al. 2013) and weight gain (Grant and Boersma 2005; Koenders and van Strien 2011; Sung et al. 2009; van Strien and Koenders, 2012, 2016). Even though obese people usually present higher rates of emotional eating, this dysfunctional eating style is not exclusive to people with obesity since it is also present in normal-weight population (Palomino Pérez 2020). Other relationships have been established between emotional eating in people who are overweight and a series of negative emotional states such as depression, stress, anxiety, attention deficit, and dysfunctional regulation of emotions. In addition to this, symptomatology in certain eating disorders, body acceptance difficulties, eating self-regulation, and eating self-efficacy in the presence of obesity can be named (Nightingale and Cassin 2019). This indicates a higher susceptibility in people with obesity toward uncontrolled emotional eating provoked by a subjective perception of stress (Wilson et al. 2015). In the analysis of the physiological responses to stress, higher levels of impulsivity, cognitive restraint, uncontrolled emotional eating, and a higher reduction in the HRV have been reported as a response to food stimuli in patients with obesity. The urge for food in the absence of caloric need is thus construed as a vagal disbalance and lack of inhibitory control. These difficulties lead to the perpetuation of unhealthy eating behaviors associated with low HRV in response to stimuli relevant to subjects with psychopathological disorders and obesity (Spitoni et al. 2017) (Fig. 1).

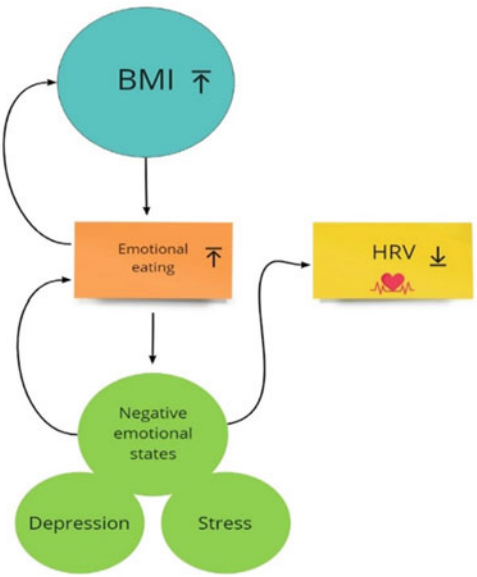


Fig. 1 HRV in the relationship between BMI and emotional eating

Emotional Eating and Food Image Stimuli

Visual food stimuli produce brain responses in the limbic centers (Ziv et al. 2020) as well as the activation of SNS under abnormal dietary conditions inducing emotional states in the subject, some of which should inhibit the eating response. By comparing a group of healthy women to others with bulimia nervosa, high caloric food craving in the clinical sample was bigger under the induction of negative emotions. Therefore, a negative mood was associated with higher brain activity in reward-related brain areas when anticipating food intake. In this way, bulimia nervosa is linked to eating in response to negative emotions during the induction of negative emotional stimuli (Lutz et al. 2021). In the analysis of biological and psycho-affective correlates of food image processing in emotional eating and as a response to the induction of negative images, an increased desire for food occurs in individuals with high levels of intake compared to individuals with low levels of intake. Additionally, the image of appetizing food influences the improvement of the emotional state, reducing negative affect (Blechert et al. 2014). It indicates that craving for food increases due to stress, which is contradictory considering that the sympathetic nervous system (SNS) is a suppressor of the digestive response regarding food intake. On the other hand, when relating BMI with food cue responses and HRV, a significant increase in food reactivity of HRV with a sympathetic predominance regarding highly caloric content in subjects with high BMI compared to subjects with low BMI. It proposes that subjects with high BMI have weaker cognitive restraint to food stimuli with high caloric content being more susceptible to food intake in response to appetizing characteristics of food, which is also common in emotionally induced feeding. It may indicate that people who are overweight are more vulnerable to identifying hunger cues and experience dysregulations in eating behaviors; this is verified through HRV (Chang et al. 2021) (Fig. 2).

Emotional Eating and Food Craving

Food craving is understood as an intense desire for one specific food (Meule 2018). Several studies report a relationship between highly palatable food cravings, external eating, and emotional eating behaviors (Blau et al. 2018). Different studies have established associations between emotional eating and food craving in individuals at risk of eating disorders, specifically in subjects with binge eating disorders and anorexia nervosa. Also, food craving can be linked to external eating behaviors in people with symptoms of anorexia nervosa, bulimia nervosa, and binge eating (El Archi et al. 2020). Hence, what eating styles such as food craving, emotional eating, external eating, and have in common is the pursuit of emotional rewards instead of responding to biological needs. Thus, an increment in emotional eating might boost a significant increase in the frequency of food cravings (Shnepper 2020). On the other hand, it is coherent with biological cues that food intake gets properly motivated by interoceptive cues of hunger or satiety since it does not depend on inaccurate mechanisms influenced by mood to be triggered. Concerning

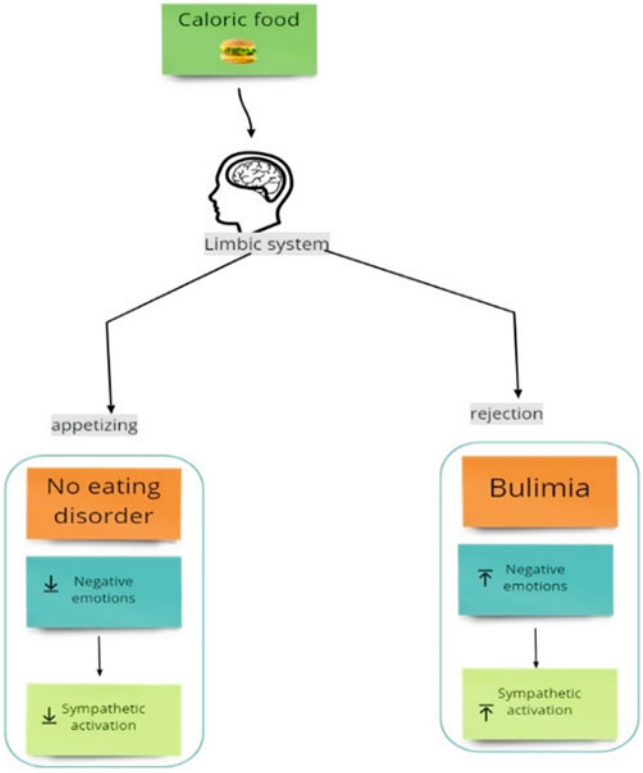


Fig. 2 Relationship between food stimuli and eating behavior. Autonomic response

HF values of HRV in the analysis of maladaptive style, Wu et al. (2020) discovered significant relationships between loss of control in eating and food craving. In this respect, an increased food craving is associated with a lower HF-HRV. This phenomenon responds to the influence that stress exerts on SNS activation over the parasympathetic nervous system (PSNS) in which the individual becomes motivated by the intake instead of suppressing the desire for food. Moreover, food craving has also been found to be associated with this HRV pattern through the lack of control over food intake. In palatable food like chocolate, a lower HRV has been found which precedes increased craving. It means that, due to a lower HRV, deficient automatic regulation plays an important role, relevant in food craving and uncontrolled eating behaviors (Rodríguez-Ruiz et al. 2009) (Fig. 3).

Emotional Eating and Loss of Control Eating

Loss of control eating is often a feature in individuals with binge eating episodes. These individuals are characterized by two different components: (a) eating an unusually large amount of food, known as overeating, and (b) feeling unable to

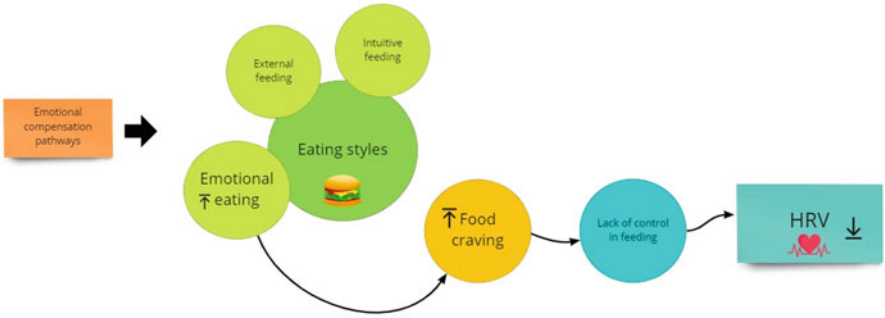


Fig. 3 Relationship between eating styles and food craving. Autonomic response

stop or resist eating, which is called "loss of control eating" (LOC) (American Psychiatric Association 2013; Vannucci et al. 2013). Emotional eating has been linked to LOC eating when predicting binge eating behavior. Also, emotional eating is usually associated with higher levels of depression, anxiety, and stress (Conceição et al. 2018). Such emotional alterations underlying food intake are commonly driven by the lack of control in eating to avoid negative emotions. In this sense, it has been identified that emotional eating is moderated by LOC eating in association with a significant increase in disordered eating patterns, BMI, and long-term adiposity (Stojek et al. 2017). Responding to stress, HRV informs how emotional regulation behaves concerning LOC eating which may lead to binge eating episodes. In this way, overeating has been associated with a lack of emotional balance and LOC as well as the nonacceptance of emotions. The high severity of these conditions is related to poor flexibility in the ANS with increased LF-HRV and decreased HF-HRV (Godfrey et al. 2019). Young et al. (2017) analyzed LOC eating as the mediator between negative emotional states and HRV. A depressed mood was connected to a lower HF-HRV rate with higher levels of disinhibited eating. For entropy effects, findings were similar to HF-HRV, connecting a reduction of it to emotional states and disinhibited eating. It is important to highlight that minor entropy indicates a minor regulatory capacity of the organism which will affect self-regulation and the control of emotions that leads to eating. It evidences HRV capacity as a stress biomarker in the identification of dysfunctional patterns of emotional regulation and food intake. Lastly, Ranzenhofer et al. (2016) determined that a critical low HRV during the 30 min before emotional eating is associated with eating and LOC (Fig. 4).

Emotional Eating and Hunger Inhibitory Control

Lack of inhibitory control impacts the suppression of food cues which causes an inability of individuals to recognize hunger cues and becomes influenced by emotions to execute food intake. The latter can be expressed by an impulsive behavior as a hasty response toward the stimuli or the lack of competence to amend inadequate

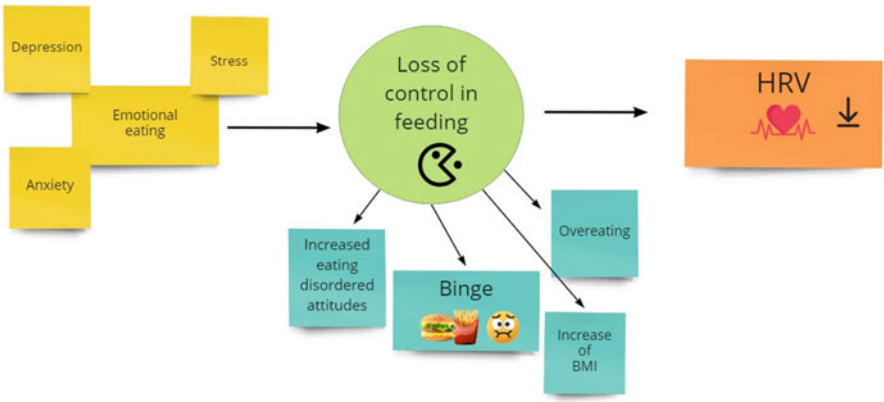


Fig. 4 Relationship between loss of control in feeding and emotional eating. Autonomic response

behaviors (response inhibition). So, this pattern has been associated with obesity and low self-control during food intake (Spitoni et al. 2017). More specifically, a higher negative affect predicts an inability to suppress desirable food cues, implying disinhibition in eating or loss of control associated, at the same time, with a higher level of emotional eating (Zhang et al. 2020). On another side, van Strien et al. (2014) found that inhibitory control moderates emotional eating over food intake. This pattern perpetuates in people who did not experience the typical hunger-reduction response after a stress episode. In this regard, inhibitory control has been related to emotional eating (Nelson et al. 2020). Different findings support these assumptions stipulating that emotional eating is connected to major behavioral inhibitory control difficulties, while negative emotions are being suppressed. Aligned to this, it is concluded that inhibiting behavioral responses during the regulation of negative emotions would contribute to a disinhibited intake (Wolz et al. 2021). Rodríguez-Ruiz et al. (2011) examined the loss of inhibitory control through food stimulation to evaluate physiological reactivity in HRV. The results confirmed a lower HF leading to a higher defensive and appetitive reflex toward food stimuli assessed as threatening (high-calorie foods) for women with bulimia nervosa. In this sense, HRV appears to modulate these reactions, which include appetite, food aversive reflex, and loss of control over eating, and supports the assumption that poor emotional and autonomic regulation plays a significant role in lack of inhibitory control (Fig. 5).

Neural Basis of Emotional Eating

Emotional eating is related to the hedonic dimension of eating behavior which has its structural and functional basis in the appetite reward systems located in the cerebral cortex and subcortex. From this neural mechanism, the search for gratification follows through food in order to relieve emotional discomfort, which is associated

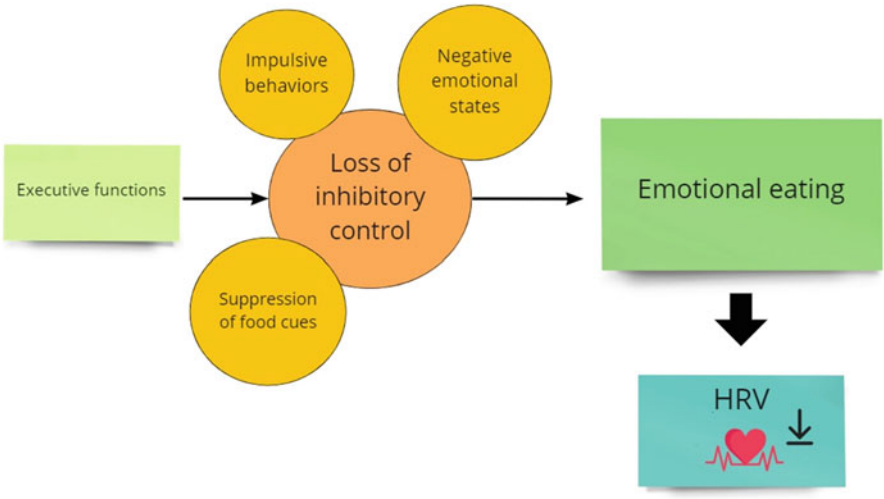


Fig. 5 Relationship between loss of inhibitory control and emotional eating. Autonomic response

with a deficit in the capacity for self-control (Suárez Palazón and Mayoral Babiano 2019). Considering this, the findings suggest that it is a tendency in people with emotional eating behaviors to have higher neural activation in response to rewards in front of food stimuli and rewards reinforcing food intake (Bohon et al. 2009). This is evident during the experience of negative emotions and during the anticipation of rewards, where activation of the right frontal lobe has been found, which could reflect the learned resource of food craving as an emotional regulator (Bletcher et al. 2014). During highly appetizing food choices, the visual system is the principal role-player, which reacts to food stimuli so the received information can travel through afferent pathways vias and activates structures such as bilateral posterior fusiform gyrus (FG), left orbitofrontal cortex (OFC), and the left mid-insula (van der Laan et al. 2011). Besides, different activation patterns have been discovered specifically in the anterior cingulate cortex (ACC), globus pallidus (GP), thalamus (Bohon et al. 2009), medial OFC, insular cortex (Killgore and Yurgelun-Todd 2006), dorsolateral prefrontal cortex (DL-PFC), and bilateral prefrontal cortex (Wood et al. 2016). Specifically, the activation of the insular cortex has been directly linked to information processing related to food's taste and its hedonic assessment, and, at the same time, it is involved in impulse control deficit in response to food incentives (Kenny 2011; Wood et al. 2016). Also related to self-control, the activation of subcortical structures such as the tonsil and basal ganglia occurs (Chechlacz et al. 2009; van Bloemendaal et al. 2015). In emotional eating condition there is styles, higher functional connectivity between the OFC - lateral hypothalamus (LH), ventral striatum, anterior insula, and medial temporal lobe networks - medial hypothalamus (MH), LH networks - nucleus accumbens, and the LH of the mesencephalon or midbrain has been detected, with the latter being also associated with the stress response. Moreover, a higher connection in the LF of the mesencephalon has been

related to a greater presence of an emotional eating style. Thus, the relationship between functional connectivity alterations in both networks, LH and MH, in eating patterns induced by emotions, particularly LH network alterations, has also been associated with higher levels of response toward stress (Martín Pérez et al. 2019). To summarize, evidence demonstrates a tendency to increase neural reactivity under induced stress conditions in the presence of food cues, which, at the same time, appears to be the basis of different background information related to binge eating as clinical symptomology (Fischer et al. 2017) (Fig. 6).

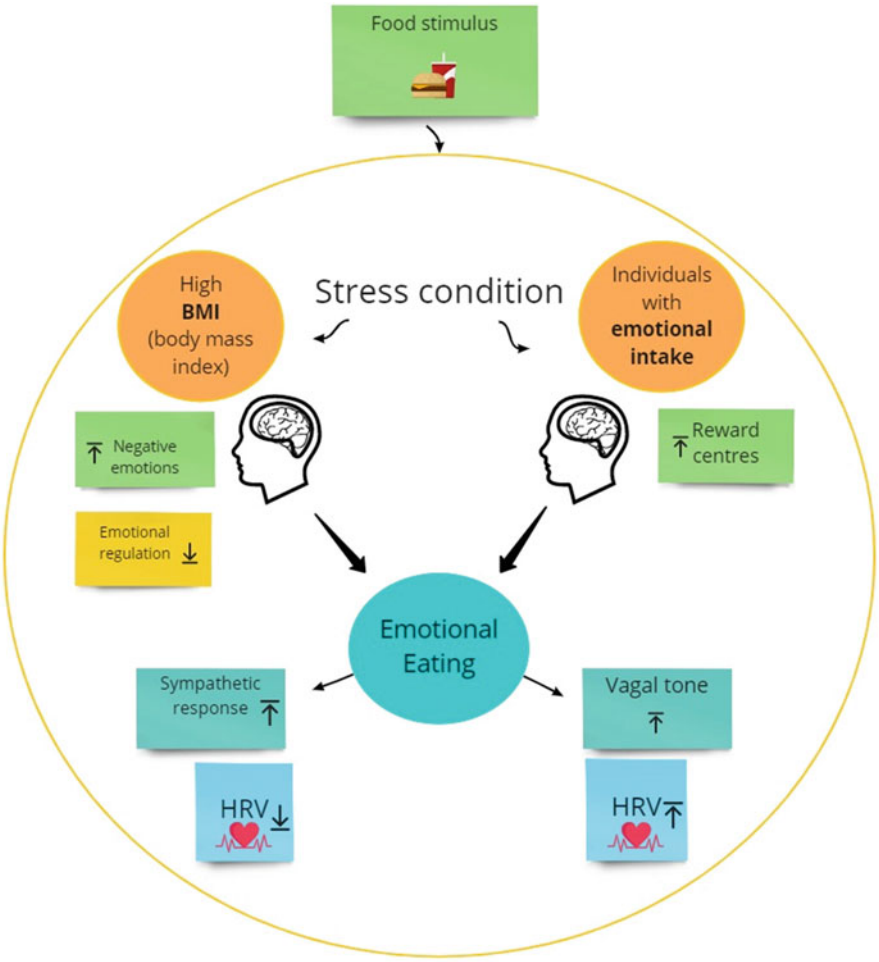


Fig. 6 Relationship between emotional eating with and without BMI mediation. Autonomic response under stress condition

Emotional Eating and HRV

In the theoretical approach to emotional eating, Kaplan and Kaplan's (1957) psychosomatic approach is positioned as one of the main explanatory theories. From this point of view, it can be established the existence of a tendency to handle negative emotions through eating concerning people who are overweight. In this regard, reference is made to SNS activation (Kaplan and Kaplan 1957), which is associated with a reduction in vagal tone, being the physiological process that would explain an adaptive difficulty of the organism when dealing with stress and that would be related to this dysfunctional eating style (Thayer and Lane 2000). Consistent with this approach, the neurovisceral integration model poses that HRV is an indicator of the self-regulation capacity in the organism in response to external demands meaning that the vagal tone reduction in HRV is connected to a deficient emotional regulation, which might be associated with dysfunctional behaviors such as emotional eating (Thayer and Lane 2000). Nonetheless, considering current findings when HRV is analyzed in people with emotional eating disorder, their physiological response is associated with an activation of the PSNS instead of the SNS. This is demonstrated through the HF band predominance in the HRV (González Velázquez et al. 2020). On another hand, Juarascio et al. (2020) found similar results in relation to changes associated with HRV in response to emotional eating episodes. In this respect, HF bands were predominating in previous moments of emotional eating episodes, suggesting vagal predominance and emerging as a principal and mainly predictive characteristic (Juarascio et al. 2020). This paradoxical response toward a stressful factor could be interpreted as a coping strategy and inadequate compensation associated with positive emotional responses in food intake (González Velázquez et al. 2020). Also, these results imply that people with emotional eating disorders apparently have higher activation of the reward centers in front of food stimuli and negative emotions induced intake (Bohon et al. 2009), explaining that the parasympathetic predominance would be linked to hedonism considering emotional eating behaviors. Likewise, the results remind us that when emotional eating is studied without BMI mediation, the psychophysiological response addressed by these theoretical references is not successfully obtained (Kaplan and Kaplan 1957; Thayer and Lane 2000). Contrary to these assumptions, the vagal response predominates from the activation of the PSNS, which would question the paradigm of psychosomatic theory in the analysis of emotional eating behaviors. Other results support Kaplan's approach (1957), where the BMI appears to mediate the relationship between food stimuli reactions and HRV, resulting in a predominance of the SNS and a reduction in HRV. In this way, these psychophysiological responses is a mechanism of emotional eating. However, this finding got restrained to people with a high BMI (Chang et al. 2021) resulting in a discrepancy between empirical evidence and theoretical information when trying to explain the psychophysiological mechanism of emotional eating behaviors. On the one hand, the psychological mechanisms involved in the interaction between HRV and emotional eating, which are associated with the self-regulation of emotions, interoception, and inhibitory control, have not yet been studied in depth. On the other hand, the approach to

emotional eating and the psychophysiological response associated with this eating disorder is restricted to people with obesity. Thus, it is concluded that explanatory reasons for emotional eating are not yet clear, and this explanation remains pending considering the limitations named above (Suárez Palazón and Mayoral Babiano 2019).

Applications to Other Areas

Los hallazgos actuales permiten sentar las bases para comprender el mecanismo a través del cual la VFC repercute en la autorregulación que conlleva a la ingesta alimentaria (Meule et al. 2012). En relación a las implicaciones clínicas, este conocimiento permite el diagnóstico de las desregulaciones emocionales que conllevan a comportamientos alimentarios compulsivos como el comer emocional. En este sentido, a través del uso de las nuevas tecnologías como es el caso de los sensores de machine learning, se incluyen métodos eficaces para detectar en tiempo real, los cambios en la VFC y el riesgo de episodios de comer emocional y de conductas alimentarias desadaptativas (Juarascio et al. 2020). Además, se pueden diseñar e implementar intervenciones como biorretroalimentación del hambre como estrategia de afrontamiento que permite a las personas con alimentación emocional, identificar sus sensaciones físicas de hambre (Kalogiratou et al. 2021; Ledoux et al. 2014). En consonancia con esto, la HRV-biofeedback podría ser una herramienta beneficiosa para atenuar el comportamiento alimentario disfuncional (Meule et al. 2012), pues posibilita el desarrollo de estrategias de regulación emocional y locus de control, lo que a su vez genera cambios favorables en el control del peso, teniendo en cuenta el alto índice de obesidad y el riesgo de enfermedades crónicas que existe hoy en día (Ledoux et al. 2014; Meule et al. 2012).

Mini Dictionary of Terms

- **Biofeedback**: Es una técnica de reconocimiento del hambre desarrollada por Mario Ciampolini. Consiste en la le administración de dispositivos portátiles de autocontrol con el que se les indica a los individuos que coman cuando confirmen el hambre física, con el objetivo de controlar el estado de peso.
- **Comer emocional**: Se considera como una tendencia a comer en respuesta a emociones negativas, siendo los alimentos elegidos principalmente ricos en energía y palatables.
- **Estrés**: Se define como una perturbación de la homeostasis e incluye el estresor, la respuesta al estresor y los cambios fisiológicos entre el estresor y la reacción corporal.
- **Índice de Masa Corporal (IMC)**: Valor que se obtiene del cálculo en base al peso y la talla y que funciona como indicador para establecer las categorías de peso.

- **Variabilidad de la Frecuencia Cardiaca (VFC)**: Es un índice de la actividad de la actividad del SNA. Se refiere a la variación latido a latido en la frecuencia cardíaca o la duración del intervalo R-R.
- **Machine learning**: Se basa en el algoritmo de funciones estadísticas a partir de conjuntos de datos multidimensionales que permiten hacer predicciones generalizables sobre individuos.

Summary Points

- The psychological mechanisms involved in the interaction between heart rate variability (HRV) and emotional eating are associated with the self-regulation of emotions, interoception, and inhibitory control.
- The approach to emotional eating and the psychophysiological response associated with this eating disorder are restricted to people with obesity.
- The evidence on the relation between the HRV and emotional eating demonstrates a predominance of the vagal response against the lower food stimulus under stress condition.

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Biologic Aspects of Rumination Syndrome, Eosinophils, and Beyond

69

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Contents

Introduction 1400
Physiology of a Rumination Episode 1402
Pathophysiology of Rumination 1403
GERD 1405
Functional Dyspepsia 1406
Rumination Syndrome 1408
Summary 1409
Mini-Dictionary of Terms 1411
Summary Points 1411
References 1412

Abstract

Rumination syndrome is characterized by repeated regurgitation with re-swallowing or spitting. It is associated with both medical and psychosocial complications. It is a disorder of gut-brain interaction resulting from complex and heterogenous interactions across biologic, psychologic, and social systems. Diaphragmatic breathing to compete with abdominal wall contractions is the current mainstay of treatment but is often only associated with partial improvement and high relapse rates. As such, there is a need to develop other treatments to supplement the current behavioral approach, particularly addressing other targets of therapy as defined within the biopsychosocial model. The purpose of this chapter is to describe current knowledge of the biology of rumination syndrome, suggesting other potential therapeutic targets including both mechanical and

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immune dysfunction. Frequent coexistence of GERD and functional dyspepsia has been demonstrated in both adults and children with rumination syndrome, and both may be triggers for rumination. Thus, the biology of both is relevant to rumination, and, as such, the biologic mechanisms of both may represent viable treatment targets in rumination syndrome. Immune dysfunction is now highly implicated in other disorders of gut-brain interaction with emerging data implicating a role in rumination syndrome independent of the presence of functional dyspepsia.

Keywords

Rumination syndrome · Gastroesophageal reflux · Functional dyspepsia · Diaphragmatic breathing · Mast cells · Eosinophils · Biopsychosocial model

Introduction

Although some variability exists across criteria defining rumination syndrome (see Table 1), rumination syndrome is generally characterized by repeated regurgitation with re-swallowing or spitting of the regurgitated material (Drossman 2016; APA 2013; Hyams et al. 2016). It usually begins shortly after eating, does not occur at

Table 1 Rome and DSM-5 criteria for rumination syndrome

Adult Rome IV:
All of the following:
1. Persistent or recurrent regurgitation of recently ingested food into the mouth with subsequent spitting or remastication and swallowing
2. Regurgitation is not preceded by retching
Supportive: effortless regurgitation events are usually not preceded by nausea; regurgitant contains recognizable food which may have a pleasant taste; the process tends to cease when the regurgitated material becomes acidic
Pediatric Rome IV:
All of the following:
1. Repeated regurgitation and rechewing or expulsion of food that:
(a) Begins soon after ingestion of a meal
(b) Does not occur during sleep
2. Not preceded by retching
3. After appropriate evaluation, the symptoms cannot be fully explained by another medical condition. An eating disorder must be ruled out
DSM-5:
Criteria for rumination disorder are:
1. Repeated regurgitation of food for a period of at least 1 month. Regurgitated food may be rechewed, re-swallowed, or spit out
2. The repeated regurgitation is not due to a medication condition (e.g., gastrointestinal condition)
3. The behavior does not occur exclusively in the course of anorexia nervosa, bulimia nervosa, BED, or avoidant/restrictive food intake disorder
4. If occurring in the presence of another mental disorder (e.g., intellectual developmental disorder), it is severe enough to warrant independent clinical attention

night, and is not preceded by retching. Like other conditions defined by Rome criteria, it is believed to be a disorder of gut-brain interaction. Previously referred to as functional gastrointestinal disorders under Rome criteria, disorders of gut-brain interaction are defined as unique symptom clusters of gastrointestinal symptoms which result from any combination of dysmotility, visceral hypersensitivity, altered mucosal barrier, immune dysfunction, dysbiosis, and/or aberrant central nervous system processing (Drossman 2016). As such, they are the result of complex interactions across biologic, psychologic, and social systems.

Rumination syndrome is believed to be underdiagnosed and quite often misdiagnosed as another gastrointestinal condition, particularly gastroesophageal reflux disease (GERD). Reported prevalence in community samples varies from 0.8% to 10.6% in adults and 0% to 9.7% in children and adolescents (Murray et al. 2019; Martinez et al. 2021). The prevalence appears to be much higher in patients seeking evaluation for gastrointestinal symptoms, particularly in pediatrics. Rumination syndrome has been found in 12.8% of adults presenting with "gastric symptoms" (Murray et al. 2019). Rumination syndrome has been reported in 44% of children believed to have treatment-refractory GERD and in 60% of children with chronic vomiting (Nikaki et al. 2020; Malik et al. 2020). These studies suggest that rumination should be considered in all patients seeking care for reflux or dyspeptic symptoms.

There is often a large delay between onset of symptoms and diagnosis of rumination syndrome with associated high costs for medical tests and ineffective treatments (O'Brien et al. 1995; Chial et al. 2003; Alioto et al. 2017). There are also high psychosocial costs with school absenteeism and avoidance of work and social settings (Murray et al. 2019; Chial et al. 2003; Malik et al. 2020; Alioto et al. 2017). Additionally, there are medical complications including dental erosions, weight loss, and electrolyte disturbances (Murray et al. 2019; Chial et al. 2003; Malik et al. 2020; Alioto et al. 2017).

Disorders of gut-brain interaction are best understood through a biopsychosocial model which states that they are the result of biologic, psychologic, and social factors which are all interactive with each other (see Fig. 1), communicating through neurologic, immunologic, and endocrinologic pathways. These disorders are more likely to respond to treatment packages that identify and treat multiple factors across the full spectrum of the biopsychosocial model. To date, most treatment approaches to rumination syndrome have been directed at psychologic aspects with behavioral interventions to create responses that compete with the abdominal contractions that initiate a rumination episode (as will be discussed).

Diaphragmatic breathing is considered the mainstay of treatment for rumination syndrome with very few studies to support other treatments currently (Murray et al. 2019). Diaphragmatic breathing, also known as abdominal breathing, involves engaging the abdominal wall muscles and diaphragm while breathing. As will be discussed, rumination episodes follow strong contractions of the abdominal wall muscles pushing stomach contents into the esophagus and mouth. Diaphragmatic breathing is believed to create a competing response to these contractions (Murray et al. 2019). The evidence for diaphragmatic breathing is meager, including three

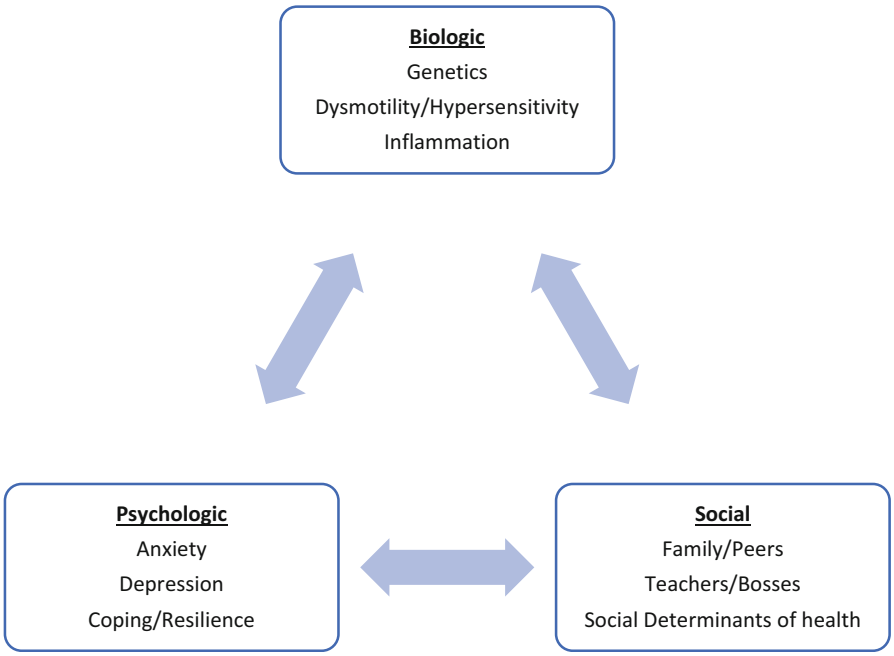


Fig. 1 The biopsychosocial model involves interactions between biologic, psychologic, and social factors in the generation of symptoms

prospective trials: two open trials containing a total of 38 patients and one randomized trial of 23 patients (Murray et al. 2019). Diaphragmatic breathing results in a decrease in rumination episodes, but most often some rumination continues, and the relapse rate is rather high, particularly in pediatrics (Murray et al. 2019; Chial et al. 2003; Malik et al. 2020; Alioto and Di Lorenzo 2018). Thus, there is a need to develop other treatments to supplement the current behavioral approach, particularly addressing other targets of therapy as defined within the biopsychosocial model. To date, there has only been one prospective trial of a medication directed at biological aspects of rumination syndrome (Pauwels et al. 2018). The purpose of this chapter is to describe current knowledge of the biology of rumination syndrome.

Physiology of a Rumination Episode

The physiologic changes which occur during a rumination episode have been well described in youth and adults during antroduodenal motility evaluations and more recently high-resolution esophageal manometry (Singendonk et al. 2017; Grunder et al. 2017; Rosen et al. 2017; Halland et al. 2020; Tucker et al. 2013; Rommel et al. 2010). Although the trigger for rumination may vary (as discussed later), the final events resulting in regurgitation are quite consistent. Episodes result from strong

voluntary (but generally unconscious) contraction of abdominal muscles which significantly increases intragastric pressure. An intragastric pressure increase greater than 30 mmHg is specific for rumination, differentiating it from a reflux episode, though a lower pressure may be seen in pediatric patients (Singendonk et al. 2017; Grunder et al. 2017; Halland et al. 2020; Tucker et al. 2013; Rommel et al. 2010). This pressure increase propels gastric contents into the esophagus and into the mouth. On manometry, rumination episodes appear as "R" or retrograde waves.

Other features seen on manometry demonstrate overlapping physiology with GERD but also differentiating features. Additionally, reflux may be a triggering event for rumination. Rumination is generally divided into primary rumination, where rumination is not associated with reflux, and secondary rumination where rumination is preceded by reflux which presumably triggers the rumination episode (Rosen et al. 2017; Tucker et al. 2013; Rommel et al. 2010). In adults with rumination syndrome, Rommel and colleagues demonstrated a consistent pattern in 86% of episodes where an initial small increase in gastric pressure was followed by retrograde flow of gastric contents with a subsequent large increase in gastric pressure due to abdominal wall muscle contraction (Rommel et al. 2010). In youth, Rosen and colleagues reported primary rumination in 55.5% and secondary in 44.5% of rumination episodes (Rosen et al. 2017). However, even in those episodes not preceded by reflux, there was often physiology similar to GERD, specifically relaxation of the lower esophageal sphincter (LES). Three patterns were noted in those with primary rumination: LES relaxation followed by an R wave before regurgitation in 51%, an initial R wave followed by LES relaxation in 20%, and an R wave without LES relaxation in 29% (Rosen et al. 2017). Whether different patterns have clinical significance remains to be determined. Rumination episodes differ from reflux episodes in that they are more likely to reach the proximal esophagus and mouth, are more frequently nonacidic postprandial events, and are more likely to be sensed by the patient and associated with symptoms (Nikaki et al. 2020).

As the physiology of a rumination episode has been well described, one pathway for treatment involves interventions to disrupt the episodes by inducing competing responses to abdominal wall contractions or to retrograde waves. This is the strategy behind diaphragmatic breathing which is performed to counteract the abdominal contractions. Hard swallows or inducing swallowing by sucking on mints or hard candy or chewing gum has been used to counteract retrograde waves. An alternative strategy would be to attempt to disrupt the pathophysiology that precedes the initiation of the abdominal wall muscle contractions.

Pathophysiology of Rumination

Three primary pathways have been proposed for development and maintenance of rumination including (1) a primary pathway where premonitory urges (uncomfortable psychologic or physical symptoms) precede and are relieved by rumination; (2) a pathway involving comorbid pathology, such as GERD; and (3) a pathway

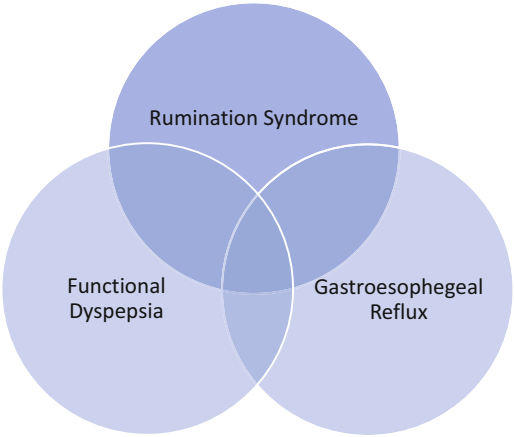


Fig. 2 There is significant overlap in the occurrence of rumination syndrome with functional dyspepsia and/or gastroesophageal reflux

involving psychosocial mechanisms where rumination initially relieves an unpleasant physical sensation due to a related condition, such as functional dyspepsia, and continues after the related condition resolves as a learned behavior to contextual clues, such as eating (Murray et al. 2019).

There is significant overlap in the presence of rumination syndrome, GERD, and functional dyspepsia which would suggest shared pathophysiology or that GERD and FD are triggers for rumination (see Fig. 2). There is evidence that both are true to differing degrees.

Frequent coexistence of GERD and functional dyspepsia has been demonstrated in both adults and children (Geeraerts et al. 2020; Fujiwara and Arakawa 2014; De Bortoli et al. 2018; Friesen et al. 2016). In adults with GERD symptoms occurring at least weekly, there is a nearly sevenfold increase in the prevalence of dyspepsia (Eusebi et al. 2018). Overlap is associated with worse physical and mental health, including increased sleep disturbance, anxiety, and depression (Lee and Chang 2021; Colombo et al. 2021). Significant overlap has been demonstrated between rumination syndrome and GERD with a substantial proportion of rumination syndrome patients having rumination secondary to reflux (Rosen et al. 2017). Significant overlap between rumination syndrome and functional dyspepsia has been demonstrated in population studies (Zand Irani et al. 2021a). In one study of children with rumination syndrome, 18% fulfilled Rome criteria for another functional gastrointestinal disorder (Rajindrajith et al. 2012). In youth with rumination syndrome, concurrent abdominal pain is reported in 23–38%, nausea in 17–30%, and constipation in 21–28% (Chial et al. 2003; Malik et al. 2020). Adults with rumination syndrome report increased postprandial nausea and discomfort as compared to healthy controls (Hoshikawa et al. 2020). Also, in adults with rumination syndrome, postprandial dyspepsia has been reported in 29% and treatment-resistant GERD in 24% (Tucker et al. 2013). As GERD and functional dyspepsia may provide the

stimulus for rumination episodes, the two conditions represent viable treatment targets in patients with rumination syndrome.

As will be discussed, GERD and rumination syndrome share common mechanical features and rumination syndrome, and GERD and functional dyspepsia share common features related to mucosal inflammation. Additionally, reflux and post-prandial symptoms seen in functional dyspepsia may be triggers for rumination, with regurgitation providing temporary symptom relief. For example, over 70% of adults report symptoms such as dyspepsia before onset of a rumination episode, symptoms which resolve once the regurgitant reaches the mouth (Tucker et al. 2013). Given the significant links between rumination syndrome, GERD, and functional dyspepsia, further discussion of GERD and functional dyspepsia is warranted.

GERD

Rumination syndrome significantly overlaps with GERD in terms of both symptoms and pathophysiology. Most often, patients with rumination syndrome are initially diagnosed with GERD and treated with acid-reducing medications (Murray et al. 2019). The clinical similarities prompted pediatric Rome III criteria to include the requirement that patients not respond to GERD treatment; this requirement was dropped under the current Rome IV criteria (Hyams et al. 2016; Rasquin et al. 2006). "GERD" patients who continue to have symptoms despite treatment are often labeled as refractory GERD before the diagnosis of rumination syndrome is entertained.

There are multiple possible explanations for why patients presumed to have GERD may be refractory to acid reduction therapy. Symptoms may be unrelated to GERD. For example, they may be the result of esophageal hypersensitivity (Clarke et al. 2018). This may be more likely with concurrent functional dyspepsia or irritable bowel syndrome which is associated with a decreased rate of symptomatic response to acid-reducing medications (e.g., proton pump inhibitors, PPIs) (Zerbib et al. 2021). As medications are not perfect, acid reflux may continue despite aggressive acid reduction therapy (e.g., twice daily PPIs) (Zerbib et al. 2021). Ultimately, a significant proportion of treatment-refractory "GERD" patients with predominantly post-prandial regurgitation will have rumination syndrome, either primary or secondary to reflux.

Up to 90% of gastroesophageal reflux episodes are initiated by transient lower esophageal sphincter relaxations (TLESRs) (Tack and Pandolfino 2018). These are both myogenic and neurogenic phenomena, most often resulting from a vagal-mediated reflex initiated by distension of the gastric fundus (proximal stomach) (Clarke et al. 2018; Tack and Pandolfino 2018). TLESRs are also influenced by intra-abdominal pressure, neuro-mediators, hormones, and dietary components (Tack and Pandolfino 2018). $GABA_B$ receptors, which can be moderated by baclofen (a $GABA_B$ agonist), have been assessed in several studies; baclofen decreases TLESRs and increases LES pressure (Clarke et al. 2018; Pauwels et al. 2018;

Blondeau et al. 2012). Baclofen has been reported to be beneficial in pediatric GERD patients with a sustained response in 81% (Vadlamudi et al. 2013).

GERD may also be associated with gastric motor dysfunction. GERD is associated with delayed gastric emptying in up to 45% of patients (Jehangir and Parkman 2020; Gonlachanvit et al. 2006). GERD is associated with proximal gastric retention of both solids and liquids and has been associated with altered gastric accommodation in some, but not all, studies (Gonlachanvit et al. 2006; Penagini 1998; Patcharatrakul et al. 2020; Pauwels et al. 2014). One method for assessing accommodation and gastric sensitivity is to inflate a gastric balloon to increasing volumes in the proximal stomach while measuring pressure and assessing symptoms. With gastric balloon distension, patients with GERD report fullness and discomfort at lower pressures and/or volumes than do controls (Penagini et al. 1998).

GERD is also associated with increased esophageal sensitivity which may be relevant given that a significant proportion of rumination episodes are preceded by reflux. Sensitivity plays an important role in symptoms generated by reflux (Tack and Pandolfino 2018). GERD is associated with disruptions in the esophageal epithelial barrier, increased nerve fiber density, and increased expression of TRPV1, a channel associated with hypersensitivity in patients with other functional gastrointestinal disorders (Tack and Pandolfino 2018). Together, these result in hypersensitivity to esophageal distension (Tack and Pandolfino 2018).

GERD can also be associated with inflammation, both in the esophagus and downstream within the gastrointestinal tract. While gastric acid may induce a chemical burn, much of the reaction resulting in esophagitis appears to be immune mediated with T cells central to the inflammatory mechanism (Rieder et al. 2007, 2010; Zavala-Solares et al. 2021; Souza et al. 2009; Zand Irani et al. 2021b; Moiseff et al. 2021). The immune response is associated with production of cytokines that can reduce esophageal muscle cell contractions (Rieder et al. 2007). It is likely that inflammation contributes to the altered mucosal barrier and increased sensitivity.

GERD has also been associated with duodenal inflammation with eosinophils, in particular, and as will be discussed, this represents an area of commonality with functional dyspepsia and rumination syndrome. In patients with functional dyspepsia, duodenal eosinophilia is associated with up to a sixfold increase in GERD (Ronkainen et al. 2019).

Functional Dyspepsia

Like GERD, rumination syndrome significantly overlaps with functional dyspepsia in terms of both symptoms and pathophysiology. Dyspeptic symptoms are frequently reported by patients with rumination syndrome; often, patients report these symptoms before a rumination episode with symptom relief once the regurgitant reaches the mouth (Tucker et al. 2013).

Functional dyspepsia has been associated with a variety of mechanical disturbances including delayed gastric emptying, decreased gastric accommodation, and visceral hypersensitivity (Rosen et al. 2014; Tack and Pandolfino 2018; Simrén et al.

2018). Approximately half of adults with FD exhibit delayed gastric emptying, and patients tend to exhibit increased retention in both the proximal and distal stomach (Park et al. 2017; Gonlachanvit et al. 2006). Delayed gastric emptying can be associated with nausea, pain, early satiety, and fullness (Vijayvargiya et al. 2019). Abnormal accommodation has been reported in over 40% of adults with functional dyspepsia and can be associated with early satiety (Park et al. 2017; Tack and Pandolfino 2018). Over 20% of adults with functional dyspepsia have both abnormal accommodation and delayed gastric emptying (Park et al. 2017).

Functional dyspepsia has been associated with inflammation including chronic inflammation involving Th17 cells (Singh et al. 2020). A large and continually growing body of literature has demonstrated increased density and activation of eosinophils and mast cells in the antrum and duodenum of both adults and youth with functional dyspepsia (Wauters et al. 2017; Friesen et al. 2013, 2021a; Singh et al. 2018; Du et al. 2018). Pesek and colleagues found mucosal eosinophilia in over 80% of patients undergoing endoscopy for moderate to severe gastrointestinal symptoms (Pesek et al. 2020). This increase occurs even in patients with mucosa that appears normal on gross endoscopic examination (Dellon et al. 2021). In particular, early satiety has been associated with mucosal eosinophilia. Nausea is also associated with increased mast cell density in children with dyspepsia, independent of abdominal pain (Friesen et al. 2020).

Inflammation appears to be an important link between functional dyspepsia and known triggers including stress and infections. Anxiety and stress have been highly implicated in the development and maintenance of disorders of gut-brain interaction, including functional dyspepsia. The stress response results in inflammation, dysmotility, visceral hypersensitivity, and alteration of central nervous system processing of nociceptive signals (Friesen et al. 2013). Corticotropin-releasing hormone (CRH) is the major mediator of the stress response. CRH receptors are widely expressed on the surface of mast cells, and CRH receptors may be expressed on the surface of eosinophils under stress conditions (as demonstrated in a rodent model), or eosinophils may be recruited and activated by mediators released from mast cells (Wallon 2009; Zheng et al. 2009). Antral mast cell density is positively correlated with anxiety and depression scores in youth with functional dyspepsia (Schurman et al. 2010b). Anxiety is common in patients with mucosal eosinophilia, and duodenal eosinophilia is associated with anxiety independent of functional dyspepsia (Reed et al. 2021; Ronkainen et al. 2021). Biofeedback-assisted relaxation training has been shown to enhance the clinical response in youth with functional dyspepsia and duodenal eosinophilia with decreased pain intensity and decreased duration of pain episodes providing further evidence for a link between eosinophilia and stress (Schurman et al. 2010a).

Mast cells appear to be an important pathway between stress and pain in adults as well (Wouters et al. 2016; Santos et al. 1998). Under physical stress conditions, adults have demonstrated jejunal intraluminal release of tryptase and histamine at a magnitude similar to that released by antigen exposure in food allergic patients (Santos et al. 1998). Upon activation, mast cells and eosinophils can release mediators which induce gastrointestinal symptoms (Friesen et al. 2013). Mast cell

infiltration and activation has been shown to induce hypersensitivity with histamine as an important mediator (Zheng et al. 2009; Wouters et al. 2016; Hou et al. 2001). Mast cell-derived histamine, which is released at biologically important rates in adults under stress, may be of particular importance as it can directly stimulate sensory nerves or lead to hypersensitivity (Coruzzi et al. 2012; Wouters et al. 2016; Santos et al. 1998).

Functional dyspepsia can be induced by an enteric infection with higher reported prevalence following both bacterial and parasitic infections (Zanini et al. 2012; Saps et al. 2008; Hanevik et al. 2009). Postinfectious functional dyspepsia appears to be due to an inability to end the inflammatory response after the pathogen is eliminated (Zanini et al. 2012). Postinfectious functional dyspepsia is associated with chronic inflammation as well as increased duodenal eosinophils, increased gastric mast cells, and increased gastric release of histamine and 5-hydroxytryptamine (Walker et al. 2011; Li et al. 2010; Lan et al. 2011; Futagami et al. 2010).

Rumination Syndrome

The overlap between GERD, functional dyspepsia, and rumination creates challenges in distinguishing which motility and inflammatory processes are directly related to rumination and which are due to an associated condition. As previously discussed, rumination episodes are frequently triggered by gastroesophageal reflux and share pathophysiology related to TLESRs. Like GERD, rumination episodes can be decreased by baclofen which decreases TLESRs and increases LES pressure (Blondeau et al. 2012; Pauwels et al. 2018). Other pathophysiologic motility processes reported in GERD and particularly in functional dyspepsia have been evaluated in several studies with mixed or inconclusive results. This should not be surprising as findings could be significantly altered by whether patients have overlapping GERD and/or functional dyspepsia.

Most often, gastric mechanical function is normal in patients with rumination, and there is a belief that medications to increase accommodation or emptying are ineffective; however, placebo-controlled trials are lacking (Murray et al. 2019; Absah et al. 2017). In one study, impaired accommodation was reported in less than 10% of adults with rumination syndrome (Bredenoord et al. 2003). In adults with rumination, balloon distension in the proximal stomach was associated with increased nausea and bloating as compared to healthy controls with no differences in accommodation at a group level (Thumshirn et al. 1998). However, decreased accommodation was demonstrated in 50% (6/12) of patients, and these patients reported increased pain with distensions (Thumshirn et al. 1998). Rumination syndrome patients do not appear to be a homogeneous group with regard to accommodation, and at an individual patient level, decreased accommodation may contribute to rumination in some patients. This is an important area for future research. Delayed gastric emptying is not uncommon in rumination syndrome and has been reported in 30–46% of children and adolescents (Chial et al. 2003; Alioto et al. 2017). It is not known whether delayed gastric emptying as measured by a

scintigraphic emptying study represents decreased gastric motor function or is an artifact created by excessive regurgitation. Again, there are no controlled trials of gastric pro-motility agents in rumination syndrome.

Similar to GERD, an altered mucosal barrier has been reported in rumination syndrome (Halland et al. 2020). Inflammation has also been more recently implicated in rumination syndrome. Abnormal upper endoscopic findings have been reported in over 30% of youth with rumination syndrome (Alioto et al. 2017). In another pediatric series, esophagitis (generally consistent with reflux esophagitis) was found in 32%, gastritis (generally chronic gastritis) in 32%, and eosinophilic duodenitis in 18% of patients (Friesen et al. 2021b). In functional dyspepsia, though there is not universal agreement in the upper limit of mucosal eosinophils, an increase in gastric or duodenal eosinophils appears to be common even in the absence of a formal pathologic diagnosis of eosinophilic gastritis or duodenitis; histologic criteria continue to evolve, and thus the 18% prevalence may represent an underestimation of the prevalence of duodenal eosinophilia in rumination syndrome (Dellon et al. 2021). Halland and colleagues studied mucosal inflammation in adults and found an increase in eosinophil density and intraepithelial lymphocytes in rumination syndrome patients as compared to controls (Halland et al. 2019). It was not known whether this was accounted for by overlapping functional dyspepsia which is highly associated with increased mucosal eosinophils (Halland et al. 2019; Du et al. 2018). A subsequent pediatric study confirmed these increases in duodenal eosinophils and intraepithelial lymphocytes while also demonstrating increases in eosinophil and mast cell densities in the gastric antrum (Friesen et al. 2021b). This study also demonstrated that increased inflammation occurred independent of the presence of abdominal pain or early satiety, hallmark symptoms of functional dyspepsia (Friesen et al. 2021b). The significant prevalence of chronic gastritis in these patients may also be relevant as chronic gastritis in children is associated with increases in mucosal eosinophils and mast cells (Singh et al. 2020).

Immune activation involving mast cells and eosinophils may be a pathway for factors that can exacerbate rumination, particularly known triggers of illness and stress (Alioto and Di Lorenzo 2018). Rumination syndrome is associated with anxiety and depression (O'Brien et al. 1995; Amarnath et al. 1986; Barba et al. 2015, 2016). Inflammation may be an important path between stress and rumination as has been demonstrated in other disorders of gut-brain interaction. As previously discussed, stress may be of particular importance in patients with concomitant rumination syndrome and functional dyspepsia. The role of inflammation in stress exacerbation of rumination syndrome is another important area for future research.

Summary

Like most disorders of gut-brain interaction, rumination syndrome is a complex and heterogenous entity. There is significant variability regarding mechanical functioning, both gastric motor function and functioning of the LES, particularly with its relationship to the onset of abdominal wall muscular contractions. Additional

heterogeneity is introduced by whether there is concomitant GERD or functional dyspepsia. It also seems likely that variation is introduced by varying triggers and differences in psychosocial factors. Consequently, patients may develop rumination syndrome by widely divergent pathophysiologic processes which may impact treatment responses. The paucity of controlled trials along with the pathophysiologic variability between patients which has not been controlled for in these studies limits the options for treating rumination syndrome in an evidence-based fashion.

There currently appear to be two treatment strategies: one directly targeting rumination episodes with competing responses (directed either at abdominal wall contractions or counteracting retrograde waves) and another identifying associated conditions with an attempt to identify relevant biologic, psychologic, and social factors. The two strategies are not mutually exclusive, and frequently both strategies are utilized, in part, in clinical practice. Diaphragmatic breathing has the most literature support, although somewhat meager, as a competing response. Other competing responses utilized in clinical practice (e.g., hard swallows, sucking on mints or hard candy, chewing gum), which are directed at counteracting retrograde waves, have not been studied prospectively nor compared to diaphragmatic breathing in treatment trials. Unfortunately, with diaphragmatic breathing, many or most patients have some residual rumination, albeit at a reduced rate, and relapse can be high. The other intervention which has been studied in a controlled trial is baclofen which improves LES function, preventing TLESRs as a trigger for some patients (Pauwels et al. 2018). With baclofen, although improvement has been noted in rumination syndrome, a significant proportion of patients continue to have symptoms. No studies have assessed combined treatment with diaphragmatic breathing and baclofen to determine if they have complementary effects. There have also not been controlled trials assessing either intervention in association with relaxation training although diaphragmatic breathing may induce a relaxation response in some patients if done properly. Teaching diaphragmatic breathing utilizing biofeedback may have the added benefit of being able to assure that it is also inducing relaxation.

Treatment utilizing a biopsychosocial model, identifying and treating relevant biologic, psychologic, and social factors, might represent a more efficacious pathway (as appears true for other disorders of gut-brain interaction), but this remains to be proven in this patient group. We have found it useful to classify patients by whether associated GERD and/or FD is still present or whether rumination syndrome represents a residual set of symptoms following adequate treatment and resolution of GERD and/or functional dyspepsia. In some patients, treatment of GERD or functional dyspepsia may be able to resolve rumination syndrome. In others, it may be helpful or even necessary but not sufficient to eliminate it. Within the biopsychosocial model, there is an implied need to identify relevant biologic contributors which is the focus of the present chapter. Similar to other disorders of gut-brain interaction, mechanical dysfunction (visceral hypersensitivity, accommodation defects, and possibly delayed gastric emptying) may be relevant in some patients and represent therapeutic targets. Immune dysfunction, particularly increased density and activation of mucosal eosinophils and mast cells, is now highly implicated in other disorders of gut-brain interaction, particularly functional

dyspepsia and irritable bowel syndrome, with emerging data implicating a role in rumination syndrome independent of the presence of functional dyspepsia (Du et al. 2018; Friesen et al. 2021a; Halland et al. 2019; Friesen et al. 2021b). Treatments targeting mast cells and eosinophils have shown benefit in other disorders of gut-brain interaction and are an important area for future studies in rumination syndrome (Dellon et al. 2020). Much of the current knowledge pertaining to rumination syndrome is related to pathophysiology; studies assessing treatments targeting the wide variety of maintaining pathways across biopsychosocial factors are strongly needed.

Mini-Dictionary of Terms

Rumination syndrome: A syndrome characterized by repeated regurgitations with swallowing or spitting which begins shortly after eating and is not preceded by retching.

Disorders of gut-brain interaction: Gastrointestinal symptom clusters resulting from any combination of aberrant motility, sensitivity, microbiome composition, intestinal barrier function, and neural processing.

Biopsychosocial model: A model explaining symptoms as resulting from variable contributions from and interactions between biologic, psychologic, and social factors.

Competing responses: Motor behaviors that oppose a habit in order to suppress the habit.

Gastroesophageal reflux: The return of stomach contents into the esophagus generally due to an incompetent sphincter or, most often, transient relaxation of the LES.

Functional dyspepsia: A disorder defined by the presence of epigastric pain, epigastric burning, early satiety, and/or postprandial bloating without a clear medical cause.

Summary Points

- The physiology of rumination episodes is well described with strong abdominal wall muscle contractions initiating retrograde or R waves; both muscle contractions and R waves are targets of current therapies utilizing competing responses
- Diaphragmatic breathing is the current mainstay of treatment but only has meager support from controlled studies, often leaves residual rumination, and is associated with significant rates of relapse
- GERD and functional dyspepsia frequently coexist with rumination syndrome and may trigger rumination episodes; as such, they represent viable treatment targets utilizing a biopsychosocial framework
- A growing body of evidence supports a role for mast cells and eosinophils in other disorders of gut-brain interaction including functional dyspepsia; emerging

data may implicate a role for inflammation in the pathophysiology of rumination syndrome
- There is a great need for controlled studies of current commonly utilized treatment strategies as well as interventions targeting biologic contributors to rumination syndrome

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Picky Eating in Normally Developing Children and Young Adults

70

Ada H. Zohar

Contents

Introduction 1418
Definitions of Picky Eating 1418
Measurement of Picky Eating 1419
What Is Not Eaten by Picky Eaters? 1420
Prevalence of Picky Eating 1420
Continuity from Childhood to Young Adulthood 1421
Trajectories of PE 1422
Parental Feeding Practices: Pressure to Eat 1422
Sensory Sensitivity 1423
Temperament, Fearfulness, and Inhibition 1424
Less-Studied Issues 1425
Practical Advice 1425
Applications to Other Eating Disorders 1428
Mini Dictionary of Terms 1428
Key Facts of Picky Eating in Children and Young Adults 1429
Summary 1429
References 1429

Abstract

This chapter deals with picky eating (PE) in normally developing children and adults. PE is a central component of avoidant/restrictive food intake disorder (ARFID) but not an eating disorder in itself. A large proportion of children go through a phase of PE, which usually resolves itself. A minority of children continue to be highly selective and neophobic. Extreme and consistent restricted eating in children can arrest development and cause severe health problems. There is (arguable) evidence that consistent picky eating from early childhood

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into preadolescence is a risk factor for restrictive eating disorders such as ARFID and anorexia nervosa. There is a growing body of research on PE in young adults; there is some evidence that adult PE is related to a less healthy lifestyle and is associated with emotional and social dysfunction and distress. This chapter reviews the definition, extent, duration, precursors, and repercussions of PE in children and young adults. It uses vignettes of picky eaters to illustrate some of the points raised in the review. In conclusion, it summarizes some of the less-studied issues that require further research and offers practical advice.

Keywords

Picky eating · Neophobia · Food fussiness · Intergenerational transmission · Children · Young adults · Parental feeding practices · Pressure to eat · Appetitive tendencies

Abbreviations

AN	Anorexia nervosa
ARFID	Avoidant restrictive food intake disorder
BMI	Body mass index
FF	Food fussiness
Pe	Picky eater
PE	Picky eating
Pes	Picky eaters

Introduction

Picky eating may constitute a health hazard, and at the very least can permeate the parent–child relationship with frustration, distrust, guilt, and anger, which may generalize to other aspects of the parent–child relationship and alter family dynamics. It is a nondiagnostic but salient problem in autism spectrum disorder (ASD); and in the absence of language in children and adults with ASD can be particularly tragic and difficult to deal with. There is a wealth of research on picky eating in the context of ASD. However, this chapter focuses on typically developing children and young adults, which is in itself a field of study that is gaining momentum and is worthy of review.

Definitions of Picky Eating

The criterion of avoidant restrictive food intake disorder (ARFID) in the DSM5 (APA 2013) includes apparent lack of interest in food, avoidance of foods based on their sensory characteristics, and concern about aversive consequences of eating, which leads to a significant weight loss or to nutritional deficiencies. Some of these have been suggested as elements of picky eating (PE). Dovey et al. (2008) include in

their definition of PE an inadequate variety of foods, rejecting many familiar and unfamiliar foods, and an aversion to specific food textures. A different definition was suggested by Brown and Perrin (2020) to include the refusal to taste new foods (neophobia), eating very little, and having one's food prepared separately or differently from other people present at the meal. Other definitions of PE include emotional responses having to do with food – such as showing no interest in food or meals, or displaying negative emotions before or during eating. These behaviors are better described as emotional undereating, although they are usually associated with PE (Tharner et al. 2014; Zickgraf and Ellis 2018; Zohar et al. 2020; Wolstenholme et al. 2020). In a systematic review of child PE and neophobia, Brown et al. (2016) conclude that the inconsistency of the definition of PE leads to great difficulty in drawing conclusions about prevalence of PE and its relationship to BMI and obesity in children.

Measurement of Picky Eating

The measurement of picky eating has evolved as interest in the phenomenon has grown. Some studies of young children (e.g., Cardona Cano et al. 2015; Zohar et al. 2019) rely on parental report via the Pre-School Child Behavior Checklist (Achenbach 1992), which includes an item on eating problems answered on a 3-point severity scale, and an open item for describing the eating difficulties. A more detailed parental report is the Child Eating Behavior Questionnaire (Wardle et al. 2001), which includes the six-item Food Fussiness (FF) subscale, with a focus on refusal to taste new foods, and can be used for children up to the age of 18. The FF score is sometimes used to define a cutoff point above which the child is defined as a picky eater (Sandvik et al. 2019; Zohar et al. 2020). Another measure is the objective tool for assessing picky eating (OTAPE; Finder 2020) for parental report on children 3–6 years of age. Parents report on the availability of various food items from a frequent foods list at meals in their home, and then on which of these were actually eaten by their child. Since it yields a quantitative ratio, it is deemed objective. However, since all these measures depend on parental report, there is potential for bias.

Observational tools are used in some studies and have the highest face validity. However, the observed behavior is study-specific, and the expense and labor involved limit the sample size studied (e.g., Abebe et al. 2017; Adamson and Morawska 2017; Jordan et al. 2020).

As children grow older, self-report becomes possible. Zohar et al. (2020) developed a scale based on a frequent foods list presented by name and picture. Children 7–9 years of age self-reported online to produce two variables: "never," the number of food items the child scores as not to be eaten; and "last week," the number of items the child endorses as having eaten over the last week. The two variables are negatively correlated and are strongly related to maternal reports of PE at earlier developmental stages as well as concurrently. Ellis et al. (2017) developed a 16-item self-report adult picky eating questionnaire (APEQ), with excellent psychometric

properties measuring sensitivity to meal presentation, the limitation of food items eaten, lack of appetite or interest in food, and aversion to sour and bitter tastes, which is in wide use in the growing research on adult PE. Zickgraf and Ellis (2018) composed a nine-item avoidant/restrictive screen (NIAS), with three items on PE, three on low appetite (Appetite, A), and three on anxiety pertaining to the gastrointestinal consequences of eating (Fear, F). The items on PE are "I am a picky eater"; "I dislike most of the foods that other people eat"; and "The list of foods that I like and will eat is shorter than the list of foods I won't eat." Each of the items is rated on a 6-point scale from strongly disagree (0) to strongly agree (5). The score on the PE subscale of the NIAS is the sum of responses, ranging potentially from 0 to 15. The NIAS has excellent psychometric properties, but as yet a cutoff point for PE has not been identified. The PE score correlates positively with food neophobia and with the food fussiness subscale of the adult eating behavior questionnaire, and negatively with the food enjoyment subscale. It does not correlate with measures of anxiety, depression, and stress (Zickgraf and Ellis 2018).

What Is Not Eaten by Picky Eaters?

Although the definitions of PE offered at the beginning of this chapter did not include what picky eaters (Pes) are not eating, this is of course of medical and health concern. By definition, the more selective a picky eater (Pe) is, the more foods she will not eat. However, a recurring theme in PE is avoiding vegetables and fruit. Most children who are Pes will not eat vegetables of any kind (Zohar et al. 2019) or will only eat a restricted range or amount of raw vegetables (van der Horst et al. 2016) and fruit. Because vegetables and fruit are crucial for vitamins and dietary fiber, this may have developmental repercussions and may also contribute to constipation (Taylor et al. 2016), which in turn will affect appetite and food enjoyment, thus constituting a positive feedback loop for PE. Ellis et al. (2018a) found that college students who self-reported as Pes were more likely to eat less vegetables and fruits. Thus, the association between PE and low vegetable and fruit consumption is found throughout the developmental span studied. Many PE interventions are targeted at extending the consumption of vegetables and fruit (e.g., Bennett et al. 2020; Jordan et al. 2020).

The avoidance of all or most vegetables and fruit is mentioned in all five vignettes included at the end of this chapter.

Prevalence of Picky Eating

Prevalence estimates of transient picky eating, present in one phase of childhood and not in another, vary from study to study, possibly because of cultural influences. A meta-analysis concluded that about 22% of children go through a picky eating phase (Cole et al. 2017a). There is some consistency, however, in the estimate of persistent picky eating over childhood, which derives from longitudinal studies. Zohar et al.

(2020) found that 3.9% of typically developing children in Israel were persistently Pes between 3 and 8 years of age. Taylor et al. (2015) found in a longitudinal study in the west of England that 3.5% of children 2–7 years of age were persistently Pes. In the Netherlands, a longitudinal study that followed children from their first year of life until they were 6 found that 4% of the children were persistent Pes (Cardona Cano et al. 2015). The prevalence of PE in young adults has been less studied. However, He et al. (2020) found that 19.4% of the Chinese college students studied could be defined as picky eaters and 3.3% as severe Pes. Ellis et al. (2018b) studied young adults in the United States and found that 18.1% could be described as picky eaters; this group also reported more social anxiety related to eating and more depressive symptoms. Thus, currently, there is a discrepancy in the prevalence estimates of PE in children and adults. While less than 5% of children are persistently picky eaters from infanthood to school age, about a fifth of young adults self-report as picky eaters. It is likely that different criteria are being used at different developmental stages; however, only extended longitudinal studies, with well-defined criteria for picky eating at the different developmental stages, can resolve this discrepancy.

Continuity from Childhood to Young Adulthood

Do individuals who are persistently picky as children become adult picky eaters? Or, are they at increased risk to develop restrictive eating disorders such as ARFID or restrictive AN? Van Tine et al. (2017) followed a small sample of children from infancy until the age of 23 and found continuity between persistent picky eating at 11 and remaining a selective eater at 23, with no evidence for increased eating pathology or obesity in the persistent picky eaters. Retrospective studies of adolescents diagnosed with ARFID (Menzel 2019) or AN (Dellava et al. 2012) suggest that childhood PE increases the risk for developing these disorders; however, there are no prospective studies showing this association. Moreover, a retrospective qualitative study of adolescents with restrictive AN (Scolnick et al. 2015) found that as children they were particularly good eaters, eating healthy, varied, vegetable-rich diets. The onset of their eating disorder could best be attributed to school-based obesity intervention programs. In young adults, PE is associated with more disordered eating, obsessive-compulsive symptomatology, and social anxiety surrounding eating (Wildes et al. 2012). Barnhart et al. (2021) found that PE as self-reported by undergraduates was correlated with overall eating pathology, with binge eating, as well as with social anxiety about eating, and symptoms of stress, anxiety, depression, and OCD. However, Zickgraf and Ellis (2018), in their validation of the NIAS, did not find that PE correlated with any measures of psychopathology in healthy young adults.

For the adult picky eaters represented in the vignettes in this chapter, there does not appear to be associated psychopathology, but there is discomfort around social eating.

Trajectories of PE

Different lines of research find partial support for a variety of antecedents and risk factors that can best be grouped as distinct trajectories to PE. In reality, they may not be mutually exclusive, but are described separately for clarity.

Parental Feeding Practices: Pressure to Eat

The dance of feeding and eating begins in the first few hours of the baby's life as both mother and child are recovering from the trauma of birth (Brody and Siegel 1992).

Some studies support the protective role of exclusive breastfeeding until 6 months of age against PE in later childhood (Shim et al. 2011; de Barse et al. 2017; Emmett et al. 2018); however, systematic review does not bear out this association (Bąbik et al. 2021). Self-weaning, letting the infant pick up and eat solid and lumpy foods when over 6 months of age rather than spoon-feeding her smooth pureed food, in the process of weaning the infant from an exclusive diet of milk or milk substitutes, is also found to be protective against later picky eating (Bąbik et al. 2021). However, waiting to begin doing so until the child is over 9 months of age is a risk factor for PE (Emmett et al. 2018), particularly so if the mother is worried or very worried about the child's eating. A possible integration of these early feeding findings is that babies and toddlers do best when they can regulate their food intake to suit their actual needs and appetite: Therefore, breastfeeding has an advantage over bottle feeding; self-weaning over spoon-feeding, but these are proxies and thus found in some studies and not in others, because the underlying protective factor is the absence of parental worry or fussing, trusting the baby/toddler to eat what and how much she needs. In an extraordinary longitudinal study of maternal feeding that followed mother–child dyads from the first year of life until the children were 18, Brody and Siegel (1992) found that mothers who were relaxed and enjoyed breastfeeding had long-term better outcomes for their children and for their children's eating behavior when they were young adults. Steinsbekk et al. (2017) found that parents offering their Pe child new foods in a calm, assertive way helped against continued PE; while responding emotionally to the child's food rejection "parental sensitivity" and accommodating to the child's food avoidance increased the risk of continued PE. This conclusion, that a relaxed confident parent who feeds her child without too much worry, fuss, or pressure has the greatest odds of not having a child who is a PE, has further corroboration in that first-born children are more likely to be described by their mother as PE than non-first-born children (van der Horst et al. 2016; Zohar et al. 2019), so that inexperienced and more anxious parenting may be the underlying factor.

Parents who identify their children as Pes self-report that they pressure their child to eat (e.g., Kutbi 2020). Common sense dictates that if the child eats less than the parent or the culture deems appropriate, or rejects many of the foods that are readily available in the home environment, a parent will try to discharge her responsibility toward the child by trying to increase the child's food intake or the range of foods the

child will eat. However, a low-appetitive child who is pressured to eat might respond to pressure by further reduced appetite and develop the attitude that eating is a chore that must be undertaken to satisfy the parent. Zohar et al. (2021) found that mothers of 6-year-old children, who were authoritarian, and practiced overt control of their child's diet, pressured their child to eat more, while the children ate less (high food satiety), had a more restricted diet (food fussiness), were slower eaters, and did not enjoy their food as much. Authoritative parenting, both loving and structured, is protective against PE (Steinsbekk et al. 2017; Jordan et al. 2020; Zohar et al. 2021).

There is also evidence that parental pressure to eat in childhood is a stronger predictor of adult PE than childhood PE (Ellis et al. 2016); this ironic reversal was noted in a retrospective study of adult eating behavior, BMI, and body image (Lev-Ari and Zohar 2013). Parental pressure to eat on children is a major predictor of adult PE (Cole et al. 2018). So, although pressure to eat is a common and understandable parental response to a child who is eating or is perceived to be eating very little, it does not seem helpful in the long run. In the short term, if meals become conflictual, with parents seeking to forcefully control their children's eating behavior, the parent–child relationship is negatively affected and the risk for continued PE and the development of eating disorders is elevated, while maintaining a positive atmosphere at family meals is moderately protective (Cole et al. 2018; Emmett et al. 2018).

It is unfortunate that particular parental feeding practices, including pressure to eat, undergo intergenerational transmission (Lev-Ari et al. 2021); so, young adults who were adversely affected by being pressured to eat when children find themselves in turn pressuring their own children to eat.

Sensory Sensitivity

Sensory sensitivity can be described as having an aversive or lacking response to stimuli that are tactile, visual, auditory, kinetic, the body's spatial orientation (proprioception), as well as to taste, smell, and food texture (Schoen et al. 2008). In the context of PE, sensory sensitivity is measured in all these domains **excluding** those that pertain directly to food (taste, smell, and food texture). Children who react aversely to sensory stimuli are more likely to be Pes at age 4, and sensory sensitivity at age 4 predicts continued PE at age 6, even when controlling for PE at age 4 (Steinsbekk et al. 2017). Sensory sensitivity seems to be congenital or genetic to some degree (van Hulle et al. 2012; Kalig-Amir et al. 2019), as does neophobia (Cooke et al. 2007; Smith et al. 2017). Pes are more prone to disgust, probably mediated by sensory sensitivity (Harris et al. 2019).

It has been suggested that individual differences in sensitivity to bitter taste may mediate PE (Jani et al. 2020; Patel et al. 2020). These differences are partly genetically determined as the ability to taste 6-n-propylthiouracil (PROP) is a Mendelian trait (Wooding et al. 2004). Cole et al. (2017b) found that variations in chemosensory genes were associated with elevated PE in preschool children. Bell and Tepper (2006) found that preschool children who were phenotypically

non-PROP tasters consumed more vegetables such as raw broccoli and black olives than PROP tasters. Moreover, Bell and Tepper (2008) found that parents of tasters and nontasters were no different in their feeding practices, suggesting that sensitivity to bitter taste contributes to PE in young children irrespective of parental influence. This line of research seems promising, but is relatively undeveloped.

This relationship between sensory sensitivity and PE has been found in preschool children (Steinsbekk et al. 2017), school-age children, adolescents, and young adults (Zickgraf and Ellis 2018). In school-age children with a diagnosed anxiety disorder, Zickgraf and Ellis (2018) found that aversive sensory sensitivity mediated completely between anxiety levels and PE; they found a similar pathway in healthy college students in their early twenties – the young adults' aversive sensory sensitivity mediated between their anxiety level and their PE. Kauer et al. (2015) found that adult Pes had more obsessive-compulsive symptoms and disgust propensity. To summarize, across development from young childhood to young adulthood, having strong aversion to sensory stimuli in realms unrelated to food is a considerable contributor to PE.

Sensory sensitivity is quite marked in vignettes I and III; in the other accounts, the sensory sensitivity is limited to taste and smell.

Temperament, Fearfulness, and Inhibition

An initial influence on the child's appetitive behavior can be due to temperament. Negative emotionality in toddlers is predictive of PE in later childhood (Hafstad et al. 2013) and cross-sectionally differentiates between toddlers who are PE and those who are not (Zohar et al. 2019). Obesity-prone children who exhibit high levels of PE have many more behavioral and emotional difficulties (Lepinioti et al. 2021).

Behavioral problems are elevated in young children who are described as PE. These include externalizing behavioral problems (Jacobi et al. 2008), as well as internalizing behavioral problems, and in particular affective problems (Zohar et al. 2019). This is also true in school-age children (Machado et al. 2016) and adolescents up to the age of 18 (Machado et al. 2021).

Typically developing children develop fears of imaginary characters, of harm to themselves or others, fear of strangers and strange situations, and may also suffer from night terrors (Zohar and Felz 2001). Children who were identified as PE at age 3 were elevated for all these normative childhood fears compared to typically developing children who were not PE (Zohar et al. 2019).

Deficiency in executive function, particularly in emotional regulation and shifting, differentiates children with PE at 3 from children without PE (Zohar et al. 2019) and predicts the persistence of PE to 8 years of age (Zohar et al. 2020). Although executive function is crucial for behavior regulation (Isquith et al. 2004), it has not been much studied in relationship to PE in children, and not at all in adults.

Children who are Pes and young adults who self-report as Pes may have a greater tendency to be shy, inhibited, anxious, and/or depressed, and these tendencies may characterize the individual and contribute to low appetite and PE.

Less-Studied Issues

Although the literature on PE is large and growing, there are several outstanding issues that bear additional scrutiny. Although there is a plethora of research on risk factors, there is less on protective factors. It is still difficult when examining a 3-year-old Pe child to predict if the individual child will outgrow this PE phase or whether the child is set on a trajectory of persistent and potentially dangerous PE. In vignette I, the mother assumed that her baby son's extreme pickiness was a phase; sadly, she was mistaken. There is a need to better understand the continuity between childhood PE and adult PE. The sensory and genetic underpinnings of PE and neophobia bear further study. And the contribution of difficulties with executive function, in children and young adults to PE, is a promising line of research that has not been pursued.

Practical Advice

For children who are low in appetite and restrictive in their food choices, and are low on their developmental trajectory, parents should first seek a medical evaluation to rule out health complications. When and if ruled out, parental common sense should prevail. Parents should avoid keeping foods in the house that they prefer their children not to eat. Parents should avoid power struggles over food and let the children lead in what and how much they eat out of the available foods that the parents deem healthy. If parents find themselves regularly pressuring, cajoling, or preparing special and different meals for their child, or for each of their children, then they are accommodating their children's pickiness and reinforcing it (Shimshoni et al. 2020). Treatment of extreme PE in children and adults can be sought in serious cases, and treatment follows the general principles of exposure (to more foods) and anxiety reduction. Young adults who seek treatment for their PE can be treated by dieticians who specialize in PE along the same principles. In the absence of distress or adverse health implications of PE, Pes should be left to enjoy their choices and their PE should not turn into a personal or social issue.

(1) A mother's account.

The only picky eater among my children was and is my youngest and fourth child. When he started sitting in a high chair and eating solids, I would put different vegetables on his tray for him to pick up and eat. He would try to pick them up and was obviously repelled by their texture. When I tried to spoon feed him he would look disgusted, and push the food out with his tongue. He absolutely rejected all vegetables and fruit, and to this day (at 26 years of age) will not eat any fruit. He was very sensitive to textures – of food and other things. He would not wear anything

with a label. I didn't concern myself too much about his diet – he was a fourth child, I was an experienced mother, and I expected it was just a phase. Our family is not particularly focussed on eating a healthy diet, and I didn't enter into conflicts with him or go to extraordinary lengths to look for vegetables and fruit that he would eat. There was a process of adaptation in which we discovered the limited list of foods that he was willing to eat, and made sure that some of them were available at meals. Sometimes I feel guilty I didn't try harder, and think he would have grown taller if he had eaten a more varied and nutritious diet. Even as an adult man, he eats very few vegetables and no fruit, but any kind of meat. I don't think he is much inconvenienced by his limited diet, except when people start fussing about it, or when he is out of the house and has difficulty finding foods that he can eat.

(II) A mother's account.

My eldest (now 27) was a very good eater as a baby and a young child. She nursed well, and loved the pureed food which at that time was the first non-milk food offered to very young children. To this day one of her favourite foods is apple puree. When she was in nursery school and kindergarten she ate with the other children and the staff never complained about her eating. I first noticed how restricted her diet was when she was a schoolchild (over 6). She would not eat any raw vegetables, very few fruits, and preferred potatoes, (white) rice, pasta and (white) bread. She would eat some proteins, chicken or beef if they were processed and had a smooth texture, and eggs in any form. Some hummus and tahini. She would eat vegetable soup if it was pureed, and particularly liked pumpkin. The restriction of her diet was a problem for her mainly when adults tried to pressure her to eat "healthy" food she could not eat. Then as now, she loved fried food. I worried about her nutrition and health. When she was about 10 or 11 years old, I consulted our paediatrician as well as a dietician. They did not have much constructive advice. As she matured, she was able to extend her diet. She has adopted tomatoes, raw, cooked, chopped and pureed. She loves basil pesto. She eats onions. She can mostly get by with food she cooks herself and eating with friends is part of her very active social life. She is very overweight, but I think this is mostly the result of not having enough physical activity, and does not result from her picky eating.

(III) A picky eater's account (30 years old at interview)

I was a picky eater from day one – my mother likes to say from the moment I was hatched. There was a wide range of things I couldn't eat – most fruit and all vegetables repelled me. When I first went to kindergarten my mother told the teacher that I could not eat tomatoes. The teacher was not deterred but several hours later had to call my mom to come and pick me up because I was vomiting so violently. Our house had a traditional cuisine, with a lot of meat, rice, and fried food, which I loved. There wasn't great emphasis on healthy eating, or on fruits and vegetables. I was a plump child, with a preference for processed food, dry hard food, and an aversion from anything that was or felt wet. Cucumbers I cannot stand to this day- they are wet and they smell. The smell of melon, watermelon, banana, can make me gag. The texture of soft fruits like plum or peach is unbearable for me. I can eat hard cheese, but it leaves my mouth feeling like sandpaper. I remember the adults around me being frustrated and angry about my pickiness, and also worrying that I was

gaining weight because I was eating a lot of junk food, and rejecting fruit and vegetables. I think it affected my body image even as a child; I also felt I was harming myself by not eating most of the foods. In the family I was ridiculed and tagged as a problem eater. When I left the house as a young adult I started working to extend my diet. I can now eat tomatoes; I can eat strawberries, and certain sautéed vegetables like broccoli. My boyfriend and his family are into healthy eating and that exposed me to more foods, some of which I now eat. My sensitivity is not restricted to food – loud sounds and especially loud talking actually hurt my ears; Although I enjoy being touched I am also extremely sensitive to touch, and this may mean that I will not be able to nurse my baby when she is born. I worry now that I am pregnant that the baby may not be getting the nutrition she needs and will suffer because of my pickiness.

(IV) An adult man's picky eater's account (55 years of age)

I am second out of four children, and although my sister is also picky, I have always been, and still am the most extreme picky eater in the family. As a child I was very sensitive and prone to moods. I would only eat a very limited number of foods; no vegetables, for fruit – only apples and carrots (laughs). I would eat processed meat, rice, and potatoes. Bread with chocolate spread. Very little else. There is a big category of foods that I call sour; I cannot abide sour food. Melon and watermelon are sour, as are many other things. When I was twelve we moved to a Kibbutz with a communal dining room. So not only was I a skinny runt (he is still extremely thin, AHZ), but there was no accommodation for my restricted diet and I had great difficulty finding things I could eat. My pickiness made me even less acceptable to my new peers and I was bullied by them. When I was in college living in the dorms I extended my diet a little – I learned to eat eggs cooked in certain ways as well as toasted cheese sandwiches. When I taste food that is unacceptable to me, I gag and spit it out. Today, my picky eating is less of a problem because I can usually determine what I will eat. I have problems when attending a social event, when I have to find things that I can eat. Being a guest in someone's home requires a lot of preparation and explanation, and sometimes is embarrassing for me and disappointing or hurtful to my hosts. However, when I go out to a restaurant with friends I can nearly always find something on the menu to eat.

(V) A young woman's account (26 years of age)

I have always been a picky eater. The list of things I can eat is very limited. My younger brother – is the opposite, he is omnivorous and a very large man. I have always been very small and skinny for my age. To be drafted into the army I made a special effort and gained weight to meet the minimal weight – 37 kilograms (81.6 pounds). I am known as a problem eater in the family. I cannot eat beef, only chicken breast; I can eat rice and potatoes. I avoid most vegetables and fruit. I love sweet processed foods like breakfast cereals, and certain candy bars. I am not very motivated to eat – I can forget to eat or not be bothered to for a whole day. During corona, when studies were on zoom, I forgot to get out of my chair and eat for entire days. But I am a nibbler and always have snacks in my backpack (shows a bag of cereal she has taken along). My best cooked food is pasta, and I can eat it with tomato sauce or with a cream sauce as long as no vegetables are included. That is

what I ate during my army service. When the family goes out for a meal, I try to study the menu in advance to identify things that I can eat. Sometimes there is a children's meal that is appropriate. My family complains a lot about my limited eating and the difficulties it poses for family events. I do not like to have my eating focused on, and find it unpleasant at family meals and social events when my restricted eating is noticed. I don't know if it effects my health, I am phobic about needles I am not monitored regularly.

Applications to Other Eating Disorders

Picky eating is not an eating disorder, yet it is linked to the restrictive eating disorders. ARFID includes aspects of picky eating in its first diagnostic criterion. AN is characterized by eating very limited amounts of food within a highly restricted range. So, picky eating can be conceived as a component of these disorders. There is some literature linking picky eating in childhood to eventual obesity, but the evidence is weak and arguable. The impulsive urges salient in bulimia and binge eating disorder seem to be in direct contradiction to the inhibited behavior seen in picky eating, and there is no research linking picky eating to the bingeing disorders. Picky eating in children is often the focus of parental feeding practices that do not promote healthy eating habits and can increase risk for the development of restrictive eating disorders.

Mini Dictionary of Terms

Appetitive tendency

- A tendency present early in development to approach and consume food; children with a low appetitive tendency are likely to eat small amounts, enjoy food less, and eat slowly, while children with a high appetitive tendency will do the reverse.

Picky eating

- Eating behavior characterized by low intake of food, rejection of new foods, food rejection because of texture or smell, and is usually exhibited by individuals with low appetitive tendencies.

Pressure to eat

- Parental feeding behavior intended to influence the child to eat greater amounts or to eat particular foods that the child rejects. The pressure might manifest in exerting parental authority, evoking guilt and shame in the child, or using food as reward or punishment,

Key Facts of Picky Eating in Children and Young Adults

- Picky eating is one of the most common presenting problems brought to the clinical attention of pediatricians in wealthy countries.
- It is difficult to untangle parental feeding behavior from child eating behavior in regard to child picky eating.
- It can cause social and emotional impairment in both children and young adults.

Summary

- About 20% of children go through a phase of picky eating, although there is great cultural variation.
- Most children will outgrow this behavior over development.
- Although cross-sectional studies show that children with picky eating are more prone to emotional and behavioral problems than their nonpicky peers, these problems tend to remit as picky eating wanes.
- Only about 4% of children persist in picky eating throughout childhood.
- Self-described picky eating is common in young adults and is associated with emotional and social dysfunction.
- There is retrospective evidence that persistent picky eating throughout childhood increases risk for restrictive eating disorders.
- Individuals who are consistently picky eaters from childhood into adulthood tend to be either under- or overweight as adults.
- Adults picky eating is a relatively new but fast-growing field of study.

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Part VI

Diagnosis, Delective Questionnaires, and Resources

Assessing Orthorexia Nervosa by Questionnaires

71

Melda Pelin Yargic and Murat Cenk Celen

Contents

Introduction 1436
Which Questionnaires Are Used in Orthorexia Nervosa Studies? 1438
Bratman Orthorexia Test 1438
ORTO-15 1439
Body Image Screening Questionnaire (BISQ) 1441
Düsseldorf Orthorexia Scale (DOS) 1441
Orthorexia Nervosa Scale (ONS) 1442
Burda Orthorexia Risk Assessment (B-ORA) 1442
Teruel Orthorexia Scale (TOS) 1443
The Barcelona Orthorexia Scale (BOS) 1444
Orthorexia Nervosa Inventory (ONI) 1444
Test of Orthorexia Nervosa (TON-17) 1444
Application to Other Eating Disorders 1445
Mini-Dictionary 1445
Key Facts of Assessing Orthorexia Nervosa by Questionnaires 1446
Summary Points 1446
References 1446

Abstract

With a growing research interest directed at orthorexia nervosa (ON), specifically at measuring it accurately, today there are many measurement tools available in the scientific literature. Due to the lack of a consensus on the diagnostic criteria of ON for many years, the early scales, which are the most commonly used ones, lack questioning some key features of the disease, in addition to lacking adequate

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validity. Researchers who noticed this shortcoming started working on developing new measurement tools. In this chapter, we will review these 10 ON measurement tools and their properties: Bratman Orthorexia Test (BOT), ORTO-15, Body Image Screening Questionnaire (BISQ), Düsseldorf Orthorexia Scale (DOS), Orthorexia Nervosa Scale (ONS), Burda Orthorexia Risk Assessment (B-ORA), Teruel Orthorexia Scale (TOS), The Barcelona Orthorexia Scale (BOS), Orthorexia Nervosa Inventory (ONI), and Test of Orthorexia Nervosa (TON-17). Our aim is to provide researchers and clinicians with the information they require regarding the content, validity, reliability, and other distinct properties of the questionnaires.

Keywords

Orthorexia nervosa · ORTO-15 · Bratman Orthorexia Test · Düsseldorf Orthorexia Scale · Teruel Orthorexia Scale

Abbreviations

ABOST	Authorized Bratman Orthorexia Self-Test
BISQ	Body Image Screening Questionnaire
B-ORA	Burda Orthorexia Risk Assessment
BOT	Bratman Orthorexia Test
DOS	Düsseldorf Orthorexia Scale
DSM-5	The Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition
ON	Orthorexia nervosa
ONI	Orthorexia Nervosa Inventory
ONS	Orthorexia Nervosa Scale
TON-17	Test of Orthorexia Nervosa
TOS	Teruel Orthorexia Scale

Introduction

Orthorexia nervosa (ON), which is often referred to as a lifestyle syndrome, is a disordered eating behavior. The word "orthorexia" was put together by Bratman in his article "Health Food Junkie" which was published in Yoga Journal in 1997 (Bratman 1997). The term implies an unhealthy preoccupation with healthy eating. There is an ever-growing interest in orthorexia nervosa, although it lacks the proper recognition in the current diagnostic classifications.

Questionnaires are a set of previously determined questions to determine the attitude, behavior, or situation on a particular topic. This topic can be related to all areas of life, as well as human health. For many years, questionnaire research has been used for many of the studies in the field of medicine and has been especially preferred by epistemologists in examining the attitude and behavior dimension of disease and health (Mandal et al. 2000). In general, questionnaires are not a preferred



Fig. 1 Orthorexia nervosa is an unhealthy preoccupation with healthy eating. (Image: Freepik)

method in the diagnosis phase of patients. It is mostly used in the self-reported, systematic determination of the factors that cause the formation of the disease (Fig. 1).

The *Diagnostic and Statistical Manual of Mental Disorders*, Fifth Edition (*DSM-5*), published by the American Psychiatric Association is the most up-to-date manual accepted as a reference when defining certain psychiatric conditions as a psychiatric disease (American Psychiatric Association 2013). Although orthorexia nervosa is a condition that is increasingly recognized and of interest as a research topic, it is still not defined as a disease in the *DSM-5*. Therefore, it is not possible to use the *DSM-5* diagnostic criteria for orthorexia nervosa, as we do for other eating disorders. Even so, Dunn and Bratman have suggested diagnostic criteria for the condition: an obsessive focus on "healthy" eating (Criterion A) and clinically impairing compulsive behavior and mental preoccupation (Criterion B) (Dunn and Bratman 2016). In this context, questionnaires assessing orthorexia nervosa are very much needed, not necessarily for making a diagnosis, but to clarify which populations are under higher risk for ON, which clinical conditions are often associated with it, and its many unknown properties (Fig. 2).

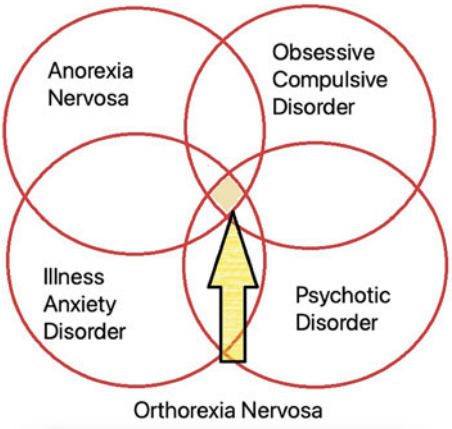


Fig. 2 Association of orthorexia nervosa with other eating-related disorders

In this section, the questionnaires used in studies on orthorexia nervosa, their compatibility with each other, and how inferences are made from the information obtained from these questionnaires will be discussed.

Which Questionnaires Are Used in Orthorexia Nervosa Studies?

The number of orthorexia nervosa questionnaires used in current studies is relatively high. The first of these questionnaires was conducted in 2000 by Bratman, who described this eating disorder condition as orthorexia nervosa (Bratman 2000). At least 10 different questionnaires appear to be used to measure ON nowadays. Although some of these questionnaires are about eating disorders in general, studies show that they can be used in the detection of ON. Important details such as the scope of the questions and the explanations suitable for the person to answer affect the reliability and validity of the scales. Translations of the questionnaires in various languages require new reliability and validity studies, in some cases resulting in extracting certain questions from the scale. Each scale used for the measurement of ON has its strengths and weaknesses. It should not be aimed to decide on one single scale which is "the best" measurement scale for ON in general but to find the best scale for each varying study purpose and condition (Table 1).

Bratman Orthorexia Test

Bratman Orthorexia Test, also referred to as Orthorexia Self-Test, was developed by Bratman and Knight, and it consists of 10 questions in dichotomous response format (Bratman 2000). Each positive answer is recorded as one point, and a higher sum score shows a higher tendency towards ON. Although the cutoff value does not have

Table 1 The scales that will be reviewed in this chapter

Name of scale	Abbreviation	Reference
Bratman Orthorexia Test	BOT	(Bratman 2000)
ORTO-15	ORTO-15	(Donini et al. 2005)
Body Image Screening Questionnaire	BISQ	(Jenaro et al. 2011)
Düsseldorf Orthorexia Scale	DOS	(Barthels et al. 2015)
Orthorexia Nervosa Scale	ONS	(Kramer 2016)
Burda Orthorexia Risk Assessment	B-ORA	(Burda 2018)
Teruel Orthorexia Scale	TOS	(Barrada and Roncero 2018)
The Barcelona Orthorexia Scale	BOS	(Bauer et al. 2019)
Orthorexia Nervosa Inventory	ONI	(Oberle et al. 2021)
Test of Orthorexia Nervosa	TON-17	(Rogowska et al. 2021a)

a valid basis, patients who score four and higher are considered to suffer from ON by Bratman. Some studies have used the BOT with a 4-point Likert scale instead of a yes/no format, to have more comparable results with other measurement tools (Meule et al. 2020). A good internal reliability was shown for BOT (Cronbach α: 0.79), but its test-retest reliability has not been measured yet. German and Swedish translations are available for the scale (Rössner 2004; Kinzl et al. 2005).

BOT is the oldest ON measuring tool available, which makes it difficult to catch up with the conceptual changes about ON. Recognizing this shortcoming, Steven Bratman updated the scale by associating it with the new diagnostic criteria, which were also set forth by him, and published ABOST (Authorized Bratman Orthorexia Self-Test) (Dunn and Bratman 2016; Rogowska et al. 2021b). The ABOST has six items instead of 10, and even one positive answer points out an increased risk of ON. One study investigated the reliability and validity of the ABOST with two answering formats (a dichotomous format and a continuous 5-point Likert scale). The latter showed a good validity and reliability, whereas the former did not meet the reliability and validity criteria (Rogowska et al. 2021b).

There has been no validity or reliability studies published regarding the ABOST yet, other than its Polish adaptation study (Rogowska et al. 2021b).

ORTO-15

ORTO-15, a 15-item questionnaire developed by Donini, is scored on a 4-point Likert scale (Donini et al. 2005). ORTO-15 uses some items of the BOT by changing the wording and adding new items to them. Therefore, there is no harm in saying that ORTO-15 was heavily inspired by the BOT. ORTO-15 has six items focusing on the cognitive factors related to eating behavior, five items related to clinical factors, and four items related to emotional factors. However, a sum score is evaluated rather than calculating separate scores for each dimension (Table 2).

Items 2, 5, 8, and 9 are scored as always 4, never 1. The rest of the items other than 1 and 13 are scored in reverse. Items 1 and 13 are scored as such: Always = 2,

Table 2 Number of questions and used Likert scale in questionnaires

Name of scale	# of questions	Likert scale
Bratman Orthorexia Test (BOT)	10	4-point
ORTO-15	15	4-point
Body Image Screening Questionnaire (BISQ)	24	5-point
Düsseldorf Orthorexia Scale (DOS)	10	4-point
Orthorexia Nervosa Scale (ONS)	47	5-point
Burda Orthorexia Risk Assessment (B-ORA)	21	4-point
Teruel Orthorexia Scale (TOS)	17	4-point
The Barcelona Orthorexia Scale (BOS)	64	Self-statement
Orthorexia Nervosa Inventory (ONI)	24	4-point
Test of Orthorexia Nervosa (TON-17)	17	5-point

Often = 4, Sometimes = 3, and Never = 1. Higher sum scores indicate a lower tendency towards ON behavior (Donini et al. 2005).

Creators of the ORTO-15 have also attempted to set a cutoff value for ORTO-15, trying out three different values (<35, <40, and <45). They observed increasing sensitivity and decreasing specificity and efficacy with increasing threshold values, so much that at the threshold value of 45, efficacy of the test was as low as 37.4%, which made it unreliable. However, when the threshold was set at 35, the sensitivity and positive predictive value were 0%. Therefore, the threshold was set at 40, where it confirmed substantial validity. A very problematic issue with ORTO-15 and its threshold is that its predictive capability covers healthy eating behavior but fails to differentiate any obsessive traits (Donini et al. 2005). The use of any cutoff values was later criticized heavily for resulting in erroneous inferences, and it was suggested that researchers should not utilize cutoff values and should not report prevalence rates with regard to these cutoff values (Rogoza and Donini 2021). This criticism was based on the many unrealistic reports of ON prevalence across different populations (many of them higher than 50%, one study even 88.7%) (Aksoydan and Camci 2009; Ramacciotti et al. 2011; Souza and Rodrigues 2014; Segura-Garcia et al. 2015). Although ORTO-15 is the most widely used measurement tool in ON research and has the most language adaptations, such as Turkish, Russian, Arabic, Polish, French, Greek, German, Spanish, and Italian (Arusoğlu et al. 2008; Alvarenga et al. 2012; Brytek-Matera et al. 2014; Missbach et al. 2015; Stochel et al. 2015; Parra-Fernandez et al. 2018; Babeau et al. 2020; Haddad et al. 2020; Gonidakis et al. 2021; Zemlyanskaya et al. 2021), its validity and reliability are very questionable. In fact, many studies reported very low internal consistency reliability and poor validity for ORTO-15 (Missbach et al. 2015; Heiss et al. 2019; Mitrofanova et al. 2021). In one study ORTO-15 had a Cronbach α value of 0.23, whereas a limited version of it (ORTO-11) had 0.74 (Roncero et al. 2017). The language adaptation studies have extracted items that had low factor loadings, and this resulted in different questionnaires with varying numbers of items included, such as ORTO-11, ORTO-9, and ORTO-6. Two recent studies addressed the factor stability issue of the ORTO-X's available and proposed two new scales: ORTO-7

and ORTO-R. Moller et al. suggested that ORTO-15, ORTO-11, and ORTO-9 have poor model fits and developed a new version consisting of seven items using exploratory factor analysis and confirmatory factor analysis in combination. Authors have reported that ORTO-7 has a strong, stable factor structure in contrast to the previous versions (Moller et al. 2019). Another revised version of ORTO-15 is the ORTO-R, which was developed using the very original data of Donini. ORTO-R also addresses the same problem, namely, the factorial instability of ORTO-15. It consists of six items, none of the items are coded reversely, and a higher score indicates a higher tendency of ON (Rogoza and Donini 2021). All versions of ORTO-15 are still being widely used in the scientific literature across various populations such as university students, athletes, artists, patients who suffer from other eating disorders, etc.; yet it is fair to suggest the use of the two newly proposed versions (ORTO-R and ORTO-7) in forthcoming research instead, which have proven factorial stability (Vuillier et al. 2020; Özdengül et al. 2021; Rodgers et al. 2021; Hallit et al. 2021b).

Body Image Screening Questionnaire (BISQ)

In 2011, the Body Image Screening Questionnaire was first used by Jenaro et al. in Spain (Jenaro et al. 2011). According to this study conducted with 395 participants, results show that the questionnaire could be used in the assessment of eating disorders such as orthorexia, anorexia, obesity, and bigorexia. Only Romanian adaptation of the mentioned assessment technique was made. This study, in which a 24-item version was applied to 156 participants, was used to evaluate the psychometric properties of the scale and reported adequate internal consistency (Tomsa et al. 2012). This questionnaire was originally made in Spanish. There is no English adaptation study. Therefore, there are very few original studies on ON assessment using this scale in the literature. Although its validity and reliability have been demonstrated, when using BISQ in your research, it should be kept in mind that there is very limited literature to compare the results. Also, BISQ's test-retest reliability has not been examined yet (Table 3).

Düsseldorf Orthorexia Scale (DOS)

Düsseldorf Orthorexia Scale consists of ten items, which are answered on a 4-point Likert scale: This does not apply to me = 1, This does rather not apply to me = 2, This does somewhat apply to me = 3, and This applies to me = 4. It was originally developed in German. It shows a good internal consistency with a Cronbach α value of 0.84 (Barthels et al. 2015). As it has a much better internal consistency, some authors suggest the use of DOS instead of ORTO-15 (Meule et al. 2020). It has Chinese, Polish, English, Italian, French, and Arabic language adaptation available (Chard et al. 2019; He et al. 2019; Brytek-Matera 2021; Cerolini et al. 2021; Hallit et al. 2021a; Lasson et al. 2021).

Table 3 Evaluation standard and Cronbach α values of questionnaires

Name of scale	Evaluation standard	Cronbach α value
Bratman Orthorexia Test (BOT)	4 or higher	0.79
ORTO-15	Higher sum lower tendency	0.23
Body Image Screening Questionnaire (BISQ)	Higher sum score higher tendency	Not found
Düsseldorf Orthorexia Scale (DOS)	Higher sum score higher tendency	0.85
Orthorexia Nervosa Scale (ONS)	Higher sum score higher tendency	.
Burda Orthorexia Risk Assessment (B-ORA)	Higher sum score higher tendency	0.97
Teruel Orthorexia Scale (TOS)	Higher sum score higher tendency	0.87
The Barcelona Orthorexia Scale (BOS)	Higher sum score higher tendency	Not found
Orthorexia Nervosa Inventory (ONI)	Higher sum score higher tendency	0.84
Test of Orthorexia Nervosa (TON-17)	61 or higher score higher tendency	Not found

Orthorexia Nervosa Scale (ONS)

Orthorexia Nervosa Scale was developed by Kramer in 2016, and it was further updated in 2019 (Kramer 2016, 2019). ONS consists of 47 items, answered on a 5-point Likert scale where 1 = Strongly Disagree, 2 = Disagree, 3 = Neither Agree or Disagree, 4 = Agree, and 5 = Strongly Agree. The purpose of the scale is to accurately measure ON in the US sample, as most of the other measurement tools are valid for European populations. Its psychometric properties were studied by Conrad, suggesting a two-factor solution after an exploratory factor analysis: behavioral dysfunction and social dysfunction. The scale has a high internal consistency (Conrad 2019).

Burda Orthorexia Risk Assessment (B-ORA)

BORA, developed by Lilo Burda, explores orthorexic tendencies. It consists of 21 questions. All questions are scored based on a 4-point Likert scale (strongly agree = 1, somewhat agree = 2, somewhat disagree = 3, strongly disagree = 4). The highest total score attainable is 84 and the lowest 21, with a higher score indicating less orthorexic tendencies. It has a good internal consistency (Cronbach $\alpha = 0.97$), which is a property that more commonly used scales often lack (Burda 2018). However, it does not have a test-retest reliability result. It was developed among

college students and has not yet been validated among other populations or cultures. Also, the lack of original studies making use of BORA is a major disadvantage when it comes to comparing your results.

Teruel Orthorexia Scale (TOS)

Teruel Orthorexia Scale, the first version of which was developed in Spanish by Barrada and Roncero in 2018, is a promising tool for distinguishing healthy orthorexia and orthorexia nervosa (Barrada and Roncero 2018). TOS is used to illuminate the relationship between psychological constructs and disorders like obsessive-compulsive disorder symptoms, negative affect, and perfectionism with orthorexia nervosa. The questionnaire includes 17 items rated on a 4-point Likert scale with Cronbach α value of 0.87 (Barthels et al. 2019). The first nine items question the healthy orthorexia and orthorexia nervosa, whereas the last eight items question the pathological dimension of orthorexia nervosa. Adaptation studies have been carried out in several languages due to its distinctive features (Chace and Kluck 2021; Mhanna et al. 2021; Roberto da Silva et al. 2021). The fact that the English adaptation study has been carried out might accelerate the research using TOS in the coming years. In the English adaptation study, with the concerns of poor differentiation, one item was extracted. The modified TOS showed a good model fit and was accepted; therefore, the English version of TOS is called TOS-16 instead of TOS-17 (Chace and Kluck 2021) (Table 4).

Table 4 Language revisions of questionnaires

Name of scale	Language revisions
Bratman Orthorexia Test (BOT)	German, Swedish
ORTO-15	Turkish, Russian, Hungarian, Arabic, Polish, French, Greek, German, Spanish, and Italian
Body Image Screening Questionnaire (BISQ)	Spanish, Armenian, no English ver.
Düsseldorf Orthorexia Scale (DOS)	Chinese, Polish, English, Italian, French, and Arabic
Orthorexia Nervosa Scale (ONS)	No other version
Burda Orthorexia Risk Assessment (B-ORA)	No other version
Teruel Orthorexia Scale (TOS)	English
The Barcelona Orthorexia Scale (BOS)	English, Spanish
Orthorexia Nervosa Inventory (ONI)	Turkish
Test of Orthorexia Nervosa (TON-17)	No other version

The Barcelona Orthorexia Scale (BOS)

The Barcelona Orthorexia Scale was developed using the Delphi method. 58 experts from 17 different countries participated in the study, and an initial item pool consisting of 105 items was evaluated in 3 rounds. Finally, 64 items were obtained. Items are grouped into 6 domains: cognitive domain (14 items), emotional domain (16 items), behavioral domain (14 items), negative consequences – health (6 items), impairment in social or academic functioning (9 items), and differential diagnosis (5 items). These items are selected due their content validity according to expert opinion, but they lack any study on their psychometric properties. Therefore these selected 64 items are not the final version (Bauer et al. 2019). BOS has two versions in Spanish and English. It is a very promising measurement tool for ON, which is currently under development.

Orthorexia Nervosa Inventory (ONI)

ONI consists of 24 items, of which 9 assess behaviors and preoccupation with healthy eating, 10 assess physical and psychosocial impairments, and 5 assess emotional distress. Items are scored on a 4-point Likert scale (very true = 4, mainly true = 3, slightly true = 2, not at all true = 1). Higher scores indicate a higher tendency towards ON. One of the strengths of ONI is that it has a very high internal consistency (Cronbach $\alpha = 0.94$) and 2-week test-retest reliability (ICC = 0.91) (Oberle et al. 2021). What makes ONI further advantageous is that it takes the physical impairments associated with ON into account. Although these impairments are agreed to be a key component of the disease, none of the previous measurement tools evaluated this aspect.

On ONI, items 10, 24, 12, 5, 19, 14, 3, 20, 7, and 16 belong to the "impairments" factor; items 17, 11, 8, 6, 22, 8, 15, 4, and 2 belong to the "behaviors" factor; and items 9, 13, 1, 23, and 21 belong to the "emotions" factor.

ONI already has a Turkish language adaptation (Kaya et al. 2021). As it is a very newly developed scale, it certainly lacks results in different populations and cultures.

Test of Orthorexia Nervosa (TON-17)

TON-17, which was initially TON-40 but was reduced to TON-17 as a result of the structural analysis, was developed in response to the need for a reliable and new method to measure ON emphasized in the literature (Valente et al. 2019; Rogowska et al. 2021a). It consists of 17 items, in 3 subscale factors (control of food quality, fixation of health and healthy diet, and disorder symptoms). Each item is answered on a 5-point Likert scale and scored as follows: 1 = Strongly disagree, 2 = Rather disagree, 3 = Undecided, 4 = Rather agree, and 5 = Strongly agree.

The authors suggest the use of a cutoff value of 61 points as an indicator for high ON risk. TON-17 currently has English and Polish versions, and this promising measurement tool for ON requires to be used in different populations and cultures.

In summary, there are many options for researchers and clinicians when it comes to assessing ON. But it should be kept in mind that most measurement tools fall somewhere in between measuring "healthy eating" and "being obsessed with healthy eating." This is especially important when using the older scales. Also, it is very interesting to see that the most commonly used tools have the poorest validity and reliability values among all. Researchers and clinicians should pay attention to the newly developed measurement tools and always make sure they check the psychometric properties of the tools they choose to apply.

Application to Other Eating Disorders

In this chapter, we have reviewed questionnaires that can be used to evaluate orthorexia nervosa. However, a similar approach is also widely used when assessing all eating disorders. For example, scoring 2 or higher in the SCOFF questionnaire (which is an acronym for Sick, Control, One, Fat, Food) raises suspicion of anorexia nervosa or bulimia. It consists of five simple questions answered with yes or no. Being developed in 1999, it has been adapted to more than 10 languages and was used among various populations, such as children, adolescents, athletes, depressed patients, and so on (Morgan et al. 1999). An even older questionnaire is the Dutch Eating Behaviour Questionnaire, which consists of 33 items and measures 3 different psychologically based eating behaviors: emotional eating, externally induced eating, and restrained eating (Wardle 1987; Bozan et al. 2011). Similarly, EDE-Q (Eating Disorders Examination Questionnaire) is a 36-item questionnaire that assesses the specific psychopathology of eating-disordered behavior (Mond et al. 2004). The Eating Disorders Inventory (EDI) and EDI-2, which is an adapted version of EDI, are also widely used self-reported measures of symptoms of eating disorders (Garner et al. 1983). A more recent questionnaire developed to examine eating disorders is the Survey for Eating Disorders (SEDs), which is another valid and reliable tool with a high positive predictive value. In summary, questionnaires have been widely used for decades in the evaluation of all eating disorders and will continue to be used due to their advantages such as ease of application, objective evaluation, and allowing for comparison of results.

Mini-Dictionary

- **Validity**: The degree to which a construct is accurately measured.
- **Reliability**: The consistency of a measure. It includes aspects such as internal consistency and stability.

- **Internal consistency**: The degree to which all items included in a test are consistent with each other. To test internal consistency, the correlation is checked one by one between all the items.
- **Stability**: The correlation between the answers of the same subject to the measure at two different times. Also called test-retest reliability.
- **Cronbach α value**: Indicates the level of internal consistency (shows excellent reliability when >0.90).

Key Facts of Assessing Orthorexia Nervosa by Questionnaires

- There are some statistical methods to make sure that questionnaires successfully measure what they aim at. With these methods, the validity and reliability of the questionnaires can be determined. If the questionnaires are used in research without paying attention to these features, it can lead to erroneous inferences and even misdiagnosis.

Summary Points

- There is an ever-growing research interest in ON; most of it focused on measuring ON accurately.
- There are numerous available scales to evaluate orthorexia nervosa.
- It is necessary to pay attention to their psychometric properties when deciding which one to use in your research or clinical practice.
- Some scales were developed before a consensus was reached on the diagnostic criteria of the disease; therefore, they do not question all the clinical features of ON.
- Some of the newly developed scales are very promising as they are based on the conceptual background of the disease, question all clinical features, and have a high validity and reliability.

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The Eating Disorder Quality of Life (EDQoL) Scale 72

Methods and Applications

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Contents

Introduction 1452
Quality of Life in Eating Disorders 1453
Applications to Other Eating and Feeding Disorders 1455
Comorbidities 1455
Treatments and Quality of Life 1456
The Eating Disorder Quality of Life (EDQoL) Questionnaire 1457
The EDQoL Domains 1457
Interpersonal Domain 1458
Application to Other Areas 1458
Future Directions 1459
Mini-dictionary of Terms 1460
Key Facts on Quality of Life in EDs 1460
Summary Points 1460
References 1461

Abstract

Patients with an eating disorder present a severe reduction of their quality of life (QoL) during the acute phase, which could also impact their treatment outcome. Different studies have pointed out the role of QoL in both physical and psychological well-being, and slight differences have been pointed out between eating disorder diagnoses, showing a transdiagnostic impairment in this specific aspect of patients' lives. Different domains have been included in the evaluation of the QoL: psychological, physical, cognitive, financial, work/school, and

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interpersonal. The relevance of the interpersonal domain is profoundly discussed in the chapter and how it has been included in the original version of the EDQoL questionnaire. Despite the role of this aspect in the patients' lives, the literature's evidence is limited, and possible future directions are discussed.

Keywords

Quality of life · Eating disorder · Health-related quality of life · Anorexia nervosa · Bulimia nervosa · Binge eating disorder · Interpersonal domain

Abbreviations

ED	Eating disorder
EDQoL	Eating disorder quality of life
HRQoL	Health-related quality of life
QoL	Quality of life

Introduction

In recent decades, eating disorders (EDs) have presented an increased epidemiological impact in young women and girls and a progressively decreased age of onset (Favaro et al. 2009). Recent evidence has also underlined the underestimation of the incidence of EDs in males, especially during adolescence, when one-third of patients are boys (Murray et al. 2017). These psychiatric disorders have consistent effects on physical, psychological, and social facets of life, especially given their tendency to evolve into chronic disorders or partial recovery, with possible relapses (Steinhausen 2002, 2009). These physical, mental, and social impairments can be long-lasting and evolve into severe difficulties in different facets of patients' lives. The medical complications of EDs have an impact on almost all organ systems. These complications are life-threatening and potentially irreversible, and they are consequences of starvation, binge eating, or purging behaviors (Rome and Ammerman 2003).

In recent decades, researchers and clinicians have moved from measures of psychopathology to looking at the impairment caused by disorders, taking into account the change of perspective suggested by patients with a long history of ED. Indeed, due to the possible roles of EDs in the everyday lives of patients, growing importance has been placed on the measurement of quality of life (QoL). Quality of life is defined as a person's perception of their position in life regarding their goals, expectations, and concerns and their quantitative evaluation of how they experience their life overall (Engel et al. 2009). The evaluation of QoL in ED patients provides indicators of their satisfaction with their lives and recovery levels (Mitchison et al. 2016). To allow the evaluation of the effects of EDs on patients' lives and the effects of psychosocial treatments, specific self-report questionnaires about health-related quality of life (HRQoL) have been validated. These instruments allow clinicians and researchers to obtain standardized data for comparison and

objective evaluation. Dedicated questionnaires also allow to find out aspects specifically linked to the symptomatology of a disorder, increasing data robustness.

Quality of Life in Eating Disorders

Even if several papers focused on QoL in EDs, the literature still seems very limited, with a predominance of cross-sectional approaches and few speculations about specific aspects linked to QoL. In a comprehensive overview, QoL appears to be compromised in EDs. Still, it is also significantly related to the different levels of insight of the patients about the existing impacts of ED symptoms on their lives.

Looking at the specific effects of EDs on the QoL of patients, a systematic review of the existing literature has suggested that there are no marked differences between diagnoses in the impairment of QoL of ED patients (Ágh et al. 2016). This evidence corroborates the results of a previous meta-analysis that showed a substantial decrease of the QoL throughout the entire ED spectrum, regardless of diagnosis (Winkler et al. 2014). The literature also underlines the shared increased healthcare system use and costs compared to controls (Agh et al. 2015). However, these results have to be taken with the consideration that the number of studies is limited and different questionnaires have been applied, with a possible bias effect on results. Moreover, ED patients – especially in patients with anorexia nervosa (AN) – have shown the presence of a reduction of the insight of the disorder. This aspect could bias the results of self-reported questionnaires due to the absence or the reduction of the patient's awareness of the negative impact of their health status (Mond et al. 2005). Indeed, in AN patients, momentary ecological assessments have found a robust relationship between ED symptomatology and QoL, showing a specific role for binge eating behaviors in worsening the perception of their life quality (Mason et al. 2018). Moreover, analysis of the published studies pointed out the need for a distinction in the binge eating spectrum between patients with bulimia nervosa (BN) and binge eating disorder (BED) due to the presence of obesity and its consequent comorbidities (Ágh et al. 2016). Looking into different domains of the QoL evaluation, patients with AN and BN have shown higher scores on social well-being (van Hoeken and Hoek 2020), with patients with AN reporting the highest impairment (Meneguzzo et al. 2020). Another interesting aspect that previous reviews have highlighted is the possibility of a reduced impact on QoL in patients with a diagnosis that do not meet the diagnostic criteria, possibly due to a modest distress (Baiano et al. 2014).

Looking at the literature, robust evidence has suggested the use of ED-specific questionnaires for the evaluation of QoL over generic ones – like the Short-Form Health Survey 36 (SF-36) – due to the possible underestimation of specific behaviors or thoughts that could have relevant roles in the assessment of self-perceived QoL, for example, in AN patients (Muñoz et al. 2009) (Table 1).

Regarding the interpersonal effects of EDs, only one study has evaluated the people who lived with patients (de la Rie et al. 2005). Caregivers and relatives of ED patients reported decreased QoL and a reduction in their psychological well-being,

Table 1 Summary of evidence on quality of life

	Global QoL	Psychological domain	Physical/ cognitive domain	Financial-work/ school domains	Interpersonal/ social domain
Anorexia nervosa	Impaired compared to general population and other EDs. Insight might have a specific role in the reliability of the results	No clear differences across ED spectrum	Impaired compared to general population and other EDs	Impaired compared to general population and to BN, BED, and OSFED	Impaired compared to general population. Some evidence of worse score than patients with BN
Bulimia nervosa	–	No clear differences across ED spectrum	–	–	Impaired compared to general population
Binge eating disorder	–	No clear differences across ED spectrum	Evidence of worse scores due to medical comorbidities	–	No clear evidence of a strong impairment of social domain
Other eating and feeding disorders	Reduced when compared to general population. Little evidence of a reduced burden than other EDs	No clear differences across ED spectrum	–	–	–

with the increase of family conflicts after the development of the disorder by their relative. The QoL of patients' relatives is a less explored aspect of QoL and EDs, even if relatives and caregivers of patients with an ED could have an essential role in treatments (de la Rie et al. 2005).

An interesting relationship between QoL and psychological distress was found in a community-based study that pointed out the bidirectional relationships between QoL and ED symptoms (Mitchison et al. 2015). The authors found that lower levels of QoL and higher psychological distress predict increases in ED symptomatology after 9 years from the first evaluation. Moreover, ED symptoms predict a reduction in QoL at the follow-up. These bidirectional relationships could help clinicians and researchers to move away from symptom-centered approaches in the evaluation of QoL. Indeed, this study helps to point out the complexity of the relationships between QoL and psychopathology and could also suggest the need for more studies

focused on possible latent variables. Moreover, these data reinforce the idea that specific interventions are needed for the improvement of QoL.

Applications to Other Eating and Feeding Disorders

Looking at the existing literature, few data is available about other eating or feeding disorders, mainly because these diagnostic categories were introduced with DSM-5. A reduction of the QoL in individuals with these diagnoses is linked to the presence of a psychiatric or psychological condition, but the levels of burden are still not clear. Indeed, going beyond merely considering them as one non-specified group, we may find different facets of impaired QoL, and, for this reason, future studies should consider this aspect in their research planning. Here is a summary of the preliminary evidence in the literature with a comparison between diagnoses, if available.

People with avoidant/restrictive food intake disorder (ARFID) have reported a reduction of their QoL compared to the general population, but with a reduced compromission of the physical domain if compared to patients with BED (Hay et al. 2017). Pica may have a negative effect on the QoL of the patients and parents, both from stigmatization that may occur and from clinical effects related to the consumption of toxic, contaminated, or inedible substances (Leung and Hon 2019; Liu et al. 2021). However, no study has been specifically conducted for the evaluation of QoL in patients with pica. Rumination disorder impaired QoL of patients due to the effects of their symptomatology on social activities, interpersonal involvement, school absence, and physical health (Mousa et al. 2014). Individuals with purging disorder are characterized by an impairment of physical, psychological, and social domains (Forney et al. 2021). However, no studies are available with a direct comparison of individuals with purging disorder and other EDs like anorexia or bulimia nervosa (Smith et al. 2017). Individuals with night eating syndrome may present an impaired quality of life due to the disruption of the circadian circle, with effects on mood and perceived stress (Vander Wal 2012). The QoL of these patients is compromised, and it has an effect on their ability to reduce their weight during treatment (Calugi et al. 2009). Finally, also individuals with orthorexia nervosa showed an impairment of their QoL in its physical and environmental domains, but the results need confirmatory studies (Strahler and Stark 2020; Sfeir et al. 2021).

Comorbidities

In recent years, there has been a growing concern about pro-eating disorder website communities, which have been cited as possible reinforcing factors in the development and maintenance of EDs (Peebles et al. 2012). In evaluating users of these sites, authors have found a relationship between time spent online in these communities and decreases in QoL and increases in dysfunctional eating behaviors even in individuals without an ED diagnosis according to international criteria. These results

could underline the role of interpersonal reinforcement in EDs, and this is a potential aspect that might be evaluated in future studies, looking for potential ways to improve patients' QoL.

Medical comorbidities like obesity in BED patients have been found to be negative factors for QoL, suggesting the possible role of psychological elements like social exposure or depression in addition to physical factors (Singleton et al. 2019). Moreover, it has been demonstrated that the presence of irritable bowel syndrome, but not functional gastrointestinal-like disorders, is highly related to the QoL reported by patients, with a significant decrease in QoL correlating with increases in intestinal symptomatology (Abraham and Kellow 2011). Similarly, psychiatric comorbidities like obsessive-compulsive behaviors have shown a moderate association with poorer QoL in AN (Young et al. 2018), as well as emotional distress in BN (Ágh et al. 2016).

Looking at demographic data, sex has been found to be a moderator for the relationship between QoL and body objectification (Sanftner 2011). Still, no studies are available with sexual orientation as a variable. Moreover, no study has looked at the possible changes in QoL in different stages of life. So little evidence is available about the demographic aspect linked to QoL.

Treatments and Quality of Life

Looking at the effects of treatments in improving perceived QoL, studies reported that current psychological approaches had modest effects in the improvement of the perceived QoL in ED patients (Linardon and Brennan 2017), and their effects are similar to other psychiatric conditions. Indeed, cognitive-behavioral approaches are tailored to improve eating psychopathology more than QoL, and this aspect should be improved in future studies (Linardon and Brennan 2017). Inpatient treatment has been found to be effective in improving the HRQoL scores in ED patients (Weltzin et al. 2015), but the number of studies is limited, and there is no definitive evidence (Linardon and Brennan 2017). Indeed, other studies have pointed out that dysfunctional elements persist after treatment in patients with EDs despite improving the perceived QoL (Padierna et al. 2000).

In severe and enduring patients with AN, QoL has been the critical element of several studies about its role in treatment approaches, especially regarding the idea that it should focus on the improvement of long-enduring disorders. Study results have reinforced this position, showing that improving patients' QoL after a long duration of the disorder is also linked to weight gain and reductions in ED symptomatology (Bamford et al. 2015). The existing connection between QoL, eating psychopathology, and weight underlines that these three elements could not be treated alone, especially in patients with a long history of disorder.

The Eating Disorder Quality of Life (EDQoL) Questionnaire

One of the first and most used HRQoL questionnaires is the eating disorder quality of life (EDQoL) scale, constructed and validated for the first time by Engel and colleagues in 2006 with the goal of introducing in the literature a validated instrument focused on the domain of QoL as it relates to the clinical impairments of patients (Engel et al. 2006). Previous studies had been conducted with generic QoL questionnaires, obtaining data with smaller effect sizes and fewer specifically related results. An interesting aspect of the transdiagnostic nature of the EDQoL, based on the theoretical perspective on EDs, is that for all the ED diagnoses, clinicians are allowed to evaluate patients across time and determine the diagnostic changes that are common in patients' lives. The EDQoL has demonstrated good psychometric properties with test-retest validity and sensitivity between patients and controls in different languages and ages. In addition, it shows a robust correlation with other psychological constructs more focused on psychosocial impairment in areas like self-perception, cognitive functioning, interpersonal functioning, and work performance. The questionnaire has been translated into different languages, including Italian and German, and all the translations have maintained good psychometric proprieties (Tagay et al. 2010; Meneguzzo et al. 2020).

The EDQoL Domains

Subjective QoL can be reported as a global measure of well-being or satisfaction, or it can be broken down into distinct domains (e.g., psychological well-being). In the development of the EDQoL domains, researchers decided to evaluate different possible domains due to the complexity of the QoL domain in patients with ED (Engel et al. 2006). The authors of the original EDQoL scale pointed out the possible areas where ED patients could be more impaired and produced a large number of items (Engel et al. 2006). The statistical validation of the scale produced four domain areas: psychological, physical/cognitive, financial, and work/school. The authors also included social and legal domains in the original version of the questionnaire, but data did not support their inclusion in the final questionnaire. This aspect could be linked to the items included in the original questionnaire, as well as in the participants of the original evaluation. Indeed, authors of different QoL scales for ED patients have pointed out the possible role of interpersonal domain in patients and included specific items in their questionnaire (Padierna et al. 2000).

Regarding the different domains, the psychological subscale of the EDQoL is focused on emotional states and feelings related to the self and one's everyday activities. The physical/cognitive subscale is related to the physical and cognitive effects that EDs could have on patients, investigating the presence of symptoms like reduced attention or concentration and headaches or weakness. The financial domain evaluates the presence of economic effects of EDs in patients' lives, which could be due to increases in spending or reductions in income. Finally, the work/school domain evaluates the effects of EDs on daily activities. In the Italian version of the

EDQoL (Meneguzzo et al. 2020), the authors increased the number of items on the physical/cognitive subscales, including, for example, teeth pain or problems, constipation, and weight. The result showed good reliability and psychometric values. Therefore, they suggest that items should also be included in different language versions of the questionnaire.

Some differences have been found looking at the impairment of the QoL domains across the ED spectrum. No differences emerged between diagnoses as regards psychological impairment, while in physical/cognitive and financial domains, the results showed worse scores in AN compared to BN, BED, and OSFED (Meneguzzo et al. 2020).

Interpersonal Domain

The interpersonal domain was included in the Italian translation of the EDQoL questionnaire (Meneguzzo et al. 2020) due to the need to evaluate the social interactions of patients, their effects on eating psychopathology, and their role in perceived QoL. The interpersonal domain has a specific role in the development and maintenance of ED psychopathology due to the role of negative social evaluation reported by patients and the effects on self-evaluation (Rieger et al. 2010). Patients reported social isolation linked to interpersonal difficulties. Dysfunctional behaviors could increase the disruption of social connections (Björck et al. 2003; Ivanova et al. 2015; Treasure et al. 2020).

For this goal, questions about interpersonal difficulties were elaborated on using ED research and clinical experts and then rated by three experts to find a consensus between ED researchers. The new items were then included in the Italian EDQoL and validated using an exploratory factor analysis approach. The result was a valid questionnaire with robust psychometric values that showed good convergence with other well-known questionnaires used for the evaluation of different life aspects like the clinical impairment assessment questionnaire (Bohn et al. 2008). The results of the first Italian application of the new EDQoL were the presence of an impaired QoL linked to the interpersonal domain, with AN patients reporting the highest (worst) scores.

The Italian authors have proposed an English version of the new EDQoL questionnaire. However, validation has not yet been performed (Meneguzzo et al. 2020).

Application to Other Areas

The EDQoL has assumed a relevant role in evaluating the ED burden, showing its centrality in clinical and health psychology as one of the main elements of the individual's well-being [1]. Today, the recent literature has pointed out new evidence

of the existing connections that may be pointed out in patients and that may have a relevant role in the treatment pathways.

Recently, in a large clinical sample of individuals with EDs, researchers have evaluated the connection between QoL and the insight of the disorder as a relevant role in the self-assessment of ED psychopathology, showing different evaluations between patients and clinicians [2]. There is still something missing in ED psychopathology that QoL might allow us to evaluate [3]. These data underlined the possible role of QoL in the definition of recovery in ED and the need for a standardized approach to QoL in the definition of treatment pathways. Indeed, the connection between QoL and health service use has already been reported, showing that even before an official ED diagnosis, patients reported a decreased QoL and higher use of services, with more drug prescriptions and medical consultations [4]. However, the literature needs specific studies about the economic and organizational aspects linked to QoL, and EDQoL may be the specific tool that could be applied due to the presence of a specific subscale.

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Future Directions

The literature about QoL in patients with ED is still insufficient. More studies are needed to evaluate the relationships between these psychological constructs and different psychopathological aspects like depression, anxiety, cognitive functioning, and specific eating behaviors. The literature has proposed QoL as a possible "back-door" approach in order to improve ED symptomatology and promote recovery in patients who did not respond to other treatment approaches by increasing insight into the effects of the disorder (Mitchison et al. 2016). However, clinical data on this hypothesis is still missing.

Mini-dictionary of Terms

- **Financial-work/school domains**. These are two different domains that are connected. Financial domain evaluates the loss of money, while the work/school domain evaluates the adverse effects of ED on everyday activities.
- **Health-related quality of life (HRQoL)**. The specific evaluation of the own QoL related to mental and physical health.
- **Interpersonal domain**. This domain evaluates the presence of social connections with friends, fiancé, and sexual experiences.
- **Physical/cognitive domain**. It is related to all the physical effects that EDs could cause, as well as to mental performances. In the statistical validation of the EDQoL, cognitive and physical aspects fall in the same domain, corroborating a psychosomatic approach to these aspects.
- **Psychological domain**. It is related to all the ideas and concerns due to the eating psychopathology that could be negatively affected in patients. It is related to past, present, and future scenarios that could be affected by specific psychopathology.
- **Quality of life (QoL)**. The degree to which individuals perceive themselves in relationship with their goals, standards, concerns, and expectations.

Key Facts on Quality of Life in EDs

- Despite the evidence that the majority of the patients have an impaired QoL, studies are still limited and with preliminary results.
- Some studies reported that patients with AN have the worst scores in QoL, and other studies reported no differences across diagnoses.
- Patients with subthreshold ED diagnosis report less impaired QoL.
- Comorbidities and insight have specific roles in the evaluation of QoL.

Summary Points

- Patients with EDs have a reduced quality of life versus their healthy peers.
- Psychological, physical, cognitive, financial, and work/school domains could be compromised by an eating disorder.
- The interpersonal domain should be included in the evaluation of the health-related quality of life of patients due to its role in the development and maintenance of the disorder.
- The evaluation of the effects of treatments on patients' QoL is still preliminary.
- More studies are needed to understand better the possible role of quality of life in treating eating disorders.

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Binge Eating Scoring Systems

73

Applications to Bariatric Surgery

Natália Luiza Kops and Rogério Friedman

Contents

Introduction 1466
Bariatric Surgery and the Prevalence of Disorders 1467
BED Diagnosis 1468
Effect of BED in Pre- and Postsurgery Patients 1468
Types of Bariatric Surgery and the Effect on Eating Behavior 1469
Binge Eating Assessment in Bariatric Patients 1471
Pros and Cons of Instruments for the Assessment of Eating Disorders 1473
Applications to Other Areas 1474
Mini-Dictionary of Terms 1475
Key Facts of Scoring Systems for Bariatric Patients 1475
Summary Points 1475
References 1476

Abstract

Bariatric surgery limits the amount of food consumed in a short period of time, and, since this is one of the diagnostic criteria for binge eating disorder (BED), the experience of loss of control (LOC) continues to be reported postoperatively. Therefore, the tools and questionnaires used to assess binge eating in these patients need to be discussed. Data regarding the presence of eating disorders in the postoperative period are scarce, due to lack of comprehensive follow-up data, screening, or standardization in the evaluation of these comorbidities. The chapter aims to discuss binge eating scoring systems in patients seeking or undergoing bariatric surgery.

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Keywords

Binge eating · Binge eating disorder · Appetite disorder · Feeding and Eating Disorders · Bariatric surgery · Bariatric medicine · Baseline survey · Surveys and Questionnaires · Impulsive behavior

Abbreviations

AgRP	Agouti-related protein
BED	Binge eating disorder
BES	Binge Eating Scale
BMI	Body mass index
DSM-5	Diagnostic and Statistical Manual of Mental Disorders
EDE	Eating Disorder Examination
EDE-BSV	Eating Disorder Examination-Bariatric Surgery Version
GLP-1	Glucagon-like peptide-1
LABS	Longitudinal Assessment of Bariatric Surgery
LAGB	Laparoscopic adjustable gastric band
LOC	Loss of control
LSG	Laparoscopic sleeve gastrectomy
NPY	Neuropeptide Y
POMC	Pro-opiomelanocortin
QEWP-R	Questionnaire on Eating and Weight Patterns-Revised
RYGB	Laparoscopic sleeve gastrectomy
TFEQ	Three-Factor Eating Questionnaire

Introduction

The global prevalence of obesity has tripled in more than 70 countries since 1975, and it is projected to continue increasing ("obesity and overweight" n.d.). Clinically severe obesity has increased at a more pronounced rate than less severe obesity. More severe forms of obesity represent a great risk for noncommunicable diseases, including approximately 200 comorbidities such as type 2 diabetes, hypertension, heart disease, sleep apnea, osteoarthritis, and several forms of cancer (Apovian 2016). Individuals with body mass index (BMI) $\geq$ 45 kg/m^2 show a decrease in life expectancy and an increase in mortality from cardiovascular causes ("Associação Brasileira para o Estudo da Obesidade e da Síndrome Metabólica Diretrizes brasileiras de obesidade 2016/ABESO - Associação Brasileira para o Estudo da Obesidade e da Síndrome Metabólica. – 4.ed. - São Paulo, SP" n.d.).

Obesity is a complex whole-body disease that involves the brain, gut, hormones, and emotions. Finding personal strategies that unlock the root causes of obesity and finding the path to sustainable health is crucial for long-term success of weight loss. The treatment must necessarily promote healthy lifestyle behaviors, and, in individual cases, the association of pharmacotherapy can be adopted. However, when these

measures do not imply improvement of severe obesity and associated diseases, bariatric surgery is a consistent option ("Associação Brasileira para o Estudo da Obesidade e da Síndrome Metabólica Diretrizes brasileiras de obesidade 2016/ ABESO – Associação Brasileira para o Estudo da Obesidade e da Síndrome Metabólica. – 4.ed. – São Paulo, SP" n.d.).

Concomitantly with the increase in obesity, the number of bariatric surgeries also increased (Ramos et al. 2019.). There has been an overall increase of approximately 60%, since 2011, in the number of metabolic and bariatric procedures (English et al. 2020). The surgery can lead to weight loss on average 26 kg greater than nonsurgical treatment (Finkelstein et al. 2009). However, the outcomes, although expressive, are not universal, varying between patients and types of surgical procedures.

Bariatric Surgery and the Prevalence of Disorders

Symptoms of stress, anxiety, depression, nervousness, and emotional problems are common in patients with obesity. There are strong associations between obesity and a range of mental disorders, such as depressive and bipolar disorders, schizophrenia, and binge eating disorder (BED) (American Psychiatric Association 2013), especially in those undergoing bariatric surgery (Horvath et al. 2015; Sarwer et al. 2021). However, the relationship between psychopathologies before bariatric surgery and postoperative results is less robust (Dawes et al. 2016).

Mood and substance use disorders, such as binge eating, share common characteristics of impulsivity. That is, the inability to inhibit automatic behavior and the tendency to discount future consequences in favor of immediate results (Sarwer et al. 2021). Lack of control can reduce the ability to inhibit automatic behavior (such as the consumption of highly palatable foods) and may increase preference for immediate rewards (as a healthier option) affecting the results of bariatric surgery (Sarwer et al. 2021).

Despite several common psychological and behavioral aspects, the disorders differ in terms of clinical course, outcome, and need for treatment (American Psychiatric Association 2013). The effects of disordered eating behaviors may differ if they occur over a time-limited versus prolonged period, for example. Therefore, it can be problematic if assessments do not address chronicity or focus only on recent experiences (Lavender et al. 2020).

Valid postsurgical assessment and monitoring have a critical role in identifying disordered eating following bariatric surgery (Parker et al. 2014). In the presurgery period, it is known that the prevalence of disordered eating behaviors is high (Sarwer et al. 2021). Among patients seeking and undergoing bariatric surgery, BED is the second most common psychiatric disorder (17% [95% CI, 13–21%]), following major depressive disorder (19% [95% CI, 14–25%]) (Dawes et al. 2016). On the other hand, data regarding the presence of eating disorders in the postoperative period are scarce, due to lack of comprehensive follow-up data, screening, or standardization in the evaluation of these comorbidities (Parker et al. 2014).

BED Diagnosis

The diagnostic criteria of BED have changed over time. Binge eating was described more than 50 years ago by Stunkard (1959). However, it was only in the fifth edition of Diagnostic and Statistical Manual of Mental Disorders (DSM-5), published on May 2013, that BED was no longer listed as an "eating disorder not otherwise specified." In DSM-5, diagnostic criteria were consistent with the previous edition, but both the frequency of episodes and the duration of eating behaviors were reduced (American Psychiatric Association 2013). In DSM-5, it is required that binge eating episodes occur at least once a week for 3 months (American Psychiatric Association 2013). These recurrent objective binge eating episodes must occur in the absence of compensatory behaviors (e.g., self-induced vomiting), accompanied by a sense of loss of control (LOC). They are defined as eating an unusually large quantity of food in a discrete period. In addition, a diagnosis requires experiencing three of five associated symptoms: (1) eating much more rapidly than normal, (2) eating until feeling uncomfortably full, (3) eating large amounts of food when not feeling physically hungry, (4) eating alone due to embarrassment, and (5) feeling disgusted with oneself or very guilty after overeating (American Psychiatric Association 2013).

Despite the difficulty in eating large amounts of food after surgery, the experience of LOC continues to be reported postoperatively. LOC is common among bariatric patients, with rates ranging from 13.3% to 61.0% prior to surgery (Colles et al. 2008; White et al. 2010) and from 16.9% to 39.0% postsurgery (Conceição et al. 2014; White et al. 2010). Evidence suggests that the experience of LOC, regardless of the amount of food ingested, may be the most important indicator in defining BED postsurgery (Mond et al. 2010). Thus, because LOC is most predictive of the level of impairment, distress, and psychopathology associated with disordered eating behaviors (Colles et al. 2008).

Currently, the diagnostic criteria for BED are the same for bariatric and non-bariatric patients. However, we leave a reflection about the amount of food ingested after surgery and how much this factor can interfere in the assessment of postsurgical patients.

Effect of BED in Pre- and Postsurgery Patients

The impact of preoperative BED in the outcomes of bariatric surgery has been a question of interest to the field. Some studies suggest an association between BED and poorer outcomes, although most have not found this association (Kops et al. 2021; Meany et al. 2014). Data from the Longitudinal Assessment of Bariatric Surgery (LABS) study showed that presurgery BED was not associated with weight change over 7 years of follow-up (Kalarchian et al. 2019). Nevertheless, patients presenting BED presurgery have higher rates of other psychopathologies, which have been associated with poorer surgical outcomes. The disorder is not a

contraindication for surgery, and its presence may not be very significant in terms of surgical success, although an indication remains to follow each case carefully.

On the other hand, the impact of BED during the postoperative period is more controversial. Little is known about the continuation of preexisting BED, incidence, or remission of the disorder. Inaccurate measures may lead to misdiagnosing symptoms and failure to identify clinically significant symptoms that have the potential to impact postsurgical psychological well-being, weight loss, and complications (Conceição and Goldschmidt 2019). As expected, after bariatric surgery, the frequency of objective binge eating episodes seems to fall, and the prevalence of full BED is lower. This prevalence depends on the diagnostic criteria of BED employed and on different assessment measures. Thus, inadequate measures also contribute to the lack of evidence in the research literature and to inconsistency in reported findings. Furthermore, they impact the evaluation of disordered eating treatments.

Undoubtedly, the anatomical alterations imposed by bariatric surgery influence the patients' ability to consume large quantities of food, as well as the types of food that can be consumed, especially in the first months after surgery (Kops et al. 2021). The postsurgical physiologically imposed restriction impacts the ability to eat unusually large amounts of food, an event that is required for the diagnosis of binge eating. Furthermore, postsurgery recommendations, including reducing portion sizes, eating slowly, and chewing thoroughly, mimic some disordered eating behavior. In addition, maladaptive eating symptoms including vomiting, regurgitation, diarrhea, and other gastrointestinal complications such as dumping syndrome can arise from a failure to adhere to postsurgical eating recommendations and may appear very similar to disordered eating (Conceição et al. 2015).

Although the predictive effect of presurgical BED is controversial, the literature that addresses the effect of BED in the postoperative period is more consistent. Still, it is unknown why the disorder recurs in some people and not others. Even so, psychosocial interventions can improve psychosocial disorders among bariatric surgery patients. The surgery alone will not improve compulsive behaviors, and patients need to understand the importance of this for effective long-term results.

Types of Bariatric Surgery and the Effect on Eating Behavior

Currently, different surgical techniques can be used. The most frequently performed procedures are either purely restrictive, such as laparoscopic adjustable gastric band (LAGB) and laparoscopic sleeve gastrectomy (LSG), or restrictive-malabsorptive, such as the Roux-en-Y gastric bypass (RYGB). Knowing the type of procedure is important since anatomical changes may modify the production of hormones responsible for satiety signals and eating until feeling uncomfortably full is one of the criteria for binge eating Fig.1.

The RYGB is the "gold standard" and most widely studied procedure (Welbourn et al. 2018). This surgery reduces food intake through the "creation of a small pouch in the top portion of the stomach which is separated from the remaining stomach." The small intestine is connected to the pouch to allow for the passage of food, while

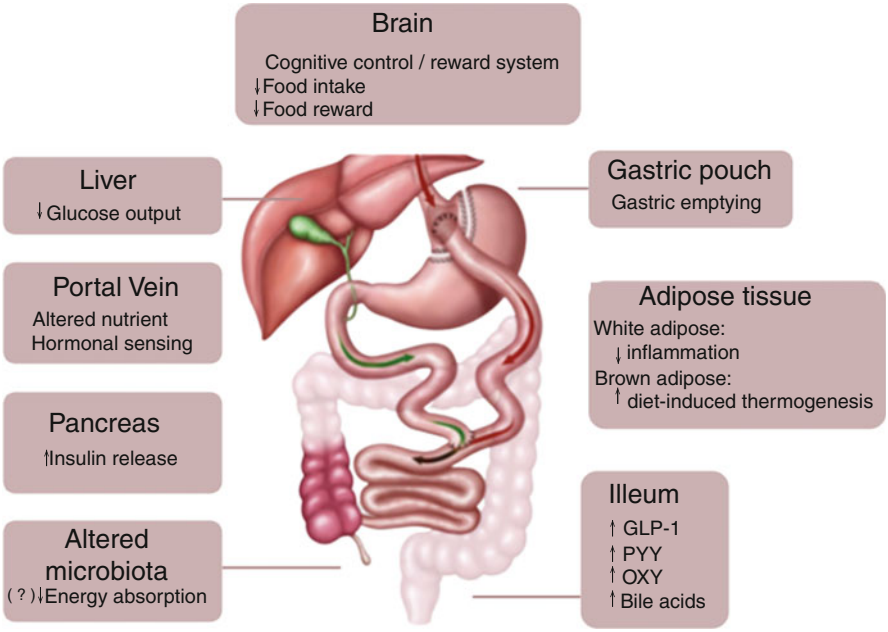


Fig. 1 Anatomical changes and representation of the physiological mechanisms after bariatric bypass surgery. The anatomical change of the gut is a major source of altered signaling to the brain, liver, pancreas, and adipose tissue. These changes lead to reduction of hunger, increase in satiation, shift in food preferences away from high-calorie foods, increase in diet-induced thermogenesis, reduction in inflammation, and improved glycemic control. Abbreviations: *GLP-1* glucagon-like peptide-1, *PYY* peptide YY, *OXY* oxyntomodulin

the remnant stomach is reattached further down the intestinal track (Mitchell and Gupta 2020). The redirection of food produces changes in intestinal hormones that promote satiety and suppress hunger. In addition to favorable changes in gut peptides and appetite hormones, the restriction of total food intake and malabsorption of macronutrients induces weight loss (Mitchell and Gupta 2020).

Energy balance requires an ability of the brain to match energy intake with expenditure. Signals from sensory organs such as vision, smell, and taste and from peripheral tissues such as gastrointestinal tract and adipose tissue, as well as signals from other central areas such as the cortex and reward system, converge on the hypothalamus (Sohn 2015). In the hypothalamus, there are two groups of neuropeptides involved in orexigenic and anorectic processes. The first increases the feeling of hunger: neuropeptide Y (NPY) and agouti-related peptide (AgRP). The other suppresses the appetite, such as pro-opiomelanocortin (POMC) neurons. Both have the function of controlling feelings of hunger or satiety and triggering endocrine, autonomic, and behavioral responses in order to maintain homeostasis (Sohn 2015).

Knowing the procedure performed on each patient is also essential to determine the postsurgical follow-up. Despite the effectiveness of bariatric surgery, weight regain may occur over time. Maximum weight loss usually occurs between 1 and

2 years after the surgery (Sjöström 2018). And long-term weight stabilization is still one of the greatest challenges as it is known that only 76% of patients receiving RYGB surgery maintain at least 20% weight loss 6 years after surgery (Adams et al. 2012). The reasons for weight regain are not fully understood but likely involve psychological, behavioral, and physiological processes.

Sanmiguel et al. (2017) showed that sleeve gastrectomy also decreased both appetite and hedonic eating, causing structural changes in various regions of the brain's reward system (Sanmiguel et al. 2017). Therefore, regardless of the type of surgical procedure performed, the anatomical and physiological changes suggest an important role in the effectiveness of weight loss. The velocity and amount of weight loss will differ between the types of surgeries; however, it is unknown if BED patients would benefit more from one procedure over another.

Binge Eating Assessment in Bariatric Patients

Tools and measures originally developed for patients outside the context of bariatric surgery may not adequately address the clinical presentation of disordered eating behaviors after bariatric surgery (Conceição et al. 2015). Validated measures are fundamental to identify and prevent the disorders and consequent poor biopsychosocial outcomes (Parker et al. 2014). Moreover, methodological inconsistencies in the literature make it difficult to determine the prevalence of the disorders and their impact on treatment outcomes.

A lack of consistency between terms and definitions has been used to describe problematic eating behavior across studies. These definitions such as "binge eating," "LOC," "hyperphagia," "craving for food," "nibbling," "picking," "grazing," and "frequent snacking" are isolated characteristics of a possible disorder and cannot be compared with the diagnosis of BED. Grazing, for example, "involves eating small/modest amounts of food in an unplanned and repetitious manner, and not in response to hunger/satiety sensations" (Conceição and Goldschmidt 2019) and is present in 33.20% of patients with obesity and 67.77% of BED patients (Heriseanu et al. 2017).

There is mixed evidence to suggest that grazing is associated with worse outcomes in weight loss treatment (Heriseanu et al. 2017) and greater weight regain (Pizato et al. 2017). After 10 years of follow-up of patients included in the Swedish obese subjects, presurgery eating behaviors were not related to subsequent weight changes (Konttinen et al. 2015). Including 26 studies, the prevalence of grazing presurgery was 33.2% (95% CI, 27.5–39.1), 28.2% (95% CI, 17.9–39.7) post-surgery, and 23.3% (95% CI 3.1–52.0) in the general population (Heriseanu et al. 2017). The Longitudinal Assessment of Bariatric Surgery-2 (LABS-2) study also showed that grazing and BED reduced right after gastric banding or RYGB but increased again with a remarkable number of new cases (25.6% e 4.8%, respectively) (Smith et al. 2019).

Besides the different terminologies, considerable variation in BED assessment measures is evident among the studies (Tess et al. 2019). A systematic review of the methods used to diagnose disordered eating in presurgical assessments identified

35 questionnaires and 23 interviews. From the 35 questionnaires identified, the Dutch Sweet-Eating Questionnaire was the only measure developed for bariatric surgery patients (however, it was not developed to evaluate BED but sweet eating) (van den Heuvel et al. 2011). From the 23 interviews identified, the only interview specific to the bariatric surgery population was the Eating Disorder Examination-Bariatric Surgery Version (EDE-BSV) (de Zwaan et al. 2004).

Other frequent methods of evaluation are the Eating Disorder Examination-Bariatric Surgery Version (EDE), Three-Factor Eating Questionnaire (TFEQ), Binge Eating Scale (BES), and Questionnaire on Eating and Weight Patterns-Revised (QEWP-R) (Parker et al. 2014):

EDE is a tool to help diagnose eating disorders in general. It addresses various food and self-image issues (e.g., objective binge eating, subjective binge eating, and LOCE) through self-reported questionnaires. The questionnaire assesses disordered eating attitudes and behaviors over the previous 28 days (Fairburn and Beglin 1994). The measure provides four subscale scores: restraint (5 items), eating concern (5 items), shape concern (8 items), and weight concern (5 items). The global score is obtained by averaging the four scores. Higher scores reflect greater eating- or body-related concerns or behaviors. Frequencies of disordered eating behaviors (e.g., binge eating and compensatory behaviors) are also assessed. The revised version of the EDE questionnaire is recommended for use in both bariatric surgery candidates and patients (Parker et al. 2015).

The TFEQ is a scale that measures three types of eating behavior: cognitive restraint, uncontrolled eating, and emotional eating (Stunkard and Messick 1985). It contains 51 items, and higher scores indicate higher levels of the factor, respectively.

The BES is a widely used self-report instrument that measures the behavioral and emotional/cognitive symptoms associated with binge eating. Each of the 16 items contains three to four response options reflecting the severity for each characteristic measured. It was validated by Grupsky (2016) for patients seeking bariatric surgery, but it must be administrated as part of a comprehensive psychological evaluation (Grupski et al. 2013). Individuals can be categorized into three groups, based on the BES total score: no binge eating (score $\leq$ 17), mild to moderate binge eating (score of 18–26), and severe binge eating (score $\geq$ 27). The cut score of 17 classifies correctly 78% of patients with BED. A higher score improved this statistic but increases the number of false negatives (Grupski et al. 2013).

The 28-item QEWP-R also assesses behavioral components of disordered eating, including frequency of objective binge eating and diagnostic information (Yanovski et al. 2015). This measure does not include additional constructs or provide a scaled severity score of disordered eating but has been shown to have reasonable agreement with interview-based measures and the EDE. However, the QEWP generally is more sensitive and less specific and, therefore, should only be used to screen for BED with its confirmation by interview (Yanovski et al. 2015) Table 1.

Among these questionnaires, the EDE is the most appropriate to be used in the pre- and postoperative surgery (Parker et al. 2015). The criteria of objectively large amount of food for BED are not always clear, which makes it difficult to interpret findings across studies (Conceição et al. 2015). For this reason, the tools in their

Table 1 Scoring questionnaires to assess binge eating

Instrument	Details
Dutch Sweet-Eating Questionnaire	Ten questions and a list of 16 sweet foods and beverages to measure intake frequency. The questions had three to maximally five options. Intake frequency varied from never to three or more times per day and had ten options
Eating Disorder Examination-Bariatric Surgery Version (EDE-BSV)	A semi-structured clinical interview adapted for bariatric patients
Eating Disorder Examination (EDE)	Four subscale scores
Three-Factor Eating Questionnaire (TFEQ)	51 items; three types of eating behavior
Binge Eating Scale (BES)	16 items containing three to four responses
Questionnaire on Eating and Weight Patterns-Revised (QEWP-R)	27-item self-administered questionnaire

adapted forms are more reliable. Furthermore, inclusion of items assessing objective and subjective binge eating and grazing enables comparison between measures of disordered eating more relevant to a postsurgical population (Parker et al. 2015).

Pros and Cons of Instruments for the Assessment of Eating Disorders

Although there are several instruments for the assessment of eating disorders, clinical interviews are the gold standard for the diagnosis of BED. However, their application is not always feasible as they are laborious and must be performed by trained mental health professionals. Therefore, self-report questionnaires are preferred as a screening method. Ideally, a good screening instrument should be highly sensitive in order to identify the majority of affected patients with BED (Tess et al. 2019). On the other hand, its specificity is less relevant, since a preliminary diagnosis of an eating disorder must be confirmed by a clinical interview – responsibility of the psychologist or the psychiatrist.

The lack of consistency impedes recognition of disordered eating behaviors and appropriate continuity of treatment by clinicians (Conceição and Goldschmidt 2019). The correct assessment could greatly improve the detection of eating disorders and behaviors and, thus, contribute to a better postoperative result. Since the effects of binge eating in the postoperative period are more recognized (related to poorer weight outcomes, psychological well-being, and greater postsurgical complications) than the preoperative period, the accurate identification at this time is perhaps even more important.

In addition, the wide range of questionnaires for the assessment of binge eating made comparison between different studies and procedures difficult. The psychometric properties, validity, and utility of these measures in bariatric surgery patients are not established. The investigators should use the same assessment measures to

ensure accuracy and comparability of findings in future studies. Further development of measures is required to find consistent and psychometrically acceptable measures for pre- and postsurgery patients.

In conclusion, bariatric surgery is recognized as an important option for obesity treatment. Although most surgical patients have disturbed eating behaviors, little is known about the effect of this in the surgery. Furthermore, the studies have important methodological limitations to evaluate the development or recurrence of eating disorders. Thus, a standardized assessment is crucial to identify these disorders considering the unique eating context created by the surgery. Meanwhile, we emphasize the importance of a clinical assessment by qualified professionals for the disturbed eating behaviors and a postsurgery follow-up by a multidisciplinary team.

Applications to Other Areas

Binge eating scoring systems are also used in other areas than bariatric surgery. Although most studies are performed in patients with obesity or undergoing weight loss treatments, the general population of different age groups, as well as clinical and nonclinical patients, can also be evaluated despite contradictory results.

Studies conducted on obese patients have demonstrated that the BES has high sensitivity and specificity for discriminating between binge eaters and non-binge eaters (Grupski et al. 2013). These findings show scales presenting similar results to those obtained by reliable and supported semi-structured interviews (Robert et al. 2013). Furthermore, a growing body of research has been showing that the BES presents good validity both in clinical and in nonclinical samples (Duarte et al. 2015), including in the youth population (Cardoso et al. 2020; Escrivá-Martínez et al. 2019; Mina et al. 2021). However, in a study with 553 non-clinical subjects, BES was not a useful tool in underweight and optimal-weight subjects (Brunault et al. 2016). Therefore, there is a need for more evidence about the scale and additional psychometric properties in this population.

A large amount of research has established a well-defined relationship between BED and addiction disorders. Impulsivity has been positively associated with BED (Mason et al. 2018) and could play an important role in comorbidity. Although there is a positive correlation between the presence of BED and food addiction (Imperatori et al. 2014), use of alcohol, and binge drinking (Fouladi et al. 2015), the applicability of each instrument cannot be confused.

The evaluation of binge eating offers some challenges due to the private nature and the difficult aspects to declare and to recall, such as shame and severity of the episodes. These challenges are even greater when evaluated by scoring systems. It is consensual that investigator-based interviews are the most valid method to accurately assess disorders regardless of the area or studied population.

Mini-Dictionary of Terms

- ***Loss of control:*** *Constantly exaggerate. Eating an unusually large amount of food in a discrete period*
- ***Grazing:*** *The habit of "pinching." Eating small amounts of food over time*
- ***Bariatric surgery:*** *Surgical procedure for weight loss and improvement of associated comorbidities*
- **Scoring systems:** Assessment instruments and questionnaires that use a score as a diagnostic criterion
- **Orexigenic neuropeptides:** They are transmitters that stimulate appetite
- **Anorexigenic neuropeptides:** They are transmitters that inhibit appetite

Key Facts of Scoring Systems for Bariatric Patients

Bariatric surgery limits the amount of food consumed in a short period of time.

The experience of LOC continues to be reported postoperatively.

Valid postsurgical assessment and monitoring have a critical role in identifying disordered eating following bariatric surgery.

Considerable variation in BED assessment measures is evident among the studies.

The wide range of questionnaires for the assessment of binge eating made comparison between different studies and procedures difficult.

Scoring systems are practical and inexpensive to apply but need attention.

Summary Points

- *The gastrointestinal rearrangement after bariatric surgery plays a role in the metabolic changes observed after surgery*
- *Valid postsurgical assessment and monitoring have a critical role in identifying disordered eating following bariatric surgery*
- *Data regarding the presence of BED in the postoperative period are scarce, due to lack of comprehensive screening or standardization*
- *Despite the difficulty in eating large amounts of food after surgery, the experience of LOC continues to be reported postoperatively*
- *Tools originally developed for patients outside the context of bariatric surgery may not adequately address the clinical presentation of disordered eating behaviors after the surgery*
- *Inclusion of items assessing objective and subjective binge eating and grazing enables comparison between measures of disordered eating more relevant to a postsurgical population*

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Conceptualizing and Evaluating the Healthy Orthorexia Dimension

74

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Contents

Introduction 1481
Conceptualizing Orthorexia 1484
Knowing Orthorexia Symptomatology 1486
Investigating the Frequency and Risk Factors of Orthorexia 1488
Evaluating Orthorexia from Psychometric Instruments 1490
What Is the Best Way to Investigate HeOr Symptomatology? 1493

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What Is the Best Way to Management Symptomatology of Orthorexia? 1494
Final Considerations 1495
Applications to Other EDs 1497
Mini-Dictionary of Terms 1498
Key Facts of Orthorexia 1498
Summary Points 1499
References 1499

Abstract

Orthorexia can be understood as a drive for eating foods perceived to be health-promoting. When this drive includes obsessive thoughts and rigid behaviors about food choices, a person can suffer physical, psychological, and social harms. In the literature, this symptomatology is known as orthorexia nervosa, as it can cause damage in different areas of people's lives. On the other hand, a drive for healthy eating can also be experienced as a guide to help people make food choices aiming to establish a health-promoting eating habit. This has been named in the literature as healthy orthorexia, but it is not clearly understood yet. The aim of this chapter was to conceptualize healthy orthorexia and explore its forms of evaluation, providing discussion about empirical evidence and practical implications. For that, a background about orthorexia nervosa was also necessary to understand how healthy orthorexia fits into this phenomenon that is still under debate in the clinical and scientific community.

Keywords

Orthorexia · Nervosa · Healthy · Disorder · Eating · Behavior · Pathological · Non-pathological · Preoccupation · Fixation · Obsession · Interest · Focus · Scales · Diagnostic Criteria

Abbreviations

AN	Anorexia nervosa
BOT	Bratman's Orthorexia Self-Test
DOS	Düsseldorfer Orthorexia Scale
DSM-5	Diagnostic and Statistical Manual of Mental Disorders, fifth edition
EDs	Eating disorders
EFA	Exploratory factor analysis
EHQ	Eating Habits Questionnaire
HeOr	Healthy orthorexia
ICD-11	International Statistical Classification of Diseases and Related Health Problems, eleventh revision
Non-ON	Non-orthorexia nervosa
ONI	Orthorexia Nervosa Inventory
OrNe	Orthorexia nervosa
P	Percentiles
TOS	Teruel Orthorexia Scale

Introduction

The beneficial effects of a nutritionally adequate eating (e.g., supplying adequate macro- and micronutrients) are undeniable (Bazzano 2006), which supports global strategies focused on promoting health through food, aimed mainly at the prevention of noncommunicable diseases (World Health Organization 2003, 2020). However, while this appeal is seen as protective and important, biological approaches focused only on health promotion (e.g., a medical recommendation) ironically may have negative implications on autonomous choices, individual values, group experiences, and others (Barnhill et al. 2014). In addition, internalizing an eating behavior with a premise to exclude all foods labeled "unhealthy" can turn into an obsession (i.e., a persistent and disturbing thought) with consequent fixation (i.e., a stereotyped behavior related to an obsessive and unhealthy preoccupation or attachment) and subsequent biological and psychosocial harm (McComb and Mills 2019; Strahler et al. 2018; Cena et al. 2019). As a result of health-focused reductionist approaches, a growing number of individuals are seeking help from psychologists, nutritionists/dietitians, and other professionals and reporting maladaptive behavior focused on "ideal eating" to promote health (Bratman 2017). This seems to be a paradox represented by the modern preoccupation with health (Devcich et al. 2007), which may result from inconsistent interpretations of official dietary recommendations that actually suggest having a diet that promotes health, psychological well-being, social interaction, and environmental sustainability, as well as respects culture (McCartney 2016; Brazil 2014; World Health Organization 2020).

The unhealthy preoccupation with healthy eating has been understood as a phenomenon called orthorexia (Mathieu 2005). Etymologically, this word derives from the Greek words *orthós* and *orexsis*, meaning "correct" and "appetite," respectively (Bratman 2017). Orthorexia-like behaviors seem to stem from global motives, values, and beliefs based on the ideological theory that food promotes good health per se (Bratman 2017), which is not an absolute truth (Barnhill et al. 2014). In 1997, Steven Bratman, an American physician who at the time practiced alternative medicine, published a manuscript in the *Yoga Journal*, where he coined initially – based on his personal and clinical experiences – the term "orthorexia nervosa (OrNe)". The use of the word "orthorexia" to represent "correct appetite" was intentional to refer to an eating practice considered healthy. Furthermore, this word would be different from "anorexia," which represents "absent appetite." The addition of the word "nervosa" to "orthorexia" forms the term OrNe representing a pathological fixation on healthy eating characterized by overconcentration on specifics of food choices, including quality, preparation, and adherence to one or another particular theory of eating. These may be conceptualized as improving everyday health, addressing specific health concerns, or reducing risk of life-threatening diseases (Bratman 1997; Hallit et al. 2021). After Bratman's first publication, a considerable number of studies sought to understand OrNe phenomenon. However, some of these studies began to conflate OrNe with adherence to a theory of healthy eating per se, such as the desire to avoid ultra-processed foods and the adoption of

eating styles, such as veganism (Bratman 2017). In part the present work is designed to address this confusion.

The present biopsychosocial understanding of OrNe indicates that it represents an extreme fixation on healthy eating, which can influence the choice and consumption of foods and, consequently, people's lives (Douma et al. 2021; Bratman 2017). Individuals who exhibit OrNe behaviors are "inflexible eaters" (i.e., they only eat what they judge to be appropriate) avoiding certain type of foods based on whatever theory of healthy eating they may follow. For example, vegans avoid all animal products, followers of the paleo diet eschew legumes and grains, and adherents of "clean eating" avoid additives (e.g., artificial colors, pesticides, and preservatives). Thus, food choice is based on self-perception of unhealthy characteristics. Concepts such as the "naturalness" of foods, their purity, and their production by certain means (such as organic farming) are often but not always employed. In addition, it is has been observed that individuals with OrNe may switch dietary theories, sometimes rather rapidly, and therefore move from one set of rigid rules to another (Bratman and Knight 2000). However, it should be noted that choosing foods believed to be healthy is not a problem per se. Most people who exhibit healthy eating preoccupations do not subject themselves to direct physical harm. The real issue emerges when the "drive for healthy eating" becomes problematic, and understanding this transition is a challenge (Koven and Abry 2015; Moroze et al. 2015).

From a psychodynamic point of view, when healthy eating becomes a permanent preoccupation and demands an inflexible choice, it provides a sense of control over the body, hunger, and health, masking anguish and acting as a kind of defense (Dolto 2014). When a person adopts an overcontrolled eating behavior, they may feel safe, but this can have a negative impact on different areas of their life, such as social (e.g., isolation to avoid eating out), psychological (e.g., feelings of guilt when eating a self-imposed forbidden food), occupational (e.g., spending a lot of time acquiring and preparing specific types of food), and biological (e.g., nutritional deficiencies due to monotonous eating and fasting as self-punishment for breaking rules). As society plays a key role in people's lives, maladaptive eating behaviors (e.g., restrict all foods supposed to be "unclean") could occur in response to societal pressure (e.g., being as healthy as possible), and this may trigger a disorder (e.g., obsessive-compulsive disorder). Therefore, a behavior that was supposed to be healthy can become a coping strategy with negative outcomes (Moroze et al. 2015; Koven and Abry 2015). However, this hypothesis has not been completely validated (Greville-Harris et al. 2020; McGovern et al. 2021; Mitrofanova et al. 2021).

At present, there is still no consensus in the literature whether OrNe is an independent mental disorder, a subtype (e.g., obsessive-compulsive disorder), or merely a behavioral or lifestyle phenomenon (Koven and Abry 2015; Strahler et al. 2018). Both the Diagnostic and Statistical Manual of Mental Disorders, fifth edition (DSM-5), and the International Statistical Classification of Diseases and Related Health Problems, eleventh revision (ICD-11), do not recognize OrNe as a mental disorder, as there are no official diagnostic criteria. Based on this, individuals who are obsessed about food to achieve good health may exhibit risky behaviors, but so far there is no sufficient evidence to describe OrNe as a disease (Cena et al. 2019;

Dunn and Bratman 2016). Nevertheless, it is still possible to identify some characteristic aspects of OrNe.

Evidence suggests that OrNe is focused on *what to eat* (i.e., quality) driven by the goal of being as healthy as possible, while eating disorders (EDs) such as anorexia nervosa (AN) are focused on *how much to eat* (i.e., quantity) in an attempt to change body shape. However, this distinction is not always so pragmatic (Domingues and Carmo 2021). For instance, an individual with AN may move their focus from quantity to the quality of food (Barrada and Roncero 2018; Segura-Garcia et al. 2015). On the other hand, a person that is primarily preoccupied with food quality may also control the food quantity (Strahler et al. 2018). Furthermore, a simultaneous preoccupation with the quality and quantity of food can occur. In this way, it is speculated that OrNe can precede, succeed, or coexist with EDs (Barthels et al. 2017; Segura-Garcia et al. 2015; McGovern et al. 2021). Individuals with AN generally hide their behaviors, while those with OrNe are proud of their conduct, and these differences are important (McComb and Mills 2019; Mitrofanova et al. 2021; Greville-Harris et al. 2020). Therefore, future research should be encouraged to better understand OrNe in the context of EDs.

When Bratman coined the term OrNe (Bratman 1997), he did not intend to determine a new ED; however, this was not clear in the literature. Thus, years later, Bratman clarified this point by reporting that orthorexia encompasses two stages (Bratman 2017). The first involves an "innocent" interest in changing eating to reduce diseases and improve overall health without physical and mental negative consequences. The second, understood as OrNe, is characterized by a further progression focused on extreme fixation with healthy eating, generating a rigid, fearful, and self-punishing lifestyle, which is the problematic component of orthorexia (Bratman 2017). From this perspective, Barrada and Roncero (2018) brought to light the bidimensionality of the orthorexia by proposing to investigate this phenomenon considering an already known pathological dimension (i.e., OrNe) and a non-pathological one called "healthy orthorexia" (HeOr).

It is worth commenting that Bratman is opposed to the use of the term healthy orthorexia and instead wishes to describe this as an interest in health. In Bratman's conception, "orthorexia" should only be used as a shorthand for OrNe, just as "anorexia" is a shorthand – at least when EDs are concerned – for anorexia nervosa. He argues that since the term "anorexia" is also used, especially in association with cancer treatment, as an indicator of lack of appetite, "orthorexia" could conceivably be used in a parallel manner as a mere indicator of healthy eating. Despite these objections to use of the term HeOr, this work will follow the general literature and employ it. Importantly, the term "non-orthorexia nervosa (non-ON)" is also used to represent signs and symptoms related to interest in healthy eating (Strahler et al. 2018; Barrada and Roncero 2018), but the term HeOr is more commonly used in the literature. However, regardless of the term used, it is important to know this dimension, as well as the whole continuum, to verify the usefulness of recognizing the symptoms of orthorexia.

The focus of this chapter is to discuss orthorexia as a phenomenon that lies on a continuum as illustrated in Fig. 1. This continuum begins with no concern for

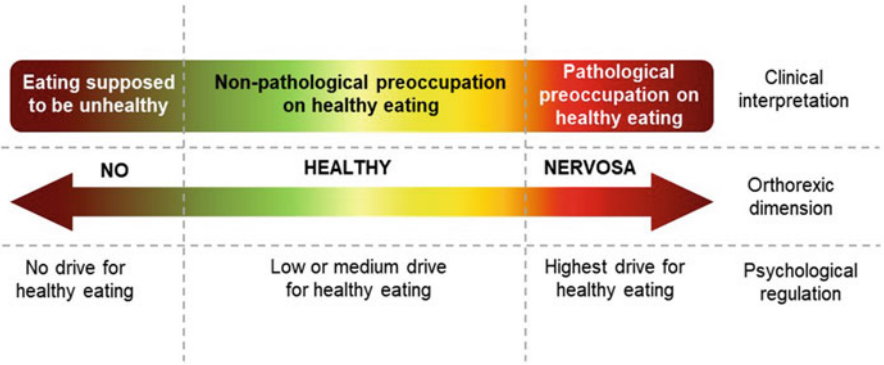


Fig. 1 The continuum of orthorexia. Note. Orthorexia is a state of excessive preoccupation with healthy eating. Here it is conceived as a continuous phenomenon ranging from none to high drive (i.e., arousal influencing beliefs and behaviors) toward healthy eating. When there is no drive for healthy eating, orthorexia is absent (this can be problematic, as it represents disinterest). When there is a low/medium drive for healthy eating, but it is not obsessive, healthy orthorexia may be found. When there is a high drive as an obsession for healthy eating, orthorexia nervosa may be found, which can cause damage in different areas of a person's life. (This figure was created by the authors of this chapter)

healthy eating, which can be seen as a maladaptive eating behavior, but it is clearly not orthorexia. Then, there is a point of balance where food choices are made consciously to promote health but without obsessive preoccupation. Note that this may involve the adoption of a nonstandard theory of healthy eating; rather than simply promoting consumption of fruits, vegetables, whole grains, and protein sources, the theory may extol raw food and eschew meats. All theories of healthy eating are equivalent from this perspective provided they supply adequate micro- and macronutrients. Finally, a stage in which extreme fixation is reached is found, and here there is a maladaptive eating behavior, as it causes significant damage. From this perspective, some drive for healthy eating may be good, but a total absence or extreme level is not. The balanced drive for healthy eating can be seen as HeOr. The aim of this chapter is to conceptualize HeOr and explore its forms of evaluation to discuss empirical evidence and practical implications. For this, it was necessary to provide a background about OrNe to understand how HeOr fits.

Conceptualizing Orthorexia

One of the first scientific articles explaining orthorexia was published by Mathieu (2005). The author described the phenomenon based on pathological dimension as a fixation on righteous eating. This was supported by an interview conducted with Bratman, who proposed the term OrNe. In addition, experts in mental disorders who cared for people with different obsessions around food were interviewed for the article. At that time, experts were not completely sure whether orthorexia should be

considered a disorder, since having a healthy eating is something positive in society (Mitrofanova et al. 2021). Despite the effort to provide a clear definition for OrNe, the article also highlighted the need of further investigation and evidence gathering, both in clinical and research settings.

Currently, OrNe encompasses an intensification of the preoccupation with healthy eating that leads to persistent and disturbing thoughts (obsession) and stereotyped behaviors (fixation), such as eating only highly specific foods, eliminating those perceived to have unhealthy properties (e.g., "highly refined" foods), constantly thinking about the origin of the food, and choosing holiday destinations based solely on local foods chosen for their supposed health-promotion properties, rather than mere regional tastes (Mitrofanova et al. 2021). Knowing this is useful for therapists to be able to recognize OrNe symptomatology, although it is worth emphasizing that official diagnostic criteria do not yet exist (Cena et al. 2019).

Twenty-one years after its initial concept, orthorexia gained a new perspective. Barrada and Roncero (2018) observed a need to clarify when the preoccupation with healthy eating ceases to be a sign of care and becomes a fixation. This approach does not appear to represent a division of orthorexia into two parts but considers it as a continuum, ranging from no concern about healthy eating to extreme fixation passing by a midpoint represented by the interest based on preoccupation (see Fig. 1). Thus, HeOr was proposed as a non-pathological dimension for orthorexia. It emerged to represent an "adaptive preoccupation," such as an interest in the consumption of nutritionally adequate and health-promoting foods. This interest involves the tendency to self-control and the ability to focus attention on food choices, as a manifestation of a health care, without overconcern, being interpreted as a protective behavior. Hence, individuals who exhibit HeOr behaviors usually have healthy eating as an important part of their lives, take responsibility for their actions, and persist in their commitment, but without exaggeration. In summary, HeOr represents the tendency to eat healthy food as an integrated part of one's life (Barrada and Roncero 2018; Zickgraf and Barrada 2022).

Unlike the extreme fixation on healthy eating, HeOr encompasses the interest in eating to promote health, but the preoccupation does not trigger behaviors that objectively cause psychological, physical, occupational, or other harm. Thus, Barrada and Roncero (2018) shed light on the understanding of orthorexia by expanding it to include two dimensions, one represented by the interest in healthy eating (HeOr) and the other represented by extreme preoccupation (OrNe), which are part of the continuum seen in Fig. 1. Some studies (Depa et al. 2019; Silva et al. 2021; Zickgraf and Barrada 2022; Yakin et al. 2022; Strahler 2020, 2021; Barthels et al. 2019; Mhanna et al. 2022) bring up this supposed bidimensional nature of orthorexia, providing further support for decipher it. However, this understanding remains difficult, as most research focuses on investigating only OrNe (McComb and Mills 2019). In addition, with the strengthening of official guidelines to promote health through food (Walker-Swanton et al. 2020), the concern about healthy eating seems to be something natural and acceptable, regardless of whether it is exaggerated. Thus, it is important to know the extent to which people's concerns about

healthy eating are "normal," that is, including adaptive eating behaviors based on food choices that promote physical health and psychosocial well-being.

Knowing Orthorexia Symptomatology

Research about orthorexia is growing year by year (McComb and Mills 2019; Dunn and Bratman 2016; Cena et al. 2019). However, today the body of scientific evidence is still fragmented about its etiology and clinical implications, being especially scarce in terms of investigation of HeOr. Some articles (Dunn and Bratman 2016; Barthels et al. 2015b; Moroze et al. 2015; Donini et al. 2004; Setnick 2013) have suggested diagnostic criteria to guide the clinical community to identify signs and symptoms of OrNe. Cena et al. (2019) carried out a review study and gathered the diagnostic criteria suggestive of OrNe presented in four previous studies. Based on these, "consensual" diagnostic criteria for OrNe can be found, as presented in Fig. 2. The "consensual" criteria are not exactly the same in the studies, but there are key elements (e.g., obsessive behaviors, drive for health, and psychosocial and nutritional deficiencies), which allow characterization of OrNe. These can be useful as a

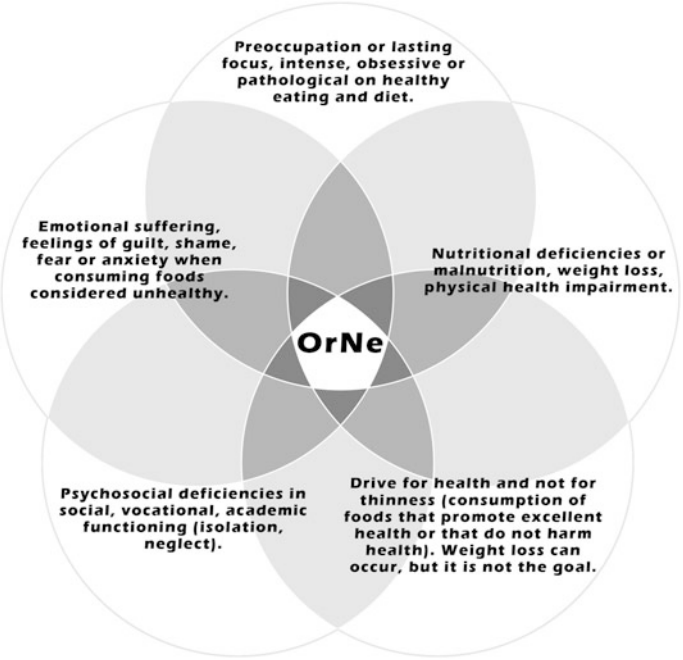


Fig. 2 Consensus criteria found in the literature for diagnosis suggestive of orthorexia nervosa (OrNe). (Note. Adapted from Cena et al. (2019) based on the criteria of Setnick (2013), Moroze et al. (2015), Barthels et al. (2015b), and Dunn and Bratman (2016). This figure was created by the authors of this chapter)

starting point for developing official diagnostic criteria that are still under debate. Despite the gaps in the literature, OrNe may already be well recognized and distinguished from eating behaviors (Cena et al. 2019).

Knowing the non-pathological dimension of orthorexia and identifying the point on which the drive for healthy eating becomes too high and negative can provide clinical benefits. Hence, recognizing signs and attitudes of HeOr is necessary. People with HeOr behaviors may be attentive to healthy eating and spend a considerable amount of effort on it, but this per se is not enough to determine that a psychopathology exists, since no extreme preoccupation emerges when it is not possible to "eating properly." Subsequent literature (Depa et al. 2019; Silva et al. 2021; Zickgraf and Barrada 2022; Yakin et al. 2022; Strahler 2020, 2021; Barthels et al. 2019; Mhanna et al. 2022) has shown consensus that HeOr is a dimension of orthorexia and this involves the general interest about healthy eating that produces behaviors as part of one's identity.

Yakin et al. (2022) mentioned that HeOr behaviors may include elimination of ultra-processed foods, as they are believed by some to negatively impact health and the environment. This can be interpreted as a lifestyle choice given that the dietary changes include the individual and the collective. According to Roncero et al. (2021), people who exhibit HeOr behaviors are able to plan the meal knowing that their food choices can have an impact in the long, medium, and short term, but they bet more on the effort that will have future and not immediate effects. In addition, the authors report that these individuals have a specific personality pattern including a tendency for responsibility, self-control, and the ability to focus, allowing them to critically evaluate guidelines, beliefs, and experiences that supposedly influence their behavior. Therefore, knowing how to differentiate individuals with HeOr behaviors from those with OrNe behaviors becomes important in terms of clinical implications, to contribute to the development of prevention or treatment strategies (Yakin et al. 2022).

Strahler et al. (2020) suggest that there are gains in the therapeutic approach when identifying HeOr behaviors. The authors showed that high scores for OrNe were significantly correlated with poor mental health, but this relationship was attenuated when there were also high scores for HeOr. This means that there was a "buffering," as the "interest" in healthy eating mitigated the obsession/fixation with eating specific foods. For example, a person who is preoccupied with healthy eating may recognize that certain behaviors are not beneficial and seek to avoid them. However, this self-awareness is not present all the time, and for this reason the individual needs help to maintain the interest in healthy eating (as absence may be also a problem), but without this becoming an extreme fixation (Hallit et al. 2021; Yakin et al. 2022). Yakin et al. (2022) showed that distinguishing between individuals with pathological and non-pathological orthorexia behaviors is significant, but also the awareness of the existence of groups of individuals with "low orthorexia" (i.e., no particular interest in healthy eating) and "in-between orthorexia" (i.e., symptomatology for OrNe and HeOr experienced together) is important to implement the most parsimonious therapeutic strategy. From this perspective, different behaviors can be seen as associated with orthorexia, and this may indicate that the concept appears to be a

multidimensional phenomenon rather than bidimensional. However, this is just a speculation that needs to be validated by future scientific evidence in different contexts.

Investigating the Frequency and Risk Factors of Orthorexia

Rates of OrNe behaviors have already been shown in different samples around the world, ranging from less than 1% to 90% (McComb and Mills 2019; Chard et al. 2019). This wide variation seems to be uncertain and may be associated with the different ways of measurement, such as instruments (e.g., scales) with poor psychometric properties (Valente et al. 2019; Chard et al. 2019) and suggestive clinical evidence based on preliminary diagnostic criteria (McComb and Mills 2019). Rates of HeOr behaviors are practically nonexistent, with few studies finding it (Silva et al. 2021; Awad et al. 2022b). This indicates that studies are focused on identifying maladaptive behaviors, and this strategy may not be the best way to understand orthorexia, as it separates the findings into the presence or absence of a problem. As mentioned previously, knowing whether there is an interest in healthy eating can be useful for preventive therapeutic plans that seek to prevent maladaptive behaviors from appearing. Thus, knowing the number of people interested in healthy eating and the number of individuals obsessed with the quality of their food provides room for the development of more assertive public health intervention plans.

Besides knowing the frequency and type of behavior found, knowing whether specific characteristics can be considered a risk factor may be interesting to prevent attitudes driven by extreme fixation on healthy eating. Table 1 shows a distinction between OrNe and HeOr considering the main predictors for symptomology and relationships found in the literature (Astudillo 2021; Cena et al. 2019; McComb and Mills 2019; Awad et al. 2022b; Hallit et al. 2021; Roncero et al. 2021; Strahler 2021; Zickgraf and Barrada 2022; Mitrofanova et al. 2021). In general, OrNe covers positive relationships with aspects that can compromise people's physical and mental health (e.g., restrained eating and maladaptive personality traits), as well as reducing well-being (e.g., impulsivity), while HeOr seems to be inversely associated with these aspects or leads to outcomes without significant harms. A significant relationship between OrNe and the drive for thinness and dysfunctional attitudes toward physical appearance was found in previous studies (Depa et al. 2019; Domingues and Carmo 2021), but this is not fully validated in the literature. Some relationships are unclear, such as HeOr vs. EDs. Other relationships are inconclusive, such as demographic characteristics, like sex and age, vs. OrNe and HeOr. Furthermore, somatic symptoms (e.g., anxiety, guilt feelings, and obsessive thoughts) seem to be present in OrNe, making the individual's clinical condition worrying.

Douma et al. (2021) studied the experience of Dutch health professionals to assess how OrNe develops and who typically develops it. Data showed young age, female, high level of education, perfectionism, and use of social media as baseline risks for OrNe. The authors also found that weight loss, inactive social life, and

Table 1 Distinction between pathological and non-pathological dimensions of orthorexia and the main predictors for symptomology

	Pathological dimension (orthorexia nervosa)	Non-pathological dimension (health orthorexia)
Focus	In the food quality that must be as healthy and "clean" as possible	In the food quality that is nutritionally balanced
Eating disorders	Positive relationship	Positive relationship, but weak*
Restrained and emotional eating	Positive relationship	Negative relationship
Body image disturbance	Positive relationship	Negative relationship*
Obsessive-compulsive symptoms	Positive relationship	Uncorrelated
Maladaptive personality traits and impulsivity	Positive relationship	Negative relationship
Poor mental health	Positive relationship	Negative relationship
Good mental health	Negative relationship	Positive relationship
Well-being	Negative relationship*	Positive relationship*
Mindfulness	Negative relationship*	Positive relationship*
Social media use	Positive relationship*	Untested
Exercise engagement	Inconclusive	Uncorrelated*
Body mass index	Inconclusive	Inconclusive
Age	Inconclusive	Inconclusive
Gender	Inconclusive	Inconclusive
High level of education	Positive relationship*	Untested
Socioeconomic status	Inconclusive	Inconclusive
Health-related programs/ occupations	Inconclusive	Positive relationship*
Dieting	Positive relationship	Untested
Adoption of vegetarian/ vegan food style	Inconclusive	Untested
Alcohol, tobacco, and drug use	Positive relationship*	Inconclusive
Vegetable and fruit consumption	Positive relationship*	Positive relationship*
Meat consumption	Negative relationship*	Untested

Note. Asterisk indicates that only or a small number of studies have found the relationship. Inconclusive means that the studies are not consensual about the relationship.

environment were inconclusive for OrNe, corroborating Bratman's (2017) idea that weight and exercise are not primary motivations for exhibiting high levels of OrNe. Zickgraf and Barrada (2022) found differing patterns of associations between OrNe and HeOr and ED symptoms, food intake, diet quality, nutrition knowledge, and lifestyle variables, with negative consequences for OrNe. Some studies show that OrNe is positively associated with poorer mental health (Barthels et al. 2019; Strahler et al. 2020; Awad et al. 2022a; Yakin et al. 2022), while HeOr is positively

linked to better mental health (Awad et al. 2022b; Strahler 2021; Yakin et al. 2022). Therefore, the literature is still inconsistent in terms of risk and protective factors for orthorexia dimensions.

A relationship that could be explored in greater depth in the future is whether orthorexia is associated with socioeconomic status. Some studies (Mathieu 2005; Varga et al. 2013; Hyrnik et al. 2016) suggest that it is expensive to eat the kinds of foods classified as healthy. According to McComb and Mills (2019), it is possible that OrNe is more prevalent among high-income individuals. In this way, would people who cannot afford to shop at an organic health food store be less likely to develop orthorexia? Perhaps, as people with lower or lack of income generally make food choices based on price and not on the desire to be healthier per se. Furthermore, low socioeconomic status may be associated with other problems that are more relevant than just healthy eating. However, the answer to this question is not yet clear, which requires further investigation to determine whether income influences orthorexia-like behaviors.

Evaluating Orthorexia from Psychometric Instruments

To screen orthorexia-like behaviors, it is essential to have adequate tools to produce valid and reliable data. In this chapter, only psychometric instruments with a suggestive capacity to simultaneously investigate both OrNe and HeOr symptomatology will be explored. At the time of this writing, most tools do not allow a clear interpretation about the dimensions of the orthorexia (Valente et al. 2019; Hallit et al. 2021; Niedzielski and Kazmierczak-Wojtas 2021). However, the Teruel Orthorexia Scale (TOS) (Barrada and Roncero 2018), the Eating Habits Questionnaire (EHQ) (Gleaves et al. 2013), the Düsseldorfer Orthorexia Scale (DOS) (Barthels et al. 2015a), and the Orthorexia Nervosa Inventory (ONI) (Oberle et al. 2021) seem to include items that may be able to identify both OrNe and HeOr behaviors. The following information about these instruments is to help clarify to the reader their reasoning and usefulness.

TOS. The TOS was developed by Barrada and Roncero (2018) in the Spanish culture based on key elements extracted from literature. The researchers constructed the items as statements (e.g., "Thoughts about healthy eating prevent me from concentrating on other tasks") and found from exploratory factor analysis (EFA) two balanced item sets, one with eight items to investigate the negative consequences of extreme fixation on healthy eating, i.e., OrNe (e.g., "If I ever eat something I consider unhealthy, I punish myself for it"), and the another with nine items to investigate the interest, but not obsessive, in following an eating style considered by the individual as healthy, i.e., HeOr, (e.g., "I mainly eat foods that I consider healthy"). Table 2 shows the distribution of items for each factor of the TOS. A 4-point *Likert*-type response scale ranging from 0 (completely disagree) to 3 (completely agree) is used, and higher scores indicate greater likelihood of presenting OrNe and/or HeOr. Importantly, when there is evidence about the multidimensionality of an instrument, as in the case of the TOS, it is necessary to compute

Table 2 Potential instruments to assess the bidimensionality of orthorexia

Instrument	Items[a]	
	Health orthorexia dimension	Orthorexia nervosa dimension
Teruel Orthorexia Scale (TOS)[b]	1, 2, 3, 6, 7, 8, 11, 13, 15	4, 5, 9, 10, 12, 14, 16, 17
Eating Habits Questionnaire (EHQ)[c]	1, 2, 3, 11, 12, 15, 19	6, 7, 8, 10, 13, 17, 18, 20
Dusseldorf Orthorexia Scale (DOS)[c]	1, 2, 3	4, 6, 7, 8, 9, 10

Note
[a]The content of the items can be found in the scientific articles
[b]Barrada and Roncero (2018)
[c]Hallit et al. (2021)

Table 3 Classification used in Silva et al. (2021) to interpret scores of "orthorexia nervosa" (pathological) and "health orthorexia" (non-pathological) using the Teruel Orthorexia Scale

Percentile	Mean score	Likelihood for presenting health orthorexia- and orthorexia nervosa-like behaviors
≤25	≤0.75	Extremely unlikely
25–50	0.75–1.50	Unlikely
50–75	1.50–2.25	Likely
>75	>2.25	Extremely likely

Note. Silva et al. (2021)

a score for each latent factor (i.e., dimension). The TOS has been tested in different contexts, such as Spanish college students (Barthels et al. 2019; Depa et al. 2019; Barrada and Roncero 2018), German and/or Lebanese community (Strahler et al. 2020; Strahler 2020, 2021; Awad et al. 2022a, b), US college students (Chace and Kluck 2021), English-speaking adults from different countries (Domingues and Carmo 2021; Zickgraf and Barrada 2022), adolescents residing in Lebanon (Mhanna et al. 2022), French female adults (Yakin et al. 2022), and Brazilian gym users (Silva et al. 2021).

Despite the advance brought by the TOS with the bidimensional approach, the methodology to determine HeOr scores is unclear. At the present, only two studies (Silva et al. 2021; Awad et al. 2022b) used the TOS to show the frequency of HeOr behaviors among participants with distinct approaches. Awad et al. (2022b) indicated the frequency of HeOr for each independent variable studied (e.g., presence of HeOr separated by gender: male = 37.6%, female = 45.2%) based on mean scores; however, the allocation of participants in present/absent HeOr was unclear. Silva et al. (2021) calculated the mean scores for each factor of the TOS and classified participants according to the likelihood of presenting HeOr and OrNe behaviors using percentiles (P) of *Likert*-type response scale. Table 3 shows this classification. Importantly, the authors emphasized that the strategy used was for the study, which requires future evaluation to verify whether the suggested classification is adequate in other contexts, as this may change when there is a "gold standard," i.e., an official

diagnostic criteria. Using their classification, Silva et al. (2021) found that 5.3% of participants were more likely (>P50) to present OrNe. These individuals were extremely preoccupied with healthy eating, and clinical follow-up would be very helpful to confirm and understand the symptomatology. On the other hand, 41.2% of participants were more likely (>P50) to present HeOr. They are people who are interested in healthy eating and seek to follow it but without exaggerations. In addition, the study found that 4.4% of participants exhibited both OrNe and HeOr behaviors (>P50). This overlap may indicate the validity of considering orthorexia as a continuum phenomenon (Strahler 2020), as participants with high OrNe and HeOr scores are probably people interested in healthy eating, but at certain times they may be more preoccupied than usual with the quality of food.

EHQ. The EHQ was developed in a US context by Gleaves et al. (2013) based on evidence about orthorexia indicated by Bratman and Knight (2000) and on the importance attributed to healthy eating by undergraduate students in introductory psychology and nutrition classes and apparent symptoms of the phenomenon reported by graduate students in clinical psychology. A pool of 21 items composed the final version of the EHQ, which included 12 items to measure problems associated with healthy eating (e.g., "I am distracted by thoughts of eating healthily"), five items to measure knowledge of healthy eating (e.g., "I am more informed than others about healthy eating"), and four items to measure positive feelings about healthy eating (e.g., "I feel in control when I eat healthily"). A 4-point *Likert*-type response scale ranging from 1 (*false, not at all true*) to 4 (*very true*) is used to the EHQ items. Individuals with higher scores on the three factors exhibit greater preoccupation with healthy eating. Subsequent studies (Mohamed Halim et al. 2020; Godefroy et al. 2021) evaluated the EHQ in different samples (Australian and French) and found factorial structures and distribution of items per factor not equivalent to the original study, which may indicate some factorial instability of the instrument.

DOS. The DOS was created by Barthels et al. (2015a) in Germany. Data for the items came from an inductive procedure that included discussions on different subject areas, such as knowledge about the composition and components of food, nutritional supplements, effects of food on bodily functions, psyche and diseases, and general opinions about health. The authors also used the ideas presented by Bratman and Knight (2000) to create the DOS items. A single-factor final model with 10 items (e.g., "I have the feeling of being excluded by my friends and colleagues due to my strict nutrition rules") was designed to measure orthorexia-like eating behaviors. A 4-point *Likert*-type response scale ranging from 1 (*this does not apply to me*) to 4 (*this applies to me to*) is used in the DOS, and a higher score reflects greater OrNe-like behavior. Psychometric studies (Chard et al. 2019; He et al. 2019) have evaluated the DOS and found inconsistencies regarding the adequacy of the single-factor model, which raises doubts about its dimensionality.

Considering the inconsistent data on the dimensionality of both EHQ and DOS, Hallit et al. (2021) conducted a study with a sample of Lebanese adults and found for both instruments two correlated factors interpreted as HeOr and OrNe. Table 2 shows the distribution of items and each factor. The multidimensionality of these

instruments was discovered from the EFA, which was conducted in a sample of participants. However, to date, psychometric evidence of the bidimensional structure of the EHQ and of the DOS has not been showed in different samples to support the adequacy of the models; therefore, this limitation must be taken into account. Importantly, to elaborate the items of an instrument, a clear theoretical rationale is the main guide for the formation of latent factors (Marôco 2021; Kline 2016). From this perspective, developing items with specific content to capture the symptomatology of each dimension of orthorexia would be the most parsimonious way.

ONI. The ONI was proposed in an American context by Oberle et al. (2021) to screen orthorexia-like behaviors from physical, psychosocial, and emotional aspects included in consensual diagnostic criteria for OrNe (Cena et al. 2019). As this instrument was also based on modified items of the EHQ and DOS, speculation emerges as to whether it would also be able to assess HeOr. The ONI encompasses a three-factor model composed of 10 items to assess physical and psychosocial impairments (e.g., "Health professionals have expressed concern that my diet is too restrictive"), nine items to capture behaviors and preoccupation (e.g., "I follow a healthy diet with many rules"), and five items to investigate emotional distress (e.g., "When I stray from my healthy diet, I can only think about what a failure I am"). A 4-point *Likert*-type response scale, which ranges from 1 (*definitely not true*) to 4 (*definitely true*), is used in the ONI with higher scores indicating OrNe symptomatology. The authors proposed a cut-off point using the mean value of >3 to indicate having OrNe (or at least being at high risk for OrNe). What is not clear so far is whether the ONI is an instrument capable of evaluating HeOr, and if it is, it is important to determine how to do this.

What Is the Best Way to Investigate HeOr Symptomatology?

At this point, you should be asking yourself this question. In an epidemiological context, the psychometric instruments seem to be the most prominent tools to screen orthorexia-like behaviors in the population, but caution is essential when using these as all have limitations. This is not surprising, because given that there are no official diagnostic criteria for orthorexia, it is unlikely that any instrument will be considered the best to assess the phenomenon. Psychometric evaluation of the existing attitude scales should continue. Future research should focus on clarifying differences and similarities between the TOS, DOS, EHQ, and ONI for screening OrNe and HeOr. Importantly, no psychometric instrument produces results to determine the presence/absence of orthorexia, as this would require cutoff values to be establish from diagnostic tests. For now, the TOS seems to be the most prominent psychometric tool available.

Investing in reviews of available instruments to investigate the dimensions of orthorexia may be more plausible than creating new ones without knowing exactly where HeOr fits. As the understanding of HeOr advances, the possibility of adjusting existing instruments becomes more tangible, such as improving items and factors. In addition, HeOr investigations with qualitative research design – including clinical

interviews – on healthy eating styles and other related eating habits can be substantially important to generate information to improve the instruments. These data, together with longitudinal and experimental studies (with qualitative and quantitative approaches), may help to increase knowledge about orthorexia, clarify risk factors, and determine the extent to which a pathological obsession exists. This could make preventive and therapeutic intervention strategies more successful (Douma et al. 2021).

What Is the Best Way to Management Symptomatology of Orthorexia?

The answer to this question is not clear and objective. As OrNe is not an officially recognized disorder, elaborating a therapeutic plan is a challenge. A pertinent hesitation that emerges is whether both OrNe and HeOr should be treated considering that they refer to pathological and non-pathological dimensions, respectively. In practical terms with the background of the literature, treating OrNe is probably clear and necessary, as it harms different areas of the person's life. On the other hand, treating HeOr does not seem to be appropriate.

Before guiding a patient with symptoms suggestive of orthorexia, it is important to know if you are the "right professional" for this. For example, people commonly go to a nutritionist in search of more information about food and nutrition but with a focus on receiving a "perfect diet (e.g., a list of foods written on a sheet)" that promotes several benefits, especially the control of body weight. If "diet" is the unique therapeutic approach to be followed in a case of orthorexia, treatment is not in line with projections of improvement in the disturbance. Now, if the therapeutic approach includes techniques to change maladaptive eating behaviors, this needs to be clear for that patient to evaluate their level of involvement. Individuals with OrNe symptomatology must be assisted by nutritionists aligned with this phenomenon, i.e., those trained and able to recognize healthy eating practices and when these practices cross the line toward obsession (Mathieu 2005).

A multidisciplinary team (e.g., nutritionist, psychologist, psychiatrist, physical education teacher, and social worker) is important for the management of orthorexia, as maladaptive traits can affect different areas of people's lives. This also allows for the complete treatment of the phenomenon, since "people don't stay in one spot," as they may have more than one disorder, as well as change categories such as recovering from bulimia nervosa and manifesting orthorexia-like behaviors together with symptoms of stress and anxiety (Mathieu 2005; McGovern et al. 2021). To date, studies on the effectiveness of treatment have not been identified in the literature, but some works have suggested that cognitive-behavioral therapy, exposure therapy, and group therapy can be useful to reduce extreme fixations with healthy eating. These therapies can be applied by well-trained nutritionists and psychologists who should know what patients eat, how they buy and prepare food, and what they think is important to guide/advise change of habits (McGovern et al. 2021; Walker-Swanton et al. 2020; Mitrofanova et al. 2021). In some cases, the prescription of medication –

by a properly qualified physician – may be necessary to reduce debilitating sensations, but this strategy is challenging, as the obsession with "purity" or "naturalness" can prevent the consumption of drugs. On the other hand, individuals who experience orthorexia symptomatology might be a bit more responsive to treatment because they are actually concerned about their health (Mathieu 2005; Douma et al. 2021).

As for HeOr, what therapeutic approach should be followed? Is this plausible? If a "normal" drive for healthy eating is not a problem per se, when should the therapist act? If the risk factors for OrNe and HeOr were elucidated, the answer to these questions would be clearer. For now, it is believed that public health campaigns aimed at promoting health and individual guidance carried out by trained professionals to understand the guidelines are the best paths. These are not therapeutic approaches but preventive and counseling strategies that may avoid the drive toward healthy eating as an extreme preoccupation on the edge of OrNe.

Regardless of whether or not it receives its own diagnostic category, orthorexia appears to be increasingly prominent in society. Knowing the symptomatologic framework involved in this phenomenon is important; however, helping those who suffer from a maladaptive relationship with food is also valuable. Therefore, those involved in the therapeutic process of patients who have healthy eating concerns should be constantly updated on the evolution of the concept of orthorexia. However, they must also be sensitive and empathetic to provide care that goes beyond diagnosis and biomedical therapy, being able to tap into beliefs and emotions that influence and/or determine eating behavior aiming to changing it, when relevant.

Final Considerations

Although the focus of this chapter was to describe the non-pathological dimension of orthorexia (i.e., HeOr), it was necessary to introduce the reader to the characteristics of the pathological dimension (i.e., OrNe). The background presented demonstrates a growing effort of the academic community to understand the negative consequences of OrNe and the dearth of data about HeOr. A better understanding of the non-pathological dimension would be useful in managing people's conscious eating behaviors, offering opportunities to develop prevention and intervention, when the preoccupation with health crosses the line of interest and becomes an obsession.

A focused interest on food is not inherently problematic unless maladaptive behaviors occur and cause distress or lead to impairments. In this way, OrNe and HeOr seem to be separable dimensions that individuals may experience to different degrees. Individuals with symptoms of OrNe have food as the center of life and, due to the ability to control, experience a sense of pride and superiority creating identity. This commonly leads to fixation and obsession with physically, socially, and emotionally negative impacts. On the other hand, people with symptoms of HeOr see eating as a way to promote health, but not the only way, so they are interested in eating to change maladaptive eating behaviors. These changes do not cause

significant damage to these people's life and should not be considered potentially pathological.

Importantly, it is still unclear whether orthorexia represents a disorder, the progression of a disorder, or a lifestyle. It is also unclear whether orthorexia is a multidimensional phenomenon. Therefore, understanding, conceptualizing, and showing how to assess this phenomenon is a challenge that the scientific community will have to unravel, thus making clinical practice assertive and effective. There is still much to discover about orthorexia, especially about HeOr. The conceptualization of this seems to be close to a consensus, finding no associated pathological characteristics. On the other hand, the forms to assess HeOr are still quite unclear, and few tools are available to investigate non-pathological symptoms, with the TOS being the scale that seems to be the most promising. For now, it is worth remembering that following a healthy eating is good, but if obsessive thoughts and fixation behaviors exist, the effects can be reversed, making the person's life more complicated and less long-lasting.

At this point, a final remark is important. Naming HeOr as a non-pathological healthy eating brings it too close to a pathological one. The use of the suffix "orexis" with a negative bias is so common (given to its use to name EDs) that this happens unintentionally. Note in Fig. 3 that when a group of Brazilian students was asked



Fig. 3 Word cloud associated with the terms "healthy eating" (A) and "healthy orthorexia" (B). *Note*. Answers given by Brazilian students to the questions: "When I say healthy eating, what word comes to your mind?" (A) and "When I say healthy orthorexia, what word comes to your mind?" (B). (This figure was created by the authors of this chapter)

about the meaning of "healthy eating" and "healthy orthorexia," the words "health" and "preoccupation" were present in both. Furthermore, the words used by students to characterize HeOr were mostly associated with something problematic. When Bratman (1997) first proposed the existence of orthorexia, he only made reference to what is called today as OrNe to indicate an excessive preoccupation about healthy eating. In research settings, scientists may use the terms OrNe and HeOr to operationalize the supposed bidimensionality of orthorexia in a didactic way. However, despite the theoretical enthusiasm to understand the particular dynamics about orthorexia, the impact that words may cause in the general population should be noted. The use of the term HeOr should always be used with caution, as the suffix *"*orexsis" may be misinterpreted as something harmful. Therefore, for the general public, HeOr might be translated as interest in healthy eating in order not to cause feelings of inadequacy.

Applications to Other EDs

In this chapter, we review the phenomenon of orthorexia focusing on its presumed non-pathological dimension, called healthy orthorexia (HeOr). However, we also had to explore the pathological dimension, called orthorexia nervosa (OrNe), and through this we found suggestions for therapeutic approaches that can reduce extreme fixation on healthy eating. Although OrNe is not recognized as a mental disorder, it is already possible to identify some characteristic aspects of OrNe in the context of EDs. Hence, as more about OrNe is understood, more clinicians and health professionals may add this to their body of knowledge about eating, becoming more resourceful to plan and implement therapeutic plans. Some evidence suggests that OrNe is focused on the quality of food driven by the goal of being as healthy as possible, while EDs can be focused on the quantity of food aiming at body change; however, these two focuses can coexist. Among the therapeutic and preventive approaches mentioned in this chapter for OrNe, psychotherapeutic and psychoeducational strategies stand out, which are also very relevant for the treatment of EDs. The cognitive-behavioral approach is an example of a useful therapy to reduce maladaptive thoughts about healthy eating and, consequently, promote new adaptive eating behaviors, applying to people who exhibit OrNe behaviors, and an official ED (e.g., anorexia nervosa), as they can coexist. Regarding preventive approaches, the chapter provides evidence that may also be considered for other EDs, since it is not clear yet if the controlled and fixated food selection characteristic of OrNe can act as a first sign of other EDs. If OrNe risk factors are divulged, they also may be considered in other ED investigation studies. The chapter also sheds light on a non-pathological healthy eating behavior, HeOr. Although it is conceptually associated with OrNe, the dedication, care, and commitment to healthy eating should not be seen as pathological – even if someone has some weird beliefs regarding what is a good food – if this care and commitment do not cause physical, social, and psychological impacts on one's life. Therefore, it is recommended that in clinical practice (e.g., during an appointment with a psychologist) people are not labeled as

"orthorexic" just because they take care with what they eat, as this label carries a negative perception and may cause psychological distress. People diagnosed with EDs may have excessive preoccupation with healthy eating, and in these cases the therapeutic approaches suggested in this chapter for OrNe may be useful.

Mini-Dictionary of Terms

- **Concern**: A state of interest blended with apprehension or uneasy.
- **Drive**: An arousal state that influences beliefs and behaviors related to its aim.
- **Eating behavior**: A set of cognitions and affections that support actions in relation to the act of eating and are strongly related to biological, psychosocial, cultural, and environmental aspects.
- **Fixation:** An obsessive preoccupation or attachment to making something firm or stable.
- **Healthy orthorexia**: A non-pathological interest in healthy eating behavior.
- **Maladaptive behavior:** An action that interferes with everyday activities with potential harmful effects.
- **Non-orthorexia nervosa**: Synonymous with healthy orthorexia.
- **Obsession:** A persistent and disturbing idea or thought.
- **Orthorexia nervosa**: A possible pathological fixation on healthy eating.
- **Preoccupation**: Synonymous with concern with a likely higher degree of alarm.
- **Psychometric properties**: Validity (e.g., factorial) and reliability (e.g., internal consistency) estimates that allow showing data on the capacity of an instrument to measure latent construct(s).
- **Score**: A numerical value that can be used to interpret the magnitude of a phenomenon.
- **Trigger**: Something that sets off a mechanism.

Key Facts of Orthorexia

- Orthorexia is represented by the concern with healthy eating that can be obsessive or not.
- The term orthorexia nervosa has been used to represent an extreme fixation on healthy eating that can damage various areas of a person's life.
- Orthorexia nervosa is not yet recognized as a mental disorder included in the DSM-5 and ICD-11.
- People with pathological behaviors to achieve a healthy diet can experience physical and mental impairments; therefore, therapeutic approaches used in official mental disorders can be useful.
- The term healthy orthorexia has been used to represent an interest in healthy eating without obsessive behavior; however, it is not yet consolidated in the literature.

- People who are interested in eating healthy can benefit from guidelines to direct their eating behaviors; however, these individuals do not have pathological symptoms that require intervention therapy.

Summary Points

- Orthorexia is a phenomenon that lies on a continuum, which goes from an interest in healthy eating (non-pathological) to an extreme preoccupation and control (pathological).
- Knowing the drive for healthy eating can be helpful for clinical management.
- Orthorexia nervosa encompasses an intensification of the preoccupation with healthy eating with disturbing thoughts and stereotypical behaviors.
- Healthy orthorexia involves an interest in healthy eating that does not harm the person's life.
- This chapter focuses on the conceptualization of healthy orthorexia and explores its forms of assessment and empirical evidence.
- Much is known about orthorexia nervosa behaviors, but little is known about healthy orthorexia.
- The use of proper assessment tools is necessity in the field, which is more focused on orthorexia nervosa, but a special look at healthy orthorexia is also helpful.

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The Binge Eating Scale

75

Features and Applications

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Contents

Introduction 1504
Diagnosis and Scales 1505
Binge Eating Scale 1506
Scoring 1507
Other Uses of BES 1507
Limitations 1508
Other Versions 1508
Modified Versions of BES 1509
Applications to Other Eating Disorders 1510
Mini-Dictionary 1511
Key Facts 1511
Key Summary Points 1511
Conclusion 1512
Questions in Binge Eating Scale and Scoring 1512
References 1514

Abstract

Binge eating disorder (BED) is a type of ED that is characterized by recurrent episodes of binge eating (BE) without subsequent compensatory behaviors, such as self-induced vomiting or over-exercising. The Binge Eating Scale (BES) is one of the most common instruments used to screen binge eating severity. The BES has been found to demonstrate a very good internal consistency (between 0.85 and 0.90) and a good construct validity. There have been various versions developed of BES like French, Persian, Arabic, Spanish, etc.

Keywords

Binge eating · Scale · Eating disorder

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Introduction

Eating disorder (ED) most frequently affects young Western females within high-income and industrialized Western Europe and North America, but can also occur in diverse countries and cultures worldwide to a lesser extent. The disorder is found to be more common in the population suffering from obesity, and it is usually associated with several psychiatric (anxiety, depression, obsessive-compulsive disorder) and physical comorbidities (diabetes, hypertension). It has been seen that anxiety is the most important associated factor with ED, followed by stress, body image, and depression.

Binge eating disorder (BED) is a type of ED that is characterized by recurrent episodes of binge eating (BE) without subsequent compensatory behaviors, such as self-induced vomiting or over-exercising (Zeidan et al. 2019). Very high BED prevalence rates have been reported in adolescents and young adults, with higher prevalence rates in women than in men, and recent neuroimaging studies suggest that this sex differences in binge eating may be due to the presence of some alteration in the female brain's reward system, such as the lower ability to suppress hunger in women (Escrivá-Martínez et al. 2019; Imperatori et al. 2016). Smink et al. showed that BE has two peak ages of onset, one immediately after puberty at an average age of 14, and the other at the end of adolescence (19–24 years). Average lifetime prevalence is estimated to be 1.9% for BED, making it the most common ED (Escrivá-Martínez et al. 2019).

The risk factors associated with BED are similar to those with psychiatric disorders and obesity. The most common risk factors associated with BED are as follows (Zeidan et al. 2019):

1. Adverse childhood experiences such as sexual/physical abuse.
2. Parental problems like depression.
3. Negative self-evaluation.
4. Vulnerability to obesity.
5. Repeated exposure to negative comments about shape, weight, or eating is associated with BED.
6. A positive correlation has been found between BE and food addiction.
7. Emotional eating has also been found to be positively related to BE. In fact, overeating just for emotional reasons and cravings may turn quickly into BED.
8. Family history of eating disorders is associated with higher BE. BED is found to aggregate strongly within families, which may reflect genetic influences.

Tuschen-Caffier and Hilbert model has integrated the triggering and sustaining factors of the BED in addition to the risk factors. Based on this model, different external and internal stressors like relationship conflicts, exposure to food, impulsivity, low self-esteem, and tensions have been identified that can trigger BE. BED also shares characteristics with substance use and addictive disorders (Zeidan et al. 2019).

Recent research indicates the presence of comorbidity between BE and the use of alcohol and binge drinking in young people. Impulsivity can play an important role in the comorbidity between disordered eating behavior and excessive alcohol consumption in young students and has also been positively associated with BE (Escrivá-Martínez et al. 2019).

Despite data suggesting that only a small subset of adolescents 10–13 and even fewer children 14–16 meet full DSM-IV-TR criteria for BED, binge eating and the experience of loss of control (LOC) while eating (regardless of the amount of food ingested) appear to be quite common among youth (Tanofsky-Kraff et al. 2007).

Diagnosis and Scales

Diagnosis of BED according to the *Diagnostic and Statistical Manual of Mental Disorders*, Fifth Edition (*DSM-5*), is based on the occurrence of at least one BE episode per week for three consecutive months; these episodes are characterized by the consumption of larger amounts of food in a short period when compared to the typical amounts for most people under similar circumstances, accompanied by a sense of loss of control over eating and a marked distress during these episodes (Zeidan et al. 2019).

Eating Disorder Examination (EDE) interview provides a comprehensive scheme for classifying episodes of overeating using perceived lack of control and amount of food consumed as criteria to distinguish between different types of overeating. Based on these criteria, four different types of overeating are identified: (a) objective binge eating: loss of control and objectively large amount consumed; (b) subjective binge eating: loss of control and small amount consumed even though the individual views intake as excessive; (c) objective overeating: no loss of control and objectively large amount consumed; and (d) subjective overeating: no loss of control and small amount consumed, but individual views amount consumed as excessive. Objective binge eating is used as part of the *DSM-IV* diagnostic criteria for Binge Eating Disorder (BED; American Psychiatric Association 1994; Timmerman 1999).

To assess any psychological disorder including binge eating, structured clinical interview is considered as gold standard. However, it is time-consuming, requires training, and can only be administered to one subject at any particular time (Robert et al. 2013).

Several self-report questionnaires have been developed to assess BED to replace the interview and save time. Gormally et al. (1982) developed the BES, Yanovski (1993) developed the Questionnaire on Eating and Weight Patterns (QEWP-R), and Fairburn and Beglin (1994) developed the Eating Disorder Examination Questionnaire (EDE-Q).

The Binge Eating Scale (BES) is one of the most common instruments used to screen binge eating severity.

Binge Eating Scale

The Binge Eating Scale (BES) was developed by Gormally et al. to measure severity of binge eating, the uncontrolled consumption of a large amount of food, in overweight binge eaters (Timmerman 1999). It is an interesting tool both in terms of evaluation and monitoring of these patients, as it can be used for the purposes of screening, evaluation of severity, and monitoring of the disorder (Zeidan et al. 2019). Since its inception, the BES has been used widely in research to measure binge eating severity in the non-purge binge eating population and to determine whether potential research participants meet the inclusion criteria of binge eating (Timmerman 1999).

Importantly, the BES is not intended to detect presence of Binge Eating Disorder (BED) as it was created before binge eating disorder (BED) was officially recognized as a psychiatric diagnosis (American Psychiatric Association 1994). Rather, it can be used as a brief screening tool to identify the severity of binge eating behavior in overweight and obese adults, to tailor obesity interventions, and to track treatment outcomes (Cotter and Kelly 2015).

The BES was designed as a measure of severity rather than diagnosis of BED, with the additional property of evaluating its affective, cognitive, and behavioral manifestations. It has an outstanding role as a screening measure in clinical and nonclinical populations to evaluate BE severity and intervention outcomes (Escrivá-Martínez et al. 2019). It does not specify a time frame and presents a series of differently weighted statements for each item, from which respondents select the statement that best describes their attitudes and behaviors (Celio et al. 2004).

Studies carried out in the past decade, mainly with obese patients, have shown that the BES is very sensitive and specific in distinguishing between compulsive and normal eaters (Escrivá-Martínez et al. 2019).

The BES has been found to demonstrate a very good internal consistency (between 0.85 and 0.90) and a good construct validity (Zeidan et al. 2019).

The BES items were created in accordance with the "Diagnostic and Statistical Manual of Mental Disorders, 3rd edition," criteria for binge eating. Although the BES is not designed to assess for the presence of binge eating disorder (BED), in one of the few studies that evaluated the concordance between the BES and BED in bariatric surgery candidates, BES was found to have a high sensitivity and adequate specificity in identifying those with BED (Cotter and Kelly 2015). Estimated internal consistency of the measure is generally acceptable across samples, including men and women from the community, college students, treatment-seeking adults, and racially/ethnically diverse groups (Hood et al. 2013).

The BES demonstrates a significant association with several indicators of subjective binge eating (SBE) like calories consumed during SBEs, number of SBEs, and number of SBE days. Small-to-moderate, significant correlations have also been noted between the BES and similar indicators of objective binge eating. BES scores do not correlate with overall caloric intake and is not successful in discriminating between SBEs and OBEs, but appears to be a good indicator of severity of LOC eating (Cotter and Kelly 2015).

The BES is a 16-item self-report measure designed to assess two components of binge eating: behavioral manifestations (e.g., eating quickly, overeating) and emotions/cognitions that precede or follow a binge (e.g., feeling out of control, guilt) (Hood et al. 2013).

The initial development of the scale yielded two eight-item factors representing the behavioral and cognitive/emotional aspects of binge eating. More recent examinations of the scale further support this two-factor solution, suggesting that the existing subscales remain appropriate across a range of samples (Cotter and Kelly 2015).

Scoring

The BES consists of 16 items, eight describing the behavioral manifestations of binge eating and eight describing feelings and cognitions associated with binge eating. Each item consists of four statements that reflect a range of severity (0 indicates no binge eating problem and 3 indicates a severe binge eating problem). Subjects choose the statement that best describes their perceptions and feelings about their eating behavior. The BES is scored by adding the individual values for the 16 items with the possible range of scores from 0 to 46 (Timmerman 1999).

Based on BES scores, the uncontrolled eating behavior is graded into three different levels of severity: subjects scoring 17 and less were considered non-binge eaters, those scoring between 18 and 26 were moderate binge eaters, and those scoring 27 and above were considered severe binge eaters (Robert et al. 2013).

Thus, the total score is used to differentiate among those with absent to minimal binge eating, mild to moderate binge eating, and severe binge eating (Hood et al. 2013).

Based on the BES total raw scores, Marcus et al. (1988) identified three different levels of severity: individuals scoring 17 or less were considered not reporting significant binge eating, those scoring between 18 and 26 were considered moderate binge eaters, and those scoring 27 and above were considered severe binge eaters. These categories had a 98% concordance rate with a diagnosis using a semi-structured interview (Imperatori et al. 2016).

Other Uses of BES

BES has been used as a screening measure in prebariatric surgery psychological evaluations (Hood et al. 2013). Administering the BES as part of a comprehensive psychological evaluation can help improve the assessment and treatment of patients presenting for bariatric surgery (Celio et al. 2004). BES is a reliable measure that identifies approximately one third of patients seeking bariatric surgery (Hood et al. 2013). When prescreening potential bariatric surgery patients, clinicians are likely to be interested in identifying patients who endorse significant binge behaviors, even if

they do not meet full criteria for BED. In other words, identifying false positives is often acceptable as further evaluation and appropriate presurgical cognitive/behavioral interventions can be recommended. Timmerman reported an adequate 2-week test–retest reliability of the BES in a behavioral weight loss sample. BES is an appropriate measure to screen for binge eating behaviors in nonsurgical weight loss treatment, although false positives may be common (Celio et al. 2004).

Limitations

1. Gormally et al. originally proposed a two-dimensional structure, dividing the items of the BES into cognitive and behavioral BE, but the results on its two-dimensionality use are contradictory (Zeidan et al. 2019). Most of the times it is exclusively used as a unidimensional measure of binge eating severity through the measure's total score, but studies have shown that both the unidimensional and the two-factor models provide an adequate fit to the data, in fact the fit of the two-factor model maybe better (Hood et al. 2013). Of all the models compared, the bi-factor model is more superior in its potential for replication. Various studies have cast doubt on the utility of calculating the behaviors and feelings/cognitions factors as separate scores on the BES (Imperatori et al. 2016; Hood et al. 2013).

2. Though BES questionnaire has been widely used, there is limited research on the factors and properties of the BES in the general population. There is no study examining its psychometric properties in general populations of young men and women. Research has been done to assess the validity in specific samples like clinical samples or samples of women, especially obese women who undergo bariatric surgery to lose weight (Hood et al. 2013; Marek et al. 2016), or obese and overweight patients seeking weight loss treatment (Imperatori et al. 2016).

3. BES may be adequate for screening purposes but its use solely for the diagnosis of BED is not recommended due to the high percentage of misclassifications (Celio et al. 2004).

Other Versions

The BES has been translated into a variety of languages and validated in multiple international samples.

Spanish version: Spanish version of the BES is a valid and reliable scale for the assessment of BE in a youth sample. This brief, easy-to-administer, self-report questionnaire consists of 16 items on one scale. It provides relevant information about clinically significant symptoms of BE, and it may be especially useful in prevention programs and community interventions for disordered eating behaviors (Escrivá-Martínez et al. 2019).

Persian version: The BES showed acceptable reliability and considerable sensitivity (84.8%) and specificity (80.8%). BES, also, effectively distinguished the obese participants from the normal weight subjects. These results suggest that the

Persian version of BES is a sensitive instrument for screening binge eating among the nontreatment-seeking obese population (Mootabi et al. 2009).

Indonesian version: The Indonesian version of BES has good validity. The two-factor BES was revealed to be important in Indonesia, cross-culturally. There were language and cultural differences among Indonesian ethnics, which required a scale that uses standard language. This Indonesian version of BES can be used immediately. Thus, it can help improve planning of health promotion, prevention, and treatment of binge eating (Kusbiantari et al. 2020).

French version: The psychometric properties of the French version of the BES are comparable to its original version with a one factor structure. The BES is a useful tool to assess binge eating disorder in obese patients but might not differentiate binge eating disorder and bulimia nervosa in underweight and optimal weight subjects (Brunault et al. 2016).

Arabic Version: The Binge Eating Scale in its Arabic version is a suitable instrument to screen for binge eating among the Lebanese population. Some factors (body dissatisfaction, having a history of sexual abuse, a family history of binge eating, greater depressive/anxiety symptoms, and lower self-esteem) seem to be associated with higher binge eating (Zeidan et al. 2019).

Malaya Version: A study demonstrated high levels of sensitivity (84.6%) and specificity (94.9%) of the Malay version of BES in detecting binge eating behavior within a Malay-speaking adult population, with a positive predictive value of 81.8%, negative predictive value of 95.7% and Cronbach's alpha of 0.89. Therefore, the Malay version of the BES is useful as it has been demonstrated to be a valid and reliable instrument that is easy to administer (Robert et al. 2013).

Only five of the 16 items were correlated when studies were carried out to determine possible ways to strengthen concordance of the BES with a BED diagnosis. The items that were significantly associated with a BED diagnosis measured preoccupation with eating (item 14), guilt after overeating (item 6), difficulty controlling eating (item 10), preoccupation with food (item 15), and eating when not hungry (item 5) (Celio et al. 2004).

When using the BES clinical cutoffs there is tendency to over diagnose BED so it is suggested that the BES be used as a brief screening device and not as a diagnostic indicator (Cotter and Kelly 2015).

Modified Versions of BES

1. **The Children's Binge Eating Disorder Scale** (C-BEDS) is a 7-item measure which includes Marcus and Kalarchian's criteria. For example One item asks, "Do you ever eat because you feel bad, sad, bored, or any other mood?" to which children respond "yes" or "no" (Tanofsky-Kraff et al. 2007).

This scale was developed to measure BED in children according to the provisional criteria. Both the provisional criteria and the C-BEDS may be developmentally appropriate for use with children, although the C-BEDS may be a better screening

instrument as it quickly identified children with subsyndromal BED. If used by physicians and other health providers, this brief measure may assist with identifying early onset binge eating behaviors and avoiding the associated consequences, including adult BED, obesity, and other comorbidities (Shapiro et al. 2007).

2. **The Adolescent Binge Eating Scale** questionnaire is a potential screening tool to identify adolescents with obesity at high risk of BED and guide referral to a specialist to clarify the diagnosis and provide adequate care. Binge eating disorder (BED) is associated with obesity and high rates of medical and psychopathologic comorbidity, as well as increased healthcare use. Research involving children and adolescents has shown that few meet all the criteria for BED, as described by the fifth edition of the *Diagnostic and Statistical Manual of Mental Disorders*. The ADO-BED auto-questionnaire demonstrated a good association with the clinical interview for BED, particularly for question 1, "food seeking in the absence of hunger or after satiation," which was efficient to exclude adolescents without BED when answered negatively. The first question was more indicative than the second relative to the sense of lack of control over eating (sensitivity 85.7%). This may be explained by the subjectivity of this question and the adolescents' limited capacity to recognize such a behavior, even when illustrated by a concrete example such as, "Has it ever happened that you started eating biscuits and could not stop before the end of the packet?" However, answering positively to one of these two questions was not in itself predictive of BED (specificity 27.4%) (Chamay-Weber et al. 2017).

Applications to Other Eating Disorders

The Binge Eating Scale (BES) has no direct role in the assessment of other eating disorders but may be used as an add-on scale when scales for other eating disorders are applied. This is more so as binge eating behavior may be part of other eating disorders like Bulimia and is worth evaluating in those patients. The BES may provide insights into the binge eating behavior patterns in those patients and may also provide insights into the comprehensive management of these patients. The BES may be of use in patients with obesity where there are binge eating issues, and as a result, there is weight gain and there are many instances that these patients may have guilt and shame related to binge eating. The scale may help in the management of binge eating behavior in patients with obesity and looking at weight management as a part of their treatment. The BES may be useful in patients with borderline personality disorder that may have binge eating as a coping mechanism in these patients. The scale may also be useful in adolescents that have binge eating as mechanism of coping. There is a need to study the usefulness of BES in these populations so that we are able to deduce its utility in these cases and decipher its exact applications. Detailed literature in these conditions is sparse.

Mini-Dictionary

1. **Adolescence:** Adolescence is the transitional phase of growth and development between childhood and adulthood. The World Health Organization (WHO) defines an adolescent as any person between ages 10 and 19.
2. **Binge:** a period of excessive indulgence in an activity, especially eating, drinking, or taking drugs.
3. **Disorder:** a disturbance of normal functioning of the mind or body.
4. **Eat:** put (food) into the mouth and chew and swallow it.
5. **Obesity:** A disorder involving excessive body fat that increases the risk of health problems.
6. **Overeat:** Eat too much.
7. **Screening:** the evaluation or investigation of something as part of a methodical survey, to assess suitability for a particular role or purpose.

Key Facts

- The Binge Eating Scale (BES) is one of the most commonly used instruments to screen binge eating severity.
- There are many versions of scale in many languages like French, Persian, Arabic, Spanish, etc.
- The BES has been found to demonstrate a very good internal consistency and reliability.
- The scale aids in screening, diagnosis, and to judge improvement in children and adults with binge eating problems.
- Apart from binge eating disorder, the BES has uses in other eating disorders and obesity as well as patients undergoing bariatric surgery.

Key Summary Points

- The BES is one of the most widely used scales in the screening and diagnosis of binge eating behavior and binge eating disorder.
- The scale has greater use in the measurement of severity rather than diagnosis of binge eating disorder.
- The BES has a version to assess binge eating severity in children and adolescents as well.
- Further studies of the BES in diverse populations of eating disorders are needed to validate its use better.
- The BES also has versions in many languages that allow it to be used in national and international populations across research studies.

Conclusion

The BES may identify a significant number of patients with moderate/severe binge eating who do not meet criteria for BED; this is acceptable for a screening instrument, where false positives are more desirable than false negatives. Finally, clinicians can be very confident that a patient with a negative BES screen most likely does not have BED (Grupski et al. 2013).

Questions in Binge Eating Scale and Scoring

1. Self-conscious about weight:
   - I do not think about my weight or size when I'm around other people.
   - I worry about my appearance, but it does not make me unhappy.
   - I think about my appearance or weight and I feel disappointed in myself.
   - I frequently think about my weight and feel great shame and disgust.
2. Eat Quickly:
   - I have no difficulty eating slowly.
   - I may eat quickly, but I never feel too full.
   - Sometimes after I eat fast I feel too full.
   - Usually I swallow my food almost without chewing, then feel as if I ate too much.
3. Difficulty controlling Eating Urges:
   - I can control my impulses towards food.
   - I think I have less control over food than the average person.
   - I feel totally unable to control my impulses toward food.
   - I feel totally unable to control my relationship with food and I try desperately to fight my impulses toward food.
4. Eat when bored:
   - I do not have a habit of eating when I am bored.
   - Sometimes I eat when I am bored, but I can often distract myself and not think about food.
   - I often eat when I am bored, but I can sometimes distract myself and not think about food.
   - I have a habit of eating when I am bored and nothing can stop me.
5. Eat when not hungry:
   - Usually when I eat it is because I am hungry.
   - Sometimes I eat on impulse without really being hungry.
   - I often eat to satisfy hunger even when I know I've already eaten enough. On these occasions I can't even enjoy what I eat.
   - Although I have not physically hungry, I feel the need to put something in my mouth and I feel satisfied or only when I can fill my mouth (for example with a piece of bread).

6. Guilt after overeating:
   - I do not feel guilty or regretful at all.
   - I sometimes feel guilty or regretful.
   - I almost always feel a strong sense of guilt or regret.
7. Diet and Binge:
   - When I'm on a diet, I never completely lose control of food, even in times when I eat too much.
   - When I eat a forbidden food on a diet, I think I've failed and eat even more.
   - When I'm on a diet and I eat to much, I think I've failed and eat even more.
   - I am always either binge eating or fasting.
8. Eat tilled stuff:
   - It is rare that I eat so much that I felt uncomfortably full.
   - About once a month I eat so much that I felt uncomfortably full.
   - There are regular periods during the month when I eat large amounts of food at meals or between meals.
   - I eat so much that usually, after eating, I feel pretty bad and I have nausea.
9. Diet/restrict and binge:
   - The amount of calories that I consume is fairly constant over time.
   - Sometimes after I eat too much, I try to consume few calories to make up for the previous meal.
   - I have a habit of eating too much at night. Usually I'm not hungry in the morning and at night I eat too much.
   - I have periods of about a week in which I imposed starvation diets, following periods of when I ate too much. My life is made of binges and fasts.
10. Difficulty controlling eating:
    - I can usually stop eating when I decide I've had enough.
    - Sometimes I feel an urge to eat that I cannot control.
    - I often feel impulses to eat so strong that I cannot win, but sometimes I can control myself.
    - I feel totally unable to control my impulses to eat.
11. Eat till stuffed or sometimes vomit:
    - I have no problems stopping eating when I am full.
    - I can usually stop eating when I feel full, but sometimes I eat so much it feels unpleasant.
    - It is hard for me to stop eating once I start, I usually end up feeling too full.
    - It is a real problem for me to stop eating and sometimes I vomit because I feel so full.
12. Conceal eating:
    - I eat the same around friends and family as I do when I am alone.
    - Sometimes I do not eat what I want around others because I am aware of my problems with food.
    - I often eat little around other people because I feel embarrassed.
    - I'm so ashamed of overeating; I only eat at times when no one sees me. I eat in secret.

13. Eat continually:
    - I eat three meals a day and occasionally a snack.
    - I eat three meals a day and I usually snack as well.
    - I eat many meals, or skip meals regularly.
    - There are times when I seem to eat continuously without regular meals.
14. Preoccupation with eating:
    - I don't think about impulses to eat very much.
    - Sometimes my mind is occupied with thoughts of how to control the urge to eat.
    - I often spend much time thinking about what I ate or how not to eat.
    - My mind is busy most of the time with thoughts about eating.
    - I seem to be constantly fighting not to eat.
15. Preoccupied with food:
    - I don't think about food any more than most people.
    - I have strong desires for food, but only for short periods.
    - There are some days when I think of nothing but food.
    - Most of my days is filled with thoughts of food. I feel like I live to eat.
16. Uncertain how much food is normal:
    - I usually know if I am hungry or not. I know what portion sizes are appropriate.
    - Sometimes I do not know if I am physically hungry or not. In these moments, I can hardly understand how much food is appropriate.
    - Even if I knew how many calories should I eat, I would not have a clear idea of what is, for me, a normal amount of food.

Non-binging; less than 17
Moderate binging; 18–26
Severe binging; 27 and greater

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Health-Related Quality of Life Questionnaires

76

Applications to Eating Disorders

Jelena Milic, Dunja Stankic, and Dona Stefanovic

Contents

Introduction 1518
The Short Form-36 (SF-36) 1519
Eating Disorder Examination-Questionnaire (EDE-Q) 1519
Short Form-12 Health Status Questionnaire (SF-12) 1521
Weissman Scale of Social Adjustment 1522
BDI 1523
The Eating Disorder Diagnostic Scale (EDDS) 1523
Health-Related Quality of Life in ED-Short Form (HeRQoLED-S) 1525
Conclusion 1526
Mini-Dictionary of Terms 1526
Key Fact of Health-Related Quality of Life Questionnaires: Applications to EDs 1527
Summary Points 1527
References 1527

Abstract

People suffering from eating disorders (EDs) are affected both on the somatic and psychological and social aspects. The World Health Organization used the term quality of life to define individuals' perception of their position in life in the context of the culture and value systems in which they live and in relation to their goals,

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expectations, standards, and concerns to express the broad range of changes in a person's life. Some of these changes are either triggered or suffer consequences from eating habits that are often a form of EDs. In the last few decades, there is an increasing interest in finding adequate questionnaires to help identify and measure the severity of EDs, as well as questionnaires to examine the quality of life in these patients. Several studies have been conducted on this subject, and the evolution and scientific advancement will be elaborated and discussed in the following text in order to identify the most appropriate questionnaire that will aid clinicians in their therapeutic practice. Among the first questionnaires used in practice to assess the quality of life of patients with an ED were Short Form-36 (SF-36) and the Eating Disorder Examination-Questionnaire (EDE-Q). Although the generic questionnaires were applied and yielded good results, a specific questionnaire on the quality of life of individuals with EDs is still lacking in this field. New discoveries are made as the search for highly specialized and sensitive questionnaires continues. Several instruments and questionnaires are used to obtain a final result in several studies investigating the association between the intensity of symptoms induced by EDs and quality of life. The most recent questionnaires specific to the quality of life of a patient with an ED are the Eating Disorders Quality of Life Scale (EDQLS) and the Eating Disorders Quality of Life Scale (EDQOL). We conclude that there has been great progress in evaluating and designing appropriate questionnaires to help clinicians and researchers in the diagnosing, developing treatment strategies, and prognosing EDs, as well as assessing quality of life in these patients.

Keywords

Eating disorder · Quality of life · Questionnaire · Instrument

Abbreviations

BDI	Beck Depression Inventory
EAT-26	Eating Attitudes Test
EDDS	The Eating Disorder Diagnostic Scale
EDE-Q	Eating Disorder Examination-Questionnaire
HADS	The Hospital Anxiety and Depression Scale
HeRQoLED-s	Health-Related Quality of Life in ED-short form
QoL	Quality of Life
SF-12	Short Form-12 Health Status Questionnaire
SF-36	The Short Form-36
WHO	The World Health Organization

Introduction

People suffering from eating disorders (EDs) are affected both on the somatic and psychological and social aspects. Eating problems are increasingly demonstrating potentials to cause substantial medical, mental, and social consequences. The WHO defines quality of life as the World Health Organization (WHO) defines QoL as an

individual's perception of their position in life in the context of the culture and value system in which they live and in relation to their goals, expectations, standards, and concerns (Orley et al. 1998). As a result, a wide range of related domains, such as the connection of physical health with social and psychological functioning, have an impact on quality of life. If EDs progress to a chronic stage, they can have a substantial influence on the patient's physical, social, psychological, and other aspects of life. As a result, assessing the quality of life of ED patients is an important part of the treatment process and should be incorporated into therapeutic practice.

In the last few decades, there has been more and more interest in finding adequate questionnaires to help identify and measure the severity of EDs, as well as questionnaires to examine the quality of life of these patients. Several studies have been conducted on this subject, and the evolution and scientific advancement will be elaborated and discussed in the following text in order to identify the most appropriate questionnaire that will aid clinicians in their therapeutic practice (Fig. 4).

Among the first questionnaires used in practice to assess the QOL of patients with an ED were Short Form-36 (SF-36) and the Eating Disorder Examination-Questionnaire (EDE-Q).

The Short Form-36 (SF-36)

A generic health-related quality of life questionnaire, the Short Form-36 (SF-36), examines quality of life (Fairburn and Wilson 1993). The SF-36 comprises questions concerning an individual's functioning and contentment in several areas of life. The SF-36 is a 36-question survey that examines a person's happiness with their physical, mental, social, and emotional well-being. The SF-36 scale has a range of 0 to 100 points. A higher score suggests a better quality of life (Fairburn and Wilson 1993) (Fig. 1).

Although the generic Short Form-36 (SF-36) questionnaire was applied and yielded good results, a specific questionnaire on the quality of life of individuals with EDs is lacking in this field. The questionnaire was used to assess the quality of life of patients with EDs; nevertheless, issues were found that obscured the true image of the quality of life of these patients. The fundamental concern is that the Short Form-36 is not sensitive or specific enough for patients with EDs – in other words, it does not address enough aspects relevant to how EDs can affect a patient's quality of life. Specific concerns and common symptoms associated with certain disorders, such as EDs, are assessed using disease-specific questionnaires. Disease-specific questionnaires are more likely to show substantial differences than generic questionnaires because they are more sensitive. Scientists were inspired by the challenge to create and evaluate new, more sensitive quality of life questionnaires.

Eating Disorder Examination-Questionnaire (EDE-Q)

The Eating Disorder Examination-Questionnaire (EDE-Q) is a self-assessment questionnaire adapted by Fairburn (Ware et al. 1993). The questionnaire is structured

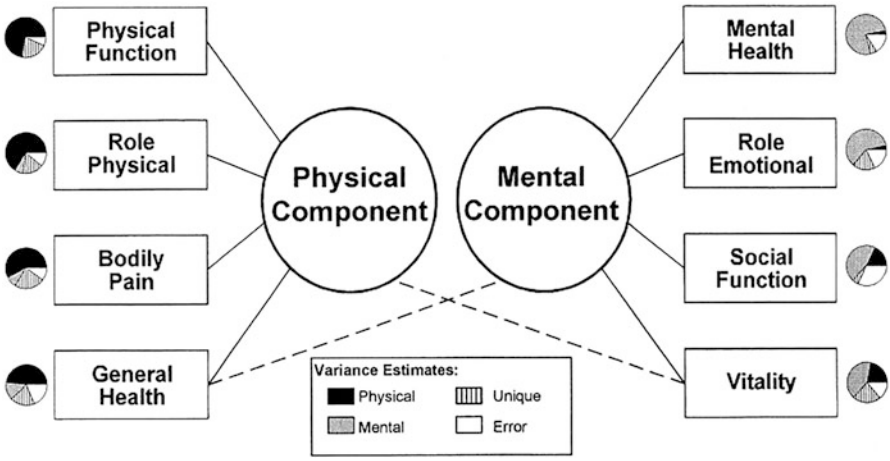


Fig. 1 Components of the Short Form-36 questionnaire. A generic health-related quality of life questionnaire (SF-36) which includes both physical and mental component (Ware and Gandek 1998)

into 36 questions about the patient's eating habits during the previous 28 days. It includes questions based on DSM-IV criteria for EDs. Feeling obese, fear of gaining weight, bulimic episodes, certain dietary restrictions, compensatory behaviors such as self-induced vomiting or laxative abuse, irrational desire to lose weight, obsessive need for a healthy diet, and the impact of physical appearance on self-esteem are all covered by the questionnaire. In regard to the frequency of symptoms in the previous 28 days, the questions were assessed on a scale of 6 points (Fig. 2).

A study published by S. Engel in 2006 was conducted on the development and validation of questionnaires designed to combine the symptoms of EDs with quality of life. In this study, the EDE-Q questionnaire proved to be more specific than the SF-36 questionnaire for determining the severity of the stage of an ED and the consequences that these disorders can contribute to the quality of life of patients (Engel et al. 2006). The EDE-Q questionnaire provides an opportunity for clinicians and researchers treating EDs to assess the degree of reduced quality of life since the questionnaire is designed to address the issues and concerns of people with EDs, and it can be very useful in clinical research to assess treatment outcomes (Figs. 3, 4, 5, and 6).

New discoveries are made as the search for highly specialized and sensitive questionnaires continues. Several instruments and questionnaires were used to obtain a final result in several studies investigating the association between the intensity of symptoms induced by EDs and quality of life. What led researchers and scientists to this approach is that a substantial percentage of patients with EDs suffer from other mental disorders in addition to EDs, most often anxiety disorders, mood disorders, depression, and others. A study conducted in 2014 looked at the

	On how many of the past 28 days	No days	1-5 days	6-12 days	13-15 days	16-22 days	23-27 days	Every day
1	Have you been deliberately trying to limit the amount of food you eat to influence your shape or weight (whether or not you have succeeded)?	0	1	2	3	4	5	6
2	Have you gone for long periods of time (8 waking hours or more) without eating anything at all in order to influence your shape or weight?	0	1	2	3	4	5	6
3	Have you tried to exclude from your diet any foods that you like in order to influence your shape or weight (whether or not you have succeeded)?	0	1	2	3	4	5	6
4	Have you tried to follow definite rules regarding your eating (for example, a calorie limit) in order to influence your shape or weight (whether or not you have succeeded)?	0	1	2	3	4	5	6
5	Have you had a definite desire to have an empty stomach with the aim of influencing your shape or weight?	0	1	2	3	4	5	6
6	Have you had a definite desire to have a totally flat stomach?	0	1	2	3	4	5	6
7	Has thinking about food, eating or calories made it very difficult to concentrate on things you are interested in (for example, working, following a conversation, or reading)?	0	1	2	3	4	5	6

Fig. 2 Eating Disorder Examination-Questionnaire EDE-Q. An example of questionnaire (EDE-Q) (Rø et al. 2015)

quality of life of a large group of people with EDs and discovered potential predictors of quality of life. The Eating Disorder Examination-Questionnaire (EDE-Q), Short Form-12 Health Status Questionnaire (SF-12), the Weissman Social Adjustment Scale, and the Beck Depression Inventory (BDI) were the four types of questionnaires that were utilized in this study (Bamford et al. 2015).

Short Form-12 Health Status Questionnaire (SF-12)

The Short Form-12 Health Status Questionnaire (SF-12) (Ware Jr et al. 1996) is a standardized measure that assesses the respondents' physical and psychological well-being. It is made up of 12 questions separated into two parts: the Physical Component Summary Scale (PCS) and the Mental Component Summary Scale (MCS). The physical component of the health condition questions assesses if the patient's physical health limits his daily physical activities, as well as his ability to function in society and whether it impacts his productivity at work and in other activities. The mental component of the questionnaire includes questions that examine how an individual's mental and emotional health affects social functioning and productivity at work, as well as how nervous, sad, or lethargic they are.

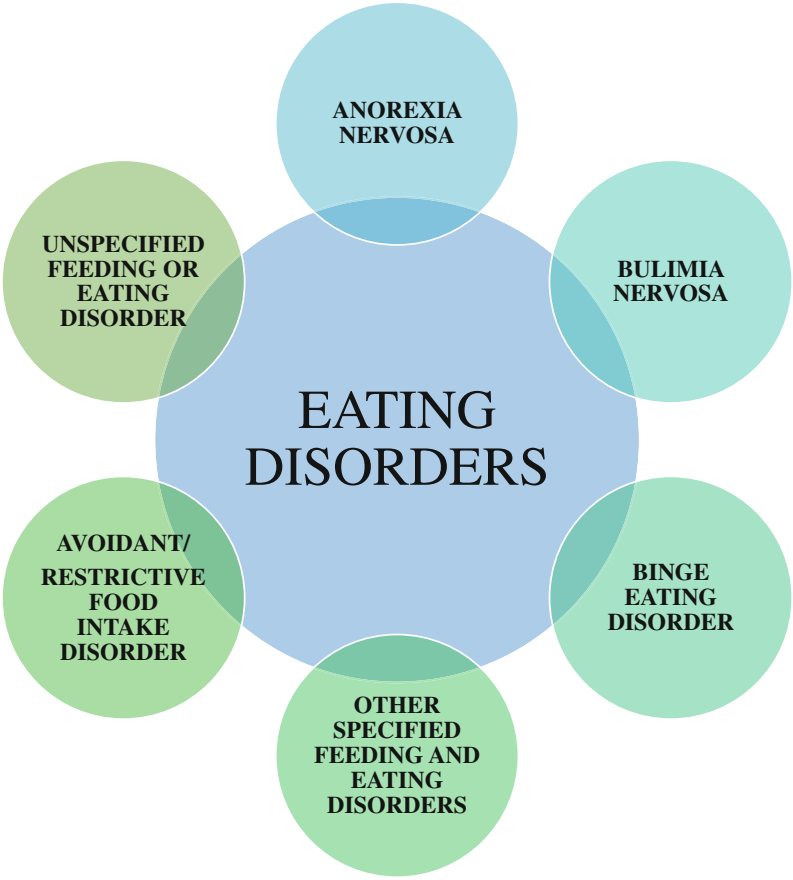


Fig. 3 Eating disorders

Weissman Scale of Social Adjustment

The Weissman Social Adjustment Scale (Weissman and Bothwell 1976) assesses an individual's social adjustment in a number of different areas of functioning, including marital, family, work, and leisure. The Weissman scale is a five-item self-assessment measure that assesses the extent to which physical or mental disorders have affected an individual's work, social and leisure activities, interpersonal relationships, and home management skills. Each item is scored on a scale of 5 points with higher grades, which indicates poorer functioning. The reliability and validity of the questionnaire was well established and used in a wide range of populations.

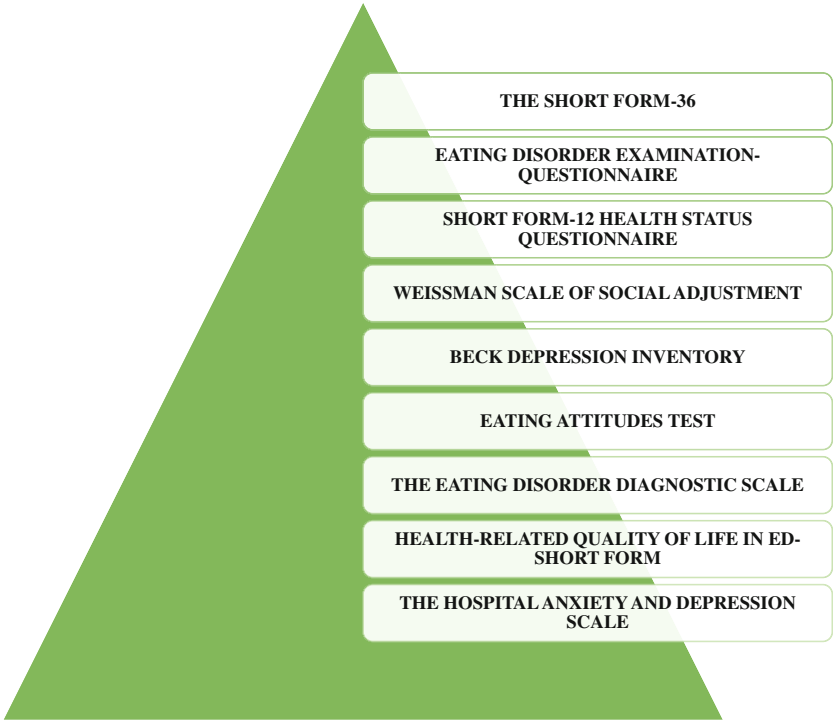


Fig. 4 Questionnaires that are used today

BDI

The BDI (Beck 1981) is a 21-question self-assessment questionnaire designed to assess depressive symptoms. Higher overall scores reflect greater depressive symptomatology.

More research into questionnaires for the discovery and prognosis of EDs, as well as the assessment of these patients' quality of life, leads to the development of new, more specific, and sensitive instruments.

Eating Attitudes Test (EAT-26) (Garner et al. 1982) evaluates behavioral and cognitive characteristics of patients with EDs. It comprises of 26 questions divided into three categories: diet, bulimia, and food worries and oral control. The result of the questionnaire might range from 0 to 76. The existence of actions or thoughts typical of people with an ED is indicated by a score of more than 20.

The Eating Disorder Diagnostic Scale (EDDS)

The Eating Disorder Diagnostic Scale (EDDS) (Castro et al. 1991) consists of 22 questions that assess the DSM-IV diagnostic criteria for anorexia, bulimia, and

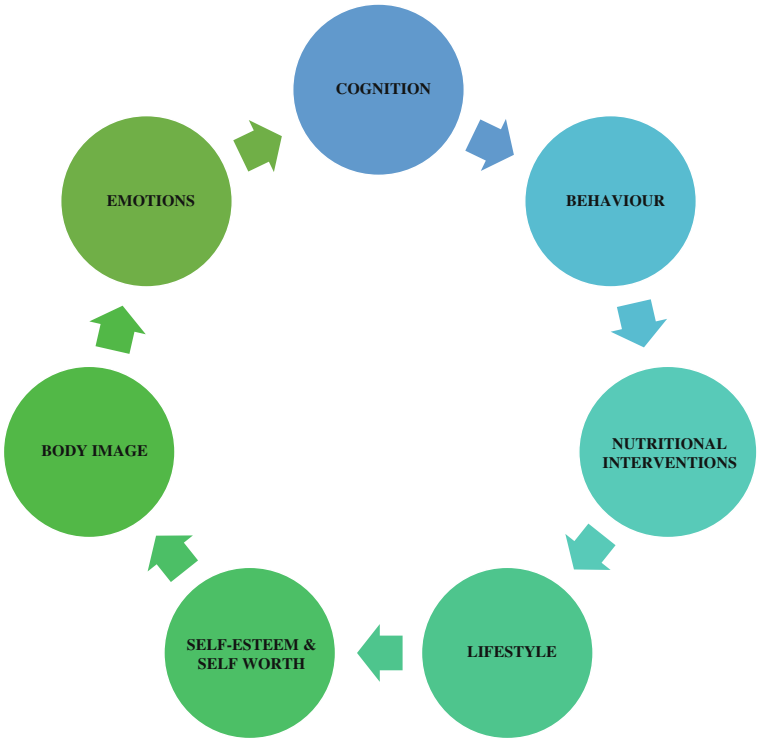


Fig. 5 Aspects affected by EDs

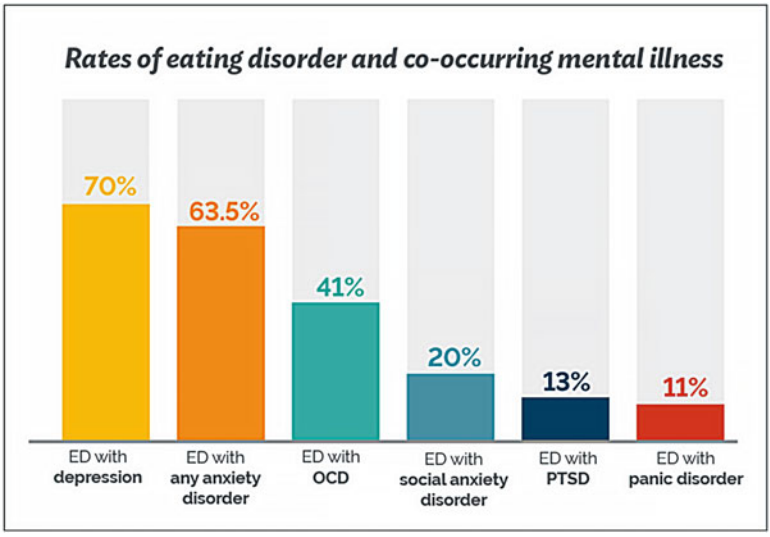


Fig. 6 Eating disorders and co-occurring mental illness (Bould et al. 2014)

binge-eating disorder. The answers can be used to make a DSM-IV diagnosis of these three disorders. There are both closed and open questions (e.g., questions about height, weight, use of contraceptive pills, etc.). This questionnaire's benefit is that it has been demonstrated to be trustworthy and valid in a population that includes both adolescents and adults (Stice et al. 2000).

Health-Related Quality of Life in ED-Short Form (HeRQoLED-S)

HeRQoLED-s (Las Hayas et al. 2010) has 20 items that are divided into two categories: social maladaptation and mental health and functioning. The higher the result of the questionnaire, the lower the quality of life related to the health condition.

The above questionnaires (Eating Attitudes Scale (EAT-26), the Eating Disorder Diagnostic Scale (EDDS), HeRQoLED-s, and the Short Form-12 Health Status Questionnaire (SF-12) described earlier in the text with the Hospital Anxiety and Depression Scale (HADS) were used in a study conducted in 2017, which looked for predictors of quality of life in patients with EDs (Martín et al. 2017). The anxiety and depression scale was employed in the study to detect anxiety and depression symptoms in ED patients in earlier stages.

The Hospital Anxiety and Depression Scale (HADS) (Zigmond and Snaith 1983) is a 14-item questionnaire that is used to test for anxiety and depression in the nonpsychiatric population (those who haven't been diagnosed with a mental illness). It's divided into two subscales. An absence of anxiety or depression symptoms is indicated by a score of 0 to 7 on any subscale, a score of 8 to 10 indicates a likely case of anxiety or depressive symptoms, and a score of 11 or higher indicates the presence of anxiety or depressive symptoms.

Further research suggests that different types of EDs cannot be defined using generic QoL questionnaires like the SF-36 and that ED-specific QOL questionnaires should be used in clinical trials to help clinicians identify behavioral patterns that are common in diseases that meet the definition of EDs. The most recent questionnaires specific to the quality of life of a patient with an ED are the Eating Disorders Quality of Life Scale (EDQLS) and the Eating Disorders Quality of Life Scale (EDQOL). The Eating Disorder Quality of Life Scale (EDQOL) has 25 items and four subscales: psychological, physical/cognitive, financial, and school/work. The EDQLS (Adair et al. 2007) is a 40-item questionnaire that assesses 12 aspects of disordered eating-related quality of life: cognitive, educational/vocational, family and close relationships, interpersonal relationships, future outlook, appearance, leisure, psychological, emotional, values and beliefs, physical, and eating. On a 5-point scale, items are scored from (Orley et al. 1998) strongly disagree to (Bamford et al. 2015) strongly agree. Higher ratings imply a better quality of life.

Before we move on to the conclusion, there is one more point to consider when assessing the quality of life of individuals with EDs. Patients were evaluated by

several specialists in most studies that evaluated the quality of life of patients with an ED prior to the beginning of the research. All patients must undergo a comprehensive physical examination, which involves determining body weight, height, and BMI, as well as discovering any organic chronic diseases such as diabetes, hypertension, obesity, heart diseases, lung diseases, and others. In order to diagnose psychiatric comorbidities such as mood disorders, anxiety disorders, substance addiction disorders, psychotic disorders, and others, a complete psychiatric assessment is also required.

Conclusion

There has been great progress in evaluating and designing appropriate questionnaires to help clinicians and researchers in the diagnosing, developing treatment strategies, and prognosing EDs, as well as assessing quality of life in these patients. What emerges in most studies and research is the knowledge that the combination of several questionnaires at the same time is the best choice for detecting and preventing impairment in quality of life in patients with EDs, as well as considering predictive factors related to quality of life. It is important to emphasize that the simultaneous occurrence of other mental illnesses, such as depression and anxiety, is very common and that instruments that help in the early detection of these accompanying disorders must be implemented in the examination.

Mini-Dictionary of Terms

- **QOL** – An individual's perception of their position in life in the context of the culture and value system in which they live and in relation to their goals, expectations, standards, and concerns.
- **Questionnaire** – A list of questions, usually printed, submitted for replies that can be analyzed for usable information.
- **Impairment** – The state of being diminished, weakened, or damaged, especially mentally or physically.
- **Instrument** – A device for measuring the present value of a quantity under observation.
- **DSM-IV** – A publication by the American Psychiatric Association for the classification of mental disorders using a common language and standard criteria.
- **Mental disorders** – Conditions that affect your thinking, feeling, mood, and behavior. They may be occasional or long-lasting (chronic).
- **Predictive factor** – As any patient characteristic that is predictive of the patient's response (outcome) to a specified treatment.

Key Fact of Health-Related Quality of Life Questionnaires: Applications to EDs

- Quality of life expresses the broad range of changes in a person's life as a result of an eating problem; it defines as an individual's perception of their position in life in the context of the culture and value system in which they live and in relation to their goals, expectations, standards, and concerns.
- Questionnaire: A research instrument consisting of a series of questions (or other types of prompts) for the purpose of gathering information from respondents through survey or statistical study.
- Evaluation of questionnaires is conducted through many of clinical research and studies in order to find the most suitable questionnaire that could help the clinicians and researchers in future treatment of EDs.
- Mental comorbidity is the presence of one or more additional mental conditions co-occurring with a primary condition – ED. Comorbidities are often coexistent with each other.
- Instrument represents a tool, often in the form of questionnaire, that is used to aid in diagnosing a variety of symptoms through the questions.

Summary Points

- People with EDs are impacted in a variety of ways by a variety of disciplines. There has been a growing interest in identifying appropriate questions to help detect and measure the severity of EDs, as well as questionnaires to assess the quality of life of these patients, throughout the previous several decades.
- The Short Form-36 (SF-36) and the Eating Disorder Examination-Questionnaire were among the first questionnaires used in practice to assess the QOL of patients with an ED (EDE-Q).
- Significant progress has been made in analyzing and constructing relevant questionnaires to assist clinicians and researchers in diagnosing, developing treatment strategies, and prognosing EDs.
- The best method for diagnosing and avoiding deterioration in quality of life in patients with EDs is to use a combination of many surveys at the same time.
- It's crucial to think about the factors that influence the outcome.

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Resources in Eating Disorders

77

Rajkumar Rajendram, Daniel Gyamfi, Vinood B. Patel, and Victor R. Preedy

Contents

Introduction 1530
Resources 1531
Other Resources 1531
Summary Points 1536
Contributions to the Development of This Resource 1536
References 1538

Abstract

Eating disorders are characterized by abnormal eating behavior which may also be associated with a preoccupation with body shape, size, and weight. They cause significant morbidity and mortality. Of all mental disorders, the mortality rate of anorexia nervosa is among the highest. In 1992, The World Health Organization (WHO) published the tenth revision of the International Classification of Diseases and Related Health Problems (ICD; ICD-10. The guidelines on eating disorders in the ICD-10 had several limitations. In 2022, the 11th revision (ICD-11) was

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officially released. Many changes had been made in an attempt to rectify these shortcomings. During the intervening 30 years between the release of ICD-10 and ICD-11, the literature on eating disorders and the evidence to inform clinical practice advanced greatly and eating disorders are still actively being studied. Thus, the knowledge and understanding of eating disorders has progressed rapidly in recent years. However, keeping abreast of current research can be difficult so we have compiled tables of the resources recommended by active practitioners and researchers. These include information on regulatory bodies, societies, organizations, and other resources.

Keywords

Books · Evidence · Professional societies · Regulatory bodies

Abbreviations

DSM	Diagnostic and Statistical Manual of Mental Disorders
ICD	International Classification of Diseases and Related Health Problems
ICD-10	Tenth revision of the ICD
ICD-11	11th revision of the ICD
WHO	World Health Organization

Introduction

Eating disorders are characterized by abnormalities of eating behavior (World Health Organization (WHO) 2022). They may also be associated with a preoccupation with body shape, size, and weight. Examples of eating disorders include binge eating, bulimia, and anorexia nervosa. Eating disorders cause significant morbidity and mortality (Arcelus et al. 2011; Field et al. 2012). Those suffering from eating disorders are at increased risk of death by suicide (Arcelus et al. 2011). Indeed, of all mental disorders, mortality rate of anorexia nervosa is among the highest (Zerwas et al. 2015).

The World Health Organization (WHO) published the tenth revision of the International Classification of Diseases and Related Health Problems (ICD; ICD-10) in 1992 (WHO 1992). There were several inherent limitations with the guidelines on eating disorders in this version of the ICD (Claudino et al. 2019). However, there are other classifications such as the Diagnostic and Statistical Manual of Mental Disorders (DSM; American Psychiatric Association 2013), and indeed, classifications can change in the light of ongoing scientific dialogue (Rajendram et al. 2022).

The management of a mental health disorder is often defined by its classification. Thus, the development of more accurate, clinically relevant tools to classify, identify, prevent, and treat eating disorders is an important public health priority (Claudino et al. 2019).

In 2022, the 11th revision (ICD-11) was officially released and is available online at https://icd.who.int/browse11/l-m/en (WHO 2022). Many changes were made in an attempt to rectify the shortcomings of the ICD-10 with respect to eating disorders (Claudino et al. 2019).

During the intervening 30 years between the release of ICD-10 and ICD-11, the literature on eating disorders and the evidence to inform clinical practice advanced greatly (Claudino et al. 2019). Several areas are covered in Patel and Preedy (2023), but eating disorders are still actively being studied. As we often highlight, even the most experienced researchers and clinicians struggle to stay up-to-date, and some new researchers need some guidance on what online resources they should use. We have therefore produced tables containing resources as recommended by active researchers and practitioners, which draws upon their wealth of experience and acumen acquired over many years. The list below acknowledges all the experts who helped to prepare these valuable resources.

Resources

Tables 1, 2, 3, 4, and 5 list the most up-to-date information on the regulatory bodies (Table 1), professional societies (Table 2), books (Table 3), and other resources of interest (Table 4) that are relevant to an evidence-based approach to eating disorders. Some organizations are listed in more than one table as they occasionally fulfill multiple roles.

Other Resources

The Wellcome Collection (https://wellcomecollection.org/collections) and The British Library (https://www.bl.uk/) also list material on topics related to eating disorders.

Other chapters on resources relevant to nutrition (recommended by authors and practitioners) may also be relevant to eating disorders. These include diet quality (Rajendram et al. 2013a) nutrition and oxidative stress (Rajendram et al. 2020), maternal nutrition (Rajendram et al. 2017), nutrition and the menopause (Rajendram et al. 2013b), biomarkers of nutrition (Rajendram et al. 2022) glutamine (Rajendram et al. 2014), branched chain amino acids (Rajendram et al. 2015), famine, starvation, and nutrient deprivation (Rajendram et al. 2019a), aging (Rajendram et al. 2019b), diet and nutrition in critical care (Alzaid et al. 2015), and the metabolism and physiology of bariatric surgery (Rajendram et al. 2016).

Other chapters on resources relevant to mental health (recommended by authors and practitioners) may also be relevant to eating disorders. These include cognitive behavioral therapy (Rajendram et al. 2022), post-traumatic stress disorder (Rajendram et al. 2015), and substance misuse (Rajendram and Preedy 2016a, b, c).

This list of material in these tables is included to provide general information only. It does not constitute any recommendation or endorsement of the activities of

Table 1 Regulatory bodies or organizations dealing with eating disorders

Regulatory body or organization	Web address
Academy for Eating Disorders (AED)	https://www.aedweb.org/home
Academy of Nutrition and Dietetics	https://www.eatright.org/
Australia & New Zealand Academy for Eating Disorders	www.anzaed.org.au
Body Dysmorphic Disorder Foundation	https://bddfoundation.org/
Body Positive	https://thebodypositive.org/
Butterfly Foundation	https://butterfly.org.au/
Centre for Eating Disorders Management, Inc. (CEDM)	https://cedm-inc.com/
Centre for Research on Eating Disorders at Oxford (CREDO)	https://www.credo-oxford.com/index.html#topic0
Centre of Excellence in Eating Disorders (CEED)	https://ceed.org.au/
Centre of Mindful Eating	https://www.thecenterformindfuleating.org
Eating Disorder Hope	https://www.eatingdisorderhope.com/
Eating Disorder Resource Centre (EDRC)	https://edrcsv.org/
Eating Disorders Anonymous	https://eatingdisordersanonymous.org/
Eating Disorders Coalition (EDC)	http://www.eatingdisorderscoalition.org/
Eating Disorders Families Australia	www.edfa.org.au
Foundation for Prader-Willi Syndrome Research (FPWR)	https://www.fpwr.org/
International Eating Disorder Action (IEDaction)	https://www.facebook.com/IEDaction.Global/
International Eating Disorders Action	http://internationaleatingdisorderadvocacy.blogspot.com
International OCD Foundation	https://bdd.iocdf.org/
International Prader-Willi Syndrome Organization (IPWSO)	https://ipwso.org/
Mental Health Europe	https://www.mhe-sme.org/
National Alliance for Eating Disorders	https://www.allianceforeatingdisorders.com/
National Alliance on Mental Illness	https://www.nami.org/home
National Centre of Excellence for Eating Disorders (NCEED)	https://www.nceedus.org/
National Eating Disorder Collaboration (NEDC)	https://nedc.com.au/
National Eating Disorder Information Centre (NEDIC)	https://nedic.ca/

(continued)

Table 1 (continued)

Regulatory body or organization	Web address
National Institute of Mental Health (NIMH)	https://www.nih.gov/about-nih/what-we-do/nih-almanac/national-institute-mental-health-nimh
Parents to Parents	http://www.parents-to-parents.org/

This table lists the regulatory bodies and organizations involved with eating disorders. The links were accurate at the time of going to press but may move or alter. In these cases, the use of the "Search" tabs should be explored at the parent address or site. In some cases, links direct the reader to pages related to eating disorders within parent sites. Some societies and organizations have a preference for shortened terms, such as acronyms and abbreviations. See also Table 2

Table 2 Professional societies relevant to eating disorders

Society name	Web address
American Psychiatric Association	https://www.psychiatry.org/
American Society for Nutrition	https://nutrition.org/
Anorexia-Bulimia Association	http://aabaphila.org/
Austrian Society for Eating Disorders (ASED)	https://www.oeges.or.at/
Bulimia Anorexia Nervosa Association (BANA)	https://bana.ca/
Deutsche Gesellschaft für Essstörungen (German Eating Disorders Society)	https://www.dgess.de/
Eating Disorders Association of Canada	https://edac-atac.com/
Eating Disorders Research Society (EDRS)	https://edresearchsociety.org/
European Psychiatric Association	https://www.europsy.net
European Psychiatric Association (EPA)	https://www.europsy.net/
Frisk & Fri (Healthy & Free – The Swedish Association against Eating Disorders)	https://www.friskfri.se/
International Association of Eating Disorders Professionals	http://www.iaedp.com/
Italian Association for Eating and Weight Disorders	https://www.aidap.org/
Italian Society of Food Psychopathology	https://psicopatologiaalimentazione.it/la-sipa/chi-siamo/
Multi-Service Eating Disorders Association (MEDA)	https://www.medainc.org/
National Association for Males with Eating Disorders	https://www.nationaleatingdisorders.org/named-merger
National Association of Anorexia Nervosa and Associated Disorders, Inc. (ANAD)	http://www.anad.org/
National Association of Eating Disorders (Italy)	http://www.consultanoidca.it
National Eating Disorders Association (NEDA)	https://www.nationaleatingdisorders.org/
Society of Biological Psychiatry (SOBP)	https://sobp.org/

This table lists the professional societies involved with eating disorders. The links were accurate at the time of going to press but may move or alter. In these cases, the use of the "Search" tabs should be explored at the parent address or site. In some cases, links direct the reader to pages related to eating disorders within parent sites. Some societies and organizations have a preference for shortened terms, such as acronyms and abbreviations. See also Table 1

Table 3 Books on eating disorders

Book title	Authors or editors	Publisher	Year of publication
Adonis Complex: How to Identify, Treat and Prevent Body Obsession in Men and Boys	Pope HG, Phillips KA, Olivardia R	The Free Press	2002
AED Report 2021 4th Edition Eating Disorders: A Guide to Medical Care	Academy for Eating Disorders' Medical Care Standards Committee	AED Report	2021
Animal Models of Eating Disorders (1st edn)	Avena NM	Humana Press, Totowa, NJ	2011
Animal Models of Eating Disorders (2nd edn)	Avena NM	Humana Press, New York, NY	2021
Anorexia and Other Eating Disorders	Musby E	Booktopia	2021
Binge Eating: The Ultimate Guide to Finally Ending Emotional Eating, Bingeing, Overeating, and Food Addiction, Including Tips on Eating Disorder Recovery, and an Introduction to Mindful Eating	McClain D	Primasta	2020
Body Dysmorphic Disorder: A Treatment Manual	Veale D, Neziroglu F	Wiley	2013
Body Dysmorphic Disorder: Advances in Research and Clinical Practice	Phillips KA	Oxford University Press	2017
Cassidy and Allanson's Management of Genetic Syndromes	Carey JC, Cassidy SB, Battaglia A, Viskochil D	Wiley-Blackwell	2021
Clinical Guide to Fertility, Motherhood, and Eating Disorders	Daigle K	Routledge	2019
Cognitive Behavior Therapy and Eating Disorders	Fairburn C	Guilford Press	2008
Cognitive Behavior Therapy for Adolescents with Eating Disorders	Dalle Grave R, Calugi S	Guildford Press	2020
Cognitive-Behavioral Therapy for Body Dysmorphic Disorder: A Treatment Manual	Wilhelm S, Phillips KA, Steketee G	Guilford Press	2013
Dialectical Behavior Therapy for Binge Eating and Bulimia	Safer DL, Telch, CF, Chen EY	Guilford Press	2009
Eating Disorders	Keel PK	Oxford University Press	2016
Eating Disorders and Obesity (3rd edn)	Brownell KD, Walsh BT	Guilford Press	2017
Eating Disorders and Obesity in Children and Adolescents	Hebebrand J, Herpertz-Dahlmann B	Elsevier	2019

(continued)

Table 3 (continued)

Book title	Authors or editors	Publisher	Year of publication
Eating Disorders in Boys and Men	Nagata JM, Brown TA, Murray SB, Lavender JM	Springer	2021
Eating Disorders in Sport	Thompson R, Sherman R	Routledge	2010
Eating Disorders Sourcebook: A Comprehensive Guide to the Causes, Treatments, and Prevention of Eating Disorders	Costin C	McGraw-Hill	2006
Eating Disorders: Obesity, Anorexia Nervosa, and the Person Within	Bruch H	Routledge and Kegan Paul	1974
Emotion Regulation for Young People with Eating Disorders: A Guide for Professionals	Nesbitt S, Giombini L	Routledge	2022
Help Your Teenager Beat an Eating Disorder	Lock J, LeGrange D	Guilford Press	2015
Hidden and Lesser-known Disordered Eating Behaviors in Medical and Psychiatric Conditions	Manzato E, Cuzzolaro M, Donini LM	Springer Nature	2022
How to Nourish Your Child Through an Eating Disorder	Crosbie C	Booktopia	2009
Inside Scoop on Eating Disorder Recovery	Reichmann C, Rollin J	Routledge	2021
Intuitive Eating: A Revolutionary Anti-Diet Approach	Tribole E, Resch E	Essentials	2020
Management of Prader-Willi Syndrome	Butler MG, Lee PDK, Whitman BY	Springer	2006
Overcoming Bulimia Nervosa and Binge Eating (3rd edn)	Cooper P	Robinson	2009
Oxford Handbook of Eating Disorders (2nd edn)	Agras WS, Robinson A	Oxford University Press	2018
Prader-Willi Syndrome	Hoybye C	Nova	2013
Prader-Willi Syndrome	Cassidy SB	Springer	1992
Prader-Willi Syndrome (Japanese)	Hasegawa T	Koudansha	2009
Prader-Willi Syndrome: Development and Manifestations	Whittington J, Holland T	Cambridge University Press	2011
Prader-Willi Syndrome: How Parents and Professionals Struggled and Coped and Made Genetic History	Hernandez-Storr J	John Hernandez-Storr	2016
The Void Inside: Bringing Purging Disorder to Light	Keel PK	Oxford University Press	2020
Trauma-Informed Approaches to Eating Disorders	Seubert A, Virdi P	Springer	2018

(continued)

Table 3 (continued)

Book title	Authors or editors	Publisher	Year of publication
What Causes Eating Disorders – And What Do They Cause?	Frank GKW	Booklocker.com, Inc.	2016
Wiley Handbook of Eating Disorders, Assessment, Prevention, Treatment, Policy, and Future Directions	Smolak L, Levine MP	Wiley	2015
Your Dieting Daughter: Antidotes Parents Can Provide for Body Dissatisfaction, Excessive Dieting, and Disordered Eating	Costin C	Routledge	2013/2021

This table lists books relevant to eating disorders

these sites, facilities, or other resources listed in this chapter, by the authors or editors of this book.

Summary Points

Eating disorders are characterized by abnormalities of eating behavior.
In 2022, the 11th revision of the International Classification of Diseases (ICD-11) was officially released and is available online at https://icd.who.int/browse11/l-m/en.
In the 30 years between ICD-10 and ICD-11, the literature on eating disorders and the evidence to inform clinical practice advanced greatly.
Eating disorders are actively being studied.
This chapter lists the most up-to-date resources relevant to eating disorders.

Contributions to the Development of This Resource

The following authors made valuable contributions to the development of this resource. We apologize if some of the suggested material was not included in this chapter or has been moved to different sections.

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Table 4 Other resources of interest or relevance for health care professionals or patients related to eating disorders

Name of resource or organization	Web address
Academy of Nutrition and Dietetics	https://jandonline.org/article/S2212-2672(20)30904-7/fulltext
Active Minds	https://www.activeminds.org/
AED's "9 Truths About Eating Disorders"	https://www.aedweb.org/publications/nine-truths
AED's "Eating Disorders: A Guide to Medical Care"	https://www.aedweb.org/publications/medical-care-standards
Anorexia – Parents to Parents	http://www.parents-to-parents.org/
Anorexia Nervosa Inventory for Self-Rating (ANIS)	https://www.lmu-klinikum.de/psychiatrie-und-psychotherapie/forschung-research/working-groups/epidemiology-and-evaluation/anis/98aedba0af1c9bf8
Assessment tools Italian versions	http://www.dallegrave.it/category/misure-di-assessment/
Disordered Eating Attitude Scale (DEAS)	https://www.midss.org/content/disordered-eating-attitude-scale-deas
DSM-5 Feeding and Eating Disorders	https://higherlogicdownload.s3.amazonaws.com/AEDWEB/27a3b69a-8aae-45b2-a04c-2a078d02145d/UploadedImages/Learn/DSM5September2016Final.pdf
e-CBT: Digital Treatment for Eating Disorders	https://www.credo-oxford.com/5.1.html
Eating Disorder Diagnostic Scale (EDDS)	https://qxmd.com/calculate/calculator_562/eating-disorder-diagnostic-scale-edds
Eating Disorder Examination Questionnaire (EDE-Q)	https://www.corc.uk.net/outcome-experience-measures/eating-disorder-examination-questionnaire-ede-q/
Eating Disorder Screening Tools	https://www.therecoveryvillage.com/mental-health/eating-disorders/related/screening-tools/
Eating Disorders – National Alliance on Mental Illness	https://www.nami.org/About-Mental-Illness/Mental-Health-Conditions/Eating-Disorders
Eating Disorders Examination Interview	https://www.cbte.co/for-professionals/measures/
Eating Disorders: About More Than Food – NIH	https://www.nimh.nih.gov/health/publications/eating-disorders
Healthy and Free (In Czech with English Translation)	http://www.healthyandfree.cz/
ESPEN Guidelines for Nutrition Screening 2002	https://espen.info/documents/screening.pdf
List of Organizations Worldwide	https://www.worldeatingdisordersday.org/get-involved/participating-organisations/
Masters in treatments for Eating Disorders (English)	https://www.credo-oxford.com/index.html#topic5
Masters in treatments for Eating Disorders (Italian)	http://www.dallegrave.it/category/corsi/master/

(continued)

Table 4 (continued)

Name of resource or organization	Web address
Mindful Eating Resources	https://www.thecenterformindfuleating.org/Mindful-Eating-Resources
Munich Eating Disorders Questionnaire (Munich ED-Quest)	https://www.lmu-klinikum.de/psychiatrie-und-psychotherapie/forschung-research/working-groups/epidemiology-and-evaluation/munich-ed-quest/7c7bbcfc393d516d
National Institute for Health and Care Excellence Guidelines for Eating Disorders: Recognition and Treatment	https://www.nice.org.uk/guidance/ng69
NICE Clinical Guidelines for Obsessive Compulsive and Body Dysmorphic Disorder	https://www.nice.org.uk/guidance/cg31
NSW Eating Disorders Toolkit	https://www.health.nsw.gov.au/mentalhealth/resources/Publications/nsw-eating-disorders-toolkit.pdf
Project Heal	https://www.theprojectheal.org/
Questionnaire on Eating and Weight Patterns-5 (Italian version)	http://www.dallegrave.it/wp-content/uploads/2015/04/QEWP-5-Verisione-Italiana.pdf
Recovery Record	https://www.recoveryrecord.com/
Resources and links – Centre of Excellence in Eating Disorders (CEED)	https://ceed.org.au/resources-and-links/
Screening for Mental Health, Inc.	https://philanthropynewsdigest.org/npo-spotlight/screening-for-mental-health-inc
Structured Inventory for Anorexic and Bulimic Eating Disorders (SIAB-EX and SIAB-S)	https://www.lmu-klinikum.de/psychiatrie-und-psychotherapie/forschung-research/working-groups/epidemiology-and-evaluation/siab-ex-and-siab-s/43c8f5577c4c0c68
The SCOFF Questionnaire Screens for Eating Disorders	https://www.verywellmind.com/the-scoff-questionnaire-1138316
The Yale-Brown Obsessive-Compulsive Scale Modified for Body Dysmorphic Disorder (BDD-YBOCS; used to assess BDD symptom severity)	https://pubmed.ncbi.nlm.nih.gov/9133747/
UNICEF Nutrition	https://www.unicef.org/nutrition
World Eating Disorders Action Day	http://www.worldeatingdisordersday.org/
Worldwide List of Eating Disorders Advocacy Organizations	https://www.feast-ed.org/worldwide-list-of-ed-advocacy-organizations/

This table lists other resources of interest or relevance to eating disorders. Please note, occasionally the location of the websites or web address changes

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Index

A
A1 allele, 228
AA-derived eiCs pathways, 455
Academy for Eating Disorders, 274
Accelerometers, 426
Acceptance and Commitment Therapy (ACT), 340, 375, 380
Acculturation, 216
Acid-base balance, 532
Activity-based anorexia (ABA), 558, 559
  model, 459
Activity-based rodent model of anorexia (ABA), 547
Acute insomnia, 147
Acute sleep deprivation, 1106
Acylghrelin (AG), 571
Adaptive physical activity, 415
Adaptive preoccupation, 1485
Adaptive response, 703, 704
Adolescent Binge Eating Scale, 1510
Adolescents, 866–868, 870, 874–876
  with ADHD, 128, 130
Adrenal hormones, 557
Adrenocorticotropic hormone (ACTH), 54, 67, 85, 776
Adult Autism Subthreshold Spectrum (AdAS), 646
Adult picky eating questionnaire (APEQ), 1419
Adults, 314, 338–341, 345
Affect, 1007
  regulation model, 808
Affectionless control, 968, 969, 971, 972, 974, 975
Agouti-related peptide (AgRP), 55, 67, 85, 571, 1470
Agouti-related protein, 543
Alcohol consumption, 1340
Alexithymia, 648, 649, 651
  anorexia nervosa, 339
  bulimia nervosa, 339
  case-control studies findings, 322
  cohort studies, 338, 339
  future lines of research, 343
  limitations, 343
  longitudinal findings, 340, 341
  longitudinal variation, 341
  research findings, 316, 317
  structure and rationale of the current review, 317, 322
  synthesis of the previous reviews and meta-analyses, 318
  therapeutic implications and applications, 342
  types, 315, 316
Alexithymia Questionnaire for Children, 336, 344
Alpha-melanocyte-stimulating hormone (α-MSH), 505
Alpha-methylparatyrosine (AMPT), 563
Amenorrhea, 440, 925
  functional hypothalamic, 605, 607
American Psychiatric Association (APA), 203, 206, 1064
γ-aminobutyric acid (GABA), 777
AMP-activated protein kinase (AMPK) signaling, 55, 67
Amphetamine-regulated transcript (CART), 544
Amygdala, 57
Anandamide (AEA), 84, 455
Androgen receptor (AR), 771, 778
Androgens, 770, 780, 836
Androstenedione, 771

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V. B. Patel, V. R. Preedy (eds.), *Eating Disorders*,
https://doi.org/10.1007/978-3-031-16691-4

Anemia, 929
in pregnancy, 611
Animal model, AN, 558–559
ANKK1 gene, 81
Ankyrin repeat, 78
Ankyrin repeat and kinase domain containing 1 (*ANKK1*), 81
Anorexia, 685, 686
disease model, 574
disorder, 683, 684
Anorexia nervosa (AN), 96, 99, 201, 202, 208, 250, 254, 256, 265, 270, 317, 323, 338–344, 397–399, 442, 556, 558–562, 624, 686–688, 692, 703, 752, 772, 816, 865, 925, 947, 1004, 1192, 1251, 1306, 1315–1317, 1319, 1320, 1332, 1343, 1365, 1366, 1483, 1530
acute stage of, 571
and adverse perinatal outcomes, 613
applications, 650, 651
attention-deficit/hyperactivity disorder, 130
BF estimation and measurement, 443–445
binge-eating episodes, 9
BMI determination, weight, height and standard for, 441
body composition, 443
characteristics, 571
clinical based studies, 678, 679
clinical implications, 680, 681
clinical study, 645
clinical traits, 648, 649
clinicians, 643
core eating-disorder maintenance processes, 9
depressive disorders, 681–683
development of, 504, 505
discharge and follow up, 635
epidemiology, 646
feeding and eating disorders, 642, 643
and fertility, 605
follow-up studies, 470
gestational, 29
Gothenburg AN study, 470
growth hormone resistance in, 705–709
gut microbiota, 491
hallmark of, 605
health policymakers, 643
hospitalization criteria, 625–626
insomnia disorder, 149
integrated treatment, 626–632
interventions, 650
knockout models for genes encoding, 459
malnutrition, 645
management of pregnant women with, 615
mental health comorbidities, 643, 644
motivation to treatment, 632
neurodegenerative findings, 476
neuropsychological impairments, 652
nutritional rehabilitation, 627–628
ominous variant of, 5
osteoporosis and restoration of BMD, 446–447
outcomes, 649, 650
outpatient CBT-E, 18
pathogenesis of, 453
population-based studies, 677, 678
and pregnancy complications, 610, 611
prevalence, 610, 643, 650
probiotics on, 502
psychiatric comorbidities, 650
psychiatric morbidity, 476
psychiatry, 646
psychodiagnostics, 646–648
psychological treatment, 630–631
psychology, 646
psychopathological features, 652
psychopathology, 633
psychopharmacological treatment, 631
quality of life, 634
refeeding process, 628–630
rehospitalization, 634–635
remission, recovery and risk of relapse, 446
renutrition, 632–633
reproductive health, 605
resumption of menses and reproductive functions, 446
starvation symptoms, 9
Sten Theander's study, 470
theoretical implications, 679, 680
theories, 648, 649
transdiagnostic cognitive-behavioral theory, 9
treatments, 632–635, 649, 650
Anorexia nervosa, binge eating/purging subtype (AN-BP), 1175
Anorexia nervosa (AN), male
application, 532
awareness, 531
course, 524
dietary intake, 517
dietitian, 525, 531
environmental (Societal & cultural) risk factors, 515, 516
features, 514
females, 518, 519
genetic factors, 515
hormonal factors, 515

medical complications, 522–524
parameters, 517
prevalence, 514, 533
prognosis, 524
psychiatric comorbidities, 518
risk factors, 517
treatment, 525–528
Anorexigenic peptides, 84
Antepartum haemorrhage, 618
Anthropometry, 440
Anti-androgens, 829
Antidepressants, 823, 824
Antiepileptics, 824, 827
Anti-inflammatory dietary pattern, 61
Antisaccade task, 591
Anxiety, 97, 542, 546, 1237, 1294, 1296, 1407
and bulimia nervosa, 733
Anxiety disorders (AD), 253, 643, 680, 684, 685, 688, 691
Anxiolytic medications, 665
Appearance preoccupation, 1307
Appetite, 539, 541, 543–545, 547, 548
regulatory system, 84
Arachidonic acid (AA), 61, 453
2-Arachidonoylglycerol (2-AG), 455
Arcuate nucleus (ARC), 543, 548
ARFID in children
assessment, 1242
characteristics, 1237, 1238
cognitive-behavioral approaches, 1243, 1249
differential diagnosis, 1240, 1241
etiology, 1241, 1242
family-based treatment (FBT), 1243
hospital-based feeding programs, 1250
impact, 1239, 1240
parent-based treatments, 1249, 1250
pharmacotherapy, 1250
prevalence, 1238, 1239
treatment, 1243
Arginine-vasopressin (AVP), 1267, 1270
Assessment, 1126
Athlete
anorexia nervosa in, 115
ATHLETE questionnaire, 118
binge eating disorder, 116
bulimia nervosa, 116
eating disorders not otherwise specified (EDNOS), 119
ED
in female, 113
in male, 113, 115
prevalence studies, 113
risk factors, 113
sports disciplines, 115
male runners obligatory runners, 115
nutrition and eating disorders, 113
orthorexia nervosa in, 116
Attachment style, 848–849
Attachment Styles Questionnaire Relationship, 1049
Attentional bias tasks, 596
Attention-deficit disorder (ADD), 1292
Attention-deficit/hyperactivity disorder (ADHD), 827, 1241
anorexia nervosa, 130
avoidant/restrictive food intake disorder (ARFID), 130
behavioral symptoms, 125
binge eating disorder, 129
body satisfaction and eating behaviors, 134
bulimia nervosa, 130
comorbidities, 126
diagnosis and etiology, 125
eating and weight-related problems, 130
eating patterns of children with, 127–129
ED
applications, 138–139
in children and adolescents with, 131
clinical implications/clinical management, 137–138
environmental risk factors, 126
inattention features of, 133
management of, 126
vs. obesity, 128
prevalence, 125
vs. sleep disturbances, 134
Atypical anorexia, 250, 255, 258
Autism, 1273, 1276
Autism Diagnostic Observation Schedule-2nd Edition (ADOS-2), 646–651
Autism quotient (AQ) questionnaire, 646
Autism spectrum disorder (ASD), 475, 644, 645, 651, 1237, 1251
Autism spectrum quotient (AQ), 646, 651
Autonomic nervous system (ANS), 54, 67, 1382
Avoidant/restrictive food intake disorder (ARFID), 216, 279, 354, 404, 1332, 1367, 1368, 1418, 1421, 1455
ARFID in children (*see* ARFID in children)
assessment tools, 1251
attention-deficit/hyperactivity disorder, 130
characteristics, 1251
clinical profiles, 1251
diagnosis, 1236
diagnostic criteria, 1236
early childhood, 1236

Avoidant/restrictive food intake disorder (ARFID) (*cont.*)
eating disorders, 1237
epidemiological research, 1252
family accommodation, 1252
feeding and eating disorder of infancy and early childhood, 1252
heterogeneity, 1251
infancy, 1236
psychosocial domain, 1251
quantity of foods, 1236
restricted eating, 1236
tertiary care, 1253
treatment approaches, 1251

B

Balanced diet, 396
Barcelona Orthorexia Scale (BOS), 1444
Bariatric and metabolic surgery (BMS), 1084, 1095
definitions and indications of, 1087–1090
Bariatric surgery, 1084–1089, 1091–1097
Beck Depression Inventory (BDI), 1523
BED's increased brain reaction to food imagery, 1074
Behavioral addiction, 1340–1346
Behavioral change, during pregnancy, 27
Behavioral interventions, 261, 262
Behavioral phenotype, 1288
Bermond-Vorst Alexithymia Questionnaire (BVAQ), 316, 329, 341
Binge eating (BE), 1004, 1016, 1086, 1504
LOC eating, 128
occurrence of, 1087
Binge eating disorder (BED), 96, 99, 206, 216, 226, 323, 338, 341, 389, 401–404, 749, 754, 816, 823, 947, 1044, 1086, 1090–1092, 1122, 1192, 1251, 1467, 1504, 1506, 1510
adulthood, 972
in athlete, 116
attachment liability, 960
attention-deficit/hyperactivity disorder, 129
behavioral and dietary reorganization, 1096–1098
BES, 1095
bulimia nervosa, 1064
CBT-E, 15
childhood, 974
chi-square test, 962
clinical functional imaging and cognitive studies, 1064
clinical implications, 970, 971
clinical interview, 1094
criterion B symptoms, 1125–1127, 1131, 1132
deficit attachment, 975
diagnosis and scales, 1505
diagnostic criteria, 1123, 1124
disgusted, 1130
during pregnancy, 30
eating disorders, 963, 965, 966
EDE-Q, 1094
embarrassment, 1129, 1130
epidemiology, 959
etiopathogenesis, 1064
expression, 969, 970
implications, 973, 974
insomnia disorder, 149
maternal and paternal parenting styles, 968, 969
medical and psychiatric comorbidities, 974
non-authoritative parenting styles, 975
non-pharmacological, 1132, 1133
neuroimaging findings, 1064
obesity, 963, 965, 966, 975
ODD ratio (OR), 964
overprotection, 962, 963, 967, 972
parenting characteristics, 961
parenting influence, 966, 968
parenting styles, 973
physical discomfort, 1128
physical hunger, 1129
prevalence, 958
prevalence of BED in bariatric patients, 1092–1093
prevalence studies, 1064
preventions issues, 972
primary care, 958
psychiatric classification systems, 1031
psychiatric disorders, 962, 963
psychoeducational efforts, 973
psychopathological aspects, 959
QEWP-5, 1095
recurrent binge-eating episodes, 1031
risk factors, 1504
self-administered questionnaires, 1094
self-monitoring instrument, 1094
treatment, 960, 963, 967, 971
voxel-based morphology of brain volume, 1065
Binge Eating Scale (BES), 1094, 1095, 1472, 1506–1507, 1510
ADO-BED, 1510
Arabic version, 1509

C-BEDS, 1509
French version, 1509
Indonesian version, 1509
limitations, 1508
Malaya Version, 1509
Persian version, 1508
scoring, 1507
Spanish version, 1508
uses, 1507–1508
Binge eating scoring systems, 1475
anorexigenic neuropeptides, 1475
assessment, 1471–1474
bariatric patients, 1475
bariatric surgery, 1467, 1475
body mass index (BMI), 1466
disorder diagnosis, 1468
eating behavior, 1469–1471
loss of control, 1475
noncommunicable diseases, 1466
non-surgical treatment, 1467
obesity, 1466
orexigenic neuropeptides, 1475
physiological mechanisms, 1470
pre-and post-surgery patients, 1468, 1469
prevalence of disorders, 1467
scoring questionnaires, 1473
scoring systems, 1475
treatment, 1466
types of bariatric surgery, 1469–1471
Binge eating symptomatology, 1111
Binge/purge subtype (AN-BP), 226
Bioelectrical impedance analysis (BIA), 444
Biofeedback-assisted relaxation training, 1407
Biological and neural changes implicated in increased dietary intake or altered eating behavior, 1105
Biology of anorexia nervosa (AN)
adolescents, 538
applications, 548
children, 538
clinical manifestations, 540
clinical presentation, 539, 541, 542
depression, 549
DMS-V criteria, 538
energy homeostasis, 543, 544
gastrointestinal symptoms, 549
genetic studies, 549
gonadal function, 546, 547
heterogeneity, 547
hypoleptinemia, 544–546
kisspeptin, 549
metabolic state, 546, 547
multi-organ complications, 539, 549
neurohormonal regulation, 542, 543
NPY/AgRP neurons, 548
pathogenesis, 547
peripheral and central dysregulation, 547
POMC/CART neurons, 548
psychiatric disease, 539
psychiatric diseases, 549
psychotherapy, 549
renourishment, 549
risk of mortality, 539
Biopsychosocial model, 1251, 1401, 1402, 1410
Bipolar disorder, 683, 684
Bisacodyl, 1165
Black and Latinx communities, 377
Block design, 757
Blood brain barrier, 770
Blood-oxygen-level-dependent (BOLD), 994
Body density (BD), 443
Body dissatisfaction, 187–189, 191, 192, 891, 892, 917, 1011, 1180, 1181, 1309, 1312, 1317
Body dysmorphic disorder (BDD), 1306
clinical characteristics, 1315, 1316
comorbidities, 1308
core symptoms, 1307
diagnosis, 1313, 1314
eating disorders, 1312
functional impairment, 1309
gender differences, 1309, 1310
insight, 1308
muscle dysmorphia, 1310
prevalence, 1307
Body fat (BF), 442, 443, 445, 524, 533
AN, 443–445
definition, 441
Body image, 516, 517, 525, 527, 846–848, 852, 1312
disturbance, 847
Body Image Screening Questionnaire (BISQ), 1441
Body mass index (BMI), 38, 206, 415, 442, 445, 446, 517, 533, 647, 737, 888, 890, 917, 1126, 1145
ADHD, 127
AN, 441
definition, 441
eating disorders, 9
and emotional eating, 1383–1384
level after sleep deprivation, 1112
pre-gravid, 29
Body project, 183, 184, 187, 189–191, 193
Body satisfaction and eating behaviors, 134

Body weights and mass, 1192–1201
Bone mineral density (BMD), 447, 709, 710, 713, 714
Books on eating disorders, 1534
Borderline personality disorder, 253, 259
Bradycardia, 660, 662
Brain-derived neurotrophic factor (BDNF), 78, 81, 558
Bratman Orthorexia Test (BOT), 1438, 1439
Buffering capacity, 787, 790
Bulimarexia, 5
Bulimia nervosa (BN), 96, 201–203, 210, 211, 226, 250, 265, 274, 317, 320, 323, 327, 331, 333, 338–340, 342, 399–401, 563–564, 635, 668, 688, 714, 753, 786, 790, 807–815, 942–944, 946, 947, 949, 1004, 1134, 1158, 1161, 1175, 1252, 1307, 1357, 1365
  in adolescents, 731, 734
  amenorrhea, 927, 928
  androgen's role, 776–778
  antiandrogenic treatment, 775, 776
  antidepressants, 823, 824
  antiepileptics, 824, 827, 828, 837
  anxious and depressive experiences, 733
  applications, 778
  in athlete, 116
  attachment style, 848–849
  attention-deficit/hyperactivity disorder, 130
  biological mechanisms, 769
  CBT-BN, 6
  CBT-E, 18
  characteristics, 9
  cholesterol, 769
  clinical features, 6
  cognitive-behavioral therapy, 865
  cognitive distortion, 734
  comorbidity, 867, 868
  definition, 5, 844
  demographics, 866
  development of, 725, 726
  diagnostic criteria, 865
  diagnostic crossover, 877, 878
  dietary restriction, 400
  as a disorder of embodiment, 846–850
  eating disorders, 769, 931
  family-based approaches, 868
  features, 5
  fertility, 925
  fluoxetine, 823, 835
  during gestation, 29
  hormonal, 829, 831
  hormonal changes, 773, 774
  individual approaches, 868, 870
  insomnia disorder, 149
  key facts, 779, 780
  late adolescence, 740
  late-luteal phase, 773
  LH-stimulated thecal cells, 770
  lifetime prevalence, 823
  management of pregnant women, 931, 932
  medications, 823, 832–834, 836, 837
  menstrual cycle, 773
  mid-luteal phase, 773
  mixed/negative findings, 831
  multifactorial etiology, 864
  negative feelings, 823
  neural correlates, 847–848
  open-label trial, 836
  pathophysiology, 772
  perfectionism and, 732
  pharmacology, 834, 835, 837
  pharmacology youth, 833, 834
  pharmacotherapy, 823, 836, 874
  physical and psychosocial impacts, 400
  polycystic ovary syndrome, 774, 775, 925, 926
  postpartum period, 930, 931
  pregnant women, 930
  pregnenolone, 770
  prevalence, 866
  prevalence of pregnancy, 929
  primary characteristic of, 733
  prokinetic agent, 836
  psychiatric disorder, 776–778, 864
  psychodynamics of, 727
  psychological characteristics, 729
  psychotherapy, 823, 834, 835, 837
  purgative, 731
  randomized control trial, 879
  reproduction, 928
  self-esteem and, 731
  sex steroid hormones, 769, 772
  stimulants, 827, 829, 830
  tempo-spatial dynamics, 849–850
  topiramate, 836, 837
  transdiagnostic treatment, 20
  transdiagnostic view, 866, 867
  treatment, 868, 872
  treatment considerations, 400–401
  treatment moderators, 874–877
  unplanned pregnancies, 27
  visceral interoception, 846–847
  weight bias, 878, 879
Bulimic Investigatory Test of Edinburg (BITE), 795
Burda Orthorexia Risk Assessment (B-ORA), 1442

C
Calcium foods, 393
cAMP-response element binding protein (CREB), 986
cAMP-responsive element-binding protein H (CREBH), 706
Cancer, and binge eating
  alcohol consumption, 1033
  behavioral, environmental, and biomedical risk factors, 1026, 1027
  behavioral risk factors, 1028, 1032
  cigarette smoking, 1030
  correlational or causational effects, 1032
  directional relationships, 1035
  healthcare and screening behaviors, 1033
  low and middle-income areas, 1026
  maladaptive coping mechanisms, 1032
  mental and emotional consequences, 1033–1035
  mental and emotional health risks, 1035
  metabolic abnormalities, 1033
  modifiable risk factors, 1031
  nutrition and diet quality, 1028, 1029
  obesity, 1028
  pathways, 1034
  physical activity, 1029, 1030, 1032
  physical and mental health impacts, 1026
  physical health, 1026
  poorer nutrition and dietary intake, 1031
  protective effects of exercise, 1032
  protective factors, 1030
  in psychiatric classification systems, 1036
  psychological impacts, 1027
  public health issues, 1028
  screening behaviors, 1030
  screening rates, 1033
  secondhand smoke, 1030
  shared risk factors, 1036
  smoking and alcohol use, 1032
  substance use behavior, 1030
  utilization of health care, 1033
  workplace carcinogens, 1026
Cannabinoid-like G-coupled receptors, 84
Cannabinoids (*CNR1*) genes, 78
Cannabinoid type 1 receptor (CB1R), 461
Carbohydrates, 396, 522, 1161
Cardiac arrhythmia, 657
Cardiac complications, 541
Caregivers, 294
Case-control study, 322, 338, 339, 345
Catecholamine, 67
Catecholamine-O-methyl transferase (*COMT*) genes, 78
Catechol-O-methyltransferase (COMT) gene, 229
Center for Disease Control and Prevention (CDC), 645
Central coherence, 751, 753
Central Coherence Index (CCI), 756
Central nervous system, 171
Cerebellar dentate nucleus, 1270
Cerebellum, 1268
Cerebrospinal fluid (CSF), 171
Cerebrum, 1270
Child–Adolescent Perfectionism Scale (CAPS), 736
Child Eating Behavior Questionnaire, 1419
Childhood impulsivity, 136
Childhood obesity and early onset of being overweight, 1031
Children
  eating patterns with ADHD, 127
  school-aged, with ADHD, 125
  with ADHD, 128
Children and adolescents, 284, 286, 288, 292, 294, 295, 298, 300, 305, 306, 316, 344
Children's Binge Eating Disorder Scale (C-BEDS), 1509
Cholecystokinin (CCK), 85, 1160
Cholesterol, 769
Chronicity, 946, 949
Chronic sleep deprivation and binge eating, 1110, 1111
Chronic sleep deprivation and sleep disturbances, 1108
Chronic starvation, 703, 704, 707, 708
Circadian clock genes, 1198
Circadian control of feeding by the master and the secondary clocks, 1194
Circadian disruptions in shift work, 1195
Circadian rhythm of food intake, 1194–1196
Clinical sample, 322, 338, 339
CNR1 and *CNR2* genes, 83
Cocaine and amphetamine regulated transcript (CART), 86
Coenaesthesia, 845, 847
Cognitive-behavioral approaches, 1243, 1249
Cognitive behavioral model, 809
Cognitive-behavioral strategies, 370
Cognitive behavioral therapy (CBT), 4, 279, 391, 402, 824, 865, 868, 870, 992, 1150, 1152, 1243, 1252, 1318
Cognitive Behavioral Therapy–Enhanced (CBT-E), 853
Cognitive Behavioral Therapy for eating disorders (CBT-E), 1185
Cognitive-Behavioral Treatment (CBT), 376
Cognitive-behavioral treatment for ARFID (CBT-AR), 1249

Cognitive dissonance (CD), 279
Cognitive functioning, of EDs, 749
Cognitive states, 1011
Cohort study, 338, 345
Collaborative Care Skills Workshops, 301
College Health Related Information Survey (CHRIS-73), 117
Combination devices, 427
Combined oral contraceptives (COC), 776
Community sample, 338, 339
Comorbidity, 633, 634, 867, 1308
Compensatory behavior, 865, 868
Competing response, 1401, 1403, 1410
Compulsive behavior and mental preoccupation, 1437
Compulsive exercise test (CET), 420
Computer gaming, 1341
Computerized Tomography (CT), 1065
Concentration networks, 1216
Confident Body, Confident Child, 296
Consequences of binge eating, 1012
Corticosterone-insulin interaction, 56
Corticotropin-releasing factor (CRF), 54, 67
Corticotropin releasing hormone (CRH), 1407
Cortisol, 85
CREST treatment, 340
Criterion B symptoms, 1123, 1133
Cronbach alpha values of questionnaires, 1442
Culture bound syndrome, 216
Cyclooxygenases (COXs), 455
Cytochrome P450 epoxygenases, 456
Cytochrome P450 monooxygenases (CYP), 455
Cytokines, 67

D

Danish National Birth Cohort (DNBC), 43
D-cycloserine (DCS), 1250
Dehydration, 252, 253, 259
Dehydroepiandrosterone sulfate (DHEA-S), 770, 779
Deliberate Denial of Disordered Eating Behaviors Scale (DDEBS), 374, 380
DeltaFosB, 983, 984
  binge eating, 983
  chronic stimulation, 984
  expression, 986
  neuronal activity, 987
Denial of disordered eating
  applications, 378, 379
  assessment, 369, 371, 373, 375, 376, 378, 380
  behaviors, 378
  black women, 377
  clinical and non-clinical samples, 377
  comorbid diagnostic consequences, 372
  concealment, 369, 374, 375, 379
  definition, 368, 369
  diagnosis, 368, 371, 372, 375, 378, 380
  diagnostic consequences, 371, 372
  eating behaviors, 368
  etiology, 369, 370
  face stigmatization, 378
  factors, 379
  health care providers, 377
  help-seeking consequences, 371
  infancy, 378
  insight, 368, 369, 372, 373, 375, 378, 379
  interpersonal formulation, 379
  legal system, 378
  lethal consequences, 370, 371
  lying, 373
  mental illness, 378
  retrospective, 374, 375
  self-report, 373, 374
  social consequences, 370
  underreporting, 373, 379
Dental caries
  biological and clinical aspects, 792
  concepts and epidemiology, 792
  dental caries and bulimic symptomatology, 796
  etiology, 793
Dentate gyrus, 556, 558, 559
Depression, 542, 546, 678, 776, 777, 918
  bulimia nervosa, 733
Depressive and bipolar disorders, 1467
Depressive disorders, 253
Depressive emotional eating consumed overall fewer Kcal and carbohydrates, 1112
Depressive symptoms, 892
Desacyl-ghrelin (DAG), 571
Describe, express, assert, and reinforce (DEAR), 376
Developmental Origins of Health and Disease, 38
Dextroamphetamine, 829
Diagnostical and Statistical Manuals (DSM), 265
Diagnostic and Statistical Manual for Mental Illness (DSM-5), 371
Diagnostic and Statistical Manual of Mental Disorders, fifth edition (DSM-5), 643, 689, 1044, 1145, 1505

Diagnostic and Statistical Manual of Mental Disorders (DSM), 533, 769, 777, 1123, 1468, 1530
Diagnostic and Statistical Manual of Mental Disorders (DSM)-III, 203
Diagnostic and Statistical Manual of Mental Health Disorders (DSM), 1236, 1252
Diagnostic and Statistical Manual version 5 (DSM-5), 514, 532
Diagnostic criteria, 1482, 1485–1488, 1492, 1493
Diagnostic crossover, 878
Dialectical behavior therapy (DBT), 340, 376, 814, 834, 873, 971
Diaphragmatic breathing, 1401–1403, 1410
Dietary assessment, 389
Dietary cholesterol, 769
Dietary psychopathology, 1086
Dietary restraint, 892, 893, 918, 1009, 1010, 1160, 1161
  macronutrient deficiencies, 1163
  micronutrient deficiencies, 1162, 1163
Diet-induced hypoglycaemia, 62
Dieting, 1006, 1009
Dietitians, 1165–1167
Differential diagnosis, 1252
Difficulty in Describing Feelings (DDF), 316–318, 322, 325, 330, 338–340, 342
Difficulty to Identifying Feelings (DIF), 316–319, 322, 326, 328, 330, 333, 338–342
Diffusion Tensor Imaging (DTI) study, 563, 1076
Digital media use, 135
Dihydrotestosterone, 770
5-α-Dihydrotestosterone (DHT), 770
Dihydrotestosterone (DHT), 771
Disordered eating, 55, 66, 68, 296, 304, 305
Disordered eating behaviors, 129
  and binge eating, 1109
Dissonance-based interventions, 185, 187, 189
Distress tolerance, 814
Diuretic misuse, 1165
Dopamine (DA), 81, 777
  function, 136
  SUD and ED, 228, 230
Dopamine D3 receptor (*DRD3*), 82
Dopamine receptor 2, 3 and 4 (*DRD2*, *DRD3* and *DRD4*) genes, 81
Dopamine receptor family, 78, 81
Dopamine reward pathway, 57
Dopaminergic signaling system, 136
Dorsolateral prefrontal cortex (DLPFC), 994
Dove Parents, 297
Dove Self-Esteem Project Website for Parents, 297
DRD4 gene, 82
Driven exercise, 430
Drospirenone, 776
Dual-energy X-ray absorptiometry (DXA), 444–445
Dual Pathway Model (DPM)
  applications, 917
  bivariate relationships, 893
  BN risk factors, 918
  body dissatisfaction, 889, 891, 892
  bulimia nervosa (BN), 888
  caloric deprivation, 889
  clinical and prevention implications, 916
  cross-lagged model, 913
  cross-sectional studies, 893, 894, 901, 902
  dietary restraint, 892, 893
  disordered eating symptoms, 918
  limitations, 914–916
  longitudinal studies, 902, 911–913
  negative affect, 892, 893
  negative mood state, 889
  path-modelling, 893
  predictive utility, 914
  risk factors, 916, 917
  sociocultural pressure, 888, 890
  thin-ideal internalisation, 888, 891, 918
Duration of untreated ED (DUED), 270
Duration of untreated illness (DUI), 273, 274
Düsseldorfer Orthorexia Scale (DOS), 1441, 1492–1493
Dutch Eating Behaviour Questionnaire, 1445
Dysbiosis, 489
Dysmorphic concern, 1315
Dysmorphophobia, 1306, 1321
Dyspeptic symptoms, 1406
Dysthymia, 689

E

Early adolescence
  anorexia nervosa, 740
  bodily changes, 740
  psychosexual identity in, 725
Early detection
  adolescence, 285
  adolescents, 290–292, 303
  anorexia nervosa, 285
  applications, 305
  barriers, 292–295, 303

Early detection (*cont.*)
behavioral symptoms, 290, 291, 303
caregivers, 285, 290, 303, 304
categories, 286
childhood, 285
children, 290, 291, 303
COVID-19 pandemic, 303, 305
early cognitive symptoms, 290
early interventions, 286, 288
Eating Disorder Continuum, 287
eating habits, 292
education, 307
energy intake, 292
expenditure changes, 292
family involvement, 284
interventions, 285, 307
linear progression, 287
literature, 303
longitudinal research, 289
mental illnesses, 284
mood changes, 292
online programs, 305
parent-focused early intervention programs, 295
parent-led early detection, 306
parent-led early intervention programs, 295
parent-led early interventions, 304
parent-led prevention, 303
parent-led risk factor reduction, 295–298
parent-led treatments, 298, 299
parents, 284, 285, 292, 294
parent support, 300–302, 307
phases of illness, 286
research and clinical interventions, 302
risk factors, 285, 289, 304
role of parents, 288, 289
symptoms, 285, 289, 303
time-based parameters, 287
treatment, 284
Early disorder phase, 306
Early Metabolic programming, 38
Eating Attitudes Test (EAT-26), 131, 1523
Eating Attitudes Test (EAT), 373
Eating disorder (ED), 250, 251, 254, 255, 257, 258, 261, 263–267, 315, 322, 338–344, 346, 1085, 1504
Eating Disorder Diagnostic Scale (EDDS), 1523
Eating Disorder Examination (EDE), 1505
Eating Disorder Examination-Bariatric Surgery Version (EDE), 1472
Eating Disorder Examination-Questionnaire (EDE-Q), 532, 1519–1521
Eating Disorder Inventory (EDI), 373
Eating Disorder Not Otherwise Specified (EDNOS), 338, 340, 769, 943, 1211
Eating Disorder Not Otherwise Specified of Purging type (EDNOS-P), 777
Eating disorder quality of life (EDQoL) questionnaire, 1457
Eating Disorder Quality of Life (EDQoL) scale
complications, 1452
domains, 1457, 1458
health-related quality of life, 1452
inpatient treatment, 1456
interpersonal domain, 1458
medical comorbidities, 1456
pro-eating disorder website communities, 1455
psychological approaches, 1456
QoL and body objectification, 1456
quality of life, 1452, 1454
treatment approaches, 1456
weight gain and reductions in ED symptomatology, 1456
Eating disorders (ED), 96, 97, 101, 182–183, 225, 270, 387, 415, 544, 556, 557, 563, 564, 625, 627, 631, 633, 786, 807–810, 812, 881, 942, 945, 1004, 1192, 1314, 1315, 1331, 1332, 1342–1346, 1361
in ADHD, 125
in adolescents, 5
anorexia nervosa, 201, 202, 354
application, 20, 216, 952
in athlete
female, 113
male, 113, 115
prevalence studies, 113
risk factors, 113
sports disciplines, 115
beliefs and behaviours, 390
binge, 947
binge eating disorder, 354
body mass index, 9
books on, 1534, 1536
bulimia nervosa, 202, 203, 354
chronicity, 949
clinical features characteristic of, 8
cognitive behavior therapy, 4
culture-bound syndromes, 200
diagnostic category of, 9, 18

diagnostic criteria, 203
epidemiological studies, 215
etiological theory, 207
etiology, 270
features of, 8
and fertility, 27
food and nutrient administration, 390
food and nutrient intake, 389
gene-environment interaction studies, 101–102
genetics, 201
health care, 206, 213
incidence, 206, 207
inpatient dietetic treatment, 397–399
laboratory studies recommended and potential findings, 277
maintenance of, 7
medical consultations, features of, 272–276
medication and complementary medicine, 390
men, 214, 215
methodological issues, 206
middle-aged women, 213, 214
mortality, 270, 951
non-Western countries, 200
nutrition assessment, 388–390
nutrition education and counselling, 391
nutrition intervention, monitoring and evaluation, 390–391
and OCD, 1361
and ON, 1365–1368
other resources of interest or relevance to, 1538
outpatient dietetic treatment for, 392–397
in pregnancy, 28–29
prevalence, 206, 207
prevention of eating disorders, intervention programs and impact, 276–279
professional societies, 1533
psychiatric disorders, 201
psychosocial change, 200
regulatory bodies or organisations, 1532
remission, 945
risk factors and prodromes, 271–272
serotonin in, 97
signs and symptoms, 275
sociocultural, 200
SUD and ED, 226
time-related changes, 215, 217
uric acid in, 172–174
validated screening tool, 277
Western countries (*see* Western countries, EDs)
Western culture, 200
Eating Disorders Examination (EDE), 371
Eating Disorders Inventory (EDI), 1445
Eating Disorders in Youth-Questionnaire, 1242
Eating Disorders Quality of Life Scale (EDQLS), 1525
Eating Habits Questionnaire (EHQ), 1492
Eating patterns
behavior outcomes, 59
drinking and smoking, 59
eating behavior, 59
food consumption, 59
mood, 59, 60, 62
stress/negative mood, 59
stress, 59, 60, 62
Ecological momentary assessment, 808, 811, 1005, 1015
EDE-Q, 1094, 1095
EDI-2, 1445
ED-related psychopathology, 1150
ED-specific questionnaires for the evaluation of QoL, 1453
Egosyntonicity, 369
Egosyntonic personality, 80
Eicosanoids (eiCs), 67, 453
in ABA model, 460
and neuroinflammation, 457
receptors, 456
Electrocardiogram (ECG)
anorexia nervosa (AN), 656
applications, 668
bradycardia, 659, 660, 662, 668
cardiac abnormalities, 659
cardiac manifestations, 656
cardiac risk, 669
clinical care of patients, 667
clinical use, 666, 668
computer-generated parameters, 658
electrolyte imbalances, 668
exercise, 664, 665
heart rate (HR), 657
heart rate variability (HRV), 662
heart rhythm, 657
impact of refeeding, 664
interpretation, 658
normal electrocardiogram values, 659
parameters, 659
patients, 667
prescribing QT prolonging medications, 665

Electrocardiogram (ECG) (*cont.*)
psychopharmacotherapy, 659, 665, 666, 668
QT interval, 663
refeeding, 659
skin electrodes, 657
spatial and temporal information, 659
sudden unexpected death (SUD), 666
symptoms, 657
T-wave changes, 664
Electrophysiological studies, 1272
Embedded Figures Test (EFT), 757
Embodiment, 850, 851
bulimia nervosa, 846–850
clinical perspectives, 853–854
definition, 845
and sexuality, 852–853
Emotional activation, 1383
Emotional eating, 1382
and body mass index, 1383–1384
and food craving, 1385–1387
and food image stimuli, 1385–1386
and HRV, 1391–1392
and hunger inhibitory control, 1387–1389
and loss of control eating, 1386–1388
neural basis of, 1388–1390
Emotional regulation difficulties (ERD), 133
Emotion dysregulation, 808, 810, 815
Emotion regulation, 807, 809–811
in SUD and ED, 236
Emotion Regulation Group Therapy, 340
Emotion-related eating, 64
Empathy, 651
Endocannabinoids (eCBs), 83, 461
pathway, 83–84
Endocrine system, 67
Energy expenditure, 544
Energy intake, 389, 398, 1045, 1051, 1055, 1058
Enhanced Cognitive Behavior Therapy (CBT-E)
for adolescents, 15
CBT for Bulimia Nervosa (CBT-BN), 4
challenges, 19
definition, 4
forms of, 14
goals, 12
implications for clinical services, 19
inpatient, 17
integral parts of, 15
intensive outpatient, 15
origin of, 5
outpatient version of, 15
post-inpatient outpatient, 18
psychological model, 13
psychological treatment, 9
rationale, 5
status of, 18
transdiagnostic theory, 8
transdiagnostic treatment, 20
treatment, 4
for underweight patients, 15
Enhanced version of CBT (CBT-E), 1150
Ensemble coding findings, 1074
Enteral feeding, 1252
Environment, 98, 102
Enzymatic deficiency, 171
Eosinophils, 1406–1411
EPHX2, 88
Erosive tooth wear (ETW)
biological and clinical aspects, 788
concepts and epidemiology, 787, 788
epidemiology, 787
erosive tooth wear and bulimic symptomatology, 794
etiology, 790–791
ESR2, 88
Estradiol, 709
Estrogen receptor (ER), 771, 778
Estrogen Related Receptor Alpha gene (*ESRRA)*, 88
Estrogens, 770
Evening awakenings with ingestions, 1211
Evidence, 1531, 1536
Excessive exercise, 423, 424
Executive function deficits
common features of, 234
in SUD and ED, 235
Exercise, 1370
addiction, 1341, 1342, 1345, 1346
chronic physical, 576
Exercise addiction inventory (EAI), 420
Exercise Motivations Inventory-2 (EMI-2), 419
Exogenous GH, 703
Experienced Carers Helping Others (ECHO), 301
Exploratory factor analysis (EFA), 1490
Exposure and response prevention therapy (ERP), 262
Expressive writing, 191, 192
External context, 1011
Externally Oriented Thinking (EOT), 316, 317, 322, 338, 339
Exteroception, 848

F
Facebook, 911
Facial emotion recognition task, 474, 477
Familial aggregation, 1198
Family-based treatment (FBT), 284, 299, 306, 375, 380, 865, 868, 873, 876, 877, 1243
Fasting, 1009
FAST (The Female Athlete Screening Tool), 118
Fat, 1161
  catabolism, 539
Fat mass (FM), 445
Fat mass and obesity-related gene (FTO)
  adolescents, 1050–1052, 1057
  adult and pediatric populations, 1057
  adults, 1046–1050
  alleles and neural studies, 1054, 1055
  anorexia nervosa, 1058
  binge Eating, 1058
  binge nating, 1058
  bulimia nervosa, 1058
  children, 1050–1052, 1057
  compensatory behavior, 1044
  development, 1046
  diabetes, 1045
  eating disorders, 1044
  emotional eating, 1057, 1058
  etiology, 1045
  food craving, 1058
  food enjoyment, 1058
  food responsiveness, 1058
  food reward, 1058
  high-energy food items, 1045
  higher food reinforcement, 1045
  homeostatic and reward circuits, 1052, 1053, 1056
  hypothalamus, 1045
  limitations, 1056, 1057
  metabolic syndrome, 1045
  morbidity, 1045
  mortality, 1045
  neural systems, 1052
  neurobiological evidence, 1057
  pediatric and adult population, 1046
  relative reinforcing value, 1058
  strengths, 1056, 1057
Fatty acid amide hydrolase (FAAH) enzyme, 455
FBT for the anorexia nervosa prodrome, 299
Fecal microbiota transplantation, 500, 501, 503
Feeding and eating disorders, 642, 643
Feeding and Eating Disorders Examination-Bariatric Surgery Version (EDE-BSV), 1472
Feeling and Body Investigators-ARFID Division (FBI-ARFID), 1249
Fertility, 446
  anorexia nervosa and, 605
  eating disorders in, 615
  long-term effect on, 608
Fibroblast growth factor (FGF)-21, 707
First Episode Rapid Early Intervention for Eating Disorders (FREED), 301, 302
First Night Eating Symposium, 1211
Fixation, 1481–1485, 1487, 1488, 1490, 1494–1497
Fluid replacement, 259–261
Fluid restriction in eating disorders
  behavioral interventions, 261, 262
  demographic characteristics, 253
  fluid replacement, 259–261
  Holliday-Segar formula, 252, 253
  inpatient or residential setting, 253
  intentional fluid restriction, 251, 252
  internet, 254
  patient fluid needs, 252, 253
  psychiatric symptoms, 255
  psychological interventions, 262, 263, 265
  water weight, 254
Fluoxetine, 824, 834, 837
Focused ultrasound stimulation (FUS), 993
Follicle stimulating hormone (FSH), 772, 926
Food addiction, 1342–1343, 1345
  ADHD, 133
  rate of, 136
Food craving, 1006, 1010, 1385, 1387
Food enjoyment, 1050–1052, 1058
Food fussiness (FF), 1419, 1420, 1423
Food insecurity, 390, 400
Food intake, 250, 253, 265, 1193, 1194
Food intake and energy expenditure, 1192
Food literacy, 389
Food responsiveness, 1050, 1052, 1058
Food rewarding, 1057, 1058
FTO (Fat mass and obesity-associated) gene, 86
Functional dyspepsia, 1406–1408, 1410
Functional hypothalamic amenorrhea (FHA), 605, 772, 924, 925, 928
Functional MRI studies (fMRI), 563, 1065, 1068, 1074–1076
Fused Graphical Lasso (FGL) method, 1224

G
Gambling, 1332, 1341
Gaming, 1332, 1341
Gamma amino butyric acid (GABA), 1267
Gastric bypass, 1131
Gastroesophageal reflux disease (GERD), 1401, 1403–1406, 1410
Gastrointestinal problems, 1237
Gastrointestinal symptoms, 1241
Gender, 532, 1309
Genetic(s)
  imprinting, 1264
  SUD and ED, 227, 229
  variants, 98, 102, 103, 545
Gene variants, in ED, 79
Genomic-wide association studies (GWAS), 79, 1199–1200
Gestation, OFSED during, 28
Gestational anorexia nervosa, 29
Gestational bulimia nervosa, 29–30
Gestational diabetes mellitus (GDM), 39, 42
Gestation weight gain (GWG), 27, 39
Ghrelin, 84, 542, 543, 546, 549, 571, 705–706, 1267
  antagonism, 576
  chronicity and, 577
  clinical evidence of, 575
  genetic factors, 576
  insomnia disorder, 153
  physiological effects, 572
  resistance, 576
  and reward signaling in AN, 573
Ghrelin gene (GHRL), 84, 571
GHSR1a receptor, 571
Glucocorticoid receptors (GR), 57
Glucocorticoids (GCs), 54–56, 67, 68
Glutamatergic neurotransmission, 83
Glycaemic load (GL), 62
Go/no-go saccade task, 592
Godin Leisure-Time Exercise Questionnaire (GLTEQ)., 418
Gonadotropin, 770
Gonadotropin-releasing hormone (GnRH), 774
Gothenburg anorexia nervosa study, 471
G protein-coupled receptors (GPCRs), 456
Group Embedded Figures Test (GEFT), 757
Growth hormone (GH), 571
Growth hormone (GH) resistance, in anorexia nervosa, 705
  bone mineral density, 709
  CREBH, 706
  estradiol, 709
  FGF-21, 707
  ghrelin, 705–706
  insulin, 707
  leptin, 708–709
  protein deficiency, 705
  recombinant human growth hormone, 710
  recombinant human IGF-1, 710–714
  SIRT1, 706
  testosterone, 709
  triiodothyronine, 707
Growth hormone-insulin-like growth factor-1 (IGF-1) axis, 703, 706, 714
Growth hormone secretagogue receptor 1a (GHSR1a), 706
Gut microbiome, 62

H
Head circumference, 930
Healthful eating, 1329
Health-Related Quality of Life in ED-short form (HeRQoLED-s), 1525
Healthy eating, 1354–1358, 1360, 1364, 1365, 1370
Healthy Girls Project, 296, 297
Healthy orthorexia (HeOr), 1484, 1485, 1489, 1491, 1493–1497
  psychometric evaluation, 1493
Heart rate sensors, 427
Heart rate variability (HRV), 662, 1383–1388, 1391
Help-seeking, 379
Heterogeneity, 1237
Hippocampal atrophy, 542
Hippocampal cell proliferation, 557
Hippocampal neurogenesis, 557, 558
Hippocampus, 55
  in animal model of AN, 558–559
  bulimia nervosa (BN), 563–564
  functional studies, 561, 562
  in neurobiology, 557
  psychiatric disorders, 557
  role, 556
  structural studies, 559–561
  with short ($\leq$1 year) or long duration of anorexia nervosa, 561
Histone deacetylase 4 (*HDAC4*), 88
Holliday-Segar formula, 252, 253
Hormonal, 829, 831
  disbalance, 359
Hospital Anxiety and Depression Scale (HADS), 1525
Hospital-based feeding programs, 1250

5-HT2A receptor gene (re6311), 80
5-HTTLPR, 97–102, 228
5-HT transporter (5-HTT), 80
Human adipocytes, 546
Hunger hormone, *see* Ghrelin
Hydroloading, 265
5-Hydroxytryptamine (5-HT) system, 80
Hyperactivity, 539, 678
Hypercortisolaemia, 542
Hyperemesis gravidarum, 929
Hyperphagia, 1263, 1264, 1288, 1291, 1293, 1296
Hypocalcaemia, 657
Hypocretin receptors and NE, 1199
Hypokalemia, 657
Hypoleptinemia, 544–546, 548
Hypomagnesemia, 657
Hyponatremia, 657
Hypoproteinaemia, 541
Hypothalamic amenorrhea, 542, 779
Hypothalamic-pituitary-adrenal (HPA) axis, 54, 67, 774, 776
  dopamine reward pathway, 57
  glucocorticoids, 55, 56
Hypothalamic-pituitary-gonadal (HPG) axis, 546, 774
Hypothalamic–pituitary-ovarian axis, 772
Hypothalamic-pituitary-thyroidal axis, 772
Hypothalamic reactivity, 548
Hypothalamus, 55, 543, 544, 547, 548, 1265
Hypovitaminosis, 541
Hypoxanthine-guanine phosphoribosyltransferase, 171

I

ICD-10, 1530, 1531
ICD-11, 1123–1125, 1531
IDentity and EAting disorders (IDEA) questionnaire, 852
Image of one's own body, 730, 733, 742
Immediate early genes (IEGs), 984
Immune activation, 1409
Implementation, 189–191
Impulsivity, 807, 808, 1182, 1183, 1505
  SUD and ED, 233, 234, 236
Incidence, 192, 216
Individualized approaches, 1014
Inflammation, 1407
  resolution of, 454
Inhibitory control, 987–989
Inpatient dietetic treatment, for eating disorders
  goals, 397
  nutrition support for inpatients, 398–399
  refeeding syndrome, 398
Inpatient treatment, 624, 625, 627, 632–635
Insomnia disorder, 1192
  anorexia nervosa, 149
  avoidant/restrictive food intake disorder (ARFID), 150
  binge eating disorder, 149
  bulimia nervosa, 149
  categories, 147
  characteristics, 146
  definition, 147
  and eating disorders, 146
  hypothesized psychological factors, 151
  night eating syndrome, 150
  prevalence, 148
  social timing and behaviors, 154
  and symptoms in eating disorders, 149
  as transdiagnostic across psychopathology, 148–149
  treatment implications, 155
Insulin, 546, 707, 708
Insulin like growth factor-1 (IGF-1), 571, 703–710, 714
Insulin resistance, 774
Integrative cognitive-affective therapy for bulimia nervosa, 815
Intelligence quotient (IQ), 645
Intentional fluid restriction, 250–252, 254, 265–267
Interaction, 97, 102
Interest, 1483, 1485, 1487
Inter-generational transmission, 1423
International Classification of Diseases 10th Revision (ICD-10), 206
International Classification of Diseases and Related Health Problems (ICD), 1530
International Classification of Diseases (ICD-11), 1236
International Physical Activity Questionnaire (IPAQ), 416
International research meeting, 1193
International Society for Nutritional Psychiatry Research, 60
International units (IU), 829
Internet addiction, 1345, 1346
Interoception, 847, 848, 854
Interpersonal therapy (IPT), 834
Intervention outcomes, 315, 340, 342–344
Interventions, 1015
Intrauterine growth restriction (IUGR), 38
Iodine deficiency disorders, 40

K
Kinase domain containing 1 (*ANKK1*), 78
Kisspeptin (KISS1), 546, 548
Kutcher Adolescent Depressive Scale (KADS), 736

L
L-allele, 82
Language revisions of questionnaires, 1443
Laparoscopic adjustable gastric band (LAGB), 1469
Laparoscopic sleeve gastrectomy (LSG), 1469
Large-for-gestational-age (LGA) babies, 30
Late adolescence, bulimia nervosa, 740
Lateral hypothalamic area (LHA), 543
Lateral parabrachial nucleus, 544
Laxatives, 1164
Leptin, 544, 546, 549, 708–709, 1193
  in cerebrospinal fluid, 85
  insomnia disorder, 153
Leptin gene (LEP), 85
Lesch-Nyhan syndrome)LNS), 171
Leukotrienes, 456
Light neglect obesity (LNO), 965
Likert Scale in questionnaires, 1440
Lipoxygenases (LOXs), 455
Lisdexamfetamine (LDX), 823, 993
Lisdexamfetamine dimesylate (LDX), 829
Lithium, 831
Lived corporeality, 845, 846, 848, 850–853, 855
Liver, 769
Longitudinal Assessment of Bariatric Surgery (LABS) study, 1468
Longitudinal study, 322, 340, 341, 343, 345
Loss of control (LOC), 1468
Loss of control eating
  binge eating, 128–129
  and emotional eating, 1386–1388
Loss of control while eating (LOCE), 1086, 1091–1097
Low-density lipoproteins (LDLs), 769, 926
Low Energy Availability in Females Questionnaire (LEAF-Q), 118
Luteinizing hormone (LH), 772, 926

M
Macronutrients, 1163, 1252
Magnesium hydroxide, 1165
Magnetic resonance imaging (MRI), 1065
Magnetic resonance spectroscopy, 1272
Magnetoencephalography studies in BED, 1076, 1079
Major depressive disorder (MDD), 557, 560, 689
Maladaptive physical activity, 415
Malnutrition, 358, 387, 388, 399, 440, 539, 542, 546, 547, 549
Mania, 678
Mast cells, 1407–1411
Matching Familiar Figures Test (MFFT), 758
Maternal-fetal relationship, 27
Maternal postnatal depression, 30
Medical conditions, 1241
Medical consultations, 273
  eating disorders, 272–276
Medical foods, 629
Medical model paradigm of disease, 1209, 1213
Mediterranean diet (MD), 42, 60
Medium spiny neurons (MSNs), 986
Melanocortin (MC) system, 505
Memory and learning, 1053
Memory-guided saccade task, 593
Menses, 440, 446
Mental Component Summary Scale (MCS), 1521
Mental health
  of cancer patients, 1027, 1028
  eating disorders, 354
  protection in, 360
Mesolimbic dopaminergic system, 67
Meta-analysis, 339, 343, 345
Methodological considerations, 1012
Methylamphetamine, 829
Methylphenidate, 829
Microbiome, of AN patients, 493
Microbiota
  with AN, 492–496
  development in infancy, 492
  dysbiosis, 489
  gut, 489, 492, 493
  host relationship, 490
  lean, 500
  manipulations in animal models, 491
  microbiota-gut-brain axis, 490
  obese, 500, 506
Microbiota-gut-brain axis, 490–492
Micronutrients, 1163, 1252
Mineral oil, 1165
Minerals, 1161
Minnesota Multiphasic Personality Inventory (MMPI), 374
Model-based recursive partitioning, 1225
Modeling Network structure, 1216

Monoamine oxidase inhibitors (MAOI), 824, 836
Monosodium urate (MSU), 169, 170
Mood and substance use disorders, 1467
Mood disorders, 643, 688
Mood intolerance, 809, 813
Morbid obesity and eating disorders, 1079
Morning anorexia, 1192–1193, 1209
Mortality, 942, 951
Motivational interviewing (MI), 375, 380
Motivation to eat, 1059
Multidisciplinary follow-up, 1085
Muscle dysmorphia, 1312
  characteristics, 1310, 1311
  steroid abuse, 1311

N
N-arachidonoylethanolamine (AEA), 84, 455
Narrative review, 317, 345
Nasogastric (NG) feeding, 398
Nasogastric (NG) tube, 260, 1252
Negative affect, 807–809, 892, 893, 918, 983
Nental illness, 368
Neonatal outcomes, 608
  AN on, 614
Neophobia, 1419, 1420, 1423, 1425
Nervous vomiting, 202
Network analysis, 1215, 1217
  accuracy and stability, 1218
  centrality indices, 1217, 1218
  models, 1225
Network Approach to Psychopathology in Eating Disorders, 1218
Network Approach to Psychopathology in NES, 1219, 1221, 1223
Network dynamics, 1226
Network structure, 1216, 1217, 1223
Network theory, 1213–1215
Network Theory of Psychopathology, 1213
Neural correlates, 847–848
Neural tube defects (NTDs), 42
Neurobiology
  of ED, 230, 231
  of ED-SUD, 231
  of SUD, 230
Neurodevelopmental disorders (NDD), 643, 644
Neurofilament light chain protein (NfL), 473
Neurogenesis, 556
Neuroimaging, 561, 565
Neuroimaging studies, 1064
Neuroinflammation
  in animal models of AN, 460
  eiCs receptors, 456
Neuromodulation, 992, 993, 995, 1274
Neuronatin (NNAT) gene, 87
Neuropeptides, 55
Neuropeptide Y (NPY), 55, 67, 85, 543, 571, 1470
Neuropsychiatric disorders, 171–172
Neuropsychology, 644
Neurotransmitter, 777
  intestinal, 492
  metabolomic analysis, 503
Nicotine consumption, 1340
Night Eating Questionnaire (NEQ), 1196
Night eating syndrome (NES), 1192
  BMI, 1197
  bootstrapped strength difference, 1222
  centrality plot for the psychopathology network, 1221
  clinical impairment/distress, 1223
  clinical observation of individuals with obesity, 1212
  clinical versus subclinical thresholds, 1224
  compensatory behaviors, 1197
  conceptual and clinical utility, 1223
  conceptualization, 1223, 1224
  conceptualization and etiology, 1212
  conceptualization and unique features, 1209
  daily caloric intake, 1196
  daily rhythms of food intake and sleep, 1193
  delayed timing of eating, 1195
  diabetes, 1197
  diabetes management, 1198
  disrupted circadian rhythm, 1224
  emotional regulation, 1198
  environmental influences, 1200
  genetic determinants, 1200
  genetic studies, 1198, 1199
  genetic susceptibility, 1200
  history of, 1209
  hormone profiles, 1195, 1196
  insomnia disorder, 150
  isolated phenotype, 1193
  long-term effects, 1197
  meal anticipation, 1195
  and network analysis
    circadian pattern of food intake, 1209
    disrupted circadian rhythm, 1209
    medical model approach, 1209
    mood or sleep disturbances, 1209
    network approach to psychopathology, 1209

Night eating syndrome (NES) (*cont.*)
network approach, 1224
nocturnal awakenings and food consumption, 1225
out-of-phase eating, 1195
phenotyping, 1196
poor sleep quantity and quality, 1111
prevalence, 1193
prevalence rates, 1212
psychological factors, 1198
psychological treatments, 1223
psychopathology network, 1220
recognition of, 1210
research and clinical implications, 1209, 1224
research diagnostic criteria, 1211
sleep-wake cycle, 1195
symptom network, 1214
symptoms, 1210, 1212
treatment, 1200
variation in operationalized diagnostic criteria, 1210
Nighttime eating, 1193, 1198–1200
Nine-item avoidant/restrictive screen (NIAS), 1420
Nocturnal eating, 1196
Nocturnal hyperphagia, 1192
Nocturnal ingestion of food, 1211
Nomophobia, 136
Non-communicable diseases (NCDs), 40
Non-compensatory purging, 1182, 1184
Non-pathological dimension, 1485, 1487, 1489, 1494, 1495, 1497
Non-specific symptoms, 276
Non-suicidal self-injury (NSSI), 370
Non-Western countries, EDs
Africa, 213
East Asia, 211, 212
epidemiology, 211
Latin America, 212, 213
West Asia, 212
Norepinephrine (*NE*), 78
Nucleus accumbens (NAcc), 57
Nutrition, 1293
assessment, 388–390, 440
counselling, 391
deficiencies, 41
education, 391, 392
intervention, 390–393, 397, 400
rehabilitation, 391, 393, 397, 398, 627–628
status, 387, 400
support, for inpatients, 398–399
Nutrition Care Process, 387, 388

O

Obesity, 1084, 1087, 1089–1093, 1095, 1131, 1294, 1296
ADHD and, 127
and daytime dysfunction, 134
hyperinsulinemia, 774
Object Assembly, 757
Objective binge episodes (OBEs), 226
Objective measures, 1013
Obligatory exercise questionnaire (OEQ), 420
Observation Alexithymia Scale (OAS), 317, 338, 342, 344
Obsession, 1481, 1484, 1485, 1494, 1495
Obsessive-compulsive disorder (OCD), 643, 685, 686, 691, 1241, 1360, 1361
and EDs, 1361
lifetime prevalence rate, 1361
and ON, 1364–1365
Obsessive-compulsive personality disorder (OCPD), 1368
Obsessive-compulsive symptoms, 678
disorder, 1331, 1347
Oculomotor delayed response task, 593
Oestrogen, 515, 532
Oleoylethanolamide (OEA), 461
Opioid antagonists, 83
Opioid delta 1 receptor (*OPRD1*), 83
Opioid peptides, 83
Opioids (*OPRD1*) genes, 78
Oppositional defiant disorder (ODD), 1241
Oral-sensory motor problems, 1237
OR eating behavior, 1104
Orexins, 85
Organic alexithymia, 315, 344
Orthorexia, 1436
Orthorexia nervosa (ON), 31, 1328, 1331, 1332, 1339–1344, 1354, 1355, 1359–1361, 1372, 1481–1486, 1489, 1491, 1497
in athletes, 116
definition, 1355
diagnostic criteria, 1358–1360, 1486
DOS, 1492–1493
with eating disorders, 1365–1368
EHQ, 1492
and exercise, 1370
frequency and risk factors, 1488–1490
and healthy living behaviors, 1370–1371
management symptomatology, 1494–1495
with mental disorders, 1368–1369
negative effects of orthorexia on health and functionality, 1356–1357

with obsessive-compulsive personality disorder, 1368
and OCD, 1364–1365
ONI, 1493
prevalance, 1357–1358
with psychotic disorders, 1369
questionnaires, 1438
smoking and alcohol use, 1371
and social media, 1370–1371
with somatoform disorders, 1368–1369
symptomatology, 1364, 1486–1488
symptoms of, 1355–1356
TOS, 1490–1492
treatment and management, 1372–1374
unique features, 1369
vegeterian diet, 1371
Orthorexia Nervosa Inventory (ONI), 1444, 1493
Orthorexia Nervosa Scale (ONS), 1442
Orthorexia Self-Test, 1438
Orthorexic eating, 1329–1332, 1339, 1341, 1343, 1345, 1346
ORTO-15, 1439–1441
Osteopenia, 447
Osteoporosis, 447
Other specified feeding and eating disorder (OSFED), 226, 279, 354, 476, 1152, 1252, 1253
categories, 1145, 1211
diagnostic classification, 1176
Outcome, 183–185, 189–193
Out-of-phase eating, 1195
Outpatient dietetic treatment, for eating disorders
calcium foods, 393
carbohydrates, 396
diet foods and fillers, 397
fluids, 396
fruit and vegetables, 396
fun foods and social eating, 397
goals, 392
nuts, oils and fats, 396
protein, 393–396
Overeating, 1181
act of, 732
episodic, 733
in respondents, 736
uncontrolled, 728
and vomiting, 728
weight fluctuations and, 726
Overlapping Figures Test, 757
Oxidative stress, 68
Oxytocin (OXT), 829, 836, 1267

P

Paffenbarger Physical Activity Questionnaire (PPAQ), 419
Palmitoylethanolamide (PEA), 84, 461
Paranoia, 678
Paraventricular nucleus (PVN), 54
Parental Bonding Instrument (PBI), 962
Parental feeding practices, 1422–1423
Parent-based treatments, 1249, 1250
Parenting style, 962, 963
Parents Act Now, 298
Partial hospitalization program (PHP), 1239
Partial sleep deprivation on executive functions, 1113
Path-analyses, 918
Pathological dimension, 1483, 1484, 1495, 1497
Pediatric autoimmune neuropsychiatric disorders linked to streptococcal infections (PANDAS), 504
Pedometers, 427
Peptide tyrosine tyrosine (PYY), 1161
Perfectionism and bulimia nervosa, 732
Perinatal outcomes, anorexia nervosa and adverse, 613
Peroxisome proliferation-activated receptor α (PPARα), 84
Peroxisome proliferator-activated receptors (PPARs), 456
Persistent insomnia, 147
Personality, 959, 965–968, 971, 973, 974
Personality disorders, 643, 688, 689
Perth Alexithymia Questionnaire, 344
PGE receptor, 456
Pharmacotherapy, 992, 995, 1250
Phenomenological research, 846
Phenomenology, 846, 854
Phoenixin (PNX), 547, 549
Phospholipase A2 (PLA2) superfamily, 455
Physical activity (PA)
adaptive, 415
eating disorders, 415
ecological momentary assessment, 421–424
maladaptive, 415, 419, 420
objective components, 415
objective measurement, 426–429
psychological components, 415
reasons for exercise inventory, 419
self-report measurement, 416, 417, 419, 421
semi-structured interview, 424, 425
Physical appearance, 1010
Physical Component Summary Scale (PCS), 1521

Phyto-9 cannabinoid-tetrahydrocannabivarin, 83
Pica, in pregnancy, 30–31
Picky eaters (Pes), 1420
Picky eating (PE), 1418, 1425
  childhood to young adulthood, 1421
  definitions, 1418–1419
  measurement, 1419–1420
  parental feeding practices, 1422–1423
  prevalence, 1420–1421
  sensory sensitivity, 1423–1424
  temperament, fearfulness and inhibition, 1424–1425
  treatment, 1425
Pituitary disease, 202
Polish adaptation study, 1439
Polycystic ovary syndrome (PCOS), 774, 775, 924–926
Polyunsaturated fatty acids (PUFAs), 40, 453
POMC gene, 86
Positron emission tomography (PET), 1079
Postpartum period
  depressive and anxiety symptoms, 614
  pregnancy and, 611, 616
Post-traumatic stress disorder, 253
Prader–Willi syndrome (PWS), 1263, 1271, 1273, 1288
  adulthood, 1293, 1294
  behavioral interventions, 1298
  behavioral phenotype, 1265, 1266
  BP1-BP2 microdeletion syndrome, 1266
  brain stem, 1268
  cerebellar contribution, eating disorders, 1276
  cerebellum, 1268
  cerebrum, 1270
  diagnostic criteria, 1264
  early childhood period, 1290–1292
  electrophysiological studies, 1272
  functional imaging studies, 1272, 1274
  genetic susceptibility, 1265
  ghrelin, 1267
  5-hydroxytryptamine, 1267
  hyperphagia, 1265
  hypothalamic dysfunction, 1265
  hypothalamus and pituitary gland, 1268
  neurochemical alterations, 1267
  neurological features, 1264
  neuromodulation, 1274
  nutritional stages, 1296, 1297
  pharmacotherapy, 1299, 1300
  phenotype, 1294, 1295
  prenatal period, 1289
  psychiatric comorbidities, eating disorders, 1276
  psychiatric disturbances, 1265
  schaaf-Yang syndrome, 1266
  self-injurious behavior, 1296
  structural connectivity, 1270
  teenage and adolescent period, 1292, 1293
Prebiotics, 501, 502
Prefrontal cortex (PFC), 57, 985
Pregnancy, 446
  anemia in, 611
  behavioral change during, 27
  binge eating disorder, 30
  birth outcomes, 38
  complications, 611
  dietary patterns, 42–44
  disease course in, 611
  eating behaviors in, 27
  eating disorders in, 28–29
  ED/OFSED during, 27
  feto-maternal outcomes, 42–44
  industrialized countries, 41, 42
  macronutrient, 44
  maternal anthropometrics, 38–40
  maternal nutrition, 38
  micronutrients, 44
  nausea and vomiting in, 612
  nutrition, 38–40
  pica during, 30–31
  and postpartum period, 605
  prevalence of anorexia nervosa in, 610
  U/OSFED, 27
  in women with ongoing AN, 605
Pregnenolone, 770
Pregorexia, 31
Preoccupation, 1481–1485, 1487, 1492, 1493, 1495, 1497, 1498
Pre-School Child Behavior Checklist, 1419
Pressure to eat, 1423
Preterm delivery, 614
Prevalence, 216
Prevention of eating disorders
  cognitive dissonance theory and implication for prevention, 185
  dissonance-based intervention and Body Project, 187–188
  efficacy and effectiveness of Body Project, 189
  influencing public health, 189–190
  Internet and digital techniques, 190
  prevention strategies, 184–185
  vBP, 190–193
Primary alexithymia, 315, 344, 345

Primary care, 271–274, 276, 279
Primary caregivers, 284, 285, 288, 289, 294, 303, 306
Primary prevention, 278
"Pro-ana" behaviors, 254
Probiotics, 501
  on anorexia nervosa, 502
  effect of, 502
Prodromal phase, 306
Prodromes, 271–273, 276, 278
Professional societies, 1533
Pro-inflammatory cytokines, 61
Prolactin, 85
Proopiomelanocortin (POMC), 86, 543, 1470
Prosaccade task, 591
PROSPERO, 317
Prostacyclin (PGI2), 456
Prostaglandin (PG)-H2, 455
Prostaglandins, COX-derived, 461
Protein, 393–396, 1161
  deficiency, 705
  synthesis, 541
Psychiatric comorbidity
  AN-depression association, 692
  anorexia disorder, 683, 684
  anorexia nervosa (AN) (*see* Anorexia nervosa (AN))
  anxiety, 692
  application, 688, 689
  bipolar disorder, 683, 684
  bulik hypotheses, 679
  clinical and psychopathological fields, 676
  clinical setting, 675
  definition, 675
  depressive disorders, 690
  eating core symptoms, 692
  eligibility criteria, 687
  epidemiological studies, 676
  epidemiology, 677
  evaluation, 677
  hierarchical diagnostic rules, 689
  internal medicine, 675
  liability spectrum model, 676
  mental disorders, 676, 692
  mental health professionals and researchers, 675
  mortality, 681, 689, 692
  multi-axial system, 675
  neurodevelopmental disorders, 677
  outcome, 678, 681, 683, 684, 689, 692
  persistence, 679, 683, 688
  psychiatric language, 675
  psychopathology, 675
  recovery, 690
  relapse, 689, 690
  substance abuse, 693
  suicidality, 690
  time limits, 676
  transposition, 676
  treatments, 675, 677, 678, 680–684, 686, 687, 691, 692
Psychiatric disorders, 202, 556, 557, 560, 962, 963, 1452
Psychiatric illness, QoL and ED, 358
Psychoanalytic theory, 264
Psychological disorder, 1505
Psychological interventions, 262–265
Psychological treatment, 630–631
Psychopathology, 625, 631, 633, 690, 959, 963, 965–968, 970, 973, 974
Psychopharmacological treatment, 631
Psychopharmacotherapy, 665, 666
Psychosis, 686, 687, 691, 692
Psychotherapy, 264, 532
Psychotic disorders, 1369
Purging, 864, 865, 867, 872, 874, 876, 878, 881
  analysis, 1184
Purging disorder (PD), 807–810, 812, 813
  anorexia nervosa, 1158
  anxiety-related traits, 1148
  behavioral strategies, 1181
  biological correlates, 1160, 1161
  biological factors, 1146
  bulimia nervosa, 1158
  CBT, 1150
  with CBT-E, 1184
  clinical characteristics, 1180
  clinical significance, 1145
  clinical techniques, 1184
  defined, 1176
  demographic characteristics, 1177
  development and maintenance, 1175
  developmental and socio-cultural factors, 1146
  diagnosis, 1176
  diagnostic phenotypes, 1152
  diagnostic subtype, 1145
  diagnostic systems, 1152
  differential diagnosis, 1175, 1176
  diuretic misuse, 1165
  diuretics, 1175
  dysfunctional personality traits, 1148
  eating disorder, 1158
  ED diagnostic subtype, 1145
  emotion regulation, 1181

Purging disorder (PD) (*cont.*)
endocrine and psychological factors, 1145
etiopathogenesis, 1147
evidence-based treatment targets, 1151
functional impairment, 1146
general psychopathology and emotional distress, 1147
heterogeneous etiopathogenesis, 1146
hunger and preoccupation with food, 1181
impulse control disorders, 1148
inclusion criteria, 1176
inclusion of loss of control, 1176
laxatives, 1164, 1165, 1176
lifetime prevalence rates, 1145
maladaptive coping, 1181
management, 1150
mass media influence, 1146
medical and pharmacological approach, 1150
medical complications, 1148, 1149, 1177, 1178
medications, 1150
misuse of laxatives, 1175
nutrients, 1178
overarching statements, 1179
parent-perceived childhood overweight, 1146
pervasive weight control strategy, 1180, 1181
physiological processes, 1184
postprandial gut satiety peptide, PYY, 1181
premorbid overweight conditions, 1147
prevalence, 1159, 1177
prevention and intervention modalities, 1152
psychoeducational and motivational aspects, 1150
psychological factors, 1146
psychopathological, and personality features, 1148
recurrent purging behaviors, 1175
risk factors, 1146
salient risk factor, 1182
self-induced vomiting, 1163, 1164, 1175, 1176, 1178
shared psychopathology and personality traits, 1145
subthreshold bulimia nervosa (BN), 1145
topographical similarities, 1175
treatment adherence, 1151
treatment outcome, 1151
treatment response, 1185
treatment studies, 1183, 1184

Q
Quality of life (QoL), 634
BDI, 1523
definition, 1518
in eating disorders, 1453, 1454
EDDS, 1523
EDE-Q, 1519–1521
HADS, 1525
HeRQoLED-s, 1525
SF-12, 1521
SF-36, 1519
Weissman Social Adjustment Scale, 1522
Quality of life related to health (HRQoL), 361
Questionnaire, 1005
Questionnaire on Eating and Weight Patterns-5 (QEWP-5), 1095
Questionnaire on Eating and Weight Patterns-Revised (QEWP-R), 1472
Questionnaires, orthorexia nervosa, 1436–1438
Quetelet Index, 441

R
7R/7R homozygotes, 82
Randomized controlled trials (RCTs), 1243, 1253
Rare genetic variants, 87–88
REAL Food Guide, 393
Reasons for Exercise Inventory (REI), 419
Recombinant human growth hormone, 710
Recombinant human insulin like growth factor-1 (rhIGF-1), 710–714
Refeeding process
caloric prescription, 629
nasogastric feeding and parenteral nutrition, 630
nutrient quality and nutrient supplementation, 629–630
Refeeding syndrome, 387, 389, 398
Regional cerebral blood flow (rCBF), 1075
Regulatory bodies, 1532, 1533
Rehospitalization, 634–635
Relative energy deficiency in sport (RED-S), 117
Renutrition, 627, 629, 630, 632–633
Reproduction, after recovery from AN, 608
Resting energy expenditure (REE), 399
Restrictive and dieting goals, 1112
Reward deficiency syndrome (RDS), 136
Reward sensitivity, 233
SUD and ED, 233
Reward system, 988–990, 994, 996

Rey-Osterrieth Complex Figure (ROCF), 756
Risk factors, 270–272, 278, 279, 306
Ritual, 1355, 1365
Rorschach Alexithymia Scale, 317
Rosenberg Self–Esteem Scale (RSE), 736
Roux-en-Y gastric bypass (RYGB), 1087–1089, 1469
Rumination disorder impaired QoL of patients, 1455
Rumination syndrome, 1401, 1408–1409
  pathophysiology, 1403–1405
  physiology, 1402–1403

S
Saccade
  characteristics, 588
  tasks, 589
Saliva UA measurement, 170
S-allele, 82
Scan path, 594
Schaaf-Yang syndrome, 1266
Schedule for the Assessment of Insight (SAI), 373
Schizophrenia, 1467
SCOFF questionnaire, 1445
Secondary alexithymia, 315, 344, 345
Secondary prevention, 278
Selective serotonin reuptake inhibitor (SSRI), 665, 775
Self-awareness, 368
Self-disclosure, 368, 376
Self-Disclosure about Body Satisfaction scale (SDBS), 373
Self-Disclosure about Restrained Eating scale (SDRE), 373
Self-esteem, 680, 724, 726, 729–731, 901
  and bulimia nervosa, 731
Self-harm, 688
Self-indicating depressive symptoms, 678
Self-induced vomiting, 1163
Self-injurious behavior, 1292, 1296
Self-injury, 256
Self-paced saccade task, 594
Sensor technology, 426
Sensory sensitivity, 1423–1424
Serotine receptor family, 78
Serotonergic system dysfunction, 80
Serotonin (5-HT), 62, 80, 97, 777
  pathway, 80
  SUD and ED, 230
  System, 228
Serotonin reuptake inhibitor (SSRI), 823–825, 827, 836, 837
Serotonin transporter gene *SLC6A4* (5-HTTLPR), 80
Serotonin transporter (SERT), 97–99
Serum electrolytes, 657
Serum uric acid (SUA), 169–174
Set shifting, 651
Severe neglect obesity (SNO), 965
Sex hormone-binding globulin (SHBG), 771, 775, 926
Sex steroid hormones, 772
Sexuality, and embodiment, 852–853
Sexual orientation, 515, 532
Short-chain fatty acids (SCFA), 490, 498, 499
Short Form-12 Health Status Questionnaire (SF-12), 1521
Short Form-36 (SF-36), 1519
Simmonds' disease, 202
Single-frequency BIA (SF-BIA), 444
Single photon emission computed tomography (SPECT), 1079
Sirtuin 1 (SIRT1), 706
Skinfold thickness (ST), 443–444
SLC6A4 gene, 80, 87
SLC6A4 serotonin transporter gene, 98–99
  gene-environment interaction studies, in eating disorder, 101–102
  genetic association studies, 99–101
  psychopathological traits, in eating disorders, 101
  studies of sequence, 102
Sleep and eating behavior, 1104
Sleep cycle and intrinsic timing system, 1106
Sleep deprivation, 557
  and altered eating behavior, 1110
  behavioral factors, 1108
  and binge eating
  bidirectionality, 1114
  experimental evidence, 1112
  experimental studies, 1114
  impairment in inhibitory control in response to food stimuli, 1113
  population groups, 1113
  biological mechanism, 1106
  biological mechanisms, 1106
  cognitive and neural mechanisms, 1106
  defined, 1105
  detrimental long-term effect, 1105
  dietary patterns, 1108
  and eating behavior, 1109
  emotional and behavioral mechanisms, 1108, 1109
  emotion regulation and vice versa, 1108
  executive and cognitive functioning, 1107

Sleep deprivation (*cont.*)
executive functions and eating self-regulation, 1107
and food intake, 1105
impairment in emotional functioning or sleep quantity, 1108
metabolic consequences, 1106
sleep and the circadian rhythms, 1106
unrecognized sleep loss, 1107
Sleep disturbances, and ADHD, 134
Slow stabilizing eye movements, 586
Small for gestational age (SGA), 29, 43, 614
Smartphone, 1006
Smooth pursuit, 586
Snack-type foods, 64
Social anxiety, 678
Social desirability, 1112
Social functioning, 942, 950
Social media, 1370, 1371
addiction, 1343–1344
Sociocultural pressures, 890, 918
Sociotropy, 894, 911
Somatoform disorders, 1368–1369
South London and Maudsley Foundation Trust, 681
Sports nutrition, 112
Standardized mortality ratio, 951
Starvation-induced protein, 539
State–Trait Anxiety Inventory (STAI), 737
Steroids, 1312, 1318
Strength centrality, 1217
Stress, 546, 557, 1006, 1008
addictive properties of food, 58, 59
adverse health outcomes, 53
applications, 67
coping strategies, 66
eating behavior, 55
eating patterns (*see* Eating patterns)
fight-or-flight pattern, 53
food intake response, 68
gastrointestinal tract, 55
harsh environmental conditions, 53
hedonics, 58, 59
high stress levels, 68
mental health crisis, 53
mental wellbeing and evidence-based recommendations, 53
non-communicable diseases, 53
overeating, 64, 65
physiological and behavioural responses, 55
physiological changes, 54
physiological homeostasis, 54
prevalence, 68
pro-inflammatory dietary patterns, 68
responses, 53, 54
self-management approaches, 53
undereating, 63
Stress-related psychological factors, 1028
Structural equation modelling (SEM), 893, 918
Subjective binge eating (SBE), 1147, 1506
Subjective QoL, 1457
Substance abuse, 688
Substance-related disorder, 1340, 1344
Substance use, 1339, 1340
Substance use disorders (SUDs), 225, 227
Sudden unexpected death (SUD), 656, 666
Suicidal ideation, 688
Supporting Carers of Children and Adolescents with Eating Disorders in Austria (SUCCEAT), 301
Supportive therapy (SPT), 872
Surrey Early Intervention, 300
Survey for Eating Disorders (SEDs), 1445
Sympathetic nervous system (SNS), 54
Synbiotics, 501
Systematic review, 317, 340, 345

T
TaqIA polymorphism, 229
Temporal group-level models, 1225
Temporal time-series networks, 1225, 1226
Tempo-spatial dynamics, 849–850
Tertiary prevention, 278
Teruel Orthorexia Scale (TOS), 1443, 1490–1492
Test of Orthorexia Nervosa (TON-17), 1444, 1445
Testosterone, 533, 709, 770, 771
deficiency, 771
Theory of mind (TOM), 649, 651
Thin-ideal internalisation, 918
Three Factor Eating Questionnaire (TFEQ), 1045, 1065, 1472
Thromboxane, 461
Thromboxane A2 (TXA2), 456
Thyroid-binding globulin, 542
Thyroxine, 542
Time-to-conception, 27
Time trends, 201, 206, 210, 211, 213, 216, 217
Topiramate, 824
Toronto Alexithymia Scale (TAS), 316, 317, 323, 338, 341–343
Toronto Structured Interview for Alexithymia, 317

Total body water (TBW), 444
Total sleep deprivation, 1107
Transcranial alternate current stimulation (tACS), 993
Transcranial direct current stimulation (tDCS), 993
Transcranial magnetic stimulation (TMS), 993
Transcription factor nuclear factor-κB, 68
Transdiagnostic approaches, 239
Transdiagnostic cognitive behavioral theory of eating disorders, 1180
Transient lower esophageal sphincter relaxations (TLESRs), 1405, 1408
Trauma, 254–256, 263, 265, 267
Traumatic events, 237
Treatment, denial of disordered eating
  approach, 376
  empirically supported treatment, 375, 376
  modality, 376, 377
  systematic review, 375
Tricyclic antidepressants (TCA), 824, 835, 836
Triglycerides, 769
Triiodothyronine, 542, 707
Tube feeding, 630, 635

U
Underfeeding syndrome, 399
Undernutrition, 614
Underreporting of disordered eating behaviors scale (UDEBS), 374
Underweight, 440–444, 447
Unified Protocol, 340
Uniparental disomy (UPD), 1264
Unspecified feeding or eating disorder (UFED), 354
Unspecified/other specified eating and feeding disorders (U/OSFED)
  in pregnant women, 27
Uric acid (UA), 168, 174
  body fluids, measurement in, 170
  in central nervous system, 171
  in eating disorders, 172–174
  gender effects on SUA, 170–171
  in neuropsychiatric disorders, 171–172
  physiological roles and general pathophysiological aspects, 169–174

V
Val158Met polymorphism, 229
Vegetarian diet, orthorexia nervosa, 1371
Ventral frontostriatal hypoconnectivity, 1068
Ventral tegmental area (VTA), 57, 544, 574, 985
Vergence, 586
Virtual Body Project (vBP), 187, 188, 191–193
Visceral interoception, 847
Visual attention, 594–596
Visual scan path tasks, 594
Visuospatial difficulties, 748
  failure, 749
  inefficiencies, 750
  and mental rotation, 750
Vitamins, 1161
Voxel-based morphometry (VBM), 563

W
Water, 1161
  weight, 254, 258, 260
Wearable sensors, 426
Weight, 441, 443, 445–447, 514, 515, 517, 518, 522, 525, 527, 532, 534
  gain, 624, 627, 629–633, 635
  loss, 1084
  normalization, 445–447
  regain, 1085, 1086, 1092
  restoration, 443, 445–447
Weissman Social Adjustment Scale, 1522
Western countries, EDs
  anorexia nervosa (AN), 207, 209, 210
  bulimia nervosa (BN), 210, 211
  epidemiological data, 207
Westernization, 216
Whole-exome sequencing analysis, in AN patients, 87
Whole-exome sequencing (WES), 102
Whole-genome sequencing (WGS), 102
World Health Organization (WHO), 206, 1354, 1530

X
Xanthine oxidoreductase (XOR), 169–172

Z
Zonisamide, 827