EXTREME EATING BEHAVIOURS

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EXTREME EATING BEHAVIOURS

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EDITORIAL
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Editorial: Extreme Eating Behaviours

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Keywords: eating disorders, anorexia nervosa, bulimia nervosa, binge eating disorder, obesity

Editorial on the Research Topic

Extreme Eating Behaviours

IMPORTANCE OF EXTREME EATING BEHAVIORS

Extreme eating behaviors are an increasing global health threat, as their prevalence is rising (1). If we take a look at both ends of the spectrum, ∼650 million people are obese according to the World Health Organization (WHO) (2), and anorexia nervosa (AN) is one of the most common chronic disorders in adolescence. It is also the most lethal psychiatric disorder with a risk of death that is five times higher compared to people of the same age and gender without AN (3, 4).

In recent decades, our diagnostic knowledge of various eating disorders (EDs) has increased. These disorders include AN, bulimia nervosa (BN), binge eating disorder (BED), avoidant-restrictive food intake disorder (ARFID), pica and rumination. The latest edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) provides clinically useful and distinct diagnostic criteria for these disorders (5). Nonetheless, treatment options are still limited. For example, the only psychopharmacological treatment options for all EDs approved in some countries are fluoxetine for BN and lisdexamfetamine for BED (6).

We are currently increasing our understanding of how obesity and EDs are associated with changes in the composition of gut microbiota, in the intake of macro- or micro-nutrients, the immune, endocrine and nervous systems, and how these changes lead to physical and mental health consequences (7–10). However, the treatment outcome for EDs and their physical and mental health consequences is still unsatisfactory. A recent cohort study showed that only 30% of patients with AN recovered after 9 years (11).

This special collection is dedicated to disorders associated with extreme eating behaviors—the EDs and obesity. It consists of a variety of articles and study types including a historical study, an animal study, a case series, a feasibility study, cross-sectional and longitudinal clinical studies, surveys, meta-analyses, and systematic reviews; and it addresses historical, social, psychological, and biological aspects as well as symptoms and therapeutic options for extreme eating behaviors.

CONTENT OF THE SPECIAL COLLECTION

Historical Aspects of Extreme Eating Behaviors

Bergner et al. performed an in-depth historical review of the most significant German-language psychiatric textbooks throughout the past 200 years, regarding ED diagnoses and descriptions of disordered eating behavior. Interestingly, the authors found that nineteenth and early twentieth century psychiatrists such as Kraepelin, Bumke, Hoff, Bleuler, and Jaspers reported symptom clusters of extreme eating behavior such as food refusal and vomiting which show striking similarities to the description of specific eating disorder subtypes in current diagnostic manuals such as DSM-5. However, these historic psychiatrists partly classed those behavioral symptom

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clusters as features of diagnoses which are no longer used by the majority of psychiatrists, such as neurasthenia, hypochondria, and hysteria (Bergner et al.).

Social and Psychological Aspects of Extreme Eating Behaviors

Five articles in this special collection focus on significant social and psychological factors of extreme eating: culture change, executive functions, temporal discounting, loss aversion, and Theory of Mind (ToM).

Shekriladze et al. conducted a survey on culture change and eating patterns, which showed that moving to Western countries (UK, USA) increased dietary restriction among Georgian women. They concluded that integration problems in the new host culture predict elevated eating, shape and weight concerns among women and that acculturation conditions may be linked with integration and well-being outcomes.

Gisbert Cury et al. conducted a systematic review and meta-analysis on executive functions in BED and ascertained that, based on current scientific literature, BED patients had worse performance on working memory tasks compared to obese individuals without BED. Kekic et al. reported data derived from an online survey that examined temporal discounting, which is the tendency to act on immediate pleasure-driven desires, due to the devaluation of future rewards. Their data revealed that temporal discounting correlated with the frequency of compulsive overeating, food addiction, ED psychopathology, and body mass index (BMI). Sagiv et al. performed a clinical study which revealed that loss aversion scores were lower among participants with EDs (AN, BN) compared to healthy controls and that this feature was related to non-suicidal self-injury and suicidal ideations. Sedgewick et al. focused on ToM in a cross-sectional clinical study involving healthy controls and patients with AN with and without autistic features. Interestingly, they did not find any quantifiable ToM difference between these groups as one would have expected from autism studies in people without AN. Studies in people with an autism spectrum disorder but without an ED usually indicate difficulties with ToM.

Biological Aspects of Extreme Eating Behaviors

Obesity and AN are the two ends of the spectrum of extreme eating behaviors with manifold biological causes including genetic factors, the microbiome, metabolic and endocrine mechanisms, the immune system, and the brain, which are influenced by environmental and nutritional factors (12). We received three articles mainly concerned with the immune and the endocrine systems. Schmidt et al. conducted a longitudinal clinical study in normal weight, overweight and obese people (BMI range: 18.3–61.4 kg/m^2) on depressiveness, body weight, physical activity, and cytokine levels. They confirmed previous results from human (13) and animal studies (14, 15) showing that depressiveness was positively associated with certain pro-inflammatory cytokine levels. Furthermore, physical activity was negatively associated with interleukin (IL)-4, IL-5, IL-10, granulocyte-macrophage colony-stimulating factor (GM-CSF), interferon (IFN)-γ, and tumor necrosis factor (TNF)-α; and BMI predicted IL-12 and IL-13 levels. Stanikova et al. reported data from an epidemiological cohort study that included 3,124 adult women. They found higher testosterone levels in obese vs. normal-weight women and in women with vs. women without anxiety symptomatology. Tyszkiewicz-Nwafor et al. looked at growth factors and hormonal changes in people with AN in a longitudinal clinical study. In their sample, brain-derived neurotrophic factor (BDNF) serum levels were decreased in malnourished AN patients, which normalized with weight recovery. Oxytocin serum levels, however, were increased in malnourished AN patients and did not normalize with partial weight recovery.

Symptoms Related to EDs and Obesity

Baldofski et al. analyzed data from two large European multi-center studies: MooDFOOD and NESDA. In their sample of more than 500 people, somatic and vegetative depressive symptoms such as pain, changes in appetite and weight, gastro-intestinal symptoms and arousal-related symptoms were associated with both a higher BMI and a higher waist-to-hip ratio (WHR). In a clinical study by Minkwitz et al., subjective sleepiness did not differ much between obese and non-obese people, whereas depressed and non-depressed people differed significantly with regard to subjective sleepiness. Objective sleepiness measures, however, did not differ significantly between people with obesity, people with depression, people with both obesity and depression, and healthy controls.

A systematic review and quantitative analysis by Riedlinger et al. deduced that gastrointestinal (GI) symptoms and impaired gastric transit are frequent features of EDs and that serious GI complications such as gastric dilatation have been observed. Stein et al. provided a case series describing risk-taking behavior in four female patients with long-standing binge-purge type AN. The description of these patients and their history, course of the disease and risky behaviors expound important environmental vulnerabilities, purging behavior as well as other impulsive and non-impulsive comorbidities.

Therapies for EDs and Obesity

This special collection on extreme eating behaviors also sheds light on experimental and potential future treatment strategies. Kan et al. contributed a systematic review and meta-analysis of dropout and metabolic effects of antipsychotics used in AN. In their analysis, drug-related factors, such as side effects, played a lesser role than personal reasons for the discontinuation of antipsychotic treatment under trial conditions. This highlights the importance of patients' personal motivation for drug treatment in AN. Lu et al. reported in an experimental animal study that electroacupuncture reduced food intake and body weight, and improved laboratory parameters in obese mice. Thus, electroacupuncture might be an innovative approach to treat extreme eating behaviors and their health consequences. An innovative psychotherapeutic approach was presented by Rudolph and Hilbert. Their clinical pilot study tested a short-term cognitive behavior therapy (CBT) approach, which was based on manuals for BED and depressive disorders. This

treatment for patients following bariatric surgery led to a significant reduction of body weight, improvement of ED psychopathology, depressive symptoms, and self-esteem.

THANKS TO ALL AUTHORS, REVIEWERS, EDITORS AND FRONTIERS

The articles in this Research Topic provide a comprehensive, cutting-edge and inspiring view on research and clinical practice in the field of extreme eating behaviors. We would like to express our thanks to all authors for their hard work, excellent manuscripts, and for submitting work to this special collection. The call attracted authors from Australia, Brazil, China, Georgia, Germany, Ireland, Israel, the Netherlands, Poland, Slovakia, Spain, Sweden, and the United Kingdom. We also thank all the reviewers and editors involved in the preparation of this special issue as well as the publisher Frontiers and their team for always being supportive. We hope that this special collection presents a useful and appealing overview of current knowledge about extreme eating behaviors, which will reach many readers and inspire future research.

AUTHOR CONTRIBUTIONS

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Similarities and Differences in Theory of Mind Responses of Patients With Anorexia Nervosa With and Without Autistic Features

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Theory of Mind (ToM) is the ability to understand and represent mental states of others, a skill that plays a key role in how we interact with people around us. Difficulties with ToM have been posited as an underlying mechanism for autism and implicated in difficulties faced by those with anorexia nervosa (AN). This study examined, both quantitatively and qualitatively, the responses of women between the ages of 14 and 25 years on the Frith-Happé Triangle Animations, a well-validated test of ToM. Participants were split into healthy controls (HCs), AN patients (AN), and AN patients with high levels of autistic features (AN+ASF). We found no significant quantitative differences between groups in performance on the task. Qualitatively, there were differences between groups such that AN patients, especially those in the AN+ASF group, were more focused on describing the videos than creating narratives, were more negative in their interpretations, and were much more anxious about their performance. These qualitative differences have clinical implications, including that not all AN patients with autistic features should be assumed to have difficulties with ToM.

Keywords: eating disorders, autism spectrum disorders, women, Theory of Mind, emotional valence

INTRODUCTION

Theory of Mind (ToM) is the ability to represent mental states, such as beliefs and intentions, in order to predict and explain people's behavior (1, 2). ToM difficulties have been theorized as an explanatory mechanism for the social difficulties that are a defining diagnostic criteria for autism spectrum disorder (3). Large numbers of studies, using a range of ToM tasks, have consistently found that autistic people score lower than neurotypical counterparts in terms of their ability to extrapolate the mental states of characters [e.g., Refs. (4–6)]. A steady accumulation of evidence has shown that people with anorexia nervosa (AN) show similarities in cognitive profile to autistic individuals (7–9). Cognitive features such as poor flexibility and detail-focus (or weak "central coherence") have been documented in both AN and autistic groups relative to healthy controls (HCs) (9, 10). People with AN and autistic people appear also to share deficits in social–emotional functioning, including ToM (11). A recent review of the literature comparing autistic people and those with AN (12) reported a number of

similar difficulties, particularly in complex social situation tasks. Other meta-analyses have suggested that those with AN may have difficulties empathizing with fictional characters in ways similar to those seen in autistic people (13). Cognitive and social–emotional difficulties have been suggested to fuel the illness progression in AN by increasing isolation and making it difficult to see the big picture or change their thinking around food and exercise (14).

Although there is a solid body of research suggesting links between autism and anorexia going back to the 1980s (15, 16), most research to date on ToM in AN has not considered the potential influence of autistic features. This means that those differences and difficulties identified in previous work cannot confidently be associated with AN itself, rather than co-occurring autistic features—something that is an issue, as there is evidence that up to 23% of women with AN may also be autistic (17).

Therefore, we aimed to investigate whether AN patients who reported high levels of autistic features and those who reported low levels of autistic features differed in ToM ability, and also whether their ToM performance differed from that of HCs, either quantitatively or qualitatively. We expected that those with high levels of autistic features would perform poorly on ToM tasks, similarly to autistic participants in other studies, but that AN participants with low levels of autistic features would perform similarly to HC participants.

METHODS

Participants

Data from 57 women between 14 and 25 years old were included in this analysis. Participants with AN and high levels of autistic features [scoring above 6 on the Autism Quotient-10 item version (AQ-10)] were first identified from a larger dataset (BEACON Study, MRC-MRF MR/R004595/1) of 171 participants, resulting in 17 participants meeting criteria. Matched samples of HCs and those with AN and low autistic traits were then identified from within the same dataset and included in this study.

Three groups [HCs, patients with AN with low levels of autistic features, and patients with anorexia and high levels of autistic features (AN+ASF)] were matched in terms of age and IQ, and each group had a similar ethnic makeup (see **Table 1**). There was a significant difference between the HC participants and all AN participants on BMI, all p's < 0.001, but no difference between the AN and AN+ASF groups. Participants were recruited from a range of clinical and community sites across London under ethical approval from the London-Surrey Research Ethics Committee (17/LO/2071). Written informed consent was obtained from all participants, and written informed consent was obtained from the parents of all participants under the age of 16. All AN participants had current clinical diagnoses of AN according to the criteria of the *Diagnostic and Statistical Manual*—5th edition (3).

To investigate the impact of autistic features, the AN group was split into those with high-autistic (AN+ASF) and low-autistic features (AN), as measured on the AQ-10 (18). Those who scored 6 or more on the AQ-10 were categorized as AN+ASF, using the cutoff for likely autism suggested by the authors of the measure (18), and those with a score of 3 or less were categorized as AN only.

TABLE 1 | Demographic information about participants by group.

	HC	AN	AN+ASF
n	20	20	17
Age			
Range	14.24–24.21	14.43–25.06	14.00–23.26
M (SD)	19.16 (2.73)	19.41 (3.40)	18.62 (2.51)
IQ			
Range	101.27–127.70	93.83–125.22	102.92–115.31
M (SD)	112.09 (7.64)	110.71 (7.86)	109.22 (3.57)
BMI			
Range	18.26–26.81	16.00–23.43	14.98–25.16
M (SD)	21.54 (2.67)	18.04 (1.80)	18.59 (2.83)
Ethnicity			
White n (%)	15 (75)	19 (95)	16 (94.12)
Black n (%)	2 (10)	0 (0)	0 (0)
Asian n (%)	1 (5)	1 (5)	1 (5.88)
Latinx n (%)	1 (5)	0 (0)	0 (0)

HC, healthy control; AN, anorexia nervosa patients; AN+ASF, AN patients with high levels of autistic features.

We did not include participants who scored 4 or 5 in this study due to their being close to the cutoff score, as they may be among those women who are "missed" by diagnostic measures due to presenting in a non-stereotypical manner (19). HC participants were all subject to a screening call prior to taking part to ensure that they had no eating disorder past or present, and all scored less than 2 on the AQ-10 and therefore were considered a valid comparison group, without either AN or autism.

Measures

AQ-10: The Autism Quotient-10 item version (18) is a 10-item questionnaire assessing autistic symptomatology. Participants respond on a four-point Likert scale, from "strongly agree" to "strongly disagree," and items are scored either 1 or 0, depending on the direction of the endorsement. This results in a maximum score of 10 for the measure, and 6 is used as the threshold to indicate potential autism (18).

Theory of Mind: The Frith-Happé Triangle Animations (20, 21) are a series of 10 short silent animations (each 30–40 s long) showing two triangles moving. In two videos, the triangles move at random and do not interact. In four videos, the triangles move in a simple or goal-oriented manner, for example, pushing each other back and forth. In the other four videos, the triangles move in a way that can be interpreted as a complex interaction, such as one triangle encouraging the other to leave an enclosure. These three categories of video—Random, Goal-Oriented, and Complex/ToM—are designed to elicit different levels of ToM description from participants, who are asked to narrate the videos as they appeared on screen in line with European Autism Interventions - A Multicentre Study for Developing New Medications (EU-AIMS) methodology (22). Answers are then scored 0–2 for Accuracy and 0–2 for Mental State Terms and summed for each video type. Transcripts of participant responses allow for both quantitative and qualitative analysis. The Frith-Happé Triangle Animations have previously been used to assess ToM ability in clinical groups including autism (e.g., 23) and anorexia (24, 25).

The narrative responses were recorded and transcribed for further quantitative and qualitative analysis. Transcription was conducted by one of the authors (FS) who is a native English speaker and was checked for reliability by two other authors (JL and FG). Any disagreements regarding the transcription were brought to the whole team for discussion.

EDE-Q: The Eating Disorder Examination Self-Report (26)-Questionnaire is a 36-item self-report questionnaire assessing eating disorder psychopathology over the past 28 days. Suggested clinical cutoff for the EDE-Q is 2.3 (27).

HADS: The Hospital Anxiety and Depression Scale (28) is a 14-item self-report questionnaire assessing levels of anxiety and depression over the past 2 weeks. Suggested clinical cutoff for the HADS is 8 or above on either subscale or 10 or above on the subscales combined (29).

General Procedure

Participants were all seen at the university as part of a larger study (BEACON Study, MRC-MRF MR/R004595/1). Participants completed demographic information, the EDE-Q, and the HADS as part of online questionnaires. The larger testing session lasted approximately 3 h, including an autism assessment, a range of neurocognitive tests (including the Frith-Happé Triangle Animations), and a structural and functional MRI scan.

Data Analysis

Quantitative data were analyzed using R (R Core Team). Group differences in clinical and demographic characteristics were assessed with ANOVA, and Hedges' g was calculated to estimate the effect size. Group differences in ToM task accuracy and mentalizing ability were examined using Poisson regression. Finally, we also explored whether performance on the ToM task was related to eating disorder psychopathology, anxiety and depression, or body mass index (BMI) using Spearman's correlation tests. Due to the large number of exploratory correlation analyses, the p-threshold was adjusted for multiple comparisons using the false discovery rate with q = 0.05. P-value less that 0.004 was considered significant.

Qualitative data were collected by recording the spoken responses of participants to the Frith-Happé Triangles and transcribing these verbatim. Thematic analysis of the transcripts was conducted by two authors, one acting as first coder (FS) and the second (FG) carrying out reliability coding of 20% of the transcripts. Both the first and second coder conducted the thematic analysis blind to both group and codes, so that the second individual was not aware of the themes the first had identified, and the two authors then met to discuss and agree on the results. There were no notable differences between the themes the two authors found in the participants transcripts, and the themes presented below are their consensus coding.

RESULTS

Quantitative Analyses

Self-Report Questionnaires

There were significant differences between the groups on EDE-Q Global score, HADS Anxiety, and HADS Depression (see **Table 2** for scores). *Post hoc* t-tests revealed that both AN and AN+ASF groups scored significantly higher than HC participants on the EDE-Q Global score, HADS Anxiety, and HADS Depression. There was no significant difference between the AN and AN+ASF groups on the EDE-Q, $t(35) = -1.85$, $p = 0.07$. There were significant differences between the AN and AN+ASF groups on HADS Anxiety, $t(35) = -4.21$, $p < 0.001$, and HADS Depression,

TABLE 2 | Scores on mental health measures by group.

	HC	AN	AN+ASF	F-statistic *p-value*	Hedges' g ES [95% CI]
AQ-10 Range M (SD)	 0–2 1.00 (1.00)	 1–2 2.00 (1.00)	 6–10 7.00 (1.00)	 $F(2) = 268.03$, $p < 0.001$*	HC vs. AN: −0.76, [−1.42, −0.09] HC vs. AN+ASF: −5.58 [−7.06, −4.10] AN vs. AN+ASF: −5.48 [−6.93, −4.02]
EDE-Q Global Range M (SD)	 0–0.73 0.23 (0.20)	 0.28–5.12 2.63 (1.52)	 0.35–5.12 3.54 (1.44)	 $F(2) = 38.37$, $p = < 0.001$*	HC vs. AN: −2.17, [−2.98, −1.36] HC vs. AN+ASF: −3.03, [−4.01, −2.05] AN vs. AN+ASF: −0.60, [−1.28, 0.09]
HADS Total Range M (SD)	 1–21 8.15 (5.76)	 3–27 14.65 (5.67)	 14–42 24.12 (6.74)	 $F(2) = 32.29$, $p = < 0.001$*	HC vs. AN: −1.11, [−180, −0.43] HC vs. AN+ASF: 2.48, [−3.37, −1.59] AN vs. AN+ASF: −1.48, [−2.23, −0.72]

AQ-10, Autism Quotient-10 item version; EDE-Q, Eating Disorder Examination Self-Report Questionnaire; HADS, Hospital Anxiety and Depression Scale.
**Denotes a significant result.*

$t(35) = -3.81$, $p = 0.001$, such that AN+ASF participants were more anxious and more depressed than AN participants. There were no correlations between AQ-10 and BMI in the HC group ($\rho = 0.13, p = 0.581$), AN group ($\rho = 0.00, p = 1.00$), or the AN+ASF group ($\rho = -0.19$, $p = 0.475$). There were no correlations between AQ-10 score and EDE-Q score in the HC group ($\rho = -0.02$, $p = 0.949$), AN group ($\rho = 0.17$, $p = 0.485$), or AN+ASF group ($\rho = -0.39$, $p = 0.117$). There was also no significant correlation between AQ-10 scores and HADS scores within the HC group ($\rho = -0.04$, $p = 0.862$), the AN group ($\rho = -0.022$, $p = 0.355$), or the AN+ASF group ($\rho = 0.11$, $p = 0.675$).

Theory of Mind: Accuracy

On Accuracy, there was no significant difference between the three groups on either the Random, the Goal-Oriented, or the ToM animations (see **Table 3** for scores).

Theory of Mind: Mental State

On Mental State, there were no significant differences between the three groups in any of the video conditions (Random, Goal-Oriented, Complex, Total; see **Table 3** for scores).

Clinical Measures and Theory of Mind

We explored whether levels of eating disorder behaviors, anxiety and depression, autistic features, and BMI had an impact on either accuracy or on number of mental state terms, negative, and positive terms participants used in their narrations. Due to there being no significant group differences between the HC, AN, and AN+ASF, all participants were included in the exploratory correlation analyses. There were no significant correlations between Accuracy or Mental State Language and any clinical measures across all participants (see **Table 4**).

Qualitative Analysis

Qualitatively, there were notable differences between the three groups. These differences can be characterized as coming under the themes of *detail focus*, *negative interpretation bias, inaccurate emotional labels*, and *anxiety* and are visualized in **Figure 1**.

Detail focus. The most obvious difference between the patients and the HC participants was their different level of focus on the detailed geometry and *movement* in the videos. AN patients, particularly those with high AQ scores, gave greater focus to precisely where items were on the screen, for example, saying "the smaller box with the open side is now in the bottom right hand corner" (AN+ASF; Chasing) or "the little triangle is moving in a clockwise direction and the bigger triangle in an anti-clockwise direction" (AN; Bouncing). While some HC participants also described where the triangles were throughout the videos, these descriptions tended to relate their positioning to each other—"the little one is above the big one" (HC; Floating). In contrast, AN participants often described the triangles independently of each other, even in interaction videos—"the little one is in the box and the big one is going in and out of the box" (AN+ASF: Coaxing).

AN participants also placed more emphasis on describing the *appearance* of the triangles, rather than creating a narrative around their actions. For example, the patient group said things like "the lines keep getting smoother" (AN+ASF; Bouncing), "they are drawn in graphite" (AN; Surprise), and "they've squashed so they aren't isosceles triangles anymore, they're more like obtuse triangles" (AN+ASF; Fighting). While some HC participants did describe the layout of the screen—"there's a smaller box with an open side" (HC; Coaxing)—this was far less common and was usually instrumental to describing the action, rather than being a standalone comment. In the above example, the sentence was finished by adding "and the triangles are inside

TABLE 3 | Accuracy and Mental State Language scores by group and video type.

	HC	AN	AN+ASF	X^2-statistic *p-value*	Cramer's *V*
Accuracy Random Range Median (IQR)	2–4 3.0 (2.0)	0–4 3.0 (2.0)	0–4 4.0 (1.5)	$X^2(2) = 0.65$, *p = 0.721*	0.08
Accuracy Goal-oriented Range Median (IQR)	1–9 5.0 (2.0)	2–7 6.0 (1.0)	3–7 5.0 (1.5)	$X^2(2) = 0.45$, *p = 0.799*	0.06
Accuracy Complex Range Median (IQR)	2–7 4.0 (0.5)	1–6 4.0 (2.0)	0–7 3.0 (2.0)	$X^2(2) = 1.03$, *p = 0.599*	0.10
Mental State Random Range Median (IQR)	0–1 0.0 (0.0)	0–2 0.0 (1.0)	0–1 0.0 (0.0)	$X^2(2) = 2.30$, *p = 0.317*	0.14
Mental State Goal-oriented Range Median (IQR)	0–2 1.0 (2.0)	0–4 0.0 (2.0)	0–3 0.0 (1.0)	$X^2(2) = 1.12$, *p = 0.572*	0.10
Mental State Complex Range Median (IQR)	0–7 3.0 (1.5)	0–7 3.5 (2.0)	0–6 2.0 (3.0)	$X^2(2) = 5.89$, *p = 0.053*	0.28

Italicisation is a convention of the field.

TABLE 4 | Correlations between self-reported mental health and Theory of Mind.

	Accuracy	Mental State Language	Negative terms	Positive terms
EDE-Q Total	ρ = –0.20, p = 0.135	ρ = –0.19, p = 0.155	ρ = –0.01, p = 0.932	ρ = 0.11, p = 0.409
HADS Total	ρ = –0.18, p = 0.190	ρ = –0.17, p = 0.195	ρ = –0.01, p = 0.949	ρ = 0.03, p = 0.813
AQ-10 Total	ρ = –0.09, p = 0.518	ρ = –0.13, p = 0.320	ρ = –0.12, p = 0.354	ρ = –0.06, p = 0.614
BMI	ρ = 0.23, p = 0.091	ρ = 0.29, p = 0.030	ρ = 0.22, p = 0.107	ρ = 0.21, p = 0.125

it" (HC; Coaxing), whereas AN participants tended to focus on describing the physical appearance of the objects on the screen rather than providing a narrative.

Negative interpretation bias. Another key qualitative difference between the groups was the prevalence of *negative emotional words*. Both AN and AN+ASF participants used far more negative terms and gave more negative interpretations of the triangles' movements than HC participants, describing them as "crying," "fighting," and "angry" more often than HC participants. They gave more involved descriptions of these negative emotions and cognitions than for positive ones—"he's hiding in the corner shaking 'cos he's scared and trapped" (AN; Seduction) compared to "they're happy they've found each other" (HC; Surprise). AN+ASF participants were most likely to give these negative interpretations, with AN participants representing a "mid-point" between the AN+ASF and HC groups in terms of the negative emotions they assigned to the triangles. Rather than the negative emotions common among AN+ASF participants, AN and HC participants mostly used emotionally neutral terms—"wants to get out," "is looking for the other one," or "tries to get in the box." These terms all imply a mental state or goal of the character, without giving much emotional weight to those mental states and desires.

Beyond the individual negative terms used by the patient group, the AN+ASF group gave much more *negative interpretations of the videos* overall. For example, one participant described the Coaxing scenario (where the big triangle pulls the little one out of the "house" to spin and play in the "garden") as the two triangles fighting and the "small one crying in the corner because it was scared," then spinning because it was "scared and confused." This is both inaccurate and a negative way of seeing the situation, which is supposed to show two characters having fun. More AN+ASF participants gave these unhappy interpretations of either neutral or positive scenarios compared to AN and HC participants who were more positive.

As a specific example of this negative interpretation, the "Surprise" video is supposed to represent a game of "knock and run"—the larger triangle is inside the "house" by itself, and then the smaller one enters and bumps several times on the "door" ("knocking"). The larger triangle opens the door (side of the box), comes part way out, and bends from side to side, "looking" for the one who knocked, while the small one "hides" behind the door. The large triangle goes back inside, and the sequence is repeated. On the third time of "knocking," the small triangle "surprises" the large one by coming out from behind the door, and then the two triangles enter the box together and spin (intended to represent hugging or being pleased to see each other).

The authors of the animations expected participants to see this as a game of knock and run between a grandmother and grandson (or similar characters), and to give answers relating to the game and the small triangle surprising or tricking the large triangle. Instead, AN participants frequently interpreted the scenario negatively. Common narratives were that the large triangle was "trapped" in the box and "can't get out," or that the small triangle was "locking it in," "turning a switch to keep it in," or that the large triangle "is locking [the small one] out when it wants to get in." When they used ToM terms to describe how the triangles felt about the scenario, they used terms associated with negative emotions such as "sad," "worried," and "feels unwanted," rather than the positive emotions of surprise and joy that the authors intended to be seen in the video. This was true for all AN participants, rather than being affected by ASF status.

Inaccurate emotional labels. Linked to this negative interpretation bias, participants often misinterpreted the emotional valence of videos, seeing them as negative when they were neutral or positive in nature. Participants generally used more negative

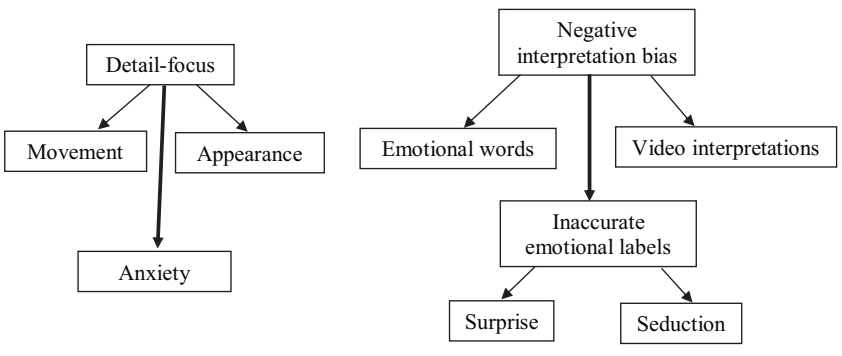

FIGURE 1 | Qualitative map of themes arising from narrations of the Frith-Happé Triangle Animations.

than positive emotional labels when narrating the videos, and the negative words they used were more intense than the positive terms, i.e., "[the triangle is] shaking and scared" or "[it looks like it's been] murdered" compared to "[the big one is] pleased" and "[they're having] fun."

Interestingly, the Seduction scenario was also interpreted very differently by participants than intended according to the scoring manual. The interpretation given in the scoring manual is that of a princess tricking a guard into letting her escape—a situation that could be interpreted negatively, although there is a happy ending. This video, which would seem to lend itself to the negative interpretations shown by AN+ASF participants elsewhere, did not elicit the same kind of strong negative responses. Instead, AN+ASF participants tended to simply describe the geometry of this video, as discussed above. In contrast, AN and HC participants tended to describe the small triangle as "escaping" or "running away," and the large triangle as "confused"—terms that imply mental states being attributed to the characters, even if they were presented in terms with neutral emotional valence.

Anxiety. Another notable pattern, possibly linked to the detail-focus discussed above, was that the patient group was much more likely than HC participants to ask questions of the examiner during the administration of the task, focused on making sure that they were getting things "right" or performing as expected. Several AN and AN+ASF participants asked questions such as "Is that what you wanted?," "Is that right?," or "Have I got it all?" Participants in both the AN+ASF and AN groups were notably more anxious about saying the right thing, giving the right interpretation, and simply whether they were completing the task correctly than HC participants were. This desire to give "perfect" responses, and the accompanying anxiety about not doing so, was not present in HC participants.

DISCUSSION

The findings of this study suggest that while there were no statistically significant quantitative differences between HC participants, AN participants, and AN+ASF participants on the Frith-Happé Triangle Animations, there are some interesting qualitative differences. This suggests that people with AN may not have significant difficulties in ToM, regardless of their level of self-reported autistic features. Although several studies have reported significantly reduced ToM in people with AN using a variety of tasks (12), more recently a few larger studies using a variety of different measures have found no group differences (24). Together, these findings suggest that women with AN may have specific social–emotional difficulties that may not extend to explicit labeling and recognition of emotions and mental states, but may rather be reflective of more subtle qualitative difficulties, such as interpretation biases.

Contrary to our hypothesis, there were no significant differences between the high-AQ and low-AQ groups in terms of Accuracy or Mental State Language, regardless of AN status. It should be pointed out, however, that scoring above cutoff on the AQ-10 is distinctly different to receiving a clinical diagnosis of being autistic, meaning that these individuals may not be as similar in performance on the task to autistic people as might be expected. Further to this, the AQ-10 is a basic screening tool and, while widely used, has been shown to be less reliable than the longer versions of the AQ, such as the AQ-50 or AQ-28 (30, 31), or other self-report questionnaires such as the Social Responsiveness Scale—2nd Edition (32). However, we can be confident in this sample that the AQ-10 was reflective of autistic features rather than mental health issues, as there was no correlation between AQ-10 score and HADS score in any group.

It is also worth noting that previous research that has supported the effectiveness of the Frith-Happé Triangle Animations as a measure of ToM ability, and as revealing differences between autistic and neurotypical groups, has had mainly male participants. The non-significant quantitative findings in this study may therefore actually represent a gender difference according to the scoring method that focuses on accuracy in explicit labeling and recognition. What little evidence there is as to gender differences in ToM ability suggests that girls score more highly than boys (20, 21, 33). Among neurotypical children, one study found that 3- to 5-year-old non-autistic girls scored better on ToM tasks than non-autistic boys (34) on the Sally-Anne False Belief task, and this gender difference is also seen in late childhood (35). Most work that finds autistic people struggle with ToM has used majority-male participant samples, as is the case for much autism research (36). This means that we know very little about ToM ability in autistic girls and women, or in girls and women with high levels of autistic features. There is, to date, little research on the ToM skills of older girls and women with eating disorders, regardless of their autism status, a lack that this paper seeks to somewhat redress. Future work should seek matched groups of males with AN and autistic males and females without AN in order to establish the true nature of the similarities and differences in ToM in AN and any potential relationship to autistic features. It is also worth noting that all participants in this sample had relatively high IQ scores, something that may ameliorate difficulties with ToM traditionally seen among autistic individuals.

The findings of this research suggest that the Frith-Happé Triangle Animations (20) may not be the most sensitive measure of ToM to use in a female neurotypical population, similar to other research findings (37). All women in this study scored similarly on both Accuracy and Mental State, regardless of levels of self-reported autistic features. Also, most participants did not create story-like narratives for the videos, instead describing the screen and the movements of the triangles, something that may have been induced in part by the direction to describe the video as it was happening. This suggests that although the task seeks to examine ToM skill—looking at the intentions and motives assigned to the two triangles—the administration instructions do not explicitly ask for this, and therefore, some participants may not show their actual level of ToM skill. While some participants did create stories and use a range of ToM terms, most did not create complex narratives, instead giving individual mentalizing terms or inconsistently using designating the triangles as characters.

The qualitative findings of this study echo those of other work that has suggested similarities between the social and

cognitive experiences of autistic people and patients with AN. The differences in the negative interpretations of the scenarios between HC/AN participants and AN+ASF participants were clear. That AN+ASF participants generally use more negative terms and give more negative interpretations to the Frith-Happé Animations aligns with previous findings of negative interpretation bias in AN (38–40). This is further evidence that AN patients with co-occurring autistic traits may need extra or individually tailored support in their treatment programs, as social support can be crucial to recovery (41–43), but if they are consistently interpreting their social experiences negatively, they may be struggling to access that support. Difficulties with negative interpretation are potentially further exacerbated by the higher levels of depression and anxiety in the AN group, as individuals with depression (44, 45) and anxiety (46, 47) have been shown to interpret situations negatively. Therefore, patients who have co-occurring AN, depression, and autism may be particularly negative in their views of their social experiences, which creates a self-fulfilling cycle where they interpret a situation negatively and withdraw or react inappropriately; therefore, those around them are less supportive, reinforcing the idea that they do not have social support, and giving the impression that their initial negative interpretation was correct. This interpretation is supported by work showing that those who are "affective deviants," i.e., who react in non-normative ways to social situations, are judged more negatively by those they interact with and are more likely to be avoided by others (48).

Other qualitative work examining emotions in anorexia found that patients had difficulties with emotional expression and negative emotions (49), all of which are also seen among autistic people (50–52). Similarly, patients with AN have been shown to have difficulties with their friendships and social relationships, which predate the onset of their illness (53, 54), and challenges with social relationships and imagination are a key diagnostic feature of autism (3). Importantly, recent research has shown that these difficulties are present for autistic women and girls (55–57), meaning that these experiences are directly comparable to those of female AN patients.

The focus of AN participants, particularly AN+ASF participants, on describing the layout of the screen and the movements of the triangles provides qualitative evidence of the detail-oriented processing and weak central coherence that has been previously seen in both those with AN (10, 58, 59) and those on the autism spectrum (60–62). It may be that individuals at the intersection of the two conditions, potentially represented by the AN+ASF group, would have that much more of a focus on details rather than the overall narrative. Knowing that this is a potential cognitive profile, as with the tendency to negative interpretation bias, has clinical implications. Detail-oriented processing over global processing is a known factor in many treatment programs designed to support AN recovery, but if a patient also has high levels of autistic features, they may find it particularly difficult to move on from this thinking style, as it may be linked not only to their illness but also to their underlying neurotype. This means that clinical teams would need to adapt treatment approaches to their particular needs and may need to reframe the ways in which these approaches are presented (63).

The fact that AN patients asked far more questions than the HC participants points to the much higher anxiety levels of the patient group. These higher anxiety levels are borne out in the quantitative as well as qualitative data, with AN and AN+ASF participants being more anxious than HC participants. There is a wealth of research evidencing higher anxiety levels in AN patients (64, 65) and autistic people (66–68). The emphasis in these questions on whether participants were "doing the right thing" or "giving the right answer" suggests that AN and AN+ASF participants were especially anxious about their performance on the task rather than how to complete it, an attitude that may be linked to the high levels of perfectionism seen in those with AN (69–71).

LIMITATIONS

While there were limitations to this study, such as the small sample size, the number of participants is sufficient for the analyses conducted, as shown by the range and consistency of the group differences identified. In the quantitative analysis, there is, however, the possibility of type II errors when working with a small sample size, as there may be insufficient power to detect a true effect leading to a negative finding. Therefore, larger studies are needed before firm conclusions regarding ToM difficulties in people with AN and ASF can be drawn. Future quantitative studies may also benefit from including a larger sample to assess the impact of eating disorders psychopathology, illness stage, and subtype along with other mental health measures on ToM scores to gain a more holistic picture of social–emotional difficulties in AN.

Another issue is the potential lack of sensitivity of the AQ-10, but it is widely used as a screening measure both clinically (17, 72) and in research (18, 73, 74). The fact that the use of the AQ-10 cutoff did not make a statistically meaningful difference to the outcome measures also suggests that the AQ-10, while quick to administer, may not be the most effective screening tool in a clinical setting, and therefore it may be worth clinical teams taking more time to use more thorough measures. In future work, it will be crucial to have a comparison group of people with AN who also have clinician-verified autism diagnoses, and a comparison group of autistic people without AN, to more fully examine the impact of autistic features on social–emotional difficulties in AN and place these in the context of autism itself. The all-female nature of this sample is also a limitation of the study. While most ToM work has had majority-male samples, as it comes from the autism field, most AN work has majority-female samples, as these are the people who are most often diagnosed with eating disorders. Conducting research with gender-balanced samples will be important in the future to redress the existing gender imbalance in both autism and eating disorder research and will allow us to more accurately evaluate and describe group- and gender-based differences in these skills.

CONCLUSION

Overall, the findings of this study suggest that while there may not be quantitative differences in task performance between HCs, AN patients with low-AQ scores and patients with high-AQ scores on the Frith-Happé Triangle Animations test of ToM, the qualitative differences between the groups may have

clinical implications. The findings also bring into question the assumption that everyone with high levels of autistic features will have difficulties with ToM tasks, highlighting that this may instead be a feature of autism in males rather than females.

DATA AVAILABILITY STATEMENT

The datasets generated for this study are available on request to the corresponding author.

AUTHOR CONTRIBUTIONS

FS and JL conducted data collection, analysis, and primary write-up of the manuscript. HH and FH contributed to initial research design and editing of the manuscript. FG contributed to data transcription and analysis, and to edits of the manuscript. KT was PI for the project, was awarded the funding which made it possible, was responsible for initial study design and contributed to recruitment and edits of the manuscript.

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Electroacupuncture Reduces Body Weight by Regulating Fat Browning-Related Proteins of Adipose Tissue in HFD-Induced Obese Mice

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Objective: This study investigated the influence of electroacupuncture (EA) and its potential underlying mechanisms on adipose tissue in obese mice.

Methods: Three-week-old male C56BL/6 mice were randomly divided to feed or not to feed high-fat diet (HFD), named HFD group and chow diet (CD) group, respectively. After 12 weeks, CD and HFD mice were randomly divided into two groups, respectively, to receive or not receive EA for 4 weeks. Body weight (BW) was monitored. Intraperitoneal glucose tolerance test and metabolic chamber recordings were performed. Blood samples and adipose tissue were collected for the analysis of leptin, triglyceride levels, and fat browning-related proteins.

Results: EA significantly reduced food intake, BW, and white adipose tissue (WAT)/BW ratio; decreased the adipocyte size and serum concentrations of triglyceride (TG) and cholesterol; and increased oxygen consumption in HFD mice. Compared with the CD mice, the HFD mice had elevated fasting serum glucose level and impaired glucose tolerance; however, these parameters were decreased by EA treatment. Meanwhile, EA promoted the protein and mRNA expressions of UCP1, PRDM16, and PGC-1α in adipose tissue, and activated sympathetic nerves *via* p-TH, A2AR, and β3AR in white adipose tissue.

Conclusions: EA reduced food intake, BW, TG, and cholesterol, and improved glucose tolerance in HFD mice. This ameliorative effect of EA on obesity-related symptoms associated with its promoted adipose tissue plasticity *via* activating sympathetic nerves.

Keywords: electroacupuncture treatment, weight loss, adipose tissue browning, obese mice

INTRODUCTION

Obesity and overweight are closely related to cardiovascular disease, type 2 diabetes mellitus, hypertension, and cancer, which have severely threatened human health and life and attracted much attention in many countries (1–3). Acupuncture for treatment of obesity in China for centuries is the most rapidly growing complementary and alternative therapy that is recognized by both the

NIH and the WHO. In addition to reducing body weight (BW), body mass index, and waist-to-hip ratio effectively, there is a growing body of evidence showing that acupuncture improved obesity-associated dyslipidemia, leptin concentration, and inflammation, suggesting that acupuncture is as effective for obese individuals (4–7). Experimental studies also showed that acupuncture treatment effectively decreased BW of high-fat diet (HFD)-induced obese rats or mice by affecting the satiety center (8), the neuroendocrine system (4), and regulating inflammatory responses (9), although the underlying mechanism is not yet entirely clear.

Fat is the largest energy reserve in mammals. During periods of excessive caloric intake, almost excess energy is stored as triacylglycerol (TAG) in lipid droplets during lipogenesis. Under fasting conditions or high energy needs, the stored TAG in adipocytes is hydrolyzed into free fatty acids (FFAs) and glycerol *via* activation of lipolytic pathways (10). Catecholamines stimulate lipolysis through activating β-adrenergic receptors in target tissues, predominantly adipose tissue and muscle (11). Therefore, effectively activating sympathetic nervous system (SNS) and adipocyte metabolism has become an effective way to control obesity. In mammalian species, there are three types of adipocytes: white, beige/brite, and classical brown. They differ in lineage origin, morphology, abundance of mitochondria, number of lipid droplets, gene expression, and functions (12). In recent years, it has been observed that the adipose tissue is more dynamic than previously believed (13), especially the browning of white adipose tissue (WAT) in response to appropriate stimulation has aroused widespread interest and has become a new target for obesity therapeutics (14–17).

Our previous work implied that electroacupuncture (EA) can induce the expression of uncoupling protein-1 (UCP-1) in WAT (18) by stimulating Zusanli (ST36) and Neiting (ST44). Does EA stimulation induce WAT browning and adipose tissue plasticity? What is the possible mechanism involved? In this study, we employed HFD-induced obese mice as the animal model and treated them with EA on ST36 and ST44 acupoints. We aimed to observe the effect of EA on obesity and determine the expression of brown-related proteins, and then evaluate the level of adipose tissue plasticity and metabolic phenotype in EA-treated obese mice. Our results may provide evidence for the field to understand how EA clinically exerts its anti-obese role.

METHODS

Animals and Grouping

Three-week-old male C57BL/6J mice (n = 63) were purchased from the Experimental Animal Center of Nanjing University of Chinese Medicine and were randomly divided into the common diet group (CD, n = 21) and the high fat diet food group (HFD, n = 42). Mice in the CD group were fed normal diet, and mice in the HFD group were fed D12451 Rodent Diet with 45 kcal% fat (supplied by Shanghai SLAC Laboratory Animal Co. Ltd). All mice were maintained at 24 ± 2°C in a 12-h light/dark cycle and given free access to water and food. Mice were weighted each week after 12 h of fasting. After 12 weeks, obese mice were defined by a 20% increase in total BW compared to control mice in the CD group and were then randomly divided into HFD (n = 9) and HFD + electro-acupuncture (EA) treatment group (HFD + EA, n = 14). Meanwhile, CD mice were randomly divided into the CD group (n = 8) and the CD + EA group (n = 13). This study was approved by the Institutional Animal Care and Use Committee of Nanjing University of Chinese Medicine and followed the latest NIH guidelines for the Care and Use of Laboratory Animals.

EA Treatment

Mice in the CD + EA and HFD + EA groups were applied EA on ST36 and ST44 after physically restraining, while mice in the CD and HFD groups were restrained in the same way, without EA treatment. According to the standard published in Experimental Acupuncturology, ST36 is located in the anterior tibia muscle, about 3 mm distal to the knee joint, and ST44 is located between the second and third phalanges on the dorsum of the foot. For the EA mice, two stainless-steel needles 0.18 mm in diameter and 10 mm in length were separately inserted into each acupoint. An electric current was provided to the needles by a Han's Acupoint Nerve Stimulator (Han Acuten, WQ1002F, Beijing, China), and EA frequency was set at 2/15 Hz with an intensity level of 1 mA for 30 min, once a day, 6 days per week, for a total of 4 weeks. The EA procedure was carried out with extremely gentle operation for avoiding any unnecessary stimulus and stress to the mice. BW and ingested food were monitored every week.

All of the mice were sacrificed with intravenous injection of high-dose pentobarbitone after 4 weeks of EA treatment, and samples were collected. The adipose tissue, including brown adipose tissue (BAT) in the interscapular region, epididymis WAT (Epi-WAT), and inguinal WAT (Ing-WAT), were dissected, weighted, and snap-frozen immediately in liquid nitrogen and stored at −80°C until further analysis.

Morphological Analysis of White Adipose Tissue

The Epi-WAT tissues were fixed in 4% paraformaldehyde and embedded in paraffin, sectioned at 8-μm thickness. Hematoxylin and eosin staining (H&E staining) were performed according to the standard process. Images were acquired by a light microscope (Nikon, Japan). For adipocyte area analysis, 10 image fields per mouse were collected by Image-Pro Plus software (19). We manually selected for adipocytes (more than 250 cells per animal) and measured adipocyte area (20).

Rectal Temperature Measurement and Cold Endurance Experiment

At the end of 4 weeks of EA treatment, the rectal temperature of the mice was recorded three times at 3 PM by an instrument at room temperature. Additionally, cold endurance experiment was performed as described previously (21). Mice were settled in a 4°C room, and rectal temperature was detected after 3, 6, 9, and 12 h.

Intraperitoneal Glucose Tolerance Test

All mice were fasted for 12 h overnight at the end of EA treatment, and then glucose (2 g/kg BW) was administered intraperitoneally and blood glucose levels were measured at 0, 15, 30, 60, and 90 min.

Metabolic Chamber Recordings

At the end of 4 weeks, 12 mice (3 each group) were given 2 days of acclimation in metabolic chambers before the trial and then continuously recorded for 24 h with the following measurements being taken every 40 min: food intake, water intake, ambulatory activity (in *X* and *Z* axes), and gas exchange (O_2 and CO_2). All measurements were taken automatically through the use of the LabMaster Phenotyping system (TSE PhenoMaster Systems, Germany). Oxygen consumption (VO_2), carbon dioxide production (VCO_2), heat production, and energy expenditure were calculated according to the manufacturer's guidelines (PhenoMaster Software, TSE Systems). The respiratory exchange rate (RER) was estimated by calculating the ratio of VCO_2/VO_2.

ELISA Detection of Serum Cholesterol, Triglyceride, Leptin, and LDL-c Level

Enzyme-linked immunosorbent assay (ELISA) kits were purchased from ShangHaiQiaDu Biotechnology Co. Ltd. Serum parameters were detected according to the manufacturer's recommendations as described previously (18).

Real-Time PCR Analysis

Total RNA was isolated from adipose tissue using Trizol reagent (Invitrogen, Cat#15596-026, USA) according to the manufacturer's recommendations. RNA concentrations were quantified and synthesis of first-strand cDNA was reverse-transcribed using the ThermoScript™ RT-PCR System (Invitrogen, Cat#11146-016) (42°C, 1 h; 70°C, 5 min). The primer sequences are listed in **Table 1**. Real-time PCR (ViiA7 Real-time PCR, Life Technologies, USA) was performed with diluted cDNAs in a total reaction volume of 20 μl (per well) and measured in triplicate. Relative mRNA levels were calculated by ΔΔCt and compared with housekeeper GAPDH as internal control. The cDNA was denatured at 95°C for 10 min followed by 40 cycles of PCR (95°C for 15 s, 60°C for 60 s).

TABLE 1 | The sequences of experimental primers used for q-PCR.

Gene	Forward primer	Reverse primer
Ucp1	GGCCCTTGTAAACAA CAAAATAC	GGCAACAAGAGCTGAC AGTAAAT
Pgc-1α	ACCATGACTACTGTCA GTCACTC	GTCACAGGAGGCATC TTTGAAG
Prdm16	CCACCAGCGAGG ACTTCAC	GGAGGACTCTCGTA GCTCGAA
Teme26	TGTTTGGTGGAGTCC TAAGGTC	ACCCTGTCATCC CACAGAG
Tbx1	GGCAGGCAGACG AATGTTC	TTGTCATCTACGGG CACAAAG
β3ar	ATCATGAGCCAGTGGTGG CGTGTAG	TCTAGTTCCCAGCGGAGT TTTATCG
Gapdh	GGCACAGTCAAGGCT GAGAATG	ATGGTGGTGAAGAC GCCAGTA

Western Blotting Analysis

Total proteins were extracted from the adipose tissue using the Total Protein Extraction Kit (Sigma, Cat# R0278). Protein concentrations were measured using the BCA Protein Assay Kit (Thermo scientific, Cat#23227). Twenty micrograms of proteins were resolved by 10% SDS-PAGE and transferred to PVDF membranes (Merck&millipore, Cat# SLGVV255F). Membranes were blocked with 5% bovine serum albumin (Merck&millipore, Cat#12659-500GM) in Tris-buffered saline with Tween 20 for 2 h followed by overnight incubation at 4°C with primary antibodies against UCP1 (Abcam, Cat#ab10983), PGC-1α (Santa Cruz, Cat#sc-13067), and PRDM16 (Abcam, Cat# ab106410). After three times washing with Tris buffered saline Tween20 (TBST), suitable HRP-labeled secondary antibody was incubated for 2 h at room temperature. Immunoblotting signals were visualized by ECL Kit (Thermo scientific). Bands were quantified by using the Image J software (NIH, Bethesda, MD, USA). Immunodetection of endogenous Glyceraldehyde-3-phosphate dehydrogenase (GAPDH) was utilized to estimate that equal amounts of protein were present in samples.

Statistical Analysis

The data are presented as the mean ± standard deviation (SD) unless otherwise stated. All statistical analyses were performed using SPSS Version 17.0 statistic software. One-way repeated-measures analysis of variance (ANOVA) was used to compare the difference in BW among groups, followed by a *post hoc* Fisher test. Multiple group comparisons were made by one-way ANOVA, followed by the Turkey–Kramer HSD test. $P < 0.05$ was considered statistically significant between the comparing groups.

RESULTS

EA Treatment Significantly Reduced Body Weight and Fat Accumulation

After 12 weeks of high-fat diet, compared with the CD group (26.2 ± 1.3 g), the BW of the HFD group (31.3 ± 2.4 g) increased significantly (**Figure 1A**), in which 23 mice (54.76%) reached more than 20% of the average BW of the CD group (**Figure 1B**). During the 4 weeks of EA intervention, BW of the mice was recorded weekly. We observed that EA significantly reduced the HFD mice's BW (from 32.5 ± 0.7 to 26.8 ± 0.7 g), especially at weeks 3 and 4 (**Figure 1C**). Interestingly, EA treatment also reduced the BW of the CD mice to some extent (**Figure 1C**). Additionally, we measured weight of the Epi-WAT, Ing-WAT, and BAT from each group and calculated the ratio of each type of adipose tissue to the BW. The results indicated that the Epi-WAT volume in the HFD group (0.67 ± 0.05 g) was larger than that in the CD group (0.38 ± 0.08 g), and EA significantly decreased the Epi-WAT/BW ratio (1.77 ± 0.4% vs. 2.29 ± 0.5%, $P < 0.05$) (**Figure 1D**). Moreover, H&E staining showed that the size of adipocyte in mice of the HFD group was larger than those in the

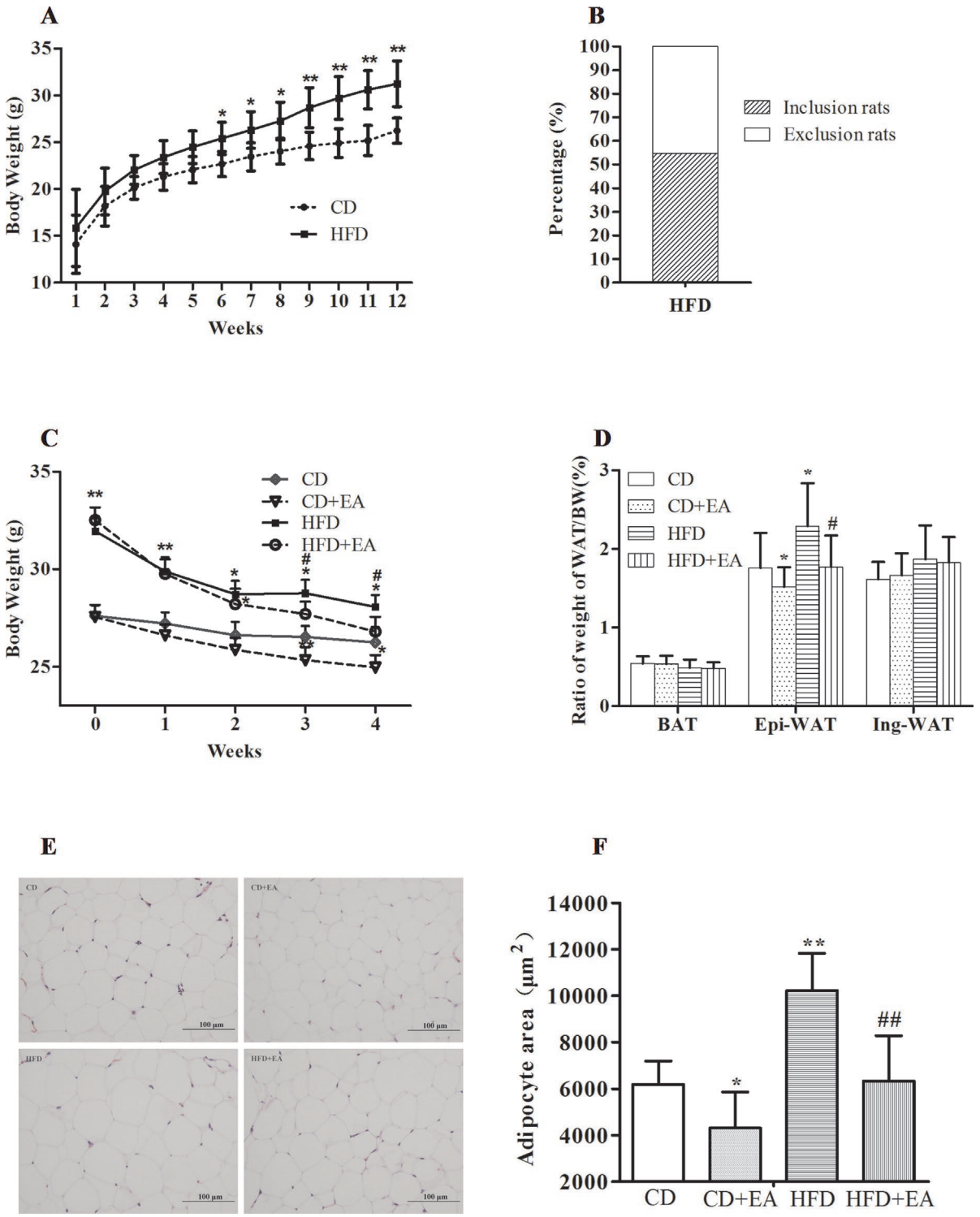

FIGURE 1 | EA treatment significantly reduced body weight and fat accumulation. High-fat diet increased body weight **(A)**, and mice weigh more than 20% of the average BW of the CD group **(B)**. Mice were fed a common diet (CD) and high-fat diet (HFD) for 12 weeks. EA decreased body weight **(C)** and Epi-WAT weight **(D)**. Furthermore, EA treatment can also decrease obese mice adipocyte size **(E** and **F)**. Data represent the mean ± SD of 8–14 animals per group besides morphological analysis (n = 5). *P < 0.05, **P < 0.01 vs. the CD group; #P < 0.05, ##P < 0.01 vs. the HFD group.

CD mice ($P < 0.05$), and EA notably decreased adipocytes' area in HFD + EA group (10,231.87 ± 1,602.23 vs. 6,337.77 ± 1,950.30 μm^2, $P < 0.01$). It is interesting that EA also affected the CD mice ($P < 0.05$) (**Figure 1E** and **F**).

EA Treatment Boosts Energy Metabolism in Obese Mice

For investigating how EA treatment affected energy expenditure, indirect calorimetry, considered the gold standard for the assessment of resting energy expenditure, was performed by measuring oxygen consumption and carbon dioxide production. The results showed that EA significantly increased oxygen consumption (5,201.99 ± 182.06 vs. 4,015.09 ± 121.77, $P < 0.05$) over a 24-h period (**Figure 2A**), whereas there was no statistically significant difference in RER between the HFD group and the HFD + EA group (**Figure 2B**). Similarly, EA did not affect the locomotor activity (**Figure 2C**). Furthermore, heat production and rectal temperature (37.7 ± 0.2°C vs. 36.9 ± 0.2°C, $P < 0.05$) were markedly increased by EA treatment (**Figure 2D** and **E**), and EA also decreased the food intake (2.99 ± 0.36 g vs. 2.53 ± 0.23 g, $P < 0.05$) of obese mice (**Figure 2F**).

EA Treatment Significantly Reversed Impaired Glucose Tolerance, Serum Leptin, Cholesterol, Triglyceride, and Insulin Level of Obese Mice

EA treatment reduced blood glucose levels during the Intraperitoneal glucose tolerance test (IGTT) in obese mice. As shown in **Figure 3A**, after 4 weeks of EA treatment, compared with other groups, the serum glucose in the HFD group increased significantly within 15 min (22.44 ± 1.83 mmol/L) after intraperitoneal glucose, while the decline was slower within 30 min (17.93 ± 2.6 mmol/L) and 60 min (10.62 ± 2.7 mmol/L). After further calculation of area under the curve (AUC), the results showed that the AUC of the serum blood glucose at 120 min was obviously increased in HFD mice in comparison with CD mice (**Figure 3B**). EA decreased the AUC in comparison with HFD mice (**Figure 3B**). Meanwhile, the serum levels of cholesterol, triglyceride (TG), leptin, and LDL-c were detected by ELISA kit, and the results indicated that, compared with CD mice, cholesterol (2.03 ± 0.14 vs. 3.77 ± 0.6 mmol/L), TG (0.62 ± 0.11 vs. 1.56 ± 0.35 mmol/L), and leptin (11.97 ± 1.13 vs. 19.29 ± 2.27 mmol/L) levels were all significantly elevated in HFD mice; however, 4 weeks of EA treatment completely reversed these levels to normal (3.77 ± 0.6 vs. 2.17 ± 0.47 mmol/L, 1.56 ± 0.35 vs. 0.75 ± 0.18 mmol/L, and 19.29 ± 2.27 vs. 13.22 ± 2.37 mmol/L, respectively), just as in mice of the CD group (**Figure 3C–E**). However, it did not change the serum LDL-c level in HFD mice.

EA Treatment Induced the Expression of Thermogenesis-Associated Genes and Encoded Proteins in Adipose Tissue

The 4-week EA treatment promoted thermogenesis-associated genes and proteins in obese mice. The results showed significantly increased expression levels of UCP1 mRNA and protein in BAT after EA treatment (**Figure 4A** and **C**). Moreover, UCP1 mRNA and protein expression was also enhanced in the Epi-WAT in the HFD + EA group (**Figure 4B** and **D**). In addition, the expression levels of beige adipocyte marker genes, including peroxisome proliferator-activated receptor γ coactivator 1α (Pgc1α), PR domain containing 16 (Prdm16), and Tmem26, were elevated in BAT and WAT of mice treated by EA (**Figure 4C** and **D**). Interestingly, T-box transcription factor 1 (Tbx1), recently defined as the beige adipocyte marker, was also significantly induced in WAT by EA treatment (**Figure 4D**).

EA Treatment Activated Sympathetic Nerves of WAT in HFD Mice

After 4 weeks of EA treatment, sympathetic activation-related protein expression increased in WAT of obese mice. Compared with the CD group, the expression of p-TH and $A_{2A}R$ decreased in the HFD group, but were reversed by EA treatment (**Figure 5A** and **B**). Moreover, EA also promoted the expression of β3 AR mRNA level of Epi-WAT (**Figure 5C**). Meanwhile, we also observed that EA increased rectal temperature of obese mice at 12 h markedly but did not affect that of CD mice (**Figure 5D**), indicating that EA treatment could affect the autonomic nervous system of obese mice and enable them to adapt to cold temperature.

DISCUSSION

Mammals have three types of adipose tissues: white, brown, and beige adipose. WAT is the main tissue of energy storage, while BAT is specialized for dissipating chemical energy by generating heat to maintain adequate core body temperature. Beige adipose is genetically different from both BAT and WAT but burns calories to release energy like BAT. Some factors such as cold exposure, SNS activation, and pharmacological conditions recruit a distinct type of thermogenic fat cell called beige adipocytes to the white fat through a process called "browning" (12, 22). Generally, WAT is characterized by its metabolic and endocrine functions for regulating energy homeostasis and insulin sensitivity. However, in the context of sustained obesity, WAT undergoes fibro-inflammation, which compromises its functionality, contributing to increased risk of type 2 diabetes and chronic cardiovascular conditions. Conversely, improving adipose tissue plasticity, either by expanding anabolic functions of WAT or by increasing tissue thermogenesis through activation of pre-existing BAT, and inducing beige adipocyte formation represent potential therapeutic approaches (23, 24). In this study, our results show that EA stimulation can significantly restore obese phenotype, promote adipose tissue plasticity, and activate sympathetic excitability in obese mice. Additionally, EA can also induce adipose tissue plasticity *via* promoting the expression of fat browning-related proteins, such as UCP-1, PRDM16, and PGC-1α in adipose tissue.

Consistent with findings from previous studies, EA treatment prevented the development of obesity (21, 25–28); however, the mechanisms remain unclear. The brain has always been a hot spot in acupuncture weight loss research; however, as the main target organ of obesity, adipose tissue has not gained enough attention. Growing body of evidence shows that inducing the formation of beige fat or WAT browning can reduce diet-induced BW gain and control obesity-related diseases (15, 29, 30). The most important

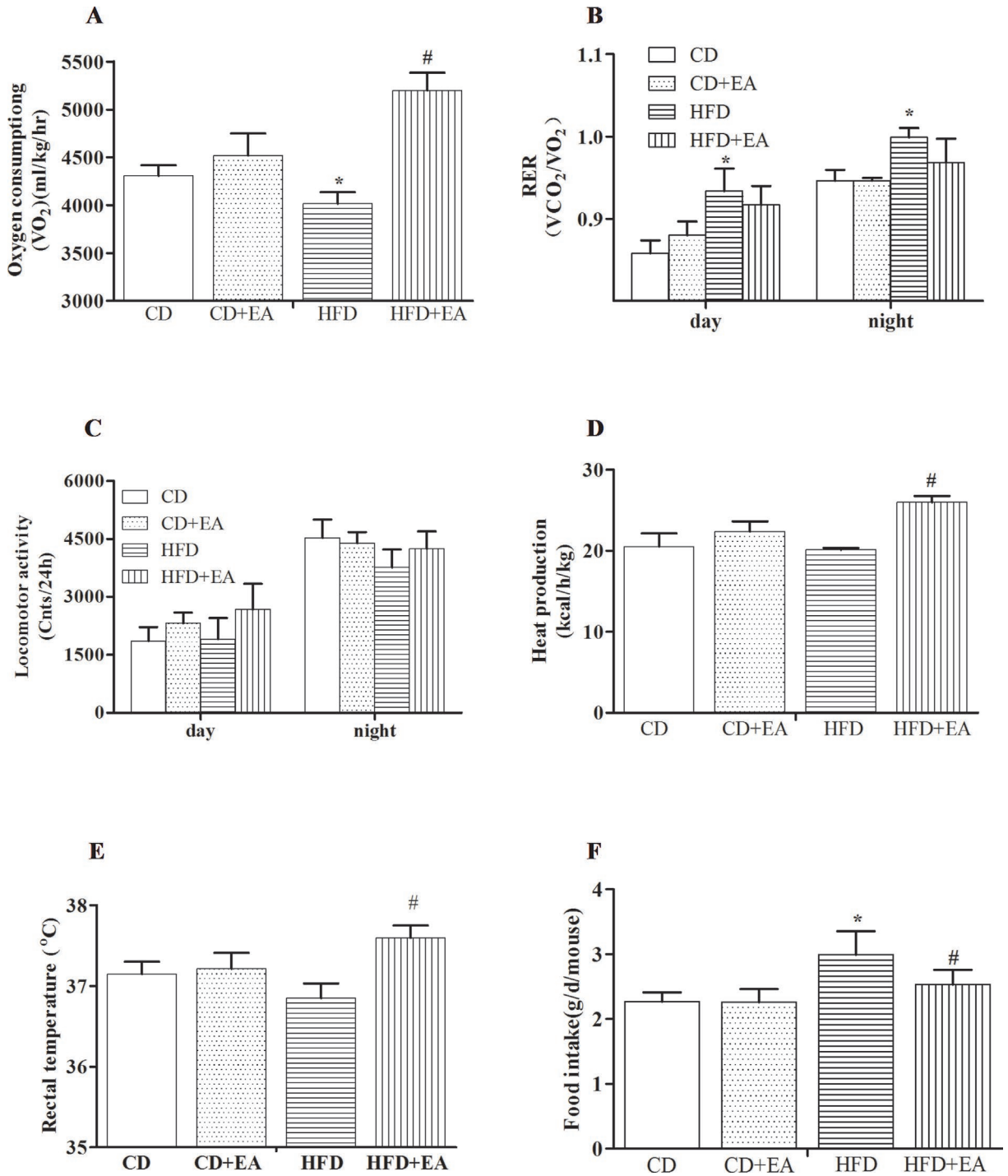

FIGURE 2 | EA treatment affects metabolic phenotype in HFD mice. EA increased oxygen consumption **(A)**, but it did not affect the respiratory exchange rate **(B)** and locomotor activity **(C)**. Meanwhile, EA can increase heat production **(D)** and rectal temperature **(E)** and decrease food intake **(F)**. Data represent the mean ± SD of three animals per group. *$P < 0.05$ vs. the CD group; #$P < 0.05$ vs. the HFD group.

characteristic of WAT browning is the elevated expression of UCP1, which is specifically BAT marker genes. As a major determinant to BAT thermogenic activity, any increase in UCP1 is commonly considered as the trademark of energy expenditure (31). Similar to UCP1, PGC-1α is also involved in the process of browning WAT (32). As a transcriptional coactivator of the nuclear receptor PPARγ, it is considered to be an integral regulator of genes that participate in mitochondrial biogenesis and oxidative metabolism (33). Moreover, increased expression levels of PRDM16 in white adipocyte precursors induce a full brown adipocyte gene programming and stimulate

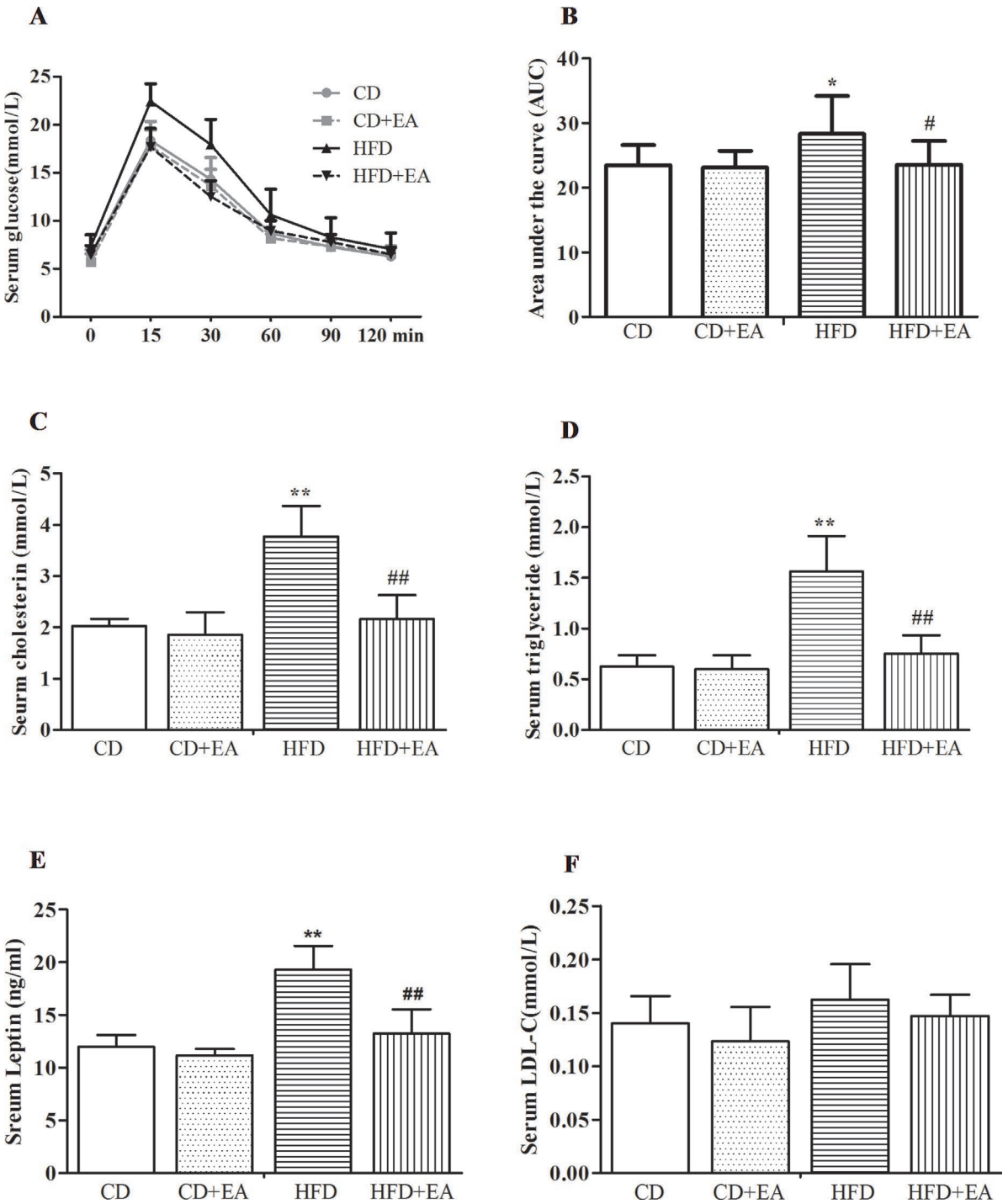

FIGURE 3 | EA significantly reversed impaired glucose tolerance **(A)** and decreased the area under the curve (AUC) **(B)**. Meawhile, EA can decreased serum cholesterol **(C)**, TG **(D)** and leptin **(E)** levels, but it did not affect the serum LDL-c **(F)** level. Data represent the mean ± SD of five animals per group. $^{*}P < 0.05$, $^{**}P < 0.01$ vs. CD; $\#P < 0.05$, $\#\#P < 0.01$ vs. HFD.

both mitochondrial biogenesis and uncoupled cellular respiration (34), and ablation of PRDM16 caused metabolic dysfunction (35). Browning of WAT or the recruitment of beige adipocytes can be brought about by hormones, cytokines, nutrients, and drugs (31, 33, 36). Our results show that 4 weeks of treatment with EA can promote WAT and BAT plasticity in obese mice through inducing the expression of UCP1 and PRDM16, thus promoting WAT lipolysis and decreasing adipocyte size. Meanwhile, PGC-1α, TMEM26, and TBX1, as beige markers (37), are greatly induced in WAT by EA. Since UCP1 and PRDM16 are responsible for energy dissipation

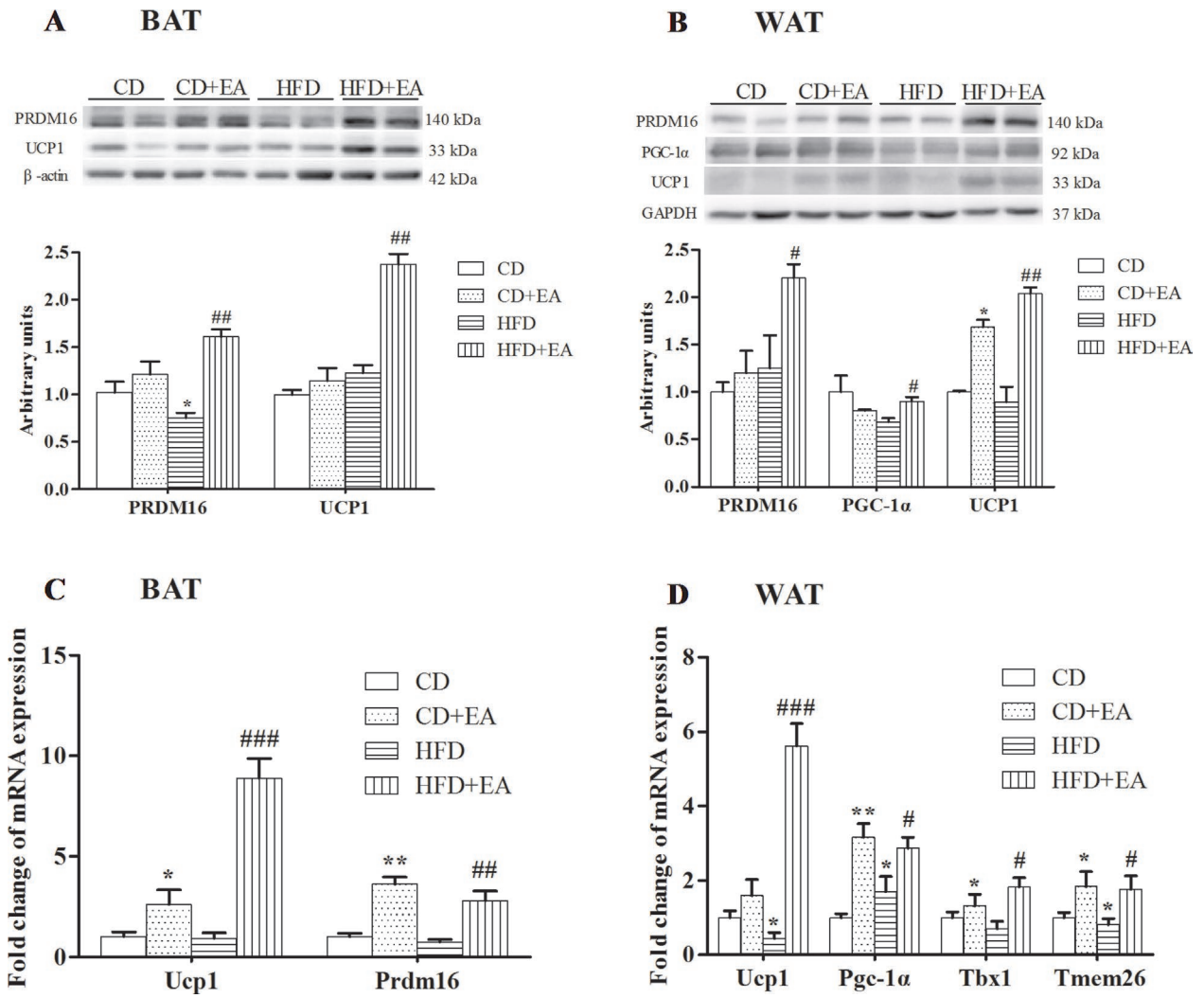

FIGURE 4 | EA treatment promoted adipose tissue plasticity in HFD mice. EA treatment induced UCP1 and PRDM16 protein expression in BAT **(A)** and Epi-WAT **(B)**. EA also induced UCP1 and PRDM16 mRNA expression in BAT **(C)** and Epi-WAT **(D)**. EA induced beige adipocyte-specific gene expression in Epi-WAT **(D)**. Data represent the mean ± SD of five to six animals per group. *$P < 0.05$, **$P < 0.01$ vs. CD; #$P < 0.05$, ##$P < 0.01$, ###$P < 0.001$ vs. HFD.

via nonshivering thermogenesis, mice with higher UCP1 and PRDM16 expression can generate heat more efficiently to maintain body temperature under cold circumstances. Therefore, impaired glucose tolerance improved in obese mice. Meanwhile, with the WAT browning, serum leptin level is significantly decreased, as did the TG and cholesterol levels. Our experiment provides evidence of adipose tissue plasticity by EA on obese mice.

Historically, the control of WAT lipolysis has mainly focused on the adrenal medullary catecholamines epinephrine (EPI) and norepinephrine (NE). Existing research indicates that WAT is innervated by SNS, and its activation is responsible for lipolysis in WAT (38, 39); nevertheless, parasympathetic innervation is not supported (38). Fully executed SNS-NE-mediated WAT lipolysis is dependent on β-adrenoceptors (βARs), especially the β3AR, which received significant attention (40, 41). This subtype is predominantly expressed on white and brown adipocytes in rodents and on brown adipocytes in humans, and its selective ligands have marked anti-obesity actions in rats and mice (42). Moreover, the SNS is fundamental in the control of daily energy expenditure *via* the regulation of resting metabolic rate and thermogenesis in response to physiologically relevant stimuli, that is, changing energy states, carbohydrate consumption, food intake, hyperinsulinemia, and cold exposure (43). Tyrosine hydroxylase (TH), a marker of sympathetic nerves, reflects the density of nerve fibers effectively (39, 44). Additionally, the adenosine 2A receptor (A2AR), as the most abundant adenosine receptor in adipose tissue, was affected during stimulation of sympathetic nerves. Pharmacological stimulation of A2AR or injection of lentiviral vectors overexpressing the A2AR into white fat induces brown-like cells, which are called beige adipocytes (15). Importantly, mice fed an HFD and treated with an A2AR agonist are leaner, with improved glucose tolerance and increased energy expenditure (15). Our results support that EA can increase the expression of TH, A2A receptor, and β3AR mRNA in WAT. At the same time, it also

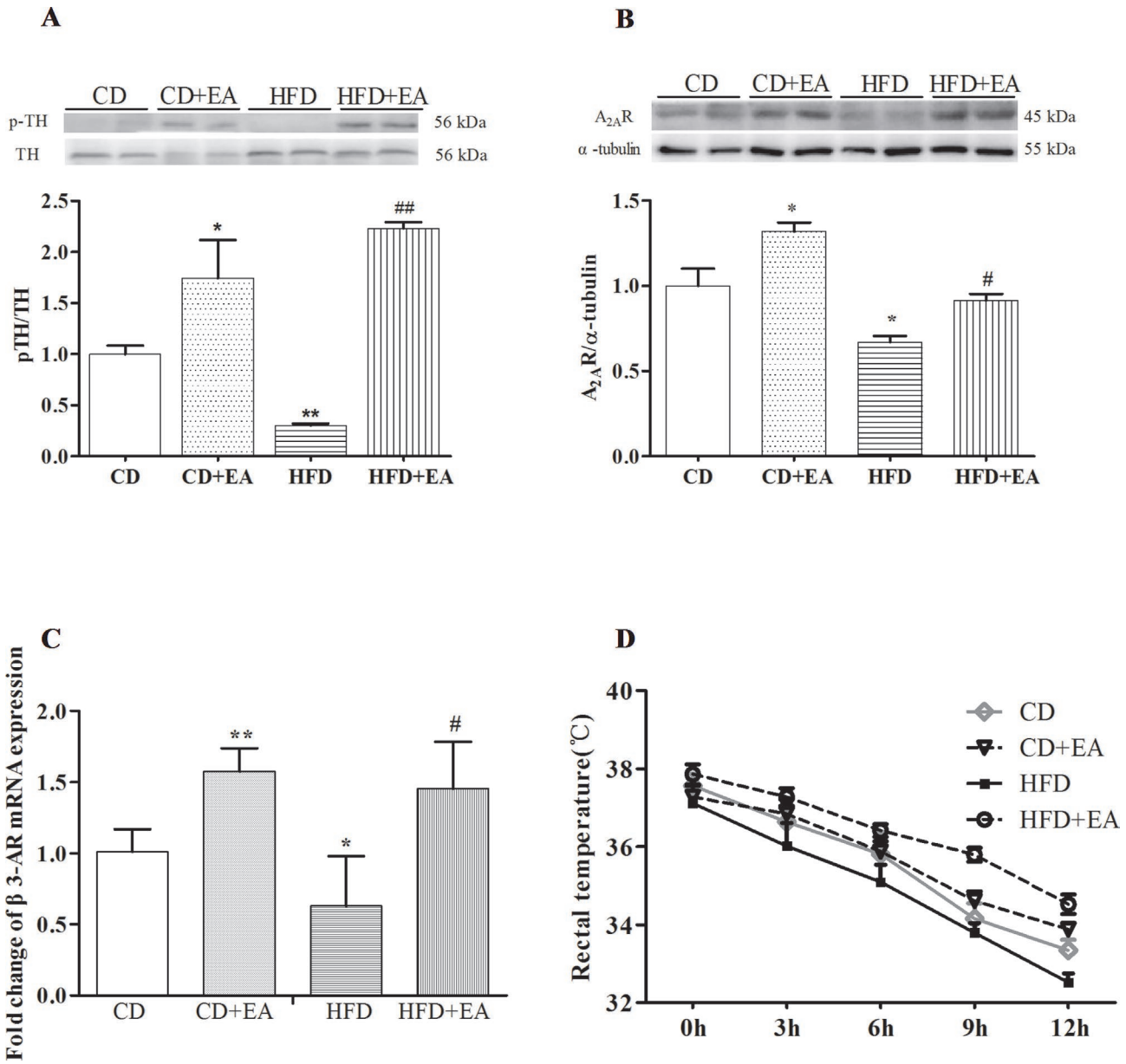

FIGURE 5 | EA treatment activated sympathetic nerves of WAT in HFD mice. EA treatment promoted p-TH **(A)** and A2AR **(B)** protein expression in Epi-WAT. EA also increased the β3-AR mRNA expression in Epi-WAT **(C)**. Moreover, EA can affect the ability of cold endurance **(D)**. Data represent the mean ± SD of five to six animals per group. *$P < 0.05$, **$P < 0.01$ vs. CD; #$P < 0.05$, ##$P < 0.01$ vs. HFD.

enhances the body's ability to tolerate cold exposure. The findings suggest that the activity of SNS in obese mice could be increased after 4 weeks of EA treatment.

Of course, this study also has some limitations. First, the number of examined cases is modest, which will limit the possibility of drawing generalizable conclusions to some extent. Second, EA, which is characterized by partial electrical stimulation, could induce muscle contraction and consequently consume energy, which is similar to physical exercise to a certain extent. Emerging evidence showed that muscle contraction causes an immediate increased glucose uptake in skeletal muscle and adipose tissue (45, 46), although EA can increase the whole-body glucose uptake by activated autonomic nervous system (47). We cannot rule out the anti-obesity effects of muscle contractions induced by EA in this study. In addition, HFD can induce the inhibition of sympathetic outflow to BAT (48), and future studies will observe sympathetic activity in BAT and evaluate WAT sympathetic drive measured by electrophysiological and neurochemical (NE turnover) means (38). In particular, the exact mode of signaling by which leptin triggers changes in WAT function was yet to be identified, and it also showed that the SNS is the fine effector of leptin's action on WAT (39). Serum leptin level increased after 4 weeks of EA treatment in this study, suggesting that leptin

may be involved in the SNS-mediated adipose tissue plasticity, but it requires further experimentation to reveal the hypothesis.

CONCLUSIONS

Taken together, EA treatment enhances sympathetic nerve activity *via* activation of TH and A2AR, thereby promoting adipose tissue plasticity and increasing energy expenditure through inducing UCP1 and PRDM16 expression, and this may be one of the mechanisms by which EA treatment decreases BW gain and fat accumulation.

DATA AVAILABILITY STATEMENT

All datasets generated for this study are included in the manuscript and the supplementary files.

ETHICS STATEMENT

The study was approved by the Institutional Animal Care and Use Committee of Nanjing University of Chinese Medicine, and all procedures were conducted in accordance with the guidelines of the NIH Animal Care and Use Committee.

AUTHOR CONTRIBUTIONS

B-MZ, S-FL, and M-LY conceived and designed the experiments. S-FL, Y-XT, TZ, S-PF, HH, YC, and X-YJ performed the experiments. Y-XT, S-FL, M-LY, and H-XX analyzed the data. S-FL, M-LY, and B-MZ wrote the paper. All authors have read and agreed with the manuscript.

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Associations Between Anxiety, Body Mass Index, and Sex Hormones in Women

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Background: Several studies have shown a positive association between anxiety and obesity, particularly in women. We aimed to study whether sex hormone alterations related to obesity might play a role in this association.

Patients and methods: Data for this study were obtained from a population-based cohort study (the LIFE-Adult-Study). A total of 3,124 adult women (970 premenopausal and 2,154 postmenopausal) were included into the analyses. The anxiety symptomatology was assessed using the GAD-7 questionnaire (cut-off ≥ 10 points). Sex hormones were measured from fasting serum samples.

Results: We did not find significant differences in anxiety prevalence in premenopausal obese women compared with normal-weight controls (4.8% vs. 5.5%). Both obesity and anxiety symptomatology were separately associated with the same sex hormone alteration in premenopausal women: higher total testosterone level (0.97 ± 0.50 in obese vs. 0.86 ± 0.49 nmol/L in normal-weight women, $p = 0.026$ and 1.04 ± 0.59 in women with vs. 0.88 ± 0.49 nmol/L in women without anxiety symptomatology, $p = 0.023$). However, women with anxiety symptomatology had non-significantly higher estradiol levels than women without anxiety symptomatology (548.0 ± 507.6 vs. 426.2 ± 474.0 pmol/L), whereas obesity was associated with lower estradiol levels compared with those in normal-weight group (332.7 ± 386.5 vs. 470.8 ± 616.0 pmol/L). Women with anxiety symptomatology had also significantly higher testosterone and estradiol

Abbreviations: GABAA, Gamma-Aminobutyric Acid A; BMI, body mass index.

composition (p = 0.006). No associations of sex hormone levels and BMI with anxiety symptomatology in postmenopausal women were found.

Conclusions: Although both obesity and anxiety symptomatology were separately associated with higher testosterone level, there was an opposite impact of anxiety and obesity on estradiol levels in premenopausal women. We did not find an evidence that the sex hormone alterations related to obesity are playing a significant role in anxiety symptomatology in premenopausal women. This could be the explanation why we did not find an association between obesity and anxiety. In postmenopausal women, other mechanisms seem to work than in the premenopausal group.

Keywords: anxiety, body mass index, obesity, sex hormones, testosterone, estrogen, women

INTRODUCTION

Anxiety disorders affect 25% of the population in the Western world, which makes them the most frequent psychiatric condition these days (1). They are chronic and more prevalent in females than males and are typically complicated by coexistent mental and somatic disorders (2). Moreover, there are also differences in comorbidities, symptoms, and how these disorders affect each gender (3).

Differences in prevalence, as well as the fact that puberty, pregnancy, and menopause are important precipitants for onset, exacerbation, recurrence, and relapse of anxiety disorders, further indicate an important role of hormones, including and in particular sex hormones (2).

As for hormones, testosterone is reported to have a crucial influence on the course of anxiety disorders (4). Testosterone, often referred as a male hormone, is also present in women, although in about 10 times lower concentrations (5). It is hypothesized that its higher concentrations in males might be one of the reasons for the sex differences in prevalence of anxiety (4). The effects of testosterone are mediated through the stimulation of estrogen receptors, androgen receptors, or GABAA receptors in several brain regions, resulting in various biological outcomes (6). It has been reported in the literature that testosterone can relieve anxiety and depression while inducing subjective feeling of an improved mood in both genders (2).

Testosterone's anxiolytic (7, 8) and anxiogenic (9, 10) effects have been studied in several animal studies as well. Various activational effects of testosterone on the anxiety-like behavior have been observed in adult male rodents. Gonadectomized adult male rodents showed increased anxiety-like behavior, and this effect could be reversed by testosterone replacement (11). Moreover, it was shown that testosterone replacement had the exact same anxiety-relieving effect as the administration of the typical tricyclic antidepressant in male rats (12). However, very inconsistent outcomes of studies investigating testosterone's anxiolytic effect in female rodents have been published. Some studies provide supporting evidence for a beneficial role of testosterone in intact adult female rodents (13).

Women with anxiety disorders were previously proved to have decreased testosterone levels. When compared with healthy controls, women with social phobia, generalized anxiety, or agoraphobia produced lower levels of testosterone in their saliva (14).

On the other side, also an association between higher testosterone levels and anxiety has been shown in women with polycystic ovarian syndrome (state of hyperandrogenism) (15).

Contradictory results from preclinical and clinical research were published regarding the association of anxiety with estrogen levels as well (16, 17). Higher estrogen levels were significantly associated with anxiety and anxiety-like behaviors in some studies (18). The risk for developing of any anxiety disorder significantly increases at menarche, as the circulating estradiol abruptly increases from prepubertal to its adult levels during the stage of sexual development (19).

On the other hand, increased anxiety symptoms were also noticed in women after surgical or natural menopause (20) and close to the end of the luteal phase of the menstrual cycle (21) – periods characterized by decline in circulating estradiol levels. The most probable explanation is that the effect of estradiol on anxiety behavior is dose dependent and varies from anxiogenic (22) to null (23) to anxiolytic (24).

Several conditions might be associated with changes in sex hormone levels in women. The most prevalent is obesity, which might be associated with changes in hypothalamic–hypopituitary–gonadal axis and also altered testosterone and estradiol levels (25). This is also due to the fact that fat tissue *per se* represents an intracrine source of sex hormones, and this was shown to be gender specific. Body mass index (BMI) is positively associated with testosterone levels in women, while there is an inverse association of BMI and estrogen (26). It has been reported that severity of obesity is directly linked with the amplitude of hormonal changes (27), which can be reversed by the reduction of weight (28).

A positive association between overweight and anxiety disorders has been shown in several studies (29, 30), although the underlying mechanisms of this association are still not completely understood. Alterations of testosterone levels (higher levels in women) associated with increased BMI might represent one of the possible risk factors in the etiopathogenesis of anxiety.

We hypothesized that all three factors – anxiety, BMI, and sex hormones – might be strongly interconnected. To the best of our knowledge, all three factors have not been studied together so far.

In the present study, we (1) focused on associations between anxiety symptomatology and BMI, (31) focused on associations between anxiety symptomatology and sex hormones and to compare them with sex hormone alterations in obesity, and (2) studied the impact of both BMI and altered sex hormone levels on anxiety in one regression model.

PATIENTS AND METHODS

Study Population

Data presented in this study were obtained from the (LIFE)-Adult-Study conducted by the Leipzig Research Centre for Civilization Diseases. This study included >10,000 participants selected randomly. The objective of the LIFE-Adult-Study is to investigate the prevalence, markers of early onset, genetic factors, and lifestyle determinants of major civilization diseases, including metabolic diseases and depression (32). The study was approved by the responsible institutional ethics committee of the Medical Faculty of the University of Leipzig (PV 2016-274-04). All participants provided written informed consent. The data privacy and safety concept of the study were endorsed by a responsible data protection officer.

Medical History and Medications

A structured interview was performed in all participants of the study, where they were asked about 70 common medical diagnoses, which were previously confirmed by their physician. In women, data on menstrual cycle [number of days/months/years since the last menstrual period (LMP)], history of bilateral oophorectomy and hysterectomy, and past or present use of contraception pills or hormonal replacement therapy were included. Data on all other medications taken within past 7 days before study day were gathered. Medications were identified by bar codes, following ATC classification.

Anthropometry

Trained study personnel measured the body weight and height according to standardized protocols. For measuring body weight, an electronic scale (SECA 701, Seca Gmbh & Co KG) with a precision of 0.01 kg was used; body height was assessed by means of a stadiometer (SECA 240) to the nearest 0.1 cm (32). Underweight was assessed as BMI < 18.5 kg/m^2, normal weight as BMI ≥ 18.5 and < 25 kg/m^2, overweight as BMI ≥ 25 kg/m^2 (pre-obesity BMI > 25 and 29.9 kg/m^2 and obesity ≥ 30 kg/m^2).

Hormonal Analyses

Blood samples were collected in all participants of the study between 7:30 and 10:30 a.m. after more than 10 hours of fasting). Analyses of levels of selected hormonal (sex hormone-binding globulin and total testosterone) and biochemical (albumin) parameters (for calculation of free testosterone) were performed on fresh serum samples in a highly standardized manner (32). Biochemical analysis was performed by fully automated Cobas system (Roche, Mannheim). Intra-assay and inter-assay coefficients of variation were given exemplarily by 100 subsequent analyses during the time of recruitment study of probands: results of sex hormone-binding globulin were <3.4% for the range between 25.4 and 54.2 nmol/L, results of estradiol were below 4.3% for the range between 387 and 2,052 pmol/L, and results of total testosterone were below 4.9% for the range between 3.73 and 19.07 nmol/L. Free testosterone was calculated using Vermeulen's formula (33). Composition of estradiol and total testosterone or free testosterone was calculated by multiplying serum estradiol levels by total or free testosterone serum levels, respectively.

Assessing of Anxiety Symptomatology

We used a German version of the established self-report questionnaire Generalized Anxiety Disorder 7 (GAD-7) to screen the presence of anxiety symptomatology. The GAD-7 questionnaire (covering symptoms of generalized anxiety disorder, panic disorder, social anxiety disorder, and post-traumatic stress disorder) consists of seven items asking patients how often, during the last 4 weeks, they were bothered by each symptom. The answer options were "not at all," "several days," "more than half the days," and "nearly every day" scored from 0 to 3 points. A total score of ≥10 indicates the presence of an anxiety symptomatology (34).

Exclusion Criteria

We excluded all women 1) using medications possibly influencing either hormonal or mental status, including 1A) external hormones [ATC groups: G02, other gynecologicals (n = 210); G03, sex hormones and genital modulators (n = 766); H02, systemic corticosteroids (n = 109); and L02, endocrine therapy (n = 60)], 1B) CNS or psychotropic drugs [N03, antiepileptics (n = 143); N04, antiparkinsonics (n = 61); N05, psycholeptics (n = 344); N06, psychoanaleptics (n = 516); and N07, other CNS drugs (n = 61)]; (31) individuals with hypothyreosis or hyperthyreosis (n = 11); 2) perimenopausal (6–12 months since LMP, n = 136) and postpartal (1 year after delivery, n = 28) women, as both periods are significantly related to increased onset and prevalence of anxiety disorders (35); 3) underweight individuals (n = 40) because of small numbers; 4) all individuals with severe renal/hepatal/neurologic disease or cancer in the last year (n = 276); and 5) individuals diagnosed or/and treated for depression (n = 462).

Classification Process

Women were classified according to age and LMP into premenopausal (0–6 months since LMP or <45 years) and postmenopausal (>12 months since LMP or ≥55 years or bilateral oophorectomy), in accordance with guidelines used by Breast Cancer Consortium (36).

Cohort Description

The study sample included 3,124 women of whom 970 (31.0%) were premenopausal (45.0 ± 6.6 years) and 2,154 (68.9%) were

postmenopausal (64.2 ± 8.0 years). In the group of premenopausal women, 53.7% were of normal-weight (mean BMI 22.1 ± 1.6 kg/m^2), 28.1% were pre-obese (mean BMI 27.1 ± 1.4 kg/m^2), and 17.0% were obese (mean BMI 35.2 ± 5.0 kg/m^2). In the group of postmenopausal women, 32.5% were normal weight (mean BMI 22.8 ± 1.6 kg/m^2), 37.9% were pre-obese (mean BMI 27.4 ± 1.4 kg/m^2), and 29.0% were obese (mean BMI 34.2 ± 4.1 kg/m^2).

Statistical Analyses

Values for the sample description are given as mean ± SD. Comparison between groups was tested using *t*-test for metric variables and by Fisher's test or chi-square test for binary variables. Logistic regression analysis was performed using presence of anxiety symptomatology (GAD-7 ≥ 10 points) as a dependent variable, and BMI, testosterone, and age as independent variables. *p* values less than 0.05 were considered as statistically significant. Statistical analyses were performed with SPSSv25 software (IBM, NY, USA). Graphs were plotted with GraphPad Prism 7.04 (GraphPad Software, CA, USA).

RESULTS

Prevalence of Anxiety in Women

In all women included into the study, the prevalence of anxiety symptomatology was 5.0%, with no significant differences between the premenopausal and postmenopausal groups (**Figure 1A**).

Association Between Anxiety Symptomatology and BMI

We did not find any significant differences in the prevalence of anxiety symptomatology between normal weight, and obese premenopausal, postmenopausal women (**Figure 1B**).

Associations of Anxiety Symptomatology and BMI with Sex Hormones

Premenopausal women with anxiety symptomatology showed higher total testosterone levels than did women without anxiety symptomatology (1.04 ± 0.59 vs. 0.88 ± 0.49 nmol/L, $p = 0.023$) (**Figure 2A**). Free testosterone and estradiol levels were also higher in the women with presence of anxiety symptomatology; however, the differences were not significant (**Figure 2B**, **C**). Significant differences in anxious versus non-anxious women were observed in compositions of estradiol with total and free testosterone, respectively (**Figure 2D**, **E**).

In postmenopausal women, no significant association between anxiety symptomatology and testosterone (as well as with other sex hormones) was found (**Figure 2A**–**E**).

Premenopausal women with obesity showed higher total testosterone (0.97 ± 0.50 vs. 0.86 ± 0.49 pmol/L, $p = 0.026$) and free testosterone levels (12.8 ± 8.3 vs. 8.9 ± 6.2 pmol/L, $p < 0.001$) and lower estradiol levels (332.7 ± 386.5 vs. 470.8 ± 516.0 pmol/L, $p = 0.004$) than did normal-weight women (**Figure 2A**–**C**).

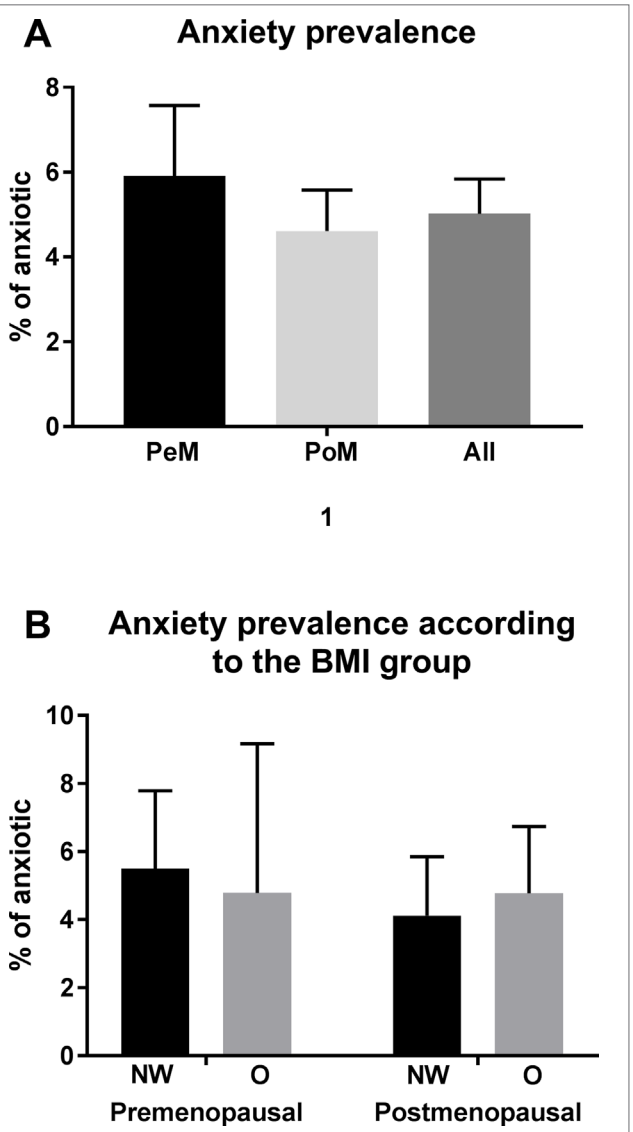

FIGURE 1 | Prevalence of anxiety. Displayed in % with 95% confidential intervals (calculated with the Wilson–Brown method). Significant differences are marked with * (*p* between 0.05 and 0.01), ** (*p* between 0.01 and 0.001), and *** (*p* < 0.001). Abbreviations: PeM, premenopausal; PoM, postmenopausal.

Association Between Anxiety Symptomatology, BMI, and Sex Hormones

In the logistic regression analysis, anxiety symptomatology was significantly associated with total testosterone ($\Delta R^2 = 0.016$, OR = 1.773, $p = 0.025$), but not BMI (**Table 1**).

In postmenopausal women, total testosterone, estradiol, and BMI were not associated with anxiety symptomatology (**Table 1**).

DISCUSSION

Both anxiety symptomatology and obesity were associated with higher testosterone levels but had opposite impact on the estradiol

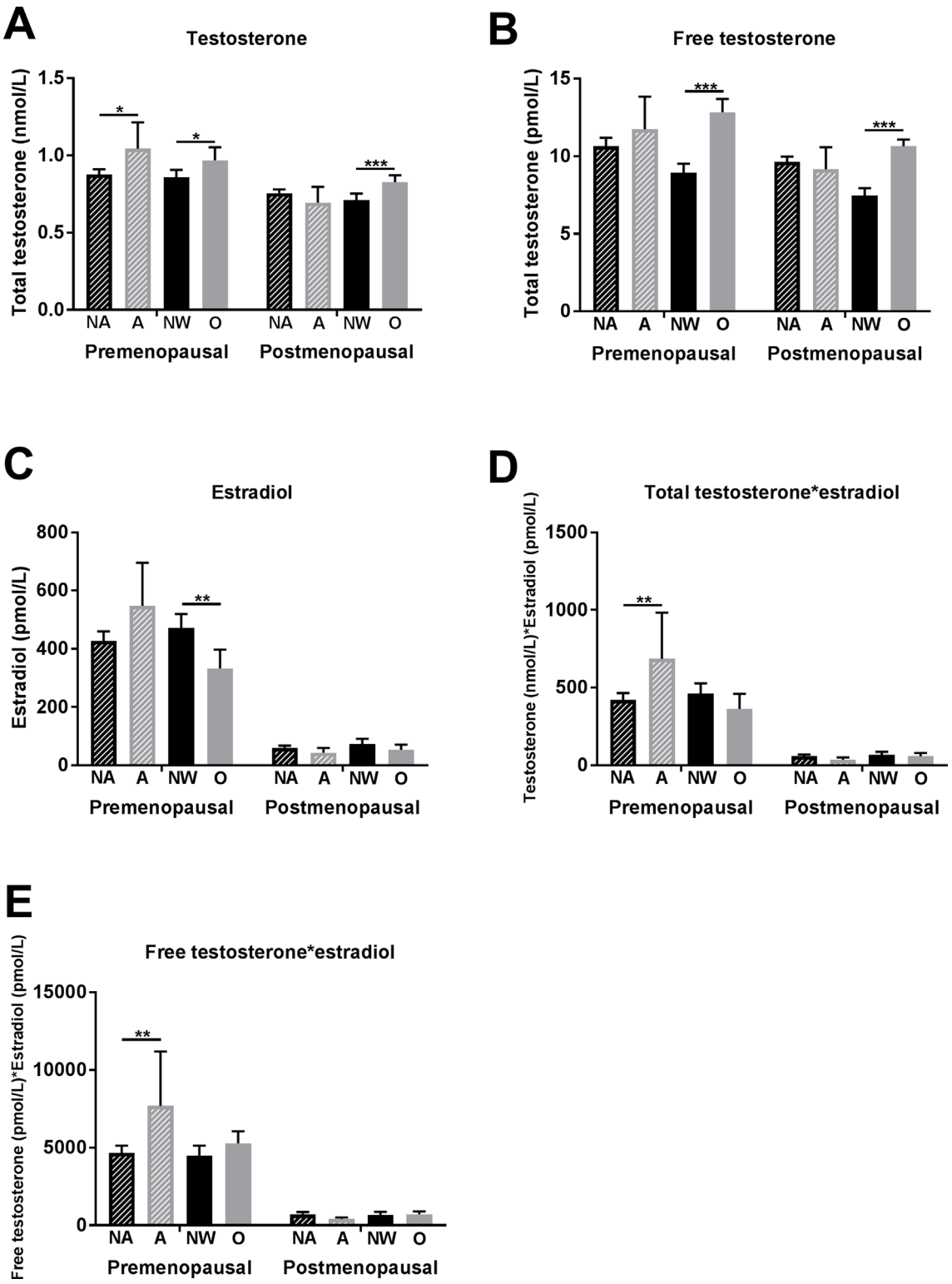

FIGURE 2 | Associations of anxiety symptomatology and obesity with testosterone and estradiol levels in premenopausal and postmenopausal women. **(A)** Total testosterone levels, **(B)** free testosterone levels, **(C)** estradiol levels, **(D)** composition of total testosterone with estradiol levels, and **(E)** composition of free testosterone with estradiol levels. Significant differences are marked with * (p between 0.05 and 0.01), ** (p between 0.01 and 0.001), and *** ($p < 0.001$). Abbreviations: NA, non-anxious (anxiety symptomatology not present = GAD-7 < 10 points); A, anxious (anxiety symptomatology present = GAD-7 ≥ 10 points); NW, normal weight (BMI between 18.5 and 25 kg/m^2); O, obese (BMI ≥ 30 kg/m^2).

TABLE 1 | Logistic regression analysis of anxiety symptomatology and co-factors in women. Anxiety symptomatology (assessed as 0–1, cut-off GAD-7 ≥ 10 points) was set as dependent variable. Independent variables were total testosterone, estradiol, and BMI. Stepwise model was used for all analyses. Abbreviations: BMI, body mass index; ΔR^2, *R* square change; OR, odds ratio; CI, confidence intervals; *n*, number of analyzed individuals; *p* value, significant if <0.05.

Dependent variable: *anxiety symptomatology* **Independent variables: *total testosterone, estradiol, BMI***	**Included independent variable**	**ΔR^2**	**OR**	**CI (95%)**	***p***
Premenopausal women. Model summary: $R^2 = 0.016$, $p = 0.033$, $n = 799$	**1. Total testosterone**	0.016	1.763	1.074–2.895	**0.025**
	Not included: estradiol ($p = 0.230$), BMI ($p = 0.124$)				
Postmenopausal women. Model summary: $n = 1{,}708$	Not included: total testosterone ($p = 0.278$), estradiol ($p = 0.423$), BMI ($p = 0.628$)				

levels in premenopausal women. However, BMI was not associated with anxiety symptomatology. No significant associations between anxiety symptomatology and sex hormone levels were found in postmenopausal women.

Anxiety Symptomatology and Testosterone

The positive association between anxiety and testosterone levels in women, found in our study, has been observed in several others, particularly in studies of women with polycystic ovarian syndrome (state of hyperandrogenism) (37, 38). A similar association has also been found in animal studies. In a study by Goel and Bale (9), an anxiogenic effect after administration of testosterone in female mice was observed. Increased androgen levels in prenatal period were proved to be associated with anxiety-like behavior in rats. This effect was reversible by the administration of estrogen receptor modulators and androgen receptor blockers. This study also reported anxiety-like behavior in female rats after they were injected testosterone into the amygdala (39).

Females were proved to have more sensitive receptor binding testosterone despite about 10 times lower levels of testosterone than have males (2, 5). This can be seen also in our study—premenopausal women with anxiety symptomatology had higher total testosterone levels, but the mean levels were still within the reference range. This is implying that women might be sensitive not only to extreme but also to more subtle alterations of testosterone levels. The fact that this association was observed in premenopausal women only might be related to physiological changes of testosterone levels over a woman's lifespan. Between 20 and 40 years, a steep decline of testosterone levels can be seen in women (40). Premenopausal women could be therefore more sensitive to the (pathophysiological) increase of testosterone level.

On the other hand, it is necessary to say that several studies have found an association between lower testosterone and anxiety (or some specific subtypes) in women (14, 41).

The most possible explanation is that the association between anxiety and testosterone levels might be not linear and that the effect is dose dependent. This was observed in one of the most cited animal study focused on the effect of testosterone on anxiety (42). Differences in the study design (e.g., with regard to the menopausal status of women) as well as studied samples might also play a role in the various outcomes.

Anxiety Symptomatology and BMI

Several large epidemiologic studies have found a positive relationship between anxiety disorders (or some specific subtypes) and overweight or obesity in women and men, i.e., increasing prevalence with increasing BMI (29). A moderate but positive relationship between overweight and anxiety disorders was also observed in large epidemiological studies and meta-analyses (30, 43).

In our study, no significant association between BMI and prevalence of anxiety symptomatology regardless of gender or menopausal status in women was found.

There might be several possible explanations for these contradictory results. The first possibility is the way that anxiety was measured. Most of the published studies focused on the lifetime or on the 12-month prevalence of anxiety (29, 44), and only a few studies focused on current anxiety symptomatology with current BMI. In the study by Jorm et al. (45) investigating the association between current anxiety symptomatology and current BMI status, similar results to our study have been found. Anxiety symptomatology and BMI are largely time-dependent phenotypes; e.g., higher anxiety symptoms earlier in life may contribute to increased BMI later in life and vice versa. To the best of our knowledge, a study investigating the association between BMI in the age of the onset of anxiety disorder is missing.

Another possible explanation for these contradictory findings of above-mentioned studies and our study is that most of them did not use any exclusion criteria, which may have an impact on the results of anxiety and weight of an individual as well. In our study, by contrast, all individuals treated with psychotropic or selected CNS drugs, as well as with severe somatic conditions (e.g., cancer), were excluded. Also, comorbidity of depression and anxiety is high (29); it could be that the positive association described also in other studies of increased BMI and anxiety could be driven by comorbid depression.

Anxiety Symptomatology, BMI, and Testosterone

A well-established fact is that increased BMI is associated with higher testosterone levels in women and decreased levels in men (28, 46). First, we hypothesized that there might be a mediation of the positive association between anxiety and overweight (described in several studies) through altered testosterone levels associated with increased BMI. If this hypothesis would be true, this could change the therapy approach of anxiety disorders in obese women, as higher testosterone level might maintain

anxiety symptomatology. Therefore, obese women with anxiety symptomatology could benefit from androgen receptor blockers or weight loss as an additive therapy.

However, we did not find a significant association between anxiety symptomatology and BMI in either premenopausal or postmenopausal women in our study. There could be several explanations of this finding:

a. Hormonal changes associated with gradually increasing BMI are slow, so a certain "adaptation mechanism" might develop and could explain why the BMI-associated sex hormone alterations were not proven to play a significant role in anxiety pathogenesis in overweight individuals.
b. Hormonal changes associated with obesity might be "protective" against anxiety. Therefore, we have looked at the concentrations of other sex hormones. Estradiol levels were significantly lower in obese premenopausal women compared with the normal-weight group, and non-significantly (p = 0.086) higher in the group of women expressing anxiety symptomatology than in the women without anxiety symptomatology. Therefore, lower estradiol levels associated with obesity could be protective against anxiety in premenopausal women. To support our hypothesis, we calculated total and free testosterone * estradiol index, as higher levels of both hormones were associated with anxiety. Higher values of this index (using both total and free testosterone) were significantly associated with anxiety symptomatology in premenopausal women, but there were no significant differences between obese and normal-weight groups.
c. The association between increased testosterone levels and anxiety symptomatology independent of BMI might indicate that other conditions related to higher testosterone level in women [e.g., stress (47), smoking (48), polycystic ovarian syndrome (37), insulin resistance (49), and hypothyreosis] could be involved in the pathomechanism of anxiety in premenopausal women, and most of these conditions are highly influenceable by lifestyle changes.
d. Another speculation could be that anxiety *per se* might lead to increased testosterone levels in women, so this might be secondary to anxiety. Further studies are required to establish causal relationships and to elucidate possible neural and molecular mechanism underlying testosterone's actions in anxiety.

In postmenopausal women, no association between testosterone and anxiety, as well as anxiety and BMI, was shown in our study. Several other factors (e.g., partnership or being married and socioeconomic status) might play a more significant role in the mechanism of anxiety besides those two factors.

Strengths and Limitations of the Study

To our best knowledge, this is the first study investigating associations between anxiety, BMI, and sex hormones in women together. It is based on a large cohort of more than 3,000 individuals, where strict exclusion criteria were employed. A further strength is that anthropometric measurements were taken by study personnel rather than self-report, which is related to higher reliability. As a limitation, the cross-sectional nature of the study with a relatively healthy population sample might have hampered the study of these associations. The studied associations might be more pronounced in a sample of patients with clinical diagnosis of anxiety disorder. Further limitation could be the fact that the sex hormone levels were not measured in the same phase of the menstruation cycle. However, our aim was not to study association of the anxiety symptomatology with the menstruation cycle but to study the presence of anxiety symptomatology with levels of sex hormones, which was performed on the same day. Another limitation could be the polycystic ovary syndrome. However, in our cohort, we did not have any female participants labeled with polycystic ovary syndrome that was associated with anxiety in several studies (37).

CONCLUSIONS

Although both obesity and anxiety symptomatology in premenopausal women were separately associated with the same hormonal phenotype – higher testosterone levels – there was an opposite impact of anxiety and obesity on estradiol levels. This could be the explanation why we did not find a relationship between anxiety symptomatology and obesity. This suggests that there is no direct link between anxiety, BM, and sex hormones and that sex hormone alterations in obese women do not play a significant role in developing or maintaining anxiety. As the prevalence of obesity and mental disorders is increasing, further studies investigating other factors associated with anxiety might bring light into the pathomechanism of anxiety in young women. In postmenopausal women, other mechanisms seem to work than in the premenopausal group.

DATA AVAILABILITY STATEMENT

All datasets generated for this study are included in the manuscript and the supplementary files.

ETHICS STATEMENT

Data included in the study were obtained from the Leipzig Research Centre for Civilization Diseases (LIFE)-Adult-Study. The study was approved by the responsible institutional ethics board of the Medical Faculty of the University of Leipzig (PV 2016-274-04). Written informed consent was obtained from all participants. The data privacy and safety concept of the study were endorsed by the responsible data protection officer.

AUTHOR CONTRIBUTIONS

All authors reviewed the manuscript critically and approved the final version. DS was responsible for the conception and design of the study, analysis of the data, and writing of the manuscript. YJB, JK, JT, UC, CEng, and KW acquired the data. TL, JSt, AP,

AH, HG, JSa, CEnz, and SR-H contributed to the interpretation of the data and critical revision of the manuscript.

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Culture Change and Eating Patterns: A Study of Georgian Women

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Introduction: Immigration and culture change have been thought to affect various aspects of psychological well-being, including eating behaviors. This study aimed to examine the association between immigration, acculturation strategies and eating patterns.

Materials and Methods: Acculturation was conceptualized and measured by acculturation strategies of integration (maintaining original culture and adopting the new culture), assimilation (adopting the new culture and leaving behind the old), separation (sticking with the original culture only) and marginalization (maintaining/adopting neither culture). Eating patterns were conceptualized by dietary restriction, eating concern, shape concern, and weight concern. Links between demographic variables, acculturation strategies, and eating patterns were also examined. Five hundred and six Georgian women took part in the study: 253 living abroad (UK and USA) and 253 living in Georgia. Measures included East Asian Acculturation Measure (EAAM) for acculturation strategies (assimilation, integration, separation, and marginalization subscales) and Eating Disorder Examination Questionnaire (EDEQ) for eating patterns (dietary restriction, eating concern, weight concern, shape concern subscales, and global score). Relevant demographic variables and Body Mass Index (BMI) were recorded.

Results: Comparisons of immigrant and nonimmigrant groups using Multivariate Analysis of Covariance (MANCOVA) with BMI as a covariate found a difference in dietary restriction only, with immigrants yielding higher mean score than non-immigrants. The global EDEQ scores of immigrant and nonimmigrant groups were almost identical though. Correlations between separation and marginalization and four EDEQ scores were statistically significant and positive, while correlations between integration and two EDEQ subscales were marginally significant and negative. Regression analysis showed that separation and marginalization strategies of acculturation were significantly linked with EDEQ eating concern, shape concern, weight concern, and global scores thereby representing predictors of elevated eating outcomes.

Discussion: Findings suggested that moving to Western countries increased dietary restriction among Georgian women. Furthermore, while living abroad, the lack of integration in a host culture, as a common denominator of separation and marginalization strategies of acculturation, may predict elevated eating, shape, and weight concerns among women relocated over six years ago. Acculturation conditions may also be linked with integration or well-being outcomes.

Keywords: acculturation, immigration, eating patterns, disordered eating, Eastern Europe, cross-culture, transition

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INTRODUCTION

Disordered eating patterns represent eating related unhealthy behaviors (e.g., excessive concern about weight and shape, excessive dieting, self-induced vomiting) that resemble Eating Disorders (ED) but are exhibited in a smaller degree in terms of frequency and intensity (1). Traditionally believed to be affecting women of affluent societies (2, 3), the prevalence of EDs has been increasing among diverse populations and cultures (4–8). While researchers are trying to find out more about the main determinants, risk and protective factors of EDs, it is recognized that they are culturally influenced (9–13). Among other factors, disordered eating has been linked with immigration, acculturative stress and Western beauty standards of thinness (5, 14, 15).

Acculturation as a complex and interdisciplinary phenomenon has been defined in multiple ways, all implying meeting of cultures and the subsequent changes in individuals or groups (16). Psychological acculturation refers to the changes an individual experiences as a result of culture change while adjusting to a new dominant culture [Graves, 1967 as cited in Ref. (17)]. One of the prominent acculturation models introduced by Berry and his colleagues is a fourfold model of acculturation proposing four acculturation strategies that individuals might apply when exposed to culture change: assimilation – preference in adopting and maintaining only new cultural identify, separation – preference in maintaining only original cultural identity, integration – preference in both maintaining original and adopting new cultural identities, and marginalization – no interest in maintaining/adopting either cultural identity (16, 18–20).

Migration-related psychological distress and mental health vulnerability of immigrants and refugees have been recognized by an abundance of research prompting researchers to propose that culture change and adopting to Western lifestyles posed certain risks for psychological well-being among diverse populations (21–24). Empirical evidence suggests that once individuals are subjected to acculturation, engagement in both cultures leads to better outcomes compared to the engagement in one culture only, while engagement in neither culture has been linked with the poorest health outcomes (18, 20, 25).

The link between culture change and disordered eating has attracted researchers' interest towards the end of the twentieth century as EDs started emerging in non-Western countries, including Eastern Europe, and among immigrant/minority populations (8, 26–29). Cases of EDs in some parts of the world, e.g., the island of Curacao and South America, appeared very low primarily affecting elite groups exposed to North American and European influence (14, 27, 30), which further strengthened the hypothesis linking EDs with acculturation to Western culture and values.

While several researchers suggested that eating disturbances might take place in the process of adapting to a new culture (31, 32), some have linked increased ED symptomatology with initial years of immigration and lower levels of acculturation to a mainstream culture (33–36), while others identified higher risks at later stages of immigration and higher levels of acculturation (37–40). Similarly, some studies comparing various immigrant and nonimmigrant groups identified higher ED susceptibility among westernized immigrants (35, 39, 41–43), whereas others have found no associations between culture change and disordered eating (10, 44–47).

Nevertheless, the ways these studies defined and measured acculturation varied significantly (some using proxy measures such as length of residence in a new country) and many of them did not sufficiently examine acculturation variables relevant to the well-being outcomes (48–50). As the process of acculturation is multifaceted, the impact of a variety of factors (e.g., acculturative stress, internalizations of Western cultural values, acculturation variables) on one's well-being tends to be accumulative and the individual influence of each is hard to determine. Thus, more studies are needed encompassing diverse populations to advance the knowledge on the associations between immigration, acculturation and eating patterns, and to examine the unique ways of responding to culture change by each group.

Located on the crossroads of Eastern Europe and Western Asia, with a population of less than 4 million, Georgia is a small lower middle income country (51). After regaining independence in the 1990s, Georgia went through multiple wars and economic crises prompting large numbers of people to leave the country in search of economic prospects. With the oldest history of wine-making and a distinguished national cuisine, many cultural values of Georgia, including social interactions, revolve around eating and feasting (52–54). Overall, female beauty ideals tend to be pro-slimness. While EDs were considered non-existent in Georgia until the end of 20th century, later studies identified increased ED susceptibility (55, 56).

The Present Study

The study examined the links between immigrating to a Western country, the strategy of acculturation established and eating patterns. For the purposes of this study, Western encompasses the UK and the USA only. Under acculturation types, four strategies of acculturation were examined – integration, assimilation, separation, and marginalization (57). Under eating patterns, dietary restriction, eating concern, weight concern, and shape concern were examined. It was hypothesized that: a) females who immigrated from Georgia would exhibit more disordered eating patterns compared to nonimmigrants, and b) among those who immigrated, the acculturation strategy of integration would be associated with lowest risk/healthiest outcomes, and strategy of marginalization would be linked with the highest risk/the least healthy outcomes. Two hypotheses were tested for which quasi-experimental cross-sectional design and correlational analysis were used.

Based on the framework of the assessment of psychological acculturation (58), the variety of situational and individual factors

Abbreviations: ANOVA, Analysis of Variance; EAAM, East Asian Acculturation Measure; BMI, Body Mass Index; CFA, Confirmatory Factor Analysis; ED, Eating Disorder; EDEQ, Eating Disorder Examination Questionnaire; FDR, False Discovery Rate; MANCOVA, Multivariate Analysis of Covariance; MANOVA, Multivariate Analysis of Variance; SEM, Structural Equation Modeling.

of acculturation (acculturation conditions) impact migrants' home-country and new-country orientations (acculturation orientations), which, in turn, affect their psychosocial well-being (acculturation outcomes). In line with the above, the study also explored several demographic/acculturation variables and examined their links with both acculturation strategies and eating patterns. Overall, considering that our study sample was non-clinical and no cut-off values had been established for Georgian population, we refrain from making clinical judgments about EDs.

MATERIALS AND METHODS

Participants and Procedure

In total, 506 Georgian females aged 18–55 participated in the study. Among them were 253 women residing in the UK and the USA, and 253 were residing in Georgia (control group). Inclusion criteria for both groups were: female, aged 18–55, of Georgian ethnicity, born and raised in Georgia, and first language must be Georgian. Additionally, for the immigrant/sojourner group it was necessary for a participant to be residing in UK or USA for at least 6 months, while nonimmigrant participants must not have lived abroad (short stays excluded).

The selection method used was a combination of convenience sampling and snowball sampling. Since no unified database of Georgians residing in the UK or the USA existed, it was impossible to perform probability sampling. An electronic version of the survey was created and distributed among Georgians living in the US and the UK electronically. An extensive search was performed to locate corresponding communities, groups, individuals, and forums for posting and distributing the study link. Mail-outs were sent to The Society of British Georgians, The Georgian embassy in the UK, The Society of US-Georgians. Social media was also used. A similar recruitment process was applied to control (nonimmigrant) group: electronic version of survey was created and distributed among participants electronically. Nonimmigrant group survey did not include acculturation measurement. The survey was anonymous to encourage participation.

Data was first collected from immigrant/sojourner group and then from nonimmigrant/control group. Composition of the latter, as a matched group, was tailored to the age distribution of the former. The second sample consisted of 345 nonimmigrants, out of which 92 entries were removed and 253 remained with matched age group distribution. Inter-group equivalence was preserved with respect to education and marital status as well (see **Table 1**).

Measures

Demographics

Demographic variables for both immigrant and nonimmigrant groups included age, marital status, highest education achieved, employment status, height and weight. Body Mass Index (BMI) scores were calculated for all participants (see **Table 1**).

Additionally, for the immigrant group, information was gathered on a number of acculturation variables, including length of residence in the new country, age of relocating to the new country, current financial status, history of marriage with a representative of a mainstream culture (i.e., British or American), history of being undocumented (i.e., illegal immigration status), among others. These variables were regarded to have potential to influence the acculturation process and the individual's well-being. A few of them, such as length of residence and age of relocation, have been linked with both acculturation and ED outcomes in other studies (36, 39, 59, 60).

Acculturation Strategies

To measure acculturation strategies, the East Asian Acculturation Measure (EAAM) (61, Georgian translation Shekriladze, I., 2015) was used. EAAM is a four-dimensional self-report measure of acculturation with 29 statements on a 7-point Likert scale (e.g., "at home I usually speak English" or "Asians (in our case Georgians) should not date non-Asians (non-Georgians)") which measures the degrees of assimilation, separation, integration, and marginalization on corresponding four subscales. The tool consists of general statements examining one's cultural orientations (original vs host) that can be applied to any cultural group. Higher scores indicate higher degrees of corresponding acculturation strategies. The tool has been reported to have decent psychometric properties – Cronbach's alpha (by subscale) equals to.77/.76/.74/.85 respectively (61).

TABLE 1 | Descriptive data of participant demographics.

Group	Age (18–55)		Highest education obtained			Marital status				Body Mass Index		
	Mean	SD	Higher	Incomplete uni-vocational	High school or less	Single	Married	Divorced	Widow	Mean	SD	Percentage per category
Immigrant (N = 253)	41	8.31	224	23	6	47	159	36	11	24.12 range 30.37	4.71	3.6% < 18.5 61%-norm 23.1%-overweight 11.9%-obese
Nonimmigrant (N = 253)	41	8.64	234	15	3	51	158	33	11	24.94 range 29.54	5.44	6.8% < 18.5 48%-norm 27.6%-overweight 16.4%-obese

Total number of participants is 506.

The instrument was validated through Confirmatory Factor Analysis (CFA) (Structural Equation Modeling [SEM] in MPLUS software) and was slightly modified. Fit indices were as follow: $\chi^2 = 690.09$, df = 316, p = 0.000, RMSEA = 0.07, CFI = 0.81, TLI = 0.79. Cronbach's alpha amounted to 0.78 for assimilation subscale, 0.73 for separation subscale, 0.64 for integration subscale, and 0.82 for marginalization subscale (62). Initially developed for the East Asian population, the tool has been used to measure the links between acculturation strategies and eating patterns (45, 63). It has also been used to measure acculturation strategies of various cultures, including Eastern European (60, 64, 65).

Eating Patterns

The Eating Disorder Examination Questionnaire (EDEQ) (66, 67) was selected as a widely used measure of disordered eating patterns. This tool has previously been used with the Georgian population (55). It is a 36-item self-report measure that assesses individual's experiences within the last 28 days with answers on a 7-point scale from 0 to 6, in which 0 corresponds to never/no day and 6 corresponds to every day (e.g., "Have you been deliberately trying to limit the amount of food you eat to influence your shape or weight?", "have you tried to exclude from your diet any foods that you like in order to influence your shape or weight?"). It generates scores on four subscales – dietary restraint, eating concern, shape concern and weight concern – and a global score representing the mean of all subscale scores. Higher scores indicate more disordered eating psychopathology. The measure has shown good psychometric properties (66–68). Suggested clinical cut-off for the EDEQ global score is 2.3 (69).

Statistical Analyses

Data was analyzed using the statistical package IBM SPSS version 21.00. First, data was assessed for normality and for outliers. Several extraneous variables were controlled for, including BMI. Bivariate correlations were performed to explore the links between demographic variables (e.g., lengths of residence, age of relocation to a new country) and EDEQ/EAAM scores. Mean EDEQ scores were compared between immigrant groups based on immigration status and the history of marriage with the representative of a host culture (i.e., British or American). Mean EDEQ scores of immigrant and nonimmigrant groups were compared. Correlational and regression analyses were performed between immigrant acculturation strategies and EDEQ scores. Collinearity was checked between the acculturation strategies prior to conducting multiple regression analyses. In line with broader research examining the links between culture change and eating patterns, probability level of 0.05 was used in all statistical tests of significance. Nevertheless, we adjusted p-values using False Discovery Rate (FDR) method producing more conservative significance threshold at q = 0.01. Thus, we decided to deem probability levels of $p < 0.05$ marginal.

RESULTS

Participant Demographics and Their Links With Acculturation and Eating Outcomes

The immigrant group mostly consisted of adult females who moved to a Western country in their late twenties and had been residing there for about a decade. Fewer than 18% were under 30 years old and only about 20% of participants resided in a new country for the period of up to 5 years (10% – for the period of up to 3 years), whereas 80% had been living there for the period of 6+ years. More than a quarter of women reported being married to a British/American man, while one fifth reported experience of being undocumented (see **Table 2**). Nearly half (47.3%) of the participants reported having normal/average financial status.

Length of residence was found to have a statistically significant positive correlation with integration (r = 0.26, p = 0.000) and a statistically significant negative correlation with separation (r = −0.20, p = 0.001). Age of relocation was significantly negatively correlated with both assimilation (r = −0.20, p = 0.002) and integration (r = −0.24, p = 0.000). None of these variables, however, had any statistical significance in terms of ED outcomes. Therefore, they were not further analyzed as covariates.

Out of the categorical variables, it was speculated that history of being undocumented might have a negative impact with one's integration and well-being outcomes, whereas history of being married to a representative of mainstream culture might be linked with more favorable outcomes.

Analysis of variance (ANOVA) was used to examine differences with respect to acculturation strategies, eating patterns and BMI of immigrant women with a history of being undocumented and those without such a history. Comparisons showed no significant differences with respect to acculturation strategies or eating patterns (although the tendency was for all mean EDEQ scores to be higher for women with the history of being undocumented); however, the mean BMI of women with the history of illegal immigration status appeared markedly

TABLE 2 | Demographics of immigrant group.

Variables	Mean	Median	SD	Minimum	Maximum	N
Age of relocation	29.43	29	7.47	10	54	
Length of residence	11.56	12	6.30	0.6	25	
Body Mass Index	24.12	23.24	4.71			
Resides in UK						105
Resides in USA						148
Married to British/American						67 (26.5%)
Undocumented						50 (20%)

Total number of participants is 253.

higher (M = 25.86, SD = 4.59) than of those with no such history (M = 23.69; SD = 4.87; F (1, 249) = 8.59, p = 0.004, $\eta^2 = 0.03$).

Furthermore, ANOVA was used to compare acculturation and EDEQ outcomes of immigrant women with the history of being married to British/American and those without such a history. The comparison yielded between-group differences in some EDEQ outcomes, as well as assimilation, separation and integration scores (see **Table 3**). More specifically, women who had a history of marriage with the representative of mainstream culture, showed marginally lower (i.e., healthier) EDEQ weight concern and global scores than those with no such history. Furthermore, they scored significantly lower on the EAAM separation and had higher integration and significantly higher assimilation outcomes compared to women with no such history. In other words, women with a history of being married to British/American, showed somewhat more favorable eating patterns and higher host culture orientation.

Immigration and Eating Patterns

We expected EDEQ scores to be higher among immigrant/sojourner population compared to nonimmigrant group due to the experience of immigration to Western countries. Eating patterns were measured by 5 scores – dietary restriction subscale, eating concern subscale, shape concern subscale, weight concern subscale, and global score.

Even though we do not consider it appropriate to apply the recommended cut-off value of 2.3 of EDEQ global score to our sample, we still checked how many participants in each group scored higher just for the purposes of shedding light on the distribution of extreme eating patterns. Findings showed that EDEQ global scores of 33.2% (84) of immigrants and 31.6% (80) of nonimmigrants exceeded the recommended cut-off value with rather similar distribution of the data in the two groups.

Comparisons of the two groups were performed by one-way between-groups Multivariate Analysis of Variance (MANOVA), which showed notable difference between the EDEQ restriction scores (F (1, 504) = 6.27, p = 0.013, partial η2 = 0.012) only and marginal difference between EDEQ eating concern scores (F (1, 504) = 4.03, p = 0.045, partial η2 = 0.008), with the former being higher among immigrants, and the latter being higher among nonimmigrants. It should be noted though that nonimmigrant group had marginally higher mean BMI (24.94) than immigrant group (24.12). To ensure the equivalence of the groups, BMI as a confounding variable was controlled. Before checking links between BMI and EDEQ scores, the linearity of their relationship was checked. BMI appeared significantly correlated with all the EDEQ outcomes (r = 0.27, r = 0.39, r = 0.55, r = 0.50, r = 0.51, n = 504, p < 0.001 in all cases) and thus linearity was observed.

Next, a multivariate analysis of covariance (MANCOVA) with BMI as a covariate was performed, which showed that the marginal difference between the two groups with respect to eating concern disappeared (it appeared to be explained by BMI), whereas the difference with respect to dietary restriction became stronger (see **Table 4**). In other words, as immigrant group with lower BMI produced a higher restriction score than nonimmigrant group with higher BMI, the deference between the groups' restriction scores became more important. Thus, for Georgian women, moving to Western countries for a prolonged period increased dietary restriction. Hence, in the context of EDEQ outcomes, moving to the West appeared to affect only one out of five EDEQ subscales: restriction of food intake. The global EDEQ scores of immigrant and nonimmigrant groups, however, were almost identical.

Since EDEQ cut-off values had not yet been established for Georgian women, no clinical judgments were made about disordered eating. Although the norms of our study groups (both immigrant and nonimmigrant) were markedly higher than UK (66) and Australian (70) community norms, we did not deem appropriate to make comparisons neither from cultural, nor from an age perspective.

Acculturation and Eating Patterns

Among immigrant/sojourner population, we expected the strategy of acculturation with the mainstream culture to be linked with eating patterns: namely, integration associated with the lowest EDEQ scores (most favorable patterns) and marginalization with highest EDEQ scores (the least favorable outcomes).

Correlational Analyses

Bivariate correlations between the strategies of acculturation and EDEQ scores were performed through controlling BMI as a confounding variable. Prior to correlational analyses,

TABLE 3 | Links between the history of marriage with British/American, acculturation, and EDEQ outcomes.

	Married to local		Not married to local		*F (215)*	η^2
	M	*SD*	*M*	*SD*		
Food restriction	1.57	1.55	2.00	1.58	3.61	0.01
Eating concern	0.55	0.90	0.85	1.10	3.84	0.01
Shape concern	2.12	1.48	2.50	1.73	2.57	0.01
Weight concern	1.72	1.43	2.21	1.65	4.70†	0.01
Global score	1.49	1.11	1.89	1.30	4.97†	0.01
Assimilation	3.48	1.22	2.86	1.26	12.25***	0.04
Separation	2.56	0.88	3.38	1.24	24.36***	0.08
Integration	5.68	0.97	5.26	1.19	6.89**	0.02
Marginalization	2.22	1.08	2.38	1.18	0.953	0.00

$^{***}p < 0.001$, $^{**}p < 0.01$, $^{\dagger}p < 0.05$.

TABLE 4 | EDEQ scores of immigrant and nonimmigrant groups.

EDEQ scores	Group ID	M	SD	N	MANCOVA *F*	Partial η^2
EDEQ Restriction score	Immigrant	1.89	1.59	253	7.53**	0.02
	Nonimmigrant	1.55	1.50	253		
EDEQ Eating concern score	Immigrant	0.78	1.06	253	2.45	0.01
	Nonimmigrant	0.97	1.10	253		
EDEQ Shape concern score	Immigrant	2.40	1.68	253	0.43	0.00
	Nonimmigrant	2.50	1.61	253		
EDEQ Weight concern score	Immigrant	2.08	1.61	253	0.15	0.00
	Nonimmigrant	2.03	1.56	253		
EDEQ Global score	Immigrant	1.79	1.27	253	0.06	0.00
	Nonimmigrant	1.76	1.19	253		

***p < 0.01.*

the linearity of the relationship between BMI and EDEQ scores was checked. Immigrant group BMI appeared significantly correlated with all the EDEQ outcomes (r = 0.22, r = 0.37, r = 0.55, r = 0.49, r = 0.49, n = 251, p < 0.01 in all cases), and thus linear relationship was observed.

Correlational analyses showed that marginalization and separation appeared to have strong statistically significant positive correlations with eating concern, shape concern, weight concern, and global scores. Integration appeared to have marginal negative correlations with eating concern and shape concern outcomes (see **Table 5**). No correlations were identified between EDEQ restriction concern and any acculturation strategy. The strategy of assimilation was not linked with any EDEQ score either.

Regression Analyses

Finally, multiple regression analyses were conducted to examine the extent to which the different acculturation strategies may predict unhealthier eating in our sample. For each of four EDEQ outcome, a stepwise selection method was used to enter BMI and acculturation scores into the model. The results of regression analysis showed that separation and marginalization strategies were linked with EDEQ eating concern, shape concern, weight concern and global scores. Out of the two, marginalization was linked mildly, while separation showed stronger links (see **Table 6**). No associations were identified between integration and eating and shape concern scores.

Thus, regression analysis further showed that two strategies of acculturation, separation and marginalization — can be considered predictors of higher EDEQ scores on four out of five EDEQ subscales, with separation having strongest predicting value.

TABLE 5 | Correlations between EAAM acculturation scores and EDEQ Outcomes.

EDEQ outcomes	Marginalization	Separation	Integration	Assimilation
EDEQ eating concern	0.30***	0.30***	–0.14†	0.06
EDEQ shape concern	0.26***	0.27***	–0.16†	–0.04
EDEQ weight concern	0.24***	0.28***	–0.07	0.01
EDEQ global	0.26***	0.27***	0.30	0.02

****p < 0.001, †p < 0.05; N = 253.*

Summary of Results

In summary, the findings on the links between immigration, acculturation strategies and eating patterns of Georgian immigrants showed that: (a) moving to a Western country appeared to increase restriction of food intake; (b) while living in a Western country, acculturation strategies of separation and marginalization were associated with higher eating concern, shape concern, weight concern and global scores of EDEQ (**Figure 1**); in addition, history of marriage with a representative of host culture was linked with higher host culture orientation and lower EDEQ scores.

DISCUSSION

Acculturation Conditions

Length of residence, education, cultural distance and expectations were reported to be important factors in adjustment by various prominent acculturation researchers (71–73). Consistent with above evidence, in a present study, both length of residence and early relocation age have been correlated with higher levels of integration. They were not linked with eating patterns.

Surprisingly, history of being undocumented (illegal status) as an acculturation condition generally impeding one's integration into society of settlement, was not linked with acculturation strategies or poorer scores in EDEQ. It was, however, associated with higher BMI. On the other hand, history of marriage with a representative of mainstream Western culture, as an acculturation variable evidently facilitating one's integration, was associated with higher host culture orientation and somewhat healthier eating outcomes.

It needs to be recognized that the cases of the USA and the UK, as societies of settlement, might be different from other Western countries in many ways (from one another as well) and, therefore, while formulating interpretations, it is important to avoid generalizations to all "Western" world, especially when the characteristics of the society of settlement have not been duly explored.

TABLE 6 | Stepwise regression analysis results of EDEQ outcomes and EAAM acculturation scores.

Model	Eating concern	β	T
1	BMI	.37	6.34***
2	BMI	.35	6.32***
	Separation	.22	3.46**
	Marginalization	.15	2.38*
Model	**Shape concern**	**β**	**T**
1	BMI	.55	10.64***
2	BMI	.53	10.67***
	Separation	.16	2.84**
	Marginalization	.14	2.39*
Model	**Weight concern**	**β**	**T**
1	BMI	.49	8.89***
2	BMI	.46	8.79***
	Separation	.21	3.58***
	Marginalization	.13	2.08*
Model	**Global EDEQ score**	**β**	**T**
1	BMI	.49	8.87***
2	BMI	.46	8.83***
	Separation	.20	3.35**
	Marginalization	.15	2.46*

$^{***}p < 0.001$, $^{**}p < 0.01$, $^{*}p < 0.05$.

Culture Change and Eating Patterns

The results of the present study on the links between immigration, acculturation and eating patterns can generate significant new insights. Putting together the findings of comparisons of immigrant vs nonimmigrant groups, on the one hand, and within-immigrant group (based on their acculturation strategies or other variables), on the other, allows us to see a bigger picture.

Our findings allowed us to conclude that higher dietary restriction (the only difference between immigrant and nonimmigrant groups out of five EDEQ indicators showing statistical importance) among immigrants could be attributed to moving to the West. It is questionable, however, whether increased restriction is a manifestation of eating pathology (as it did not affect EDEQ global score). Furthermore, based on the findings, eating concern, shape concern, and weight concern, can go up if individual applies separation or marginalization strategies of acculturation. In other words, restriction (behavioral by nature) is increased for all immigrants/sojourners irrespective of their acculturation strategies, whereas eating concern, shape concern and weight concern (all cognitive by nature) tend to go up when individual strategy of acculturation implies lack of integration in a host culture (low host culture orientation) (see **Figure 1**). The importance of integration into mainstream society with respect to healthy eating is further strengthened by additional findings linking the history of marriage with a representative of host

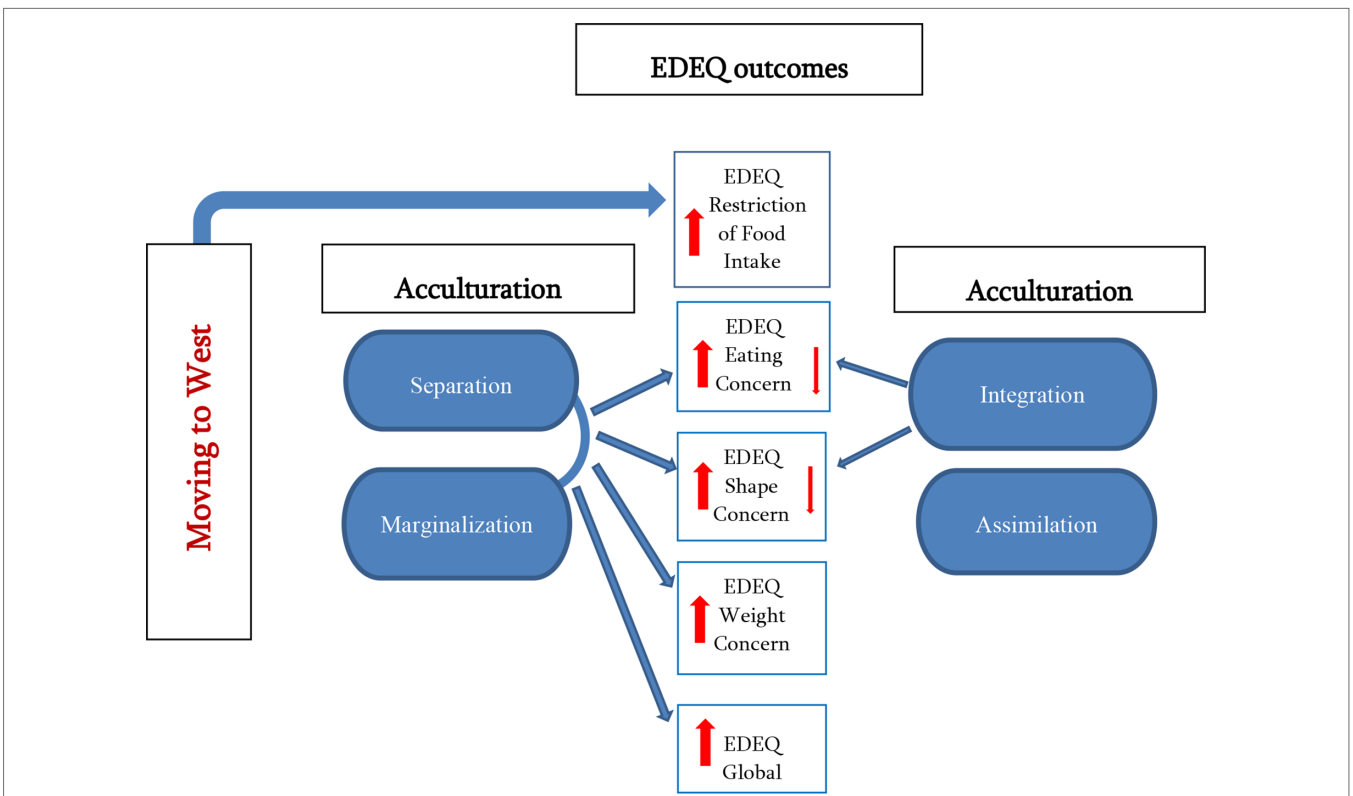

FIGURE 1 | Links between moving to West, acculturation strategies and five eating pattern indicators (EDEQ outcomes). **Moving to West** linked only with restriction of food intake; **Separation** and **marginalization** considerably linked with eating concern, shape concern, weight concern and global EDEQ outcomes; **Integration** mildly linked with eating concern and shape concern outcomes; **Assimilation** not linked with any EDEQ outcomes.

culture with higher host culture orientation and more favorable eating outcomes.

Based on the findings, we might speculate that Western context puts more restrains on food intake as opposed to Georgian context, thereby contributing to increased dietary restriction for all. On the other hand, taking into consideration the fact that the nonimmigrant sample had a higher number of participants with out-of-normal BMI, we might also envisage elevated restriction among immigrants as a means of ensuring more normal BMI (presumably due to the higher emphasis on healthy eating more prevalent in the West than in Georgia). Nevertheless, BMI could not explain the differences in EDEQ scores between immigrant and nonimmigrant groups; neither could it explain the links between EDEQ and acculturation strategies, as it was controlled as a covariate in both cases. Thus, the findings allow us to pinpoint the higher predicting value of a lack of integration in the society of settlement in developing higher eating, shape, and weight concerns among Georgian sample. In other words, it is not moving to the West per se that can contribute to unhealthier eating, but maintaining the low host culture orientation in a new country of residence (**Figure 1**).

Immigration

Overall, our findings were consistent with the evidence supporting minor or no differences between ED vulnerability of immigrant and nonimmigrant populations (44–47). Nevertheless, the reasons for generating such findings might be sample specific. First of all, multiple studies have shown that most people integrate after a certain period of time (20, 74, 75), while acculturative stress and culture shock are highest during the initial periods of firsthand contact with another culture [(57, 59, 76); Oberg, as cited in Ref. (71)]. In addition, it is recognized that forced migration and uprooting complicates psychological well-being of migrants (22), while voluntary migration in search of a better future is associated with favorable adjustment outcomes (Richmond, as cited in 71). Considering above, our sample is in an advantageous position: it consisted of relatively veteran (6+ years) immigrants, as average length of residence was 11.5 years, who by the time of our study had presumably adjusted one way or another. Besides, for this sample, relocation to Western countries was a preferred choice in search of economic and life prospects. Had there been different composition of participant length of residence and different circumstances of relocation, the outcomes might have differed as well.

Some research evidence suggests that the higher the distance between home and host cultures, the stronger the acculturative stress and the poorer the well-being outcomes (25, 77, 78). Culture encompasses what constitutes culinary and mealtime traditions as well as esthetic ideals. Even though, on average, Georgians eat more than Europeans, Georgian mealtime sequence (breakfast, lunch, and dinner) as well as most culinary ingredients are similar to European and slimness is admired in females. Therefore, as certain similarities and slender beauty ideals are present, the impact of cultural clash caused by internalization of Western habits and beauty standards may not be as dramatic as in case of some other groups examined in ED research. Its relative cultural proximity to contemporary Western world may play part in lowered risks of disordered eating.

In addition, Georgians, as invisible minorities, publicly may be perceived as representatives of mainstream culture, which gives them a considerable advantage over some other immigrant groups that have been popularly studied in the field of acculturation and EDs (e.g., Chinese, Africans, East Asians). Studies show that being a visible minority is associated with higher perceived discrimination and poorer adjustment outcomes (24, 79), including ED patterns (80).

Thus, to summarize, our findings suggest that prolonged residence in Western countries is associated with increased dietary restriction among Georgian women. This, however, may not be necessarily a manifestation of disordered eating. Variety of sample-specific factors, such as, longer length of residence, voluntary immigration, being white, and Christian, and less dramatic distance between cultures are speculated to have played protective functions making the process of acculturation less stressful. These variables have been linked with higher levels of integration and better well-being outcomes in other studies [Richmond as cited in Refs. (25, 71, 81)].

Acculturation

Our findings were consistent with studies linking unhealthier eating with lower levels of acculturation to the host culture (33–36). Namely, in case of Georgians, a weak mainstream-culture orientation, as a common feature of separation and marginalization strategies, appeared to predict higher EDEQ scores, thereby making strong mainstream-culture orientation a protective factor (**Figure 1**). These findings also corresponded to evidence of a meta-analysis on acculturation and mental health showing that orientation to mainstream culture was linked with favorable adjustment outcomes (82, 83) and lower levels of depressive and anxiety symptoms (84). Likewise, in 2014 study on 7,000 Canadian immigrants, Berry and Hou (75) found that both integration and assimilation strategies were linked with the highest scores of life satisfaction, whereas separation and marginalization were associated with significantly lower scores.

Nevertheless, perhaps the most important finding of the study was that, unlike Berry's model, separation was associated with higher EDEQ outcomes than marginalization, representing the strongest predictor of elevated eating, weight, and shape concerns (and EDEQ global score), whereas assimilation was not at all linked with disordered eating. While marginalization is generally regarded the least favorable strategy of acculturation (20, 25, 84, 85), the reasons why in the present study it was outweighed by separation might be context specific.

While separation strategy is a natural reaction on culture change at the initial stages of immigration, one might speculate that after years of living in another country, it might be indicative of serious internal or external difficulties of adjustment. In contrast to separation, marginalization as a condition that implies cultural identity confusion, might be more natural after spending a substantial period away from one's home as opposed to early stages of relocation. Moreover, in the long term, assimilation may turn into another conventional and authentic acculturation strategy and, as demonstrated by our findings, linked with favorable outcomes. Therefore, it might be argued that acculturation is a dynamic

process (25, 86) and it is time and stage-specific which strategy of acculturation is most appropriate for an individual or group.

Furthermore, as some researchers argue, different acculturation strategies might work in different contexts (82, 87) as context-specific characteristics may determine which acculturation strategy is most relevant. For instance, separation might be natural and even externally driven option for representatives of cultures/nations with big communities in the societies of settlement, such as the US Latin American populations, who have huge Spanish-speaking communities. In contrast, Georgians are few and scattered in the US and UK and do not necessarily enjoy strong ties with their ethnic population. Thus, for our sample with average length of stay of 11.5 years and 80% of participants living in a new country for 6+ years, to carry on a separation strategy after years of relocation may indeed entail considerable adjustment difficulties, isolation and inability to live in the present (e.g., excessive reminiscing about old times in the country of origin and/or excessive dreaming about returning to the home country), all contributing to the least favorable EDEQ outcomes.

Summary

To conclude, the findings on the links between immigration, acculturation and eating patterns of Georgian women showed that dietary restriction is increased for all immigrants/sojourners regardless of their acculturation strategies, whereas eating concern, shape concern, and weight concern go up when individual's strategy of acculturation implies lack of integration in a host culture (low host culture orientation). Hence, our evidence suggested that a weak host culture orientation may be considered as a risk factor of unhealthier eating, thereby reiterating critical value of immigrant integration into mainstream culture with respect to dietary health and potentially better overall well-being. The results also supported that acculturation is a very multifaceted process affected by a number of acculturation conditions (e.g., arrival age, length of residence, etc.) among which, history of marriage with the representative of a host culture was linked with higher host culture orientation and more favorable eating behaviors. Since a variety of acculturation conditions are related with how people adjust to new cultures and how their psychosocial functioning proceeds, determining the impact of culture change should entail a comprehensive approach addressing acculturation attitudes/behaviors, well-being outcomes, and major acculturation variables.

LIMITATIONS AND FUTURE DIRECTIONS

The main limitation of the study was sampling bias due to the impossibility of probability-sample that limits the generalizability of findings. Our study could not be free of limitations associated with self-report e-surveys. Despite friendly instructions, inaccurate completions are possible.

In addition, fewer than 18% of the sample were under 30 years old and only 20% of our sample appeared to be residing in a new country for 5 or less years. Thus, the findings cannot be generalized to a younger age group during which typically EDs emerge, or to a newly relocated. Therefore, it would be valuable for future studies to target younger and newly relocated groups of Georgian immigrants/sojourners and examine their response to culture change and acculturative stress.

Furthermore, the study could not explore potential comorbidities and the variety of important acculturation variables potentially affecting well-being outcomes, such as, command of a language of a host country, ties with original culture and characteristics of the society of settlement (e.g., perceived discrimination, food industries, etc.). Future direction of research might look at the differences between the countries of the so-called Western world, including British and American, examining the above characteristics.

Another important future research direction might be looking more closely at immigrant and nonimmigrant samples with regards to eating patterns and elaborating on why behavioral (dietary restriction) pattern appeared universal for immigrant group in terms of being elevated and the cognitive ones (eating concern, shape concern, weight concern) – subjected to conditionality (only in cases of lower mainstream culture orientation).

Finally, our findings suggested that for Georgian women who have been residing in a Western country for 6+ years having high host culture orientation is important with respect to healthier eating patterns. As culture change is a very multifaceted process, duly examining variety of factors (e.g., circumstances of relocation, cultural distance between original and host cultures, social support, etc.) that shape the adjustment and well-being outcomes, including eating patterns, seems essential for seeing a bigger picture.

DATA AVAILABILITY

The datasets generated for this study are available on request to the corresponding author.

ETHICS STATEMENT

Study ethics (03-11563/15) permission was obtained from Ilia State University Ethics Committee, in line with the Declaration of Helsinki, providing for the rights of participants, including anonymity of individuals and their data protection.

AUTHOR CONTRIBUTIONS

IS carried out the study, performed the analysis and drafted the manuscript. NJ took part in the data processing and analysis. KT was the lead supervisor of the study helping with the recruitment, training, design and write-up, and editing the manuscript. All authors provided feedback and contributed to the final manuscript.

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The Fear of Losing—Nonsuicidal Self-Injury as a Protective Mechanism in Eating Disorders

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Background: This study examined the moderating role of loss aversion (LA) on the relationship between impulsivity, nonsuicidal self-injury (NSSI), suicidal attempts, and ideations among Eating Disorder (ED) patients.

Methods: Data was collected on 81 ED patients and 37 healthy controls. ED patients were divided into 2 groups: 25 AN-Rs, 56 AN-BPs and BNs. Measurements of trait impulsivity, LA, NSSI, suicide attempts, and suicide ideations were collected.

Results: The rate of attempting suicide was highest in the AN-BP/BN (34.8%), lower in the AN-Rs (8%), and the lowest in the controls (2.7%). Suicide ideation was also higher in AN-BP/BN compared to both AN-R and controls. NSSI was higher in the AN-BP/BN group compared to both AN-R and control groups. LA scores were lower among participants with EDs compared to controls. BMI and depression were positively associated with suicide ideation and NSSI. Impulsivity was associated to suicide attempt and suicide ideation. Contrary to our hypothesis, LA scores were positively correlated with NSSI and SI. A stepwise regression revealed that contradictory to our hypothesis, higher LA predicted NSSI prevalence severity of NSSI and suicide ideation.

Limitations: (1) Cross-sectional design; (2) Relatively small sample size of clinical subjects and only female participants; (3) Heterogeneity of treatment status.

Conclusions: EDs are associated with lower levels of LA compared to general population. Although high LA is considered a protective factor against "high damage" decisions, it may serve as a facilitator of lower risk decisions which help the individual soothe and communicate his or her own suffering such as NSSI.

Keywords: eating disorder, anorexia, loss-aversion, impulsivity, nonsuicidal self-injury, suicidal behavior

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INTRODUCTION

Eating disorders (EDs) are a serious public health problem with long-term effects on physical and mental health (1). Its prevalence ranges between 2–4% (2). Self-harm behaviors, including nonsuicidal self-injury (NSSI) (3), completed suicide (4, 5), and suicide attempts (6, 7) are considered common in individuals with EDs.

Anorexia nervosa (AN) of the restrictive (AN-R) and binge–purge subtypes (AN-BP), and bulimia nervosa (BN) have common neurobiological mechanisms (8, 9). Yet challenges arise when attempting to discriminate between AN and BN using contemporary classification methods (i.e., Diagnostic and Statistical Manual of Mental Disorders, 5th edition; International Statistical Classification of Diseases and Related Health Problems, 10th revision), which rely on observable symptoms [e.g., body mass index (BMI)] and behaviors (10, 11), due to similarities in these diagnoses. While an AN-BP patient may be much closer in nature to a BN patient than a AN-R patient, he or she may be given the same diagnosis as an AN-R patient. The need to find a more effective way to diagnose and differentiate between AN and BN patients accords with the novel approach proposed by the United States National Institute of Mental Health, which aims to find a framework beyond categorical and symptom-based approaches (12–14).

Studies on impulsivity and EDs have suggested impulsivity as a potential transdiagnostic concept (15, 16) that may facilitate a better understanding of psychological profiles in EDs. Impulsivity can be conceptualized as either a stable state or a dynamic-temporal state (17–19). Several studies have found impulsivity to be a key behavioral characteristic among individuals with EDs, in general (20–23), and particularly in AN-BP and BN patients who report higher percentages of impulsive behavior compared to AN-R patients (24, 25, 15, 26). Moreover, studies show that patients who exhibit binge–purge behaviors are more inclined to present other impulsive behaviors as well as emotional swings and emotional disturbances compared with those who do not exhibit binge–purge behaviors (27, 28). Impulsive behaviors such as bingeing and purging are often attributed to an escape mechanism adopted to evade an unpleasant situation (29). Various studies have shown impulsivity to be a major risk factor in carrying out NSSIs and suicide attempts (30, 31).

NSSI is defined as self-inflicted harm to one's body (e.g., cutting, incising, burning) without the intent of suicide (32). NSSI is associated with a history of childhood abuse, emotional overreaction, difficulty in problem solving, and communication difficulties. It is considered a coping strategy to gain control over impulses, affect regulation, interpersonal communication when previous attempts have failed, and self-punishment resulting from self-criticism or externalization (33). A functional approach suggests that self-harm is sustained by negative intrapersonal reinforcement (avoiding and deflecting emotions and negative thoughts), positive intrapersonal reinforcement (producing desired emotions or stimuli), negative interpersonal reinforcement (escaping and avoiding undesirable social situations), and positive interpersonal reinforcement (eases the ability to ask for help) (33, 34).

A recent meta-analysis found that 27.3% of individuals with an ED had a history of NSSI. Among those suffering from AN, prevalence of NSSI was 21.8%, while among those suffering from BN, the prevalence was 32.7% (3). Among ED patients who exhibit binge or purge behavior, there was a significantly higher number of self-injury symptoms than other ED patients (35). Research also suggests that self-harm is correlated with self-reporting impulsivity (36). Among ED patients, 38.9% reported at least one type of NSSI (37).

NSSI is closely related to suicidal behavior, which is defined as an act of intentionally ending one's own life (38, 39). Suicide may be preceded by suicidal ideation, threats, and gestures, nonsuicidal self-injuries, and suicide attempts with various degrees of lethality (40). According to the National Association of Anorexia Nervosa and Associated Disorders, EDs have the highest mortality rate of any mental disorder. Given that both suicidal behaviors and EDs are body-focused disorders, over the past decade, many studies have turned to investigate their co-occurrence (30).

While personality assessment tools can help characterize individuals who fit the impulsive trait profile, the existence of additional manifestations of impulsivity oblige clinicians to seek out alternative methods to define and measure impulsive tendencies and behaviors. The process underlying these attempts is studied through models of decision-making (41, 42). People suffering from AN or BN turn to food or refuse food intake for reasons that are unrelated to their nutritional needs. Such decisions can be attributed to faulty decision-making patterns. ED symptomatology comprises a variety of behaviors, such as bingeing, purging, fasting, or self-injury, that lead to immediate satisfaction despite their long-term adverse effects. These behaviors have been shown to be related to a specific component of decision-making, namely delayed discounting (43, 44), which describes the substantial overvaluation of immediate, as opposed to delayed, rewards. Another well-known bias that influences decision-making processes is loss aversion (LA). Human beings are driven by the avoidance of losses rather than by procuring equivalent gains. This universal behavioral pattern was described by (45, 46) who demonstrated that the subjective impact of losses appears to be roughly twice that of gains in human subjects. The pervasiveness of LA has been found in many empirical studies (47), and has been evaluated by having participants gamble a certain amount of money on the outcome (win or lose) of tasks they perform (e.g., 48, 49). The extent of potential gains and losses are then varied for each gamble, and participants are asked if they are willing to gamble.

The literature on the association between LA and EDs is very scarce. Moreover, to the best of our knowledge, a comparative study of LA in the different subtypes of AN and BN has yet to be conducted, although we can infer from previous studies that individuals with AN-R made less risky choices on the Balloon Analogue Risk Task compared with healthy controls (50). Chan et al. (51) found that individuals with BN show greater relative sensitivity to gains as opposed to losses on the Iowa Gambling Task, when compared to a group of AN patients and healthy controls. Research in the field of skin conductance responses in ED patients (52) has shown that prior to choosing cards on the Iowa Gambling Task, patients with AN had decreased anticipatory skin conductance responses compared to a group of recovered anorexics and a healthy control group, thereby suggesting that they were less anxious about aversive outcomes.

Although previous studies have made major contributions to the understanding of NSSI and suicidal behavior among

ED patients, to the best of our knowledge, so far, no work has examined the association between decision-making processes and self-harm behaviors in ED patients, in general, and the moderating role of LA, in particular. Intuitively, it is reasonable to assume that individuals with a greater aversion to potential loss (e.g., body pain, long-term or irreversible damage to the body, scarring as a result of cutting, health risks, hospitalization, sorrow inflicted on family, etc.) would find the options of either NSSI and suicide less advantageous. On the other hand, in cases in which the potential gains of NSSI or suicide (ceasing pain, anxiety, and fear) are evaluated as higher than the potential losses, either act will be carried out. The clinical presentation of AN-R, as characterized by more rigidness and less impulsivity compared to AN-BP and BN, suggests that there may be an underlying cognitive bias of higher sensitivity to potential negative outcomes (losses) than positive outcomes. On the other hand, the clinical presentation of individuals with AN-BP and BN, as characterized by more impulsivity, suggests that there may be an underlying bias of a lesser sensitivity to potential negative, rather than positive, outcomes (losses).

In this study, we aimed to investigate the moderating role of LA in the association between impulsivity and self-harm behavior (NSSI and suicidal behavior) among ED patients. Consequently, we aimed to examine several hypotheses: first, we hypothesized that EDs of the AN-BP and BN groups will score higher on impulsivity, NSSI, and suicide attempts and ideation compared to AN-R and healthy controls. Second, we hypothesized that higher measures of LA will be displayed in the AN-R subjects compared to AN-BP and BN subjects, while healthy controls will display higher measures of LA compared to the research group. Third, we hypothesized a negative association between LA, NSSI, and suicide attempts among ED patients, and that the effect of LA will increase the risk of suicide attempts and NSSI among these patients, over and above the contribution of diagnosis, depression, BMI, and impulsivity.

METHOD

Study Sample

The study described in this report refers to patients with a current diagnosis of AN or BN being treated at the department for EDs in adults in a general hospital. A control group of students from Bar Ilan University was recruited. All 132 subjects were women who were divided into two groups: 93 clinical subjects and 39 healthy controls. Out of the EDs group, 12 were excluded from this study due to an irrelevant diagnosis or a failure to meet all the inclusion/exclusion criteria. ED patients were divided into two groups, the first group was made out of 25 subjects diagnosed with AN-R. Due to the previously mentioned similarities between the AN-BP and BN populations, and in line with recent literature (14), we combined 30 subjects diagnosed with AN-BP and 26 subjects diagnosed with BN into a single binge/purge group of 56 subjects. Four subjects out of the ED group and one subject out of the controls did not complete the behavioral task measuring LA due to administration difficulties.

Measures

Diagnosis

The psychiatric diagnoses were given by clinicians who interviewed the subjects in an intake session to assess suitability for treatment. Diagnoses were based on Diagnostic and Statistical Manual of Mental Disorders, 5th edition, criteria and excluded comorbidity with other non-ED diagnoses.

Self-Rating Questionnaires

A variety of questionnaires were used to capture demographic information, traits, states, and suicide attempt characteristics.

Demographics

Information on age, country of birth, marital status, number of children, type of residence (urban/rural), years of education, employment status, psychiatric medication, psychotherapy treatment, and attention-deficit/hyperactivity disorder (ADHD) diagnosis was collected from the participants by self-report.

Suicide Attempts

Past suicide attempts and their severity were assessed by the Suicide Behaviors Questionnaire developed by Osman et al. (53). Composed of four items, each tapping a different dimension of suicidality, items are scored on a 5- to 7-point scale and are summed up to an aggregate score. Reliability scores of the original questionnaire range between 0.87–0.88 in adolescents and 0.76–0.87 in the adult population. The Suicide Behaviors Questionnaire instrument was translated to Hebrew for research purposes by way of double translation.

NSSI

A modified version of the Deliberate Self-Harm Inventory (54) was used to assess engagement in self-injurious behaviors. This self-report questionnaire addresses six different self-injury items: cutting of the body, self-burning, carving into the skin, preventing the healing of wounds, and banging the head against hard objects. An additional item assessed whether the injury was severe enough to require medical treatment. Items were followed by 0–3 Likert scales for rating the frequency of each behavior; ranging from 0 ("never") to 3 ("five times or more"). The total score was calculated as a mean of the six items. The updated version of this instrument was translated into Hebrew [71]; in the current research reliability was found to be 0.83.

Depression

Depression was screened by using the depression module of the Patient Health Questionnaire. This questionnaire is based on DSM-IV criteria for major depressive disorder and includes nine items, each scored on a three-point scale (0 = "not at all" to 3 = "nearly every day"). Total scores of 5, 10, 15, and 20 have traditionally represented cut-off points for mild, moderate, moderate–severe, and severe depression, respectively. A score of 10 has been used as a cut-off point for an indication of a positive screening for clinical depression [73]. Values of reliability in previous research were found to be 0.89 and 0.84 and test–retest

reliability was 0.84 [73]. In the current study, reliability was found to be 0.82.

Impulsivity

Impulsivity was measured by the Barratt Impulsiveness Scale (BIS-11: 55; BIS-11-A: 56) which is comprised of the scores of three separate constructs: attentional, motor, and nonplanning, and an additive score. The Hebrew BIS-11 has been found to have adequate reliability (a = 0.79, 57). In this study, reliability was found to be 0.85.

Loss Aversion

A behavioral procedure was used to assess LA based on the procedure introduced by Sokol-Hessner et al. (58). Each participant was exposed to a series of 90 trials in each of which they were instructed to choose either a risky or riskless option. The risky option constituted a gamble with a 50:50 chance of winning or losing a certain amount of money, whereas the riskless option was a choice of neither winning nor losing ($0). For example, a participant could be instructed to choose between a 50% chance of winning $40 (and 50% chance of winning nothing) or a guaranteed choice of $0. LA was estimated for each participant by calculating the mean loss/gain ratio for the accepted gambles in the entire task. The higher average ratio reflects a higher preference for a "lower but safer" (i.e. more averse to losses) choice, whereas a lower ratio reflects a tendency to ignore the potential losses and choose the gamble (i.e. less averse to losses).

Procedure

The study was conducted in accordance with the 1989 revised Helsinki Declaration and received International Review Board approval from the medical center involved in the study. All participants in the clinical group were recruited during a 24-month period (March 2016–January 2018), were 18 years old or older, and had active ED diagnosed by a certified clinician. Patients were excluded from the study if they were suspected to be in a psychotic state, if they had a BMI lower than 12, due to a possible cognitive impairment, or if they had other cognitive impairments or language difficulties that did not allow for the independent completion of the study assignments. Candidates were identified by the medical staff to ensure their suitability for the study. They were approached by research assistants (M.A. level) who explained the aims and purposes of the project, and were asked for their written consent to participate. The interviews and questionnaires were each administered over the course of a hour-long session. If a patient demonstrated acute distress, the interviewer requested assistance from the medical staff. Participants in the healthy control group were students with neither psychiatric diagnoses nor histories of ED related behavior who volunteered to participate in the research as part of completing their graduate degree requirements.

Data Analysis

Statistical analysis was performed using SPSS software, version 23. Group differences in demographic and medical variables were explored using ANOVA, followed by Bonferroni post-hoc tests, t-tests, $\chi 2$ for independence, Fisher's exact test, and Kruskal–Wallis's test in accordance with the variables' scales. The relationships between EDs, suicidality, and self-injury were explored using ANOVA, followed by Bonferroni post-hoc tests. EDs, LA, and impulsivity were explored using ANOVA followed by Bonferroni post-hoc tests. Predictors of suicidality and self-injury among ED patients were discovered using Pearson correlations. Finally, linear and logistic regression analyses for the prediction of suicidality and self-injury among two groups of ED patients were conducted.

RESULTS

Participant Characteristics

Participants in all study groups did not differ in terms of marital status, occupation, and age. Significant differences were found in level of education, psychiatric medication, psychotherapy, ADHD, and depression. As demonstrated in **Table 1**, participants from the control group were more educated, less depressed, and had a lower probability of ADHD, psychiatric medication, and psychotherapy compared to participants with EDs ($p < .001$). Diagnosis groups did not differ in terms of any of these variables, or in terms of other illness variables, besides BMI, which was higher among binge/purge patients compared to AN-R patients ($p < .001$).

NSSI and Suicide

In line with our first hypothesis, differences between participants with different types of EDs (AN-R vs. binge/purge group) and participants without EDs were detected in all the suicidality and NSSI measures. The rate of participants who had attempted suicide was significantly different in all groups (FET = 17.22, $p < .001$): highest in the binge/purge group (34.8%), lower in the AN-R group (8%), and lowest in the control group (2.7%). Suicide ideation frequency was also significantly higher [$F(2,114) = 33.44$, $p < .001$, $\eta 2 = .370$] in the binge/purge group ($M = 2.04$, $SD = 1.41$) compared to both the AN-R group ($M = 0.64$, $SD = 0.99$) and the controls ($M = 0.22$, $SD = 0.63$; $p < .001$). The rate of participants with self-injurious behavior was higher [$\chi 2(2) = 35.53$, $p < .001$] in the binge/purge group compared to both the AN-R and control groups. The rate of severe injuries was highest (FET = 12.16, $p = .001$) in the binge/purge group (21.8%), lower in the AN-R group (4%), and 0% in the control group. Self-injury frequency was higher [$F(2,114) = 21.89$, $p < .001$, $\eta 2 = .277$] in the AN-BP/BN group ($M = 3.26$, $SD = 2.12$) compared to both the AN-R ($M = 0.92$, $SD = 1.86$) and control ($M = 0.84$, $SD = 1.73$) groups ($p < .001$) (**Figure 1**).

Differences between study groups in trait impulsivity were explored using ANOVA. Significant group effects were found in the attentional [$F(2,114) = 14.34$, $p < .001$, $\eta 2 = .201$] and motor [$F(2,114) = 9.72$, $p < .001$, $\eta 2 = .146$] factors, and in the total score [$F(2,114) = 10.42$, $p < .001$, $\eta 2 = .155$] of the impulsivity questionnaire. Attentional and motor impulsivity scores, as well as the impulsivity total score, were higher among AN-BP/BN patients compared to AN-R patients and controls ($p < .05$), which did not differ from each other.

TABLE 1 | Sample description*.

Variable	AN-R (N = 25)	AN-BP/BN (N = 55)	Control (N = 37)	Group differences
Marital status				
Married	2 (8%)	6 (10.9%)	5 (13.5%)	FET = 1.76, p > .05
Single	23 (92%)	48 (87.3%)	32 (86.5%)	
Divorced	0 (0%)	1 (1.8%)	0 (0%)	
Education level				
High-school	10 (40%)	28 (50.9%)	0 (0%)	K-W $\chi^2(2) = 18.83$, p < .001
Higher edu.	10 (40%)	11 (20%)	22 (59.5%)	
Academic	2 (8%)	10 (18.2%)	14 (37.8%)	
MA	1 (4%)	3 (5.5%)	1 (2.7%)	
Other	2 (8%)	3 (5.5%)	0 (0%)	
Occupation				
Employed	12 (48%)	33 (60%)	24 (68.6%)	$\chi^2(2) = 2.57$, p > .05
Unemployed	13 (52%)	22 (40%)	11 (31.4%)	
Psychiatric medication				
Yes	12 (50%)	29 (54.7%)	2 (5.4%)	$\chi^2(2) = 23.04$, p < .001
No	12 (50%)	24 (45.3%)	35 (94.6%)	
Psychotherapy				
Yes	22 (88%)	53 (96.4%)	14 (37.8%)	$\chi^2(2) = 44.11$, p < .001
No	3 (12%)	2 (3.6%)	23 (62.2%)	
ADHD				
Yes	8 (32%)	19 (34.5%)	1 (2.7%)	$\chi^2(2) = 13.46$, p < .001
No	17 (68%)	36 (65.5%)	36 (97.3%)	
Age (years)	22.54 (4.43)	24.55 (5.81)	23.16 (2.96)	$F(2,114) = 1.84$, p > .05, $\eta^2 = .031$
Disorder onset age (years)	18.14 (3.56)	20.02 (5.75)	–	$t(70.45) = -1.77$, p > .05
Hospitalizations number	1.40 (2.20)	1.30 (2.51)	–	$t(77) = 0.18$, p > .05
Chronicity	4.40 (4.34)	4.18 (5.35)	–	$t(78) = 0.18$, p > .05
BMI	16.07 (3.12)	20.09 (4.79)	–	$t(68.09) = -4.48$, p < .001
Hospitalization (days)	4.90 (3.34)	4.61 (5.65)	–	$t(64) = 0.21$, p > .05
PHQ-Depression	17.35 (7.05)	19.90 (4.70)	4.38 (2.48)	$F(2,102) = 123.80$, p < .001, $\eta^2 = .708$

Categorical variables are presented in frequencies (and percentages). Continuous variables are presented in means (and standard deviations).

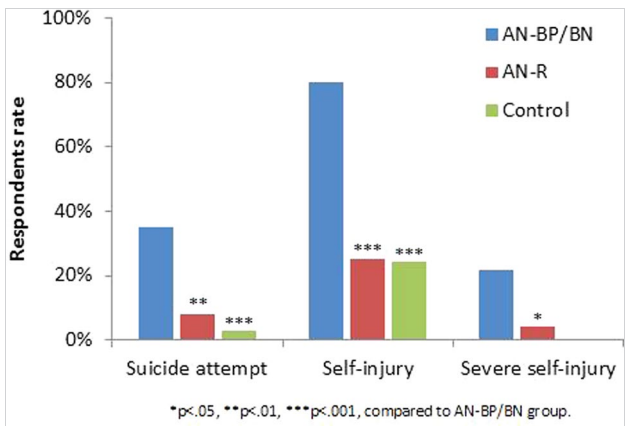

FIGURE 1 | Suicide attempts, self-injury, and severe self-injury occurrence by group.

Loss Aversion

Differences in LA between study groups were explored using ANOVA. Significant group effects were found in LA [$F(2,111) = 11.41$, p < .001, $\eta 2 = .171$], while the Bonferroni post-hoc test showed lower LA scores among participants with EDs (AN-R or AN-BP/BN) compared to participants from the control group ($p \leq .001$) as presented in **Figure 2**.

Correlations Between Study Variables

To identify potential predictors of suicidality and self-injury, Pearson correlations between suicidality and NSSI and background variables, LA, and impulsivity were calculated.

As demonstrated in **Table 2**, older and unemployed participants reported higher frequency of suicide ideation, and an ADHD diagnosis was related to a higher probability of a suicide attempt. Higher BMI and depression scores were related

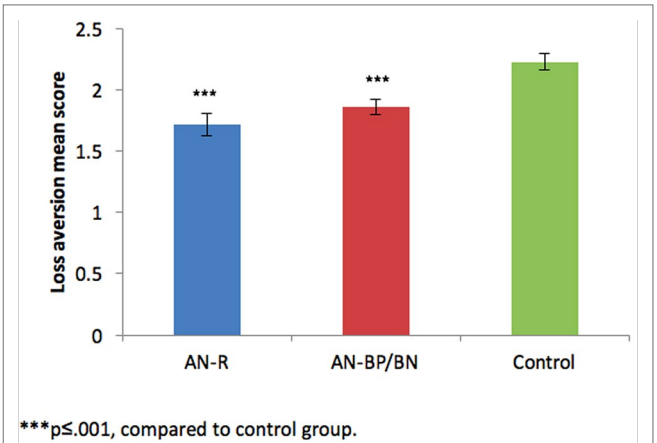

FIGURE 2 | Loss aversion score by group.

TABLE 2 | Correlations between suicidality and self-injury measures and potential predictors.

	Suicide attempt	Suicide ideation	Self-injury	Self-injury frequency
Age	.12	.24*	.05	.04
Work	–.07	–.31**	–.22	–.12
ADHD	.29**	.17	.09	.01
BMI	.18	.25*	.36***	.28*
PHQ-Depression	.21	.40***	.40***	.37**
Loss aversion	.01	.28*	.31**	.31**
BIS attentional	.30**	.31**	.38***	.21
BIS motor	.27*	.21	.32**	.17
BIS planning	.23*	.06	.18	–.05
BIS total	.31**	.22	.34**	.12

*$p < .05$, **$p < .01$, ***$p \leq .001$.

to a higher probability of self-injury attempt, higher frequency of suicide ideation, and higher frequency of self-injury. Higher impulsivity scores were related to higher probabilities of suicide and self-injury attempts and higher frequency of suicide ideation. Interestingly and contrary to our hypothesis, LA scores were positively correlated with the probability of self-injury, frequency of self-injury, and frequency of suicide ideation.

Predictors of NSSI and Suicidal Behavior: Regression Analysis

Linear and logistic regressions were conducted for the prediction of suicide and NSSI variables in the ED group. Each analysis consisted of two steps. The first step included diagnostic and background variables, which were found to be correlated with the dependent variable. The second step included the LA and impulsivity variables. Taking into account multicollinearity considerations, only the BIS total score (not its subscales) was entered into the regression analysis. Diagnosis remained a significant predictor in all the analyses: an AN-BP/BN diagnosis predicted a higher probability of suicide and NSSI attempts, as well as higher frequencies of suicide ideation and NSSI compared to an AN-R diagnosis. An ADHD diagnosis contributed significantly to the prediction of suicide attempts, whereas the depression level explained other variances in NSSI attempts and frequency. Unemployment was recognized as another risk factor for suicide ideation. While impulsivity scores did not significantly contribute to the prediction of suicide and NSSI variables beyond the background measures, higher levels of LA were related to an increased risk for attempting NSSI, higher frequencies of NSSI, and suicide ideation (**Tables 3** and **4**).

An additional set of regression analyses were conducted to determine whether the effect of the predictors on suicidality and self-injury differed between the diagnosis groups. While the regressions were identical to those presented in **Tables 3** and **4**, they also included an additional step of interactions between diagnosis and the other predictors. The interaction variables did not contribute significantly to the prediction of any of the dependent variables. Thus, the contributions of the abovementioned variables to the prediction of suicidality and self-injury seemed to be similar in both diagnosis groups.

To determine effect sizes that could be detected in this regression analysis, a *post hoc* power analysis was conducted using the software package, GPower (59). The sample size of 81 was used for the statistical power analyses and a eight predictor variable equation was used as a baseline. The recommended effect sizes used for this assessment were as follows: small (f2 = .02), medium (f2 = .15), and large (f2 = .35) (see 60). The alpha level used for this analysis was $p < .05$. The *post hoc* analyses revealed the statistical power for this study was.15 for detecting a small effect, whereas the power exceeded 0.82 and 0.99 for the detection of a moderate and large effect sizes, respectively. Thus, there was adequate power (i.e., power *.80) at the moderate to large effect size level, but less than adequate statistical power at the small effect size level.

DISCUSSION

The Relationship Between Self-Harm and Impulsivity in EDs

Our first hypothesis addressed the differences in self-harm behavior and trait impulsivity between the various ED subgroups.

TABLE 3 | Logistic regression analysis for the prediction of suicide and self-injury attempts.

Step	Predictor	Suicide attempts			Self-injury		
		B (SE)	Wald	Odds ratio	B (SE)	Wald	Odds ratio
1	Diagnosis	1.91 (0.83)	5.48*	6.78	2.38 (0.82)	8.39**	10.79
	ADHD	1.47 (0.57)	6.69**	0.23			
	BMI				0.08 (0.10)	0.58	1.08
	PHQ				0.16 (0.07)	5.98*	1.18
	$R^2 = .24$, $\chi^2(2) = 14.25$***				R2=.49, χ^2(3)=27.56***		
2	Diagnosis	1.64 (0.84)	3.81*	5.13	3.42 (1.29)	7.03**	30.73
	ADHD	–1.29 (0.58)	4.91*	0.28			
	BMI				0.04 (0.11)	0.10	1.04
	PHQ				0.19 (0.08)	5.37*	1.22
	Loss aversion				3.74 (1.48)	6.35*	42.21
	BIS total	0.04 (0.02)	2.71	1.04	0.06 (0.03)	3.39	1.06
	$R^2 = .28$, $\chi^2_{step}(1) = 2.91$, $\chi^2_{model}(3) = 17.16$***				R2=.67, χ^2step(2)=13.96***, χ^2model(5) = 41.52***		

*$p \leq .05$, **$p \leq .01$, ***$p \leq .001$.

TABLE 4 | Linear regression analysis for the prediction of suicide ideation and self-injury frequencies.

Step	Predictor	Suicide ideation		Self-injury frequency	
		B (SE)	β	B (SE)	β
1	Diagnosis	1.00 (0.37)	.32**	2.35 (0.58)	.47***
	Age	0.02 (0.03)	.07		
	Occupation	–0.71 (0.33)	–.25*		
	BMI	0.01 (0.03)	.05	–0.01 (0.05)	–.02
	PHQ	0.06 (0.03)	.23*	0.12 (0.04)	.29**
	R^2 = .35, F(5,59) = 6.31***			R2=.35, F(3,61)=10.97***	
2	Diagnosis	0.89 (0.36)	.29*	2.27 (0.56)	.45***
	Age	0.02 (0.03)	.09		
	Occupation	–0.70 (0.31)	–.24*		
	BMI	0.01 (0.03)	.03	–0.02 (0.05)	–.04
	PHQ	0.04 (0.03)	.17	0.11 (0.04)	.28*
	Loss aversion	0.72 (0.30)	.25*	1.21 (0.47)	.26*
	BIS attention	0.03 (0.03)	.09	–0.04 (0.05)	–.07
	ΔR^2 = .07, F(2,57) = 3.25*			ΔR2=.07, F(2,59)=3.52*	
	R^2 = .41, F(7,57) = 5.78***			R2=.42, F(5,59)=8.53***	

*p < .05, **p < .01, ***p < .001.

In line with contemporary literature (7, 61–63), notable differences between the subgroups in self-harm behavior were found: individuals in the binge/purge group were more likely to demonstrate NSSI behaviors of a severer nature. Individuals in the binge/purge group also attempted suicide more often and were more preoccupied with suicide ideation compared to the AN-R group and healthy controls. The AN-R group had a higher rate of past attempts compared to the healthy controls, however, they were not significantly different from the controls in terms of NSSI prevalence or severity and suicide ideation. These results are in line with previous studies (30, 64, 65).

The trait impulsivity assessment points to a discrepancy between the ED subgroups. The binge/purge group scored higher on the impulsivity questionnaire, in general, and on the attentional and motor constructs of the BIS-11, in particular. These results support existing literature in the field (26, 65). AN-R patients did not differ from controls in trait impulsivity, thereby reinforcing previous findings which largely associate these patients with a compulsive cluster (21, 66).

Is LA a Protective Mechanism?

Our second hypothesis regarding differences in LA between ED subgroups was partly confirmed. ED patients scored lower in LA than controls, suggesting that potential losses have a lower effect on the decisions of ED patients compared to controls. To the best of our knowledge, LA has not been linked to EDs prior to this study. The direction of the relationship corresponds with studies investigating impulsivity-prone populations, such as pathological gamblers and cocaine users, who have also been shown to display reduced levels of LA compared to healthy controls (67, 68). However, contradictory to our hypothesis, there were no differences in levels of LA between the AN-R and binge/purge subgroups (despite the difference in impulsivity). This may imply that decreased levels of LA are global in ED patients, and that whether characterized by either a loss of control or restraint, these individuals' decisions tend to be less affected by potential negative outcomes compared to a healthy population.

LA as a Predictor for Self-Harm Behaviors

Finally, we hypothesized a negative relationship between LA and self-harm behaviors among ED patients. Our reasoning was that those with high LA scores would be more likely to avert from self-harm due to its potential negative outcomes, such as physical injury. Conversely, as the decisions of patients with low scores in LA would be guided primarily by potential gains (i.e., release of anxiety, or end of suffering), we expected them to be more likely to engage in self-harm behaviors. Interestingly, the emerging results were the opposite of what we predicted: LA was positively correlated with the prevalence and severity of NSSI and with suicide ideation in the ED research group, while no significant association was found between past suicide attempts and LA. In addition, higher levels of LA were found to be a significant contributor to the prediction of NSSI behavior and frequency, and suicide ideation, over and above background variables and impulsivity. It is interesting to note that impulsivity was neither correlated with LA nor did it represent a unique contribution to the prediction of self-harm behaviors, perhaps due to overlap between this concept and other variables entered into the regression analysis.

How can this positive relation between LA and NSSI and suicidal ideation be explained? At face value, this finding contradicts recent findings according to which a high level of LA was shown to constitute a protective mechanism against suicidal behavior in a cross-sectional and longitudinal sample (42, 69). Two important factors may shed light on the causes for the contradictions in these findings: first, the distinction between non-suicidal self-injury and self-injury with an intent to die [see (70)], and second, differences between the populations studied in our and (69). Theorized that high levels of LA may avert the decision to attempt suicide due to its negative outcomes (e.g. death, pain to family members, etc.) superseding the positive outcomes associated with the act (putting an end to suffering). Individuals who display high levels of LA are therefore at a lower risk for carrying out an attempt. Compared to suicide, NSSI is a behavior that entails more moderate negative consequences

(mainly physical pain and cosmetic damage), and perhaps less dramatic and somewhat advantageous consequences. Nock (33), for instance, suggests that although NSSI is considered a pathological behavior, it serves several intrapersonal and interpersonal purposes. Other studies have shown that a major intrapersonal gain of NSSI is affect regulation (71, 72). Another important positive aspect of NSSI is its communication-related function (73): studies concerning social media found NSSI to be driven by peer support (74, 75).

If we apply Hadlaczky et al.'s logic to NSSI, a decision-maker with a high level of LA should still be less likely to carry out NSSI than more so (as demonstrated by our data): even if the potential losses and gains are somewhat lower/different in NSSI, a high LA level should still play a preventive role. However, what if the decision is not related to carrying out or abstaining from NSSI? Given the high prevalence of suicidal ideation in the ED population, the decision may pertain to engaging in NSSI rather than carrying out a suicide attempt. In this case, participants with high LA levels may be redirected from the "bad" alternative of attempting suicide (with significant potential negative consequences) to the "less bad" alternative of carrying out a NSSI.

Taken together, the choice of NSSI as a better alternative over an intently driven suicide attempt relies not only on several predisposed variables, including hopelessness, depression, and the individual's communication aptitude, but also on his or her ability to assess potential losses. For individuals in need of immediate affect regulation, a tendency toward higher LA may safeguard them from choosing a self-regulation behavior with a higher potential for a negative consequence (suicide attempt), while motivating them toward a communicative act. Thus, although a high level of LA is considered a protective factor against high risk decisions, it may serve as a facilitator of lower risk decisions that help the individual soothe and communicate his or her own suffering (76, 77). This explanation is congruent with the results of a study conducted by Gómez-Expósito et al. (78), which demonstrated that while bulimic-spectrum patients with past suicide attempts scored high on impulsivity, bulimic patients with NSSI presented lower impulsivity, most probably as a manifestation of a different mechanism of self-regulation. Models that determine the transition from NSSI to suicide attempts may support this hypothesis as well (79)—a growing sense of capability for self-harm may decrease levels of LA and lead the individual to choose a more lethal option. It is also possible that while LA remains constant, the option of suicide becomes increasingly suitable for patients whose suffering persists and intensifies.

Regarding the positive relation between higher levels of LA and the preoccupation with suicidal thoughts, further study is required. Research on suicide ideation has failed to discriminate between suicide attempters and non-attempters (80), thereby leading to the notion that it is an independent variable. Taking this a step forward, we suggest that suicide ideation is part of a repertoire of actions, which, under certain circumstances, may serve as a satisfactory alternative to the carrying out of an intentional suicide attempt. The understanding of the individual in pain that death is an alternative to suffering, can, to some extent, alleviate suffering and allow him or her to go on with their lives. This idea reinforces the notion offered in work presented by Hadlaczky et al. (69) proposing that LA can be found as an important variable in understanding the transition from suicidal thoughts to attempts. Further study in this field is required to confirm these results. It would also be interesting to investigate the relationship between LA and suicidal using other measures than the lottery task in this study, which has a quite specific economic/statistical character. An example could be to use for instance a "mug-task" type paradigm (81), and perhaps through the endowment effect investigate other domains such as the loss of relationships or status.

Limitations

A major drawback of this study is its cross-sectional design, which prevents us from drawing conclusions regarding cause and effect. Additionally, considering difficulties in the recruitment of EDs patients, due to limited cooperation and medical complications, a relatively small sample size of participants (93) were recruited in the research group. This could explain why we did not find a direct LA effect on attempted suicide in our data, contradictory to previous studies (69), possibly due to a lack of statistical power. Moreover and in favor of this option, the number of attempted suicides in the data was relatively low (21 out of 81 subjects in the research group). In addition, future studies with a larger sample size might determine an interaction effect between the contributing variables and the diagnosis which was not found in this research.

Although all participants were recruited from the same medical center, some were patients already in treatment, while others were patients interviewed prior to treatment as a part of an intake procedure. This might affect the temporal state of the patients and result in alterations in the performance of the behavioral task. Due to the fact that some of the potential participants refused to participate we cannot rule out a sampling bias in our study sample. By including female participants only, compared to our study does not account for potential differences in coping mechanisms and behavioral tendencies attributed to gender differences, which were found to be significant (82). Further study that involves the participation of male subjects could help resolve this ambiguity.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this manuscript will be made available by the authors, without undue reservation, to any qualified researcher.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by IRB SHEBA Tel Hashomer. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

ES and YG planned and conducted the research, assessed the data, and wrote the paper. GH took a part in analysis of the data and contributed to the discussion, specifically in specialty areas of decision making paradigms. NS was responsible for data collection and contributed to analysis of the data. EG took a part in theoretical and practical aspects of research planning and data collection. NH was involved in the formulation of the initial research.

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Depressive Symptom Clusters in Relation to Body Weight Status: Results From Two Large European Multicenter Studies

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Background: There is strong evidence for a bidirectional association between depression and obesity. Several biological, psychological, and behavior-related factors may influence this complex association. Clinical impression and preliminary evidence suggest that patients with a diagnosis of major depressive disorder may endorse very different depressive symptom patterns depending on their body weight status. Until now, little is known about potential differences in depressive symptoms in relation to body weight status.

Objective: The aim of this analysis is the investigation of potential differences in depressive symptom clusters (mood symptoms, somatic/vegetative symptoms, and cognitive symptoms) in relation to body weight status.

Methods: Cross-sectional baseline data were derived from two large European multicenter studies: the MooDFOOD Trial and the NESDA cohort study, including persons with overweight and obesity and normal weight reporting subthreshold depressive symptoms (assessment *via* Inventory of Depressive Symptomatology Self-Report, IDS-SR30). Different measures for body weight status [waist-to-hip ratio (WHR) and body mass index (BMI)] were examined. Propensity score matching was performed and multiple linear regression analyses were conducted.

Results: A total of n = 504 individuals (73.0% women) were analyzed. Results show that more somatic/vegetative depressive symptoms, such as pain, change in appetite and weight, gastrointestinal symptoms, and arousal-related symptoms, were significantly associated with both a higher BMI and higher WHR, respectively. In addition, being male and older age were significantly associated with higher WHR. Mood and cognitive

depressive symptoms did not yield significant associations for both body weight status measures.

Conclusions: Somatic/vegetative symptoms and not mood and cognitive symptoms of depression are associated with body weight status. Thus, the results support previous findings of heterogeneous depressive symptoms in relation to body weight status. In addition to BMI, other body weight status measures for obesity should be taken into account in future studies.

Clinical Trial Registration: www.ClinicalTrials.gov, identifier NCT02529423.

Keywords: depression, depressive symptoms, obesity, overweight, body mass index

INTRODUCTION

Major depressive disorder (MDD) is among the most prevalent and disabling mental disorders, one of the leading causes of disability worldwide, and a major contributor to the overall global burden of disease (1). One of the most prevalent somatic comorbidities of MDD is obesity (2, 3). Several studies have provided evidence for a bidirectional link between depression and obesity in a way that the presence of one is increasing the risk of developing the other (3–6). Further, as stated by Milaneschi et al. (3), there is strong reason to believe that these conditions are interconnected through a vicious, mutually reinforcing cycle of adverse physiological adaptations.

Several factors, such as biological, psychological, and behavior-related ones, may influence this complex association between depression and obesity (e.g., 7, 9–12). Moreover, depression and obesity are two major risk factors of negative health outcomes (10, 13, 14).

The inter-individual heterogeneity of depressive symptoms in different patients with MDD grants to a greater variability in its association with obesity. This association seems to be stronger in certain subgroups of patients (3, 6, 15, 16); for example, the association between depression and obesity is found to be stronger for abdominal obesity, and in some studies and certain populations, it was found to be inverse or even absent (17–19). Several (e.g., genetic and inflammatory) factors and mechanisms are being discussed in the international literature to date (3, 10, 20–22). Genetic factors influence likewise depression and obesity, with additive effects explaining the phenotypic variation for both depression and body mass index (BMI) (3, 23, 24). To sum up, there is emerging evidence that the relationship between depression and obesity has its origins in partially overlapping genetic bases (3).

The clinical impression also supports the hypothesis that patients with the same MDD diagnosis may endorse very different symptom patterns depending on their body weight status (3). For example, obesity seems to be associated with fatigue in the sense of tiredness (lack of drive and sleepiness), which may result from somatic reactions to the condition of obesity, whereas typical depression is associated with inhibition of drive and long sleep latencies (25–27).

In the past decades, quite some efforts have been made to determine and establish different depressive symptom patterns or clusters and examine their influence on various health-related outcomes. In most of these studies, depressive symptom patterns or clusters were distinguished as follows: a) two symptom clusters: cognitive-affective (e.g., pessimism, guilt, and self-dislike) and somatic-affective (e.g., insomnia, fatigue, and work difficulty) depressive symptoms (28, 29) or b) three symptom clusters: cognition/mood, anxiety/arousal, and vegetative symptoms (or sleep) (30, 31). However, other distinctions were also proposed, such as a differentiation between atypical and melancholic depressive subtypes (32–34).

As mentioned above, a growing body of evidence indicates that abdominal obesity is a more important risk factor of MDD than general obesity (35). It seems to be the key mediator in the relationship between obesity and depression (36). Results indicate a positive association between abdominal fat distribution [measured by waist-to-hip ratio (WHR)] and prevalence of depression, and further that abdominal obesity is a risk factor of depression independently of general obesity (measured by BMI). Nevertheless, some epidemiological studies report no association between unfavorable waist circumference and mental disorders (in particular depression) (17). Considering these differential associations, it seems beneficial to take into account different measures for body weight status, not only BMI (37).

However, only a few studies have addressed anthropometric measures in relation to different depressive symptoms so far (38), with equivocal results: one study reported that BMI was associated with both cognitive-affective and somatic-affective depressive symptom patterns of the Beck Depression Inventory I (BDI-I), whereas waist circumference and WHR were only associated with somatic-affective, but not cognitive-affective symptoms (39). Another study reported as a secondary result that BMI at baseline was significantly correlated with improvement in neurovegetative and cognitive symptoms of depression (2). It has also been shown in a population-based study that only the somatic, not the cognitive-affective, symptoms of depression are positively associated with anthropometric measures of obesity (35).

The aim of this study is the investigation of self-rated depressive symptoms (assessed with the Inventory of Depressive Symptomatology Self Report, IDS-SR30 clusters: mood symptoms, somatic/vegetative symptoms, and cognitive

symptoms) in relation to body weight status in persons with overweight and obesity and normal-weight individuals reporting subthreshold depressive symptoms. Different measures for body weight status (WHR and BMI) will be examined.

METHODS

Study Design

This publication includes baseline data from two large European multicenter studies: the MooDFOOD Trial ("Multi-country cOllaborative project on the role of Diet, Food-related behavior, and Obesity in the prevention of Depression") and the NESDA Study ("The Netherlands Study of Depression and Anxiety"), respectively.

The MooDFOOD Trial for the prevention of depression in individuals with overweight and obesity reporting subclinical depressive symptoms is a 2 × 2 factorial randomized controlled trial. It was carried out between July 2015 and October 2017 in four European countries (Germany, Spain, United Kingdom, and the Netherlands). For full details of trial design and protocol see Roca et al. (40), and for primary outcome results see Bot et al. (41). The trial was approved by the Human Research Ethics Boards of all four study sites. All participants provided written informed consent prior to participation.

The NESDA Study is an ongoing multicenter, longitudinal, naturalistic cohort study examining the 9-year course and consequences of depressive and anxiety disorders (for details of study design and protocol, see 42). Baseline assessments of NESDA took place between 2004 and 2007. The study includes persons with a current or lifetime diagnosis of depression and/or anxiety disorder, persons being at risk for these disorders because of a family history or subthreshold depressive or anxiety symptoms, and healthy controls, respectively. Ethics approval was provided by the local review boards of all study sites and written informed consent was obtained from all participants prior to participation.

For this publication, baseline data from both the MooDFOOD Trial (total N = 1,025) and the NESDA Study (total N = 2,981) were combined to provide a sample with a wide range of body weight status. To this end, only the data of normal-weight participants from the NESDA Study were used to provide a matching sample to the MooDFOOD data of individuals with overweight and obesity (see below for details on propensity score matching procedure).

Recruitment and Eligibility Criteria

Participants for the MooDFOOD Trial were recruited from the general population *via* websites, advertisements, and press releases as well as *via* other studies conducted at the study sites and mailings to registered subjects in the general practice setting or in city registers. Inclusion criteria were age 18-75 years, BMI in the range of 25–40 kg/m^2, and subclinical depressive symptoms as operationalized by a Patient Health Questionnaire (PHQ-9) score of ≥5 (43). Main exclusion criteria included a current (including the past 6 months) MDD episode according to the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV; (44), as assessed by the Mini-International Neuropsychiatric Interview (MINI 5.0; 45), current use of antidepressants, current eating disorder or a severe life-threatening physical disease (e.g., cancer), and a history of psychosis, bipolar disorder, substance dependence, or another severe psychiatric disorder (40). All eligible participants were invited for a baseline interview, physical measurements, and blood sampling conducted by trained research assistants/nurses and the completion of self-report questionnaires. Follow-up assessments took place at 3, 6, and 12 months.

Participants for the NESDA Study were recruited from community samples, primary care practices, and mental health organizations, in order to represent diverse settings and developmental stages of psychopathology. Participants aged 18–65 years were included in the study. Further inclusion criteria were a current (including the past 6 months) or lifetime diagnosis of depression (minor or major depression, dysthymia) or anxiety disorders according to the DSM-IV, as assessed by the Composite International Diagnostic Interview (CIDI, WHO version 2.1; 46). In addition, persons with a family history of depression or anxiety disorders and with subclinical depressive or anxiety symptoms were included, as well as healthy controls without any depressive or anxiety symptoms. Main exclusion criteria were psychosis, obsessive compulsive disorder, bipolar disorder, severe addiction, and a history of stroke (42). Eligible participants were invited for a baseline assessment including clinical interviews and physical measurements conducted by trained research assistants and the completion of self-report questionnaires. Follow-up assessments took place every 2 years after baseline and are currently ongoing.

Propensity Score Matching and Study Sample

The baseline data of the MooDFOOD Trial included N = 1,025 participants in total. To match these data with the data of the NESDA Study, n = 35 participants had to be excluded from the dataset [n = 14 with normal body weight and n = 21 with history of stroke (exclusion criterion in the NESDA sample)], resulting in a dataset of n = 990 participants from the MooDFOOD Trial.

Baseline data of the NESDA Study included N = 2,981 participants. Of these, n = 2,544 had to be excluded during data preparation for the following reasons: n = 1,481 not normal body weight, n = 540 with current MDD (as this was an exclusion criterion in MooDFOOD), n = 113 with antidepressant medication, n = 94 with alcohol dependence, and n = 316 with anxiety disorders. Thus, the final selected sample out of the NESDA Study comprised n = 437.

To obtain a final sample with a wide range of body weight status, including persons with overweight and obesity from the MooDFOOD Trial as well as normal-weight persons from the NESDA Study, propensity score matching was performed (47). Based on their propensity scores calculated by logistic regression (nearest neighbor matching algorithm, caliper 0.2), samples were matched according to sex, age, and distribution of IDS scores. The final matched sample comprised n = 504 participants (n = 252 from the MooDFOOD Trial and n = 252 from the NESDA Study).

Measures

Depressive Symptoms. In both the MooDFOOD Trial and the NESDA Study, the 30-item Inventory of Depressive Symptomatology Self-Report (IDS-SR30; 30, 48) was administered to assess depressive symptoms (0 = *no problems* to 3 = *severe problems*). The two separate items on weight loss and weight gain were recoded into a single variable. The two items on increased and decreased appetite, respectively, were recoded similarly, resulting in a total of 28 items for the IDS (9, 31). A total sum score was calculated (range, 0–84), with higher scores indicating higher levels of depressive symptomatology. In accordance with previous studies, individual symptoms were categorized into three depressive symptom clusters (deductively defined): mood symptoms, cognitive symptoms, and somatic/vegetative symptoms (9, 49, 50). A sum score was calculated for each cluster (mood symptoms: 10 items, range 0–30; cognitive symptoms: 4 items, range 0–12; somatic/vegetative symptoms: 14 items, range 0–42; see **Supplementary Table**).

Body Weight Status. Body weight, height, and waist and hip circumference were measured objectively according to written, standardized protocols (identical measurement in both subsamples). BMI (in kilograms per square meter) and WHR (waist circumference divided by hip circumference) were calculated.

Presence of Lifetime MDD. The presence of a lifetime diagnosis of MDD according to the DSM-IV (44) was assessed in all study participants using clinical interviews, specifically the MINI 5.0 (45) in the MooDFOOD Trial and the CIDI [WHO version 2.1 (46)] in the NESDA Study.

Demographic Variables. Sex and age were assessed in the baseline interview in both, MooDFOOD and NESDA.

All applied interview and questionnaire instruments demonstrated good reliability and validity (51–53). The IDS showed good internal consistency with Cronbach's $\alpha = .80$.

Statistical Analysis

Statistical analyses were performed using IBM SPSS Statistics version 24.0. Differences in sample characteristics between participants from MooDFOOD and NESDA, respectively, were examined using general linear model analyses for continuous variables (age, BMI, WHR, and IDS scores) and χ^2 tests for categorical variables (sex and prevalence of lifetime MDD). To analyze the relationship between depressive symptoms and body weight status, two separate multiple linear regression analyses were computed with the anthropometric measure (BMI and WHR) as the continuous dependent variable and the depressive symptoms (clusters: mood symptoms, cognitive symptoms, and somatic/vegetative symptoms) and sociodemographic variables (sex and age) as the independent variables. Tests for assumption of collinearity of the independent variables showed that multicollinearity was not a concern. The independent variables were entered into the models simultaneously. Effect size of prediction was evaluated according to Cohen (54), R^2: small, .01; medium, .09; large, .25. A two-tailed $\alpha = 0.05$ was applied to all statistical testing.

RESULTS

Sample Characteristics

Participants from MooDFOOD (n = 252) and NESDA (n = 252), respectively, did not differ regarding sex, age, prevalence of lifetime MDD, IDS total scores, and IDS symptom clusters (all $p > .05$; see **Table 1**). As expected, participants from MooDFOOD showed significantly higher BMI and WHR than participants from NESDA (all $p < .05$).

The total sample comprised n = 504 individuals (73.0% women) with a mean age of $M = 41.93$ years (SD = 13.61), a mean BMI of $M = 26.62$ kg/m^2 (SD = 5.33, range = 18.56–42.10 kg/m^2), and a mean WHR of $M = 0.86$ (SD = 0.09, range = 0.66–1.12; see **Table 1**). Criteria for a lifetime MDD diagnosis were met by n = 150 (29.9%). Based on IDS cutoff scores for clinical severity of depressive symptoms, no values fell in the categories of severe or very severe depressive symptoms. Of the total sample, n = 292 (58%) participants had no or low severity of depressive symptoms, n = 175 (35%) had mild severity, and n = 37 (7%) displayed moderately severe depressive symptoms, respectively.

TABLE 1 | Sample characteristics for the MooDFOOD and NESDA subsamples and the total matched sample.

	Total sample (n = 504)	MooDFOOD (n = 252)	NESDA (n = 252)	Test	p
Sex (*N* female, %)	368 (73.0)	185 (73.4)	183 (72.6)	$\chi^2(1) = 0.04$	.841
Lifetime MDD (*N*, %)	150 (29.9)	76 (30.4)	74 (29.4)	$\chi^2(1) = 0.06$	.800
	M (SD)	*M* (SD)	*M* (SD)	*F*(1, 502)	
Age	41.93 (13.61)	42.52 (12.85)	41.35 (14.33)	0.93	.335
Body mass index (kg/m^2)	26.62 (5.33)	31.04 (3.86)	22.19 (1.66)	1,117.92	**<.001**
Waist-to-hip ratio	0.86 (0.09)	0.89 (0.09)	0.82 (0.07)	92.42	**<.001**
IDS total score	13.47 (7.52)	13.69 (7.52)	13.25 (7.53)	0.44	.508
Mood symptoms	4.11 (3.41)	4.13 (3.41)	4.10 (3.41)	0.01	.927
Cognitive symptoms	1.66 (1.67)	1.64 (1.57)	1.69 (1.78)	0.12	.730
Somatic/vegetative symptoms	7.67 (4.03)	7.92 (4.02)	7.41 (4.03)	2.07	.151

Using propensity score matching, samples from the MooDFOOD Trial and the NESDA Study were matched according to sex, age, and distribution of IDS sum scores. Tests for group differences refer to differences between the MooDFOOD and NESDA subsamples, respectively.
M, mean; SD, standard deviation; MDD, major depressive disorder; IDS, Inventory of Depressive Symptomatology Self-Report.
Bold type p < .05.

Multiple Linear Regression Analyses

Two separate multiple linear regression analyses were calculated to predict BMI and WHR, respectively, based on sociodemographic variables and depressive symptom clusters. The first analysis with BMI as the outcome variable did not yield a significant regression equation: $F(5, 498) = 2.01$, $p = .076$, $R^2 = .02$, adjusted $R^2 = .01$; see **Table 2** and **Supplementary Figure**). While sociodemographic variables as well as mood and cognitive symptoms were not significantly associated with BMI (all $p > .05$), results showed that the somatic/vegetative symptom cluster had a significant effect ($p = .013$). More somatic/vegetative symptoms were associated with a higher BMI.

Results of the second analysis with WHR as the outcome variable indicated that there was a collective significant association of the independent variables: $F(5, 496) = 50.11$, $p < .001$, $R^2 = .34$, adjusted $R^2 = .33$; see **Table 2** and **Supplementary Figure**). Examination of the individual variables showed that sex, age, and somatic/vegetative symptoms yielded significant effects in the model (all $p < .01$). Being male, older age, and more somatic/vegetative symptoms were associated with a higher WHR.

In both models, standardized regression coefficients (beta) for somatic/vegetative symptoms were larger than those for mood and cognitive symptoms, respectively (see **Table 2**).

DISCUSSION

The aim of this study was to investigate the relationship between depressive symptom clusters (mood symptoms, somatic/vegetative symptoms, and cognitive symptoms) in relation to body weight status, measured by BMI and WHR, in individuals with subthreshold depressive symptoms. Using a sample comprising two large European multicenter studies, the current study is, to our knowledge, the first to address this question.

Results showed that the significant regression model with WHR as the outcome variable yielded a reasonably high model fit, explaining 33% of the variance. It revealed that being male, being of older age, and reporting more depressive symptoms of the somatic/vegetative symptom cluster were significantly associated with higher WHR. Mood and cognitive symptoms did not show any significant contribution. To sum up, age, sex, and somatic/vegetative symptoms, but not mood or cognitive symptoms, were significantly associated with WHR. This finding is in line with previous research indicating that the somatic/affective symptoms of depression rather than the cognitive/affective ones are consistently related to anthropometric measures of obesity (35).

The regression model with BMI as the outcome variable did not reach statistical significance overall, meaning that the majority of the variables did not contribute to BMI. Nevertheless, the factor somatic/vegetative symptoms yielded a significant effect, which points towards the fact that this factor is associated with BMI, but the others do not.

Overall, the results of this study provide further evidence that somatic/vegetative symptoms rather than mood/cognitive symptoms of depression are associated with WHR, and potentially of BMI as well. Somatic/vegetative symptoms include pain, change in appetite and body weight, gastrointestinal, and several arousal-related symptoms (sleep and energy level) (see **Supplementary Table**). The latter are depressive symptoms that are mainly manifested in the somatic area, which might overlap or coincide with complaints and symptoms accompanying or resulting from overweight or obesity and co-occurring somatic conditions.

Moreover and also in line with the international literature, the results suggest that future research should take different body weight status measures (such as WHR) for obesity into account, not only BMI, as other measure index abdominal obesity, which is proposed to be the key factor in the obesity–depression relationship (35, 36).

The current study has important strengths. It included a large, multicenter, multi-country, and propensity score-matched sample and further used standardized assessment instruments. However, there are also some limitations. First, the results might not be generalizable to the full spectrum of depressive disorders and specifically to individuals currently suffering from MDD, as the study population comprised individuals with subthreshold symptoms of depression, but indeed 30% with a lifetime MDD diagnosis. Nevertheless, the full range of body weight state was included in the analysis. Due to the cross-sectional design, causal inferences are not possible and not all potentially relevant control variables (e.g. physical activity) could be included into the analysis. The depressive symptoms being analyzed in this study are administered *via* self-report measures, which might be biased by social desirability and other factors. Also, self-report instruments and clinician-rated scales differ regarding content and weighting of different symptom dimensions. Also, the potential role of certain medical comorbidities regarding this association is not addressed within this analysis.

In conclusion, the present study provides further evidence that there is heterogeneity in depressive symptoms in relation to body weight status, especially as assessed by the WHR. Future studies could investigate the longitudinal course of different depressive symptom clusters and their differential associations with body weight status in the long term. Treatment strategies

TABLE 2 | Linear regression analyses of depressive symptom clusters and weight status ($n = 504$; matched sample from MooDFOOD and NESDA)

	Total sample ($N = 504$)			
	β	B	SE B	p
Body mass index				
Sex	0.04	-0.46	0.54	.369
Age	0.07	0.03	0.02	.117
Mood symptoms	-0.03	-0.04	0.10	.650
Cognitive symptoms	-0.04	-0.13	0.18	.476
Somatic/vegetative symptoms	0.13	0.18	0.07	**.013**
Waist-to-hip ratio				
Sex	-0.50	-0.10	0.01	**<.001**
Age	0.30	0.00	0.00	**<.001**
Mood symptoms	-0.05	0.00	0.00	.293
Cognitive symptoms	-0.02	0.00	0.00	.704
Somatic/vegetative symptoms	0.12	0.00	0.00	**.006**

Bold type p < .05.

of both depression and obesity should take the present results into account, e.g., by adapting and targeting interventions to the presented (heterogeneous) symptoms displayed by the individual patient.

DATA AVAILABILITY STATEMENT

The datasets analyzed in this manuscript are not publicly available. Requests to access the datasets should be directed to www.nesda.nl; www.moodfood-vu.eu.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by MooDFOOD sample: Research Ethics Committee Govern de les Illes Balears, Palma, Spain (10th of March 2015), the Ethics Committee of the University of Leipzig, Germany (2nd of April 2015), VU Medical Center Amsterdam, the Netherlands (8th of July, 2015) and the NHS National Research Ethics Service (NRES) Committee, SouthWest, UK (Research Ethics Committee number- 15/SW/0153) for University of Exeter (3rd of August 2015). NESDA sample: Ethical Review Board of the VU University Medical Centre. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

SB and UH were the lead authors on the manuscript and SB and EK analyzed and interpreted the data. MV and IB obtained funding for the MooDFOOD project, designed the MooDFOOD prevention trial, and, together with MC, coordinated the MooDFOOD project. BP, MB, and EW contributed to the design of the MooDFOOD prevention trial. EW led the development and training of the MooDFOOD Food-Related Behavioural Change Intervention. EK and UH coordinated the recruitment, interventions, and follow-ups at the trial center in Germany, University Leipzig. BP and MB coordinated the recruitment, interventions, and follow-ups at the trial center in the Netherlands, VU University Medical Center Amsterdam. EW and MO coordinated the recruitment, interventions, and follow-ups at the trial center in the United Kingdom, University of Exeter. MR and MG coordinated the recruitment, interventions, and follow-ups at the trial center in Spain, University of Balearic Islands. GG set up the logistics for the trial's data collection. All authors contributed to the writing of the manuscript and approved the final version. Please see www.moodfood-vu.eu for a complete list of the MooDFOOD Prevention Trial Investigators.

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Bad Things Come to Those Who Do Not Wait: Temporal Discounting Is Associated With Compulsive Overeating, Eating Disorder Psychopathology and Food Addiction

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The tendency to act on immediate pleasure-driven desires, due to the devaluation of future rewards [a process known as temporal discounting (TD)], has been associated with substance use disorders (SUD) and with conditions characterised by compulsive overeating. The study involved a large inclusive participant sample (i.e., no diagnostic or exclusion criteria were applied). They were recruited/assessed online and we investigated whether TD was related to compulsive overeating and associated problems. Participants [*N* = 432, (48 males)] completed an online survey, which included a hypothetical monetary TD task, the Eating Disorder Examination-Questionnaire (EDE-Q), the Yale Food Addiction Scale (YFAS) and the Depression Anxiety and Stress Scales (DASS). TD correlated with frequency of compulsive overeating and compensatory behaviours, with eating disorder psychopathology, with scores on the YFAS, and with body mass index (BMI). As our study shows that elevated rates of TD are associated with a range of behaviours/measures, we propose that it is more likely that elevated TD rates are a predisposing factor rather than a consequence of the behaviour, i.e., elevated rates of TD contribute to pathological eating-related behaviours; however, a bi-directional explanation is also possible. Future research should investigate whether interventions aimed at reducing TD have clinical potential for treating problematic eating behaviours.

Keywords: compulsive overeating, food addiction, obesity, temporal discounting, impulsivity

INTRODUCTION

Compulsive overeating, binge-eating, and loss-of-control eating are behaviours used to describe the aberrant patterns of feeding that characterise the binge-purge subtype of anorexia nervosa (AN), bulimia nervosa (BN), binge-eating disorder (BED) and some forms of obesity Thus, compulsive overeating is not a diagnosis, rather, it is an umbrella term in common parlance. It refers to excessive food consumption that is accompanied by a perceived loss of control (LOC) over intake—not necessarily in a discrete period of time, as per binge-eating disorder (BED) (1). Compulsive

overeating is sometimes accompanied by unhealthy compensatory behaviours such as self-induced vomiting and laxative misuse. Compulsive overeating, like other compulsive behaviours, can be broadly defined as a trait in which actions are persistently repeated despite adverse consequences (2). As such, it can have serious health consequences: conditions encompassing this behaviour are associated with medical problems (e.g., obesity and diabetes), psychiatric morbidity (e.g., emotional distress and affective illness), and with significant functional impairment (e.g., mobility) (3–5). Our participants did not have to have any eating disorder (ED) diagnosis and in our study, the term compulsive overeating was used to describe a category of behaviour.

The cause(s) of compulsive overeating are unclear. It has been proposed that in some individuals, compulsive overeating may result from a physical and psychological dependence on certain foods, i.e., highly palatable, energy-dense foods may have addictive properties similar to drugs of abuse (6). Indeed, parameters used to describe compulsive overeating mirror the Diagnostic and Statistical Manual of Mental Disorders (DSM), Fifth Edition criteria for substance use disorder (SUD) (1). Thus, people who compulsively overeat report experiencing intense food cravings; food is often consumed in larger amounts than intended; unsuccessful efforts to cut down or control one's overeating are commonplace; lastly, dysregulated eating continues despite knowledge of it being a physical or psychological problem that is likely to have been caused by this behaviour. Behavioural/neurobiological and neurocognitive studies that provide some support for "food addiction" are described below; however, although there are overlaps in the clinical characteristics of food and substance addiction (7, 8), whether food can actually be addictive remains a subject of debate (9).

There are overlaps in brain regions involved in responding to food and drug cues, e.g., in areas that are involved in reward processing including the striatum, amygdala, and anterior insula (10, for rev) and secondly, for the involvement of dopaminergic systems in these areas in relation to susceptibility to diet induced obesity (11). Furthermore, compulsive overeating and drug abuse are associated with reward-circuitry dysfunction, e.g., reward system hyper-responsivity during exposure to high-calorie tastes has been associated with compulsive overeating behaviour in overweight and obese individuals (12), which is similar to what has been reported in response to the presence of drug-related cues in SUD (13, 14). Results are also broadly consistent with the proposal that repeated exposure to potentially addictive substances renders reward circuits hypersensitive to associated stimuli or cues (15, 16).

Neurocognitive similarities also exist between people who are compulsive overeaters and substance abusers. Both groups appear to have deficits in temporal discounting (TD)—an aspect of impulse control defined as "the observed tendency for the value of reinforcers to decrease as a function of the delay to their delivery" (17). The concept of TD originated from the well known Stanford Marshmallow Test in which young children could choose to eat one marshmallow immediately or wait indefinitely for two marshmallows (18). Contemporary TD tasks typically consist of multiple binary choices between smaller rewards available sooner and larger rewards available later. A stronger preference for smaller-sooner (SS) rewards denotes a greater degree of TD, which is considered to reflect higher impulsivity and lower self-control.

People with BN, BED and obesity, [like those with SUD (19, 20)] are reported to exhibit steeper rates of TD compared to healthy controls (21–29). In drug addiction, TD has also been used to gauge illness severity and treatment outcomes (19, 20). In relation to problematic eating behaviour, an increased propensity to act on immediate pleasure-driven desires has been linked to greater energy intake (30), to a higher probability of binge-eating (30), and poorer treatment response (31) in people who are overweight/obese, to increased eating disorder (ED) psychopathology in heavy drinkers (32), and to a higher BMI in the general population (32–35). Lastly, in people who frequently crave food, the tendency to discount the value of delayed rewards is reported to negatively influence susceptibility to the anti-craving effects of neuromodulation (36).

Research into neurocognitive markers of disordered eating has usually involved participants being separated/investigated as diagnostic groups. However, problems in executive function (including impulse control) may be better investigated across a spectrum of pathological eating behaviour, as they appear to be present transdiagnostically and also in subclinical cases (37, 38). Accordingly, we examined whether TD was linearly related to compulsive overeating and associated psychological and physiological disturbances. We recruited a large inclusive online sample and took into account a number of potential confounding variables. We hypothesised that increased rates of TD would be associated with a) increases in the frequency of compulsive overeating and compensatory behaviours, b) the severity of ED psychopathology, c) "food addiction", and d) BMI. We predicted these relationships would be independent of differences in demographic (age, sex, income, and education) and clinical (depression, anxiety, and stress) factors reported to influence TD behaviour (39–45).

MATERIALS AND METHODS

Participants

Male and female volunteers (≥18 years of age) were invited to complete an online survey investigating "impulsivity in ED and obesity" for the chance to win an Apple® iPad Mini™. They were recruited *via* online advertisements on a number of research recruitment webpages—including those of King's College London (KCL), Beat™ (Eating Disorders Association, United Kingdom), and the In-Mind Foundation—as well as on social media (Twitter® and Facebook®). Importantly, the advertisements stated that individuals could participate regardless of whether they had been diagnosed with an ED, i.e., the study involved a large inclusive participant sample, i.e., no diagnostic or exclusion criteria were applied. They were recruited/assessed online and we investigated whether TD was

related to compulsive overeating and associated problems. Questionaires were completed before the TD task. A total of 870 surveys were started and 432 (49.7%) of these were completed (perhaps due to the survey's relatively lengthy nature; data from uncompleted surveys are available on request).

This study was approved by the KCL Nursing and Midwifery Research Ethics Subcommittee, and data were obtained in compliance with KCL regulations. All participants were required to give electronic informed consent before they could gain access to the survey.

Measures

Demographics Questionnaire

This 23-42-item (19 items were response-dependent) self-report survey of general descriptive information included questions relating to sex, age, height, weight, ethnicity, income, education, and ED status. BMI = weight (kg)/(height (m)^2. was calculated for each participant.

Eating Disorder Examination-Questionnaire (EDE-Q) Version 6.0

This 33-item self-report inventory, derived from the EDE investigator-based interview, measures specific ED psychopathology over the past 28 days (46). It generates frequency data on key behavioural features of ED (e.g., compulsive overeating, vomiting, laxative misuse, over-exercising) and four subscale scores reflecting the severity of aspects of ED psychopathology (restraint, eating concern, shape concern, and weight concern). A global score is obtained by averaging subscale scores. Responses to items addressing ED severity are made on a 7-point scale (0–6), with scores ≥ 4 surpassing the recommended clinically relevant cut-off points (47). EDE-Q frequency data were used (in addition to subscale and global scores) to quantify compulsive overeating episodes and compensatory behaviours. The frequency of compulsive overeating episodes was defined as the number of times participants reported eating "what other people would regard as an unusually large amount of food, given the circumstances" accompanied by a "sense of having lost control over (their) eating, at the time (they) were eating" during the past 28 days (item 14). Frequency of compensatory behaviours was defined as the number of times participants reported making themselves "sick (vomit)…/taken laxatives as a means of controlling (their) shape or weight" or "exercised in a driven or compulsive way as a means of controlling (their) weight, shape or amount of fat, or to burn off calories" during the past 28 days (sum of items 16, 17, and 18).

Yale Food Addiction Scale (YFAS)

This self-report questionnaire measures addictive eating behaviour within the past 12 months (48). It contains 25 items (17 five-point frequency scales and eight binary choices) which map on to the DSM, 4th Edition, Text Revision criteria for substance dependence. It provides a continuous symptom count (0–7) and a dichotomous score (yes or no) denoting whether its criteria for food addiction have been met (a "diagnosis" is given if at least three symptoms and a clinically significant impairment or distress are present).

Depression Anxiety and Stress Scales-21 (DASS-21)

This self-report inventory assesses the frequency/severity of negative emotions experienced during the previous week (49). It consists of three 7-item subscales that measure depression, anxiety, and stress. Responses are made on a 4-point scale (0–3), and a separate score is generated for each dimension by summing values for relevant items and multiplying the total by 2. Scores indicate moderate to extremely severe levels of depression, anxiety and stress.

Temporal Discounting (TD) Task

TD behaviour was assessed with a hypothetical monetary choice task modelled on a paradigm developed previously (50, 51). Eighty binary choices were administered in succession: for each one, participants indicated whether they would prefer to receive a smaller amount of money available immediately (SS reward) or a larger amount available after a 3-month time delay [larger-later (LL) reward]. Two types of decision framing were employed: Accelerate and Delay. In the Accelerate set, the LL reward remained at £100 and the SS reward increased from £20 to £98 in £2 increments, resulting in a total of 40 binary choices. Alternatively, in the Delay set, the SS reward was fixed at £50 while the LL reward increased from £52 to £130 in £2 increments, also resulting in a total of 40 binary choices. The 80 choices were presented in a random order, which was the same for each participant.

TD was quantified by determining participants' discount factor (DF)—the magnitude of reduction in the present value of a future reward—for each choice set using a two-step procedure (23, 36, 50) (global DF was also calculated as the mean of the two DFs). First, the "indifference point" was established. This is the amount of money that the participant judged as equivalent to the fixed reward—i.e., the value of the variable reward when the participant switched from LL to SS in the Accelerate set and from SS to LL in the Delay set (50). Second, a formula was fitted to the indifference point: $\delta = (x_1/x_2)^{(1/(t2-t1))}$, where x_1 is the SS reward, x_2 is the LL reward, and t_2-t_1 is the delay to reward presentation (in years), which in this case was 0.25 (50, 51) This is a sensitive measure of TD that is independent of hyperbolic modelling and area under the curve analyses (50, 51)The values obtained can range from 0 to 1, with smaller numbers indicating greater TD and thus a greater tendency to choose the immediate reward. When no indifference point was calculable (i.e., when no switch was made between SS and LL rewards) a default score was assigned: 0 if the SS reward was always selected and 1 if the LL reward was always chosen.

Data Analysis

Statistical analyses were performed, according to recommendations from a biostatistician at KCL, using IBM® SPSS® software (Version 22). All tests were two-tailed: the level of significance was set at $\alpha = 0.05$.

Inspection of histograms indicated that TD data were positively skewed. Square-root transformations were performed to Accelerate and Delay DFs, and these were effective in normalising the data. The global DF was then calculated as the mean of the transformed scores (GlobalSqrtDF). To test for potential confounders, a series of multiple linear regressions were conducted with GlobalSqrtDF as the dependent variable. Age, annual personal income, highest level of education, sex, and depression, anxiety, and stress DASS-21 subscale scores were entered as independent variables (the former three were dummy coded) in a forward manner based on statistical significance. Since no model was able to predict changes in GlobalSqrtDF ($R^2 < 0.06$, $p > 0.10$ for all models), these variables were excluded from further analyses.

Bivariate correlations were used to investigate the relationships between raw DFs, the frequency of compulsive overeating episodes and compensatory behaviours (as reported in the EDE-Q), subscale and global EDE-Q scores, continuous YFAS score, and BMI. Pearson's r (parametric) and Spearman's rho (non-parametric) correlation coefficients were employed.

RESULTS

Demographic Characteristics

For the income and education variables, "prefer not to say" (n = 77) and "other" (n = 56) responses were coded as missing values, respectively. When there were obvious reporting errors, e.g., height values outside the expected range, these were removed from the dataset (n = 16). [These were defined as observations lying ±3 SD from the average adult male (177.2 cm, SD = 8.1) and female (163.0 cm, SD = 7.8) heights in the UK (52)]. To eliminate the remaining suspected erroneous BMI data, entries ±3 SD from the sample mean (M = 25.71, SD = 10.45) were discarded (n = 6). National averages were not used here as the sample contained individuals with extreme weight conditions (AN and BED).

The sample consisted of 384 females and 48 males: 52.8% were aged between 18–24 and 70.4% self-defined their ethnicity as "white". After presumed erroneous entries were removed (n = 22, see above), the mean BMI [weight (kg)/(height (m)^2] was 24.91 (SD = 7.76, range: 12.76-56.80): 12.2% of participants were underweight (<18.50); 55.4% were of normal weight (18.50–24.99); 13.2% were overweight (25–29.99); and 19.3% were obese (≥30) (NHS, 2014). Of the participants who declared their annual personal income (n = 355), 60.3% earned <£20,000 and, of those who specified their highest level of education (n = 376), 65.7% had Higher Education qualifications. More detailed demographic information is provided in **Table 1**.

TABLE 1 | Demographic characteristics.

	n (M)	% (SD)
Sex	432	100
Male	48	11.1
Female	384	88.9
Age	432	100
18–24	228	52.8
25–34	138	31.9
35–44	36	8.3
45–54	20	4.6
55–64	6	1.4
65+	4	0.9
Ethnicity	432	100
White	304	70.4
Mixed	23	5.3
Asian	44	10.2
Black	20	4.6
Arab	29	6.7
Other	12	2.8
Annual personal income	355	82.2
<£20,000	214	60.3
£20,000–£39,000	94	26.5
£40,000–£59,999	19	5.4
£60,000–£99,999	15	4.2
>£100,000	13	3.7
Highest level of education[a]	376	87.0
No qualifications	17	4.5
Secondary/Further Education	112	29.8
Higher Education	247	65.7
BMI	410 (24.91)	94.9 (7.76)
Underweight	50 (16.85)	12.2 (1.37)
Normal weight	227 (21.55)	55.4 (1.79)
Overweight	54 (27.16)	13.2 (1.49)
Obese	79 (38.14)	19.3 (6.96)
Self-reported eating disorder diagnosis	432	100
No eating disorder	301	69.7
Anorexia nervosa	42	9.7
Bulimia nervosa	36	8.3
Binge eating disorder	24	5.6
Other	29	6.7

M, mean; SD, standard deviation; BMI, body mass index.
[a]*Categories used correspond to UK Education System.*

Clinical Features and Temporal Discounting

Table 2 summarises scores on the TD task and outcomes for each of the clinical measures in the survey. The full range of possible scores was observed across all scales excepting the YFAS continuous symptom count, for which the maximum value of seven was not obtained by any participant. The mean global EDE-Q score was 2.94 (SD = 1.70), and 32.6% of participants had clinically relevant scores (≥4; Rø et al., 2012). One third of participants (33.1%) met criteria for food addiction according to the YFAS [see above; (48), and the mean continuous score for the sample as a whole was 2.88 (SD = 1.87)]. Mean DASS-21 scores were within the moderate range for depression (14–20; M = 16.25, SD = 13.42) and anxiety (10–14; M = 12.25, SD = 11.00), and within the mild range for stress (15–18; M = 16.25, SD = 13.42). Severe or extremely severe levels of depression (≥21), anxiety (≥15), and stress (≥26) were reported by 38.2%, 37.3%, and 31.0% of participants, respectively. The mean DF was 0.37 for the Accelerate set and 0.34 for the Delay set. The difference between these scores was significant (z = -4.72, p < .001): individuals discounted the future reward more when asked to delay consumption than when given the opportunity to accelerate consumption.

Correlations between TD rates and other variables are shown in **Table 3**. Accelerate DF and Delay DF were highly positively

TABLE 2 | Clinical features and temporal discounting.

	Mean	*SD*	Range
EDE-Q	–	–	–
Restraint	2.61	1.80	0.00–6.00
Eating concern	2.25	1.82	0.00–6.00
Shape concern	3.65	1.86	0.00–6.00
Weight concern	3.26	1.89	0.00–6.00
Global	2.94	1.70	0.00–6.00
Number of compulsive overeating episodes[a]	6.13	12.88	0.00–100.00
Number of compensatory behaviours[b]	11.44	24.20	0.00–295.00
YFAS	–	–	–
Continuous	2.88	1.87	0.00–6.00
Dichotomous (yes/no)	*n* = 143/289	% = 33.1/66.9	–
DASS-21	–	–	–
Depression	16.25	13.42	0.00–42.00
Anxiety	12.25	11.00	0.00–42.00
Stress	17.13	12.32	0.00–42.00
Temporal discounting (DF)[c]	–	–	–
Accelerate	0.37	0.33	0.00–1.00
Delay	0.34	0.29	0.00–1.00
Global	0.35	0.29	0.00–1.00
Sqrt accelerate	0.52	0.30	0.00–1.00
Sqrt delay	0.52	0.26	0.00–1.00
Sqrt global	0.52	0.26	0.00–1.00

SD, standard deviation; EDE-Q, Eating Disorders Examination-Questionnaire; YFAS, Yale Food Addiction Scale; DASS-21, Depression Anxiety and Stress Scales 21; DF, discount factor; Sqrt, square-root transformed.

[a]EDE-Q item 14: "On how many of these times did you have a sense of having lost control over your eating, at the time you were eating?" (Follows the question "Over the past 28 days, how many times have you eaten what other people would regard as an unusually large amount of food, given the circumstances)?

[b]Sum of EDE-Q items 16, 17 and 18: "Over the past 28 days, how many times have you [Item 16] made yourself sick (vomit) as a means of controlling your shape or weight/[Item 17] taken laxatives as a means of controlling your shape or weight/[Item 18] exercised in a driven or compulsive way as a means of controlling your weight, shape or amount of fat, or to burn off calories?

[c]Smaller discount factors indicate greater temporal discounting.

and significantly correlated. Furthermore, all eating-related outcomes (EDE-Q scores, EDE-Q frequency data, the YFAS continuous score) were significantly positively interrelated with each other. Global DF was modestly but significantly negatively related to the frequency of compulsive overeating episodes and with compensatory behaviours (as reported in the EDE-Q). Global DF was also modestly but significantly negatively related, to eating, shape and weight concern (EDE-Q subscale scores), to the global EDE-Q score, to the YFAS symptom count, and to BMI. Lastly, a greater tendency to choose the SS reward (increased TD) was associated with higher scores across these outcome measures.

DISCUSSION

This research sought to extend studies examining relationships between TD and eating-related pathological behaviours. We used a large inclusive sample of participants (i.e., no diagnostic or exclusion criteria were applied). They were recruited and

TABLE 3 | Correlations between temporal discounting rates and clinical variables.

		1	2	3	4	5	6	7	8	9	10	11
1	Accelerate DF[a]	–	–	–	–	–	–	–	–	–	–	–
2	Delay DF[a]	.71**	–	–	–	–	–	–	–	–	–	–
3	Global DF[a]	.90**	.94**	–	–	–	–	–	–	–	–	–
4	EDE-Q restraint	-.04	-.08	-.08	–	–	–	–	–	–	–	–
5	EDE-Q eating concern	-.15**	-.16**	-.17**	**.73****	–	–	–	–	–	–	–
6	EDE-Q shape concern	-.14**	-.18**	-.18**	**.75****	**.82****	–	–	–	–	–	–
7	EDE-Q weight concern	-.14**	-.16**	-.18**	**.73****	**.84****	**.94****	–	–	–	–	–
8	EDE-Q global	-.12*	-.15**	-.16**	**.87****	**.92****	**.95****	**.95****	–	–	–	–
9	Compulsive overeating episodes[b]	-.11*	-.11*	-.12*	.39**	.59**	.50**	.50**	.53**	–	–	–
10	Compensatory behaviours	-.12*	-.11*	-.12*	.60**	.54**	.53**	.49**	.58**	.32**	–	–
11	YFAS continuous	-.17**	-.13**	-.16**	**.45****	**.70****	**.62****	**.62****	**.65****	.57**	.35**	–
12	BMI[c]	-.09	-.10	-.10*	-.12*	-.05	-.00	.04	-.03	.13**	-.25**	.05

DF, discount factor; EDE-Q, Eating Disorder Examination-Questionnaire; YFAS, Yale Food Addiction Scale; BMI, body mass index.

*Coefficients in normal text are Spearman's Rho; coefficients in bold text are Pearson's R. **p < 0.05; ***p < 0.01*

[a]Smaller discount factors indicate greater temporal discounting; [b] n = 428; [c] n = 410

assessed online. Using our dimensional and symptom based (rather than diagnostic) approach, we found that an increase in TD rate were linearly associated with a) an increase in the frequency of compulsive overeating and compensatory behaviours, b) the severity of "food addiction", c) ED psychopathology (eating, shape and weight concerns), and d) BMI. These findings were not confounded by demographic (age, sex, income, and education) or clinical (depression, anxiety, and stress) factors reported to affect TD behaviour (39–44). The results on measures of are consistent with literature reporting that excessive TD is involved in addictive behaviour and related disturbances (53–55) and consistent with our hypotheses.

The idea that excessive TD operates as an antecedent to compulsive overeating seems plausible, e.g., an individual may choose to overeat having decided that immediate gratification outweighs any adverse effects on future health and well-being. Several studies are consistent with this proposal. In a longitudinal study spanning mid-adolescence to young adulthood (56), it was reported that baseline TD predicted adoption of smoking in later life. A second study (57) demonstrated that male social drinkers who displayed steeper rates of TD when they entered a bar showed greater increases in blood alcohol levels when they exited. Thirdly, it has been reported (58) that 4-year-olds who were less able to delay gratification had higher BMI when followed-up approximately 30 years later.

Several models have been proposed to explain how the initiation of compulsive overeating could be related to. failures in self-control. According to one study (59), a disposition to act rashly when distressed is likely to increase the risk of impulsive engagement in bulimic behaviours when it is coupled with a psychosocial learning history that emphasises the benefits of eating and of thinness. On the other hand, it has been proposed that impaired self-regulatory control (underpinned by dysregulation of frontostriatal circuitry) interacts with hunger to release eating behaviour from control systems, and this results in binge eating (60). Lastly, it has been hypothesised that compulsive overeating results from an imbalance between "top-down" (cognitive) and "bottom-up" (appetitive) neural systems. In this scenario, exposure to relevant cues or ingestion of hyperpalatable foods would heighten activity in subcortical reward regions such that prefrontal self-control mechanisms will be less able to regulate behaviour (61): negative affect and resource depletion might amplify this effect (61).

Although TD rate is seen as a relatively stable personality trait, there is evidence that it can be modified by behavioural, pharmacological, and neuromodulatory techniques (for revs, see 62, 63). Moreover, experimentally induced improvements in TD behaviour have been reported to occur alongside reductions in ED symptoms in people with AN and BN and with energy intake in overweight/obesity (64, 65). Given the linearity of the relationships seen in this study, manipulations promoting adaptive intertemporal decision-making could also serve as preventative measures if implemented in at-risk groups. One approach could include a focus on early, pre-syndromal stages of illness as this time period is reported to be associated with better outcomes in ED and obesity (66–68).

As this study is cross-sectional, it does not allow for causal inferences. Another possible limitation is the self-report nature of its demographic data. For example, only 50% of participants completed the survey and secondly, the accuracy of BMI values may be somewhat compromised by the tendency of people to overestimate height and underestimate weight: however, such unidirectional response biases have little impact on correlational analyses. The clinical data were also obtained *via* self-report methods: however, the instruments used (DASS-21, EDE-Q, and YFAS) are standardised measures with adequate criterion and/or construct validity (48, 69, 70).

In relation to the TD task, evidence indicates that discounting rates for real and hypothetical rewards do not differ significantly, and that results from experiments with hypothetical rewards apply to everyday life (71). However, our paradigm may have been limited by its restriction to choices between immediate rewards and rewards delayed by three months, i.e., a replication study might be better if it involved using titration procedures that collect data across multiple delay periods. In this context, it is also of note that differences in TD paradigms also hinder comparisons between different TD studies, such as those related to SUD versus those investigating compulsive overeating.

Although we had no exclusion criteria, the location of the adverts and the topic ("impulsivity in ED and obesity") may have biased recruitment towards particular individuals (e.g., university students and/or people with an ED/obesity). It is therefore not surprising that there was quite a high percentage of participants who met criteria for food addiction and also for severe depression. Similarly, the chance to win an Apple® iPad Mini™ may have had more motivational value for certain groups (72). Thus, our sample may have been somewhat unrepresentative in terms of age, sex, income, and education, and this could have contributed to these variables' lack of influence over TD. Furthermore, in the context of the participant cohort, it could be argued that only participants with greater executive control would persevere with completing the online survey: however, this possible effect is likely to be cancelled out as the participants did not have a diagnosis and were compared with each other. Lastly, it is perhaps surprising that BMI and measures of TD are not significantly correlated: it is possible; however, that only certain phenotypes (especially those associated with loss-of-control or addictive eating) would show increased delay counting.

In summary, our study advances understanding of the relationships between TD and eating-related pathologies. We have replicated previous studies demonstrating linear associations between TD rate and a) ED psychopathology (based on the data from the EDE-Q), and b) BMI. We have also shown, that TD is unambiguously and linearly related to compulsive overeating, to compensatory behaviours, and lastly to "food addiction" based on scores from the YFAS).

Future studies should determine whether TD predisposes individuals to compulsive overeating and associated psychological and physiological disturbances, and whether prevention and intervention programmes aimed at helping people lower the rate at which they discount the value of future health benefits can induce clinically meaningful behavioural change.

DATA AVAILABILITY STATEMENT

The datasets generated for this study are available on request to the corresponding author.

ETHICS STATEMENT

This study was approved by the KCL Nursing and Midwifery Research Ethics Subcommittee, and data were obtained in compliance with KCL regulations. All participants were required to give electronic informed consent before they could gain access to the survey. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

MK, JM, SB, and RC were involved in conducting the study. MK, JM, and SB were involved in analyzing the data and writing the paper. IC and US were involved in writing the paper and supervising the project.

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BRIEF RESEARCH REPORT
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Cognitive-Behavioral Therapy for Postbariatric Surgery Patients With Mental Disorders: A Pilot Study

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Background: Binge-eating disorder (BED) and major depressive disorder (MDD) following bariatric surgery are significant predictors for less post-operative weight loss and/or weight regain, however, cognitive-behavioral therapy (CBT) addressing these disorders following surgery has not been investigated so far.

Objective: This study examined feasibility of a short-term CBT based on evidence-based manuals for BED and MDD that were adapted to patients following bariatric surgery, and investigated its effectiveness in improving weight loss outcome, psychopathology, and psychosocial functioning.

Materials and Methods: In an uncontrolled proof-of-concept study, the CBT manual was piloted in N = 7 patients who had undergone roux-en-Y gastric bypass surgery at least 6 months before. Weight loss, eating disorder psychopathology, depressive symptoms, and self-esteem were assessed using clinical interviews and self-report questionnaires at pre-treatment, post-treatment, and in a 3-month follow-up.

Results: A significant reduction of body weight was found as well as medium to large effects in the improvement of eating disorder psychopathology, depressive symptoms, and self-esteem from pre-treatment to post-treatment were found. Most of those changes remained stable during the 3-month follow-up period. Study retention was 71.4%.

Conclusions: Feasibility and effectiveness of CBT were documented for patients with BED or MDD following bariatric surgery. Adaptations of the study procedure for proof-of-efficacy in randomized-controlled studies are discussed.

Keywords: cognitive-behavioral therapy, psychotherapy, bariatric surgery, binge-eating disorder, major depressive disorder

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INTRODUCTION

Bariatric surgery is the only efficacious treatment for patients with severe obesity (body mass index, BMI ≥ 40 kg/m^2 or ≥ 35 kg/m^2 with comorbidity), resulting in substantial long-term weight loss up to 20 to 35% of initial body weight and decreased morbidity and mortality (1–4). However, research has shown that 20% of patients experience only minor weight loss 1 year after surgery (5, 6) and 33%

of patients experience minor weight loss 10 years after surgery (7). Additionally, up to 50% of patients experience weight regain within 2 years after surgery (8).

Significant predictors for less post-operative weight loss and/or weight regain have been identified with post-operative eating disturbances or disorders (9–13), e.g. binge-eating disorder (BED) or loss of control (LOC) eating as well as major depressive disorder (MDD) in up to 27% (14) and 17% (15) of the patients, respectively. For example, post-operative LOC eating leads to a ≥ 8 lesser BMI loss and weight regain in the long-term (16, 17) and post-operative MDD was associated with ≥ 10% lesser percentage of weight loss in the third year following surgery (15). In addition to insufficient weight loss outcome, patients with post-operative LOC or MDD suffer from increased eating disorder and general psychopathology, and impairments in quality of life (16, 17).

Although recommended in clinical guidelines for bariatric surgery (18–20), post-operative behavioral management is not performed systematically and is not sufficiently based on evidence. Two meta-analyses on randomized-controlled trials (RCTs) documented the positive effect of post-operative behavioral management on post-operative weight loss compared to usual care. However, primarily addressing diet and physical activity in patients unselected for psychopathology, neither study comprehensively addressed post-operative mental disorders diagnosed with clinical interviews (21, 22). To the best of our knowledge, only one uncontrolled study examined a six session telephone-based cognitive-behavioral therapy (CBT) and found patients following bariatric surgery unselected for psychiatric symptoms experiencing significant reductions in depressive and anxious symptoms pre- to post intervention (23, 24).

Despite the clinical relevance of BED and MDD following bariatric surgery, there is no study to date that examined psychological treatment for patients with diagnosed post-operative mental disorders. Therefore, we aimed at piloting a CBT, the most established treatment for patients with BED (25) and MDD (26). The CBT manual comprised evidence-based interventions focusing on BED and MDD adapted to the specific needs of patients following bariatric surgery. In an uncontrolled proof-of-concept study, we examined feasibility (e.g. acceptance, retention) and sought to evaluate the effects of the CBT manual in improving weight loss outcome (e.g. BMI). Furthermore, changes in eating disorder and general psychopathology, as well as psychosocial functioning, were assessed.

METHODS

Patients, Recruitment, and Study Procedure

Patients (aged ≥ 18 years) were eligible if they had undergone roux-en-Y gastric bypass (RYGB) surgery at least 6 months ago and were post-operatively diagnosed with BED and/or MDD. Patients were excluded when they were diagnosed with psychotic disorder, bipolar disorder, substance-related disorder, current suicidal ideation, and ongoing psychotherapy. The study was approved by the local institutional review board and written informed consent was obtained from all patients prior to study enrollment. Patients were recruited at the obesity outpatient clinic of the Integrated Research and Treatment Center Adiposity Diseases, University of Leipzig Medical Center, Germany. During their regular post-operative follow-up visits, the interdisciplinary team informed all patients about the study. Patients who were interested were screened via telephone interview. Eligible patients were invited to a diagnostic session. Assessments included objective measurements of weight and height, structured clinical interviews, and self-report questionnaires, and were conducted at pre-treatment and post-treatment (in-person visits), and at 3-month follow-up (telephone interviews and posted questionnaires) by a trained and supervised assessor.

Cognitive-Behavioral Therapy (CBT)

We compiled a modular short-term psychotherapy manual selecting interventions from two evidence-based CBT manuals for BED (27) and MDD (28), in order to meet the needs of patients with post-operative mental disorders. In addition to these established interventions for BED (e.g. self-monitoring of food intake) and/or MDD (e.g. thought records), the POSTBAR manual (Post-operative CBT for bariatric surgery patients) included adaptations focused on nutritional and behavioral recommendations following bariatric surgery (e.g. portion sizes, supplementation). The CBT manual comprised 15 individual face-to-face sessions à 50 min within 5 months. Within the first 3 months, sessions were scheduled weekly, while the last three sessions were scheduled biweekly. The initial treatment phase aimed for motivational enhancement (three sessions), the intensive treatment phase comprised modules on BED and/or MDD (nine sessions), and the final self-management phase focused on relapse prevention (three sessions). All sessions were delivered by a licensed cognitive-behavioral therapist (first author), and were regularly supervised (second author). Therapy adherence was defined as the attendance of at least 12 sessions (29).

Measures

BMI

At pre- and post-treatment, BMI was calculated from measured body weight and height. At 3-month follow-up, body weight was self-reported.

Diagnosis of BED and eating disorder psychopathology

Post-operative eating behavior within the last 3 months was assessed using an adapted German version of the semi-structured Eating Disorder Examination interview (EDE) (30). The EDE–Bariatric Surgery Version (EDE-BSV) comprised diagnostic items as well as additional items to assess eating behavior following bariatric surgery (17). According to the fifth edition of the *Diagnostic and Statistical Manual of Mental*

Disorders (31), BED is defined through recurrent objective binge-eating episodes (OBEs; eating an objectively large amount of food accompanied by a sense of LOC over eating in the absence of compensatory behaviors). As the patients' ability to consume an objectively large amount of food following bariatric surgery is limited, subjective binge-eating episodes (SBEs; eating a subjectively large amount of food with concomitant LOC) were allowed for full-syndrome diagnosis of BED in addition, in line with previous research (17). Further, subsyndromal BED (i.e. presence of two behavioral indicators or lack of distress) (29), and BED of low frequency/limited duration were diagnosed (i.e. binge-eating episodes less than once per week) (31). Furthermore, the German version of the EDE-Questionnaire (EDE-Q) was administered to assess eating disorder psychopathology during the past 28 days with 22-items answered on a seven-point scale (0 = feature was absent, 6 = feature was present to an extreme degree) (32). A global mean score was computed with higher scores indicating higher levels of global eating disorder psychopathology.

Diagnosis of MDD and depressive disorder psychopathology

The Structured Clinical Interview for DSM-5 diagnoses (33) was used to diagnose current MDD. The severity of depressive symptoms during the past two weeks was measured using the nine items of the depression module of the German version of the Patient Health Questionnaire (PHQ-9) (34). The nine items were answered on a four-point scale (0 = not at all, 3 = nearly every day) with a higher sum scores indicated higher levels of depressive symptoms.

Quality of life

Obesity-specific quality of life was assessed with the German version of the Impact of Weight on Quality of Life–Lite (35). Patients answered the 31 items on a five-point scale (0 = never true, 4 = always true). Higher sum scores indicated poorer quality of life during the last week.

Self-esteem

Overall liking of oneself was measured with the ten items of the German version of the Rosenberg Self-Esteem Scale (36). Items were answered on a four-point scale (0 = strongly disagree, 3 = strongly agree), and higher mean scores indicated higher levels of self-esteem.

Feasibility

To assess acceptance, patients answered the questions "How satisfied have you been with the treatment?" and "How helpful was the treatment for your problem?" on ten-point scales (0 = not at all; 10 = very much) at post-treatment.

Data Analysis

Data analysis was carried out using the Statistical Package for the Social Sciences (SPSS 24.0 for Windows; (37). Descriptive analyses were used to report feasibility and to present patients' characteristics. Inferential analyses were based on all patients applying intent-to-treat analyses using last observation carried forward methods for the two patients who did not finished treatment nor assessments, a patient who did not return the questionnaires at 3-month follow-up and for a patient who received an unplanned revision surgery during treatment (i.e. pre-revisional body weight carried forward for post-treatment and 3-month follow-up). Changes from pre-treatment to post-treatment and 3-month follow-up were analyzed using nonparametric Fisher's exact tests for categorical variables and Friedman tests for continuous variables. For the latter, Wilcoxon signed-rank tests including Bonferroni-Holm corrections were run in order to calculate effect sizes. Effect sizes φ and r with ≤ 0.3, ≤ 0.5, and ≥ 0.5 correspond to small, medium, and large effects, respectively (38). Significance was determined at a two-tailed $p < 0.05$.

RESULTS

Sample Characteristics

Seven patients were included (four females, M ± SD: age 48.6 ± 10.0 years, BMI 41.85 ± 4.34 kg/m^2). Two patients were diagnosed with MDD as primary diagnosis and BED as a secondary diagnosis, four patients were diagnosed with BED only, and one patient was diagnosed with MDD only (**Table 1**).

Feasibility

During 3 months of recruitment, 98 patients with at least 6 months since RYGB surgery were scheduled for regular post-operative follow-up visits. Overall, 16 patients were identified as in need of psychological treatment and were screened by the study team. From those patients, nine were excluded for organizational reasons (i.e. lack of time; N = 3), travel distance (N = 3), and lack of psychopathology (N = 3). Seven patients completed treatment and follow-up assessments, however, two patients (F, G) dropped out before end of treatment (session 10 and session 6, respectively), resulting in a retention rate of 71.4%. Individual treatment sessions were scheduled according to the study protocol. Patients indicated good acceptance of treatment (satisfaction: 7.2 ± 4.2; helpfulness: 7.4 ± 3.0).

Pre- to Post-Treatment and Follow-Up Changes

Individual and overall changes in clinical variables are presented in **Tables 1** and **2**. For weight loss, we found significant changes: with large effects, weight loss increased from pre- to post-treatment as well from pre-treatment to 3-month follow-up.

Changes in the frequency of BED and MDD diagnoses were not significant (all ps > 0.05), however, small to medium effect sizes indicated decreases in the frequency of diagnoses from pre- to post-treatment (φBED = 0.3; φMDD = 0.4), as well as from pre- and post-treatment to 3-month follow-up (all φs ≥ 0.4). In detail, one patient was diagnosed with BED of low frequency/limited duration with SBEs and one patient fulfilled MDD criteria at post-treatment. At 3-month follow-up, only one patient was diagnosed with a BED of low frequency/limited duration with OBEs and none of the patients fulfilled MDD criteria.

For self-reported eating disorder psychopathology, depressive symptoms, and quality of life no significant changes were found

TABLE 1 | Patient characteristics and individual changes in clinical variables for pre-treatment, post-treatment, and 3-month follow-up assessments.

Patient characteristics	**Patient A**			**Patient B**			**Patient C**		
Age	60–65			30–35			50–55		
Diagnosis	BED with SBEs; MDD			BED with SBEs (sub); MDD			BED with SBEs		
Months since RYGB	8			7			21		
Weight (kg) before RYGB	166			195			117		
Weight regain in kg after nadir[a]	4			None			6		
Individual changes	Pre-treatment	Post-treatment	3-month follow-up	Pre-treatment	Post-treatment	3-month follow-up	Pre-treatment	Post-treatment	3-month follow-up
Body weight in kg	139.9	129.0	127.0	134.9	123.9	121.2	95.3	93.7	91.6
BMI in kg/m^2	51.4	47.4	46.7	38.6	35.4	36.2	37.7	37.1	36.2
%EWL	43.0	61.0	64.3	78.2	92.5	96.0	37.7	40.5	44.2
BED/MDD diagnosis[b]	1/1	0/0	0/0	1/1	0/1	1/0	1/0	1/0	0/0
EDE-Q	4.1	2.3	2.5	0.9	0	0	2.6	3.5	3.8
PHQ-9	17	11	12	12	9	9	7	7	11
IWQOL	101	92	92	3	3	3	38	29	35
RSES	1.8	2.3	2.5	3.1	3.7	3.7	3.1	3.1	3.4

Patient characteristics	**Patient D**			**Patient E**			**Patient F[c]**	**Patient G[c]**
Age	46–50			36–40			46–50	56–60
Diagnoses	BED with SBEs (sub)			MDD			BED (sub)	BED
Months since RYGB	63			19			25	78
Weight in kg before RYGB	155			180			180	146
Weight regain in kg after nadir[a]	20			None			4	38
Individual changes	Pre-treatment	Post-treatment	3-month follow-up	Pre-treatment	Post-treatment	3-month follow-up	Pre-treatment	Pre-treatment
Body weight in kg	122.0	120.0	120.0	139.6	131.0	130.0	128.5	115.9
BMI in kg/m^2	38.9	38.3	38.3	43.6	40.9	40.6	40.6	42.1
%EWL	46.6	49.4	49.4	56.2	68.2	69.5	72.2	49.1
BED/MDD diagnosis[b]	1/0	0/0	1/0	0/1	0/0	0/0	1/0	1/0
EDE-Q	4.0	2.7	2.6	2.8	3.6	2.5	3.1	4.4
PHQ-9	12	0	6	17	6	5	14	16
IWQOL	83	47	36	41	70	70	29	85
RSES	2.2	2.9	3.5	1.7	2.5	2.6	2.8	1.3

[a]Nadir = lowest weight after bariatric surgery. [b]Dichotomous: 0 = no, 1 = yes. [c]Patient did not complete treatment and diagnostic assessments, for all further analysis, intention-to-treat analysis with last observation carried forward method was applied. BED, binge-eating disorder; BMI, body mass index; EDE-Q, Eating Disorder Examination-Questionnaire (0–6); IWQOL, Impact of Weight on Quality of Life (0–4); MDD, major depressive disorder; PHQ, Patient Health Questionnaire (0–3); RSES = Rosenberg Self-Esteem Scale (0–3); SBE, subjective binge-eating episodes; sub, subsyndromal; %EWL, percentage of excess weight loss.

TABLE 2 | Differences in clinical variables for pre-treatment, post-treatment, and 3-month follow-up assessments.

	***M* (*SD*)**			χ^2**(2)**	***Z* (*r*)**		
	Pre-treatment	**Post-treatment**	**3-month follow-up**		**Pre-treatment vs. post-treatment**	**Pre-treatment vs. 3-month follow-up**	**Post-treatment vs. 3-month follow-up**
Body weight in kg	125.2 (15.9)	120.3 (12.9)	119.2 (13.2)	9.6**	−2.0* (0.8)	−2.0* (0.8)	−1.8† (0.7)
BMI in kg/m^2	41.8 (4.7)	40.2 (3.9)	39.9 (4.0)	9.6**	−2.0* (0.8)	−2.0* (0.8)	−1.8† (0.7)
%EWL	54.7 (15.2)	61.8 (17.6)	63.5 (18.0)	9.6**	−2.0* (0.8)	−2.0* (0.8)	−1.8† (0.7)
EDE-Q	3.0 (1.5)	2.8 (1.4)	2.7 (1.4)	0.6	−0.7 (0.3)	−1.2 (0.5)	−0.1 (0.0)
PHQ-9	13.6 (3.6)	9.0 (5.4)	10.4 (4.0)	4.8†	−1.8† (0.7)	−1.5 (0.6)	−1.3 (0.5)
IWQOL	54.3 (35.7)	50.7 (32.9)	50.0 (32.8)	1.7	−0.7 (0.3)	−0.7 (0.3)	−0.4 (0.2)
RSES	2.3 (0.7)	2.7 (0.7)	2.8 (0.8)	9.0*	−1.8† (0.7)	−2.0* (0.8)	−1.8† (0.7)

*N = 7; BED, binge-eating disorder; BMI, body mass index; EDE-Q, Eating Disorder Examination-Questionnaire (0–6); IWQOL, Impact of Weight on Quality of Life (0–4); MDD, major depressive disorder; PHQ = Patient Health Questionnaire (0–3); RSES = Rosenberg Self-Esteem Scale (0–3); %EWL = percentage of excess weight loss; χ^2 = Friedman chi-square statistics; Z = Wilcoxon Z-statistics; r = effect size (r) interpreted as small ≤ 0.3, medium ≤ 0.5, large ≥ 0.05. **p < 0.01, *p < 0.05, †p < 0.10.*

from pre- to post-treatment as well as from pre-treatment to 3-month follow-up. Self-esteem significantly increased from pre-treatment to 3-month follow-up. Effect sizes, however, indicated small to large effect changes: For eating disorder psychopathology, a small effect decrease from pre- to post-treatment and a large effect decrease from pre-treatment to 3-month follow-up was found. From pre- to post-treatment as well as 3-month follow-up, a large effect decrease in depressive symptoms was found. Although there was an increase of depressive symptoms from post-treatment to 3-month follow-up. For quality of life, medium effect changes between pre- and post-treatment as well as pre-treatment and 3-month follow-up indicated a decrease of impact of weight on quality of life. Finally, large effect sizes indicated increasing levels of self-esteem from pre- to post-treatment and from pre-treatment to 3-month follow-up.

DISCUSSION

We examined feasibility and effects of CBT addressing BED and MDD in patients following bariatric surgery. The POSTBAR manual comprised evidence-based CBT interventions in 15 individual sessions that aimed for improving long-term weight loss outcome, psychopathology, and psychosocial functioning. Recruitment of patients was manageable, acceptance of treatment was high, and retention rates were comparable with those previously published (13, 21). Our results showed significant reductions in body weight and medium to large effect sized improvements in eating disorder psychopathology, depressive symptoms, and self-esteem. More importantly, most of these changes remained stable during 3-month follow-up. Overall, findings extended evidence for the positive effect of behavioral management on weight loss outcome and psychosocial functioning (21).

A major strength of the study is the thorough psychopathological assessment, as BED and MDD were assessed via clinical expert interviews. Additionally, inclusion and exclusion criteria allowed for the recruitment of a diverse sample of RYGB surgery patients with regard to age, body weight, weight loss, and interval since surgery. Thus, the study procedure and the adapted manual are applicable to patients independently of whether they are within their initial weight loss phase or whether they have already gained weight. However, further research should investigate when post-operative CBT should best be delivered.

The results need to be interpreted with regard to several limitations. First, the study likely had insufficient power to detect statistically significant differences. Therefore, we provided effect sizes for interpretation of the non-significant test statistics in the small sample. Second, the significant decrease of body weight should be interpreted with caution. Four of five patients have had surgery less than 2 years before study inclusion and might therefore still have been in their initial weight loss phase. Pre-treatment characteristics, however, documented that half of them already reported weight regain following their lowest post-operative body weight. Nevertheless, following CBT treatment, all of them had lost body weight at post-treatment and 3-month follow-up. Third, given the uncontrolled study design, we could not draw causal interpretation in the way that improvements could be solely attributed to the CBT interventions. Psychosocial changes could also be attributed to patient and setting biases, expectancy and demand characteristics, and time and assessment effects (39).

Further research avenues arise from the results and limitations described above. This feasibility study provides valuable information to adapt the study procedure for proof-of-efficacy in a randomized-controlled trial (RCT) taking the following considerations into account: First, recruitment data suggest that more than one half of the eligible patients were unable to attend weekly therapy sessions due to a lack of time and travel distance. Therefore, new methods such as telephone-based (23) or Internet-based CBT (27) might increase access to treatment for these patients. Moreover, previous studies found post-operative BED and MDD in up to a quarter of the patients, thus, instruments for reliable and valid assessment of mental disorders should be part of routine aftercare. Second, weight loss is consistently reported as primary outcome in trials on post-operative behavioral interventions (21), however, weight loss is also influenced by surgical procedure (e.g. gastric bypass vs. gastric sleeve) and interval since surgery (e.g. before or after honeymoon phase) (40). Therefore, inclusion criteria for an RCT examining the efficacy of CBT on weight loss outcome should be considered carefully. For example, the variety of surgical procedures should be limited to a small number and interval since surgery should be as homogenous as possible. Alternatively, both factors could be controlled for in statistical analysis requiring a larger initial sample size. Third, future studies should not solely focus on weight loss outcome. Due to the fact that CBT interventions aimed at both reducing psychopathology and improving patients' psychosocial adaptations, diverse aspects of psychopathology and psychosocial functioning should be examined using reliable and valid structured clinical interviews and self-report questionnaires. In doing so, efficacy of CBT for post-operative mental disorders could be established reliably.

To conclude, successful management of post-operative BED and MDD resulted in improvements of long-term weight loss outcome following bariatric surgery, as well as lower levels of psychopathology and higher levels of psychosocial functioning. Thus, treatment of post-operative BED and MDD is likely to prevent poor weight loss and weight regain associated with a recurrence of medical comorbidities after initial remission (41, 42) and, consequently, might limit additional costs from continued health care management, revision surgeries, and decreased work productivity (43, 44).

DATA AVAILABILITY STATEMENT

The datasets for this article are not publicly available due to data safety restrictions. Requests to access the datasets should be directed to the corresponding author.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Ethical Committee at the Medical Faculty, Leipzig University (Az. 228-12-02072012). The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

Study conception and design: AR, AH. Data acquisition and analysis: AR. Data interpretation: AR, AH. Drafting the work: AR. Critical revision for important intellectual content: AH. Final approval of the version to be published: AR, AH. Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved: AR, AH.

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CASE REPORT
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Extreme Risk-Taking Behaviors in Patients With Eating Disorders

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Background: Patients with eating disorders (EDs) engage in different self-inflicted at-risk behaviors, including suicide, attempted suicide and non-suicidal self-injury. Our aim was to describe the occurrence and underlying motivations of non-suicidal extreme risk-taking behaviors in patients with EDs.

Methods: Four cases from different treatment centers in Israel were analyzed.

Results: All patients were females hospitalized in inpatient settings because of long lasting anorexia nervosa (AN) with either binge/purge or purging episodes (AN-B/P/AN-P), including in most cases both self-induced voting and laxative abuse. Case [1] was an adolescent also diagnosed with type 1 diabetes mellitus. She abused insulin, both omission and overdose, was highly suicidal, and suffered from comorbid oppositional behavior, depression and anxiety. Case [2] was a 24-years old woman, transitioning from restricting to AN with vomiting and laxative use during inpatient treatment. She was also diagnosed with attention deficit hyperactivity disorder, depression, anxiety, and suicidal thoughts. In hospital, she developed excessive water consumption, leading to very low urine concentrations and sodium levels, and one episode of loss of consciousness. Case [3] was in her late thirties, demonstrating particularly massive laxative abuse. She also suffered from alcohol addiction, sexual trauma, and one attempted suicide. During hospitalization she developed laxative-abuse-related rectal prolapse that was successfully operated. Nonetheless, after operation she resumed laxative abuse. Case [4] was a 23-year old pregnant women with highly active AN-B/P during pregnancy. She was hospitalized at 23 weeks of gestation following abdominal pressure. She only partly complied with inpatient treatment, discharged herself against medical advice after 5 weeks, and gave birth at week 34.

Discussion: All cases were females with long-standing B/P type AN, often with multiple purging behaviors, other impulsive and non-impulsive comorbidities, and many environmental vulnerabilities. Different motivations were found for these extreme behaviors in addition to ED-related factors, mostly not related to suicide. The severity of the medical and psychological condition required multimodal medical and psychological

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inpatient interventions. The patients mostly did not comply with their treatment, showing considerable indifference to their grave medical condition.

Keywords: anorexia nervosa, attempted suicide, non-suicidal self-injury, self-harm, suicide

INTRODUCTION

Eating disorders (EDs) show a lifetime prevalence of around 4% for DSM-5 diagnoses of anorexia nervosa (AN), and 2% each for bulimia nervosa (BN), and binge eating disorder (BED) (1, 2). AN, BN, and BED are associated with numerous physical (e.g., osteoporosis, fluid electrolyte imbalance, and metabolic syndrome) and comorbid mental health (e.g., affective and anxiety disorders), conditions (1, 3). Actually, the medical complications caused by EDs may involve almost all organ systems and can be viewed as consequences of: undernutrition, purging behaviors, and binge eating. The medical complications of EDs are significant and potentially life-endangering and irreversible (4). Moreover, medical complications may account for more than half of all deaths in patents with AN (5). Last, patients with all types of EDs have significantly elevated mortality rates compared with the standard population norms (3, 6). Actually, AN is associated with the highest rate of mortality among all mental disorders (7).

Dangerous Behaviors in Patients With EDs

Patients with EDs are at a high risk for endangering their life and overall health. Suicide is likely the most dangerous behaviors, being particularly frequent in AN (3). Actually, AN is considered the mental health disorder with the highest suicide rates (8). Completed suicide is less frequent in BN than in AN (3), and highly infrequent in BED (9).

In contrast to completed suicide, attempted suicide is more frequent in patients with BN than AN, and in AN of the binge/purging type (AN-B/P) compared with restrictive-type AN (AN-R) (8). The frequency of attempted suicide and the severity of the medical threat of the attempts in AN and BN are comparable to those found in major depression and conduct disorder, and greater than those found in schizophrenia and anxiety disorders (10). Attempted suicide in EDs is particularly elevated in the context of impulsivity (8).

Many factors have been associated with the increased suicide risk in AN. Disturbances in body image and body dissatisfaction represent one major factor for elevated suicidal risk in patients with EDs (11). Nonetheless, according to 12, it is not merely the fear of gaining weight and the pursuit of thinness that increase suicidality in EDs. Thus, incorrect interpretation of interoceptive stimuli, insensitivity to bodily functions, and lack of bodily control may eventuate in a detachment from the body, leading, in turn, to self-neglect and facilitation of self-destructive behaviors (12).

Another dangerous self-destructive behavior in EDs is non-suicidal self-injury (NSSI). This is a direct and deliberate destruction of one's bodily tissue without suicidal intent. Although NSSI and suicidal behavior (completed and attempted suicide) are distinct in many ways, including their primary motivation, the method employed in the self-destructive behavior, and the medical severity involved in each, the presence of NSSI is associated with an increased risk of suicide (1, 13).

Up to 68% of patients with EDs may engage in NSSI, and between 25% and 54% of people who engage in NSSI report comorbid disordered eating (14). Similar to attempted suicide, NSSI is associated with a greater risk of B/P pathology (15, 16) and elevated impulsivity and emotion dysregulation (8, 16, 17). Self-injurious patients with EDs may in addition represent with more dysfunctional personality traits, particularly, higher levels of harm-avoidance and lower levels of self-directedness (17).

In general, NSSI, including in EDs, may be understood as a means to adapt to inner and outer demands (18). Several models, potentially accounting for the occurrence of NSSIs in mental disorders, including in EDs, have been proposed (18, 19):

The affect regulation model regards NSSI as a maladaptive emotion regulation strategy, designed to prevent the escalation of negative affects such as anxiety, or, alternatively, to evoke emotions when feeling numb or dissociated (8, 16, 18, 19). Indeed, NSSI in ED patients may be preceded by high-activation unstable affective states (20). Moreover, the regulatory character of this strategy is suggested by the self-injurers' claim that the sight of blood, or alternatively the sense of physical pain (against detachment or mental pain), helps them to calm down.

Second, the environmental model focuses on the behavior learning process and its power to reinforce NSSI, viewing it as socially learned behavior, employed to communicate, manipulate, or influence one's immediate environment. The contention that individuals who self-injure have poor communication and social skills (18) is of particular relevance in patients with AN, who may present with elevated levels of autistic features and inability to identify and communicate thoughts, emotions, and sensations (21).

Third, the self-punishment model relates to the high prevalence of childhood maltreatment (abuse and neglect) found among individuals who self-injure (18), including in patients with EDs, as well as to the guilt feelings of patients with AN that the place they occupy in the world is at the cost of others (22). Last, the interpersonal boundaries model stipulates that individuals who self-injure are not only likely to have suffered childhood maltreatment, but have also been separated from primary caregivers in early years—whether due to divorce, death, or parental neglect. Such losses of early important objects are highly prevalent in patients with EDs (23). Consistent with these findings, self-injurers may fail to achieve sufficient levels of self and object-representation differentiation, leading them to experience the loss of others as if it is loss of their own self (18).

Other motivations may also increase the risk of endangering behaviors in patients with EDs. These include indifference to what might happen with their immediate life (24), owing, perhaps, to reduced attraction to life (25), detachment from one's body because of reduced interoceptive sensation awareness (21), reduction of emotional involvement (16, 21), and the greater likelihood of inhibited over-controlled affective responses in patients with AN (26).

To summarize, ED patients with concurrent NSSI behaviors may have psychopathological, cognitive, and emotional characteristics that differ from patients with EDs only (8, 17).

CASE DESCRIPTIONS

The present article describes four women with AN developing different extreme at-risk behaviors during the course of their illness. An attempt will be made to summarize common as well as specific aspects of these behaviors. Written informed consents have been obtained from the participants (and from the parents of one participant who was younger than 18) for the publication of these case reports.

Three cases of the four described here suffered from different medical derangements that were either a direct result of the ED, or appeared in the context of the ED: These include comorbid type 1 diabetes mellitus (T1DM) and AN, psychogenic polydipsia in a patient with AN, and rectal prolapse resulting from massive laxative abuse in another patient with AN. The fourth patient suffered from active AN during her pregnancy.

Regarding the development of AN in young people with T1DM, as shown in case [1], each disorder may adversely influence the course of the other. Malnutrition in AN may lead to hypoglycemia and increase insulin resistance, whereas insulin administration may lead to increase in weight due to increased metabolic efficiency, likely worsening the ED (27). The contrasting weight fluctuations associated with T1DM (reduction in weight) and insulin treatment (increase in weight) represent a considerable burden for girls with AN (28), increasing their body dissatisfaction, weight preoccupation and drive to lose weight (29). Hence, adolescents with comorbid AN and T1DM show considerable difficulties in handling their illness (30), and their compliance and adherence with their treatment is limited (31).

Psychogenic polydipsia, described in case [2], is characterized by excessive oral fluid intake in the absence of physiologic stimuli to drink, or any underlying related organic disease (32). It may represent a potentially at-risk condition, associated with severe hyponatremia and hypokalemia, potentially culminating in loss of consciousness, convulsions, and cardiac arrythmias. Although psychogenic polydipsia is common in patients with AN, and only rarely leads to serious clinical complications (24, 33, 34), if such complications do occur, as shown in case [2], they might become highly dangerous (24, 33–40).

The most frequent motivations associated with psychogenic polydipsia in patients with AN include intentional falsifying of low weight in routine weight measurements, a form of "purging behavior" to purify the body with diuresis, and as a means to reduce calories, suppress hunger, drink instead of eating, and induce vomiting (24, 33, 35, 39). Last, it might also represent a variant form of BN (35, 40).

As shown in case [3], patients with EDs use laxatives to get rid of calories and lose weight. In other cases, laxative abuse may be synonym to other maladaptive self-harm self-soothing behaviors such as cutting (8). Over time, the intestines build up resistance to laxatives, hence dosages must be increased to obtain the same result. The renin-aldosterone system is activated by the massive fluid loss; consequently, when laxative use is discontinued, edema and rapid weight gain occur because of fluid retention. Feelings of fullness and weight gain cause intense anxiety for patients with EDs, further reinforcing laxative abuse.

Laxative abuse may occur in 10%–60% of patients with EDs (41–43). Changes in electrolyte and acid-base balance associated with laxative misuse, mainly metabolic acidosis and hypokalemia, may involve the cardiovascular system and kidney, and are potentially life-threatening (41, 44). Chronic laxative use can cause irreversible damage to the smooth muscles comprising the intestine (41), inducing in rare cases, as shown in our patient, rectal prolapse, where the entire bowel wall protrudes from the anus (45–47). Factors increasing the risk of rectal prolapse in patients with EDs include recurrent bingeing behaviors, constipation, laxative abuse, intense effort during physical exercise, and increase in intra-abdominal pressure related to intentional vomiting or to prolonged periods of sitting on the toilet during defecation (42, 47).

The fourth patient shows a different type of ED-related at-risk behavior, i.e., endangering the course and outcome of pregnancy occurring during active AN. Until relatively recently, the occurrence of pregnancy in women with AN would have been considered inconceivable—both psychologically and physiologically (48). However, in the past decade, there is a significant increase in the frequency of pregnancy among active AN patients (48, 49), mainly because of greater accessibility to fertility treatments (49).

Many problems may stem from the occurrence of pregnancy in women with AN, first and foremost, that pregnancy and low weight and a flat stomach cannot coexist. Some women fail to make the choice of having a baby over losing their perfect AN body. Others might go to extremes in their desire to have both, even at the cost of possibly endangering themselves and/or their offspring.

Case 1: Anorexia Nervosa and Type 1 Diabetes Mellitus: the Oxymoron of Comorbidities

L. is 17.8 years old, the oldest of three girls, with T1DM, celiac disease and lactose sensitivity. She was hospitalized in a specialized inpatient ED department at the age of 16.3 because of AN.

L. was described from an early age as having a hard temperament and was treated in a child developmental clinic because of communication difficulties. She had social difficulties since early age, being introverted and shy, and having minimal

contact with her peers. Her parents described in addition oppositional behavior at home, followed by temper outbursts and family conflicts.

At the age of 13, L. was diagnosed with celiac disease, having to change her eating regimen. She had difficulties in maintaining her weight and experienced secondary amenorrhea. In a psychiatric consultation, she was diagnosed with social anxiety disorder and a depressive episode and was treated with cognitive behavioral treatment. Her relationship with her parents deteriorated to constant control-struggles, followed by long periods of no communication.

Later, L. developed T1DM. Insulin therapy was initiated, and L. started to gain weight, achieving menstrual stability. She was very unhappy with her weight gain, exhibiting severe restrictive behavior, followed by self-induced vomiting and laxative abuse.

L. was brought to an emergency room when the reduction of food intake culminated in an almost complete starvation. She was hospitalized and diagnosed with purging disorder. When her physical condition stabilized, L. was admitted to an ED daycare program. As she did not cooperate with this program. L. and her parents agreed to hospitalize her in a specialized inpatient ED department.

At admission, L. weighted 40 kg, her height was 1.63 m, and her body mass index (BMI) 15.4 kg/m^2 (less than 5% BMI percentile for her age). She was diagnosed with AN purging type (AN-P). Her target weight was set at 53–56 kg, representing a BMI of 19.9–2, kg/m^2 respectively. When she refused eating, nasogastric feeding was applied, and Fluoxetine 40 mg/day was initiated because of severe depression and eating-related obsessionality. During the first 3 weeks of inpatient treatment, L. was under constant 24-h supervision and was taken off responsibility for her T1DM treatment, being administered by the nursing staff. She made continuous efforts to influence her feeding program by slowing down the rate of the nasogastric feeding or tying up the feeding tube around her legs or neck. L. was asked to measure blood glucose levels with a sensor that was usually locked at the nursing room, in front of a nurse, which then would determine the amount of insulin required. Twice a day, she had to calibrate a sensor that measures glucose levels underneath the skin, providing dynamic glucose information and sending the data wirelessly to her parent's phone.

A few weeks after admission, following the resumption of oral feeding. L. started confronting new challenges. She had difficulty completing her meals, tried to hide food in her clothes or in her glucose sensor. Later, non-ED obsessional behaviors emerged: L. refused sitting on certain chairs or touch the pillows on a sofa, and separated the clothes in her closet with papers. A diagnosis of obsessive-compulsive disorder (OCD) was added. L.'s obsessional thinking also involved internal "rules" regarding her glucose levels, followed by repeated measures of glucose as part of related compulsions. Fluoxetine dosage was raised to 60 mg/day, with only a partial response of her OCD symptoms.

During her psychotherapy sessions, L. slowly began to address emotionally charged issues, revealing a long-standing body image disturbance that started already at the age of six. It seemed that the obsessional occupation with nutrition, weight, and appearance avoided her from confronting with T1DM-related difficulties, i.e., the strain caused by her highly intense dietary regimen, insulin treatment fidelity and family conflicts.

L. continued to restrict caloric intake, and started to omit insulin, or dilute her insulin with water during her visits home. She resumed nasogastric feeding and constant 24 hr supervision. Soon thereafter, L. disclosed to the staff about irritable suicidal thoughts, accompanied by non-suicidal self-injurious behaviors (NSSIs), laxative use and skin picking behavior. In the following weeks, she started disclosing her self-destructive behaviors throughout inpatient treatment: poor compliance with her medications, laxative pills hidden in her room together with shaving blades for cutting herself, and another glucose sensor in which she used to take blood samples directly from her self-injury wounds. During her home visits, episodes of hypoglycemia returned. In treatment, she described a desire for low glucose levels, feeling excited from putting her life in danger, and being disappointed that the hypoglycemic episodes only rarely led to unconsciousness.

As she kept gaining weight, L. expressed more and more depression, and wrote farewell letters to some staff members. She described self-infliction and insulin abuse as a means to "transfer pain from the mind to the body", making her focus on nothing else but the cut or hypoglycemia.

Treatment with Fluoxetine was replaced with Venlafaxine 225 mg, and Quetiapine XR 150 mg was added, as an augmentation therapy for her depression. Gradually, L. started to cooperate with the diabetic program, and her mood stabilized. She began administering herself her insulin injections, and urine and blood glucose levels indicated that her diabetes was under good control. A year after her admission, L. was discharged to a day-care program. She took full responsibility for her diabetes treatment and avoided from NSSIs. Nevertheless, she still refused to tell her parents about her daily blood glucose levels, did not let them watch her calibrate her sensor, and rejected to eat her meals under their supervision.

Surprisingly, her HbA1c levels began to be much lower than the expected 4.8% norm. On her next visit to the endocrinology clinic, her sensor was taken for investigation, exposing multiple unreported episodes of hypoglycemia during the past 2 months. Her glucose levels were as low as 25 mg/dl, explaining her low HbA1c levels. As supervision was tightened once again, L. reacted with repeated caloric restriction. A short time later, she informed the staff about the resurgence of vomiting and laxative abuse and was re-hospitalized. She is currently still in inpatient treatment, with overall lack of cooperation, necessitating once again strict supervision.

Comment

L. is a 17.8 years old girl encountering multiple psychiatric and medical complications - AN, social anxiety disorder, depression, OCD, celiac disease, and T1DM. As highlighted in this case, youngsters with T1DM show considerable difficulties in handling their illness (50) and experience a multitude of psychiatric problems, likely interfering with the course of T1DM and with its treatment (51).

The picture becomes even more complicated in T1DM adolescents with comorbid EDs. Body image disturbances may increase the risk for a host of maladaptive weight-reduction behaviors. These may lead to lack of control over glucose levels, hence recurrent hypoglycemia, hyperglycemia, and unstable HbAIC levels (52).

As shown in the present case, intentional inappropriate handling of insulin administration to prevent insulin-related weight gain may occur in adolescents with comorbid T1DM and EDs (52). Recurrent insulin omission may be associated with diabetic ketoacidosis, whereas intentional insulin overdosing following high-calorie meals may induce hypoglycemia. If both insulin omission and insulin overdosing occur in the same ED patient because of faulty ED-related behaviors and cognitions, a vicious cycle of alternating ketoacidosis and hypoglycemia represents a particularly high-risk condition (51, 53). Alternatively, as in the present case, intentional insulin overdosing may serve as a destructive anxiety-reducing behavior in stressful situations.

In this patient's complex characterological and psychosocial constellation, the bidirectional insulin abuse likely involves multiple motives, in addition to weight reduction and body-image related motivations. L. associated her intentional insulin abuse with a wish to die (see her suicide letters) (54), or alternatively with an indifference to whether she would live or die, making this behavior highly life-endangering (53).

Third, intentional faulty insulin handling can serve as a means of communication to significant others (in the present case L.'s parents), when more adaptive communication means are lacking (37). In this respect, it can be regarded as an idiom of distress., i.e., as a way for this non-talking girl to express and communicate her distress, by repeatedly endangering her life (55).

Fourth, like many other maladaptive behaviors in AN, including NSSIs, intentional insulin abuse can serve to reduce mental pain by increasing psychic numbness, or alternatively, by conveying unspoken emotions. Last, the likelihood of insulin-overdose hypoglycemia for feeling "high" has been reported also elsewhere (53). Such a complex constellation in the face of conflictual motivations (L. did agree to be hospitalized) requires long-term inpatient treatment with recurrent hospitalizations, with questionable long-term outcome.

Case 2: Psychogenic Polydipsia in a Patient With Anorexia Nervosa

S. is a 24-year-old single woman from a Jewish Ultra-orthodox background. She was accepted for treatment in an outpatient eating disorder (ED) service at the age of 22 because of a DSM-5 (1) diagnosis of AN-R.

S. is the second of four children. Her father is overweight, diagnosed with obsessive-compulsive disorder. Her older sister is diagnosed with binge/purge type ED.

Her development in younger years was uneventful, and she had no significant medical disturbances. She was always described as a shy child, with no friends, and as an average student. She was always on the lean side, but no disordered eating behaviors and preoccupations were reported.

After finishing high-school, she began studying in a seminar, where, for the first time, she was living outside of her home. She had no basic experience of cooking, and gradually started to eat less, at the beginning not because AN-related reasons. She gradually lost weight from 46 kg to 38 kg. Her height was 1.64 m. When this condition continued, she was referred to our outpatient clinic at the age of 22. Her menses ceased several months before admission. She was socially secluded, although living with other girls in her apartment, and was not interested to start with the process of "schiduchim"—getting acquainted with men for marital purposes.

On admission to outpatient service she reported of no wish to weigh more, or less, than her current weight. She was not concerned with her low weight (BMI-14.2 kgs/m^2) or with the cessation of her menses. During outpatient treatment, no change occurred in her condition. Therefore, she was offered inpatient treatment, and, contrary to the therapists' expectations, agreed.

Her physical and laboratory examinations on admission were all within normal ranges. During inpatient treatment she gradually gained weight, until reaching the weight of 51 kg. (BMI-19 kg/m^2), with gradual return of her menses. In contrast to the constant indifference and lack of emotional engagement during outpatient treatment, she became increasingly depressed, anxious and agitated, in inpatient treatment, with severe emotional dysregulation, and occasional suicidal preoccupations.

Psychotropic medications have been prescribed for the first time in inpatient treatment. She has been treated with Fluoxetine, Sertraline, Duloxetine, Aripiprazole, and Clotiapine, which reduced her anxiety and dysregulation, but had only minimal effect on her depression. Currently she receives Citalopram 40 mg/day, with some antidepressive effect, and Ritalin LA 30 mg/day because of attention deficit hyperactivity disorder.

During inpatient treatment, S. reported of starting to use laxatives, because of feeling bloated and distressed with her increase food intake. Later, she also admitted of self-induced vomiting for similar reasons. These behaviors were not present before inpatient treatment. Eventually these purging behaviors ceased following adequate supervision in the department and not allowing her to leave it.

The course of treatment seemed uneventful in the next weeks, until, in a routine examination before weighing, her urine concentration was unexpectedly very low (1.000, normal range in our laboratory is defined as 1.015–1.030). In a subsequent examination, it was still low (1.003), and she also presented with severe hyponatremia [serum sodium level of 120 meq/L (32), where normal values in our laboratory are 135–145 meq/L]. Physical examination and all other laboratory tests were normal.

In contrast with her cooperation in reducing laxative use and self-induced vomiting, S claimed that she was not drinking large amounts, although the staff noticed a recent increase in water consumption. Against her will, she was supervised for her water consumption, showing that she was drinking daily around 4 L, double the average amount required in the Israeli climate.

She was put on a strict water consumption regimen, and her urine concentration and sodium values gradually stabilized.

Thereafter, she stated going out again from the department, with occasional reduction in her urine and serum sodium concentrations, requiring supervision again.

The association of her serum sodium and urine concentration levels with the extent of water consumption during supervision, likely precluded the diagnosis of inappropriate antidiuretic hormone hypersecretion as the cause of hyponatremia. This was likely the case also with respect to her use of psychotropic medications. Theoretically, antidepressant and antipsychotic medications may induce hyponatremia by excess water intake provoked by a sensation of dryness of mouth from anticholinergic adverse effects (tricyclic antidepressants and neuroleptics), as well as from inappropriate ADH secretion due to selective serotonin reuptake inhibitors use (56).

One day, without the staff knowledge, she went to s swimming pool, and had what seemed like a loss of consciousness while being in the water. People who put her out of the water were not sure whether she was convulsing or not, but she bit her lips, and was bleeding from her mouth. She did not pass urine or stool and was not judged to be drowned.

S. was brought to the emergency room, while already being awake but somewhat confused. She was disoriented to time. Her speech was slurred, and she had no memory of what has happened to her. Her last memory was of entering the pool's surroundings, not of being in the water.

Physical and neurological examination performed in the emergency room, including fever, pulse, and blood pressure, was normal. She had further no evidence of subcutaneous edema. Laboratory examinations were within normal ranges, except for sodium level of 119 meq/L, and urine concentration level of 1.000. Chest-ray examination was intact. Electrocardiogram and later Holter electrocardiogram showed no evidence of arrythmias. EEG revealed diffuse slow wave activity, with no localization, later returning to normal. Later Holter EEG was normal. MRI showed no evidence of cerebral edema, space occupying lesion or of past/recent trauma. She was diagnosed with loss of consciousness resulting from water intoxication and hyponatremia, requiring only ongoing supervision.

Upon her return to the department, S. was put again on constant supervision. Upon re-stabilization, she was put on plan where she was supervised for her urine concentration every other day, and had a bi-weekly check of her serum sodium levels. If urine concentration was normal, she was put on a daycare regimen. If, not, she was re-hospitalized until her next urine concentration check.

On the one hand, this plan increased her motivation to cooperate with the water consumption plan, and her serum sodium and urine concentration levels were mostly normal. On the other hand, when likely having no at-risk behaviors to counteract her cooperation with weight gain and eating (she chose to stay in the department although she could leave it any minute), S. became more depressed and frustrated. Although having a place to go after her release (her previous apartment), and although having a job plan and a financial support (learning to become a professional secretary), S. felt she had no real goal in her life, and began questioning about the meaning of her living. It seemed that once she became relatively asymptomatic with her eating, her existential depression and sense of futility increased. Currently, psychotherapy focused mainly on dealing with these issues under day-center placement. It is of note, that S. hardly related to the event at the pool. She was not concerned with the possibility that she could have died, and she did not relate to the event as an attempted suicide, but was afraid of possible resulting medical complications.

Comment

The process of events occurring in the life and treatment of S. highlights several important points. Although living within her family and being part of her community, S. always felt that she was keeping herself on the verge of living, with no real inner direction. She did things feeling that this was expected form her and left her home unprepared. The reduction of eating in the beginning was not intentional, but rather reflected her overall lack of acquaintance of and indifference to her own needs (22), thus not taking any notice that she was not eating for long hours.

S. agreed to outpatient treatment similar to her previous matter of-fact attitude, as another meaningless station in her life. It was not surprising that it had no effect on her illness. Her agreement to inpatient treatment was however, highly different. On the one hand, she cooperated with the treatment plan, and did not leave the department, although having the possibility to do so. On the other hand, she began to be involved in constant at-risk behaviors, developing from laxative use and self-induced vomiting to psychogenic polydipsia. These behaviors reflected mainly her inability to live with the emotions and physical sensations induced by her increased eating and weight. Typical to patients with AN, she was unable to deal with these distressing feelings and sensations and communicate them to others (16, 21), but rather to act out on them.

The indifference of S. to the almost fatal results occurring in the swimming pool, while partly associated with her not remembering the event, mostly reflected her lack of interest as to what might have happened with her immediate life (23). Such an indifferent attitude, leading to recurrence of water intoxication following hospitalization because of grave medical complications of this behavior, has been reported in AN patients also elsewhere (24). This indifference likely reflects the inability of the AN patient to look at herself from the outside and grasp what she is really doing to herself, i.e., deficiencies in reflective mentalization and theory of mind capabilities (57, 58).

Despite these reservations, the agreement of S. to cooperate with the treatment plan, while simultaneously actively involved in at-risk behaviors opposing it, was a change in her overall aloofness. It could, however, take place only in the strictly supervised, organized, predictable and safe inpatient environment. There, likely for the first time, she was able not to block her emotions, as often occurs in patients with AN (59), but rather to really feel. The overwhelming flooding of unclear, unknown, and highly distressing emotions likely increased her at-risk behaviors (59). Nonetheless, her connectedness with her emotions (22) might increase, in due time, the chance of improving with psychotherapy in the flexible and safe environment of moving from daycare to inpatient treatment as required.

Case 3: Laxative Abuse Leading to Rectal Prolapse

N, is in her late thirties, single, unemployed, living with her parents, despite a complicated relationship with them. She reports domestic violence and feelings of fear, alongside dependence, and excessive closeness. Her ED appeared when she was 14. She began restricting her eating and vomiting and became underweight (minimal BMI was 14.7 kg/m^2). Diagnosed with AN-P (1), she was hospitalized in a specialized ED unit. After discharge, her condition improved, but she still experienced occasional patterns of fasting, bingeing, and vomiting, meeting DSM 5 (1) criteria for BN.

Following graduation from high school, she began working; she then suffered of sexual abuse, perpetrated by her supervisor at work. Since then, her ED symptoms worsened considerably. She developed bingeing, vomiting, and use of large quantities of laxatives daily, leading to two additional hospitalizations in a specialized ED department; another hospitalization was in a psychiatric department following a suicide attempt using pills. Over the years, she also became addicted to alcohol.

Approximately 2 years before her current hospitalization, she completed an addiction treatment program and continued to attend Alcoholics Anonymous meetings. She was re-hospitalized because of severe deterioration in her ED symptoms, including massive laxative use.

N. was hospitalized with a BMI of 18.4 kg/m^2. Psychopharmacotherapy included Topiramate 200 mg/day, Quetiapine 500 mg/day, Fluoxetine 60 mg/day, and Clonazepam 1.5 mg/day. At admission, her blood potassium level was 3.1 mmol/L, gradually rising to normal levels, likely reflecting discontinuation of laxatives use and vomiting.

After 2 months of inpatient treatment, hypokalemia was observed again (potassium levels decreased to 2.9 mmol/L). When questioned, the patient denied reverting to laxative use or vomiting, and her reports of diarrhea accompanied by general ill feeling were interpreted at that time as being of viral origin. However, shortly thereafter, she reported that when sitting on the toilet, she felt organs protruding from her anus. She was extremely frightened when a substantial bowel segment protruded, and had difficulty reinserting it. N. was examined by a surgeon, who diagnosed rectal prolapse. Surgery was recommended. It was explained to the patient that renewed vomiting and laxative use after surgery would endanger her, and that the surgery would only be performed if she could unequivocally commit to avoiding any return to vomiting and laxative use. in her psychotherapy sessions, she expressed full understanding of these risks and motivation for treatment. The conclusion of department's staff was of a high probability that she could control her symptoms. N. was transferred to the surgical department, where she had undergone laparoscopic sigmoidectomy with rectopexy.

Ten days after surgery, she was readmitted to the ED unit, where she rapidly resumed regular nutrition, and attained normal weight. She then began to build a rehabilitation plan, including transition to an ED residential rehabilitation center. Soon thereafter, her blood tests indicated hypokalemia again, but in consultation with the surgeon, this result was attributed to surgery-related watery discharge. However, near to her discharge from inpatient treatment, laxatives that she had hidden, were discovered in her possession. The patient admitted that 2 weeks after surgery, she started using laxatives again. She related this abuse to the distress she felt after surgery, in the anticipation of her soon-to-come discharge. She was referred for laxative addiction treatment in a group setting following her discharge.

Comment

N. suffers from a severe and enduring B/P-type ED, exhibiting a combination of restricting, bingeing, self-induced vomiting and laxative abuse, alongside additional alcohol addiction. Similar to our patient, other studies have also shown that the combined presence of vomiting and laxatives/diuretics misuse (multiple purging behaviors) is associated with greater ED severity, more comorbidity with depression and post-traumatic stress disorder (PTSD), greater use of alcohol and drugs, and a high incidence of sexual or other traumatic events, usually predating the development of the ED and the comorbid substance abuse (60, 61).

The presence of multiple purging behaviors may enable the patient to dissociate from and ignore her overwhelming trauma-related thoughts and emotions, thus potentially cleansing herself of the experience (62). From a different perspective, the lack of emotional regulation typical of such patients (16, 21), may be related also to problematic early life attachment relations (63). N. has constantly turned during her life course to the abuse of various substances and to a multitude of ED symptoms to soothe and regulate her turbulent emotions, as well as to turbulent abusive relationships, almost always ending in explosive fights and recurrent abandonments.

Bromberg (62) points to the damage to trust and to the belief in the possibility of repair within a therapeutic relationship in patients with EDs who have experienced early developmental disturbances and later traumatic harm. N. developed ED symptoms by the age of 14. Her fragile self-structure was insufficient to cope with the sexual trauma she later suffered, at the age of 20, leading to escalation of her multiple symptoms—restricting, bingeing, vomiting, laxative abuse, alcohol addiction, depression, and suicidality. Within the supportive environment of the inpatient setting, N. was able to use psychotherapy to identify the way in which she turned to objects, such as laxative abuse, for emotional regulation instead of to human relations (22). However, when she had to be separated from the therapeutic support she had only started to learn to rely on, her almost automatic, impulsive reliance on objects (laxatives) to regulate her anxiety re-emerged (8, 16, 17, 22). This led to renewed laxative abuse, despite her understanding of the high risk involved in it and the possible disruption of the results of her surgery (62, 64).

Case 4: Pregnancy and Anorexia—Which Has the Upper Hand?

M. aged 23, has been suffering from AN-B/P since the age of 12. Born to an Ultra-Orthodox Jewish family and married at the age

of 20, M. tried to conceive in the first 2 years of her marriage and had one natural miscarriage before succeeding, following fertility treatments. She kept the fertility treatment a secret so as not to impair with her sisters' marriage prospects.

Her ED was prominent throughout her upbringing. M. recalls how people would complement her for her slim figure. Her low weight gained her special attention among her family members, as well as constant worries by her mother, who kept certain items in the family refrigerator reserved solely for M., and absolve her from certain house chores. Her husband was described as supportive, but unaware of her illness.

At 23 weeks of gestation, M. was referred to the emergency room after having fallen in the street, complaining of abdominal pressure. Her BMI at that time was 17. She had virtually not gained any weight during pregnancy, while reporting of self-induced vomiting. The fetus was 8 weeks delayed in development. M had at that time anemia, hypoglycemia, and protein C deficiency. After 2 days of failed attempts to feed M. at the high-risk pregnancy unit, she consented to be hospitalized in a specialized inpatient ED department.

M's treatment plan included complete bed rest, nasogastric tube feeding and cardiac monitoring. M reported she was happy to begin psychotherapy. In the sessions she disclosed of multiple weight-reduction behaviors during her pregnancy, for example going up and down the stairs for 2 hr daily, followed by abdominal exercises.

In the second week of inpatient treatment, M gained 1 kg. She reported trying to view her weight gain as part and parcel with the keeping of her pregnancy, but this understanding did not alleviate the difficulty and fear of gaining weight. She feared the weight gain and the related post-natal struggle to lose weight. On the one hand, M described her body as "good", insofar as it carried a baby, to whom she has much to provide. She did not want to harm the baby. At the same time, however, she felt huge. She touched her belly and asked whether her fat percentage could be checked.

During the third week of inpatient treatment M was caught trying to spill the nasogastric tube content down the toilet. She expressed her wish to terminate the hospitalization. The staff explained her the severe consequences to the development of the fetus that could ensue from this decision. M. agreed to continue hospitalization only after her husband, who had become involved in her treatment, convinced her to remain in the hospital. In the following psychotherapy session, she described a feeling of loneliness, and that the staff were trying "to shake her" not to think of herself, but to change her priorities to caring for the fetus. This, however, evoked in her a wish to restrict eating, to vomit, to prove the importance of her own needs, and to convey the suffering she was experiencing.

M. confides to her therapist that she fears also her criticism. The therapist admits to herself that there is some truth to her patient's fear. She recalls her dismay upon hearing of her patient's abdominal exercises and intense physical activity she has undertaken during her pregnancy. When being informed of the delay in the development of the fetus, the therapist finds herself angry at her patient, and cannot stop thinking about the baby. She is alarmed of the intensity of her negative feelings towards her patient and expresses this fear in her supervision.

In the following 2 weeks, M. becomes more and more upset. It appears that despite the fear of not feeding her fetus properly, the fear of weight gain overwhelms everything. At 28 weeks gestation, M. decides to discharge herself against medical advice. This time even her family and husband are unable to convince her to stay in treatment. M has gained 2 kg during her 5-weeks hospitalization.

M gave birth at 34 weeks, needing a blood transfusion during delivery. Her hemoglobin level decreased to 6.9 g/L. The baby weighed 1.6 kg at birth, with an Apgar score of 4, and evidence of microcephaly.

Comment

Women suffering from AN may refuse to abandon the dream of motherhood, and some believe in and achieve recovery with the child they are bearing (48, 65–69). Nonetheless, this dream can be easily shattered in the face of bodily and hormonal changes, putting the pregnant woman with AN against stressful dramatic challenges: rapid weight gain, expansion of her bodily contour, rounding of her breasts, and an overall feeling of lack of control over her body. Research frequently points out to the dangerous coexistence of the two, whereby pregnant women with EDs show greater risk of miscarriage, delayed intrauterine growth, premature labor, forced caesarian deliveries, low birth weight, and abnormally small head circumference at birth (67, 69–76).

In this respect, pregnancy in women with an ED is a high-risk pregnancy (49). In the present case, M. has not sought for any help for her ED, until 23 weeks of gestation. Thus, the low hemoglobin levels during the first trimester have been likely associated with the intrauterine growth delay and low weight at birth (77).

The present case demonstrates the danger of pregnancy becoming unbearable for a woman suffering from active AN, as it may stand against the core goal of the ED - having a perfectly thin body. The conflict of M. between her need to care for the fetus and her fear of the change pregnancy has induced in her body and in her own well-being, has been evident throughout pregnancy. Unfortunately, as in the present case, the ED has prevailed.

The psychological challenges of a woman with AN during pregnancy can be challenging also to her therapist, particularly in young female therapists who are themselves mothers or future to be mothers. Sometimes, the fears of the pregnant AN patient may not be apparent to the therapist, who is torn between the caring for the needs of her patient—the mother vs. the needs of the fetus. In the case of M., the therapist has been overwhelmed with strong emotions of concern for the future-to-be baby's wellbeing, with accompanying anger toward the abusive mother. Thus, the therapist has become a mother who fails to nurture her own child, her patient.

Medical and psychological support for pregnant women with severe EDs should be based on a multi-professional team, including experts from both the gynecological and ED professions. Hospitalization in specific ED facilities should be an option in severe cases such as ours. The present case exemplifies the great

difficulty in dealing with pregnant ED women who refusing treatment even in an environment that is safe for them and their babies. In these cases, it is advisable to seek support from people that are most meaningful to the patient, including the patient's spouse, family, and her community at large (in the present case a religious authority could have been an option). Should the patient release herself from inpatient treatment against medical advice, it is important to continue with physical and psychological monitoring in specialized ambulatory community treatment environments to provide support for the mother and the baby, during and after birth. Compulsory treatment in such cases is not a possibility under the Israeli law.

DISCUSSION

The present article described four women with EDs who were engaged in extreme self-inflicted behaviors that endangered their life and health (all cases) and that of their future-to-be baby (case 4). They were of different ages, from 17.8 to the late 30th, had engaged in different types of extreme at-risk behaviors, and were treated in different specialized ED centers in Israel.

These specific cases were chosen because they reflected the broad spectrum of severe medical complications associated with their ED-related at-risk behaviors. These medical complications, alongside the patients' severe ED symptomatology and comorbid psychiatric disturbances, required prolonged, often repeated, hospitalizations in medical and/or specific ED departments. The patients mostly did not comply with the many medical and psychological opportunities they were offered. This required particularly fine-tuning, determination and patience from the multi-professional treatment providers. Unfortunately, none of the patients showed any inclination toward remission of their ED. Hence, all were at risk to continue with their life-endangering behaviors.

Several factors were common to all or most patients:

1. All patients were diagnosed with AN with B/P pathology (case 2 switched from restricting to B/P pathology during inpatient treatment). Second, three patients (cases 1–3) had evidence of more than one purging behavior, i.e., both self-induced vomiting and laxative abuse; this suggests the likelihood of considerable impulsivity associated with multiple purging presentation (8, 60, 78). Third, several patients had evidence of non-ED-related impulsive behaviors (case 1: oppositional behavior, NSSIs; case 2: attention deficit hyperactivity disorder; case 3: alcohol addiction). Altogether, although impulsivity was not directly assessed, the extreme self-endangering behaviors in our cases were likely carried out in the context of severe impulsivity.
2. In addition to impulsivity, most patients suffered from other comorbidities and from multiple vulnerabilities. Case [1] was diagnosed with social anxiety disorder, depression, and OCD. She was introverted and shy, had communication problems as a child and almost no friends, and her relations with her parents were highly conflictual. At times she was highly suicidal. In addition to the ED, she also suffered from celiac disease and T1DM. Case [2] suffered during inpatient treatment from depression, anxiety, and occasional "giving-up"-related suicidal preoccupations. Case [3] had abusive, violent, overly-dependent relations with her parents, as well as undergoing sexual trauma as a young adult. Altogether, as demonstrated in our patients, extreme at-risk behaviors in patients with AN seem to occur in the context of a long-standing extremely harmful background. In support of this contention, it has been repeatedly found that sexual trauma in patients with EDs is associated with the occurrence of multiple purging behaviors, comorbid depression, PTSD, substance abuse, and elevated suicide risk (60, 61, 79)
3. In most patients, the extreme at-risk behaviors developed on a background of long-standing severe AN, often requiring multiple hospitalizations (case 3): duration from onset to around 4 years in cases [2] and [3], and 9 years in case 4. Most, although not all, extreme at-risk behaviors were carried out in the purpose of weight reduction and body image disturbances. In case [1], insulin omission was used to lose weight, in addition to restricting and purging behaviors. In case [2], although the patient claimed that her excessive water consumption was not done to reduce her eating, it nevertheless appeared after the cessation of vomiting and laxative misuse. In cases [3] and [4], the grave consequences (rectal prolapse and early birth, respectively), were the direct result of multiple problematic eating-related behaviors.
4. Nonetheless, the most important finding related to these case descriptions was that multiple co-occurring non-ED motivations and faulty emotional handling, may lie at the base of the extreme endangering behaviors described here, above and beyond ED-related factors. In general, although most patients were suicidal (cases 1–3), except for patient [1], who directly attached her faulty insulin handling with her wish to die, or with an indifference to whether she would live or die (53, 54), none of the other patients attached their severe at-risk behaviors with suicide wishes. Second, whereas the motivations inherent in the severe self-destructive acts here were like those found in NSSIs (8, 16–18), in contrast to NSSIs, the symptoms caused by these behaviors almost always involved massive medical disturbances.
5. The problems and motivations underlying these extreme behaviors included: 1.) difficulties in emotional regulation and expression, and extreme unexpected moves from emotional blocking to emotional flooding [(16, 21, 59); cases 1–3]. The handling of these conditions likely required extreme self-destructive acts for anxiety reduction and self-soothing, and for avoiding contact with overwhelming emotions (case 3), mental pain (case 1), or depression [(case 2) (62); 2.)] as an idiom of distress, to indirectly communicate one's suffering to the environment in individuals with communication problems [all cases to some extent; (55), and 3.] as potentially related to early maltreatment, leading to problematic attachment relationships with significant others throughout life [cases 1, 3; (63)], specifically when separation is imminent upon the improvement of the ED (case 3).

6. Other motivations may also potentially account for the extreme at-risk behaviors described here: In case [1], the use of insulin overdose to create hypoglycemic episodes to feel "high" and excited from endangering her life (53). In case [4], the ongoing multiple faulty eating-related behaviors, signify the unresolved conflicts of caring for oneself and fostering one's own space and self-identity vs. being a good mother and caring for her future-to-be child.
7. In all cases, the patients seemed to be indifferent to the potentially harmful consequences of their repeated extreme self-endangering acts. This indifference might be associated with the motivations to the extreme behaviors described here. Specifically, it might reflect the tendency of patients with AN to deny the severity of their illness (1), that might be generalized to other medical disturbances. It might be further associated with the patients' deficient emotional, mentalization and theory of mind capacities [(21), 58.59], as well as their reduced attraction to life (25), when having no immediate or long-term fulfilling meaningful goals.
8. The treatment of all four cases required inpatient settings specializing in the treatment of severe long-standing EDs, as well as of severe self-endangering behaviors often requiring intensive medical interventions. The treatment in all centers described here is multidimensional and multi-professional. The patients receive a structured nutritional rehabilitation program, as well as multimodal individual, family and group interventions tailored for the treatment of the ED, comorbid disorders, and different psychosocial difficulties
9. At the beginning of hospitalization, individual psychotherapy in most centers was supportive, to assist the patients in in their nutritional rehabilitation, alongside cognitive behavioral therapy (CBT) and dialectical behavior therapy (DBT) elements as required. DBT was of particular relevance for emotionally dysregulated patients involved in impulsive life-endangering behaviors such as ours (80). At later stages, treatment included motivational and different types of psychodynamic psychotherapies. For the present cases, psychodynamic interventions were considered to compensate for the patients' long-standing emptiness, loneliness, frustration, lack of self-fulfillment, and severe enduring relational difficulties. These interventions were also considered to potentially enhance the developmental abilities of our patients in front of the challenges of discharge from inpatient treatment, which was highly difficult for them. Whereas adolescent patients usually return to their home, adult patients may receive rehabilitation interventions preparing them for referral to post-discharge ED-related rehabilitation centers. Unfortunately, all the cases described here, lacked the motivation and resources to be referred to such rehabilitation centers.

DATA AVAILABILITY STATEMENT

The datasets generated for this study are available on request to the corresponding author.

ETHICS STATEMENT

Ethical review and approval was not required for the study on human participants in accordance with the local legislation and institutional requirements. Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

AUTHOR CONTRIBUTIONS

All authors (DS, SK, II, TS, AT, MP, EW) contributed to the conception and design of the study. SK, II, TS, AT, and MP contributed the different case reports. DS and EW contributed the introduction and general remarks and were responsible for the organization of the article. All authors read and approved the final draft of this article.

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Brain-Derived Neurotrophic Factor and Oxytocin Signaling in Association With Clinical Symptoms in Adolescent Inpatients With Anorexia Nervosa—A Longitudinal Study

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Introduction: Brain-derived neurotrophic factor (BDNF), as well as oxytocin (OXY), are centrally secreted neuropeptides regulating a range of physiological processes, including food intake and metabolism. Moreover, numerous reports suggest their role in affective and cognitive symptoms of various psychiatric disorders. Thus, the study aimed to measure the serum level of BDNF and its receptor—tropomyosin-related kinase B (TrkB) and OXY in the malnourished anorexia nervosa patients and following partial weight-recovery. The correlations between levels of these proteins with the primary symptoms of the anorexia nervosa (AN) were also analyzed.

Methodology: Eighty-four adolescent AN patients were recruited into the study, but only forty-two AN patients completed it. The control group comprises of thirty age- and height-matched girls (CG). Serum BDNF, TrkB, and OXY levels were measured in AN group in two time-points—at the beginning of the hospitalization in malnourished patients (AN-T1) and again after partial weight normalization, on the day of discharge (AN-T2). The severity of eating disorders, as well as depressive and obsessive-compulsive symptoms, were assessed at the same two-time points.

Results: Body mass index (BMI) differed significantly between the AN-T1, AN-T2, and CG. BDNF levels for the AN-T2 increased significantly in comparison to the AN-T1, but at two-time points were significantly lower than in the CG. The OXY level did not change with weight gain and in both groups AN-T1 and AN-T2 were statistically significantly higher than in the CG. Statistically significant negative correlations between BDNF and the severity of eating disorders symptoms were found. Depressive and obsessive-compulsive symptoms did not show significant correlations with levels of studied proteins for either malnourished or partially weight recovered AN patients.

Conclusions: BDNF serum levels were decreased in the malnourished AN patients and tended to normalize with partial weight recovery. OXY serum levels were found to be increased in the malnourished AN patients and did not normalize with partial weight recovery, confirming previous reports about its role in the etiopathogenesis of AN. BDNF can be related to aberrant eating behaviors occurring in AN. Our results do not support the role of serum levels of BDNF, TrkB, or OXY in the modulation of depressive or obsessive-compulsive symptoms.

Keywords: eating disorders, anorexia nervosa, brain-derived neurotrophic factor, oxytocin, tropomyosin-related kinase B

INTRODUCTION

Anorexia nervosa (AN) is common (1), poorly understood metabo-psychiatric disorder with a high relapse rate (2) and excessive mortality (3). Biological, psychological, and sociocultural factors may affect the development, progression, and outcome of AN, and recently a role for the abnormalities in centrally and peripherally produced regulatory peptides in the AN pathogenesis has been suggested (4). Regulatory proteins play an essential role in the monitoring of food intake, affecting homeostatic, mainly hypothalamic control of feeding. Moreover, they may also influence non-homeostatic food intake *via* their receptors in the cortico-limbic system. Processes like emotions, motivation, physical activity and reward assessment, associated with higher order brain structures are also relevant for the regulation of food intake and AN etiology (5).

Oxytocin (OXY) is a nine-amino acid neuropeptide and neuromodulator mainly produced in the paraventricular nucleus (PVN) (6) and the supraoptic nucleus (SON) (7), which primarily regulates reproductive behaviors and mother–infant interactions (8). It is released into the bloodstream, entering peripheral circulation, as well as directly into the nervous system (9). In the brain, OXY binds to a G-protein-coupled receptor expressed in the limbic system so its role in learning, anxiety, memory, regulation of emotions, and social cognition has been suggested (10). Moreover, its receptors are also present peripherally in pancreas, gastrointestinal tract, or adipocytes (11), which may point to its importance for metabolism and food intake (12). In animals, OXY-deficiency or OXY receptor-deficiency increased food intake and body weight (13). Moreover, central or peripheral OXY administration attenuated food intake and led to sustained weight reduction (14). It was also demonstrated that OXY activates pro-opiomelanocortin neurons (POMC) and acts as the downstream mediator of the leptin effects. Peris et al. proposed that the peptide might attenuate eating behavior by modulating reward-related signaling (15). Serotonin has been found to increase OXY concentrations (16), while dopamine and glutamate interactions with OXY were found to modulate the activity of the reward circuitry of the brain (15). The serum OXY levels in obese patients were found to be increased (17). However, if obesity was associated with diabetes then the serum OXY levels were decreased (18). Moreover, in both healthy-weight and obese subjects, OXY administration can cause a reduction in caloric intake and consumption of palatable snacks (19), as well as improved glucose and lipid metabolism (20, 21). OXY increased the cognitive control and reduced food craving, which might suggest its role in the reward system (22). Thus, the above results support the interest in the role of OXY as an anorexigenic factor both in healthy humans and patients suffering from eating disorders.

Brain-derived neurotrophic factor (BDNF) is produced in the brain and plays an essential role in neuronal survival and growth, serves as a neurotransmitter and neuromodulator, and participates in neuronal plasticity (23). BDNF protein and its receptor tropomyosin-related kinase B (TrkB) have been identified in most brain areas including the olfactory bulb, cortex, hippocampus, basal forebrain, mesencephalon, hypothalamus, brainstem, and spinal cord (24). Furthermore, it was shown that BDNF is involved in the regulation of food intake and metabolism and, together with TrkB, is expressed in several regions that influence feeding behavior including the PVN, arcuate nucleus (ARC), ventromedial nucleus (VMN), dorsomedial hypothalamus (DMH), and lateral hypothalamus (LH) (25, 26). BDNF affects the motivated and reward-seeking behaviors in the mesolimbic dopamine system (27, 28) and thus regulate the food intake (29). Animal studies have shown that BDNF or TrkB depletion results in hyperphagia, obesity, and metabolic syndrome (30). Moreover, peripheral or ventricular administration of BDNF suppresses energy intake and reduces body weight (31). In humans, BDNF haploinsufficiency or inactivating mutations of the BDNF receptor result in the hyperphagia and childhood-onset obesity (32, 33). Moreover, large genome-wide association studies have strongly implicated the BDNF gene locus in the regulation of body mass index (BMI) (34). It was postulated that BDNF could have an anorexigenic effect on food intake and metabolism.

The majority of previous studies examined the role of OXY, BDNF, and TrkB in adult patients with AN. It is not clear whether the regulation of food intake in the developing adolescents is the same as in adults. Nevertheless, the assessment of the adolescent population may allow to observe the regulatory mechanisms before the neuroplastic changes caused by long duration of illness.

Therefore, the presented study aimed to measure the serum levels of OXY, BDNF, and TrkB in malnourished and partially

weight-recovered adolescent AN inpatients. We investigated the correlations between level of proteins and several symptomatic dimensions of AN, namely eating disorder, depression, and obsessive-compulsive symptoms. Due to the lack of previous studies in this population, unclear results of animal models, and exploratory nature of the project no *a priori* hypotheses of correlation were proposed.

METHODOLOGY

Participants and Procedures

Eighty-four adolescent patients admitted in the acute phase of AN to the Child and Adolescent Psychiatric Department were enrolled in the study. Diagnosis of the restrictive type of AN was made according to the ICD-10, DSM-IV, and DSM-5 criteria after a semistructured interview conducted by a child and adolescent psychiatrist. A physical examination and basic laboratory assessments were performed. The exclusion criteria comprised physical illnesses and laboratory abnormalities not resulting from the prolonged restriction of food as well as other psychiatric comorbidities. For the first time during the study, in 1 to 3 days after admission in malnourished AN patients (AN-T1), a psychometric assessment was conducted, heights and weights were checked, and 15 ml blood samples were obtained. The same procedures were repeated for the same patients in the second time point 11.2 ± 2.3 weeks later, on the day of discharge, after partial weight normalization (AN-T2). Then the exclusion criteria were as follows: failure to obtain target body weight (minimal appropriate for particular height and age) and an increase of BMI less than 2 kg/m^2. Only forty-two weight-recovered amenorrhoeic patients completed the study, and the remaining forty-two subjects who did not gain weight or discharged themselves against medical advice were excluded. The control group (CG) comprised of thirty normal-weight, eumenorrheic, healthy girls with no history of psychiatric disorders that were recruited from middle school students. They underwent the same procedures as physical and psychiatric examination, anthropometric and psychometric assessment, and blood analysis, only once. The BMI was calculated as a ratio of body weight (kg) to height (m^2) and the percentage of ideal body weight (%IBW) as a ratio of actual to ideal body weight (IBW) × 100%, where IBW (kg) = [height (cm) −100]−{[height (cm)−150]/2} according to Lorentz's formula. Considering Polish growth references, the additional inclusion criterion was a BMI of lower than 15 kg/m^2 (35). All measurements were taken from fasting females in a standing position. The Eating Attitudes Test (EAT-26), Hamilton Depression Rating Scale (HDRS), Beck Depression Inventory (BDI), and Yale-Brown Obsessive-Compulsive Scale (YBOCS), all commonly used in clinical practice as well as scientific research in the Polish adolescent patients, were used to assess the symptoms of eating disorders, depression, obsessions and compulsions, respectively.

All patients were enrolled in a behaviorally oriented nutritional rehabilitation program. The daily caloric intake was 2,000–2,500 kcal and increased gradually to 3,500–4,000 kcal depending on weight gain (1.0–1.5 kg per week). Group and family therapy were available. The patients with acute symptoms such as severe agitation, anxiety, or insomnia received medication, mostly hydroxyzine, benzodiazepines, or small doses of atypical antipsychotics, only temporarily.

The methodology of this study is similar to other studies previously published by our team (36, 37). Written informed consent was obtained from all participants and their guardians. The research protocol was approved by the Bioethics Committee of Poznan University of Medical Sciences (1029/13). All procedures were conducted in accordance with the 1964 Helsinki Declaration.

Biochemical Analysis

Venous blood was collected upon morning admission (7–8 am) from overnight fasting malnourished AN patients (AN-T1) and again on the day of discharge, after partial weight normalization (AN-T2). Serum was immediately separated from the blood by centrifugation at 1,000 × g for 15 min at 4°C, aliquoted into Eppendorf tubes, frozen at -70°C, and assayed afterward.

A quantitative assay of OXY was performed using a commercial immunoenzymatic test (General Oxytocin Elisa kit cat no. E9802Ge, EIAab Science Inc, Wuchan, Hubei, China), following the manufacturer's instructions. The measurement range of the kit was 32.1–2,000 pg/ml. The minimum detectable dose of general OXY is typically less than 0.39 pg/ml. Optical density was read *via* a spectrophotometric plate reader (Biochrom Asys UVM 340 Microplate Reader) at a wavelength of 450 nm ± 10 nm. Every assay was repeated twice, and the mean value of the two assays was used for statistical evaluation. A four-parameter algorithm (four-parameter logistic) was used to assay concentration in the tested samples. The intra-assay coefficient of variation was <4.5%, whereas the inter-assay coefficient of variation was <7.5%.

Enzyme-linked immunosorbent assay analyses were performed using BDNF DuoSet (cat. No DY 248) and TrkB DuoSet (cat. No DY 397-5) ELISA Development Kit (R&D System, Minneapolis, MN, USA) according to the manufacturer's instructions. All samples and standards were run in duplicates. Standard curves ranged from 1,500–23.4 pg/ml (for BDNF) to 3,000–46.8 pg/ml (for TrkB). Intra-assay and inter-assay variability were <5% and <10% coefficient of variation (CV), respectively.

Statistical Analysis

Results were analyzed using the SPSS 21 statistical package. The data were reported as mean ± standard deviation (SD). Results are also presented as boxplots where the dark line in the middle of the box is the median, the bottom of the box indicates the 25th percentile, and the top the 75th percentile with whiskers extended to the minimum and maximum values. The distribution of results was tested for normal distribution using the Shapiro–Wilk tests. For variables with normal distribution (age CG, weight CG, BMI AN-T1, BMI CG, %IBW CG, %IBW AN-T1, OXY AN-T1, OXY AN-T2, TrKB CG), the significance of differences was assessed using the Student's t-test for dependent (AN-T1 vs. AN-T2) and independent groups (AN-T1 vs. CG and AN-T2 vs. CG). The other variables were analyzed using the Mann–Whitney test for independent groups (AN-T1

vs CG and AN-T2 vs. CG) and the Wilcoxon test for dependent groups (AN-T1 vs AN-T2). Correlations were tested using the Spearman tests. All analyses were two-sided, and p-values ≤0.05 were considered significant. The *post hoc* power was calculated using GPower program (38).

RESULTS

Demographic and Clinical Characteristics

The demographic characteristics of all participants are presented in **Table 1**. Studied groups did not significantly differ in age–AN patients were 15.76 ± 2.15 years old and the CG was 15.38± 1.47 years old ($p < 0.360$) or height–AN group was 1.63 ± 0.06 m and the CG was 1.64 ± 0.05 m ($p < 0.281$). Body weight, BMI, and % IBW were significantly lower in the AN-T1 than in the AN-T2 and CG.

The AN-T1 group obtained statistically significant higher results on the HDRS than the AN-T2 group ($p < 0.000$) and CG ($p < 0.000$), but there was no statistically significant difference between the AN-T2 group and CG ($p < 0.080$). The AN-T2 group scored statistically significantly lower in BDI than the AN-T1 group ($p < 0.000$) but still significantly higher than the CG ($p < 0.004$). There were no statistically significant differences in EAT-26 between the AN-T1 and AN-T2 group ($p < 0.067$), but the results in the AN-T1 and AN-T2 group were statistically significantly higher than in the CG ($p < 0.000$ and $p < 0.007$, respectively). The results from the YBOCS were higher in the AN-T1 group than in the CG ($p < 0.000$), but there were no statistically significant differences between the AN-T2 group and CG ($p < 0.158$), as well as the AN-T1 and AN-T2 group ($p < 0.158$).

Serum Levels of OXY, BDNF, and TrkB

As presented in **Table 2**, serum OXY concentrations were significantly higher in the AN-T1 and AN-T2 group than the CG ($p < 0.000$ and $p < 0.008$ respectively). In AN patients, the OXY levels remained unchanged; there were no statistically significant differences between the AN-T1 and AN-T2 group ($p < 0.973$) (**Figure 1**). The mean serum BDNF concentrations were statistically significantly higher in the CG than in the AN-T1 group ($p < 0.001$) and AN-T2 group ($p < 0.047$). There were no statistically significant differences in the BDNF levels between the AN-T1 and AN-T2 group ($p < 0.057$), but the tendency to increase with body weight normalization was observed (**Figure 2**). Moreover, there were no statistically significant differences in TrkB concentrations in the AN-T1 group and CG ($p < 0.584$) or AN-T2 group and the CG ($p < 0.147$). However there was a statistically significant difference between the AN-T1 and AN-T2 group ($p < 0.000$)—the TrKB concentrations increased with body weight normalization to the level higher than in the CG (**Figure 3**).

Correlations Between Analyzed Variables

A statistically significant negative correlation between BDNF and BMI was found for the AN-T1 group ($p < 0.036$; $r = -0.372$) but not the AN-T2 group. A statistically significant negative correlation between BDNF and EAT-26 ($p < 0.042$; $r = -0.292$) was obtained. TrkB showed no statistically significant correlation with any of the analyzed variables in the AN-T1 or AN-T2 groups. However, a positive correlation between TrkB and BMI was found in AN ($p < 0.000$; r = 0,369). There were no statistically significant correlations between OXY and BMI, HDRS, BDI, EAT-26, or YBOCS in any of the patient groups or CG.

DISCUSSION

The adolescent inpatients with the restrictive type of AN included in the presented study were hospitalized for about 11 weeks and gained, on average, 8 kg. After partial weight recovery, they showed improvement in obsessive-compulsive and depressive symptoms assessed by a psychiatrist—the AN-T2 group and the CG showed no statistically significant differences in HDRS and YBOCS. Conversely, the AN-T2 group still presented higher than the healthy controls, score in self-reported depression (BDI) and eating disorder (EAT-26) scales. These results are partially in line with previous studies (39), which showed that weight restoration alone is insufficient for long-term recovery (40, 41). Many psychopathological symptoms and biological abnormalities, including alteration in peripheral and central neuropeptides, still occur long after weight normalization and may affect disease course and prognosis (42).

The existing literature examining OXY in AN subjects is small (43). To the best of our knowledge, none of the studies assessed

TABLE 1 | Anthropometric and psychometric data, in the adolescent anorexic inpatients in acute stage of the disease (AN-T1) as well as after partial weight recovery (AN-T2), and in the control group (CG).

	AN-T1	AN-T2	CG	AN-T1 vs CG	AN-T1 vs AN-T2	AN-T2 vs CG
					p<	
Age (years)	15.76±2.15		15.38±1.47		0.360	
Height (m)	1.63±0.06		1.64±0.05		0.281	
Weight (kg)	37.76±4.42	45.83±4.64	53.73±11.22	0.000	0.000	0.001
BMI (kg/m2)	14.03±1.58	17.19±1.25	19.81±3.85	0.000	0.000	0.001
%IBW	52.63±8.35	65.79±6.15	74.99±14.24	0.000	0.001	0.003
HDRS	12.80±7.09	5.46±4.94	3.07±5.08	0.000	0.000	0.080
BDI	16.24±12.25	9.81±10.39	3.53±4.24	0.000	0.000	0.004
EAT-26	25.87±20.15	15.35±19.20	5.20±5.55	0.000	0.067	0.007
YBOCS	10.10±7.84	6.84 ± 8.66	3.53±4.24	0.000	0.158	0.071

TABLE 2 | The serum oxytocin (OXY), brain-derived neurotrophic factor (BDNF), and tropomyosin-related kinase B receptor (TrkB) levels in the adolescent anorexic inpatients in the acute stage of the disease (AN-T1) as well as after partial weight recovery (AN-T2), and in the control group (CG).

	OXY (pg/ml)	BDNF (ng/ml)	TrkB (ng/ml)
AN-T1	127.46 ± 58.68	28.66 ± 6.70	1.67 ± 0.54
AN-T2	127.90 ± 106.13	30.75 ± 8.34	1.93 ± 0.53
CG	70.72 ± 39.75	34.66 ± 7.40	1.74 ± 0.53
		AN-T1 vs. CG	
df	58	67	67
p	0.000	0.001	0.584
t	4.385	-3.521	-5.551
md (95% cl)	56.740	-5.998	-0.071
	(30.760–82.719)	(-9.398–(-2.597)	(-0.330–0.187)
power	0.99	0.98	0.09
		AN-T1 vs. AN-T2	
df	29	38	38
p	0.973	0.057	0.000
t	-0.034	-1.965	-4.102
md (95% cl)	-0.447	-2.087	-0.260
	(-27.274–26.379)	(-4.239–0.063)	(-0.388–(-0.131)
power	0.05	0.30	0.72
		AN-T2 vs. CG	
df	58	67	67
p	0.008	0.047	0.147
t	2.764	-2.025	1.468
md (95% cl)	57.187	-3.910	0.188
	(15.769–98.604)	(-7.764–(-0.056)	(-0.067–0.445)
power	0.83	0.55	0.31

levels of OXY in AN patients below 18 years old, though the highest incidence rate subgroup for AN includes girls aged 15–19 years old and accounts for about 40% of all identified cases. Results from studies conducted in adult AN patients are conflicting. In one study, no differences in basal OXY levels between AN and control groups were demonstrated (44). However, in most of the investigations, it was found that OXY levels were decreased in AN adult patients in serum (17, 45), as well as in CSF (not in binge-purge subtypes) (46). Moreover, postprandial OXY level was also discovered to be elevated in AN patients (47). The results of the present research are contradictory—serum OXY levels were higher in the AN-T1 and AN-T2 than in the healthy controls. Moreover, the OXY level did not normalize with weight gain, and after partial weight normalization remained higher than in the CG. A high level of anorexigenic OXY might suggest disturbances in transferring information about the metabolic status and be co-responsible for maintaining low body weight. It could also be an adaptive mechanism to reduce the level of cortisol and anxiety. Previous studies have shown that OXY reduces the level of adrenocorticotropic hormone and cortisol under basal and stress conditions (48) and acts as an antianxiety factor.

The link between OXY levels and psychopathology in AN has also been explored. Studies in AN women have identified an association between genetic variation in the OXY receptor and eating disorders, thoughts and behaviors, and food preoccupation (49, 50). Moreover, basal OXY levels in patients after partial weight recovery, but not in the acute stage, were negatively associated with disordered eating psychopathology and anxiety symptoms (45), but postprandial OXY levels were positively associated with disordered eating, anxiety, and depressive symptoms (47, 51). In the present study, we did not find any correlation of OXY with symptoms of eating disorders, depression, obsessions or compulsions.

Using various methodological approaches might be the simplest explanation for the inconsistency in the results of studies. However, it has been postulated that OXY levels might be not only sex-dependent but also age-dependent (52, 53) and this could justify conflicting results as well. Different actions of

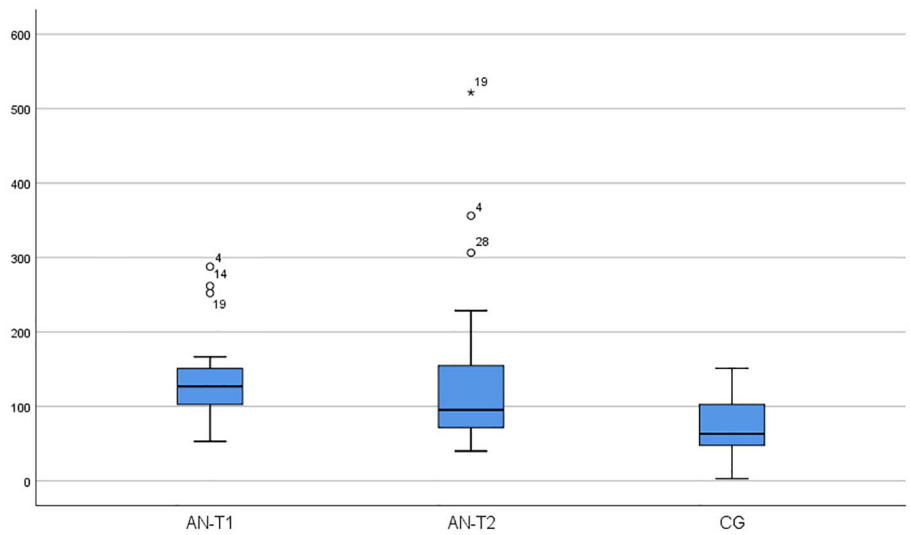

FIGURE 1 | Serum oxytocin (OXY) concentration in the adolescent anorexic inpatients in acute stage of the disease (AN-T1) as well as after partial weight normalization (AN-T2), and in the control group (CG).

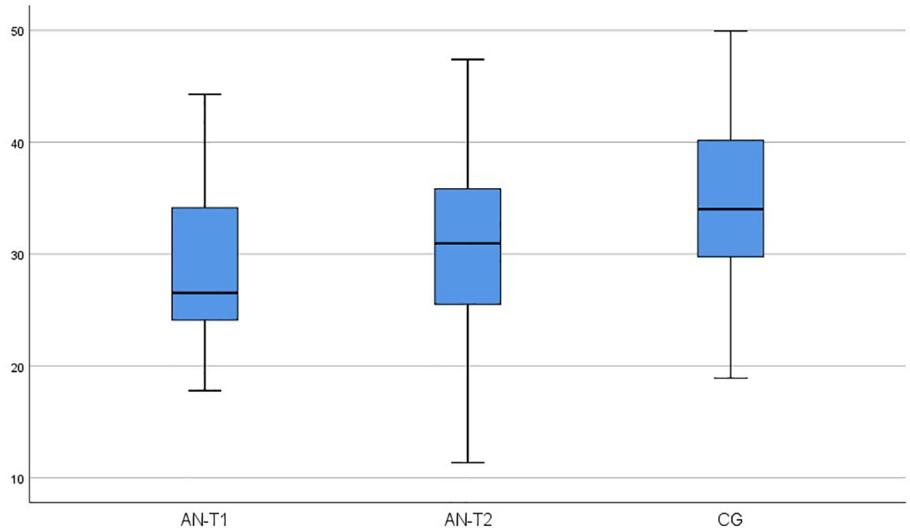

FIGURE 2 | Serum brain-derived neurotrophic factor (BDNF) concentration in adolescent anorexic inpatients in the acute stage of the disease (AN-T1) as well as after partial weight normalization (AN-T2), and in the control group (CG).

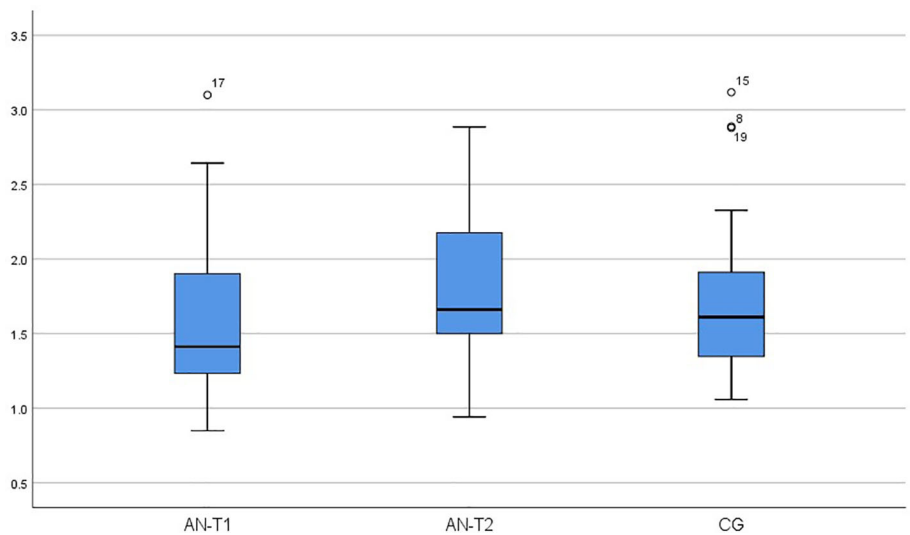

FIGURE 3 | Serum tropomyosin-related kinase B receptor (TrkB) concentration in adolescent anorexic inpatients in the acute stage of the disease (AN-T1) as well as after partial weight normalization (AN-T2), and in the control group (CG).

OXY related to age has been suggested in both animal (54) and human studies (55). Intranasal administration of OXY can lead to a reduction in body weight when given to obese adults but not to obese children; thus, it was postulated that young individuals might respond differently to OXY than older ones (56). Therefore, it is necessary to study OXY levels in adolescent girls because, in many ways, it appears to be a critical period for biological and psychological development.

BDNF levels have been intensively studied in eating disorders, mostly in small groups of adult patients. In the previous investigations, serum BDNF levels were decreased in the acute stage of AN (57–61), what was also confirmed in a meta-analysis (62). The results were opposite in only one study, probably due to heterogeneity of the included patients and the fact that plasma and not serum was assayed (63). After partial or full weight normalization, BDNF levels were increased (27, 59, 64, 65),

unchanged (58), or even decreased (65, 66). In the present study in the acute stage of the disease, BDNF levels were reduced compared to the healthy controls and tend to normalize with weight gain. Moreover, a negative correlation between BDNF and BMI was found in the AN-T1 patients but not in AN-T2. There was also a positive correlation between BMI and TrkB in AN patients. Previously, either no association of BDNF with BMI (58, 59) or a positive relationship (60, 61, 66) was shown in the analysis of all patients regardless of body weight and the stage of the disease. Lower levels of BDNF could be an adaptive mechanism to promote food intake in chronic starvation. However, its role in non-homeostatic regulation of food intake could also be important in terms of an explanation. This was shown in genetic studies where the Val66Met BDNF polymorphism was associated not only with BMI (67) but also with a higher reward value of starvation in AN (68).

Moreover, negative correlations between the severity of symptoms of eating disorders measured with EAT-26 in AN patients were found ($p < 0.042$; $r = -0.292$). This is contradictory with other results where Eating Disorder Examination Questionnaire (EDEQ) or Eating Disorders Inventory two (EDI-2) were used and no correlations with eating disorder symptoms were found (59, 61). We did not see an association between BDNF and depressive symptoms measured with HAM or BDI or obsession and compulsions measured with YBOCS. These findings confirmed previous studies where BDNF did not correlate with the severity of the depressive (57, 60, 61) or obsessive-compulsive symptoms (59) in AN patients. We speculate that BDNF could be related to aberrant eating behaviors occurring in AN.

The authors of the presented study are aware of its limitations and recall the most important of them. Only weight-recovered patients were included in the study, and it would be relevant to include also those who did not reach appropriate body weight or discharge themselves against medical advice. The OXY, BDNF, and TrkB levels should be examined several times at the different time points as well as after long-term weight restoration what could help draw the final conclusions.

Conclusions

BDNF serum concentration was lower in the malnourished AN patients and tended to normalize its level with weight gain. The serum of OXY was higher in adolescent inpatients with AN and did not normalize its level; thus, it could contribute to persistent psychopathology after partial weight recovery from AN.

BDNF levels correlate with the severity of eating disorder symptomatology and, thus, could be related to aberrant eating behaviors occurring in AN. Our results do not support a role for serum level BDNF in the modulation of depressive and obsessive-compulsive symptoms.

DATA AVAILABILITY STATEMENT

The datasets generated for this study are available on request to the corresponding author.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Bioethics Committee of Poznan University of Medical Sciences (1029/13). Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

AUTHOR CONTRIBUTIONS

MT-N, AS, and FR contributed conception and design of the study. MD-W, AD and EP organized the database. MT-N and MS performed the statistical analysis. MD-W and MS performed biochemical analysis. All authors contributed to manuscript revision, read and approved the submitted version.

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SYSTEMATIC REVIEW
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A Meta-Analysis of Dropout and Metabolic Effects of Antipsychotics in Anorexia Nervosa

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Background: Second-generation antipsychotics are often used off-label in the treatment of anorexia nervosa (AN) across the clinical spectrum. Patients with anorexia nervosa often cite concerns about metabolic effects, such as weight gain, as reasons for their reluctance to start or continue second-generation antipsychotics. Improving our understanding of the metabolic effect patients experience and reasons underlying their disinclination will enable us to build rapport and guide our clinical decisions. We therefore aimed to conduct a comprehensive review of dropouts, metabolic effects, and patient-reported outcomes associated with second-generation antipsychotic in people with AN.

Method: EMBASE, Medline, and PsycINFO were searched for all relevant studies published until 2019, and retrieved studies were assessed for eligibility as per predefined inclusion criteria. A random-effects meta-analysis was conducted to assess overall dropout rates.

Results: Of 983 citations retrieved, 21 studies met the inclusion criteria for the systematic review and 10 studies had appropriate data for meta-analysis. Using the random effects model, the pooled dropout rate in the intervention arm (95% confidence interval) from psychopharmacological trials was 28% (19 to 38%) in people with AN. Personal reasons or factors associated with study were commonest reason for dropout, not adverse events or metabolic effects as hypothesized.

Conclusion: Compared to personal reasons, drug-related factors such as side effects seem to play a lesser role for the discontinuation of antipsychotic treatment under trial conditions. This suggests an urgent need to consider and fully examine potential individual and patient-related factors that influence dropout rates in psychopharmacological trials and treatment compliance in clinical settings.

Keywords: anorexia nervosa, dropout, antipsychotic, metabolic effect, meta-analysis

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BACKGROUND

Anorexia nervosa (AN) is a debilitating illness with a median duration of 7–10 years. Approximately 20% of individuals with AN develop a severe and enduring form of the illness (1) and a 22 years follow-up study found that only 68.2% of participants with AN have recovered (2). Treating AN successfully is a challenge. Admissions have continued to rise exponentially in the UK (3), even though National Institute for Health and Care Excellence (NICE) recommended outpatient treatment as a first line of management since 2004 (4, 5).

Various forms of outpatient psychological therapies have been developed. A recent meta-analysis of 35 randomized controlled trials (RCTs) concluded that specialised AN treatment was not superior to standard treatment at follow-up [effect size (95% CI) for i) for weight outcomes: 0.11 (-0.04 to 0.27) and ii) psychological outcomes: -0.001 (-0.11 to 0.11)] (6). A recent Cochrane Review also reported that there is little or no difference between specialist inpatient care and active outpatient or combined inpatient and outpatient care in weight gain at 12 months after the start of treatment [standardised mean difference (SMD): -0.22 (-0.49 to 0.05)] (7).

Second-generation antipsychotics are often used off-label in the treatment of AN. For example, a recent self-reported survey of prescribing practice in the UK reported that psychotropic medications are commonly prescribed to a minority of children and adolescents with AN, with olanzapine being the most frequent psychotropic drug (8). The rationale for their use includes weight gain and symptom relief such as reducing anxious feelings and weight/shape concerns. The clinical effectiveness of antipsychotics for people with AN is, however, unclear at present. To date, there have been four meta-analyses examining this effect (9–12). None of the meta-analyses reported a statistically significant differences for weight or changes in body mass index (BMI) between antipsychotics and active control/placebo groups.

The metabolic effects of second-generation antipsychotics are serious and wide-ranging. They have been associated with weight gain, dyslipidemia, hypertension, hyperglycemia, and type 2 diabetes in people with schizophrenia (13). Genetic vulnerability may be relevant in developing metabolic effects. A recent genome-wide association study reported significant genetic correlations between metabolic-related phenotypes with AN, with the authors encouraging a reconceptualization of AN as a metabo-psychiatric disorder (14). This concept is further supported by a meta-analysis of clinical studies showing that AN is associated with increased insulin sensitivity [effect size (95% CI): 1.66 (0.79 to 2.54)].

Patients with AN often cite metabolic effects as reasons for their reservations towards second-generation antipsychotics (15). For example, weight gain is a desired side effect for AN from a clinician's perspective, but patients are often reluctant to start or continue with them. Drop-out rate in clinical trials is defined as the proportion of participants who begin, but do not complete the full course of recommended treatment. It is a useful metric in determining the tolerability of a treatment. We therefore conducted a meta-analysis on the drop-out rates from psychopharmacology trials with second-generation antipsychotics. It can serve as a proxy indicator of the likelihood of a patient with AN in continuing second-generation antipsychotics. We also explored self-reported side effect, as patient-reported outcomes provide a unique window in directly understanding patients' experience and guide clinical decision-making (16). The main aim of this review is therefore to conduct a comprehensive review of dropouts, metabolic effects, and patient-reported outcomes associated with second-generation antipsychotic in people with AN.

METHOD

Eligibility Criteria

Abstracts were considered eligible for full manuscript data extraction if the study met all the following criteria: i) they compared the treatment outcomes of second-generation antipsychotics for AN; ii) the design was RCTs, open label trials, or observational studies; and iii) published in English. Participants of any age and any sex, with a diagnosis of AN were considered. For the meta-analysis, only studies with information about the proportion of participants who begin but do not complete the full course of recommended treatment in the intervention arm were considered.

Study Selection

We searched the Embase (1985 to 2019), PsycInfo (2005 to 2019), and Medline (1982 to 2018), using Ovid Database. We also hand-screened reference lists of all included articles to identify additional studies that were not found during the initial search. Keywords used in the searches included, but not limited to "anorexia nervosa", "atypical antipsychotic", "second generation antipsychotic", "amisulpride", "aripiprazole", "asenapine", "brexpiprazole", "cariprazine", "clozapine", "lurasidone", "olanzapine", "paliperidone", "pimavanserin", "quetiapine", "remoxipride", "risperidone", "sertindole", "ziprasidone" (exhaustive list of keywords in Appendix 1).

Data Extraction

Using a standardized data extraction sheet, the following information (if available) was extracted and recorded for each study: authors; year of publication; country of origin; treatment setting; study design; duration of intervention; age; sex; total numbers of participants in each treatment group; drop out in intervention group; reasons for dropouts; adverse event reporting; duration of intervention and concurrent treatment.

Dropout was defined as the number of participants who started treatment and were defined as having dropped out according to the definition of the study. We did not distinguish the time point of the dropout, as participants can drop out prior to starting the intervention, during the intervention, and after completing the intervention but fail to attend follow-up. The metabolic effects considered included but not limited to weight/BMI, glycaemic control, electrocardiogram (ECG) reports, lipids profile, liver function tests, prolactin, and self-reported side effects.

Quality of Study

To assess the quality of studies, the Cochrane Collaboration's tool for assessing risk of bias was applied to randomized trials and Risk Of Bias In Non-randomized Studies-of Interventions (ROBINS-I) assessment tool for non-randomized studies (17, 18). These include adequacy of study design (observational or open label trails or RCT with an adequate control group); recruitment of sample and control for cofounding variables, such as age, sex, socioeconomic status. A study was considered to be of high quality if the study design consists of a control group; consecutive or random sampling method was used; adequate blinding of participants and personnel; appropriate reporting of outcome variables.

Statistical Analysis

All statistical analyses were performed using the "Metafor" package (19) in open source software programme R. We first transformed the proportion data using the Freeman-Tukey (double arcsine) transformation. This approach is recommended for proportion data as it produces more stable estimates of corresponding sampling variances for the sampling distribution of proportions close to 0 or 1 (20, 21). The transformed proportions and corresponding sampling variances were used in the meta-analysis and then back-transformed using the equation derived by Miller (22) for ease of interpretation.

To estimate the average overall dropout rate from active treatment, a weighted pooled event rate was calculated ("escalc" function in "Metafor"). The meta-analysis was conducted using a random effects model. Given the likely significant differences in study design, a fixed-effects model was deemed inappropriate. Significance threshold was set at $p < 0.05$. A Cochran Q test was performed to assess between-study heterogeneity of effect size (23). Publication biases were investigated with visual inspection of the funnel plots and Begg's rank correlation tests for funnel plot asymmetry (24).

RESULTS

Study Selection

The literature search resulted in 983 studies (**Figure 1**). After reviewing their titles and abstracts, 51 studies met the inclusion criteria and were retrieved for full text. Of these, 33 studies were excluded from the systematic review as they did not meet the inclusion criteria. Upon closer inspection of the remaining 18 studies, two studies utilized the same study population (25, 26). The study with the main aim of reporting the findings of olanzapine in people with AN was selected (25). One study was published as an abstract and the journal is now defunct (27). We therefore did not have access to any information about sampling method, baseline clinical characteristics of the sample population and variables of interest. Five additional studies that fulfilled the inclusion criteria were found from searches of the reference lists of included articles. In total, 21 studies were included in the systematic review and summarised in **Table 1**.

11 studies were excluded from the meta-analysis because they did not report information about the proportion of participants in the intervention arm who did not complete the study. Raw data were therefore not available to generate a standardized effect size for dropout rates. This resulted in 10 datasets being included in the meta-analysis.

Qualitative Summary

Of the 21 datasets included in the systematic review, 11 were RCTs (25, 28, 32–35, 39, 42, 46, 47), 5 open label trials (29, 40–43, 45), 1 prospective study (38) and 4 retrospective cohort studies (31, 36, 44). Sample size varies substantially, with a range between 8 and 152. The median number of participants was 31 with an interquartile range of 18 and 39. There were only 3 studies with a sample size over 100 (106, 152, and 152 respectively). In addition, the majority of the studies included in the systemic review (n = 10) have been conducted in USA, with the rest being in Canada only (n = 3), Canada/US (n = 1), Australia (n = 3), and Italy (n = 4). In terms of sample populations, 6 studies focused on adolescents, with the mean age ranging from 13.7 to 17.1, while 15 studies focused on adults, with a mean age ranging from 20.5 to 38. Of the 14 studies with information on gender, 6 studies recruited only females, while the proportion of females in the remaining 8 studies range between 88.9 and 97.0%.

In terms of treatment setting, 6 studies were conducted in inpatient, 7 in outpatients, 1 in day-care, and 7 across all three settings. For concurrent treatment, 20 studies reported adequate information for extraction. 10 studies allowed for concurrent medication, mainly antidepressants and benzodiazepines, 3 studies combined psychotherapy with second generation-antipsychotics and 6 studies was part of a comprehensive eating disorder treatment programme or its participants receive multidisciplinary team inputs which can include psychotherapy and meal support. One study recorded that no participants received psychotherapy or any other psychiatric treatment during the study. For second-generation antipsychotics as the study drug in the intervention group, 13 studies examined olanzapine, 4 quetiapine, 1 risperidone, 1 aripiprazole, 1 amisulpride, and 1 study compared olanzapine with aripiprazole. Their associated treatment duration ranges from a minimum of 2 weeks to a maximum of 20 weeks. Descriptive data from the datasets are summarized in **Table 1**.

For the meta-analysis, 7 were RCT (25, 28, 32, 34, 35, 37, 39) and 3 open label trials (40, 41, 45). Total number of participants in the intervention group ranged between 6 and 75. The majority of the studies have been conducted in USA (n = 6), with the rest being in Canada only (n = 1), Canada/US (n = 1) and Australia (n = 2). Two studies focused on adolescents, with the mean age ranging from 16 to 17.1. 8 focused on adults, with a mean age ranging from 20.5 to 34. In terms of second-generation antipsychotics as the study drug in the intervention group, 5 studies examined olanzapine, 4 quetiapine and 1 risperidone.

Meta-Analysis

The pooled dropout rate in the intervention arm was estimated to be 28% (95% CI: 19 to 38%; $p < 0.01$) in a random effect model. Results were not statistically significant heterogeneous (Q: 11.96,

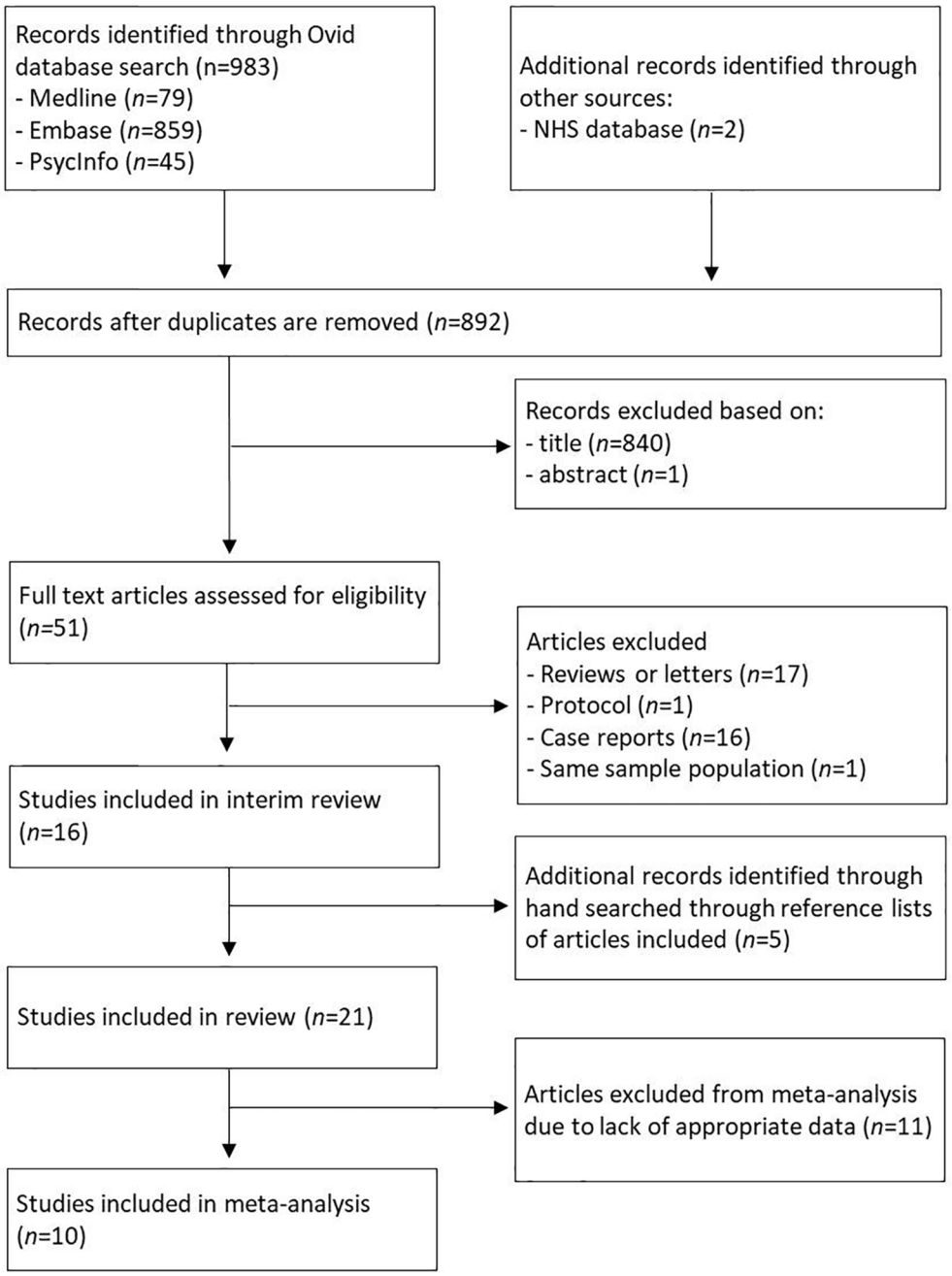

FIGURE 1 | Flow chart of studies included in systematic review.

df: 9, p: 0.02, I^2: 33.1%). Visual inspection of the funnel plot suggested asymmetry, but the Begg's rank correlation test was statistically insignificant (τ: 0.27, p: 0.28), indicating no publication bias.

Outcome of Interest: Dropout

Ten studies specified reasons for dropout. The percentage of each dropout reason, as a proportion of all the reasons given, are described below from most prevalent to least prevalent. The commonest reason for dropout was personal choices (43.5%; 27/62), such as participants' voluntarily withdrawal from a study or preference of a different intervention. This was closely followed by study reasons, for example being lost to follow-up or failure to adhere to protocol (25.8%; 16/62). Of interest, 16.1% (10/62) of dropouts were due to poor response to the intervention or deterioration in mental state, with 6

TABLE 1 | Summary table of primary studies included in the systemic review.

Author	Setting	Study type	Adults/ Adolescent Age mean (SD)	% of female	Number of participants	Dropout in intervention group	Reasons for dropout	Adverse event	Intervention dosage mean (SD)	Duration of intervention (weeks)	Concurrent treatment
*Attia (28)	US/Canada; Outpatient	RCT	Adults Cx: 30.0 (11.0) Ix: 28.0 (10.9)	96 (146)	Cx: 77 Ix: 75	34/75	Hospitalisation: 5 Side effect: 4 Suicidal ideation: 3 Other: 1 Voluntarily withdrawal: 12 Lost to follow-up: 9	Hospitalisation: 5 Suicidal ideation: 3	Olanzapine 7.77 (1.07)	16	Psychotropics (41.4% in sample)
Spettigue (29)	Canada; Mainly Inpatient	Open label trial	Adolescents 15.48 (1.45)	90.6 (29)	At baseline, Cx: 18; Ix: 14 8 participants switched to Ix At end of study, Cx: 10; Ix: 22	NA	Incapable to participate: 1 Unable to adhere to protocol: 1 Preferred a different Ix: 4	None	Olanzapine 5.28 (NA)	12	Individual and family therapy
Frank (30)	US; Inpatient/ partial inpatient	Retrospective chart review	Adolescents Cx: 14.4 (2.5) Ix: 15.0 (2.2)	NA	Cx: 84 Ix: 22	NA	NA	NA	Aripiprazole 3.59 (1.85)	Minimal 3	Specialized eating disorders program
Marzola (31)	Italy Inpatient	Retrospective chart review	Adults 25.43 (9.4)	90.7 (68)	Cx: 25 Ix-A: 23 Ix-B: 27	NA	NA	None	Ix-A: Aripiprazole 9.13 (6.33) Ix-B: Olanzapine 6.11 (3.27)	Mean: 4.96 (1.62)	Antidepressants
*Powers (32)	US; Outpatient	RCT	Adults 34 (13.48)	93.3 (14)	Cx: 9 Ix: 6	2/6	Hospitalisation: 2	Hospitalisation: 2	Quetiapine 177.7 (90.8)	8	NA
Attia (33)	US/Canada; Outpatient	RCT	Adults 27.7 (9.1)	95.7 (22)	Cx: 12 Ix: 11	NA	NA	None	Olanzapine 7.95 (2.7)	8	Antidepressants; no psychological therapy
*Hagman (34)	US; Inpatient, outpatient and daycare	RCT	Adolescents 16 (NA)	100 (40)	Cx: 22 Ix: 19	3/19	Requested active Ix: 1 Reasons unrelated to study: 2	None	Risperidone 2.5 (1.2)	Mean: 8.6 (4.2)	Antidepressants (40% in sample)
*Kafantaris (35)	US;Inpatient, outpatient and daycare	RCT	Adolescents 17.1 (NA)	100 (20)	Cx: 10 Ix: 10	3/10	Sedation: 1 Stopped Ix: 2	None	Olanzapine 8.5 (NA)	10	Comprehensive eating disorders programme; no group/family therapy
Norris (36)	Canada; Inpatient, outpatient and daycare	Retrospective cohort study	Adolescents Cx: 14.8 (1.6) Ix: 14.4 (1.9)	100 (86)	Cx: 43 Ix: 43	NA	NA	None severe	Olanzapine 5.0 (3.75- 7.5)	Minimal 2 In subgroup	Antidepressants (39%) +/- benzodiazepine (7%)
*Court (37)	Australia; Outpatient and inpatient if needed during stay	Open label RCT	Adults 22.53 (NA)	97.0 (32)	Cx: 18 Ix: 15	5/15	Withdrawn consent: 1 Adverse event: 1 Side effect: 1 Non-response: 1 Failure to attend: 1	None severe	Quetiapine 322.5 (NA)	12	Antidepressants +/- benzodiazepine
Leggero (38)	Italy; Outpatient	Prospective cohort study	Adolescents 13.7 (2.3)	NA	Ix: 13	NA	NA	NA	Olanzapine	Unclear	Multimodal including psychotherapy, assisted feeding, psychoeducation,

(Continued)

TABLE 1 | Continued

Author	Setting	Study type	Adults/ Adolescent Age mean (SD)	% of female	Number of participants	Dropout in intervention group	Reasons for dropout	Adverse event	Intervention dosage mean (SD)	Duration of intervention (weeks)	Concurrent treatment
											and prolonged control of somatic conditions
*Bissada (39)	Canada; Daycare	RCT	Adults Cx: 29.67 (11.59) Ix: 23.61 (6.50)	100 (34)	Cx:18 Ix: 16	2/16	Discontinued daycare: 1 Stopped Ix: 1	None	Olanzapine 6.61 (2.32)	10	Comprehensive day programme Including group therapy
Brambilla (25)	Italy; Outpatient	RCT	Adults Cx 26.3 (8.5)	100 (30)	Cx: 15 Ix: 15	NA	NA	NA	Olanzapine 7.77 (1.07)	12	CBT
*Bosanac (40)	Australia; Inpatient/ outpatient	Open label trial	Adults 33.25 (7.65)	100 (8)	Ix: 8	3/8	Own request: 1 Substance misuse: 2	None	Quetiapine 520 (277.49)	8	Specialised and multidisciplinary treatment
*Powers (41)	US; Outpatient	Open label trial	Adults 26.8 (11.2)	94.7 (18)	Ix: 19	5/19	Unknown: 1 Seek treatment elsewhere: 1 Weight gain: 1 Moved out of area: 1 Non-response: 1	None severe	Quetiapine 150-300 (NA)	10	None
Mondraty (42)	Australia; Inpatient	RCT	Adults 25.3 (NA)	NA	Cx: 7 Ix: 8	NA	NA	NA	Cx: Chlorpromazine 50 (NA) Ix: Olanzapine 10 (NA)	Mean: (Unit: days) Cx: 53 (26) Ix: 46 (31)	Antidepressants (63% in Ix arm)
*Barbarich (43)	US; Inpatient & outpatient	Open label trial	Adults 20.5 (5.1)	NA	Ix: 17	5/17	NA	NA	Olanzapine 4.7 (1.6)	6	CBT and DBT mainly, with 1 participant being on antidepressants
Malina (44)	US; Inpatient	Retrospective cohort study	Adults 22 (7)	NA	Ix: 18	NA	NA	NA	Olanzapine 4.7 (2.4)	Range: 17-20	Antidepressants, benzodiazepine
*Powers (45)	US; Outpatient	Open label trial	Adults 26.8 (12.3)	88.9 (16)	18	4/18	Hospitalisation: 1	NA	Olanzapine 10 (NA)	10	Psychotherapy for 1 participant and benzodiazepine for 2 participants
Ruggiero (46)	Italy; Inpatient	Single blind RCT	Adults Cx-A: 23.69 (4.57) Cx-B: 24.5 (50.6) Ix: 24.33 (5.76)	NA	Cx-A: 13 Cx-B: 10 Ix: 12	NA	NA	NA	Cx-A: Clomipramine 57.69 (25.79) Cx-B: Fluoxetine 28 (10.32) Ix: Amisulpride 50 (NA)	12	Weight gaining programme

(Continued)

TABLE 1 | Continued

Author	Setting	Study type	Adults/ Adolescent Age mean (SD)	% of female	Number of participants	Dropout in intervention group	Reasons for dropout	Adverse event	Intervention dosage mean (SD)	Duration of intervention (weeks)	Concurrent treatment
Beasley (47)	US; Inpatient & outpatient	RCT	Adults 38	NA	Cx: 50 Ix-A: 52 Ix-B: 50	NA	NA	SCZ worsen: 1 Hyponatraemia: 1 Hypotension: 1 Urticaria: 1 Allergic reaction: 1 PD: 1	Ix-A: Olanzapine 1 Ix-B: Olanzapine 10	6	Benzodiazepam and anticholinergic agent

NA, Not Available; SD, Standard Deviation; Ix, Intervention Group; Cx, Comparison Group; RCT, Randomized Controlled Trial; CBT, Cognitive Behavioural Therapy; DBT, Dialectic Behavioural Therapy; SCZ, Schizophrenia; PD: Personality Disorder.
**Studies included in meta-analysis.*

participants requiring hospitalization during the study. Adverse events were cited as a reason for dropouts in only 12.9% cases, with weight gain being mentioned once. There were, however, three incidences of suicidal ideations (4.8%) as a reason for dropout from one study (28).

Outcome of Interest: Metabolic Effects

All studies included in the systematic review provided some information for weight/BMI/ideal body weight. This information was, however, difficult to interpret due to heterogeneity between studies. This included different duration of intervention and measures of weight, with some focus on weight gain over time or changes in pre- and post-intervention BMI between groups. In addition, the handling of missing data analysis was often not discussed, leading it hard to summarize the results in a systematic manner. In brief, 6 studies reported a statistically difference between intervention and comparison groups in either weight/BMI increase over time (28–30, 33, 36, 47) whereas 9 studies concluded the opposite (25, 32, 34, 46, 47). Six studies focused on the intervention group only, with 4 reporting a statistically significant weight gain/BMI increase or a greater proportion reaching their ideal body weight (38, 40, 43, 45). One study did not observe any statistically significant change in weight between baseline and end of treatment (41) while one study did not report any significance testing (44).

For glycaemic control, seven studies reported their findings. One study reported a statistically significant increase in fasting glucose in the intervention group (olanzapine) between baseline and end of study (35) whereas one study reported that 4 participants reported hypoglycaemic events with olanzapine (42). For ECG results, four studies reported their findings. One study reported that QTc prolongation was observed in one participant from both intervention (olanzapine) and comparison groups (29) whereas another study reported that one participant developed borderline QTc prolongation with olanzapine (31).

For other routine metabolic effects, there was limited information, with some studies stating that no abnormalities were observed during routine laboratory investigation. In summary, 5 studies reported lipid profiles, 5 for liver function test, and 2 on prolactin. Most studies did not report any statistically significant difference between intervention and comparison groups. One study reported that 3 participants developed raised cholesterol and one participant developed raised low-density lipoprotein in the intervention group (olanzapine) during the study period (31). One study concluded that more participants in the intervention group (olanzapine) experienced clinically significant abnormalities in lipid profiles, liver function tests and prolactin than comparison group, but the differences did not reach statistical difference (29). Another study reported that there is statistically difference in prolactin level between intervention (risperidone) and comparison groups (34), while another study reported that two participants in one study developed raised liver enzymes with olanzapine (38).

Outcome of Interest: Patients Reported Physical Side Effects

Second-generation antipsychotics are associated with a range of physical side effects which may not be captured by biometric investigations. All studies included in the systemic review were examined for any description of patient reported physical side effects. In brief, 14/21 (67%) studies documented physical side effects or adverse events. There was no information on the duration of the side effects, except for two studies describing them as mainly transient (37, 41).

In the intervention group, the most common side effect was sedation which was reported in 12 out of the 21 studies (57%). This was followed by dizziness (n = 7 studies, 33%), headache (n = 7, 33%), gastrointestinal problems (n = 6, 29%), insomnia (n = 5, 24%), fatigue (n = 4, 19%), muscular problems (n = 4, 19%). A few studies also reported dry mouth (n = 3, 14%), blurred vision (n = 2, 10%), poor concentration (n = 2, 10%), agitation (n = 2, 10%), respiratory problems (n = 2, 10%), lower extremity oedema (n = 2, 10%), difficulty in staying still (n = 1, 5%), paraesthesia (n = 1, 5%), and dental problems (n = 1, 5%). Of interest, participants who received placebo also reported physical side effects (n = 3, 14%) (28, 29, 34). These included troubles concentrating, subjective restlessness, agitation, sleep problems, headache, constipation, dizziness, muscle stiffness, somnolence, dry mouth, fatigue, dizziness, gastrointestinal complaints, and headache.

Risk of Bias and Strength of Evidence Quality

For randomized trials, two studies did not blind participants and personal adequately (37, 42). For non-randomized trial, six studies did not have a comparison group as they were observation studies (25, 38, 40, 44, 45). Other sources of bias were which could potentially threaten the external and internal validity of the findings include heterogeneous demographics across groups during baseline, a short duration of treatment, wide range of medication dosage, or confounding variables such as concurrent treatment. In addition, sample sizes of each individual studies were generally small and of the 21 studies included in the systematic review, only 10 studies reported appropriate dropout rates for the meta-analysis, further reducing the sample sizes. The challenges of small sample size were further compounded by the significant dropout observed and only missing data analysis was often not clearly detailed. The overall risk of bias was therefore low to medium (**Figure 2**).

DISCUSSION

To our knowledge, this is the first systematic review and meta-analysis of dropout associated with second-generation antipsychotics in people with AN. Our finding of 28% dropout rate (95% CI: 19 to 38%) from psychopharmacological trial is low when compared to 48.1% reported in a meta-analysis of second-generation antipsychotics in people with schizophrenia or schizoaffective disorder (48). Our dropout rate is, however, high when compared to psychotherapy. Meta-analyses have reported dropout rates of 24% for cognitive behaviour therapy in people eating disorders (49), 18.7% for interpersonal therapy in eating disorders (50) and 19.9% for individual psychotherapy in unipolar depression (51). Of interest, personal choices and factors associated with individual trials are the main reasons for dropout, not metabolic effects such as weight gain as initially hypothesised. Thus, our findings prompt the need to consider how specific patient and study characteristics may influence dropout rates in psychopharmacological trials in people with AN.

It is important to interpret our findings in the context of difficulties of recruiting and retaining participants with AN in psychopharmacological studies. For example, in a study of quetiapine, only 10.4% of the adult patients (21/217) consented to treatment (32). A study in adolescents examining risperidone was ended after 4 years due to slow recruitment and exhausted funding (34). Thus, the extent of generalizability of our findings to those who declined to participate is at present unclear.

Limitations

A major source of heterogeneity is study design, given only 11 out of the 21 studies included in the systematic review were RCT in design. Another source of heterogeneity is concurrent treatment and study setting. The regimen of the second-generation antipsychotics also varies substantially between and within studies. The dosage is often flexible and individual-tailored within studies. A major limitation of our review is that most studies included in the systematic review (67%) and meta-analysis (80%) were from USA/Canada, rendering it difficult to generalize our findings. In addition, most studies were small in size. Another major limitation of our review is that most studies included were small in size. This is further compounded by the significant proportion of participants who did not complete a study. Thus, adopting the "intention-to-treat" in data analysis according to the treatment groups being assigned at randomization, with appropriate handling of missing data is important. In addition, the long-term metabolic effects of second-generation antipsychotics in people with AN is currently unclear, as only two studies discussed follow-up beyond 3 months (37, 38).

Clinical Implications

Recruitment and retainment rates are a major challenge for psychopharmacology studies in AN. To encourage patients to consider second-generation antipsychotics as part of their treatment plan, it is important to explain the potential side effects experienced and stress the transient nature. Given that adverse events such as suicidal ideation were observed (28), it is important that patients are reviewed after being commenced on second-generation antipsychotics and address any side effects experienced promptly. Including family members in discussions about treatment and potential risks can allow for a more balanced appraisal of possible costs and benefits.

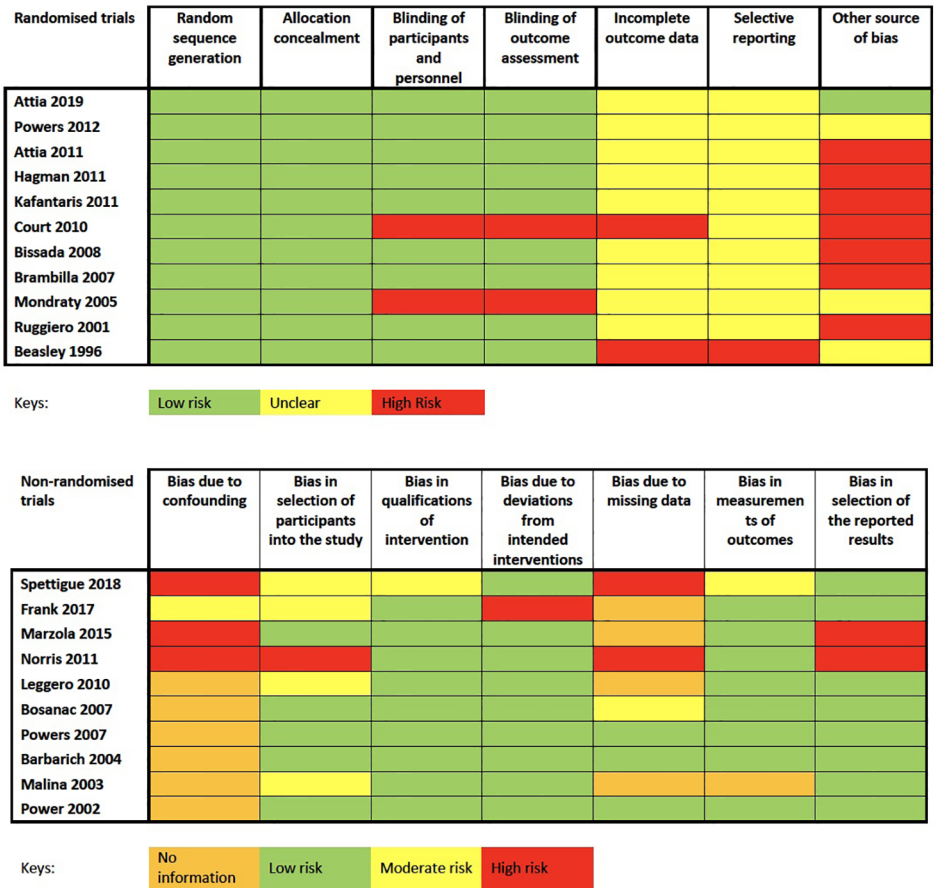

FIGURE 2 | Cochrane Collaboration's tool for assessing risk of bias for randomized trials and Risk of Bias in Non-randomized Studies-of Interventions (ROBINS-I) assessment tool for non-randomized studies.

CONCLUSION

Our study echoes the need to conduct high-quality psychopharmacological studies in people with AN. There are severe major limitations in the quality of the studies included in our meta-analysis. Future psychopharmacological studies for AN need to be large-scale and involve multiple centres while including qualitative feedback from patients and patient-related outcomes to address these limitations. Involving patients and their families in the co-design process will potentially lead to better engagement and lower dropout rates. Overall, patient-related factors may explain drop-out rates in psychopharmacological trials even better than drug-related factors and side effects.

AUTHOR CONTRIBUTIONS

All authors were involved in the conception of the study. CK and JT designed the protocol for this analysis. CK performed the statistical analysis. CK and LE wrote the manuscript. All authors reviewed/edited the manuscript.

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

APPENDIX 1 EXHAUSTIVE LIST OF KEYWORDS FOR SEARCH

1. 'anorexi*' OR 'anorexia nervosa'
2. 'atypical antipsychotic' OR 'atypical neuroleptic' OR 'second generation antipsychotic' OR 'second generation neuroleptic' OR amisulpride OR aripiprazole OR asenapine OR brexpiprazole OR cariprazine OR clozapine OR lurasidone OR 'lurasidone hydrochloride' OR olanzapine OR paliperidone OR 'paliperidone palmitate' OR primavenserin OR quetiapine OR 'quetiapine fumarate' OR remoxipride OR risperidone OR sertindole OR ziprasidone.
3. metaboli* OR BMI OR 'body mass index' OR obesity OR hba1c OR 'blood pressure' OR hypertension OR cholesterol OR QTc OR prolactin OR hyperglycemi* OR diabetes OR 'weight gain' OR 'weight increase' OR 'metabolic side effects of drugs and substances' OR 'metabolic diseases' OR 'metabolic syndrome' OR 'weight gain — drug effects' OR 'metabolic networks and pathways — drug effects' OR 'body weight — drug effects
4. 1 AND 2 AND 3
5. Limit 4 to humans + English language

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ORIGINAL RESEARCH
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Reported and Recorded Sleepiness in Obesity and Depression

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Background: Obesity and depression are both associated with changes in sleep/wake regulation, with potential implications for individualized treatment especially in comorbid individuals suffering from both. However, the associations between obesity, depression, and subjective, questionnaire-based and objective, EEG-based measurements of sleepiness used to assess disturbed sleep/wake regulation in clinical practice are not well known.

Objectives: The study investigates associations between sleep/wake regulation measures based on self-reported subjective questionnaires and EEG-derived measurements of sleep/wake regulation patterns with depression and obesity and how/whether depression and/or obesity affect associations between such self-reported subjective questionnaires and EEG-derived measurements.

Methods: Healthy controls (HC, N_{HC} = 66), normal-weighted depressed (DEP, N_{DEP} = 16), non-depressed obese (OB, N_{OB} = 68), and obese depressed patients (OBDEP, N_{OBDEP} = 43) were included from the OBDEP (Obesity and Depression, University Leipzig, Germany) study. All subjects completed standardized questionnaires related to daytime sleepiness (ESS), sleep quality and sleep duration once as well as questionnaires related to situational sleepiness (KSS, SSS, VAS) before and after a 20 min resting state EEG in eyes-closed condition. EEG-based measurements of objective sleepiness were extracted by the VIGALL algorithm. Associations of subjective sleepiness with objective sleepiness and moderating effects of obesity, depression, and additional confounders were investigated by correlation analyses and regression analyses.

Results: Depressed and non-depressed subgroups differed significantly in most subjective sleepiness measures, while obese and non-obese subgroups only differed significantly in few. Objective sleepiness measures did not differ significantly between the subgroups. Moderating effects of obesity and/or depression on the associations between subjective and objective measures of sleepiness were rarely significant, but associations between subjective and objective measures of sleepiness in the depressed subgroup

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were systematically weaker when patients comorbidly suffered from obesity than when they did not.

Conclusion: This study provides some evidence that both depression and obesity can affect the association between objective and subjective sleepiness. If confirmed, this insight may have implications for individualized diagnosis and treatment approaches in comorbid depression and obesity.

Keywords: obesity, depression, EEG, sleepiness, VIGALL

BACKGROUND

With over 1.9 billion adults affected worldwide (1), overweight and obesity cause significant negative health outcomes (2). Obesity is a well-known risk factor for somatic diseases such as diabetes, heart attacks, cancer, or sleep apnea (3). However, obesity also often co-occurs with mental illness, especially affective disorders like depression, and causes an enormous burden of disease (4) due to the deterioration in both the quality of life and the level of social functioning it entails.

Similar physiological processes are involved in the development and maintenance of both diseases (5). Nevertheless, associations between obesity and depression are very complex and not equally applicable to all people affected (6). This might be due to the fact that depression is a heterogenous disorder with multiple aetiological pathways interacting with genetic, neuroendocrinal, neurochemical, and neuroimmunlogical processes (7).

To further our understanding of how depression and obesity interact from a clinical perspective, the present paper is concerned with the link between depression and obesity focusing on sleep/wake regulation as a symptom complex that might connect both diseases, specifically, the occurrence and severity of disturbed sleep patterns. To do so, the following paragraphs provide precise definitions of brain arousal regulation, depression, atypical depression, and our operationalizations of these constructs before we describe our hypotheses in more detail.

According to the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5, 8), diagnosing a severe episode of depression requires five or more symptoms that can affect both the mental and physical well-being of the individual to persist for at least two weeks.

Symptoms include depressed mood, loss of interest, joylessness, feelings of worthlessness, and cognitive impairment, but also describe changes in activity levels, appetite, and sleep quality. Interestingly, the clinical manifestations of the heterogenous cohort of depressed patients differ particularly with regard to different characteristics of disturbances in sleep/wake regulation and appetite.

Therefore, atypical depression (AD) was included as a separate diagnosis in the fourth edition of Diagnostic and Statistical Manual for Mental Disorders in 1994 (DSM-IV, 9). AD defines a distinct symptom complex in depressed patients including mood reactivity, increased appetite and hypersomnia (10).

In fact, it is theorized that atypical depressed patients often suffer from significant weight gain or an increase in appetite with excessive sleep all through the day, whereas non-atypical depressed patients are characterized by significant weight loss or decrease in appetite and decreased sleep duration with early morning awakening. From a clinical perspective, varying symptoms with regard to sleep and appetite have a decisive influence on the choice of the individual treatment approach. Although a substantial body of literature already describes possible links between depression and body weight and/or sleep/wake regulation (e.g., 11–13), a deeper understanding of the connections between depression, obesity and sleep/wake regulation is likely to have important implications for individualized psychopharmacological and psychotherapeutic treatment of comorbid obesity and depression.

Sleepiness is the main consequence of insufficient sleep and dramatically influences the daytime brain arousal regulation. Brain arousal regulation, in turn, plays an important role in order to understand disturbed sleep/wake regulation in depression and describes a key process required to stabilize vigilance for higher cognitive performance. Vigilance as it is used here defines a tonic neurophysiologic arousal level rather than a function of attention. Besides, "arousal" has been defined as a relevant dimension investigating mental illness by the Research Domain Criteria project (14). Therefore, especially brain arousal regulation has recently become an important focus of interest in understanding the psychopathology of affective disorders.

The working group of Hegerl and colleagues defined the term EEG-vigilance in order to examine brain arousal regulation by means of electroencephalic activity (15). They found significantly more stable EEG-vigilance regulation in depressed patients compared to healthy controls and established the EEG-based "vigilance regulation model for affective disorders" (16).

The model hypothesizes that depressed patients (DEP) show less and later declines of brain arousal in resting state EEG recordings than healthy controls (HC). Thus, depressed patients are assumed to be characterized by a hyperstable EEG-vigilance regulation, whereas manic patients are assumed to have an unstable brain arousal regulation. Hegerl and colleagues (16, 17) characterize disturbed brain arousal regulation as a pathophysiological factor for depressive symptom complexes, such as sleep disturbances and daytime sleepiness. Furthermore, their model provides psychopathological explanations for, e.g., sensation avoidance and withdrawal in depression as a consequence of an autoregulatory attempt to handle hyperstable brain arousal.

In line with the predictions of the vigilance regulation model for affective disorders, several studies that apply electroencephalography-

based approaches provide evidence for a hyperstable brain arousal regulation in depressed patients (18–20). Regarding disturbed sleep/wake regulation in depression, Hein and colleagues reported that approximately half of depressed patients suffer from excessive daytime sleepiness (EDS; 21) and that AD is a significant risk factor of EDS in major depression.

Moreover, previous findings of Bixler et al. (22) support the hypothesis that extreme daytime sleepiness (EDS) is more strongly associated with affective disorders and obesity than with sleep disordered breathing or sleep disruption per se. In a polysomnographic study, Fernandez-Mendoza et al. (23) showed that objective sleep disturbances predict incident daytime sleepiness in depressed individuals, whereas an increase in physiological sleep propensity predicts incident daytime sleepiness in those without depression.

Interestingly, results of a study by Plante et al. (24) indicate divergent associations between subjective and objective sleepiness in depression. Thus, self-reported sleep duration and EDS were positively associated with severity of depression, whereas objective sleepiness parameters were negatively associated with depressive symptoms.

Plante et al. (24) quantified objective sleepiness by the multiple sleep latency test (MSLT), which usually takes about 7 h in the course of a day and requires multiple devices. Although the MSLT is the gold standard for measuring daytime sleepiness, its applicability in a clinical setting is limited by its complex testing protocol. Moreover, the MSLT only assesses sleep onset, but does not provide information about the dynamics of brain arousal regulation before sleep onset. Therefore, measurements of resting state EEG activity constitute a preferable operationalization of objective sleepiness.

Resting state EEG activity is recorded typically for 15–20 min in eyes-closed condition and the dynamics of EEG-vigilance levels are recorded over time. To standardize this measurement, the working group of Hegerl and colleagues established an automatic tool for the classification of brain arousal regulation called VIGALL (Vigilance Algorithm Leipzig). VIGALL is an EEG- and electrooculography (EOG)-based algorithm which allows to objectively determine the level of EEG-vigilance and its dynamics within EEG recordings (25). It automatically classifies seven EEG-vigilance stages from wakefulness to varying degrees of drowsiness to sleep onset in a 1s-resolution (also see **Table 1**).

TABLE 1 | Characteristics of EEG-vigilance stages according to VIGALL (Vigilance Algorithm Leipzig).

Brain arousal state	VIGALL		Score	EEG characteristics
High alertness	Stage 0		7	Low voltage EEG without α-activity, no horizontal SEM
Relaxed awake	Stage A	A1	6	Predominant occipital α-activity
		A2	5	High temporal and parietal α-activity
		A3	4	Predominant frontal α-activity
Drowsiness	Stage B	B1	3	Low voltage EEG without α-activity with horizontal SEM
		B2/3	2	Increase of δ- and θ-power
Sleep onset	Stage C		1	K-complexes and sleep spindles

AIMS AND HYPOTHESES

To date, there exists no VIGALL-based study investigating brain arousal regulation in depressed patients with comorbid obesity, although the literature clearly indicates that both diseases affect sleep/wake regulation. Manifestations of sleep disturbances in depressed patients are complex and so far, it remains unclear how they are linked to obesity and subjective and objective sleepiness.

Moreover, based on the authors´ clinical expertise, obese depressed patients may subjectively suffer more often from severe daytime sleepiness and massive sleep disturbances than normal-weighted depressed patients. Nevertheless, it is currently unresolved whether such differences of subjective level of suffering can also be detected in objective EEG-based brain arousal regulation parameters or whether obese depressed patients assess subjective sleepiness differently and may overestimate the severity of disturbed sleep/wake regulation compared to normal-weighted depressed patients.

To shed some light on the psychopathological manifestation of disturbed sleep/wake regulation in depression and comorbid obesity, the aim of the present study is to investigate the relationship between subjective reported sleepiness and objective measured sleepiness in depressed and obese patients.

Therefore, a sample of healthy controls (HC), obese patients without depression (OB), depressed normal-weighted patients (DEP), and patients with depression and obesity (OBDEP) were examined via self-rating questionnaires and resting-state EEG recordings applying VIGALL.

We compared subjective parameters of sleepiness (subjective daytime sleepiness and subjective current states of sleepiness before and after EEG recordings) with objective EEG-based parameters of brain arousal regulation within and between these four subgroups.

Taken together, we hypothesize that obesity and depression affect the association between objective and subjective sleepiness.

METHODS

Sample

As part of the OBDEP (Obesity and Depression) project volunteers were consecutively recruited between February 2011 and November 2012 from the outpatient clinic of the Integrated Research and Treatment Centre (IFB) for Adiposity Diseases Leipzig, from the Department of Psychiatry and Psychotherapy of the University Hospital Leipzig and via announcements (intranet, internet, local newspapers). One aim of the OBDEP project was to investigate the role of sleep and wakefulness regulation in the relationship between obesity and depression. The study was approved by University Leipzig Ethics Committee (#015–10–18012009).

The recruiting process for potential participants aged 18–70 years included a 20–40 min telephone interview to collect socio-

demographic data plus a screening for somatic disorders and severe psychiatric conditions, using the German version of the checklist of the Structured Clinical Interview for DSM-IV (SKID; 26). Then, a full SCID-I was performed in cases of positive SCID screening.

The following inclusion criteria were defined: free from (a) psychiatric or neurological disorders other than depression, (b) history of head injury with loss of consciousness exceeding 1 h, (c) psychiatric medication, (d) acute or chronic infections, (e) current medication with a recognized major impact on the immune system, and (f) use of illegal drugs or abuse of alcohol within the past 6 months. After inclusion in the study, participants underwent a full physical examination by a study physician with weight and height measurements under standardized conditions.

The sample consists of N = 193 participants. We included N_{HC} = 66 healthy controls, N_{OB} = 68 obese patients without depression, N_{DEP} = 16 depressed normal-weighted patients, and N_{OBDEP} = 43 patients with comorbid depression and obesity.

Subjective Sleepiness

We measured two subjective sleepiness parameters: daytime sleepiness [see *Day Time Sleepiness* Via *Epworth Sleepiness Scale (ESS)*] and situational sleepiness for a current state immediately before and after EEG recordings (see *Subjective Situational Sleepiness* Via *Self-Rating Questionnaires: KSS, SSS, VAS*).

Day Time Sleepiness via Epworth Sleepiness Scale (ESS)

The self-administered eight-item questionnaire "Epworth Sleepiness Scale (ESS)" was applied as it is proposed as a simple method for measuring subjective daytime sleepiness in adults (27) over the course of an entire day. Patients rate how likely they are to fall asleep in differing circumstances. Responders rate usual chances of dozing off or falling asleep while engaged in eight different everyday situations on 4-point scales with each item scored from 0 (not at all) to 3 (very likely). The ESS score can range from 0 to 24, whereas total scores of more than 10 points represent increasing levels of excessive daytime sleepiness (EDS). Internal consistency (Cronbach's α: 0.73–0.86) of ESS is good, whereas external validity (0.11–0.43), and test-retest reliability (0.73–0.82) is described to be only weak to moderate (28).

Subjective Situational Sleepiness via Self-Rating Questionnaires: KSS, SSS, VAS

In addition to the ESS, participants were asked to rate their self-assessed current state of subjective sleepiness via the ordinal 1-item questionnaires Stanford Sleepiness Scale (SSS, 29) and Karolinska Sleepiness Scale (KSS; 30) before and after EEG recordings as both of these scales are sensitive to short-term fluctuations.

The KSS is a 10-point scale (1 = extremely alert to 10 = extremely sleepy, falls asleep all the time) and was found to be highly correlated to EEG and behavioral variables (30).

The SSS requires respondents to select one of seven (31) statements on a 7-point scale (1 = feeling active, vital, alert or wide awake to 7 = no longer fighting sleep, sleep onset soon, having dream-like thoughts) best representing their level of perceived current sleepiness. However, Akerstedt and colleagues (31, 32) criticize that several of the seven statements actually refer to fatigue or boredom rather than sleepiness.

As both SSS and KSS are applied in several recent studies for assessing self-reported sleepiness, we used both questionnaires for ordinal measurements of subjective sleepiness, although this might be redundant.

Historically, sleepiness was assessed using visual analogue scales (VAS, 33). Thus, we also used a VAS to evaluate the individual sleepiness of each participant on a metric scale from 0 (= not at all) to 100 (= very much).

SSS, KSS, and VAS were assessed twice. Score differences (ΔSSS, ΔKSS, ΔVAS) of measurements before (SSS_{pre}/KSS_{pre}/VAS_{pre}) and after (SSS_{post}/KSS_{post}/VAS_{post}) EEG recordings were calculated.

After the EEG recordings, participants were further asked to assess whether they had fallen asleep (variable ASLEEP) by choosing one of the four options: 1 = I definitely fell asleep, 2 = I may have fallen asleep, 3 = I probably did not fall asleep, 4 = I certainly did not fall asleep.

Covariates: Subjective Sleep Duration (SSD) and Subjective Sleep Quality (SSQ)

To control for confounding effects on subjective and objective sleepiness, we additionally assessed subjective sleep duration (SSD) of the last night before EEG recordings and subjective sleep quality (SSQ). SSQ is defined as the current degree of relaxation after last night sleep. SSQ was determined using the subscale "restedness" of a German sleep questionnaire SF-A ("Schlaffragebogen A"; 34), which consists of 8 items. Participants were asked to evaluate on a 5-point-scale (1 = not at all, 5 = very much) to what extent adjectives describing the sleep quality of the last night and well-being in the morning applied to them. SSQ was calculated by the quotient [sum score subscale "restedness"/8], where higher values correspond to higher degree of feeling relaxed after night sleep.

Objective Sleepiness Parameter—EEG Vigilance Regulation

EEG analyses are a well-established approach for assessing levels of brain arousal and for monitoring sleep patterns. The EEG vigilance concept we refer to in our study relates unspecific activation patterns of the brain to a continuum from high alertness to sleep onset.

Early on, Loomis et al. (35) classified different states of cerebral activation on the basis of specific EEG patterns on a continuum ranging from a concentrated waking state to a deep sleep state. Bente (36) and Roth (37) further subdivided these EEG vigilance levels depending on the frequency and topographic distribution of the EEG waves (A1, A2, A3, B1, B2/3).

For an automatic classification of EEG vigilance, Hegerl and colleagues developed the computer-based algorithm VIGALL (Vigilance Algorithm Leipzig), which categorizes different EEG-vigilance stages on the basis of the frequency and topographical distribution of cerebral activity on a high temporal resolution. The

algorithm was validated and further improved by simultaneous recordings of EEG and functional magnetic resonance imaging (fMRI) data (38) and by including EEG-power source estimates using sLORETA (standardized Low Resolution Brain Electromagnetic Tomography). VIGALL classifies each second of the EEG recording into one of seven EEG-vigilance stages ranging from high alertness (stage "0"), to relaxed wakefulness (stages "A1", "A2", "A3"), to drowsiness (stage "B1", "B2/3") up to sleep onset (stage "C"). **Table 1** defines EEG characteristics for each of these EEG-vigilance stages.

EEGs were recorded in eyes-closed condition for 20 min. All of the resting-state EEG recordings were taken between 08:00 and 18:00. They were recorded in a darkened and soundproofed room where participants sat in a comfortable chair in an upright position. The participants were instructed to keep their eyes closed, to relax and not to try to resist the urge to fall asleep.

EEG setup and recording: To record the EEG, 31 electrodes (sintered silver/silver chloride) with impedances below 10 kOhm were attached according to the international 10–20 system. The data were sampled at a rate of 1 kHz with a low-pass filter at 280 Hz, using the common average as a reference measure. An electrocardiogram (ECG) and an electrooculogram (EOG) were also recorded to monitor cardiac and ocular artifacts. For EOG recording, one electrode was placed on the forehead and a reference electrode on the cheek below the eye. The ECG electrodes were attached to the right and left wrist. The recordings were amplified with a 40-channel QuickAmp device and post-processed with BrainVision 2.0 software (BrainProducts, Gilching, Germany) installed on a Microsoft Windows XP-compatible computer system.

We then applied VIGALL to classify the EEG-vigilance stages at a 1s-resolution for each participant. Artefacted segments were excluded from further calculations based on established pre-processing protocols.

For more detailed information about EEG data recording and processing as well as operational methodology of VIGALL please refer to Huang et al. (39) and the VIGALL 2.1 manual (25).

Several objective sleep/wake regulation parameters were calculated on the basis of the VIGALL EEG-vigilance stages (18, 39).

a. The proportion of time spent in each EEG-vigilance stage over 20 min.
b. The mean vigilance values (MVV, range 1–7), i.e., averages of EEG-vigilance scores over 20 min, based on assigning a numeric value from 1 (lowest EEG-vigilance stage "C") to 7 (highest EEG-vigilance stage "0") to each EEG-vigilance stage.
c. The criteria for the calculation of the arousal stability score (ASS, range 1–11) are described in **Table 2**.

Obesity and Depression

Body mass index (BMI, [kg/m^2]) was assessed according to WHO guidelines (40, 41). To assess symptoms and severity of depression, participants completed the revised Beck Depression Inventory, 2nd edition (BDI-II; 42)

According to established cut-off values of BMI (40, 41) and BDI-II scores (43) participants were classified as: (1) HC = healthy controls (BMI < 30, BDI-II score < 14), (2) OB = obese non-depressed patients (BMI > 30, BDI-II score < 14), (3) DEP = normal-weighted, depressed patients (BMI < 30, BDI-II score > 13), and (4) OBDEP = obese depressed patients (BMI > 30, BDI-II score > 13).

TABLE 2 | Criteria of the arousal stability score (ASS).

Score	Stability level criterion	Operational definition
11	less than 1/3 of all segments	rigidity, only 0 and A1 stages
10	not classified as 0 or A/A1 stages	rigidity, only 0 and A stages
9	at least 1/3 of all segments	stage B emerged in minute 11–15
8	classified	stage B emerged in minute 6–10
7	as B stages	stage B emerged in 1–5
6	at least 1/3 of segments	stage B2/3 emerged in minute 11–15
5	classified	stage B2/3 emerged in minute 6–10
4	as B2/3 stages	stage B2/3 emerged in 1–5
3	occurrence of at least 1 C stage	stage C emerged in minute 11–15
2		stage C emerged in minute 6–10
1		stage C emerged in 1–5

Statistics

Statistical analyses were performed using R version 3.5.3 (44) using packages cocor (45) and ordinal (46). Univariate between-group differences of location for metric and ordinal variables (see 2.1) were assessed using Kruskal-Wallis tests.

To assess the existence of a global association between subjective (SSS_{pre},KSS_{pre},VAS_{pre}, SSS_{post},KSS_{post},VAS_{post}, ΔSSS, ΔKSS, ΔVAS, ASLEEP) and objective (Proportions of VIGALL Stages 0, A, B, C, MVV, ASS) measures of sleepiness, canonical correlation analysis (CCA) between these two sets of variables was performed. The null hypothesis of no association was tested by means of the Pillai-Bartlett-Trace test (47), as implemented in R package CCP (48). The reported p-value for this test was computed based on a bootstrap approximation (9999 replications) of the null distribution to avoid unrealistic Gaussianity assumptions.

Bivariate associations of subjective measures of sleepiness or sleep quality and EEG vigilance-based measures (proportion of EEG-vigilance stages, MVV, ASS) were quantified via Spearman rank correlations and tested for significance as in Best and Roberts (49). Inter-group differences of group-specific estimated correlations were tested for significance based on Diedenhofen and Musch (45).

vRegression analyses of measures of subjective situational (VAS, KSS, ASS, sleep) or daytime sleepiness (ESS) were performed in order to assess between-group heterogeneity of their associations with objective EEG-vigilance based measures of situational sleepiness (MVV, ASS). These analyses corrected for the effects of age, gender, and sleep quality (SSQ) and included main effects as well as interaction effects of depression, obesity, and either MVV or ASS. The null hypothesis of homogeneity of association between subjective and objective measures of sleepiness across the groups defined by their (combined) depression and obesity status was assessed by testing for the presence of significant interaction effects between depression and/or obesity and the respective objective measure (MVV/ASS) on the respective subjective sleepiness

parameters. For metric dependent variables (VAS, ESS), Gaussianity assumptions were validated using graphical regression model diagnostics and the significance of interaction effects was assessed by standard ANOVA F-tests. Proportional odds cumulative logit models (cf. 50) were used for ordinal dependent variables (KSS, SSS, ASLEEP) and the significance of interaction effects was assessed using Chi-Square likelihood ratio tests. Reported p-values were not corrected for multiple comparisons.

RESULTS

Descriptive Statistics

Descriptive statistics for age, gender, SSD, SSQ, and subjective sleep parameters for all four subgroups are presented in **Tables 3A–C**.

We included 132 female and 61 male participants in the study. The mean age of all subjects was M = 37.6 years (SD = 12.4 years). Subgroups differed in age (p =.057) and in terms of gender distribution (p =.016). Mean BDI-II scores were 4.4 (SD = 4.5) for HC, 5.4 (SD = 4.0) for OB, 24 (SD = 8.2) for DEP and 24 (SD = 8.8) for OBDEP. Mean BMI was 24 (SD = 2.9) for HC, 43 (SD = 7.5) for OB, 24 (SD = 3) for DEP, and 45 (SD = 8.9) for OBDEP.

Group differences were also found for SSQ (p =.005), although SSD did not differ between subgroups (p =.44).

Subjective Sleepiness.

Subgroups differed significantly in several subjective sleepiness parameters: self-reported daytime sleepiness (ESS, p =.010), self-reported sleepiness before (VAS_{pre}, p =.004; KSS_{pre}, p =.003; SSS_{pre}, p < .001), and after EEG recordings (SSS_{post}, p =.007) as well as in KSS score differences post and pre EEG (ΔKSS, p =.004), but did not differ in reported likelihood of having fallen asleep.

Moreover, we calculated correlations between subjective daytime sleepiness and subjective situational sleepiness. Overall, Spearman rank correlations were significantly positive between ESS – and SSS_{pre} (r =.26, p < .001), KSS_{pre} (r =.33, p < .001), VAS_{pre} (r =.25, p < .001), SSS_{post} (r =.19, p =.008), and KSS_{post} (r =.27, p < .001). Score differences after and before EEG recordings (ΔSSS/KSS/VAS) did not correlate significantly with ESS.

TABLE 3A | Descriptive statistics (metric variables).

	HC (N=66)		OB (N=68)		DEP (N=16)		OBDEP (N=43)		
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	p (Kruskal-Wallis)
Age	34	12	39	12	38	13	41	13	0.057
VAS (pre-EEG)	29	25	34	27	39	29	47	25	0.0039
VAS (post-EEG)	32	24	33	27	39	26	41	30	0.41
Δ VAS (post - pre)	3.3	26	-0.96	31	-0.31	37	-5.8	27	0.56
Δ KSS (post - pre)	0.52	1.4	-0.21	1.6	0	1.7	-0.4	1.7	0.0035
Δ SSS (post - pre)	0.21	1	-0.088	1.2	-0.19	1	-0.14	0.97	0.22
SSD (minutes)	432	69	427	81	462	74	436	75	0.44
SSQ	3.3	0.65	3.3	0.68	2.9	0.67	3	0.82	0.005
ESS	7.7	3.1	8.1	3.9	8.4	3.5	9.8	3.3	0.01

TABLE 3B | Descriptive statistics (categorical variables).

		HC (N=66)		OB (N=68)		DEP (N=16)		OBDEP (N=43)		
		N	%	N	%	N	%	N	%	p (χ^2)
Gender	female	40	60.6	54	79.4	7	43.8	31	72.1	0.02
	male	26	39.4	14	20.6	9	56.2	12	27.9	
ASLEEP	definitively	9	13.6	5	7.4	1	6.2	9	20.9	0.11
	possibly	14	21.2	18	26.5	4	25	6	14	
	probably not	9	13.6	17	25	0	0	9	20.9	
	surely not	34	51.5	28	41.2	11	68.8	19	44.2	

TABLE 3C | Descriptive statistics (ordinal variables).

	HC (N=66)		OB (N=68)		DEP (N=16)		OBDEP (N=43)		
	Median	IQR	Median	IQR	Median	IQR	Median	IQR	p (Kruskal-Wallis)
KSS (pre-EEG)	3	3 – 4	3	3 – 5	4.5	3 – 6	5	3 – 6	0.0027
KSS (post-EEG)	4	3 – 5	3	2 – 4	4	3 – 5	4	3 – 6	0.12
SSS (pre-EEG)	2	2 – 2	2	1 – 3	3	2 – 4	3	2 – 4	9.4e-05
SSS (post-EEG)	2	2 – 3	2	2 – 3	3	2 – 3	2	2 – 4	0.0073

TABLE 3D | Distributions of EEG-vigilance stages, mean vigilance value (MVV), and arousal stability score (ASS).

	HC (N=66)		OB (N=68)		DEP (N=16)		OBDEP (N=43)		
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	p (Kruskal-Wallis)
Proportion Stage 0	0.07	0.12	0.088	0.12	0.12	0.19	0.12	0.18	0.62
Proportion Stage A	0.47	0.3	0.48	0.33	0.54	0.31	0.47	0.32	0.85
Proportion Stage B	0.43	0.29	0.4	0.3	0.3	0.3	0.39	0.28	0.37
Proportion Stage C	0.012	0.044	0.012	0.048	0.012	0.033	0.0077	0.03	0.66
MVV	3.5	0.99	3.6	0.98	4	1.1	3.7	0.96	0.25
ASS	3.9	2.2	3.7	1.9	3.2	1.9	3.3	1.5	0.52

We further calculated correlations between subjective daytime/situational sleepiness and the covariate subjective sleep quality (SSQ). Overall, Spearman rank correlations were significantly negative between SSQ - and SSS_{pre} ($r = -.44$, $p < .001$), KSS_{pre} ($r = -.45$, $p < .001$), VAS_{pre} ($r = -.42$, $p < .001$), SSS_{post} ($r = -.35$, $p < .001$), KSS_{post} ($r = -.34$, $p < .001$), and VAS_{post} ($r = -.29$, $p < .001$). Score differences pre and post EEG recordings (ΔSSS/KSS/VAS) did not correlate significantly with SSQ. Furthermore, Spearman rank correlations between SSQ and ESS were significantly negative ($r = -.28$, $p < .001$).

Objective Sleepiness

Subgroups did not differ significantly in objective sleepiness parameters. Specifically, normal-weighted depressed and obese depressed patients did not differ significantly in objective sleepiness parameters according to results of the Wilcoxon rank sum test (MVV: $p = 0.39$; ASS: $p = 0.7$). Detailed information on distributions of EEG-vigilance stages, MVV and ASS are presented in **Table 3D**.

Inference Statistics

Correlations Between Objective and Subjective Sleepiness Parameters

Canonical correlation analysis results indicate the existence of highly significant global association between subjective (SSS_{pre}, KSS_{pre},VAS_{pre}, SSS_{post},KSS_{post},VAS_{post}, ΔSSS, ΔKSS, ΔVAS, ASLEEP) and objective (Proportions of VIGALL Stages 0, A, B, C, MVV, ASS) measures of sleepiness (Pillai-Bartlett-Trace test, $p = 0.001$). For ease of interpretation, we report the relevant bivariate objective-subjective correlations in the following.

Proportion of EEG Vigilance Stages

Correlations between the proportions of time spent in EEG-vigilance stages "0," "A," "B," and "C," respectively, and subjective sleepiness parameters were calculated.

Over all subjects, correlations revealed significant associations of the proportion of time spent in EEG-vigilance stages "A," "B," and "C" with the reported likelihood of having fallen asleep ("A": $r = .22$, $p = .002$; "B": $r = -.31$, $p < .001$; "C": $r = -.34$, $p < .001$) and ESS ("A": $r = -.15$, $p = .04$; "B": $r = .15$, $p = .035$; "C": $r = .16$, $p = .026$). In addition, proportion of time spent in stages "A" or "C" was associated (marginally) significantly with SSS_{pre} ("A": $-.14$, $p = .052$; "C":.18, $p = 0.014$). Furthermore, proportion of time spent in EEG-vigilance stage "A" was associated with pre-post changes in SSS ($r = .15$, $p = .037$) and proportion of time spent in EEG-vigilance stage "C" was associated significantly with both KSS_{pre} ($r = .22$, $p = .002$) and KSS_{post} ($r = .2$, $p = .0062$). None of the subjective sleepiness parameters were correlated significantly with proportion of time spent in EEG-vigilance stage "0."

Correlations between EEG-vigilance stage proportions and subjective sleepiness parameters did not differ significantly between DEP and OBDEP. Significant correlation differences were found between DEP and HC for the correlations of time spent in EEG-vigilance stage "0" with pre-post changes in KSS (corr. difference:.55, $p = 0.05$), for the correlations of time spent in "A" with VAS_{post} (corr. difference: $-.56$, $p = 0.05$) and for the correlations of time spent in "B" with VAS_{pre} (corr. difference:.63, $p = .02$), VAS_{post} (corr. difference:.69, $p = .01$), and SSQ (corr. difference: $-.61$, $p = .03$). Significant correlation differences were found between OB and OBDEP for the correlations of time spent in stage B with KSS_{pre} (corr. difference: $-.41$, $p = .03$) and for the correlations of time spent in stage C with VAS_{post} (corr. difference:.46, $p = .02$) and pre-post changes in VAS (corr. difference:.48, $p = .01$).

MVV

Over all subjects, correlations revealed significant associations between MVV and the reported likelihood of having fallen asleep ($r = .37$, $p < .001$), MVV, and ESS ($r = -.14$, $p = .05$), and marginally significant associations between MVV and KSS_{pre} ($r = -.13$, $p = .07$).

Correlations between MVV and VAS_{pre} (correlation difference $= -.66$, $p = .01$) as well as between MVV and SSQ (correlation difference $= .69$, $p = .01$) differed significantly between HC and DEP. Correlations between objective and subjective sleepiness parameters did not differ significantly between DEP and OBDEP or between OB and OBDEP.

ASS

Over all subjects a significant correlation was found between ASS and the reported likelihood of having fallen asleep ($r = -.37$, $p < .001$).

Comparing HC and DEP, correlations between ASS and VAS_{pre} differed significantly (correlation difference $= .60$, $p = .03$), whereas correlations between ASS and SSQ (correlation difference $= -.54$, $p = .06$) differed marginally. Moreover, correlations between ASS and KSS_{pre} ($r = -.38$, $p = .04$) differed significantly between OB and OBDEP. No statistically significant correlation differences were found between DEP and OBDEP.

Correlations between objective and subjective sleepiness parameters for each subgroup are presented in **Table 4**.

ANOVAs

MVV/ASS and Subjective Situational Sleepiness (SSS; KSS, VAS)

Main Effects "age". Regression analyses with either MVV or ASS as independent variables showed significant main effects of age on VAS_{post}, ΔSSS, ΔKSS and ΔVAS (MVV: ΔVAS: F = 5.99, p =.015; ΔKSS: F = 12.80, p < .001; ΔSSS: F = 7.99, p < .001; VAS_{post}: F = 16.60, p < .001; ASS: ΔVAS: F = 5.71, p =.018; ΔKSS: F = 13.30, p < .001; ΔSSS: F = 7.91, p =.006; VAS_{post}: F = 16.10, p < .001). Moreover, regression analyses of MVV as independent variable revealed a significant main effect of age on KSS_{post}(F = 4.99, p =.026), whereas regression analyses of ASS as dependent variable revealed a significant main effect of age on SSS_{post}(F = 3.91, p =.048).

Main effect "SSQ". Regression analyses with either MVV (ΔVAS: F = 4.50, p =.035; KSS_{pre}: F = 5.92, p =.015; VAS_{pre}: F = 39.80, p < .001; SSS_{pre}: F = 40.90, p < .001; SSS_{post}: F = 22.60, p < .001; VAS_{post}: F = 13.80, p < .001; KSS_{post}: F = 23.60, p < .001) or ASS (ΔVAS: F = 4.29, p =.040; KSS_{pre}: F = 5.31, p =.022; VAS_{pre}: F = 39.80, p < .001; SSS_{pre}: F = 42.40, p < .001; SSS_{post}: F = 24.10, p < .001; VAS_{post}: F = 13.40, p < .001; KSS_{post}: F = 23.50, p < .001) as independent variables revealed significant main effects of SSQ on almost all parameters of subjective situational sleepiness except ΔSSS and ΔKSS.

Main effect "gender". Regression analyses with either MVV or ASS as independent variables revealed significant main effects of gender on ΔVAS (MVV: F = 4.92, p =.028, ASS: F = 4.69, p =.032) and KSS_{pre} (MVV: F = 5.92, p =.015, ASS: F = 6.19, p =.013) Regression analyses with MVV as independent variable further revealed a significant main effect of gender on ΔKSS (F = 4.92, p =.028).

Main effect "depression". Regression analyses with either MVV (VAS_{pre}: F = 6.49, p =.012; VAS_{post}: F = 4.14, p =.043, KSS_{pre}: F = 5.96, p =.015, SSS_{pre}: F = 11.90, p < .001, SSS_{post}: F =7.17, p =.007) or ASS (VAS_{pre}: F = 5.31, p =.022; VAS_{post}: F = 4.14, p =.043, KSS_{pre}: F = 6.20, p =.013, SSS_{pre}: F = 11.60, p < .001, SSS_{post}: F = 7.74, p =.005) as independent variables revealed a significant main effect of depression on almost all parameters of subjective situational sleepiness pre and post EEG recordings, except KSS_{post}, but not on score differences of subjective sleepiness (ΔSSS, ΔKSS, ΔVAS).

Main effect "obesity". Main effects of obesity on VAS_{pre} were found to be significant (MVV: F = 3.76, p =.054; ASS: F = 3.85, p =.051). Regression analyses of MVV as dependent variable revealed a significant main effect of obesity on ΔKSS (F = 4.09, p =.045). Furthermore, a significant main effect of obesity (F = 3.73, p =.053) on ASLEEP was found.

Associations between subjective and objective sleepiness parameters. Moreover, regression analyses revealed a significant association between MVV and ASLEEP (F = 23.40, p < .001) as well as between ASS and ASLEEP (F = 27.90, p < .001).

Interaction Effects. Regression analyses revealed a marginally significant interaction effect of depression on the association of MVV with VAS_{pre} (F = 3.73, p =.055).

Moreover, results showed a significant interaction effect of obesity on the association between of ASS with VAS_{pre} (F = 2.79, p =.042).

MVV/ASS and Subjective Daytime Sleepiness

Main Effects "SSQ". Main effects of **SSQ** on ESS (F= 15.30, p < .001) were found to be significant.

Main effect "depression". Regression analyses with MVV as independent variable revealed a significant main effect of depression on ESS (F = 4.84, p =.029).

Associations between subjective and objective sleepiness parameters. Moreover, regression analyses revealed a marginally significant association between MVV and ESS (F = 3.68, p =.057).

Interaction Effects. Regression analyses revealed no interaction effects on the association between objective sleepiness and subjective daytime sleepiness.

TABLE 4 | Correlation between EEG-based and subjective sleepiness, per subgroup.

EEG-Based	Subjective	HC	OB	DEP	OBDEP
MVV	SSS (pre-EEG)	−0.062	0.112	0.297	0.195
	KSS (pre-EEG)	0.040	0.058	0.230	0.435
	VAS (pre-EEG)	−0.103	0.029	0.498	0.160
	SSS (post-EEG)	−0.017	−0.079	0.450	−0.005
	KSS (post-EEG)	0.067	−0.009	0.276	0.213
	VAS (post-EEG)	−0.125	0.059	0.352	0.043
	Δ SSS (post - pre)	0.027	−0.206	0.135	−0.256
	Δ KSS (post - pre)	0.080	−0.042	0.115	−0.254
	Δ VAS (post - pre)	−0.029	−0.048	−0.173	−0.060
	ASLEEP	−0.301	−0.512	−0.517	−0.257
	ESS	0.034	0.127	0.322	0.148
	SSQ	0.099	−0.107	−0.438	−0.107
ASS	SSS (pre-EEG)	−0.062	0.112	0.297	0.195
	KSS (pre-EEG)	0.040	0.058	0.230	0.435
	VAS (pre-EEG)	−0.103	0.029	0.498	0.160
	SSS (post-EEG)	−0.017	−0.079	0.450	−0.005
	KSS (post-EEG)	0.067	−0.009	0.276	0.213
	VAS (post-EEG)	−0.125	0.059	0.352	0.043
	Δ SSS (post - pre)	0.027	−0.206	0.135	−0.256
	Δ KSS (post - pre)	0.080	−0.042	0.115	−0.254
	Δ VAS (post - pre)	−0.029	−0.048	−0.173	−0.060
	ASLEEP	−0.301	−0.512	−0.517	−0.257
	ESS	0.034	0.127	0.322	0.148
	SSQ	0.099	−0.107	−0.438	−0.107

DISCUSSION

In the present study, we investigated the relationship between obesity, depression, subjective reported sleepiness, and objective measured sleepiness.

To investigate this, we examined reported daytime and situational sleepiness as well as objectively measured EEG-based sleepiness parameters in normal-weighted depressed, obese depressed, obese non-depressed patients, and healthy controls.

Generally speaking, subjective sleepiness parameters differed significantly between the four subgroups, whereas objective

sleepiness parameters did not. Similar phenomena have previously been reported by Denton et al. (51), who reported weak correlation only between subjective but not objective sleepiness and affective disorders and also by Plante et al. (24, 52) who reported divergent associations between subjective and objective measures of hypersomnolence and depression. In addition, the fact that "[…] only objective but not subjective sleepiness was significantly associated with the reported likelihood of having fallen asleep during EEG recordings […could suggest that some] patients may have rated depression related tiredness or apathy as sleepiness," as one reviewer put it.

Descriptive analyses showed that both subjective daytime sleepiness and subjective sleep quality were associated with reported situational sleepiness. However, directions and magnitudes of changes in reported sleepiness before and after EEG recordings did not vary systematically with subjective daytime sleepiness or with subjective sleep quality. Counterintuitively, 20 min of resting in eyes-closed condition seem to change reported situational sleepiness pre and post EEG recordings in the same way regardless of subjective daytime sleepiness or reported sleep quality.

Furthermore, ANOVA results provide evidence that both depression and obesity are associated with subjective sleepiness.

While depression significantly affects both subjective daytime sleepiness, i.e., ESS, and almost all parameters of reported situational sleepiness pre and post EEG recordings, obesity does not seem to be associated with subjective daytime sleepiness and only with reported situational sleepiness before EEG recordings when evaluated using the metric visual analogue scale.

These findings partly contradict the results of previous studies exploring the role of obesity in excessive daytime sleepiness. Thus, a study by Slater and colleagues (53) identified obesity as an independent predictor for subjective daytime sleepiness. Similarly, Maugeri and colleagues (54) investigated a non-depressed cohort and found short sleep duration and EDS to be associated with greater odds of overweight and obesity, independent of diet and physical activity.

Moreover, ANOVA results show that both depression and obesity affect the association between objective measured sleepiness and subjective reported sleepiness before EEG recordings when assessed by the metric visual analogue scale, but not when assessed by KSS or by SSS.

To summarize: In the present study, reported situational sleepiness before EEG recordings was associated with obesity only when the former was assessed by the metric VAS. Similarly, depression and obesity were found to affect the association between objective measured sleepiness and subjected reported sleepiness before EEG recordings only when the latter was assessed by the metric VAS. We now discuss two possible explanations for this surprising result, which may also be related to methodological shortcomings of our study.

As participants were asked to evaluate their situational sleepiness simultaneously on a metric scale (VAS) displayed as a horizontal line with a range from 0 to 100 on which the participants mark how tired they are, and on two ordinal scale (KSS and SSS), this triple query may distort the recorded responses. KSS and SSS are very similar questionnaires requiring responders to select one of 10 (KSS) or 7 (SSS) statements about their situational sleepiness. Responding to KSS and SSS shortly after one another may cause cognitive dissonance avoidance behavior among the participants, in the sense that they may compare their answers to KSS and SSS in order to choose maximally consistent statements.

Therefore, KSS and SSS scores could be biased by a kind of social desirability bias, as participants may try to give reliable and valid answers. In contrast, VAS scoring might be more intuitive and easier to choose compared to KSS and SSS, where participants carefully weigh up, and potentially attempt to compare, the 7 or 10 statements that differ only slightly from each other.

Additionally, and more generally, another methodological drawback of our study is due to the fact that different concepts of sleepiness, fatigue and exertion coexist and might be cross-associated (55). Therefore, it is questionable whether both SSS and KSS are suitable for validly measuring situational sleepiness. To our knowledge, no studies exist that compare the reliability and validity of SSS and KSS to assess situational sleepiness. Taken together, the VAS is likely to provide more reliable and valid measurements to evaluate situational sleepiness.

Further results show that objective measured sleepiness was significantly associated with the reported likelihood of having fallen asleep during EEG recordings and was almost significantly associated with subjective daytime sleepiness. These results are in line with recent findings of a study by Jawinski et al. (56), which investigated the association between recorded and reported sleepiness in a population-based cohort study including 10,000 randomly selected inhabitants of Leipzig, Germany. They found moderate correlations between objective sleepiness parameters and the reported likelihood of having fallen asleep.

Although analyses revealed no significant correlation differences of objective and subjective sleepiness parameters between normal-weighted depressed (DEP) and obese depressed patients (OBDEP), we can report, nevertheless, that correlations in the OBDEP subgroup were systematically weaker than in the DEP subgroup (see **Table 4**).

Interestingly, while normal-weighted depressed patients (DEP) and healthy controls (HC) differ significantly with regard to the strengths and directions of correlations between some subjective sleepiness parameters and the objective sleepiness parameter MVV, our results show that strengths and directions of correlations between objective and subjective sleepiness parameters are very similar in the obese non-depressed (OB) and obese depressed subgroup (OBDEP). Thus, in the normal-weighted subgroup, this study provides some evidence that depression affects the association between subjective and objective sleepiness, but not in the obese subgroup.

This pattern is much less clear for correlations between the objective sleepiness parameter ASS and subjective sleepiness parameters. Indeed, this might be due to the fact that ASS is designed to measure dynamic aspects of brain arousal regulation and not just mean situational sleepiness over a 20-min time span.

Therefore, the functional course of changing EEG-vigilance over 20 min captured by ASS may conceptually define a different construct than situational sleepiness itself at a certain measure time before and after EEG recordings, as these constructs are based on different temporary conditions and may describe not just current states, but also traits of long term individual characteristics.

Thus, MVV is likely to be a valid measurement for objective situational sleepiness, whereas ASS may be better suited to describe brain arousal regulation according to the vigilance regulation model for affective disorders. Accordingly, we conclude that brain arousal regulation and consequently objective sleepiness might be more complex in depressed patients, especially with comorbid obesity, and should therefore be examined again more closely by means of more precise statistical methods. In line with such potentially complex associations of sleep/wake regulation with depression, a study by Geoffrey and colleagues (57) analyzing a nationally representative survey of the US adult population showed that insomnia sleep patterns and hypersomnia often co-occur in depressed patients. As our results show, controlling for additional covariates such as obesity may help to provide further insight into such phenomena in the depressed cohort. In a similar vein, further studies should also assess more detailed clinical characteristics of depressive symptoms to distinguish between depression and depression with atypical features in order to improve our understanding of these associations.

However, the small sample size, especially of the normal-weighted depressed subgroup is a drawback, which complicates the interpretation of the findings.

Furthermore, the present study and previous studies on brain arousal regulation using VIGALL only analyzed minute-wise pseudo-means of the ordinal high-frequency EEG-vigilance stages and fairly ad-hoc summaries of their evolution over time, which may obscure the complexity of brain arousal regulation dynamics. Taken together, for more precise analyses of both objective sleepiness and brain arousal regulation dynamics in depressed patients and their association with or confounding by comorbidities like obesity, future studies should take functional dynamics of the EEG-vigilance stages over the whole recording period in the original 1s-resolution into account in order to avoid the loss of information incurred by simply averaging EEG-segments over time (MVV) or merely analyzing first-occurrence times of lower EEG-vigilance stages and coarse categorizations of vigilance stage distributions over time (ASS).

CONCLUSION

This study provides some evidence that both depression and obesity may affect the association between objective and subjective sleepiness.

If confirmed, this insight might have future implications for individualized diagnosis and treatment approaches in comorbid depression and obesity. For example, depressive syndromes related to sleep/wake regulation may affect treatment decisions with regard to different substance classes of antidepressants that take into account their sleep-inducing effects and/or their effects on patients´ activity levels.

This clinical decision should also consider that the subjective assessment of sleep/wake regulation may be affected by obesity, as the present study indicates. To achieve optimal treatment choices, then, it might be beneficial to rely on more objective measures based on the resting state EEG recordings, which are broadly available in a clinical setting and increasingly part of the standard set of diagnostics for depressed patients. Such VIGALL-based diagnostics are a more economic and time-efficient choice that is easier to perform in clinical settings than the MSLT.

DATA AVAILABILITY STATEMENT

The datasets generated for this study are available to be shown on request to the corresponding author.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the University Leipzig Ethics Committee (#015–10–18012009). The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

HH, CS, UH, and JM contributed to the conception and design of the study. JM, JT, TC, HH, and FrS collected the data. MM, NA, IC, JT, TC, CS, FaS, and JM organized the data base. CS, JT, TC, FrS, UH, and JM carried out the EEG-analyses. FaS and JM performed statistical analyses. FaS summed up the results and created the tables. JM wrote the first draft of the manuscript. IC, MM, NA, and FaS improved the language of the manuscript. All authors contributed to manuscript revision, and read and approved the submitted version.

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Scrutinizing Domains of Executive Function in Binge Eating Disorder: A Systematic Review and Meta-Analysis

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Background: Cognitive deficits are implicated in theoretical explanatory models for binge eating disorder (BED). Furthermore, evidence suggest that alterations in executive function may underlie symptoms in BED. The current systematic review and meta-analysis provides an update on executive functioning in individuals with BED.

Methods: Literature searches (up to November 2019) were conducted in electronic databases combining binge eating or BED with executive functions. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement guidelines was used. Studies of any design comparing adults with BED with those without BED in executive function domains were selected. Methodological quality of studies was based on the Newcastle-Ottawa scale.

Results: Of 1,983 citations identified, 28 case-control studies met inclusion criteria for this review. Six meta-analyses that examined four domains (decision-making, cognitive flexibility, inhibitory control, and working memory) were conducted. The only meta-analysis to show a significant difference in executive functioning between BED and obese controls was working memory (SMD = 0.32, 95% IC: –0.60, –0.03; $p = 0.028$), with an effect size of small magnitude. Qualitative inspection of the literature indicated mixed findings for control inhibition, decision making and cognitive flexibility in individuals with BED compared to controls (obese or normal weight). In addition, people with BED showed poorer problem solving performance, but similar planning abilities to obese controls.

Conclusions: Individuals with BED were found to show worse performance on working memory tasks compared to obese individuals without the disorder. The findings did not provide definitive evidence of alterations in other aspects of executive functioning. Interest in executive functioning in people with BED is increasing but is limited by insufficient data from small studies with varied methodology. Future studies should focus on using similar

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tests and outcome measures, in order to enable more pertinent comparisons across studies.

Keywords: binge eating disorder, executive function, cognitive flexibility, decision-making, working memory, inhibitory control, problem-solving, set-shifting

INTRODUCTION

Eating disorders (EDs) affect up to 10% of young women and are associated with significant reductions in quality of life (1, 2). Binge ED (BED) is the most prevalent ED, affecting approximately 2.8% of females and 1% of males (3). BED is characterized by recurrent episodes of binge eating that are not combined with compensatory methods to avoid weight gain. Thus, the majority of BED cases are overweight or obese (4).

The aetiology of BED is not fully understood, nevertheless evidence suggests that inefficiencies in executive functions may underlie symptoms (5). The concept of executive functioning does not have a single definition and is still evolving. However, according to Friedman and Miyake (6), executive functions represent a set of control processes that regulate thoughts and behavior, dysfunctions in which are symptomatic of neuropsychiatric and behavioral disorders. Although there is some debate over which variables should be used to assess executive functioning, inhibitory control, working memory, decision-making, cognitive flexibility, planning, problem-solving are generally well established in neurocognitive research (6–10).

Difficulties to overcome habitual responses rely on top-down processes that may work as risk or maintenance factors for EDs (11). For example, inefficiencies in inhibitory control may be associated with overconsumption of highly palatable foods in individuals with BED (12, 13). Those with BED also display difficulties in decision-making, resulting in a tendency to disregard the negative consequences of binge eating in the long term (14). These deficits could increase the likelihood of binge eating episodes (short term reward)—especially when paired with a lack of adaptive emotion-regulation skills—and lead to weight gain and feelings of guilt (long term consequences) (14, 15). In addition, difficulties in problem solving may make it difficult for individuals with BED to manage and plan ahead for situations in which they are exposed to food-related stimuli (12). In addition, poor working memory, a function that modulates other cognitive abilities such as behavioral inhibition and decision making, may lead to impulsive behaviors such as overeating (16, 17). Lastly, poor cognitive flexibility is associated with difficulties in establishing new patterns of behavior, affecting engagement in therapeutic interventions that focus on changes to well established patterns (12, 18).

Attempts to understand executive functioning in those with EDs are neither exhaustive nor conclusive. One review identified that people with BED had problems in cognitive flexibility compared to obese controls without the disorder (19). Two reviews found poor decision-making performance across individuals with anorexia nervosa, bulimia nervosa and BED compared to healthy controls (20, 21). Conversely, four reviews (11, 22–24) did not find consistent evidence of diminished executive abilities in people with BED. The authors point out that the diversity in methodology, different cognitive tasks and paradigms used, and small sample sizes limit consistent findings.

A systematic review of reviews on neurocognitive functioning in EDs reported that although evidence generally suggests varying patterns of neurocognitive difficulties across EDs, there remain critical limitations regarding the methodological quality of these studies (25). For example, a few of the reviews on the topic did not follow the methodological standards of a systematic review (26, 27), one did not aggregate results in a meta-analysis (11), and others were limited by a specific focus on one task (19–24).

To date, no review and meta-analysis has summarized findings from studies that have examined different domains of executive functioning in individuals with BED.

Therefore, the aim of this systematic review and meta-analysis is to examine whether people with BED perform different to those without the disorder in executive function tasks, and discuss the potential impact of impairments found on binge eating behavior.

METHOD

The study was mainly conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) protocol (28), although the protocol drafted for this systematic review was developed for the MSc thesis of the first author (MEGC) and not published online before.

Search Strategy and Study Selection

Literature Search

Electronic searches were conducted in Pubmed, PsycINFO, Scopus, and Web of Science databases. Studies published before November 29, 2019 were included. Two terms (and their variations) were combined for the searches: one term was related to the ED diagnosis/behavior (e.g. *BED, binge eating*) and the other referred to executive functions (*executive function, executive control, cognitive control, set-shifting, cognitive flexibility, decision-making, working memory, inhibitory control, problem-solving, attention, and planning*). The descriptors were combined in Boolean operators. In addition, we carried out manual searches of reference lists in order to identify potential additional studies. We did not conduct searches in the gray literature.

Study Selection

The eligibility criteria for studies of this review were:

Population: Studies including adults (≥18 years old) diagnosed with BED based on a diagnostic criteria (e.g., DSMIII-R,

DSM-IV, or DSM-5), and established through psychiatric clinic interview or any psychiatric diagnostic tool (e.g., Structured Clinical Interview for DSM-Axis I Disorders; Eating Disorders Examination Interview);

Interventions: This review did not explore effects of treatments/interventions, however intervention studies were eligible if they provided baseline comparisons of groups as described below under "comparators" and "outcomes";

Comparators: Studies that compared participants with BED with participants without BED (either of normal weight or overweight/obese);

Outcomes: Studies that examined performance on an executive function task: set-shifting, cognitive flexibility, decision-making, working memory, inhibitory control, problem-solving and planning;

Studies: Studies with cross-sectional, case-controlled, or clinical trial designs. Additionally, publications in Portuguese, Spanish or English were eligible.

The titles and abstracts that emerged from searches were examined by three independent researchers (MEGC, JK-G, and BSS). Each study that was identified as potentially relevant by at least one of the researchers was read in its entirety to establish whether it met the inclusion criteria of the review. Where any disagreements occurred, a consensus meeting with the three researchers was held to decide on study inclusion.

Data Extraction

For each study, the first author extracted the following data (presented in **Table 1**): demographic characteristics, body mass index (BMI), psychiatric comorbidities of participants, executive function outcomes examined and their results (mean, standard deviation). In studies with missing information, study authors were contacted by email. The extracted data was checked by a second author before the statistician conducted the meta-analyses.

Quality Assessment

A standardized checklist to identify risk of bias was used to assess the quality of included studies. The checklist was based on the Newcastle-Ottawa Scale (52) and adapted by authors of this study. Only the quality items of the first two aspects ('selection' and 'comparability') were considered, given that the third domain ("exposure") was not pertinent to the focus of studies included of this review. Ratings were summed to provide a total score with a maximum value of six: four points for sample selection and assessment of potential for selection biases, and two points for comparability and controlling for confounding factors. Quality levels of evidence were defined as high (5–6 points); medium (3–4 points), and low (1–2 points). Studies were excluded if they scored in the low range. The quality assessment was conducted by the first author and revised by the last author.

Quantitative Data Synthesis

Meta-analyses were carried out aggregating results from studies that examined the same executive function subdomain. Studies using different neuropsychological tests to examine the same executive function were included in the same meta-analysis. However, separate meta-analyses were run for studies using reaction time as the outcome measure, distinct from those that used a "score" to measure the performance of the same executive function. Additionally, studies would be separated in different meta-analyses where paradigms used to examine a same domain were considered too different.

In studies where three groups were being compared (i.e., BED, normal weight controls, and obese/overweight controls), priority was given for comparisons of the BED results with those of the overweight control group, since the majority of people with BED are obese or overweight and there was interest in examining differences that could be associated with the ED itself, i.e., over and above the potential impact of the weight status (obese).

The Standardized Mean Difference (SMD) was used to calculate the mean differences between groups. The effect sizes were calculated as Hedges' g (a variation of Cohen's d that corrects for biases due to small sample sizes), and 95% Confidence Intervals (CI) were reported. The magnitude of the effects was interpreted as small (0.15–0.45), medium (0.5–0.75), and large (≥0.8).

Heterogeneity among studies was assessed using the Cochran's Q test (53). An additional measure of heterogeneity or inconsistency across studies was also applied, the Higgins and Thompson I^2 index [I^2 = (Q – df)/Q] (54). As a sample size independent measure of the inconsistency of effect sizes across studies, I^2 is more powerful with small sample sizes, compared to Cochran's Q test (54). The I^2 index describes the percentage of total variation across studies that is due to heterogeneity rather than sampling error, and ranges from 0% (no inconsistency) up to 100% (high heterogeneity). The studies are considered heterogeneous when the variability between them has a nonrandom origin, with values >50% considered as moderate heterogeneity and >75% considered high (54). The random effects model was always preferred when significant heterogeneity is observed (and I^2 > 50%) between the studies, and the fixed effects model when the heterogeneity was considered low and not significant.

The statistical program STATA 12 was used to carry out all analyses. In the forest plots, the case group refers to people with BED and the control group refers to obese controls. Forest plots present the results (SMD and CI) for each study in the meta-analysis and the measure of meta-analytic effect.

Finally, despite relatively few articles included in each meta-analysis, publication bias was assessed through visual inspection of funnel plot asymmetry (55) and by the corresponding statistical analogues: Begg's adjusted rank test (56) and Egger's test (57). The funnel plots of all meta-analyses are in **Supplementary Material**.

RESULTS

Included Studies

Out of a total of 1.983 records, 390 were selected for abstract reading after duplicates were removed. After screening of

TABLE 1 | Characteristics of included studies—case control design comparing people with binge eating disorder with obese and normal weight controls (n = 28).

Publication	Sample	Female (percentage)	Age (mean ± SD)	BMI (mean ± SD)	Tasks/Outcome variable	Summary of Findings	Quality Score (X/6)
Decision making							
Davis et al. (29)	(n = 209) BED: 65 OC: 73 NW: 71	100%	BED: 34.3 ± 6.5 OC: 35.2 ± 6.7 NW: 31.8 ± 6.3	BED: 35.7 ± 9.0 OC: 38.6 ± 7.1 NW: 21.7 ± 1.9	Iowa Gambling Test/ Net score	BED = OC BED < NW	4
Danner et al. (14)	(n = 75) BED: 20 OC: 21 NW: 34	100%	BED: 38.05 ± 10.97 OC: 44.56 ± 13.36 NW: 36.13 ± 14.09	BED: 38.74 ± 6.25 OC: 30.84 ± 3.00 NW: 22.32 ± 1.96	Iowa Gambling Test/ Net score	BED = OC BED < NW	4
Aloi et al. (30)	(n = 90) BED: 45 NW: 45	100%	BED: 30.6 ± 10.9 NW: 25.6 ± 3.5	BED: 35.2 ± 6.5 NW: 20.2 ± 1.6	Iowa Gambling Test/ Net score	BED < NW	4
Blume et al. (31)	(n = 42) BED: 19 OC: 23	BED: 73% OC: 73%	BED: 38.84 ± 9.43 OC: 40.48 ± 10.85	BED: 41.92 ± 5.25 OC: 42.84 ± 4.76	Iowa Gambling Test/ Net score	BED = OC	5
Aloi et al. (32)	(n = 93) BED: 35 OC: 32 NW: 26	BED: 77.1% OC: 50% NW: 69.20%	BED: 44.2 ± 10.7 OC: 49.6 ± 9.9 NW: 46.7 ± 11.1	BED: 38.9 ± 6.9 OC: 36.4 ± 6.8 NW: 23 ± 0.8	Iowa Gambling Test/ Net score	BED < NW BED = OC	5
Dingemans et al. (33)	(n = 81) BED: 25 (no-to-mild depressive symptoms) NW: 56	BED: 88% NW: 87.5%	BED: 32.8 ± 8.5 NW: 36.7 ± 12.3	BED: 38.5 ± 7.4 NW: 23.5 ± 2.8	Iowa Gambling Test/ Net score	BED = NW	6
Svaldi et al. (15)	(n = 35) BED: 17 OC: 18	100%	BED: 42.4 ± 12.3 OC: 38.3 ± 13.1	BED: 32.8 ± 3.54 OC: 30.7 ± 3.92	Game of Dice Task/ Net score	BED < OC	5
Wu et al. (34)	(n = 97) BED: 54 OC: 43	BED: 90.7% OC: 97.7%	BED: 40.07 ± 11.56 OC: 39.81 ± 11.26	BED: 33.95 ± 5.02 OC: 35.08 ± 5.09	Game of Dice Task/ Net score	BED = OC	4
Preuss et al. (35)	(n = 101) BED: 24 OC: 47 NW: 30	BED: 87.5% OC: 97.9% HC: 66.7%	BED: 37.44 ± 12.14 OC: 38.05 ± 9.95 HC: 36.30 ± 12.13	BED: 32.19 ± 4.45 OC: 33.48 ± 3.63 HC: 23.96 ± 2.46	Door Opening Task/ Number of doors	BED = OC = NW	5
Kollei et al. (36)	(n = 144) BED: 48 OC: 48 NW: 48	BED: 77.10% OC: 70.8% NW: 64.60%	BED: 40.69 ± 12.9 OC: 37.94 ± 12.66 NW: 37.67 ± 15.68	BED: 43.31 ± 6.31 OC: 43.58 ± 7.15 NW: 22.07 ± 1.88	Cambridge Gambling Task/ Quality of decision making	BED = OC < NW	5
Grant and Chamberlain (37)	(n = 34) BED: 17 OC: 17	BED: 64.7% OC: 64.7%	BED:25.47 ± 4.82 OC: 23.76 ± 4.09	BED: 33.87 ± 5.08 OC: 31.39 ± 6.28	Cambridge Gamble Task/ Quality of decision making	BED = OC	5
Inhibitory Control							
Duchesne et al. (12)	(n = 76) BED: 38 OC: 38	BED: 38.2% OC: 44.7%	BED: 33.29 ± 5.01 OC: 35.42 ± 7.88	BED: 35.89 ± 2.91 OC: 36.60 ± 3.75	The Stroop Test/ Color-word trial: completion time	BED = OC	4
Manasse et al. (5)	(n = 73) BED: 31 OC: 42	100%	BED: 45.06 ± 14.86 OC: 51.09 ± 8.26	BED: 36.84 ± 7.97 OC: 37.85 ± 6.27	Color-Word Interference Task/ Inhibition condition time	BED < OC	4
Eneva et al. (38)	(n = 132) BED-OB: 32 BED-NW: 23 OC: 48 NW: 29	100%	BED-OB: 36.34 ± 2.03 BED-NW: 23.34 ± 0.67 OC: 38.04 ± 1.78 NW: 24.52 ± 1.23	BED-OB: 34.2 ± 0.83 BED-NW: 22.93 ± 0.4 OC: 31.3 ± 0.56 NW: 21.56 ± 0.29	Color Word Interference Task/ Time to completion	BED-OB = BED-NW BED-OB = OC BED-OB = NW	5
Preuss et al. (35)	(n = 101) BED: 24 OC: 47 NW: 30	BED: 87.5% OC: 97.9% HC: 66.7%	BED: 37.44 ± 12.14 OC: 38.05 ± 9.95 HC: 36.30 ± 12.13	BED: 32.19 ± 4.45 OC: 33.48 ± 3.63 HC: 23.96 ± 2.46	Stroop Test/ Reaction time Stop-Signal Task/ Reaction time	BED < NW BED = OC BED > NW BED > OC	5

(Continued)

TABLE 1 | Continued

Publication	Sample	Female (percentage)	Age (mean ± SD)	BMI (mean ± SD)	Tasks/Outcome variable	Summary of Findings	Quality Score (X/6)
Dingemans et al. (33)	(n = 81) BED: 25 (no-to-mild depressive symptoms) NW: 56	BED: 88% NW: 87.5%	BED: 32.8 ± 8.5 NW: 36.7 ± 12.3	BED: 38.5 ± 7.4 NW:23.5 ± 2.8	Stroop Test/ Stroop effect	 BED = NW	6
Balodis et al. (39)*	(n = 36) BED: 12 OC: 13 NW: 11	BED: 75% OC:38.5% NW: 45.45%	BED: 47.6 ± 12.7 OC: 35.4 ± 9.3 NW: 32.7 ± 11.3	BED: 37.1 ± 3.9 OC: 34.6 ± 4.1 NW: 23.2 ± 1.1	Event-related fMRI Stroop color-word interference task/ Reaction time	 BED = OC/NW	5
Lee et al. (40)	(n = 39) BED: 12 NW: 14	100%	BED: 23.6 ± 2.6 NW: 23.3 ± 2.2	BED: 25.6 ± 3.8 NW: 20.4 ± 2.6	Stroop match-to-sample task/ Reaction time	 BED = NW	6
Galioto et al. (41)*	(n = 131) BED: 41 OC: 90	BED: 96.3% OC: 83.1%	BED: 43.58 ± 11.45 OC: 41.18 ± 10.40	BED: 45.40 ± 6.12 OC: 44.87 ± 6.58	Verbal interference color/ Words correctly identified	 BED = OC	5
Wu et al. (34)	(n = 97) BED: 54 OC: 43	BED: 90.7% OC: 97.7%	BED: 40.07 ± 11.56 OC: 39.81 ± 11.26	BED: 33.95 ± 5.02 OC: 35.08 ± 5.09	Stop-Signal Task/ Reaction time	 BED = OC	4
Svaldi et al. (42)*	(n = 60) BED: 31 OC: 29	100%	BED: 45.48 ± 12.77 OC: 40.10 ± 12.11	BED: 35 ± 5.12 OC: 32.99 ± 5.96	Stop-Signal Task/ Reaction time	 BED < OC	5
Mole et al. (43)	(n = 60) BED: 30 OC: 30 NW: 30	BED: 56.7% OC: 56.7% NW: 56.6%	BED: 42.92 ± 8.59 OC: 44.06 ± 9.70 NW: 44.12 ± 10.18	BED: 34.68 ± 5.49 OC: 32.72 ± 3.41 NW: 23.86 ± 2.74	Stop-Signal Task/ Reaction time	 BED > OC BED = NW	4
Grant and Chamberlain (37)	(n = 34) BED: 17 OC: 17	BED: 64.7% OC: 64.7%	BED:25.47 ± 4.82 OC: 23.76 ± 4.09	BED: 33.87 ± 5.08 OC: 31.39 ± 6.28	Stop-Signal Task/ Reaction time	 BED < OC	5
Bartholdy et al. (44)	(n = 39) BED: 11 NW: 28	100%	BED: 28.73 ± 11.33 NW: 24.64 ± 5.14	BED: 28.86 ± 6.92 NW: 22.04 ± 2.03	Stop-Signal Task/ Reaction time	 BED = NW	5
Aloi et al. (30)	(n = 90) BED: 45 NW: 45	100%	BED: 30.6 ± 10.9 NW: 25.6 ± 3.5	BED: 35.2 ± 6.5 NW: 20.2 ± 1.6	Hayling Sentence Completion Test/ Part B: time	 BED < NW	
Mobbs et al. (18)*	(n = 48) BED: 16 OC: 16 NW: 16	BED: 68.8% OC: 75% NW: 68.75%	BED: 45.1 ± 12.1 OC: 39.3 ± 12.2 NW: 40.2 ± 11.3	BED: 34.6 ± 3.5 OC: 33.6 ± 6.4 NW: 21.3 ± 1.8	Modified affective shifting task/ Errors Commission	 BED < OC/NW BED < OC/NW	5
Svaldi et al. (45)*	(n = 92) BED: 29 OC: 33 NW: 30	BED: 100% OC: 100% NW: 100%	BED: 46.83 ± 13.63 OC: 41.97 ± 14.34 NW: 22.00 ± 1.79	BED: 34.73 ± 4.10 OC: 32.98 ± 1.79 NW: 22.00 ± 1.79	Pictorial priming paradigm (in the context of food)/early response inhibition	BED = OC < NW	5
Hege et al. (46)*	(n = 34) BED: 17 OC: 17	100%	BED: 41.88 ± 8.46 OC: 41.35 ± 12.33	BED: 34.01 ± 5.58 OC: 36.52 ± 4.89	Food-related visual Go/No Go task/ Go trial: reaction time No Go trial: reaction time	 BED < OC BED < OC	5
Loeber et al. (47)*	(n = 57) BED: 17 OC: 20 NW: 20	BED: 100% OC: 100% NW: 100%	BED: 26.5 ± 3.5 OC: 25 ± 5.2 NW: 23.6 ± 2.0	BED: 39.3 ± 6.0 OC: 33.2 ± 3.2 NW: 22.4 ± 2.1	Go/No Go shifting task/ Commission error	 BED > NW food BED < NW neutral BED = OC neutral and food	5
Blume et al. (31)	(n = 42) BED: 19 OC: 23	BED: 73% OC: 73%	BED: 38.84 ± 9.43 OC: 40.48 ± 10.85	BED: 41.92 ± 5.25 OC: 42.84 ± 4.76	Go/No Go shifting task/ Commission error	 BED = OC	5
Kollei et al. (36)	(n = 144) BED: 48 OC: 48 NW: 48	BED: 77.10% OC: 70.8% NW: 64.60%	BED: 40.69 ± 12.9 OC: 37.94 ± 12.66 NW: 37.67 ± 15.68	BED: 43.31 ± 6.31 OC: 43.58 ± 7.15 NW: 22.07 ± 1.88	Go/No Go shifting task/ Commission errors in Response to high and low caloric stimuli	 BED = OC BED = NW	5

(Continued)

TABLE 1 | Continued

Publication	Sample	Female (percentage)	Age (mean ± SD)	BMI (mean ± SD)	Tasks/Outcome variable	Summary of Findings	Quality Score (X/6)
Working memory							
Duchesne et al. (12)	(n = 76) BED: 38 OC: 38	BED: 38.2% OC: 44.7%	BED: 33.29 ± 5.01 OC: 35.42 ± 7.88	BED: 35.89 ± 2.91 OC: 36.60 ± 3.75	Digit Span/ Backward: correct answer	BED < OC	4
Reiter et al. (48)	(n = 44) BED: 22 OC: 22	BED: 72.7% OC: 68.2%	BED: 29.0 ± 9.40 OC: 27.8 ± 4.54	BED: 28.27 ± 6.58 OC: 26.06 ± 4.35	Digit Span/ Backward: correct answer	BED = OC	4
Galioto et al. (41)*	(n = 131) BED: 41 OC: 90	BED: 96.3% OC: 83.1%	BED: 43.58 ± 11.45 OC: 41.18 ± 10.40	BED: 45.40 ± 6.12 OC: 44.87 ± 6.58	Digit Span/ Backward: correct answer	BED = OC	5
Dingemans et al. (33)	(n = 81) BED: 25 (no-to-mild depressive symptoms) NW: 56	BED: 88% NW: 87.5%	BED: 32.8 ± 8.5 NW: 36.7 ± 12.3	BED: 38.5 ± 7.4 NW:23.5 ± 2.8	Digit Span/ Backward: correct answer	BED = NW	6
Svaldi et al. (49)	(n = 67) BED: 31 OC: 36	100%	BED: 46.31 ± 14.20 OC: 40.74 ± 13.11	BED: 35.13 ± 5.08 OC: 33.31 ± 6.16	N-Back Task with lures/ Response time	BED < OC	5
Manasse et al. (5)	(n = 73) BED: 31 OC: 42	100%	BED: 45.06 ± 14.86 OC: 51.09 ± 8.26	BED: 36.84 ± 7.97 OC: 37.85 ± 6.27	Pen Letter N-Back Task/ Efficiency score (reaction time and accuracy)	BED = OC	4
Eneva et al. (38)	(n = 132) BED-OB: 32 BED-NW: 23 OC: 48 NW: 29	100%	BED-OB: 36.34 ± 2.03 BED-NW: 23.34 ± 0.67 OC: 38.04 ± 1.78 NW: 24.52 ± 1.23	BED-OB: 34.2 ± 0.83 BED-NW: 22.93 ± 0.4 OC: 31.3 ± 0.56 NW: 21.56 ± 0.29	NIH Toolbox List Sorting Working Memory/Number of items recalled and sequenced correctly	BED-NW < NW BED-OB < NW OC < NW	5
Duchesne et al. (12)	(n = 76) BED: 38 OC: 38	BED: 38.2% OC: 44.7%	BED: 33.29 ± 5.01 OC: 35.42 ± 7.88	BED: 35.89 ± 2.91 OC: 36.60 ± 3.75	Trail Making Test (B)/ Completion time The Rule Shift Cards Test/ Completion time Wisconsin Card Sorting Test/ Perseverative errors	BED = OC BED = OC BED = OC BED < OC	4
Aloi et al. (32)	(n = 93) BED: 35 OC: 32 NW: 26	BED: 77.1% OC: 50% NW: 69.20%	BED: 44.2 ± 10.7 OC: 49.6 ± 9.9 NW: 46.7 ± 11.1	BED: 38.9 ± 6.9 OC: 36.4 ± 6.8 NW: 23 ± 0.8	Trail Making Test (B)/ Completion time	BED < NW BED = OC	5
Reiter et al. (48)	(n = 44) BED: 22 OC: 22	BED: 72.7% OC: 68.2%	BED: 29.0 ± 9.40 OC: 27.8 ± 4.54	BED: 28.27 ± 6.58 OC: 26.06 ± 4.35	Trail Making Test B/ Completion time	BED = OC	4
Eneva et al. (38)	(n = 132) BED-OB: 32 BED-NW: 23 OC: 48 NW: 29	100%	BED-OB: 36.34 ± 2.03 BED-NW: 23.34 ± 0.67 OC: 38.04 ± 1.78 NW: 24.52 ± 1.23	BED-OB: 34.2 ± 0.83 BED-NW: 22.93 ± 0.4 OC: 31.3 ± 0.56 NW: 21.56 ± 0.29	Trail Making Test B/ Completion time	BED-OB < BED-NW/BED-OB < NW/BED-OB = OC	5
Aloi et al. (30)	(n = 90) BED: 45 NW: 45	100%	BED: 30.6 ± 10.9 NW: 25.6 ± 3.5	BED: 35.2 ± 6.5 NW: 20.2 ± 1.6	Wisconsin Card Sorting Test/ Perseverative errors Trail Making Test (B)/ Completion time	BED = NW BED < NW	4
Dingemans et al. (33)	(n = 81) BED: 25 (no-to-mild depressive symptoms) NW: 56	BED: 88% NW: 87.5%	BED: 32.8 ± 8.5 NW: 36.7 ± 12.3	BED: 38.5 ± 7.4 NW:23.5 ± 2.8	Wisconsin Card Sorting Test/ Perseverative errors Trail Making Test/ Part B minus Part A	BED = NW BED = NW	6
Svaldi et al. (15)	(n = 35) BED: 17 OC: 18	100%	BED: 42.4 ± 12.3 OC: 38.3 ± 13.1	BED: 32.8 ± 3.54 OC: 30.7 ± 3.92	Trail Making Test (B)/ Completion time	BED < OC	5

(Continued)

TABLE 1 | Continued

Publication	Sample	Female (percentage)	Age (mean ± SD)	BMI (mean ± SD)	Tasks/Outcome variable	Summary of Findings	Quality Score (X/6)
Blume et al. (31)	(n = 42) BED: 19 OC: 23	BED: 73% OC: 73%	BED: 38.84 ± 9.43 OC: 40.48 ± 10.85	BED: 41.92 ± 5.25 OC: 42.84 ± 4.76	Wisconsin Card Sorting Test/ Perseverative errors	 BED = OC	5
Kollei et al. (36)	(n = 144) BED: 48 OC: 48 NW: 48	BED: 77.10% OC: 70.8% NW: 64.60%	BED: 40.69 ± 12.9 OC: 37.94 ± 12.66 NW: 37.67 ± 15.68	BED: 43.31 ± 6.31 OC: 43.58 ± 7.15 NW: 22.07 ± 1.88	Intra/Extra-dimensional Set-shift Task/ Shift errors	 BED = OC BED = NW	5
Banca et al. (50)*	(n = 63) BED: 32 OC: 31	BED: 56.25% OC: 38.71%	BED: 42.81 ± 8.63 OC: 43.89 ± 9.63	BED: 34.72 ± 5.63 OC: 32.71 ± 3.59	Intra/Extra-dimensional Set Shifting Task/ Number of errors	 BED < OC	4
Grant and Chamberlain (37)	(n = 34) BED: 17 OC: 17	BED: 64.7% OC: 64.7%	BED:25.47 ± 4.82 OC: 23.76 ± 4.09	BED: 33.87 ± 5.08 OC: 31.39 ± 6.28	Intra/Extra-dimensional Set-shift Task/ Total errors	 BED = OC	5
Manasse et al. (5)	(n = 73) BED: 31 OC: 42	100%	BED: 45.06 ± 14.86 OC: 51.09 ± 8.26	BED: 36.84 ± 7.97 OC: 37.85 ± 6.27	Pen Conditional Exclusion Task/ Perseverative errors	 BED = OC	4
Mobbs et al. (18)*	(n = 48) BED: 16 OC: 16 NW: 16	BED: 68.8% OC: 75% NW: 68.75%	BED: 45.1 ± 12.1 OC: 39.3 ± 12.2 NW: 40.2 ± 11.3	BED: 34.6 ± 3.5 OC: 33.6 ± 6.4 NW: 21.3 ± 1.8	Modified affective shifting Task/ Mental flexibility	 BED = OC = NW	5
Galioto et al. (41)*	(n = 131) BED: 41 OC: 90	BED: 96.3% OC: 83.1%	BED: 43.58 ± 11.45 OC: 41.18 ± 10.40	BED: 45.40 ± 6.12 OC: 44.87 ± 6.58	Switching of attention/ Completion time	 BED = OC	5
Manasse et al. (5)	(n = 73) BED: 31 OC: 42	100%	BED: 45.06 ± 14.86 OC: 51.09 ± 8.26	BED: 36.84 ± 7.97 OC: 37.85 ± 6.27	Tower Task/ Number of move to complete each trial	 BED < OC	4
Svaldi et al. (51)*	(n = 55) BED: 25 OC: 30	BED: 100% OC:100%	BED: NA OC: NA	BED: 29.5 ± 3.89 OC: 38.0 ± 8.17	Means-Ends Problem-Solving Procedure (MEPS)/problem solutions	 BED < OC	4
Duchesne et al. (12)	(n = 76) BED: 38 OC: 38	BED: 38.2% OC: 44.7%	BED: 33.29 ± 5.01 OC: 35.42 ± 7.88	BED: 35.89 ± 2.91 OC: 36.60 ± 3.75	The Action Program Test/ Number of stages completed	 BED < OC	4
Planning							
Duchesne et al. (12)	(n = 76) BED: 38 OC: 38	BED: 38.2% OC: 44.7%	BED: 33.29 ± 5.01 OC: 35.42 ± 7.88	BED: 35.89 ± 2.91 OC: 36.60 ± 3.75	The Zoo Map Test/ Planning time-trial 1 Planning time-trial 2 Number of errors-trial 1 Number of errors-trial 2 Time to complete task-trial 1 Time to complete task-trial 2	 BED = OC BED = OC BED < OC BED = OC BED = OC BED = OC	4
Eneva et al. (38)	(n = 132) BED-OB: 32 BED-NW: 23 OC: 48 NW: 29	100%	BED-OB: 36.34 ± 2.03 BED-NW: 23.34 ± 0.67 OC: 38.04 ± 1.78 NW: 24.52 ± 1.23	BED-OB: 34.2 ± 0.83 BED-NW: 22.93 ± 0.4 OC: 31.3 ± 0.56 NW: 21.56 ± 0.29	Tower Test (D-KEFS)/Number of moves to complete trial	BED-OB = BED-NW BED-OB = OC BED-OB = NW	5
Galioto et al. (41)*	(n = 131) BED: 41 OC: 90	BED: 96.3% OC: 83.1%	BED: 43.58 ± 11.45 OC: 41.18 ± 10.40	BED: 45.40 ± 6.12 OC: 44.87 ± 6.58	Maze Task/ Number of errors	 BED = OC	5
Mean of included studies (range)	*BED: 29.3* *OC: 34.4* *NW: 31.8* *(11 – 90)*	*BED: 87.0%* *OC: 83.0%* *NW: 83.9%* *(38.2% – 100%)*	*BED: 38.0* *OC: 39.7* *NW: 32.8* *(22.0 – 51.1)*	*BED: 35.1* *OC: 35.7* *NW: 22.5* *(20.2 – 45.4)*	–	–	

** Not included in the meta-analyses.*

Findings with an > indicate a favorable result for the BED group, while those with an < indicate a favorable result for the comparison group. Results with an = indicate no significant differences between groups.

BMI, body mass index; BED, binge eating disorder; D-KEFS, Delis-Kaplan Executive Function System; OB, obese; OC, obese control; NIH, National Institutes of Health; NA, not available; NW, normal weight control; SD, standard deviation.

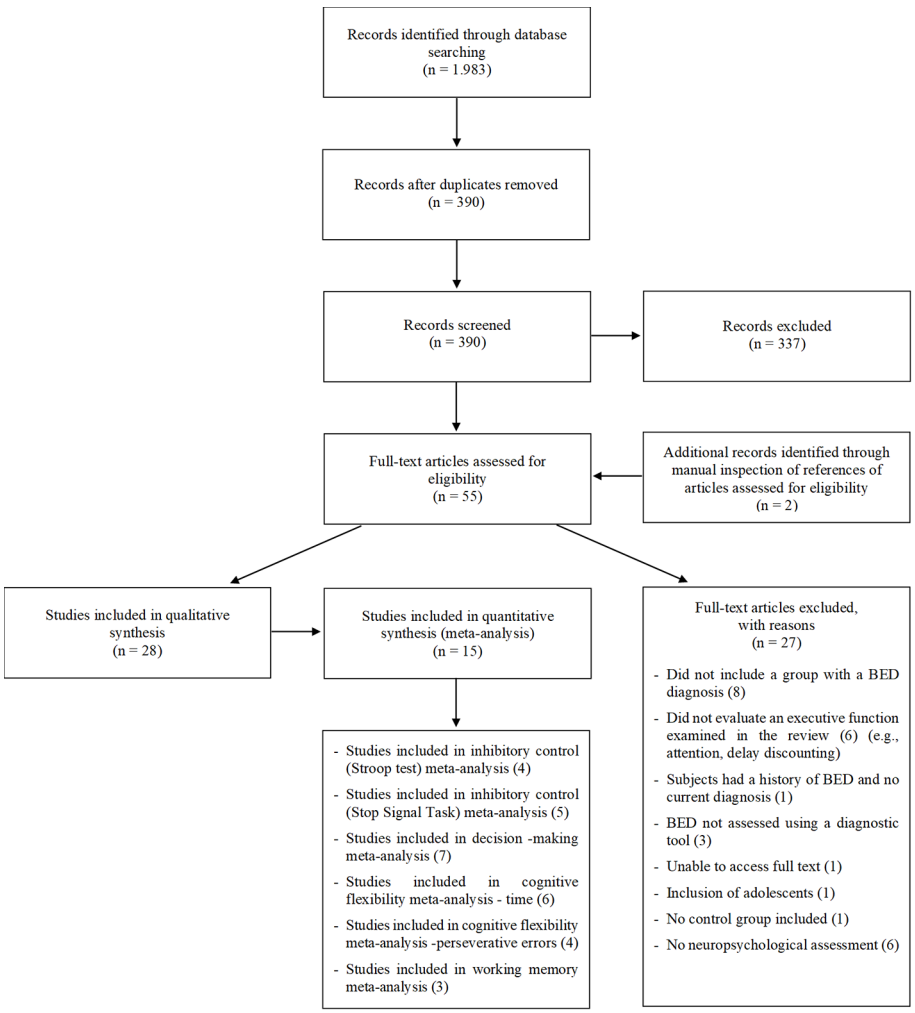

FIGURE 1 | Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow chart of study Inclusion.

abstracts, 53 potentially eligible articles for full-text reading were identified. Two additional papers were identified through manual inspection of reference lists of eligible articles. Evaluation of these full-texts resulted in 28 studies being included in this review (see **Figure 1**). All included studies were cross-sectional. Fifteen (5, 12, 14, 15, 30–32, 34–37, 43, 47–49) of the 28 studies provided sufficient data to be included in at least one of the meta-analyses conducted. Missing data were requested from authors of 15 original articles and 6 replied to requests, providing unpublished data (15, 30, 36, 39, 42, 58). Regarding psychiatric comorbidities, 25 studies reported that the BED group had some comorbidity, 2 did not provide this information (32, 48) and 1 (40) reported exclusion of individuals with a current or past psychiatric disorder. Not all studies specified the type of comorbidities.

In the methodological quality assessment, 18 studies received a "high" quality score, and 10 received scores within the "medium" range. No studies were therefore excluded due to low methodological quality. Study characteristics are summarized in **Table 1**. Some studies examined multiple executive functions and for that reason are listed several times.

Data Synthesis and Meta-Analysis of the Executive Functions

In this section, the results of meta-analyses are reported first, followed by a qualitative discussion of results from studies that could not be included in meta-analyses.

Separate analyses were conducted for studies using Stroop and Stop-Signal paradigms to measure inhibitory control, because of differences between these neurocognitive tasks. Similarly, in the cognitive flexibility domain, independent analyses were conducted for time taken to perform the Trail Making Test (TMT) and The Rule Shift Cards Test, and the number of perseverative errors in the Wisconsin Card Sorting Test (WCST), Penn Conditional Exclusion Task (PCET) and Intradimensional/Extradimensional Set-Shift task (IED).

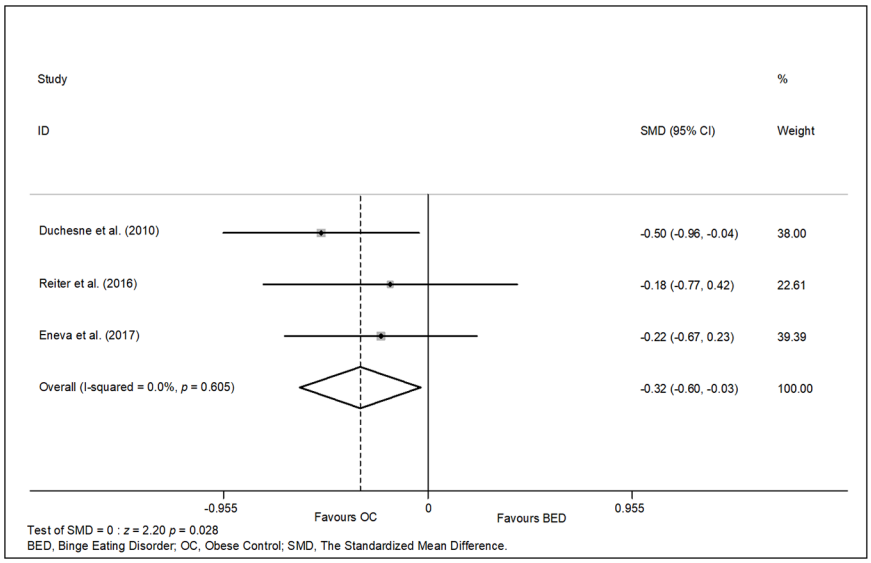

FIGURE 2 | Meta-analysis of studies examining working memory function (three studies, n = 200).

Studies Not Included in Meta-Analyses

Amongst the studies selected for the systematic review (30), 13 were not included in any of the meta-analyses conducted. Reasons for not combining data from these studies were: the use of instruments that provided scores in a different manner from the others (18, 39, 41, 42, 45–47, 51), lack of raw data (means and standard deviation) in published material which was not obtained from authors upon request (50), and studies that compared BED and normal weight control groups (32, 33, 40, 44). This last group of studies (which compared BED and normal weight control groups) could not be included in meta-analyses as there was no domain for which at least 3 studies examined the same function using comparable measures, which would enable aggregation of results. However, they were included in the qualitative description of findings. Additionally, meta-analyses could not be conducted for studies investigating planning or problem-solving, as they did not use comparable measures. Findings from all studies that examined executive function domains not aggregated in meta-analyses for any of the above mentioned reasons are presented in **Table 1**.

Inhibitory Control

Stroop Test

Four studies (5, 12, 35, 38) were included in a meta-analysis comparing Stroop test performance in individuals with BED to obese controls (n = 382). No significant differences were found between the BED group and the obese control group, with a pooled effect size of 0.18 (95% IC: −0.05, 0.42, z = 0.154, p = 0.123). No evidence of significant heterogeneity, X^2 (3, n = 250) = 3.02, p = 0.388, I^2 = 0.70%) or of publication bias was observed (Begg's test z = 0.00, p = 1.000 and Egger t (1) = 0.58, p = 0.62).

Stop Signal Task

Five studies (23, 35, 37, 43, 49) were included in a meta-analysis examining inhibitory control using the Stop Signal Task (n = 359). No significant differences between the BED group and the obese control group were found, with a pooled effect size of 0.17 (95% IC: −0.40, 0.74, z = 0.58, p = 0.562). The Cochran Q test revealed significant heterogeneity across studies, X^2 (4, n = 622) = 24.51, p <0.001, I^2 = 83.70%). No evidence of publication bias was observed (Begg's test z =0.98, p = 0.327 and Egger t (1) = 0.81, p = 0.478).

Four studies using different Go/No-Go paradigms reported mixed findings (31, 36, 46, 47). Hege et al. (46) concluded individuals with BED showed worse performance than obese controls. The other three studies did not find any evidence of altered performance in individuals with BED compared to obese (31, 36, 47) or normal weight controls (36, 47).

Mobbs et al. (18) found that inhibition problems on a mental flexibility task were more severe in the BED group compared to obese and normal weight controls. Galioto et al. (41) found no differences between individuals with BED and an obese control group in a verbal interference color test. Balodis et al. (39) used an event-related fMRI Stroop color-word interference task, finding no significant group differences to congruent or incongruent stimuli in individuals with BED compared to obese and normal weight controls. Compared with normal weight controls, individuals with BED showed worse performance on the Hayling Sentence Completion Task (HSCT) in one study (32), but no differences in another 3 studies using the Stroop test (33), the Stop-Signal task (44) and Stroop match-to-sample task (40). Svaldi et al. (45) used a Pictorial priming paradigm and found that individuals with

BED and obese controls demonstrated poorer performance compared to normal weight controls, but did not differ from one another.

Working Memory

Three studies (n = 200) were included in a meta-analysis examining working memory (12, 38, 48) based on performance on the Digit Span test (backward) and the NIH toolbox test (See **Figure 2**). A significant difference of small magnitude favouring the obese control group was found, with a pooled effect size of −0.32 (95% IC: −0.60, −0.03; $p = 0.02$). There was no evidence of significant heterogeneity, X^2 (2, n = 200) = 1.01, $p = 0.605$, I^2 = 0.0%), or publication bias (Begg's test $z = 0.00$, $p = 1.000$ and Egger t (1) = 0.54, $p = 0.686$).

Four additional studies that were not included in the meta-analysis reported mixed findings. Three showed no significant differences between individuals with BED and obese (5, 41) or normal weight controls (33), however Svaldi et al. (49) found that BED performed worse than obese controls (see **Table 1**).

Decision-Making

Seven studies (n = 649) were included in a meta-analysis examining decision-making based on the net score in the Game of Dice Task (GDT) (15, 23), the Iowa Gambling Test (IGT) (14, 29, 31, 32) and the Door Opening task (35). No significant difference between individuals with BED and obese controls was found (SMD = −0.08; 95% IC: −0.29, 0.13; p = 0.467). There was no evidence of heterogeneity between studies, Cochran Q test, X^2 (5, n = 649) = 6.07, $p = 0.300$, $I^2 = 17.60\%$). There was no evidence of publication bias (Begg's test $z = -0.94$, $p = 0.348$ and Egger t (1) = −1.41, $p = 0.231$).

Studies not included in the meta-analysis (30, 33, 36, 37) reported mixed findings. People with BED showed higher rates of decision-making impairments compared to normal weight controls in three studies. On the other hand, others reported no significant differences in this domain between BED and obese controls (36, 37) and normal weight controls (33).

Cognitive Flexibility

Time: TMT and the Rule Shift Cards Test

Data from 6 studies (n = 299) were included in a meta-analysis examining cognitive flexibility based on the measure "time" from the TMT part B. No significant difference between groups was found (SMD = 0.19; 95% IC: −0.01, 0.40, $z = 1.84$, $p = 0.065$). The Cochran Q test did not reveal significant heterogeneity, X^2 (5, n = 299) = 9.61; $p = 0.087$, $I^2 = 48\%$). Additionally, studies included did not show any evidence of publication bias (Begg's test z =1.88, $p = 0.060$ and Egger t(1) = 1.84, $p = 0.139$).

Perseverative Errors: WCST, PCET, and IED

Four studies (n = 287) were included in a meta-analysis examining cognitive flexibility based on perseverative errors (5, 12, 31, 36). Groups did not significantly differ on this measure (SMD = 0.10; 95% IC: −0.32, 0.51, $p = 0.642$). Significant heterogeneity among studies was observed ($I^2 = 66.90\%$, Cochran Q Test, X^2 (3, n = 287) = 9.06, $p = 0.02$). Included studies did not show any evidence of publication bias (Begg's test $z = 0.34$, $p = 0.73$ and Egger t(1) = −1.15, $p = 0.36$).

Six additional studies not included in the meta-analysis reported mixed findings. In three studies, there was no evidence of altered performance in the BED group compared to obese (18, 37, 41) or normal weight controls (18, 33). In one study (56), individuals with BED showed poorer performance compared to normal weight controls on all indexes of the WCST, apart from perseverative errors. In another study (50), the BED group showed worse performance than normal weight controls in the Intra/Extra-dimensional set shifting task.

Problem-Solving (Only Qualitative Analyses)

Three studies by Duchesne et al. (12), Manasse et al. (5), and Svaldi et al. (51), evaluated problem-solving using the Action Program Test, the Tower Task and Means-Ends Problem-Solving Procedure respectively. Individuals with BED demonstrated poorer performance compared to obese controls.

Planning (Only Qualitative Analyses)

Across different tasks (Zoo map, D-KEFS tower, and maze task), three studies found no significant differences in planning ability in individuals with BED compared to obese controls (12, 38, 41).

DISCUSSION

The present systematic review explored a broad range of executive functions in patients with BED compared to obese and normal-weight controls, but the meta-analyses conducted only compared BED with obese controls. In four of these domains (decision-making, cognitive flexibility, inhibitory control and working memory) it was possible to aggregate data in six meta-analyses. In five out six meta-analyses no evidence of altered executive functioning in individuals with BED was found. Overall, these meta-analyses were limited by small numbers of combined studies (maximum 6 for decision-making). Qualitative inspection of the literature indicated mixed, inconclusive findings for control inhibition, decision making and cognitive flexibility in individuals with BED compared to controls (obese or normal weight), we will discuss it later. Only one small meta-analysis (n = three studies, 200 participants in total) suggested poorer working memory performance in people with BED compared to obese individuals without BED (29, 30, 33), with a small effect size.

As far as we know, no previous meta-analysis has examined working memory in people with BED. However, studies that examined working memory and were not included in the meta-analysis were not supportive of differences between BED and obese or normal weight controls (5, 33, 41). Conversely to our meta-analysis findings, and in line with three previous reviews, there was inconsistent evidence of impairments in working memory in people with BED compared to obese controls (11, 25, 59). Working memory refers to the cognitive process that

maintains, manipulates and updates incoming information in real time to guide proximal decision-making and behavioral responses (60, 61). This function seems to play an important role in the successful self-regulation of eating behavior and body weight (62, 63). Some studies have pointed out a possible association between working memory alterations and binge eating behavior (12, 38). That is, poor working memory may impair the capacity to keep track of ongoing impulsive acts (i.e., binging) (12), and may lead to the maintenance of binge-eating by allowing distractors to overwhelm self-regulation goals (38). Despite these theories, it is important to be cautious with any attempts to associate cognition and eating behavior. Working memory is a "fluid" cognitive ability, meaning that it is susceptible to changes due to factors such as sleep alterations, medication use, or nutrition (64). For instance, a previous study in obese individuals reported that obesity was associated with deficits in working memory. Poor working memory was associated with more consumption of fatty foods, potentially contributing to the development and maintenance of obesity (65). Thus, poor performance in working memory tasks could be attributed to several factors beyond BED. Additionally, it is important to mention that the studies included in this and in other reviews used different cognitive tasks (e.g., Digit Span and N-Back Task) to assess working memory (see **Table 2** in **Supplementary Materials**). In their review, Redick and Lindsey (66) pointed out that Span and N-back tasks measure different cognitive processes. Therefore, different tasks can be used to evaluate different working memory components, and combination of results of these tasks may provide biased results and inappropriate interpretation (67). In our meta-analysis of working memory, we were careful not to combine these two tests.

The present review did not provide evidence to suggest inhibitory control is altered in BED. This is in contrast with studies reporting impulsive behavior and difficulties in controlling behavioral responses in comparison to obese individuals without the condition (5, 39). Our findings are in line with a systematic review of reviews (25), which found no differences between individuals with BED and obese or normal weight control groups using food-related stimuli for general inhibitory control. Similarly, our meta-analysis of studies using the Stop-Signal Task did not find a significant difference in performance in individuals with BED compared to obese controls. This finding has been corroborated by other reviews (11, 22, 24). Thus, although a few studies (18, 32, 45, 46) have reported that BED impacts inhibitory control task performance, this has not been supported by four reviews that examined this domain. It is worth mentioning that the Stroop task was originally constructed to assess cognitive interference and not inhibitory control, which limits the interpretation of results from this meta-analysis and might explain our null findings.

Contrary to our expectations, the decision-making and cognitive flexibility meta-analyses did not find significant differences in individuals with BED compared to controls. Nonetheless, in relation to the decision-making domain, the different types of tasks used in studies may have contributed to the overall null findings. The IGT (14, 29, 30) evaluates decision-making under ambiguity, while the GDT assesses decision-making under risk (15, 34), where risk is presented *a priori* and the subject can calculate the chances of winning or losing in each bet (68). It is not clear whether individuals with BED show poorer performance in a more intuitive-experiential mode, which is associated with automatic and emotional processing (as in IGT), than in a more rule-governed mode (as in GDT). In regard to cognitive flexibility, some of the tasks used in studies are thought to be multi-determined tasks, i.e., they reflect a wide variety of cognitive processes, rather than flexibility only (69). However, this review has assumed that the measures included (i.e. time to complete the task, and number of perseverative errors) are reliable measures of flexibility. Under this assumption, the two meta-analyses that combined results of these measures separately did not find significant differences between individuals with BED and obese controls. Thus, our results do not support reduced cognitive flexibility in people with BED, a finding that does not corroborate results of a previous systematic review (19). The differing results are likely due to the very small number of studies included in the previous review (n = 2). However, our null findings are in line with three studies included in this review that were not included in the meta-analysis (18, 33, 41).

Problem-solving has been scarcely examined in individuals with BED, with only three studies identified in this review. Findings from these studies suggest poorer problem-solving ability in people with BED compared to obese controls (5, 12, 51). Similarly, few studies (n = 3) examined planning ability. Findings from these studies do not support altered planning abilities in individuals with BED (12, 38, 41). It is important to note that the results from the meta-analyses suggest that individuals with BED do not have more deficits than obese controls, however this does not necessarily mean performance is normal or similar to a healthy control group.

The qualitative examination of findings from studies comparing people with BED and obese or normal weight controls suggest: (a) mixed findings in decision-making, cognitive flexibility and inhibitory control; (b) no differences between groups in planning. Additionally, individuals with BED showed worse problem solving abilities compared to obese controls. A hypothesis to be tested in the future research is whether p-hacking could explain these confounding findings in isolated studies.

This systematic review highlights the need for more studies examining neuropsychological performance in people with BED. The findings have several important implications. Firstly, considerable methodological heterogeneity was found among studies, also pointed out in a previous review (11). Studies used different tests and outcome measures to evaluate the same function. Secondly, there is no standardization for control groups. Obese individuals can be considered as a better control sample for future studies in the field, as BED is commonly associated with obesity. However, one-third of people with BED are of normal weight (4). Thus, it would be of interest to compare people with BED with controls of both nutritional status, and either control for the impact of BMI in analyses, or compare

people with similar BMIs. Other aspects that might have contributed to apparent inconsistencies in study findings but were not systematically reported by studies include: (a) the impact of psychiatric comorbidities of patients with BED, not usually controlled in studies (considering the fact that many different psychiatric disorders may be associated with some level of cognitive dysfunction) (70); (b) treatments that might interfere with neurocognition, such as psychiatric medication use and psychological treatments, and (c) sample type (clinical or community sample). Finally, it is important to clarify that these issues relating to methodological heterogeneity among studies are different from the criteria used for the quality assessment in this review.

Strengths and Limitations of This Review

Strengths of this systematic review include: a larger sample of overweight/obese individuals (as in Smith et al. (25) review); the extension of previous meta-analyses that focused on one specific executive function (21) or on one selected executive function task (22), as this review covered a broader spectrum of executive functions and took into account a wider range of executive function measures; and the fact that it is possibly the first study to perform meta-analysis of working memory measures in people with BED. Besides, studies were carefully examined by a standardized checklist to identify risk of bias prior to meta-analyses.

A limitation of our review was the small number of articles included, particularly in meta-analyses, restricting the strength of the evidence that emerges from the results. This was due in part to the limited number of studies available in the field to date. As mentioned above, other methodological differences across studies also limited combination and interpretation of findings. That is, even when trying to aggregate results from studies that examined the same domain, the variety of tests used and the cognitive processes that these tests reflect made comparisons difficult. It is also important to note that we were not able to compare BED with normal weight controls in meta-analyses. Comparisons between BED and obese controls are somewhat limited, as obesity itself is also associated with difficulties in several executive functions.

Clinical Implications

Cognitive deficits are implicated in theoretical explanatory models of BED, such as the transdiagnostic food addiction model (71). To examine whether differences in executive function are of causal significance, further longitudinal studies and investigation as to whether targeting them in treatment provides symptomatic benefit is required. Treatments such as inhibition training show some potential. For example, targeting impulsive actions (such as loss of control overeating) through strengthening inhibitory processes during training is a potentially valuable technique (72). Neuromodulation approaches may also work through these mechanisms. It is possible that a personalized psychiatry approach may be needed in which treatments are tailored to the underlying intermediate phenotype. More treatment studies which examine executive processes as moderators or mediators are therefore required. The development of a standardized cognitive battery through joined forces of experts from both fields (ED and neuropsychology) can potentially allow reproducibility and reduce inconsistencies of findings (73), as has been developed in the schizophrenia field (e.g., MATRICS battery) (74).

CONCLUSION

In conclusion, the findings from our meta-analysis suggest that individuals with BED may show alterations in working memory, relative to obese people without the disorder (with an effect size of small magnitude). In other domains, the meta-analyses suggest that patients with BED do not show more difficulties in executive functioning than obese controls. However, this does not necessarily indicate similar performance to healthy, nonobese controls. It is hoped that the findings from this review stimulate further research with stronger designs in the field, as well as the development of therapeutic approaches that take patients' cognitive profile into account.

DATA AVAILABILITY STATEMENT

All datasets generated for this study are included in the article/ **Supplementary Material**.

ETHICS STATEMENT

The study was approved by the ethics committee of Universidade Federal de São Paulo (case 9812050316).

AUTHOR CONTRIBUTIONS

MC performed the searches and data extraction and wrote the manuscript. AB, BS and JK-C helped with titles and abstracts and papers selection. AC and FS contributed with concept, protocol writing, revision, and interpretation of findings. JK-G also contributed with revision and edit of the manuscript.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyt.2020.00288/full#supplementary-material

SUPPLEMENTARY FIGURE 1 | The updated search of the systematic review.

SUPPLEMENTARY FIGURE 2 | Forest plot of standardized mean effect size of differences (SMD) in decision-making between individuals with binge eating disorder (BED) and obese healthy controls (OC).

SUPPLEMENTARY FIGURE 3 | Funnel plot of studies included in the decision-making meta-analysis.

SUPPLEMENTARY FIGURE 4 | Forest plot of standardized mean effect size of differences (SMD) in cognitive flexibility between individuals with binge eating disorder (BED) and obese healthy controls (OC). (Wisconsin Card Sorting Test (WCST), Penn Conditional Exclusion Task (PCET) and Intradimensional/ Extra-dimensional Set-Shift task (IED)/perseverative errors).

SUPPLEMENTARY FIGURE 5 | Funnel plot of studies included in the cognitive flexibility meta-analysis (Wisconsin Card Sorting Test (WCST), Penn Conditional Exclusion Task (PCET) and Intradimensional/ Extra-dimensional Set-Shift task (IED)/ perseverative errors).

SUPPLEMENTARY FIGURE 6 | Forest plot of standardized mean effect size of differences (SMD) in cognitive flexibility between individuals with binge eating disorder (BED) and obese healthy controls (OC). (Trail Making Test (TMT) and The Rule Shift Cards Test / time).

SUPPLEMENTARY FIGURE 7 | Funnel plot of studies included in the cognitive flexibility meta-analysis (Trail Making Test (TMT) and The Rule Shift Cards Test / time).

SUPPLEMENTARY FIGURE 8 | Funnel plot of studies included in the working memory meta-analysis.

SUPPLEMENTARY FIGURE 9 | Forest plot of standardized mean effect size of differences (SMD) in inhibitory control between individuals with binge eating disorder (BED) and obese healthy controls (OC) (Stroop test).

SUPPLEMENTARY FIGURE 10 | Funnel plot of studies included in the inhibitory control meta-analysis (Stroop Test).

SUPPLEMENTARY FIGURE 11 | Forest plot of standardized mean effect size of differences (SMD) in inhibitory control between individuals with binge eating disorder (BED) and obese healthy controls (OC). (Stop Signal Task).

SUPPLEMENTARY FIGURE 12 | Funnel plot of studies included in the inhibitory control meta-analysis (Stop Signal Task).

SUPPLEMENTARY FIGURE 13 | Data extraction form.

SUPPLEMENTARY TABLE 1 | Characteristics of excluded studies.

SUPPLEMENTARY TABLE 2 | Studies included in each executive function subdomain and in meta-analyses.

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SYSTEMATIC REVIEW
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Which Symptoms, Complaints and Complications of the Gastrointestinal Tract Occur in Patients With Eating Disorders? A Systematic Review and Quantitative Analysis

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Background: Eating disorders (ED) such as anorexia nervosa (AN), bulimia nervosa (BN), and binge eating disorder (BED) are often accompanied by a variety of psychological and physical comorbidities. Gastrointestinal (GI) symptoms are a classical feature in most patients with ED. The heterogeneity of studies on this topic is high, making it difficult to have a clear overview. The aim of this systematic review is therefore to provide an overview of subjectively and objectively measured differences and changes in the GI tract in patients with EDs, along with the occurrence of GI complications.

Methods: A systematic literature search was conducted in PubMed, Web of Science, and Google Scholar to find all relevant studies examining GI problems in AN, BN, and BED. Quantitative analyses were performed for objective GI physiology measures where applicable.

Results: The review differentiated between ED types and also between studies that report GI outcomes of ED in (i) human studies with an ED diagnosis excluding case reports that provide an overview of GI problems in ED and (ii) case reports with an ED diagnosis describing rare GI complications in ED. GI symptoms and impaired gastric transit times were frequent features of EDs with specific differences found for the ED types. During the time course of treatment, GI symptoms changed and/or improved but not completely. GI complications extended the range of GI problems observed, including a variety of serious complications such as gastric dilatation.

Conclusions: Problems of the GI tract are frequent in patients with ED and it is likely that they complicate therapy, especially in patients with AN.

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INTRODUCTION

Eating disorders (ED) include anorexia nervosa (AN), bulimia nervosa (BN), binge eating disorder (BED) and, Other Specified Feeding and Eating Disorders (OSFED) according to the Diagnostic and Statistical Manual of Mental Disorders 5 (DSM-5) criteria (1) as well as the International Classification of Diseases 11 (ICD-11) (2). EDs can be associated with being underweight or overweight and obese but also with normal weight.

AN [Body Mass Index (BMI) < 18.5 kg/m^2] is the best known ED and, together with substance abuse disorders, has the highest mortality rate of all mental illnesses (3–5). The urge to be "thin" and the fear of becoming "fat" are the driving forces for restrictive eating behavior (restrictive type) and often for other behaviors, e.g. excessive physical activity, which sometimes leads to extreme and life-threatening weight loss. Some patients regularly have binge eating episodes which are counteracted by self-induced vomiting, laxative and diuretic abuse (bulimic or binge/purging type) (1, 2). The prevalence of AN ranges between 0.9–4% in women and is about 0.3% in men (6–8).

In BN, patients are usually of normal weight and suffer from regular binge eating episodes with loss of control. This means that very large amounts of food (3000 to 5000 kcal) are consumed without interruption in a rather short period of time. Self-induced vomiting and the misuse of laxatives and other drugs serve as compensation (2). The prevalence of BN has recently been summarized as <1-2% (6).

Similarly, patients with BED have regular binge eating episodes at least once a week over a period of 3 months with loss of control. However, there is generally no compensatory behavior and many of these patients are overweight (BMI > 25 kg/m^2) or obese (BMI > 30kg/m^2) (1, 2). The prevalence of BED is <1-4% (5).

Due to the disturbed eating and food intake behavior, EDs are often associated with being under- or overweight and are accompanied by a variety of comorbidities, especially gastrointestinal (GI) tract problems (9, 10). Functional GI disorders are therefore a standard feature in most patients with EDs. EDs are associated with altered GI physiology and microbiota (11, 12). These GI problems can complicate the treatment of ED and the GI symptoms shift during the course of recovery. Some remain, others disappear, and others develop (11, 13–15). An important underlying mechanism for these observations is the microbiota-gut-brain-axis which allows bidirectional communication between the central nervous system and the gut (16, 17). Janssen (15) therefore postulated that GI physiology disturbed by an ED, in combination with other mental illnesses, could lead to the maintenance or intensification of symptoms (15).

Studies reporting GI symptoms, complaints and complications in patients with ED are extremely heterogeneous in their aims, design, participants, measurements, treatments, and outcomes (18) making it difficult to maintain a clear overview of the topic. A systematic review of the literature across the range of EDs and the GI tract is currently lacking in the literature. The objective of this review was to provide a systematic overview over the topic, applying broad inclusion criteria in order to capture the whole picture of GI problems and complications in patients with AN, BN, and BED.

METHODS

To conduct and report the systematic review, we applied the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement criteria (19, 20). The review protocol is registered in the International Prospective Register of Systematic Reviews (PROSPERO; CRD42019100585).

Literature Information Sources and Search Strategy

The review process was conducted and reported on the basis of the PRISMA statement (19, 20). PubMed and Web of Science databases were searched for literature on 3 March 2018 and 6 March 2018, respectively, and on 1 November 2019 for an update. We built two similar search terms for the two databases to find all articles related to EDs and GI problems.

The following search terms were used for 1) PubMed: (((((((anorexia nervosa[MeSH Terms]) OR bulimia nervosa [MeSH Terms]) OR binge-eating disorder[MeSH Terms]) OR anorexia nervosa) OR bulimia nervosa) OR binge-eating)) AND ((((gastrointestinal tract[MeSH Terms]) OR gastrointestinal disease[MeSH Terms]) OR gastrointestinal) OR intestinal)) AND (((((comorbidity[MeSH Terms]) OR ((signs and symptoms[MeSH Terms]))) OR comorbidity) OR symptoms) OR complaints) and 2) Web of Science: (TS=(anorexia nervosa) OR TS=(bulimia nervosa) OR TS=(binge eating)) AND (TS= (gastrointestinal tract) OR TS=(gastrointestinal diseases) OR TS=(gastrointestin*) OR TS=(intestin*)) AND (TS= (comorbidit*) OR TS=(symptom*) OR TS=(complaint*).

Additionally, we conducted a grey literature search by analyzing the first 200 search results on Google Scholar using the search terms 'eating disorders' and 'gastrointestinal symptoms' on 8 March 2018.

Eligibility Criteria

Eligibility criteria were based on the five PICOS dimensions, i.e., participants (P), interventions (I), comparators (C), outcome (O), and study design (S) (21, 22). We modified the common

PICOS scheme by inserting the item 'investigations' instead of 'interventions' for correctness.

Participants: Studies were included if they were conducted in patients with AN, BN, or BED, or if the authors reported a secured ED diagnosis with common features of the aforementioned EDs but not necessarily exactly stating which ED. Studies exclusively conducted in patients with OSFED were excluded. To meet the inclusion criteria, at least one participant above 16 years of age per study was necessary. Thus, some articles may also include children younger than 16 years of age. No restrictions were made regarding ethnicity, sex, or health status.

Investigations: Studies diagnosing or assessing at least one symptom, problem, disturbance, or complication of the GI tract, which we defined as teeth, mouth, salivary glands, pharynx, esophagus, stomach, gut with small intestine (duodenum, jejunum, ileum), and large intestine (caecum, colon, sigmoid, rectum), and the anus. Studies were excluded if they dealt with symptoms presumably provoked by any other abdominal organ (e.g. liver, pancreas, gallbladder), misdiagnosis of independent GI diseases, or exclusively with GI hormones.

Comparators: A control group of any health status was not necessary in order to meet the inclusion criteria but was allowed.

Outcome measures: All measures which are available to assess subjective and/or objective GI symptoms, problems, disturbances or complications.

Study design: In order to provide a broad overview of the topic, studies with original data were not excluded because of their study design or methodology. Thus, randomized and non-randomized, quantitative and qualitative studies with and without comparison groups, pre-post designs (with follow-up) and observational studies with any sample size (including case reports) were included.

In the screening process, articles were not considered for further evaluation if they were not peer-reviewed such as books, letters, meeting abstracts, editorials, guidelines, or if they did not report primary data (e.g. reviews). Articles meeting all criteria and written either in English, German, Spanish, or French were included. Altogether, no restrictions were imposed regarding formal study characteristics such as length of follow-up, study setting, different interventions, and outcome measures, as long as outcomes regarding the GI tract were reported to be associated with ED.

Subgroup: The possibility of performing meta-analyses on certain GI outcomes was considered but was not feasible because only four randomized controlled trials were found, in which different GI outcomes were assessed. Instead, quantitative subgroup analyses of patients with EDs versus healthy participants were performed for the following subgroups of different GI outcomes: gastric half-emptying time, serum amylase levels, and salivary flow rate. For these analyses, studies were included if the required data were reported in the text, in tables, or in figures for patients and for healthy controls. For gastric half-emptying time, studies assessing this value for liquids and solid foods by scintigraphy were considered. Studies reporting other variables for gastric emptying time which could not be converted into gastric half-emptying time or applying other techniques for gastric emptying measurement were excluded. For a subgroup analysis of serum amylase levels, studies reporting data of total serum amylase levels were included. Total serum amylase consists of salivary and pancreatic serum amylase and was reported more frequently than salivary serum amylase. Salivary and total serum amylase can be analyzed interchangeably considering our included studies, as no elevated pancreatic serum amylase levels or pancreatic damage was reported. Therefore, each included study concluded that salivary serum amylase was elevated and that elevated total serum amylase levels could not be of pancreatic origin. Subgroup analyses for salivary flow rate were conducted for studies assessing the parotid glands during resting conditions and stimulation by citric acid. Studies were excluded if it was not reported which salivary gland was investigated.

Study Selection, Data Collection, and Organization

For study selection and data collection, we used a modified PICOS scheme (21, 22). After initial literature search the duplicates were removed before titles and abstracts were screened independently by the first two authors (CR and GS) for potential inclusion and discussed in case of conflict. The first authors agreed in 96.2% (1026) of studies. A third reviewer (IM) was consulted for the remaining studies. For eligibility 364 full-text articles were evaluated. To provide a structured overview, we distinguished between subjective and objective measures and outcomes, respectively.

Due to the large variety of study types, the articles were categorized into two groups:

1. Human studies with ED diagnosis, excluding case reports: This group included articles with all types of study designs except for case reports where the diagnosis of ED was specified according to the authors, and participants were assessed for GI disturbances. Group 1 was further divided into the specific EDs: AN, BN, and BED.
2. Case reports with ED diagnosis: These articles were handled separately because they showed a very different profile of GI outcomes compared with the other studies categorized into group 1. These reports point out GI complications in EDs in particular.

Data Items and Statistics

The following information was extracted from each included article for groups 1 and 2: year of publication, ED categorization, study type, follow-up/study length, sample characterization including sample size, sex, age, and BMI, diagnostic method, subjective and objective GI problems, and intervention. In addition to these items, ED diagnostic criteria for group 1 and lethal outcomes for group 2 are reported. To provide an overview

across studies, mean (weighted for the number of participants per study) and median [interquartile range] were calculated for sample size, age, BMI, and percentage of male participants for all EDs, and also separately for each ED in group 1.

For quantitative subgroup analyses, mean values ± standard deviation for gastric half-emptying time (in min), serum amylase levels (in U/L) or salivary flow rate (in ml/min) as well as sample sizes of ED participants and healthy controls were extracted from all studies eligible for subgroup analysis. To provide a summary of the data across the studies, the values of interest were multiplied by the number of patients or healthy controls in the respective study and divided by the total number of participants or healthy controls, respectively. Finally, the total mean was calculated as a weighted sum of values from the individual studies.

Risk of Bias

For each study in group 1, a risk of bias assessment was performed using the Office of Health Assessment and Translation (OHAT) Risk of Bias Rating Tool for Human and Animal Studies checklist (23). Depending on the study type, different (applicable) items are evaluated as described in the OHAT checklist. The items include questions asking for adequate randomization, allocation to appropriate comparison groups and the accounting for confounding and modifying variables, among others. Each item is rated with one of four options: definitely low (++), probably low (+), probably high (-), or definitely high risk of bias (- -). The items were not numerically summarized into a final score for single studies in accordance with the PRISMA statement (19, 20). However, an overview for the risk of bias across the studies is reported in the results section. Risk of bias was not assessed for group 2 because we considered that the risk of bias is overall high for case reports. Articles in group 1 with a high risk of bias were not excluded since we aimed at making the overview as broad as possible.

RESULTS

Study Selection and Categorization

The detailed study selection process of our systematic literature search is shown in **Figure 1**. A total of 195 articles met the inclusion criteria. The key information from the single studies is presented in the **Supplementary Material Tables 1** and **2** due to the large amount of data. Eighty-six articles were categorized into group 1 (9, 14, 24–106), which comprises human studies with ED diagnosis (without case reports). Group 1 was further divided into the different EDs namely AN, BN, and BED as depicted in **Supplementary Material Table 1**. Group 2 consists of 109 case reports with a clear ED diagnosis (107–215) as shown with separate subheadings for the different EDs in **Supplementary Material Table 2**. This group in particular comprises studies describing rare complications of ED.

Summary of Study Characteristics

Group 1—Human Studies With ED Diagnosis, Excluding Case Reports

The articles in group 1 were published between 1967 and 2019 (AN: 1967-2019, BN: 1968-2014, BED: 1992-2017). Out of 86 studies, AN of any subtype was assessed in 52, BN in 48, and BED in 9 studies. Thirty-three were mixed studies that assessed at least two different EDs (or AN subtypes). **Table 1** summarizes the study characteristics of group 1 in terms of sample size and participants (sex, age, BMI) across all studies in group 1 and for each ED separately. Detailed information on study design among articles in group 1 are also shown in **Supplementary Material Table 1**. Sixty-seven out of 83 studies in group 1 included a non-ED control group. Only five studies used a kind of randomization. Pre-post designs were found in 30 of the studies (34.9%) of which 28 conducted an intervention. Study length was only reported for 23 of the pre-post studies of which four studies only reported the length range. Of the remaining 19 studies the median study length was 84 days [IQR=42-154].

Group 2—Case Reports With ED Diagnosis

The articles in group 2 were published between 1968 and 2019. Group 2 consists of 109 case report studies, of which 94 reported only one patient case, while 15 reported more than one case. Separated by ED types, AN restrictive subtype was reported in 16, AN binge/purge subtype in 44, BN in 25, and BED in 0 studies. The AN subtype was not clearly presented in 14 studies, and another 11 studies did not define the difference between AN with binge/purge subtype and BN. In total, 142 patient cases (130 [91.5%] females, 12 [8.5%] males) are reported in group 2. The mean age of all patients reported in group 2 was 25.8 years (median=24 [19-30]; age was not reported in two articles). The BMI was only reported in 68 out of 142 cases. Therefore, weight status was also reported in **Supplementary Material Table 2** as the lowest noted body weight (BW) or % of ideal body weight (% IBW) if BMI data were not available. Individual weight status results are presented in **Supplementary Material Table 2** for each study separately.

Summary of Study Outcomes

GI outcome measurements were extremely heterogeneous among all study groups. Subjective outcomes were assessed by self-constructed questionnaires as well as a great variety of validated questionnaires. Objective measurements ranged from physical examination to a variety of technical methods such as serum and saliva tests, radiographic and endoscopic methods, as well as the measurement of specific GI transit times, manometric measurements, and intraoperative diagnostics.

Overview of Study Outcomes at a Qualitative Level for Group 1—Human Studies With ED Diagnosis, Excluding Case Reports

Outcomes and measurements of group 1 are presented individually in **Supplementary Material Table 1** and the outcomes are also summarized in **Figure 2** and **Table 2**.

Subjective GI outcomes were assessed in 47 studies using either self-constructed (n=34) or validated questionnaires

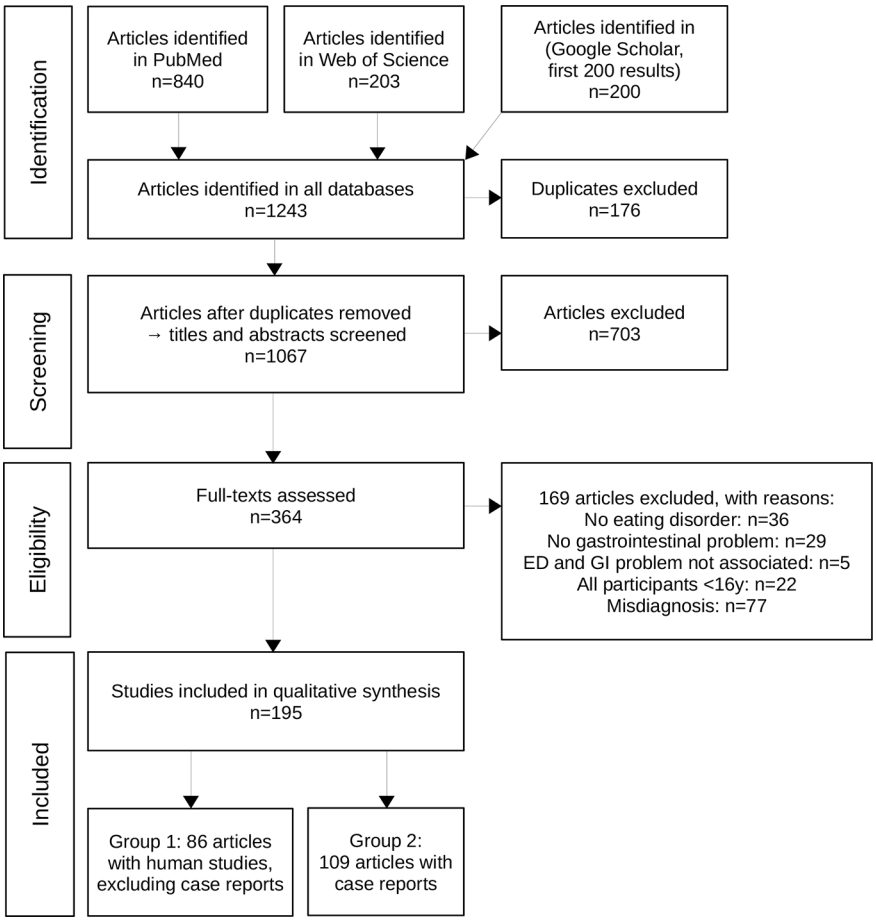


FIGURE 1 | The PRISMA flowchart shows the process of study inclusion in detail with number of studies (n) included or excluded at every step of the process.

(n=20), or both. The outcomes varied from abdominal pain and nausea to constipation and diarrhea. Patterns of GI symptoms differed between the different EDs. The data are depicted in **Figure 2**, except for BED, due to the small number of studies available. The most commonly reported GI symptom in AN was constipation (19/35.8%) and vomiting in BN (18/39.1%). GI problems reported in BED were abdominal fullness (4/44.4%), epigastric pain (4/44.4%), and nausea (4/44.4%).

Objective GI outcomes were measured in 57 studies with many different clinical methods, among which gastric emptying was reported most frequently (in 19 studies). Other frequently reported measurements were dental/oral examination (11/12.8%), salivary flow rate (5/5.8%), and serum amylase (5/5.8%). Objective GI outcomes varied from different delayed bowel transit times and esophageal reflux to increased stomach capacity. An overview of the most common outcomes for ED in general, AN, and BN is presented in **Table 2**. In BED, specific objective GI symptoms were not reported in more than one study and the individual outcomes can be seen in **Table 1** of the Supplementary Material. As depicted in **Table 2**, delayed gastric emptying was a GI condition frequently reported in AN and BN studies and delayed transit times in the small bowel (52, 56) and the colon (33, 56) were also reported. However, two studies found normal gastric emptying in AN (76) and BN (39) compared with controls and one study reported both delayed and rapid gastric emptying in BN (92).

GI outcomes over time were reported by 30 studies with a pre-post design. Different subjective GI symptoms were examined pre- and post-treatment in 15 studies. Overall, an improvement of most subjective GI symptoms was reported for all studies after treatment. The most frequently reported objective GI outcome for pre- and post-treatment was delayed gastric emptying (14 of 30 pre-post studies, 46.7%). Except for one study, delayed gastric emptying improved at least slightly upon treatment. In six of the pre-post studies with gastric emptying, medication was applied additionally. Medication administered to improve delayed gastric emptying included metoclopramide (in four studies) as well as erythromycin (39) and domperidone (95).

Overview of Study Outcomes at a Quantitative Level for Group 1—Subgroup Analysis

Quantitative subgroup analyses for gastric half-emptying time, serum amylase levels of total amylase (including salivary and pancreatic amylase), and salivary flow rate are presented in **Figure 3**.

TABLE 1 | Group 1: Summary of study characteristics.

Sample size	Mean	Median	IQR	Minimum	Maximum
All EDs (n = 86, r = 86)	55.5	24.5	[13.3 - 46.5]	3	850
AN (n = 53, r = 52)	37.3	18.0	[10.5 - 30.8]	3	293
BN (n = 46, r = 45)	21.7	16.5	[10.0 - 33.0]	2	66
BED (n = 9, r = 9)	171.8	56.0	[11.0 - 111.0]	6	850
Controls (n = 67, r = 66)	482.7	25.5	[14.0 - 56.5]	5	14647
Sex (% males)					
All EDs (n = 86, r = 77)	5.5	0.0	[0.0 - 6.3]	0.0	50
AN (n = 53, r = 44)	3.3	0.0	[0.0 - 8.2]	0.0	28.6
BN (n = 46, r = 36)	1.9	0.0	[0.0 - 0.0]	0.0	16.7
BED (n = 9, r = 6)	5.7	2.3	[0.0 - 8.8]	0.0	53.3
Controls (n = 67, r = 55)	24.0	0.0	[0.0 – 16.7]	0.0	100
Age (years)					
All EDs (n = 86, r = 70)	23.5	24.0	[22.0 - 26.6]	15.5	45.1
AN (n = 53, r = 38)	24.6	23.4	[19.8 - 26.3]	15.0	32.0
BN (n = 46, r = 29)	25.1	24.4	[23.1 - 25.8]	16.5	32.0
BED (n = 9, r = 3)	44.3	45.1	[37.1 - 45.1]	29.0	45.1
Controls (n = 67, r = 46)	21.9	26.0	[22.9 - 28.2]	11.7	41.4
BMI (kg/m²)					
AN (n = 53, r = 21)	14.5	15.1	[14.0 - 16.0]	12.0	19.2
BN (n = 46, r = 17)	22.1	22.3	[21.7 - 22.5]	15.1	22.9
BED (n = 9, r = 3)	28.0	31.1	[29.0 - 33.9]	26.9	36.6
Controls (n = 67, r = 26)	25.3	22.1	[21.4 - 22.7]	14.6	35.5

n = total amount of studies in this group, r = amount of studies reporting the variable.

TABLE 2 | Group 1: Objective GI problems reported by human studies with ED diagnosis, excluding case reports.

	ED		AN		BN	
	n	%	n	%	n	%
Caries	2	2.3	0	0	2	4.3
Delayed gastric emptying	18	20.3	13	24.5	7	15.2
Dental erosion	4	4.7	1	1.9	4	8.7
Esophagitis	4	4.7	2	3.8	3	6.5
Gastric electrical dysrhythmia	3	3.5	3	5.7	2	4.3
Gastroesophageal reflux	4	4.7	2	3.8	2	4.3
Hyperamylasemia	4	4.7	3	5.7	4	8.7
Low salivary flow rate	5	5.8	0	0	5	10.9
Salivary gland hypertrophy	2	2.3	1	1.9	2	4.3

Objective GI outcomes which were reported most frequently are presented for all eating disorders together (ED), Anorexia nervosa (AN) and Bulimia nervosa (BN). The number (n) and percentage (%) of studies reporting the specific GI outcome are shown. GI symptoms presented for ED are not the calculated sums of separate EDs shown in this figure. It is the summary of studies shown in ***Supplementary Material Table 1*** *which assessed more than one ED.*

For gastric half-emptying time, five out of potentially 19 studies remained for subgroup analysis [for AN (24, 55, 79)]; for BN (47, 55, 60). Total gastric half-emptying time was delayed in AN compared to healthy controls for both liquids and, solid foods (**Figures 3.1** and **3.2**). In BN, gastric half-emptying time of solid foods was normal among considered studies whereas for liquids, it tended to be slightly more rapid in patients compared to healthy controls (**Figures 3.3** and **3.4**).

Subgroup analysis of serum amylase levels was conducted for three out of potentially five studies including patients with BN

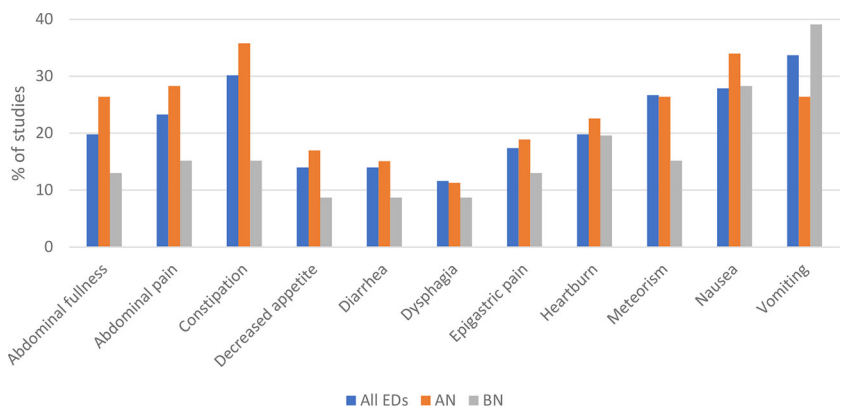
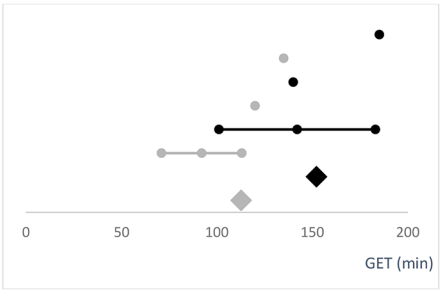


FIGURE 2 | Subjectively reported gastrointestinal (GI) outcomes of group 1 studies that were reported most frequently are presented for all eating disorders (ED), Anorexia nervosa (AN), and Bulimia nervosa (BN). GI symptoms presented for ED are not the calculated sums of separate EDs shown in this figure. It is the summary of studies shown in table 1 of the supplements which assessed more than one ED. The data of the figure are presented below as sample size/% of studies reporting the symptom. Most frequently reported subjective outcomes among all EDs were vomiting (29/33.7%), constipation (26/30.2%), nausea (24/27.9%), meteorism (23/26.7%), abdominal pain (20/23.3%), heartburn (17/19.8%), abdominal fullness (17/19.8%), epigastric pain (15/17.4%), diarrhea (12/14.0%), decreased appetite (12/14.0%), and dysphagia (10/11.6%). For each ED separately, most frequent GI outcomes were in AN: constipation (19/35.8%), nausea (18/34.0%), abdominal pain (15/28.3%), abdominal fullness (14/26.4%), meteorism (14/26.4%), vomiting (14/26.4%), heartburn (12/22.6%), epigastric pain (10/18.9%), decreased appetite (9/17.0%), diarrhea (8/15.1%), and dysphagia (6/11.3%); and in BN: vomiting (18/39.1%), nausea (13/28.3%), heartburn (9/19.6%), abdominal pain (7/15.2%), constipation (7/15.2%), meteorism (7/15.2%), abdominal fullness (6/13.0%), epigastric pain (6/13.0%), decreased appetite (4/8.7%), diarrhea (4/8.7%), and dysphagia (4/8.7%).

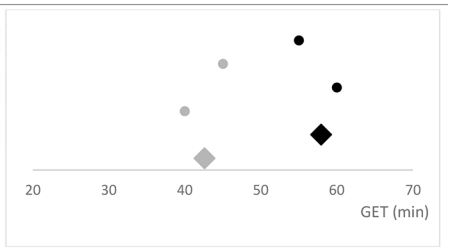
3.1 – Gastric half-emptying time of solid foods in AN

Author (Year)		GET (min)	SD	Total
Abell *et al.* (1987)*	AN	185.0	NR	8
	HC	135.0	NR	8
Hutson and Wald (1990)*	AN	140.0	NR	10
	HC	120.0	NR	15
Rigaud *et al.* (1988)	AN	142.0	41.0	14
	HC	92.0	21.0	14
Total GET	AN	152.1		32
	HC	112.6		37



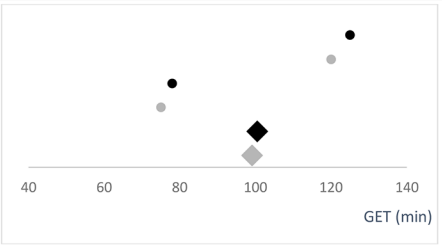
3.2 – Gastric half-emptying time of liquids in AN

Author (Year)		GET (min)	SD	Total
Hutson and Wald (1990)*	AN	55.0	NR	10
	HC	45.0	NR	15
Rigaud *et al.* (1988)	AN	60.0	NR	14
	HC	40.0	NR	14
Total GET	AN	57.9		24
	HC	42.6		29



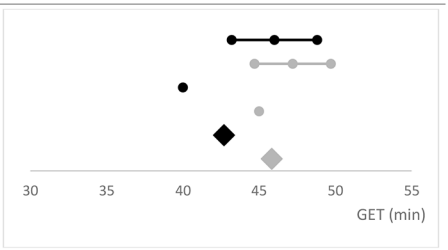
3.3 – Gastric half-emptying time of solid foods in BN

Author (Year)		GET (min)	SD	Total
Hutson and Wald (1990)*	BN	125.0	NR	11
	HC	120.0	NR	15
Koch *et al.* (1998)	BN	78.0	NR	12
	HC	75.0	NR	13
Total GET	BN	100.5		23
	HC	99.1		28



3.4 – Gastric half-emptying time of liquids in BN

Author (Year)		GET (min)	SD	Total
Geliebter *et al.* (1992)	BN	46.0	2.8	9
	HC	47.2	2.5	9
Hutson and Wald (1990)*	BN	40.0	NR	11
	HC	45.0	NR	15
Total GET	BN	42.7		20
	HC	45.8		24



3.5 – Total serum amylase levels in BN

Author (Year)		SAL (U/L)	SD	Total
Robertson and Millar (1999)	BN	88.2	NR	11
	HC	56.0	NR	37
Scheutzel and Gerlach (1991)	BN	95.8	22.2	20
	HC	55.1	NR	30
Walsh *et al.* (1990)	BN	53.1	31.0	32
	HC	38.4	18.4	25
Total SAL	BN	72.8		63
	HC	50.9		92

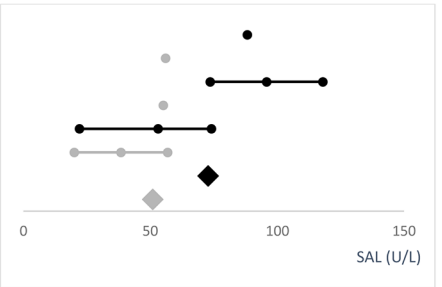
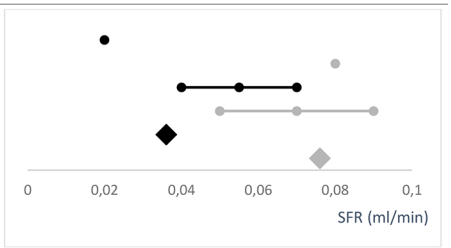


FIGURE 3 | Continued

3.6 – Resting salivary flow rate in BN

Author (Year)		SFR (ml/min)	SD	Total
Paszynska *et al.* (2006,2013)	BN	0.02	NR	33
	HC	0.08	NR	51
Riad *et al.* (1991)	BN	0.055	0.015	28
	HC	0.07	0.02	30
Total resting SFR	BN	0.036		61
	HC	0.076		81



3.7 – Stimulated salivary flow rate in BN

Author (Year)		SFR (ml/min)	SD	Total
Paszynska *et al.* (2006,2013)	BN	0.22	NR	33
	HC	0.45	NR	51
Riad *et al.* (1991)	BN	0.63	0.22	28
	HC	0.65	0.20	30
Total stimulated SFR	BN	0.41		61
	HC	0.52		81

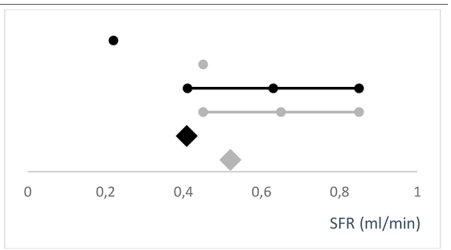


FIGURE 3 | The figures show the mean values, standard deviation (SD) if reported and, calculated weighted total values for gastric half-emptying time (GET; 3.1-3.4), serum amylase levels (SAL; 3.5) and salivary flow rate (SFR; 3.6 and 3.7) along with the number of total participants (Total). AN, Anorexia nervosa; BN, Bulimia nervosa; HC, healthy controls; NR, Not reported. *Data were taken from figures.

(82, 90, 102). Among all considered studies, total serum amylase was elevated in patients with BN in comparison to healthy controls (**Figure 3.5**).

Subgroup analysis of salivary flow rate was conducted from studies examining salivary flow rate in parotid glands. For this analysis, two out of five potential studies remained for analysis (73, 74, 78). Total resting salivary flow rate was reduced in BN patients versus healthy controls (**Figure 3.6**). Total stimulated salivary flow rate tended to be slightly reduced in BN with one study reporting values within the normal range and the other a reduced flow rate (**Figure 3.7**).

Group 2—Case Reports With ED Diagnosis

GI measurements and outcomes of group 2 are depicted in **Supplementary Material Table 2**. Diagnostic methods in group 2 differed from those used in group 1. The main subjective measurement was anamnesis/medical history which is usually taken on admission, while the use of questionnaires was rarely reported. Objective measurements were diverse and played a more important role. The most frequently reported methods were physical examination (68/62.4%), radiography (54/52.3%), computed tomography (CT) (44/40.4%), upper GI endoscopy (28/25.7%), dental/oral examination (11/10.1%), ultrasonography (10/9.2%), lower GI endoscopy (7/6.4%), and post-mortem autopsy (7/6.4%).

Subjectively reported GI problems of case reports are presented in **Figure 4** for studies with AN and BN patients. The most frequently reported symptoms were abdominal pain in both AN subtypes (AN restrictive: 9/56.3%; AN binge/purge: 16/36.4%) and vomiting in BN (15/34.1%).

An overview of the objective GI outcomes for EDs of group 2 is presented in **Table 3**. Most frequent objective outcomes among all EDs were gastric dilatation, gastric necrosis, gastric perforation, superior mesenteric artery syndrome, gastric wall ischemia, parotid gland hypertrophy, absence of bowel sounds, and duodenal dilatation. Differences between EDs could also be found and are presented in **Table 3**. Some GI problems often occurred together in the same case. The association of gastric dilatation with gastric necrosis and gastric perforation is worth mentioning in particular, as the two conditions hardly occurred without gastric dilatation.

Lethal outcomes were reported in 16 studies with 17 (12.0% of all cases) deceased patients altogether, including one suicide (164). The highest mortality among case reports was found in the AN binge/purge subtype with lethal outcomes reported in 20.5% of studies reporting an AN binge/purge subtype (9 of 44) followed by 10.7% in studies reporting a BN (3 of 28). The association of gastric dilatation with lethal outcome was also higher in the AN binge/purge subtype than in BN (26.9% of AN binge/purge subtype cases with gastric dilatation were lethal vs. 16.7% in BN) and also when adjusted for higher frequency of gastric dilatation in AN binge/purge (AN binge/purge 16.5% and BN 8.0%).

Results of Risk of Bias Assessment

Risk of bias was assessed for all studies of group 1 according to OHAT criteria. Therefore, the 10 questions listed in the **Table 4** legend were applied to each study if considered appropriate, based on OHAT criteria and depending on study design. Study designs are summarized in the section "Summary of study characteristics" and reported individually in **Supplementary Material Table 1**. Across the studies, selection bias was rated very differently, with most studies showing probably low to probably high risk of bias. For confounding bias, 58% of studies were rated with a probably low risk of bias, whereas 32% showed a probably high risk of bias. The performance bias

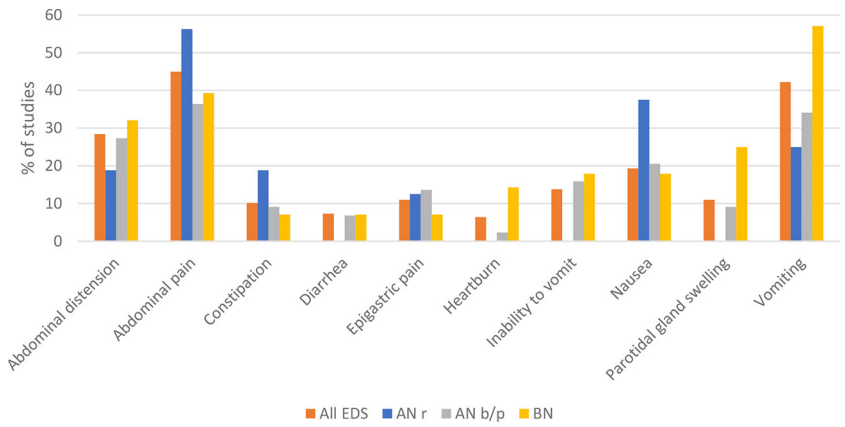


FIGURE 4 | Subjectively reported gastrointestinal (GI) outcomes of case reports that were reported most frequently among all EDs are presented for eating disorders (ED), Anorexia nervosa (AN) differentiated for restrictive subtype (r) and binge/purge subtype (b/p), and Bulimia nervosa (BN). GI symptoms presented for ED are not the calculated sums of separate EDs shown in this figure. It is the summary of studies shown in table 1 of the supplements which assessed more than one ED. The data of the figure are presented below as sample size/% of studies reporting the symptom. ED: abdominal pain (49/45.0%), vomiting (46/42.2%), abdominal distension (31/28.4%), nausea (21/19.3%), inability to vomit (15/13.8%), epigastric pain (12/11.0%), parotid gland swelling (12/11.0%), constipation (11/10.1%), diarrhea (8/7.3%), and heartburn (7/6.4%). Subjective GI outcomes differed between EDs. The most frequent were in AN with restrictive subtype: abdominal pain (9/56.3%), nausea (6/37.5%), vomiting (4/25.0%), constipation (3/18.8%), abdominal distension (3/18.8%), and epigastric pain (2/12.5%); in AN with binge/purge subtype: abdominal pain (16/36.4%), vomiting (15/34.1%), abdominal distension (12/27.3%), nausea (9/20.5%), inability to vomit (7/15.9%), epigastric pain (6/13.6%), constipation (4/9.1%), parotid gland swelling (4/9.1%), diarrhea (3/6.8%), and heartburn (1/2.3%); in BN: vomiting (16/57.1%), abdominal pain (11/39.3%), abdominal distension (9/32.1%), parotid gland swelling (7/25.0%), inability to vomit (5/17.9%), nausea (5/17.9%), heartburn (4/14.3%), constipation (2/7.1%), diarrhea (2/7.1%), and epigastric pain (2/7.1%).

TABLE 3 | Group 2: Objective GI problems reported by case reports.

	ED		AN r		AN b/p		BN	
	n	%	n	%	n	%	n	%
Gastric dilatation	53	48.6	4	28.6	25	58.1	12	42.9
Gastric necrosis	13	11.9	0	0.0	7	16.3	2	7.1
Gastric perforation	11	10.1	1	7.1	8	18.6	1	3.6
Superior mesenteric artery syndrome	14	12.8	2	14.3	4	9.3	1	3.6
Gastric wall ischemia	11	10.1	1	7.1	5	11.6	2	7.1
P-arotid gland hypertrophy	13	11.9	0	0.0	5	11.6	7	25.0
Absence of bowel sounds	10	9.2	1	7.1	5	11.6	3	10.7
Duodenal dilatation	10	9.2	3	21.4	3	7.0	1	3.6
GI bleeding	8	7.3	2	14.3	2	4.6	2	7.1
Peritonism/Peritonitis	5	4.6	2	14.3	2	4.6	0	0.0
Submandibular gland hypertrophy	7	6.4	0	0.0	3	7.0	4	14.3

Legend: Objective GI outcomes which were reported most frequently are presented for all eating disorders together (ED), Anorexia nervosa with restrictive subtype (AN r), Anorexia nervosa with binge/purge subtype (AN b/p) and, Bulimia nervosa (BN). The number (n) and percentage (%) of studies reporting the specific GI outcome are shown. GI symptoms presented for ED are not the calculated sums of separate EDs shown in this figure. It is the summary of studies shown in ***Supplementary Material Table 1*** *of the supplements which assessed more than one ED.*

was mostly probably low to low where applicable. The attrition/exclusion bias did well, with most of the studies showing low (45%) or a probably low (36%) risk of bias. Detection bias was mostly low (27%) or probably low (55%). This was similar for selective reporting bias which also scored mostly low (29%) or probably low (56%). For group 2, the risk of bias in studies which only comprised case reports was estimated to be high due to the nature of the study design.

DISCUSSION

In this review, we systematically analyzed GI symptoms and complications across AN, BN, and BED. GI problems showed overlaps among the analyzed studies between the different EDs. Frequent overlapping GI symptoms were nausea, abdominal pain, and meteorism. The reporting of vomiting also ranked high among all EDs. However, most studies did not differentiate between involuntary and ED-dependent vomiting. Apart from general symptoms that were frequent in all EDs, more specific patterns were also found.

Constipation occurred frequently in EDs but was a frequent symptom for AN in particular, most likely due to chronic food restriction. Another symptom occurring frequently in AN was abdominal fullness. On the one hand, abdominal fullness can be used as a reason for not being able to eat (216). On the other hand, this fits with objectively measured delayed gastric emptying time reported in most studies at a qualitative level and supported by our quantitative analyses. In addition, several studies also reported delayed transit times for other regions of the GI tract such as the small bowel (52, 56) and the colon (32, 33). Overall, gastric emptying time can improve after mid- to long-term rehabilitation but not after short-term refeeding (27, 79). Thus, the delayed gastric emptying time together with the experienced abdominal fullness might be a challenging GI problem in AN, making the introduction and acceptance of normal portion sizes of meals difficult.

Similarly, other pre-post design studies overall reported an improvement in most GI conditions. Interestingly, Chami et al.

TABLE 4 | OHAT: Risk of bias assessment.

Author (year)	SB			CB	PB		A/EB	DB		SRB
	1	2	3	4	5	6	7	8	9	10
Abell et al. (24)	#	#	++	+	#	#	++	+	+	++
Abraham et al. (25)	#	#	++	+	#	#	++	+	-	-
Arii et al. (26)	--	--	#	#	#	--	-	+	+	++
Benini et al. (27)	-	++	#	#	#	+	++	+	+	++
Benini et al. (28)	--	++	#	#	#	--	+	+	+	++
Bluemel et al. (29)	--	-	#	#	#	--	++	+	++	++
Bozzato et al. (30)	#	#	+	+	#	#	++	++	++	+
Chami et al. (31)	NA	NA	#	#	#	NA	+	+	+	++
Chiarioni et al. (32)	--	-	#	#	#	--	++	++	++	+
Chun et al. (33)	#	#	-	-	#	#	+	+	-	-
Coddington and Bruch (34)	#	#	-	-	#	#	-	+	+	+
Cremonini et al. (9)	#	#	+	+	#	#	-	+	-	+
Crowell et al. (35)	#	#	--	+	#	#	+	+	+	+
Cuntz et al. (36)	--	-	#	#	#	-	++	++	++	++
DeJong et al. (37)	#	#	+	+	#	#	NA	-	+	+
Devlin et al. (38)	#	#	++	+	#	#	+	++	+	++
Devlin et al. (39)	#	#	++	++	#	#	+	+	+	+
Diamanti et al. (40)	#	#	--	-	#	#	++	++	+	+
Domstad et al. (41)	#	#	-	-	#	#	+	++	-	+
Dooley-Hash et al. (42)	#	#	-	-	#	#	--	--	--	--
Dubois et al. (43)	#	#	++	+	#	#	+	++	+	-
Fernandez-Aranda et al. (44)	#	#	+	++	#	#	++	-	++	+
Fisher et al. (45)	#	#	-	+	#	#	++	+	NA	-
Garcia Aroca et al. (46)	++	-	#	#	#	-	++	++	++	++
Geliebter et al. (47)	#	#	-	+	#	#	+	++	++	+
Geliebter et al. (48)	#	#	+	++	#	#	++	++	+	++
Gowen et al. (49)	#	#	+	+	#	#	++	++	++	++
Heruc et al. (50)	#	#	++	+	#	#	++	++	+	++
Hill et al. (51)	#	#	+	-	#	#	+	++	-	--
Hirakawa et al. (52)	#	#	+	+	#	#	++	++	+	+
Holmes et al. (53)	#	#	-	+	#	#	++	+	+	-
Hotta et al. (54)	NA	NA	#	#	#	NA	++	++	+	+
Hutson and Wald (55)	#	#	-	+	#	#	++	++	-	+
Kamal et al. (56)	#	#	-	+	#	#	++	+	+	+
Keel et al. (57)	#	#	++	--	#	#	++	++	++	--
Kinzl et al. (58)	#	#	+	+	#	#	++	++	++	++
Kiss et al. (59)	#	#	NA	+	#	#	++	++	++	--
Koch et al. (60)	#	#	++	++	#	#	++	+	+	+
Lee et al. (61)	#	#	++	+	#	#	+	+	+	+
Levy et al. (62)	#	#	++	+	#	#	+	+	+	+
Lobera et al. (63)	#	#	-	+	#	#	+	+	+	+
Mack et al. (11)	NA	NA	#	#	#	NA	-	++	+	++
Mattheus et al. (64)	#	#	NA	+	#	#	+	++	++	++
McCallum et al. (65)	#	#	-	+	#	#	-	-	-	--
Metzger et al. (66)	#	#	++	+	#	#	+	+	++	+
Mond et al. (67)	#	#	++	+	#	#	+	-	-	+
Nakai et al. (68)	#	#	+	+	#	#	++	-	+	+
Nickl et al. (69)	#	#	+	+	#	#	++	+	+	+
Ogawa et al. (70)	#	#	-	-	#	#	++	+	+	+
Ogren et al. (71)	#	#	NA	+	#	#	+	++	++	--
Palla and Litt (72)	#	#	+	-	#	#	+	+	+	+
Paszynska et al. (73)	#	#	-	-	#	#	-	+	+	+
Paszynska et al. (74)	-	-	#	#	#	-	+	+	+	++
Peat et al. (75)	#	#	++	++	#	#	+	+	-	--
Perez et al. (76)	--	-	#	#	#	-	++	+	+	+
Price et al. (77)	+	-	#	#	#	-	++	+	+	+
Riad et al. (78)	#	#	-	-	#	#	-	+	-	+
Rigaud et al. (79)	--	-	#	#	#	-	+	-	+	+
Roberts and Li (80)	#	#	--	+	#	#	+	-	-	+
Roberts et al. (81)	#	#	--	-	#	#	+	+	+	+
Robertson and Millar (82)	#	#	-	-	#	#	++	+	-	-

(Continued)

TABLE 4 | Continued

Author (year)	SB			CB	PB		A/EB	DB		SRB
	1	2	3	4	5	6	7	8	9	10
Robinson (83)	#	#	-	-	#	#	-	-	+	+
Rothstein (84)	NA	NA	#	#	#	NA	++	++	++	++
Rytomaa et al. (85)	#	#	-	-	#	#	++	+	-	++
Saleh and Lebwohl (86)	--	-	#	#	#	-	+	+	+	+
Salvioli et al. (87)	NA	NA	#	#	#	NA	--	++	+	++
Santos et al. (88)	#	#	+	-	#	#	+	+	+	+
Satoh and Yoshihara (89)	#	#	+	+	#	#	+	+	+	+
Scheutzel and Gerlach (90)	#	#	+	+	#	#	+	++	+	++
Sherman et al. (91)	#	#	-	-	#	#	-	+	+	+
Shih et al. (92)	#	#	+	+	#	#	++	+	+	+
Sileri et al. (93)	#	#	+	+	#	#	++	+	-	++
Silverstone and Russell (94)	#	#	+	+	#	#	++	++	++	++
Stacher et al. (95)	-	-	#	#	#	-	++	-	+	+
Szmukler et al. (96)	-	-	#	#	#	-	-	+	+	+
Thornton et al. (97)	#	#	++	++	#	#	-	+	+	+
Thornton et al. (98)	#	#	++	++	#	#	-	+	+	++
Tylenda et al. (99)	#	#	+	-	#	#	+	+	-	+
Valena et al. (100)	#	#	-	+	#	#	+	+	+	+
Waldholtz and Andersen (101)	NA	NA	#	#	#	NA	++	++	+	+
Walsh et al. (102)	#	#	-	-	#	#	+	++	+	+
Walsh et al. (103)	#	#	+	+	#	#	++	++	++	+
Winstead and Willard (14)	#	#	--	-	#	#	-	-	-	+
Wockel et al. (104)	#	#	-	+	#	#	+	+	-	++
Wolff et al. (105)	#	#	--	--	#	#	++	+	++	++
Zimmerli et al. (106)	#	#	+	+	#	#	++	+	+	+

[++]definitely low risk of bias; [+]probably low risk of bias; [-]probably high risk of bias; (also if NR); [--]definitely high risk of bias;
[#]This criterion is not appropriate for this study type according to OHAT; NA, Not applicable.
Selection bias (SB):
1. Was administered dose or exposure level adequately randomized?
2. Was allocation of study groups adequately concealed?
3. Did selection of study participants result in appropriate comparison groups?
Confounding bias (CB):
4. Did the study design or analysis account for important confounding and modifying variables?
Performance bias (PB):
5. Were experimental conditions identical across study groups?
6. Were the research personnel and human subjects blinded to the study group during the study?
Attrition/Exclusion bias (A/EB):
7. Were the outcome data complete without attrition or exclusion from analysis?
Detection bias (DB):
8. Can we be confident in the exposure characterization?
9. Can we be confident in the outcome assessment?
Selective reporting bias (SRB):
10. Were all measured outcomes reported?

(31) reported that GI symptoms improved, but not significantly if controlled for the mediating effects of depression (31). Mack et al. (11) found a difference between upper and lower GI symptoms before and after treatment with lower GI symptoms mostly improving and upper GI symptoms tending to persist (11). Perez et al. (76) reported a decrease in irritable bowel syndrome prevalence, in addition to the general improvement of GI symptoms after treatment (76).

In BN, and to a limited extent also in AN of the binge/purge subtype, salivary gland pathologies such as parotid, submandibular or minor salivary gland hypertrophy were described in several case reports. An explanation for this is that eating large amounts of food in a short time with subsequent vomiting are stimuli for enhanced saliva production and thus enlargement of the salivary glands (58, 82, 102). Group 1 studies that measured salivary gland sizes with technical methods such as ultrasonography, overall supported the subjective findings (30, 66), except for one study with a small sample size (n=5) (77). Enhanced saliva production was also reported among studies of group 1 which was often measured as elevated total or salivary amylase in the serum. This hyperamylasemia is also supported by our quantitative analysis. In this analysis, we compared total, instead of salivary serum amylase levels because one of our included studies (82) only reported total and pancreatic serum amylase because measurement of salivary serum amylase was not feasible due to the facilities available. Analyzing total serum amylase, which is assumed to be the sum of salivary and pancreatic serum amylase (82), was possible, as pancreatic serum amylase was measured in all included studies and not found to be elevated. Thus, elevated total serum amylase resulting from pancreatic damage can be ruled out. Although salivary gland hypertrophies and elevated

total serum or salivary amylase are reported, BN patients showed reduced resting salivary flow rates. Several studies tried to find an explanation for this circumstance.

One hypothesis is that frequent vomiting leads to dehydration, which leads to reduced saliva production during resting (217). Other studies postulate that the frequent use of antidepressants in BN patients, of which some have proven anticholinergic effects (218–220), might cause a decrease in salivary gland output (74). However, the downregulation of the saliva production could also be seen as a mechanism to compensate for the high amounts of saliva required during purging episodes.

Another cluster of GI problems in BN is also provoked by frequent vomiting. These were heartburn as a subjective symptom, but also dental erosion, esophagitis, caries and gastroesophageal reflux (GER) which were examined objectively.

Although case reports as one-patient studies should be regarded with more caution, they play an important role in the overview of GI problems in EDs by highlighting rare life-threatening complications that would be difficult to examine in studies with larger sample sizes. Subjective GI symptoms in group 2 appeared to be similar to those reported in group 1. Nevertheless, objective GI disturbances in particular, extended the range of important GI problems by including a variety of serious complications which have also been discussed recently by Norris et al. (221). A frequently reported complication was gastric dilatation due to superior mesenteric artery syndrome. These patients usually presented at an emergency ward after a binge eating episode (AN with binge/purge subtype, followed by BN), often complaining about nausea and the inability to vomit, as well as abdominal pain, abdominal fullness and showing visible abdominal distension. The situation of a patient with gastric dilatation becomes even more threatening if the stomach becomes necrotic or perforated.

Besides binge eating behavior, emaciation also predisposes for the development of superior mesenteric artery syndrome, as a lack of intestinal fat lowers the aortomesenteric angle which can lead to obstruction of the upper part of the duodenum (108). The combination of these two risk factors in particular put patients with AN binge/purge subtype at risk of severe or fatal developments of superior mesenteric artery syndrome with gastric dilatation and its complications. Another contributing factor for the high lethal outcome in case reports with AN binge/purge subtype is that AN itself has a high mortality rate, which is 12 times higher than any other cause in women aged 15-24 years (150). Nevertheless, the results regarding lethal outcomes among our studies could also be due to reporting bias since a lethal case is more likely to be reported.

During the literature search, we encountered several strengths and limitations of this review which are discussed below. First, we would like to emphasize that the information of the percentage of studies that report a certain GI symptom per ED diagnosis (**Tables 2** and **3**, **Figures 2** and **4**) is limited due to the different GI symptoms/problems assessed by the single studies. Therefore, the percentages only represent the amount of studies among the included studies that reported a specific GI condition and must not be confused with prevalences.

Pre-post design studies were rare and heterogenous, making it impossible to extract specific patterns of GI problems that generally improved, persisted or worsened, especially for each ED separately. No data was available describing the development of GI problems in the time course of treatment.

Another limitation was the underrepresentation of certain groups, e.g. male patients with EDs. On the one hand, we did not find many studies with balanced sex ratios or some with even any male patients at all. On the other hand, studies as well as clinical experience show that men are indeed less affected by EDs (6), therefore it is more difficult to study the GI symptoms or any other characteristics of male EDs.

Another underrepresented group were patients with BED, as BED has only been considered a diagnosis since the publication of the DSM-5 in 2013. It was impossible to identify a certain GI pattern for BED due to the low number of studies. As obesity is a wide spread condition, BED should supposedly be as well. Presumably, the latter is rarely assessed in emergency wards due to low awareness. It is also possible that BED patients rarely develop acute complications, unlike other EDs, as BED patients develop more chronic complications due to obesity and metabolic syndrome. However, the status on GI disturbances in BED is not well examined and could be of further research interest, especially to better understand the development of the disorder.

Finally, studies were heterogenous with regard to their aims, methods, outcomes, and study designs. In particular, high-quality randomized controlled trials, which are the basis for meta-analytical approaches, were rare (n=4) and additionally, covered incomparable GI topics.

This finding highlights the importance and strength of this review to include a broad range of study designs to avoid selection bias. In order to illustrate the quality of the included studies, a risk of bias assessment was performed to help the reader estimate the quality of each individual study without the necessity to narrow down the broader picture due to exclusion of studies. In addition, observational and experimental studies also contribute valuable aspects to the state of knowledge, and RCTs are not always ethical and/or feasible as is the case in the field of EDs and GI problems. We therefore conducted quantitative analyses with controlled trials where possible. The limitations of these analyses were different applied techniques or reported parameters. However, these quantitative analyses are very valuable to support the qualitative level findings.

Although not a topic of this review but worth mentioning is the prevalence of misdiagnosis of GI related diseases in ED that we encountered during our search process. These included Crohn's disease, inflammatory bowel diseases, achalasia, celiac disease, and functional diseases such as irritable bowel syndrome and rumination syndrome. In some studies, ED diagnosis preceded the diagnosis of GI diseases whereas in others, the ED developed after GI disease diagnosis (222). In other cases, the

two diseases coexisted which sometimes led to further complications in treatment (223). To deal with this in practice, we recommend that physicians such as gastroenterologists, who usually have more contact with patients with somatic GI diseases, utilize the short SCOFF questionnaire (224) for clinical assessment of patients in whom an ED is suspected. On the other hand, psychiatrists and psychotherapists in charge of treating EDs should be aware that GI problems are common in these patients, but to only screen for other possible GI diseases if symptom patterns are fitting. GI diseases are not necessarily more prevalent in ED than in the normal population e.g. the prevalence of celiac disease is not higher than in the control population (225).

In summary, this systematic research study presents an overview of the wide-ranging topic of GI disturbances in the EDs AN, BN, and BED. Problems in the GI tract are frequent in EDs and it is likely that they protract therapy, especially in AN. Many GI problems are linked to disordered eating and food intake behavior such as chronic food restriction, binge eating, vomiting, and the abuse of laxatives and, improve after treatment.

Finally, there are research gaps which warrant further research. To date, it is not completely clear which GI symptoms and complications occur in BED. It is unknown to which extent GI problems protract ED therapy, especially in AN, and how GI symptoms change during the time course of treatment. Understanding the underlying GI physiology and problems in the course of refeeding may help to identify critical periods of GI wellbeing, which could then be addressed more adequately.

DATA AVAILABILITY STATEMENT

All datasets generated for this study are included in the article/ **Supplementary Material**.

AUTHOR CONTRIBUTIONS

IM, CR, and GS contributed to the conception and design of the study. CR, GS, and AW organized the database. CR and IM wrote the first draft of the manuscript. KG, AS, PE, and SZ wrote sections of the manuscript. All authors contributed to manuscript revision, and read and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyt.2020.00195/full#supplementary-material.

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Is There an Association or Not?—Investigating the Association of Depressiveness, Physical Activity, Body Composition and Sleep With Mediators of Inflammation

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Background: Cytokines are mediators of inflammation that contribute to a low-grade inflammation in different disorders like major depression and obesity. It still remains unclear which psychological and medical factors interact with cytokine regulation. In the current investigation, the association between levels of pro-and anti-inflammatory cytokines and anthropometrics, mood state (depressiveness), physical activity and sleep were investigated in a sample of community-dwelled adults.

Methods: Forty-nine subjects met the inclusion criteria for analyses and were assessed at two time-points (baseline (T1) and follow-up (T2), average T1-T2-interval = 215 days). Serum cytokine measures included the pro-inflammatory cytokines interleukin (IL)-2, IL-12, IFN-γ and TNF-α, the anti-inflammatory cytokines IL-4, IL-5, IL-10 and IL-13 and the granulocyte-macrophage colony-stimulating factor (GM-CSF); anthropometrics were assessed *via* physical examination, depressiveness was assessed *via* Beck Depression Inventory (BDI)2, parameters of physical activity (steps, METs) and sleep (night/total sleep duration) were measured *via* a 1-week actigraphy.

Results: Correlation analyses showed low-to moderate significant relationships between the majority of cytokines and the BDI2 at T1, positive correlation with weight and BMI at T1 and T2, and negative correlations with the number of steps and METs at T2 and T2. Regression analyses for T1 revealed that the BDI2 score was the best positive predictor for the concentrations of all nine cytokines, followed by the number of steps and the nightsleep duration as negative predictors. At T2, the amount of steps was found to be negatively associated with IL-4, IL5, IL-10, GM-CSF, IFN-γ, and TNF-α, whereas the BMI could significantly predict IL-12 and IL-13. The BDI2-score was not significantly

associated with any of the cytokines. No associations could be found between dynamics in cytokines from T1 and T2 and changes in any of the variables.

Discussion: The present results indicate an influence of physical activity, subjective well-being and body composition on inflammatory mediators. Since there was no standardized intervention targeting the independent variables between T1 and T2, no assumptions on causality can be drawn from the association results.

Keywords: cytokines, inflammation, obesity, depression, physical activity

INTRODUCTION

Cytokines are a category of heterogeneous peptides produced by various cells, such as macrophages, T lymphocytes, B lymphocytes and mast cells, which are critically involved in cell signaling and immune response. Previously, it could be demonstrated that both, subjects suffering from major depression and subjects with obesity show elevations in their cytokine profiles (1–5). This repeated finding leads to the assumption that both disorders are characterized by a low-grade inflammation which may be a common pathway that could explain the high comorbidity rates between the two disorders (6, 7). Concentrations in inflammatory cytokines may further relate to the degree of obesity (1, 8, 9), whereas results on the association of cytokines with the severity of depression or certain subtypes of depression are still conflicting (10–14). Whereas pharmaco-psychiatric treatment has not yet proven to have a consistent effect upon cytokine regulation that accompanies the therapeutic course (10, 15, 16), some non-pharmacological interventions, such as regular exercise, are effective in treating both depression and obesity and could have anti-inflammatory properties (17–19). Further, sleep properties, which are affected in depression and obesity as well as their related disorders like sleep apnea and fatigue, are discussed to interact with immune regulation (20, 21).

Although a lot of research has been performed to shed light on the multilateral facets of cytokines, and meta-analyses confirm certain assumptions [e.g. elevations of cytokines in depression (3, 4)], there are high variances of cytokine values within and between samples. The majority of investigations have been performed using a cross-sectional approach, and only few replicated the findings in the same sample or in a longitudinal design. Hence, the impact of different social, psychological and medical factors on cytokines and vice versa is yet far from clear (22).

To shed light on different factors that may be related to cytokine regulation, the associations between nine different pro- and anti-inflammatory cytokines and anthropometrics, mood states (depressiveness), physical activity, energy expenditure and parameters of sleep were examined in a sample of community-dwelled adults at two different time points. We further aimed to investigate if dynamics in these parameters between the two measurements were associated with changes in cytokine levels.

MATERIALS AND METHODS

For the present study, data were used from the OBDEP subproject (Obesity and Depression: pathogenic role of sleep and wakefulness regulation, motor activity level and neurochemical aspects), which was conducted at the Department of Psychiatry and Psychotherapy of the University Hospital Leipzig within the framework of the Integrated Research and Treatment Center for Adiposity Diseases Leipzig (IFB Adiposity). The study was approved by the Leipzig University Ethics Committee (#015–10–18012009). All participants were aged 18 to 70 years and gave written informed consent. The OBDEP project comprised of two assessment points (baseline and follow-up), in which participants were requested to fill out questionnaires related to mood and diet (including the German version of the revised Beck Depression Inventory, second edition (BDI2) (23, 24), to give a blood sample for cytokine analysis and wore an actigraphic device for one week to assess physical activity and sleep (see below). No systematic intervention took place between the two assessments, apart from many of the obese participants receiving information on healthy nutrition and physical activity while waiting for an appointment for a stomach reduction. Data from the baseline assessment has been published elsewhere (1, 2, 11, 25, 26), while results from the follow-up assessment have not yet been presented.

Sample

In total, 304 participants had been recruited for the OBDEP project either from the outpatient clinic of the IFB Adiposity, from the Department of Psychiatry and Psychotherapy of the University Hospital Leipzig and *via* announcements [details on the recruitment and pre-screening process can be found elsewhere (1, 2)]. Eligible participants were then invited to the study center, where inclusion criteria were assessed in more detail by a study physician. Assessments for current and past history of physical and mental health problems as well as current medication were performed using standardized forms. Reasons for non-inclusion were acute or chronic infections, current medication with a recognized major impact on the immune system, current psychiatric medication, psychiatric and neurological disorders apart from depression, and a history of head injury with loss of consciousness exceeding 1 h.

Participants included into the OBDEP project underwent a full physical examination (including blood sampling) by qualified healthcare professionals. Weight [kg] was determined

in underwear and without shoes using a digital scale calibrated and standardized using a weight of known mass. Height [cm] was recorded using a stadiometer with participants standing on a flat surface at a right angle to the vertical board of the stadiometer. BMI [kg/m^2] was defined as body weight [kg] divided by the square of height [m^2].

For the present study, we selected all participants who had partaken in the optional follow-up assessment (N=107). Since only 35% of the original sample took part in the follow-up assessment we compared those subjects with the non-participants. There were no statistical differences concerning sex (62% versus 66% females, p=0.401), but those subjects completing the follow-up were significantly older (41.5 versus 38.2 years, p=0.032) and had a lower T1-BMI (34.0 versus 37.2, p=0.027). We then excluded those subjects for whom at least one of the following exclusion criteria was present: a) retest interval < 150 or > 300 days (N=4); b) cytokine levels had not been measured at both assessments (N=6); c) missing BMI data (N=5); d) missing data in BDI2 questionnaires (N=10) or e) actigraphy data not fulfilling analysis quality criteria (see below) (N=36). In addition, two subjects were excluded post-hoc from the final sample because the levels of the majority of cytokines were rated as extreme outliers (> 2 standard deviations compared to the overall group average, which could indicate a current illness). In total, 49 participants were included in the subsequent analyses. When comparing the included with the excluded participants, there was a trend for differences concerning sex (53% versus 69% females, p=.092), but no statistical differences in age (41.7 versus 41.4 years, p=.925) or T1-BMI (33.4 versus 34.5, p=.607).

Cytokine Measurements

Immediately after blood drawing, serum probes were centrifuged at 3,000 rpm for 10 min. The supernatant was aliquoted and stored in non-absorbing polypropylene tubes of 300 ml, which were subsequently snap-frozen in liquid N2 and stored in freezers at −80°C until further measurement. Cytokines were measured at the Institute of Laboratory Medicine of the University Hospital of the Ludwig-Maximilians-University Munich using the Bio-Plex Pro™ human cytokine Th1/Th2 immunoassay (Bio Rad, Germany), a 96-well kit that includes coupled magnetic beads and detection antibodies. This multiplex assay detects pro-inflammatory IL-2, IL-12, GM-CSF, IFN-γ, TNF-α and anti-inflammatory IL-4, IL-5, IL-10, IL-13. The intraassay coefficient of variation (CV) for cytokines was between 1.6% and 3.8%. If cytokine levels were lower than the detection cut-off of the immunoassay (< OOR), there were assigned a value of 0.

Actigraphy

On both occasions (baseline and follow-up), a 1-week actigraphy recording was performed, using the SenseWear® Pro 3 actigraph (SWA; BodyMedia Inc.; Pittsburgh, Pennsylvania). The SWA is attached to the upper right arm and records 2-axis body acceleration, skin temperature, heat flux and galvanic skin response. Furthermore, SWA detects periods in which it is not worn (off-arm periods). Actigraphic data were analyzed using SenseWear® Professional Software Version 7 (BodyMedia Inc.). Based on validated proprietary scoring algorithms included in the software, each minute of the recorded data is scored as laying down [yes/no] or sleep [yes/no]. Furthermore, amount of steps and MET levels are given for each 1-min timeframe. Several studies have demonstrated that the SWA provides accurate estimates of energy expenditure during rest and daily life activities, comparable to the gold standards of indirect calorimetry and doubly labeled water (27–33).

Scored data were entered into a customized Excel-Template for further data preparation. Participants had kept a sleep and activity diary throughout the recording period and according to the respective information provided by the participants, nightsleep intervals (NSI) was estimated (ranging from first minute to last minute scored as laying down in close proximity to the noted bed times within the sleep diary). Accordingly, the daytime interval (DTI) was determined as duration between two consecutive NSI. Sleep duration (SD) was calculated for each NSI and each DTI (=sum of minutes scored as sleep within the NSI or DTI). Total sleep duration (TSD) was calculated by adding night sleep duration within one NSI (e.g. nightsleep from Friday to Saturday) with daytime sleep duration of the following DTI (e.g. daysleep on Saturday). In addition, for each DTI, the variables *steps* (=sum of steps per 1 min-segment) and *METs* (=mean of all MET values per 1 min-segment) were calculated. Afterwards daily values of these four measures were averaged to obtain mean values for the total week. Datasets were only included in the analysis if the averaged values comprised of at least 4 NSI/DTI-cycles, respectively, with at least one NSI/DTI-cycle during the weekend.

Statistical Analysis

The Kolmogorov-Smirnov (K-S) test was used to examine whether the cytokine levels were normally distributed or not. Therefore, in a first step, outliers cases (± 2 standard deviations) were detected and removed from the respective analysis. Since most outliers (e.g. 9 out of 10 outliers at T2) could be attributed to two specific participants, these two participants were post-hoc excluded from all analyses. After outlier removal, the K-S test still attested for non-Gaussian distribution, therefore cytokine values were normalized using a square root (SQR) or logarithmic (LN) transformation. Based on K-S results, the best transformation was determined for each cytokine level (SQR transformation: IL-2, IL-4, IL-10, IL-12, IFN-γ, TNF-α; LN transformation: IL-5, IL-13, GM-CSF).

The association between cytokine levels (response variables) and anthropometric, psychometric and actigraphic parameters (independent variables) were tested using multiple linear regression (MLR) models. The initial MLR models included all independent variables. A stepwise backwards linear regression method was used: the variables which contributed least to the aforementioned model had been removed in subsequent steps until only statistically significant variables remained ($p < 0.05$). In order to assess multicollinearity of the independent variables, tolerance statistics like the variance inflating factor were also calculated.

Changes between baseline (T1) and follow-up (T2) were quantified by calculation difference scores (Δ=T2-T1). The K-S test showed a Gaussian distribution in all cytokine change scores but Δ IL-5. This non-Gaussian distribution could be attributed to one outlier case which was therefore excluded from the respective MLR analysis.

For correlation analyses of cytokine levels and independent variables, Spearman rank correlation coefficients were calculated, since most independent variables also exhibited a non-Gaussian distribution. Therefore, non-transformed cytokine levels were used for all correlation analyses. For similar reasons, differences between T1 and T2 values were tested using the Wilcoxon test. All analyses were conducted by using the statistical software SPSS 23 (IBM SPSS Statistics for Windows, version 23 (IBM Corp., Armonk, N.Y., USA)). Also, the significance level was taken to be α=0.05 (two-tailed).

RESULTS

Forty-nine participants were included in the final analyses in this study (N=23 males (46.9%), mean age 41.64 years (SD=11.8 years, range 22–62 years). On average, the follow-up assessment (T2) of the included participants was performed 215.76 days (SD=27.24, range 170–288) after their baseline assessment (T1).

Results concerning the anthropometrics (weight, BMI), psychometric test (BDI2 score), and actigraphy results (night sleep duration, total sleep duration, as well as number of steps and average METs during the wake phase) measured at T1 and T2 are depicted in **Table 1A**. On group level, the Wilcoxon Test revealed no significant differences between T1 and T2 in all the possible predictors for cytokine changes. Cytokine levels at T1 and T2 are shown in **Table 1B**. On average, there was a numerical decrease in serum levels of all cytokines, but according to the Wilcoxon test, this decrease was only significant for IL-12, with a trend for IL-2 and IL-13.

Correlations between cytokine levels and BMI, BDI2 score and actigraphy parameters at T1 are depicted in **Table 2A**. Weight showed significant but weak associations with IL-2, IL-10, IL-12 and IL-13. BMI had still weak but slightly stronger significant associations with IL-2, IL-10, IL-12, IL-13 and also TNF-α. The BDI2-scores were positively associated with all cytokine levels except IL-4 and IL-5. Steps had moderate, negative associations with all cytokine levels apart from the growth factor GM-CSF. METs only showed significant, moderate negative associations with IL-2, IL-10, IL-12, and IL-13. For night and total sleep duration, none of the negative associations reached significance.

Correlations between cytokine levels and BMI, BDI2 score and actigraphy parameters at T2 are depicted in **Table 2B**. Weight and BMI showed significant and weak associations with all cytokines that were stronger in all cases than what had been found at T1. On the other hand, steps and METs showed significant negative associations with all cytokine levels that were

TABLE 1A | Comparison of baseline (T1) and follow-up (T2) values of anthropometrics, psychometric and actigraphic parameters.

	Baseline (T1)				Follow up (T2)				Wilcoxon
	Mean	SD	Min	Max	Mean	SD	Min	Max	Z/p
Weight (in kg)	99.2	36.25	52	179	97.4	33.57	53	170	–0.527/0.598
BMI (kg/m^2)	33.4	11.15	18.3	61.4	32.7	10.31	18.9	61.3	–0.954/0.340
BDI2-Score	6.4	6.68	0	25	6.7	8.06	0	31	–0.350/0.726
Nightsleep Duration (hh:mm)	5:53	1:03	2:53	7:56	6:01	1:02	3:51	7:45	–0.741/0.459
Total Sleep Duration (hh:mm)	6:18	1:08	3:13	8:23	6:23	1:02	4:00	8:13	–0.453/0.651
Steps	10087.1	4891.49	1787.6	21407.3	9725.7	4259.84	2355.5	18357.67	–0.831/0.406
METs	1.68	0.56	0.83	3.02	1:62	0.42	0.93	2.54	–1.457/0.145

TABLE 1B | Comparison of cytokine levels at baseline (T1) and follow-up (T2).

	Baseline (T1)				Follow up (T2)				Wilcoxon
	Mean	SD	Min	Max	Mean	SD	Min	Max	Z/p
Pro-inflammatory									
IL-2 [pg/mL]	7.16	7.11	0.00	25.96	5.76	5.62	0.00	18.19	–1.885/0.059
IL-12 [pg/mL]	10.33	8.33	0.00	40.90	8.79	6.79	0.00	31.96	**–2.072/0.038**
GM-CSF [pg/mL]	38.03	20.91	3.83	97.78	35.02	16.05	9.10	65.55	–1.323/0.186
IFN-γ [pg/mL]	121.19	64.64	0.00	280.09	112.85	57.15	19.44	269.73	–1.169/0.242
TNF-α [pg/mL]	31.19	18.73	3.71	84.87	28.21	14.78	6.34	64.95	–1.323/0.186
Anti-inflammatory									
IL-4 [pg/mL]	4.56	2.57	0.09	10.32	4.13	2.10	0.79	9.84	–1.263/0.206
IL-10 [pg/mL]	4.02	3.09	0.00	18.03	3.60	3.79	0.00	18.22	–0.850/0.395
IL-5 [pg/mL]	3.02	2.53	0.00	13.10	2.56	1.62	0.00	6.87	–1.550/0.121
IL-13 [pg/mL]	5.55	4.98	0.00	18.16	4.59	3.87	0.00	13.90	–1.707/0.088

In bold: p > 0.05.

TABLE 2A | Spearman Rank correlation coefficients between cytokine levels and antropometric, psychometric and actigraphic parameters at T1.

	Pro-inflammatory					Anti-inflammatory			
	IL-2	**IL-12**	**GM-CSF**	**IFN-γ**	**TNF-α**	**IL-4**	**IL-5**	**IL-10**	**IL-13**
Weight	0.326*	0.387**	0.224	0.273	0.278	0.248	0.277	0.371*	0.387**
BMI	0.339*	0.423**	0.236	0.277	0.289*	0.245	0.277	0.409**	0.423**
BDI2 Score	0.313*	0.330*	0.322*	0.311*	0.348*	0.281	0.278	0.334*	0.330*
Night Sleep Duration	–0.251	–0.161	–0.199	–0.227	–0.223	–0.214	–0.197	–0.260	–0.161
Total Sleep Duration	–0.244	–0.171	–0.232	–0.260	–0.219	–0.218	–0.184	–0.260	–0.171
Steps	–0.375**	–0.317*	–0.264	–0.298*	–0.350*	–0.299*	–0.305*	–0.388**	–0.317*
METs	–0.330*	–0.307*	–0.203	–0.279	–0.273	–0.252	–0.192	–0.375**	–0.307*

*Annotations: * = $p < 0.05$; ** = $p < 0.01$.*

TABLE 2B | Spearman Rank correlation coefficients between cytokine levels and antropometric, psychometric and actigraphic parameters at T2.

	Pro-inflammatory					Anti-inflammatory			
	IL-2	**IL-12**	**GM-CSF**	**IFN-γ**	**TNF-α**	**IL-4**	**IL-5**	**IL-10**	**IL-13**
Weight	0.484**	0.494**	0.348*	0.387**	0.415**	0.373**	0.394**	0.431**	0.407**
BMI	0.475**	0.479**	0.352*	0.377**	0.402**	0.361*	0.363*	0.428**	0.427**
BDI2 Score	0.075	0.154	0.029	0.025	0.058	–0.014	0.110	0.119	–0.007
Night Sleep Duration	–0.027	–0.118	0.006	–0.038	–0.030	–0.057	–0.037	–0.086	–0.092
Total Sleep Duration	–0.027	–0.094	–0.013	–0.062	–0.023	–0.072	–0.056	–0.083	–0.022
Steps	–0.517**	–0.408**	–0.438**	–0.478**	–0.497**	–0.453**	–0.486**	–0.499**	–0.317*
METs	–0.508**	–0.442**	–0.413**	–0.483**	–0.471**	–0.447**	–0.432**	–0.459**	–0.348*

*Annotations: * = $p < 0.05$; ** = $p < 0.01$.*

TABLE 2C | Spearman Rank correlation coefficients between difference values (T2-T1) in cytokine levels and antropometric, psychometric and actigraphic parameters.

	Pro-inflammatory					Anti-inflammatory			
	Δ IL-2	**Δ IL-12**	**Δ GM-CSF**	**Δ IFN-γ**	**Δ TNF-α**	**Δ IL-4**	**Δ IL-5**	**Δ IL-10**	**Δ IL-13**
Δ Weight	–0.153	–0.124	–0.077	–0.035	–0.096	–0.030	–0.051	–0.113	–0.201
Δ BMI	–0.103	–0.061	–0.038	–0.003	–0.048	0.023	0.017	–0.050	–0.122
Δ BDI2 Score	–0.021	–0.073	0.000	0.004	0.040	–0.016	–0.009	–0.066	–0.069
Δ Night Sleep Duration	–0.155	–0.234	–0.219	–0.222	–0.284*	–0.236	–0.209	–0.072	–0.094
Δ Total Sleep Duration	–0.162	–0.262	–0.205	–0.245	–0.267	–0.210	–0.208	–0.058	–0.108
Δ Steps	0.066	0.177	0.060	–0.003	–0.039	0.077	0.045	0.004	0.184
Δ METs	0.079	0.184	0.045	0.022	–0.032	0.067	0.031	0.086	0.190

*Annotations: * = $p < 0.05$; ** = $p < 0.01$.*

also stronger than those that had been found at T1. No associations with any cytokine level were found for BDI2, night and total sleep duration. Steps had moderate, negative associations with all cytokine levels except for GM-CSF. METs showed moderate, significant, negative associations with IL-2, IL-10, IL-12, and IL-13.

When changes in cytokine levels between T1 and T2 were correlated with changes in the independent variables (see **Table 2C**), none of the associations reached significance except for a weak negative association between changes in night sleep duration and changes in levels of TNF-α.

The relationship between cytokine levels and anthropometric, psychometric and actigraphic parameters (independent variables) were tested using multiple linear regression (MLR) models. As expected, several of the independent variables highly correlated (weight/BMI: $rho_{T1} = 0.954$, $rho_{T2} = 0.950$, $rho_{\Delta}=0.961$; night/total sleep duration: $rho_{T1} = 0.934$, $rho_{T2} = 0.908$, $rho_{\Delta}=0.899$; steps/METs: $rho_{T1} = 0.861$, $rho_{T2} = 0.821$, $rho_{\Delta}=0.659$). To avoid multicollinearity, only 4 independent variables (BMI, BDI2 scores, night sleep duration, and step counts during wake phase) were included in the initial MLR models.

Findings regarding initial as well as final MLR models for cytokine levels at baseline (T1) are summarized in **Table 3A**. The final MLR models demonstrated a significantly positive association of the BDI2 sum scores with cytokine serum levels for IL-2 (p=0.049), IL-4 (p=0.036), IL-5 (p=0.039), Il-12 (p=0.013), Il-13 (p=0.005), GM-CSF (p=0.022), INF-γ (p=0.024) and TNF-α (p=0.031). Moreover, there was a significantly negative association between the number of steps with cytokine levels regarding IL-2 (p=0.031), IL-10 (p=0.023) and TNF-α (p=0.029) and a significantly negative association of night sleep duration with IL-12 levels (p=0.034).

Results of the (initial and final) MLR models for cytokine levels at T2 are presented in **Table 3B**. The final MLR models showed a significant negative association of number of steps during the wake phase with cytokine serum levels for IL-2 (p <

TABLE 3A | Regression coefficients of cytokine levels on the predictor variables recorded at baseline (T1).

Predictors	Primary Model (Include)					Final Model (stepwise backwards)				
	Beta	CI⁻	CI⁺	P-Value	Stand. Coeff.	Beta	CI⁻	CI⁺	P-Value	Stand. Coeff.
IL-2 (SQR-trans.)	Model 1: N = 49/R^2 =.263/corr. R^2 = 0.196					Model 3: R^2 = 0.216/corr. R^2 = 0.182				
BMI	–0.011	–0.059	0.037	0.643	–0.097					
BDI2-Score	0.057	–0.004	0.117	0.065	0.297	0.053	0.000	0.105	0.049	0.275
Nightsleep Duration	–0.275	–0.607	0.056	0.101	–0.228					
Steps	–8.2E-5	–1.8E-4	1.0E-4	0.081	–0.315	–7.9E-5	–1.5E-4	–0.8E-5	0.031	–0.304
IL-12 (SQR-trans.)	Model 1: N = 49/R^2 = 0.224/corr. R^2 = 0.153					Model 3: R^2 = 0.222/corr. R^2 = 0.188				
BMI	–0.001	–0.048	0.047	0.982	–0.005					
BDI2-Score	0.062	0.001	0.122	0.046	0.331	0.063	0.014	0.112	0.013	0.340
Nightsleep Duration	–0.330	–0.661	0.001	0.051	–0.280	–0.337	–0.647	–0.027	0.034	–0.287
Steps	–1.0E-5	–1.0E-4	8.2E-5	0.821	–0.041					
GMCSF (LGn-trans.)	Model 1: N = 49/R^2 = 0.193/corr. R^2 = 0.119					Model 4: R^2 = 0.107/corr. R^2 = 0.088				
BMI	–0.011	–0.035	0.012	0.342	–0.209					
BDI2-Score	0.030	0.000	0.060	0.049	0.333	0.030	0.005	0.055	0.022	0.327
Nightsleep Duration	–0.110	–0.275	0.055	0.185	–0.192					
Steps	–3.7E-5			0.112	–0.298					
IFN-γ (SQR-trans.)	Model 1: N = 49/R^2 = 0.222/corr. R^2 = 0.151					Model 3: R^2 = 0.177/corr. R^2 = 0.142				
BMI	–0.037	–0.158	0.038	0.539	–0.132					
BDI2-Score	0.146	–0.007	0.298	0.060	0.311	0.148	0.020	0.275	0.024	0.315
Nightsleep Duration	–0.666	–1.500	0.168	0.114	–0.225	–0.717	–1.520	0.086	0.079	–0.242
Steps	–1.7E-4	–4.1E-4	5.6E-5	0.134	–0.276					
TNF-α (SQR-trans.)	Model 1: N = 49/R^2 = 0.288/corr. R^2 = 0.224					Model 3: R^2 = 0.233/corr. R^2 = 0.200				
BMI	–0.024	–0.085	0.037	0.429	–0.163					
BDI2-Score	0.086	0.009	0.163	0.030	0.346	0.074	0.007	0.141	0.031	0.300
Nightsleep Duration	–0.375	–0.797	0.046	0.080	–0.240					
Steps	–1.2E-4	–2.4E-4	9.9E-8	0.050	–0.348	–1.0E-4	–1.9E-4	–1.1E-5	0.029	–0.303
IL-4 (SQR-trans.)	Model 1: N = 49/R^2 = 0.223/corr. R^2 = 0.152					Model 3: R^2 = 0.175/corr. R^2 = 0.139				
BMI	–0.008	–0.029	0.014	0.478	–0.152					
BDI2-Score	0.024	–0.002	0.051	0.074	0.295	0.024	0.002	0.047	0.036	0.292
Nightsleep Duration	–0.130	–0.278	0.017	0.082	–0.249	–0.138	–0.281	0.004	0.057	–0.264
Steps	–3.3E-5	–7.4E-5	0.8E-5	0.114	–0.291					
IL-5 (LGn-trans.)	Model 1: N = 49/R^2 = 0.151/corr. R^2 = 0.073					Model 4: R^2 = 0.087/corr. R^2 = 0.068				
BMI	–0.005	–0.030	0.019	0.659	–0.099					
BDI2-Score	0.025	–0.006	0.056	0.110	0.275	0.027	0.001	0.053	0.039	0.295
Nightsleep Duration	–0.124	–0.294	0.046	0.148	–0.215					
Steps	–2.1E-5			0.383	–0.166					
IL-10 (SQR-trans.)	Model 1: N = 49/R^2 = 0.245/corr. R^2 = 0.176					Model 3: R^2 = 0.205/corr. R^2 = 0.171				
BMI	–0.007	–0.042	0.028	0.677	–0.088					
BDI2-Score	0.036	–0.009	0.080	0.113	0.257	0.033	–0.005	0.071	0.090	0.238
Nightsleep Duration	–0.182	–0.426	0.061	0.138	–0.208					
Steps	–6.3E-5	–1.3E-4	0.5E-5	0.068	–0.333	–6.1E-5	–1.1E-4	–0.9E-5	0.023	–0.324
IL-13 (LGn-trans.)	Model 1: N = 49/R^2 = 0.217/corr. R^2 = 0.146					Model 4: R^2 = 0.155/corr. R^2 = 0.137				
BMI	0.007	–0.027	0.040	0.693	0.085					
BDI2-Score	0.037	–0.004	0.079	0.078	0.292	0.050	0.016	0.085	0.005	0.393
Nightsleep Duration	–0.116	–0.345	0.113	0.314	–0.143					
Steps	–2.2E-5	–8.6E-5	4.2E-5	0.490	–0.126					

0.001), IL-4 (p=0.002), IL-5 (p=0.001), IL-10 (p < 0.001), GM-CSF (p=0.003), IFN-γ (p=0.002) and TNF-α (p < 0.001). A significant positive association with the BMI was found for IL-12 (p=0.009) and IL-13 (p=0.007).

MLR models for changes in cytokine levels (T2–T1) are presented in **Table 3C**. Out of all the independent variables, only changes in night sleep duration seemed to be somewhat negatively associated with changes in cytokine levels, however, this effect showed only a statistical tendency in the final models for IL-4 (p=0.100), IFN-γ (p=0.098) and TNF-α (p=0.085).

DISCUSSION

In this investigation, we examined the impact of the four factors BMI, depressiveness, physical activity, and sleep duration on the

TABLE 3B | Regression coefficients of cytokine levels on the predictor variables recorded at follow-up (T2).

Predictors	Primary Model (Include)					Final Model (stepwise backwards)				
	Beta	CI⁻	CI⁺	P-Value	Stand. Coeff.	Beta	CI⁻	CI⁺	P-Value	Stand. Coeff.
IL-2 (SQR-trans.)	Model 1: N = 49/R^2 = 0.340/corr. R^2 = 0.281					Model 3: R^2 = 0.314/corr. R^2 = 0.284				
BMI	0.036	–0.001	0.074	0.059	0.345	0.029	–0.003	0.061	0.079	0.271
BDI2-Score	–0.008	–0.047	0.031	0.677	–0.060					
Nightsleep Duration	0.169	–0.103	0.440	0.216	–0.162					
Steps	9.2E-5	–1.7E-4	–1.1E-5	0.027	–0.359	–9.1E-5	–1.7E-4	–1.3E-5	< 0.001	–0.356
IL-12 (SQR-trans.)	Model 1: N = 49/R^2 = 0.170/corr. R^2 = 0.095					Model 4: R^2 = 0.137/corr. R^2 = 0.118				
BMI	0.019	–0.022	0.060	0.355	0.187	0.038	0.010	0.065	0.009	0.370
BDI2-Score	0.015	0.027	0.057	0.483	0.113					
Nightsleep Duration	0.000	–0.293	0.294	0.999	0.000					
Steps	–5.5E-5	–1.4E-4	3.3E-5	0.213	–0.223					
GM-CSF (LN-trans.)	Model 1: N = 49/R^2 = 0.198/corr. R^2 = 0.169					Model 4: R^2 = 0.169/corr. R^2 = 0.151				
BMI	0.008	–0.010	0.026	0.394	0.169					
BDI2-Score	–0.007	–0.025	0.012	0.455	–0.118					
Nightsleep Duration	0.060	–0.069	0.189	0.355	0.133					
Steps	–3.9E-5	–7.8E-5	–7.9E-7	0.046	–0.356	–4.528	–7.5E-5	–1.6E-5	0.003	–0.411
IFN-γ (SQR-trans.)	Model 1: N = 49/R^2 = 0.204/corr. R^2 = 0.132					Model 4: R^2 = 0.189/corr. R^2 = 0.171				
BMI	0.042	–0.058	0.143	0.401	0.166					
BDI2-Score	–0.30	–0.133	0.074	0.566	–0.091					
Nightsleep Duration	0.149	–0.575	0.873	0.681	0.059					
Steps	–2.2E-4	–4.4E-4	–0.8E-5	0.043	–0.360	–2.7E-4	–4.3E-4	–1.1E-4	0.002	–0.434
TNF-α (SQR-trans.)	Model 1: N = 49/R^2 = 0.283/corr. R^2 = 0.217					Model 4: R^2 = 0.250/corr. R^2 = 0.234				
BMI	0.028	–0.021	0.077	0.261	0.211					
BDI2-Score	–0.016	–0.067	0.034	0.512	–0.098					
Nightsleep Duration	0.171	–0.180	0.522	0.331	0.132					
Steps	–1.3E-4	–2.4E-4	–2.8E-5	0.014	–0.419	–1.5E-4	–2.4E-4	–7.8E-5	< 0.001	–0.500
IL-4 (SQR-trans.)	Model 1: N = 49/R^2 = 0.204/corr. R^2 = 0.132					Model 4: R^2 = 0.185/corr. R^2 = 0.168				
BMI	0.007	–0.010	0.024	0.410	0.163					
BDI2-Score	–0.006	–0.024	0.011	0.487	–0.110					
Nightsleep Duration	0.036	–0.087	0.159	0.560	0.083					
Steps	–3.9E-5	–7.5E-5	–0.2E-5	0.040	–0.366	–4.5E-5	–7.3E-5	–1.7E-5	0.002	–0.430
IL-5 (LN-trans.)	Model 1: N = 49/R^2 = 0.220/corr. R^2 = 0.149					Model 4: R^2 = 0.205/corr. R^2 = 0.188				
BMI	0.005	–0.013	0.023	0.589	0.105					
BDI2-Score	0.000	–0.019	0.018	0.965	–0.007					
Nightsleep Duration	0.052	–0.078	0.181	0.424	0.113					
Steps	–4.7E-5	–8.6E-5	–0.9E-5	0.018	–0.420	–5.1E-5	–8.0E-5	–2.1E-5	0.001	–0.453
IL-10 (SQR-trans.)	Model 1: N = 49/R^2 = 0.251/corr. R^2 = 0.183					Model 4: R^2 = 0.236/corr. R^2 = 0.220				
BMI	0.015	–0.017	0.046	0.352	0.178					
BDI2-Score	–0.006	–0.038	0.026	0.716	–0.056					
Nightsleep Duration	0.024	–0.200	0.249	0.828	0.030					
Steps	–7.8E-5	–1.5E-4	–1.1E-5	0.023	–0.394	–9.6E-5	–1.5E-4	–4.5E-5	< 0.001	–0.486
IL-13 (LN-trans.)	Model 1: N = 49/R^2 = 0.178/corr. R^2 = 0.103					Model 4: R^2 = 0.145/corr. R^2 = 0.127				
BMI	0.038	0.006	0.070	0.021	0.475	0.031	0.009	0.052	0.007	0.381
BDI2-Score	–0.021	–0.054	0.012	0.210	–0.202					
Nightsleep Duration	0.004	–0.226	0.234	0.971	0.005					
Steps	–4.6E-7	–6.9E-5	6.8E-5	0.989	–0.002					

serum levels of nine different pro- and anti-inflammatory cytokines in a sample of 49 community-dwelled subjects at two different time points. Further, we investigated if dynamics in any of the variables between the two time points were accountable for changes in cytokine levels.

Regarding the correlation analyses, the majority of cytokines were found to weakly correlate with the BMI and weight in a positive direction at both time points. The number of steps and METs correlated in a negative direction at both T1 and T2. The results for the BDI2, however, were inconsistent with significant weak correlations at T1 which were absent at T2. In the regression analyses, the physical activity could explain IL-2, IL-10, and TNF-α at T1 and was negatively involved in all cytokines except IL-12 and IL-13 at T2. On the other hand, the mood state assessed with the BDI2 showed a disparity between the two cross-sectional time points, as the significant positive association

TABLE 3C | Regression coefficients of changes in cytokine levels (T2-T1) on the changes of predictor variables.

Psredictor	Primary Model (Include)					Final Model (stepwise backwards)				
	Beta	CI⁻	CI⁺	P-Value	Stand. Coeff.	Beta	CI⁻	CI⁺	P-Value	Stand. Coeff.
Δ IL–2	Model 1: N = 49/R^2 = 0.045/corr. R^2 = –0.041					Model 5: R^2 = 0.000/corr. R^2 = 0.000				
Δ BMI	–0.326	–1.014	0.362	0.345	–0.147					
Δ BDI2-Score	0.029	–0.203	0.260	0.802	0.038					
Δ Night SD	–0.900	–2.489	0.689	0.260	–0.174					
Δ Steps	–1.5E-4	–0.001	3.1E-4	0.517	–0.099					
Δ IL-12	Model 1: N = 49/R^2 = 0.045/corr. R^2 = –0.042					Model 5: R^2 = 0.000/corr. R^2 = 0.000				
Δ BMI	–0.029	–0.729	0.671	0.934	–0.013					
Δ BDI2-Score	0.006	–0.230	0.241	0.962	0.007					
Δ Night SD	–1.027	–2.644	0.591	0.208	–0.195					
Δ Steps	1.1E-4	–3.7E-4	0.001	0.650	0.069					
Δ GM-CSF	Model 1: N = 49/R^2 = 0.056/corr. R^2 = –0.029					Model 5: R^2 = 0.000/corr. R^2 = 0.000				
Δ BMI	–0.419	–2.727	1.889	0.716	–0.056					
Δ BDI2-Score	0.078	–0.699	0.855	0.841	0.030					
Δ Night SD	–4.194	–9.525	1.138	0.120	–0.240					
Δ Steps	–2.0E-4	–0.002	0.001	0.799	–0.039					
Δ IFN-γ	Model 1: N = 49/R^2 = 0.064/corr. R^2 = –0.021					Model 4: R^2 = 0.057/corr. R^2 = 0.037				
Δ BMI	–0.116	–7.485	7.253	0.975	–0.005					
Δ BDI2-Score	0.042	–2.439	2.552	0.973	0.005					
Δ Night SD	–13.859	–30.882	3.164	0.108	–0.247	–13.371	–29.327	2.586	0.098	–0.239
Δ Steps	–0.001	–0.006	0.004	0.571	–0.086					
Δ TNF-α	Model 1: N = 48/R^2 = 0.091/corr. R^2 = 0.009					Model 4: R^2 = 0.062/corr. R^2 = 0.042				
Δ BMI	–0.557	–2.523	1.409	0.571	–0.086					
Δ BDI2-Score	0.144	–0.518	0.806	0.663	0.064					
Δ Night SD	–4.153	–8.695	0.389	0.072	–0.274	–3.768	–8.078	0.542	0.085	–0.248
Δ Steps	–0.001	–0.002	0.001	0.322	–0.148					
Δ IL-4	Model 1: N = 49/R^2 = 0.061/corr. R^2 = –0.025					Model 4: R^2 = 0.057/corr. R^2 = 0.037				
Δ BMI	–0.054	–0.354	0.246	0.720	–0.055					
Δ BDI2-Score	0.004	–0.097	0.105	0.935	0.012					
Δ Night SD	–0.573	–1.266	0.120	0.102	–0.252	–0.541	–1.190	0.107	0.100	–0.238
Δ Steps	–2.8E-5	–2.3E-4	1.7E-4	0.779	–0.042					
Δ IL-5	Model 1: N = 48/R^2 = 0.024/corr. R^2 = –0.067					Model 5: R^2 = 0.000/corr. R^2 = 0.000				
Δ BMI	–0.012	–0.206	0.182	0.904	–0.019					
Δ BDI2-Score	0.003	–0.062	0.068	0.929	0.014					
Δ Night SD	–0.201	–0.649	0.247	0.370	–0.141					
Δ Steps	–3.4E-5	–1.7E-4	1.0E-4	0.616	–0.078					
Δ IL-10	Model 1: N = 49/R^2 = 0.016/corr. R^2 = –0.073					Model 5: R^2 = 0.000/corr. R^2 = 0.000				
Δ BMI	–0.002	–0.371	0.367	0.992	–0.002					
Δ BDI2-Score	0.004	–0.120	0.128	0.948	0.010					
Δ Night SD	–0.288	–1.140	0.564	0.500	–0.105					
Δ Steps	–6.3E-5	–3.1E-4	1.9E-4	0.614	–0.078					
Δ IL-13	Model 1: N = 49/R^2 = 0.032/corr. R^2 = –0.056					Model 5: R^2 = 0.000/corr. R^2 = 0.000				
Δ BMI	–0.096	–0.540	0.349	0.667	–0.067					
Δ BDI2-Score	0.030	–0.120	0.179	0.692	0.060					
Δ Night SD	–0.334	–1.361	0.693	0.516	–0.101					
Δ Steps	1.1E-4	–1.9E-4	4.1E-4	0.450	0.116					

with all cytokines at T1 could not be repeated for any of the cytokines in the follow-up assessment. For all analyses, the direction of the association of the parameters did not depend upon the pro-or anti-inflammatory characteristics of the cytokines. Concerning changes in any of the four factors included into the analyses, none was found associated with dynamics in cytokines from T1 and T2.

Although no conclusions on causality can be drawn from association studies, our results still support the assumption that physical activity could influence mediators of inflammation (17, 18) and validated previous findings of a disparity in cytokines between subjects with high versus low activity that was derived from the analyses on of the baseline assessment of the same study sample (1, 2). However, this negative association included both

cytokines with predominately pro-and anti-inflammatory properties and thus, our results do not portend that this immune-modulation is specifically anti-inflammatory. Training interventions also did not consistently show anti-inflammatory effects but rather a reduction in both anti-and pro-inflammatory cytokines (34). The effects of physical activity on the cytokine-modulating effects may result from its positive effect on the amount visceral adiposity as well as on the degree of adipose tissue inflammation, an increase of regulatory T cells in the systemic circulation, an improvement of the gut barrier function resulting in reduced endotoxaemia as well as the reduction of inflammation-associated comorbidities (17). In obesity, physical activity can decrease both the systemic and local synthesis and release of cytokines by inducing fatty acid oxidation of visceral adipose tissue, by reducing the immune cell infiltration in the adipose tissue and by reducing insulin resistance which prevents the migration of M1-macrophages (17, 35, 36). Further, training may increase the release of transcriptional factors (e.g. PGC1α) whose gene expression positively correlates with the reduction of pro-inflammatory proteins, such as IL-6 and TNF-α (37). On the other hand, the longitudinal observation could not reveal an association between changes in activity and cytokines. This may be due to the fact that the observational period did not go along with a training program whose intensity seems to be associated with the changes in cytokines (38, 39). Since the effect of training may mediate its effect *via* a reduction in adipose tissue, the missing changes in the BMI during the two points of measurement may further account for this missing association.

An association between the amount of adipose tissue and pro-inflammatory cytokine levels has been reported earlier (5, 40). We could confirm such an association at both time points. However, although there may be an association between the body composition and the cytokine profile, the backward regression analyses revealed that the BMI could only explain the levels of IL-12 and IL-13 at T2 in this group of obese and non-obese subjects. Since our previous investigation has shown that the association with anthropometrics is pronounced in samples of obese subjects and only to a lesser extend in non-obese subjects (1), we may conclude that the mix in subjects with and without obesity may, in part, account for the missing explanatory value of the BMI. Further, the assumption that obesity is simply related to a pro-inflammatory state needs to be questioned since the levels of anti-inflammatory cytokines were equally related to the BMI and weight. The increase in anti-inflammatory IL-10 with rising BMI for example may serve as a counteraction to the pro-inflammatory state, as IL-10 down-regulates TNF, IL-12 and GM-CSF (41).

Concerning the link between mood states and cytokines, the findings between the two times of measures are inconsistent. Since the BDI2, as well as the levels of cytokines, did not change relevantly between the two time points and we could not identify other factors that may have impeded the results, this connection, at least in mentally healthy subjects, has to remain open for debate. It needs to be kept in mind that the subjects included in this analysis did not suffer from a major depression but showed no or only little symptom load and for whom the plain BDI2 sum score may not be the suitable indicator. For community-dwelled samples without a clinical depression, previous results on the association between depressive symptoms and cytokine levels were also both positive (42) and negative (43). Potentially, it needs a certain threshold or symptom load of depression, which our sample did not exhibit, that leads to an immune activation, as a dependency of the cytokine levels from the depression severity and state has been found (44). Further, it may need a stimulation of the cytokine expression to correspond with the clinical picture (45), which the subjects in this sample did not experience. In clinical depression, findings were also disparate with a positive, negative or no relationship in depression (11, 13, 46). For clinical depression, which could also hold true for sub-clinical mood states, researchers have proposed a relationship between cytokines and certain symptoms or sub-groups of depression rather than a severity-dependence (12, 14, 42, 47).

Cytokines have previously been described to have sleep- or wakefulness-promoting effects (20, 21, 48), to relate to the presence of daily naps or daytime sleepiness (1, 20) and were seen to relate to the cerebral wakefulness regulation, i.e. the brain arousal (26). However, in this investigation in which the duration of sleep was measured objectively by actigraphy, as well as others (49), no such observation could consistently be found, which has to question this relationship.

A number of limitations have to be considered when interpreting our results: As a consequence of the applied quality criteria for our analysis, especially with regard to the actigraphy, the number of subjects included into the final analyses was relatively small to fully rule out type-II-errors, impeded sub-group-analyses as well as the inclusion of further parameters. The observational period varied between the subjects, which could interact with the results at T2 and the dynamics between the time points. Further, the subjects did not undergo a systematic interventional program and, thus, the changes in the psycho-biological parameters between the two time points varied distinctly. A group undergoing interventional programs concerning the factors could have added valuable information to the findings in this observational setting.

In conclusion, this investigation on the association between physical activity, subjective well-being, sleep parameters and body composition and inflammatory mediators revealed that predominately, the degree of physical activity is associated with certain cytokines. This could be relevant when focusing on anti-inflammatory treatment strategies. Since the results differed between the two assessments, although no specific intervention, but rather clinical management including a range of therapies in some patients had been performed in between, the conclusions for an association between the parameters cannot be considered as definite but give good reason for further research on this highly relevant field.

DATA AVAILABILITY STATEMENT

The datasets generated for this study are available on request to the corresponding author.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Leipzig University Ethics Committee. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

FS and CS designed the study. JM, FS, and HH recruited the participants. FS, CS, RM, and HH wrote the manuscript. LH and DT conducted the chemical analyses. CS, RM, and FS performed the statistical analyses. JM, RM, and CS revised the manuscript. All authors contributed to the article and approved the submitted version.

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Descriptions of Disordered Eating in German Psychiatric Textbooks, 1803–2017

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The most common eating disorders (EDs) according to DSM-5 are anorexia nervosa (AN), bulimia nervosa (BN) and binge eating disorder (BED). These disorders have received increasing attention in psychiatry due to rising prevalence and high morbidity and mortality. The diagnostic category "anorexia nervosa," introduced by Ernest-Charles Lasègue and William Gull in 1873, first appears a century later in a German textbook of psychiatry, authored by Gerd Huber in 1974. However, disordered eating behavior has been described and discussed in German psychiatric textbooks throughout the past 200 years. We reviewed content regarding eating disorder diagnoses but also descriptions of disordered eating behavior in general. As material, we carefully selected eighteen German-language textbooks of psychiatry across the period 1803–2017. Previously, in German psychiatry, disordered eating behaviors were seen as symptoms of depressive disorders, bipolar disorder or schizophrenia, or as manifestations of historical diagnoses no longer used by the majority of psychiatrists such as neurasthenia, hypochondria and hysteria. Interestingly, 19th and early 20th century psychiatrists like Kraepelin, Bumke, Hoff, Bleuler, and Jaspers reported symptom clusters such as food refusal and vomiting under these outdated diagnostic categories, whereas nowadays they are listed as core criteria for specific eating disorder subtypes. A wide range of medical conditions such as endocrinopathies, intestinal or brain lesions were also cited as causes of abnormal food intake and body weight. An additional consideration in the delayed adoption of eating disorder diagnoses in German psychiatry is that people with EDs are commonly treated in the specialty discipline of psychosomatic medicine, introduced in Germany after World War II, rather than in psychiatry. Viewed from today's perspective, the classification of disorders associated with disordered eating is continuously evolving. Major depressive disorder, schizophrenia and physical diseases have been enduringly associated with abnormal eating behavior and are listed as important differential diagnoses of EDs in DSM-5. Moreover, there are overlaps regarding the neurobiological basis and psychological and psychopharmacological therapies applied to all of these disorders.

Keywords: eating disorders, anorexia nervosa, bulimia nervosa, history of psychiatry, German psychiatry

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INTRODUCTION

The diagnosis and treatment of eating disorders (EDs) is an important domain of psychiatry. DSM-5 dedicates a separate chapter to eating disorder diagnoses. Anorexia nervosa (AN), bulimia nervosa (BN) and binge eating disorder (BED) are noted as the clinically most serious and prevalent conditions (1). Additional distinct EDs in DSM-5 include pica, rumination and avoidant-restrictive food intake disorder (ARFID). Prevalence rates of AN and BN are 10 and BED 2 times higher in women than men (1). One in six young women experience an ED (2). Life-time incidence is estimated up to 4% for AN and 2% each for BN and BED (3). Twelve-month prevalence is 0.4% for AN and 1–1.5% for BN. Twelve-month-prevalence of BED in adults is estimated at 0.8–1.6%. Mortality rates for AN at 5 to 20% are the highest of any psychiatric disorder (4) exceeding schizophrenia and depression [(5), p. 426]. Typical causes of death are somatic complications due to food refusal and starvation, but suicide is also common accounting for one in five deaths (4). Although mortality rates in BN are significantly lower than in AN, bulimia is associated with serious complications, such as electrolyte and pH disturbances, and tooth erosion [(5), p. 425]. Recovery rates of 52% in AN and BN in a 6-year follow up (6) indicate the need for more effective treatment.

As well as serious implications for the individual, EDs have significant economic consequences. It is estimated that ∼€ 1 trillion per year is spent on the ∼20 million patients with eating disorders in the European Union. The direct costs of health care are the same quantum as for anxiety and depression, indirect costs due to burden of disease are even higher (7).

In the English-language literature, the conceptualization of eating disorders as discrete diagnostic entities has developed over the past 150 years. Anorexia nervosa (AN) was first described in 1873 by the French physician Ernest-Charles Lasègue and by the English physician and neurologist William Gull (8). The first description of bulimia nervosa (BN), by Otto Dörr-Zegers, a Chilean of German descent, in the Revista Chilena de Neuro-Psiquiatria (1972), was exceeded in recognition and influence by the description by the British psychiatrist Gerald Russell in Psychological Medicine in 1979 (9, 10). Binge eating disorder (BED) as a separate diagnostic entity debuted as recently as 2013, the time of its inception in DSM-5 (1). The classification of eating disorders is subject to ongoing change. Diagnostic criteria for AN and BN have been subject to frequent alteration. The chapter on eating disorders was extensively revised for DSM-5 and further changes are under consideration for the upcoming edition, including possible new diagnostic entities such as Night Eating Syndrome and Purging Disorder (11, 12).

In the German-language literature, the historical development has been strikingly different. Systematic reviews have already shown that eating disorders received little attention in German-speaking psychiatry until the 20th century. This resulted in a small number of published articles, while in France and England numerous articles on this particular field were published at the same time [(13), p. 204–13, (14)].

Our aim was to investigate whether this low reception also applies to the most common textbooks of that time.

Textbook accounts of disordered eating behavior and related diagnostic entities are of particular value in discerning historical developments. Textbooks generally present a systematic account of the field of psychiatry, incorporate received views of the profession at a given time, detail perspectives promoted by the authors, and indicate formative influences and trends in education and training of psychiatrists and other medical practitioners. This article examines the representation of disordered eating behavior and EDs in German-language textbooks over the past two centuries, in particular addressing the following questions:

- When were eating disorders first mentioned as discrete diagnoses?
- Which other psychiatric diseases were associated with disturbed eating habits?
- What explanations were given for disordered eating behavior?
- In how much detail and to what extent did influential psychiatrists address these issues?
- What continuities and changes can be observed in the conceptualization of disordered eating behavior and diagnostic categories of eating disorders across these more than 200 years?

Finally, from the perspective of today's clinical practice and available research findings:

- Are there any concepts that are still valid today?
- To what extent do current research findings support or refute the ideas of the past?

MATERIALS AND METHODS

In order to gain a comprehensive picture of changing perspectives on disordered eating behavior and eating disorders in the past 200 years of German academic psychiatry, we compiled a list of 18 representative textbooks, taking into account the influence of the authors and distribution of year of publication across the period. This method has been previously applied in a longitudinal historical study (15).

For the selection of literature, we decided on the following strategy: We intentionally chose to focus on psychiatric textbooks because we wanted to present the knowledge that was considered valid at the time, representing the most common and generally accepted views within the clinical and scientific community on disordered eating in the past 200 years. Articles in journals were not taken into consideration, as they did not necessarily represent valid and widespread knowledge.

All the authors considered were professors and therefore their publications had a formative influence on psychiatry and contributed significantly to the teaching of future psychiatrists. Some of the chairs held by the authors of these historic textbooks were even considered to be the most important psychiatric chairs in the world at the time: Heinroth held the world's first psychiatric chair in Leipzig (16). Kraepelin taught in Munich and Heidelberg. He shaped German-speaking psychiatry far beyond his time, introducing clinical-empirical psychiatry and nosology. Other chairs of central importance for psychiatry have been in Vienna (Hoff), Zurich (M. Bleuler) and Breslau (Neumann).

In addition, all considered authors made significant contributions to psychiatry: Griesinger is considered the founder of the scientific and biological phase of psychiatry (17). Eugen Bleuler is considered the founder of the concept of schizophrenia (18). With Kurt Kolle and Helmut Rennert, two of the most important psychiatrists from Eastern and Western Germany are represented as well. Their textbooks have been published in numerous editions, showing their wide and long-term distribution in the field of psychiatry (19, 20). These are exemplary contributions of the cited authors to the field of psychiatry. Further important scientific contributions by the other cited authors can be found in **Table 1**, listing the cited textbooks and relevant publication data.

Inclusion criteria comprised: textbook of psychiatry in German language; authored by a professor of psychiatry at a German-speaking university; author a recognized authority in psychiatry; published between 1800 and 2017.

Eighteen textbooks were identified, spanning publication years 1803–2017. The timeline is presented in **Figure 1**.

In each textbook, relevant passages on eating disorders or their symptoms, such as food denial, emaciation or cravings, were identified, excerpted, and sorted thematically. Historical perspectives and individual views of the authors that shaped their eating disorder narrative were identified. Points of similarity and difference between these historical perspectives and present-day conceptualization of and research findings on eating disorders are summarized and discussed.

RESULTS

Eating Disorders as Distinct Diagnostic Entities

The first author to mention eating disorders as a separate disease entity in a German textbook is Gerd Huber in 1974. Huber describes "anorexia mentalis," characterized by refusal to eat, substantial weight loss, amenorrhea, use of appetite inhibitors and laxatives. This is noted to be most common in pubertal women, Huber discusses delayed "psychosexual maturation" as

TABLE 1 | List of authors, lifetime, main contributions to psychiatric science, textbook details.

Author	Life-time	Main contributions	Textbook title	Published place, year
Johann Christian Reil	1759–1813	Invented the term "Psychiatrie"	Rhapsodieen über die Anwendung der psychischen Kurmethode auf Geisteszerrüttungen	Halle, 1803
Johann Christian August Heinroth	1773–1843	First Chair in psychiatry; founder of psychosomatic medicine	Lehrbuch der Störungen des Seelenlebens oder der Seelenstörungen und ihrer Behandlung	Leipzig, 1818
Wilhelm Griesinger	1817–1868	Founder of scientific psychiatry	Die Pathologie und Therapie der psychischen Krankheiten	Stuttgart, 1845
Heinrich Neumann	1814–1884	Concept of unitary psychosis	Lehrbuch der Psychiatrie	Erlangen, 1859
Richard v. Krafft-Ebing	1840–1902	Sexology	Lehrbuch der Psychiatrie	Stuttgart, 1879
Emil Kraepelin	1856–1926	Empirical psychiatry and nosology	Psychiatrie (8th edition)	Leipzig, 1909–15
Karl Jaspers	1883–1969	Psychopathology	Allgemeine Psychopathologie	Berlin, 1913
Eugen Bleuler	1857–1939	Research in schizophrenia	Lehrbuch der Psychiatrie	Berlin, 1916
August Bostroem	1886–1944	Research in Mb. Wilson, Bostroem paralysis	Kurzgefasstes Lehrbuch der Psychiatrie (4th edition)	Leipzig, 1941
Oswald Bumke	1877–1950	Psychoanalysis, Degeneration theory	Lehrbuch der Geisteskrankheiten (6th edition)	Munich, 1944
Karl Leonhard	1904–1988	Classification of endogenous psychoses	Grundlagen der Psychiatrie	Stuttgart, 1948
Kurt Kolle	1898–1975	Combined psychiatry and neurology	Psychiatrie (4th edition)	Munich, 1955
Hans Hoff	1897–1969	Forensic psychiatry	Lehrbuch der Psychiatrie	Basel, 1956
Gerd Huber	1921–2012	First description of coenesthetic schizophrenia	Psychiatrie	Stuttgart, 1974
Manfred Bleuler	1903–1994	Endocrinologic psychiatry	Lehrbuch der Psychiatrie (15th edition)	Berlin, 1983
Helmut Rennert	1920–1994	Leading psychiatrist in German Democratic Republic	Neurologie und Psychiatrie sowie Grundzüge der Neuropsychiatrie des Kindes- und Jugendalters (8th edition)	Leipzig, 1987
Rainer Tölle	1932–2014	Sleep deprivation treatment for depression	Psychiatrie (17th edition)	Berlin, 2014
Frank Schneider	1958	Forensic psychiatry, neurobiology of schizophrenia	Facharztwissen Psychiatrie und Psychotherapie (2nd edition)	Berlin, 2017

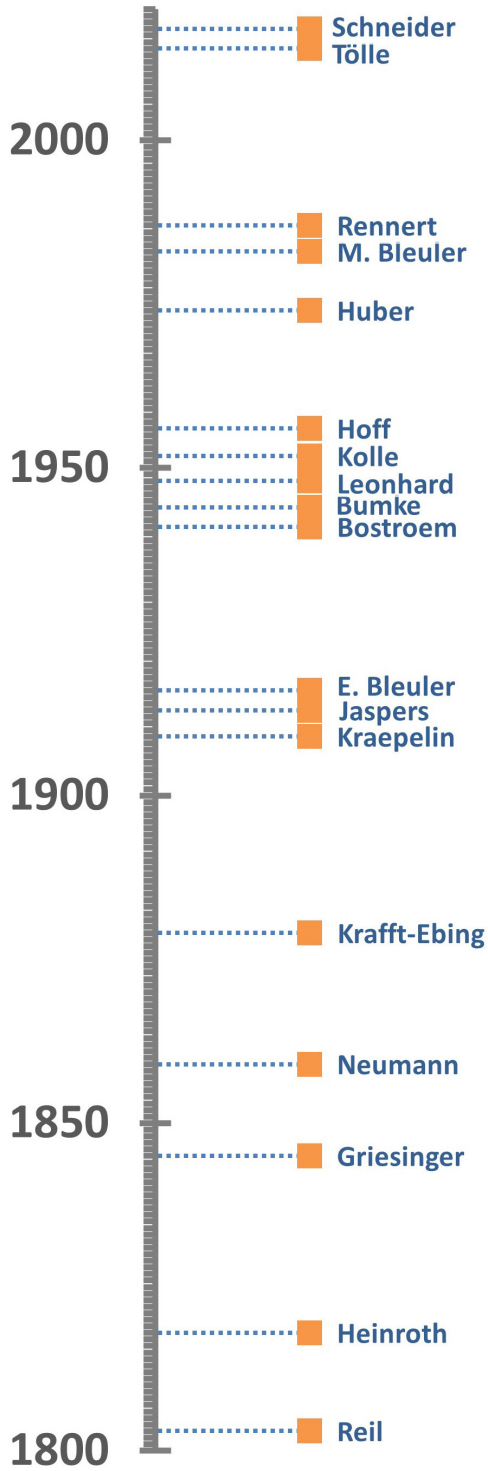

FIGURE 1 | Timeline showing the distribution of the years of publication of the textbooks in this study.

well as rejection of female roles as possible triggers [(21), p. 270]. This explanation is repeated in later textbooks by Manfred Bleuler and Helmut Rennert (20, 22). Only Rennert mentions fear of obesity as a possible causal factor (20). Tölle and Windgassen emphasize the pathophysiologic role of body image distortion in their current textbook (23).

In our sample, eating disorders as distinct diseases are found in all textbooks published after 1974. However, initially, only AN was listed as an eating disorder. Another 40 years elapsed before BED and BN appeared as independent diagnoses, in the current textbook by Tölle and Windgassen (23). Prior to 1974, disturbed eating behaviors were not categorized as a separate diagnostic condition, even though such behaviors were mentioned as symptoms accompanying a variety of psychiatric disorders.

Disordered Eating in Depressive Disorders

Abnormal eating habits are described extensively as symptoms of depressive disorders. All considered authors mention changes in appetite, food intake or body weight as symptoms of depression. As early as 1803, Johann Christian Reil described loss of weight and emaciation as symptoms of "melancholy" (24). Johann Christian August Heinroth from Leipzig added reduced appetite a few years later (25). Over the next 200 years, loss of weight and appetite are consistently mentioned as common features of depression (5, 21–35). A number of explanations of loss of appetite in depression are discussed. Several authors mention delusions of poverty, leading to patients fearing they will die of starvation (20, 24, 28, 29). Reil describes a patient who believed that voluntarily starving oneself to death was preferable to succumbing to the starvation that inevitably and inexorably accompanied (imagined) dire poverty. As a potential therapeutic approach, Reil suggested reassuring the patient the food provided was free of charge (24). Loss of appetite and weight were linked to feelings of guilt. Wilhelm Griesinger and Krafft-Ebing, the former acknowledged as a pioneer of scientific psychiatry, described fasting as a strategy of sinners to atone for their sins (26, 28). Religious motives are also mentioned by Emil Kraepelin (**Figure 2**) and persist in Rennert's 1987 textbook where the conviction of having sinned is seen as a reason for loss of appetite, along the lines of a penitential fast [(20), p. 278, (29)]. Finally, several psychiatrists mention delusions of worthlessness (*Mikromanie*) as a reason for reduced food intake. Affected patients believe they don't deserve food (27, 29, 31, 35). Krafft-Ebing describes this, in extreme form, as based on nihilistic delusions. Affected patients deny their very existence, negating the need for food [(28), vol. 2, p. 28]. Thus, delusions are presented as one definitive explanation for food refusal in depressive patients.

Krafft-Ebing formulated a remarkable approach to monitoring the course of depressive illness, regularly measuring body weight for early detection of depressive episodes. In 1879 he states that a masked depression (*larvierte Depression*) may initially present somatic symptoms, even before characteristic symptoms of depressed mood occur. Thus, "those swallowed tears, those inner wounds that have been covered by smiles, pride and lies for an extremely long time" can lead to emaciation, digestive problems, amenorrhea or irregular menstruation before mood alteration occurs [(28), vol. 1, p. 129]. Such physical findings are also referred to in Frank Schneider's current textbook as typical somatic complications of AN [(5), p. 424].

FIGURE 2 | Emil Kraepelin measured body weight attentively in order to comprehend the course and prognosis of mental disorders, at the beginning of 20th century. Source: In public domai, URL: https://wellcomecollection.org/works/mw4ah4kq.

However, food intake does not play a key role in Krafft-Ebing's account of masked depression, so it does not appear to constitute an early depiction of AN.

Food Refusal as a Suicidal Act

Beginning with Heinroth, food refusal as a suicidal act was a focus of attention in the 19th and early 20th century (25–30). Heinrich Neumann from Breslau, founder of the concept of unitary psychosis, held that the danger of suicide persisted even after beginning force feeding, since the patient could fall back on suicide methods other than food refusal [(27), p. 207]. Krafft-Ebing considered food refusal a rare form of suicidal act [(28), vol. 2, p. 28]. Kraepelin names suicide as one of the most frequent motives for the refusal to eat [(29), vol. 1, p. 618]. Kraepelin is the only author to mention suicide by eating inedible objects such as "nails, stones, fragments of glass, animals," providing the patient could consciously overcome feelings of disgust [(29), vol. 1, p. 364]. Suicide by starvation associated with depression is not mentioned in the later textbooks. It was not until 1987, that Rennert claimed that food refusal may be an accompaniment of suicidal intent in patients with anorexia [(20), p. 457]. Finally, Tölle and Windgassen explicitly mention eating disorders in their chapter on suicidality where they refer to anorexia nervosa as a form of "chronic suicide." Obesity is also noted as a possible variant of this suicide type [(23), p. 100, 126].

Disordered Eating Behavior in Schizophrenia

Altered eating behavior is also found in descriptions of schizophrenia, mostly in relation to reduced food intake. Delusions and hallucinations are implicated as valid explanations. In 1818, Heinroth states the preoccupation with intense delusions in "madness (paranoia)" may lead to neglect of sleep and eating. Furthermore, abeyance of appetite can occur as a result of incessant preoccupation with supernatural phenomena and religious writings [(25), vol. 1, p. 296–304].

A number of authors link the content of delusions to possible effects on eating (15, 17, 18, 21–24, 28). Griesinger describes delusions of poisoning and that human flesh had been offered to eat, as leading to food refusal [(26), p. 77–83]. Neumann considered delusions to be the most common reason for food refusal. In addition, he describes strategies to persuade affected patients to eat. The treating physician might partake of the food on offer to convince the patient it is safe. One patient had even devised his own strategy to circumvent starvation, solely eating eggs, since these could not contain human flesh [(27), p. 206]. Krafft-Ebing describes delusions that one's own body does not exist or has already died, and delusions of poisoning associated with paranoia as leading to food refusal. He also notes that certain delusions could lead to increased appetite. Affected patients were convinced of "having several children in their womb, or of being double bodied" [(28), vol. 1, p. 65f., 103]. Reil had previously described a patient with a delusional belief of double existence, who ate double the normal serves of food [(24), p. 80]. Overall, however, delusions causing reduction in food intake dominate in the literature considered. Describing "dementia praecox" (DP), Kraepelin mentions the example of a delusion of state-organized poisoning. Under the "paranoid form" of DP he mentions that a delusion of poisoning may result in only certain foods being eaten or food intake ceased, worsening the overall disease prognosis [(29), vol. 3, p. 696, 842, 896]. In 1941, August Bostroem emphasized food refusal not only as a complication, but also an indication for in-patient treatment in patients with schizophrenia [(32), p. 194]. Gerd Huber describes various vegetative symptoms that may occur in the course of schizophrenia: "Loss of appetite, nausea and vomiting, constipation and diarrhea." Food intake may be increased or decreased and sudden changes in eating habits may occur [(21), p. 165f.]. In the second half of the 20th century, Huber and Rennert describe delusions of poisoning as a symptom of schizophrenia [(20), p. 278, (21), p. 177]. Tölle and Windgassen also discuss a link between these conditions [(23), p. 198]. Thus, delusions of poisoning have been consistently regarded and taught as a symptom of schizophrenia in the past 200 years of German academic psychiatry and often linked to eating behavior.

Gustatory and auditory hallucinations in schizophrenia are also cited as potential triggers of disordered eating (20, 21,

26–28). This primarily involves the perception of unpleasant tastes. For example, Griesinger notes tastes that are "disgusting, metallic, pungent, rotten, earthy." Gustatory hallucinations involving a pleasant taste were much rarer [(26), p. 83f.]. In the mid-19th century, Griesinger, Neumann and Krafft-Ebing discussed gustatory hallucinations as leading to delusions of poisoning [(26), p. 83, (27), p. 115, (28), vol. 1, p. 66, 104], only for mention of this link to fall into abeyance for the next 100 years until Huber and Rennert discussed gustatory hallucinations triggering refusal to eat [(20), p. 278, (21), p. 177].

Neumann also described auditory hallucinations as the basis of a case of food denial. Voices stated there was human flesh in the food and commanded a food ban [(27), p. 116]. A few years later, Krafft-Ebing described voices prohibiting food on religious grounds [(28), vol. 2, p. 28].

Abnormal eating habits are also found in the descriptions of catatonic and hebephrenic forms of schizophrenia by the great nosologist Kraepelin. In hebephrenic schizophrenia (*läppische Verblödung*), food intake may fluctuate considerably, corresponding to phases of increased and decreased appetite. In megalomania, patients may deny needing food, insisting they are fueled by "supernatural power." In catatonia, delusions of poisoning are occasionally found [(29), vol. 3, p. 768–76, 810]. Some patients would consume inedible substances, even their own excretions. Patients may rigorously enforce refusal to eat by clenching their teeth, protesting they are neither hungry nor require food [(29), vol. 3, p. 816–29]. Three other leading German psychiatrists, Eugen Bleuler, Karl Leonhard and Manfred Bleuler, describe food denial in patients with catatonia [(22), p. 198, (31), p. 106, (34), p. 121]. Kurt Kolle mentions "pubertal anorexia" ("*Pubertätsmagersucht*") as a special form of schizophrenia in his textbook from 1955. Describing emaciation and food deprivation as its core symptoms, he discusses parallels to hebephrenic schizophrenia and a possible common pathophysiology. Eating disorders as a distinct category of mental disorders are not described by Kolle (19).

Increased Appetite in Mania

Descriptions of bipolar disorder, formerly referred to as "mixed states" or "circular insanity" report less consistent connections to eating behaviors. Many authors describe an increase in appetite during a manic phase (25, 26, 28, 29, 34, 35). Griesinger regarded increased appetite as a symptom of mania, attributing it as a lack of satiety [(26), p. 64, 224]. However, he noted that some manic patients cited their great appetite as justification for their claim not to suffer from any disease. Several authors in the first half of the 20th century described reduction of appetite during a manic phase. According to Eugen Bleuler, patients with mania ate not to appease their hunger, but rather in order to occupy themselves. "Submanic" patients with moderate activity, on the other hand, showed a diminished eating behavior [(31), p. 359]. In 1941, Oswald Bumke described a lack of appetite during mania, leading to weight loss [(33), p. 279–88]. The authors of recent textbooks again see mania linked with increased appetite. According to Leonhard, internationally known for his differentiated classification of endogenous psychoses, this could lead to a more vital appearance of the patient [(34), p. 90]. In 1987, Rennert even describes "greed" as a symptom in manic patients [(20), p. 278], however, weight gain is not described as a typical consequence of the increased appetite. Most psychiatrists rather considered weight loss a sign of mania (26, 28, 31, 33–35). A possible explanation for this apparent contradiction can be found in Hans Hoff's textbook, describing increased metabolism in manic patients [(35), p. 403]. Kraepelin alone offers the more nuanced description of increased weight in milder cases of mania, while more severe cases are associated with weight loss [(29), vol. 3, p. 1228].

Disordered Eating Behavior in Descriptions of Historical Disease Categories

In addition to these psychiatric diagnoses that are well-known today, abnormal eating habits have also been described in diseases that are no longer diagnosed in the present day, have been dissolved into other concepts or bear another name.

Kraepelin describes "neurasthenia" as a disease state, caused by overload of the human body and mind, resulting in exhaustion and loss of performance. Another symptom is lack of appetite; prolonged refusal to eat may also cause stomach discomfort, which can be counteracted by eating small amounts of food frequently [(29), vol. 4, p. 1401, 1465]. According to Oswald Bumke, malnutrition is not only a symptom but may cause neurasthenia. He also mentions stomach discomfort as a possible symptom in addition to other vegetative disorders in the cardiovascular system and gastrointestinal tract, with decreased appetite being the generic consequence [(33), p. 297]. Hans Hoff departs from this description of neurasthenia. He too describes manifold symptoms of the digestive tract, such as stomach pain or gastroesophageal reflux. However, with respect to eating behaviors, Hoff describes as typical a "ravenous appetite" at night resulting in overweight. Rumination of already eaten food may also occur [(35), p. 589]. The last textbook in our series with an entry for "neurasthenia" was published in 1974 by Gerd Huber. Therein he states that both reduced and increased appetite can be observed in this disease, manifesting as "loss of appetite" or "bulimia and polyphagia." He brackets neurasthenia and *anorexia mentalis* as typical representatives of psychiatric disorders showing both physical and psychiatric symptoms [(21), p. 258–64].

In the 19th and early 20th century, occasional descriptions of abnormal food intake are found in "hypochondria." Griesinger described heart problems, headaches and sleep disturbances as well as indigestion and lack of appetite as possible symptoms of this condition. Weight loss only occurred in cases of concurrent physical illness [(26), p.159 f.]. According to Neumann, on the other hand, patients with hypochondria focus on meticulously choosing the foods eaten [(27), p. 95, 160]. Krafft-Ebing describes a preference for inedible food. Patients consumed "spiders, toads, worms, human blood," as they hoped for a healing effect [(28), vol. 1, p. 66]. Furthermore, hypochondriacal symptoms could also occur in other psychiatric disorders. Krafft-Ebing describes "hypochondriacal melancholy" as an example: Affected patients claimed that their intestines were blocked and therefore they could not eat anything [(28), vol. 2, p. 28]. Eugen Bleuler

describes a case of "schizophrenic hypochondria": one patient was convinced that she was suffering from an ileus and that the food in the intestine was going to rot. Subsequent intake of laxatives led to weight loss [(31), p. 320]. More generally, Karl Jaspers, well-known today for his seminal work on descriptive psychopathology, mentions hypochondriacal symptoms as a complication of psychiatric illnesses that could cause severe weight loss [(30), p. 129].

Descriptions of abnormal eating habits are also found in accounts of "hysteria." Although Kraepelin viewed hysteria as an inconsistently described disease, he regarded instability of affect as its cardinal symptom, which could cause both mental and somatic sequelae. Affects could perturb body functions: Thus, "nausea, choking movements, and vomiting" would be an expression of disgust, loss of appetite a sign of sadness [(29), vol. 4, p. 1548–56]. Ingestion of food may be blocked by spasm of the esophagus, and vomiting was a frequently observed symptom. Nutritional status might only be slightly impaired, but in some cases could be greatly reduced. Further, the amount of food eaten by patients could be reduced over months or years so extensively that it was barely sufficient for survival. Young women most commonly suffered from this disease, with amenorrhea a typical complication. To treat the above symptoms, Kraepelin recommended a "mast cure" (a fattening diet regime) [(29), vol. 4, p. 1598–603, 1697]. Eugen Bleuler also saw vomiting, refusal of food and difficulty swallowing as symptoms of "hysteria." However, metabolism would be down-regulated in affected patients so that the weight remained constant [(31), p. 380–7]. Jaspers was concerned with the causes of vomiting, which he too regarded as a symptom of "hysteria." A stressful feeling that occurs during ingestion would be suppressed and could manifest later through months of vomiting [(30), p. 176]. Bumke's explanation for food refusal was that whilst a self-injurious behavior it served primarily to attract attention. On the other hand, when alone, the patient would eat secretly and deliberately, intentionally deceiving those around them [(33), p. 212f.]. Hans Hoff describes "hysterical anorexia" as a special form of "hysteria" with some parallels to AN. It typically occurred following puberty in young women, who were averse to maturing to womanhood, denying food in order to delay the development of their body. This process would happen unconsciously and might lead to an "endogenous anorexia" [(35), p. 618].

Somatic Conditions and Altered Brain Function

In addition to psychiatric disorders, somatic conditions are discussed as possible triggers of altered eating behavior, especially diseases of the gastrointestinal tract, endocrinological disorders, and lesions of the brain and pituitary gland.

Pathologies of the gastrointestinal tract were particularly seen as responsible for changes in eating behavior in the 19th century. According to Reil, increased appetite may occur due to increased activity of the nervous system in the gastrointestinal tract [(24), p. 258]. By contrast, Krafft-Ebing considered hypersensitivity of the gastric nerves to cause decreased appetite, leading to a premature feeling of satiety [(28), vol. 1, p. 66]. He also cited inflammatory changes in the gastrointestinal tract, which were also discussed by Kraepelin and Griesinger as a plausible cause of loss of appetite [(26), p. 327, (28), vol. 1, p. 204, (29), vol. 1, p. 618]. In addition, pain could trigger refusal to eat. According to Griesinger, pain sensations could impair food intake and lead to weight loss [(26), p. 29]. Neumann emphasized that abdominal pain in particular could have a significant impact on a person's nutritional status, although gastrointestinal diseases could also lead to increased appetite [(27), p. 59, 79].

In the 20th century, more attention was devoted to the brain than to the gastrointestinal tract. In particular, brain lesions were cited as a somatic cause of altered eating habits. Both increase and decrease in appetite were considered possible. According to Bumke, emaciation may occur as a result of degeneration of brain areas associated with vegetative functions [(33), p. 387]. More generally, Huber stated that a disturbed appetite may result from local brain damage [(21), p. 49]. According to Bostroem, an increased appetite could occur in the course of a frontal-brain lesion and may cause a craving for food [(32), p. 23]. Hoff described a lesion of the diencephalon as a possible trigger for periodic food cravings [(35), p. 195]. According to Leonhard, increased intracranial pressure could increase or decrease appetite [(34), p. 228].

In addition, panhypopituitarism ("Morbus Simmonds"), a hypofunction of the hypophysis, was previously considered responsible for emaciation. In the 1940's however, Bostroem and Leonhard described personality changes, altered affectivity and cognition as symptoms of the disease, but did not mention possible effects on body weight [(32), p. 60, (34), p. 140]. Not until 1974 did Huber cite pituitary disease in the differential diagnosis of "anorexia mentalis" [(21), p. 271]. Even Manfred Bleuler did not equate these two clinical pictures. Rather, he emphasized that AN is psychogenic in origin and not an endocrinopathy. Pituitary hypofunction may be considered as a differential diagnosis [(22), p. 357]. Rennert also considered "Simmond's cachexia" in 1987 as a differential diagnosis of anorexia [(20), p. 278]. In the current textbook by Frank Schneider, panhypopituitarism only receives historical attention along the lines that at the beginning of the 20th century, anorexia was attributed to malfunction of the pituitary gland according to a publication by the Hamburg pathologist Morris Simmonds. Diseased patients were treated with hormonal therapies or even pituitary transplants, whereas psychotherapy was not used [(5), p. 422].

Appetite and Body Weight as a Prognostic Factor

In the first half of the 19th century, Heinroth and Neumann regarded body weight and appetite as prognostic markers: they describe increasing appetite and weight as a sign of convalescence in patients with "melancholy" [(25), vol. 1, p. 335]. According to Neumann, the body weight may even exceed the original weight before the disease [(27), p. 189]. Krafft-Ebing, Kraepelin and Jaspers extended the prognostic significance of body weight to all psychiatric illnesses. In the presence of

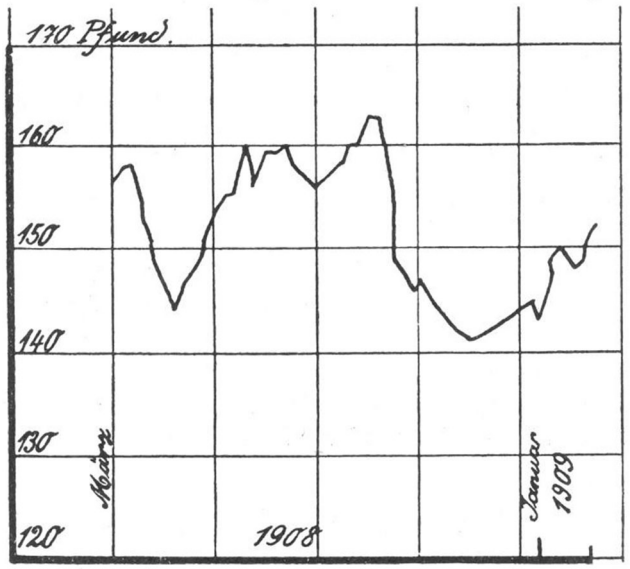

FIGURE 3 | Weight fluctuations in periodic insanity, as reported by Kraepelin. Abscissa: time [∼ 1 year]; Ordinate: bodyweight [pounds]. The first drop in weight occurred during a manic phase, with weight regained in convalescence, followed by significant weight loss during a more prolonged major depressive episode. Source: Obtained from [(29), vol. 3, p. 1231].

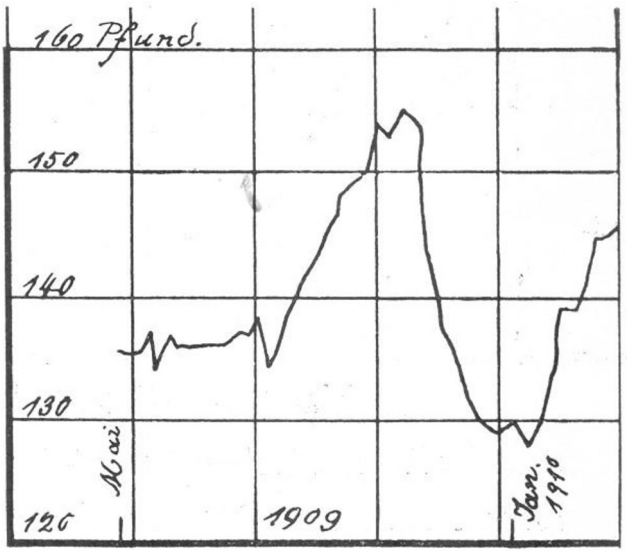

FIGURE 4 | Abscissa: time [∼ 1 year]; Ordinate: bodyweight [pounds]. According to Kraepelin, changes in weight indicate the severity of psychiatric symptoms: Whilst the first two slight weight drops occur in mild depressive phases, the following rapid and substantial weight loss represents a severe depressive episode. Source: Obtained from [(29), vol. 3, p. 1231].

improved psychopathological state, weight gain would be a sign of healing. In the views of Krafft-Ebing and Kraepelin, weight has such prominence that they doubt that successful cure of a mental illness without increase in bodyweight is possible [(28), vol. 1, p. 214f, (29), vol. 1, p. 445, (30), p. 327]. The most unfavorable constellation is considered to be increasing body weight with unimproved psychopathological state, indicating the persistence of the mental disorder [(28), vol. 1, p. 215, (29), vol. 2, p. 892, (30), p. 130].

Kraepelin reported from his clinical research that body weight could reflect the course and severity of psychiatric disorders. In his four-volume textbook there are illustrations of weight curves with descriptions of the associated course of the disease. **Figure 3** illustrates this with regard to a case of "periodic insanity," an historic diagnosis that resembles today's concept of bipolar disorder. The graph illustrates fluctuations in weight during the course of the disease. The first weight loss represents a manic phase followed by increase in weight indicating a remission. The second drop, on the other hand, represents a depressive phase. The severity of a disease can be measured by the amount of weight fluctuation. **Figure 4** describes similar observations in a recurrent depressive disorder with minor and major episodes of symptoms.

In the time following Kraepelin's interest in body weight, the tenet that weight can be a marker for severity and prognosis largely disappears from view. Bumke strongly states the contrary case, that in patients with schizophrenia, weight fluctuations are completely independent of psychiatric symptoms [(33), p. 572]. In later textbooks, weight is no longer mentioned as a prognostic factor in mental disorders.

TABLE 2 | Summary of main findings of review of eating disturbance and disorder content in textbooks.

First mention of EDs	Anorexia nervosa 1974 by Gerd Huber Bulimia nervosa 2014 by Rainer Tölle Binge eating disorder 2017 by Frank Schneider
Disordered eating symptoms described	Food refusal Food craving Weight gain Weight loss Vomiting Eating inedible things
Disordered eating behaviors as symptoms of mental disorders	Schizophrenia Depressive disorders Bipolar disorder Hysteria Neurasthenia Hypochondria
Pathophysiological explanations given for disordered eating	Psychological processes: Guilt, sin, suicidal thoughts and tendencies, attracting attention Psychopathology: Delusions of poisoning, delusions of poverty, nihilistic delusions, gustatory and auditory hallucinations Diseases in GI tract: indigestion, inflammation Dysfunction in certain brain areas: Frontal lobe, diencephalon, pituitary gland

DISCUSSION

The review of textbook entries confirms that diet and especially altered eating habits have been addressed in German psychiatric

FIGURE 5 | Richard von Krafft-Ebing addressed disordered eating extensively, dedicating a distinct chapter to this topic in his textbook of 1879. Source: In public domain, URL: http://resource.nlm.nih.gov/101420138.

textbooks throughout the past 200 years. The main findings are summarized in **Table 2**.

As early as 1879 Krafft-Ebing dedicated a separate chapter in his textbook to disordered eating (**Figure 5**). In particular, he regarded the nutritional status and appetite as markers for mental health and the prognosis of psychiatric disorders. Changed eating habits, however, were not regarded as an independent disease entity, but rather as symptoms of other mental or somatic diseases. This view has been maintained for almost a century. Only in 1974 Gerd Huber mentions "Anorexia mentalis" as a specific disorder in his textbook [(21), p. 270f.].

In German-speaking psychiatry, eating disorders were mentioned occasionally, as an article by Anton Stichl from 1892 shows: His article on the "Anorexia mentale," describes the fear of being fat as a causal factor and named self-induced vomiting and lack of insight as characteristics of the disease. This description of the AN is still valid today and let Stichl's publication appear very modern (1, 36). Overall, however, only a few German-language articles featured eating disorders well into the 20th century (14). Our review shows clearly that this also applies to the published textbooks of that time.

This is in contrast to the developments in other European countries, especially France and England: There, Gull and Lasègue described "anorexia hysterica" and "anorexia nervosa" almost simultaneously in 1873 and 1874. Their descriptions resemble today's concepts of AN in many respects, emphasizing the psychogenesis of this disease and rejecting somatic explanations like a disease of the gastrointestinal tract. They also described the therapy as difficult due to a lack of insight and mentioned typical complications such as constipation and amenorrhea (37, 38). The publications aroused great interest in France and England, and numerous articles on this "new disease" were published in specialist journals [(13), p. 204–13].

The late reception in German speaking psychiatry however is particularly noteworthy due to its leading contributions in fields like descriptive psychopathology, diagnosis and neurosciences.

In the following we want to explain reasons for this particular development in the German-speaking world.

The Role of Somatic and Psychosomatic Medicine in German-Speaking Countries

There is no single universal explanation for the sparse and late reception of eating disorders in the German-language literature. Rather, multiple factors and historical circumstances must be taken in account. An important factor is that eating disorders were not considered the preserve of psychiatrists in German-speaking countries, a review of AN treatment at the end of the 19th century indicated that pediatricians, gynecologists and in particular internists dedicated themselves to those diseases (14). It is likely the multiple physical complications of AN aroused the interest of somatic doctors, thus DSM-5 lists anemia, amenorrhea, constipation, abdominal pain, cold intolerance, hypotension and hypothermia [(1), p. 343]. Also, until the early 1900's, diseases presenting with cachexia were commonplace and sometimes occult, most notable tuberculosis. Therefore, it was a challenge for the attending physicians to determine whether emaciation was caused by reduced food intake or by a physical disorder, reducing diagnostic clarity.

Another special feature of the German health system is that psychosomatic medicine is established as a medical specialty separate from psychiatry. Psychosomatic medicine deals with psychological, social and biological influences on body functions and the development and therapy of somatic diseases (39). The term "psychosomatic" was introduced by Heinroth, whose 1818 textbook was included in our study. Heinroth urged that diseases should be grasped holistically in their somatic and psychological dimensions and special attention should be paid to the patient's biography. Thus, he saw many mental illnesses conditioned by the individual life stories of the affected patients [(40), p. 60]. Psychosomatic medicine has thrived to become an important independent medical specialty in the German-speaking world (41, 42) and has played a dominant role in the treatment of eating disorders. In the past as well as in present day, patients with eating disorders have been treated not only in psychiatric hospitals but also in psychosomatic clinics. This has resulted in a net reduction of involvement of psychiatrists in the diagnosis and treatment of ED, which may explain their reluctance to address this issue.

Coverage of Disordered Eating and Eating Disorders in Textbooks

The extent to which the authors of textbooks include disordered eating behaviors in their narratives varies widely. Analysis of the texts reveals continuities, discontinuities and differences over the two centuries. At the beginning of the 19th century, authors mentioned disordered eating behavior only sporadically. Reil, the originator of the term "psychiatry," made important contributions to neuroanatomical research and was anxious to assign the corresponding correlate in the nervous system to certain body functions and symptoms [(43), p. 19–23]. It is therefore traceable that Reil hypothesized increased appetite signified an overactive nervous system in the gastrointestinal tract in his textbook from 1803 [(24), p. 258]. In the period following Reil, German psychiatry was influenced above all by the psychicists (*Psychiker*), who regarded psychiatric illness in primarily moral terms, as a result of disobedient and godless behavior [(43), p. 35f.]. Heinroth is a leading representative of this movement, for example describing the "starvation cure" as a therapeutic procedure to make disobedient patients docile. Patients on a severely restrictive diet would perceive hunger as a punishment for their behavior, notice their need for help and dependence, and consequently end their disobedient behavior [(25), vol. 2, p. 111–24]. On the other hand, the starvation cure had not only an educational function: According to Neumann, it can be seen as a form of asceticism, which would allow the patient to concentrate on the essential. Therefore, the starvation cure was not a pure punishment, but should also encourage the patient's mindfulness. Besides promoting therapies based on strict moral elements and drawing on religious precepts, Heinroth was one of the first psychiatrists to adopt an individual, patient-oriented approach. He interpreted mental disorders as a result of past pathogenic experiences and consequences of behaviors in the patient's life. This led him to advocate consideration of the patient's biography, social circumstances and lifestyle in tailoring therapy (41). He states in his textbook: "Very much depends on detailed knowledge of the individual situation of the ill person. Often this exclusively explains the whole illness (or at least the most relevant factors) and clearly indicates what will benefit or harm them." [(25), vol. 1, p. 44]. The therapy should be arranged in a manner that "The entire treatment of the ill person is tailored to the specifics of the illness (...). The factors considered include sex, age, constitution, temperament, most importantly the personality, that is the character, cultivation of the mind, inclinations and habits, finally the individual circumstances of the ill person." [(25), vol. 1, p. 3] Additionally, he made use of activation, fostered the mental powers of his patients and applied other strategies still used in modern cognitive, behavioral and conversational therapy (44). However, despite Heinroth's promulgation of these therapeutic tools in general, there is no evidence as to whether he applied them specifically to address disordered eating behavior.

A more comprehensive study of abnormal eating behavior begins in the mid-19th century, starting with Griesinger and continuing with Neumann, Krafft-Ebing and Kraepelin with the topic increasing in importance. It is noteworthy that all four authors considered reduced food intake as a trigger for psychiatric illness. This pathophysiological approach is not represented in the earlier or later literature, with the exception of Schneider's current textbook [(5), p. 526]. For Griesinger, this approach exemplifies his psychiatric work, he was one of the leading somaticists (*Somatiker*) who aimed for a scientific basis of psychiatry and interpreted psychiatric disorders as arising from somatic conditions [(45), p. 43–9]. Therefore, it is not surprising that Griesinger considered inadequate nutrition as a possible cause of "melancholy" [(26), p. 153]. However, Griesinger was by no means a pure materialist. He also considered psychological aspects in the pathogenesis of mental disorders: "We consider psychological causes to be the most frequent and productive sources of insanity, both as predisposing factors and most importantly as immediate precipitants of the disease." [(46), p. 169]. Furthermore, Griesinger emphasized that pathogenesis is strongly subjective and that the observed triggers of mental disorders "are most diverse: sometimes it is a suddenly aroused anger, fright or sorrow in response to an insult, financial loss, shame, a sudden death" [(46), p. 169].

Another achievement of Griesinger was the establishment of asylums attached to small towns ("Stadtasyle"): He did not support the prevailing model of custody of psychiatric patients in remotely located madhouses, instead promoting asylums "preferably in the immediate neighborhood of a small town (...), in order to stay in touch with its habitants" [(46), p. 532]. This reflects Griesinger's early appreciation and enforcement of patients' personal autonomy. Kraepelin gives the most extensive account of disordered eating behavior, albeit his four-volume work is also by far the largest of the textbooks included here. Kraepelin is well-known as the founder of empirical, experimental and scientifically founded psychiatry. In particular, he was interested in the detailed study of the course of diseases [(43), p. 106ff.]. Body weight served Kraepelin as an objective parameter to understand the course of a mental disorder and to frame a prognosis, emphasizing his systematic and scientific approach to psychiatry.

By contrast, in the first half of the 20th century a markedly reduced interest in disordered eating is evident in the psychiatric textbooks selected for in this study. This may be explained by a peculiarity of German-speaking psychiatry history. From 1914 to the mid-20th century, reduced food intake in the sense of AN was not seen as a psychiatric illness, but rather as a symptom of hypopituitarism. The Hamburg pathologist Morris Simmonds had published an article in 1914 in which he reported lethal food refusal due to a malfunction of the pituitary gland, known as "Morbus Simmonds" in the German speaking world and panhypopituitarism in English (47). This publication was particularly well-received in Germany, leading to neglect of psychogenic factors in anorexia (48). Most patients with AN were treated by medical disciplines other than psychiatry. At the Charité in Berlin, the famous surgeon Ferdinand Sauerbruch performed transplantation of pituitary glands. In this case, a calf or cattle pituitary gland was transplanted into the greater omentum. A therapeutic effect, ranging from short-lasting weight gain to complete healing was described. Previously, conservative methods such as oral ingestion of pituitary extract and sugar solutions had already been attempted (49). Even during the

post-war period, changes in eating behavior made only marginal appearances in psychiatry textbooks and EDs haven't been described as distinct mental disorders in German textbooks at all (19, 34, 35). Not until the mention of "Anorexia mentalis" by Gerd Huber, did eating disorders receive increasing attention in the German literature and recognition as distinct disorders. Some perspectives still seem current from today's perspective, while others can be considered obsolete: The rejection of physical development to womanhood, as emphasized by Huber as a core symptom, is not mentioned in the DSM-5. Instead, disturbed body image as well as the fear of getting fat are included in diagnostic criteria for AN (1). On the other hand, Huber's description that "anorexia mentalis" can turn into an addiction in the course of the disease appears highly topical. It is subject of current research, which investigates possible connections between these two clinical pictures. Godier and Park identified parallels between addictions and AN in a clinical study, including loss of control, functional impairment, self-harming behavior, and occupational and social limitations as intersections of both disease entities (50).

Rennert also emphasizes an "addictive process" in 1987 in patients with AN. It is also striking that he does not list any physical illnesses, such as a disturbed pituitary function, as a possible cause of the disease. Rather, he sees "contact-weak, even defiant, idiosyncratic, ambitious, egoistic or anankastic, hypochondriacal and sensitive characters" as forming the predisposition to AN [(20), p. 457]. Describing a purely psychogenic pathophysiology, Rennert is the first of our authors to suggest psychotherapy as a therapeutic tool. The importance of circumscribed areas of the brain in appetite regulation is discussed again in Schneider's current textbook. It highlights the importance of the hypothalamus as well as orexigenic and anorexigenic hormones. However, cognitive behavior therapy is acknowledged as the most effective treatment [(5), p. 422].

The Presentation of Food Denial as a Dominant Concern

Food supply has varied markedly over the time period of this study. Between 1800 and the 1950's food was often in short supply. For example, during 1816, the "year without a summer" there was a serious famine in Central Europe (51). Later, at the time of the two world wars, food supply in many parts of Europe was catastrophic and hunger omnipresent. The economic upswing starting in the 1960's has introduced an era of unprecedented abundance of food. Over the same period diseases causing inanition such as tuberculosis and chronic anaemias have reduced markedly in prevalence. The net result has been for psychogenic refusal of food to be more conspicuous and more negatively connoted as pathological, favoring the acceptance of AN into the nosology and AN becomes a distinct diagnosis in German-language psychiatric textbooks [(21), p. 270f, (22), p. 543f.]. This change in emphasis has also resulted in reduced food intake being less commonly attributed as a symptom of other psychiatric disorders.

The more recent rise in obesity has also focused attention on disorders of excessive eating. Historically, it appears that increased food intake was not considered as deviant behavior for a long time. This is supported by the interpretation of increased food intake as a sign of convalescence in psychiatric disorders as described above, but also by the beauty ideals of past times. In the 19th century, for example, excessive body mass was still considered a sign of prosperity, even wealth, and not regarded as a sign of abnormal eating habits or even a mental disorder [(52), p. 34f.]. In our sample, mention of BN as a condition with increased food intake is found only in the current textbooks by Schneider and Tölle/Windgassen (5, 23). Although in 1879, Krafft-Ebing used the term "bulimia" in relation to increased appetite, he did not mention measures to avoid weight gain that are regarded as typical for this disease today (28). In 1974, Huber still equated "bulimia" with hyperphagia. As early as 1972, Otto Doerr-Zegers had aptly described "Bulimia nervosa" as a distinct mental disorder. He and Gerald Russell are considered to be the first to describe this disease (9, 10). As an eating disorder with increased food intake without compensatory behaviors as countermeasures, BED was first listed in DSM-5 (1). Schneider's latest textbook of 2017 is the only textbook in our sample that mentions this disorder. BED was first described by Albert J. Stunkard who published an apt description of this disease in 1959 (53). However, it took a long time for BED to be included in the DSM and considered as a discrete entity. In the selected textbooks of the past 200 years of German-speaking psychiatry, this mental disorder played practically no role at all.

Disordered Eating in Mental Disorders

In the textbooks in our sample, decreased food intake and weight loss have been regarded as symptoms of depressive disorders, schizophrenia and somatic diseases. DSM-5 mentions all of those conditions as possible differential diagnoses of AN, underlining that alterations in food intake are still today considered as crucial symptoms of these disorders (1). Additionally, further overlaps between depressive disorders, schizophrenia, medical conditions and AN have been found, regarding their symptoms, pathophysiology, genetics and possible treatment strategies.

Depression

In depressive disorders, severe weight loss can occur. Changes in weight are mentioned as a diagnostic criterion in DSM-5 (1). Furthermore, depression is the most common comorbidity of patients with AN, prevalence of mood disorders ranging from 31 to 89% (54, 55). Comorbid depressive disorder worsens the outcome and prognosis in patients with AN (56).

Besides the frequent coexistence of these disorders, they share some symptoms, notably menstruation, libido and sleep disturbances occur commonly in both disorders. Shared genetic predispositions (57) and fluoxetine as a treatment in common for both disorders have been reported (58).

The feeling of guilt is a typical symptom and a strong indicator of depression (1). Whether reduced food intake is associated with an increased perception of guilt, as described by Griesinger, Krafft-Ebing, Kraepelin and Rennert (20, 26, 28, 29) in depressed patients, is of current scientific interest in ED research. In people with AN, guilt, anguish, sadness, fear and anger have been found to be associated with eating (59). A recent systematic

review found that guilt is not consistently linked to AN and BN presentations, but the relationship is unclear due to a lack of data (60).

Suicidality

Restrictive eating or self-starvation in patients with AN are currently not interpreted as suicidal behavior, as was perceived by the 19th century psychiatrists Heinroth, Neumann, Krafft-Ebing and Kraepelin (25, 27–29). However, AN has the highest mortality rate amongst all psychiatric illnesses. This is explained by the physical consequences of the disorder, but also the high suicide rate (61). Suicide attempts are a major issue in EDs (62), with suicide the second leading cause of death among individuals with AN (63). Therefore, studies have examined possible risk factors for suicidality in patients with EDs in order to prevent suicides in these patient groups. Known risk factors include frequent purge behavior, poor emotional regulation, childhood abuse and psychiatric comorbidities (64).

Schizophrenia

Reduced food intake has been listed as a symptom of schizophrenia by numerous authors (20, 21, 23, 26–29, 33). As explanations, the authors mainly described delusions of poisoning, gustatory hallucinations and command auditory hallucinations (21, 26–29). From today's perspective, these are still valid reasons for reduced food intake in patients with schizophrenia (65). Furthermore, overlaps between AN and schizophrenia regarding their symptoms, pathophysiology, genetics, and even their therapy have been discussed recently.

In schizophrenia, eating disorders are much more common than in the general population. Disordered eating is up to 5 times more common in patients with schizophrenia (66). On the other hand, diagnosable psychotic episodes are reported in 10–15% of AN patients (67). Additionally, some symptoms of AN resemble those of schizophrenia. These include odd thinking processes, fixed illogical beliefs or deficits in work and social life that can occur in both disorders (68). Due to these reciprocal findings in AN and schizophrenia, several hypotheses have been discussed as possible explanations: psychoses could be a result of starvation, disturbed body image a result of delusions, extreme fasting a counteraction against weight gain from antipsychotics. AN could even be a prodrome of schizophrenia (69). One study took up the last thought: In the study group considered, an ED preceded 10%, in 5% this was AN. The ED occurred 4–8 years before schizophrenia in these cases; women were more frequently affected than men. As a distinguishing feature, gustatory hallucinations were found only in the group with premorbid EDs. The authors discussed the possibility that patients could represent a distinct subtype of schizophrenia (68).

There are also similarities in pathophysiology: Genome-wide association studies (GWAS) in EDs have been used to calculate genetic correlations between different disorders. It is worth mentioning that significant positive genetic correlations were observed between AN and schizophrenia which suggests an overlap in the biological pathophysiology of both disorders (70, 71).

Furthermore, there are overlaps of AN and schizophrenia concerning both psychotherapies and medication. Aripiprazole and especially olanzapine, two atypical antipsychotics, have been trialed successfully as psychopharmacological treatments of AN and might become the first approved psychotropic drugs for AN treatment (72, 73).

Historical Disorders

Although hysteria, hypochondria and neurasthenia are considered historical disorders, and their concepts have emerged in other mental disorders, we have found overlaps with eating disorders. A specific question is whether these historical disorders could represent an early appearance of eating disorders in the literature.

Hysteria was covered extensively in the textbooks published in the first half of the 20th century. Comparing the historic descriptions of hysteria with the modern view on AN, we found overlaps, especially for the binge-eating/purging type of AN. As noted above, the authors described refusal to eat as a common symptom of hysteria, resulting in amenorrhea and severe weight loss. Vomiting was considered a common symptom of hysteria, and is described as a possible purge strategy in patients with AN in DSM-5 (1, 29, 31, 33, 35).

On the other hand, we did not find the other main DSM-5 diagnostic criteria, fear of weight gain and disturbed perception of body shape in any of the textbooks. It is possible that in the past patients with AN were diagnosed with hysteria. However, due to the absence of some of the main diagnostic criteria for AN in the descriptions of hysteria, we do not regard this disorder as an early description of AN. Our findings support previous research in the history of psychiatry by Vandereycken and van Deth who discussed possible overlaps between hysteria and eating disorders (74). They also found food refusal and vomiting listed as typical symptoms of hysteria. However, they found no literature describing a disturbed body shape or a fear of gaining weight in this context. Further, vomiting in hysteria was not primarily directed at weight loss, rather it was demonstrative, aiming to attract attention. This is in direct contrast to the behavior of patients with eating disorders, who vomit and purge covertly. On these grounds, Vandereycken and van Deth considered hysteria to be a historical precursor of conversion disorder and not EDs. In conversion disorder, a shift of psychic conflicts to somatic symptoms is seen as the critical trigger for its manifestation (74). This pathophysiological explanation was already in use for hysteria: Karl Jaspers wrote that the hysterical vomiting would be a result of "a painful affect that arises during the meal, but is suppressed, then provokes nausea and vomiting, which persists for months as hysterical vomiting" [(30), p. 176]. Hysteria is not viewed as a distinct disorder in the present day, its precepts having been scattered across dissociative or conversion disorder, neurotic disorders or psycho-reactive syndromes, and histrionic personality disorder.

Gastrointestinal Symptoms and Eating Disorders

The textbook authors described numerous gastrointestinal medical conditions as possible triggers for food refusal, especially

in the 19th century. Most common explanations for reduced food intake were hypersensitivity of the gastrointestinal nervous system, abdominal pain and gastrointestinal inflammation (26, 28, 29). To the present day, somatic diseases are listed as important differential diagnoses of AN in DSM 5, requiring careful evaluation (1).

The combination of restricted eating and gastrointestinal symptoms is commonly observed in patients with EDs and often leads to additional pharmacological treatment with antacids, proton-pump inhibitors, antispasmodics, gastroprokinetics, non-absorbable sugar laxative or hyperosmotic laxatives in patients with EDs (75).

As described by the cited authors in their historic textbooks, the enteric nervous system has a significant impact on appetite. Being part of the "gut-brain-axis," it registers the amount of consumed food to the CNS. The vagus nerve plays a key role, taking part in the regulation of the digestive system, satiety and food intake (76). Abnormal function of the enteric nervous system has been described in patients with AN, including increased sensitivity to gastric expansion and nutrients in the small intestine (77). This may contribute to the manifestations of eating disorders, though etiological implications are unclear and further research is needed.

Krafft-Ebing, Kraepelin and Griesinger discussed inflammatory changes in the gastrointestinal tract as pathophysiological factors resulting from changes in food intake and eating behavior (26, 28, 29). This could be seen as an early scientific hypothesis that inflammation is involved in the pathophysiology of eating disorders. This idea is currently followed by researchers focusing on cytokine changes in EDs (78), discovering immunologically important genes as relevant in AN (79) and exploring the role of the gastrointestinal microbiome in the development of EDs (80).

EDs and Brain Areas

In the German textbooks of the 19 and 20th century, brain areas with vegetative functions, frontal areas, the diencephalon, and the pituitary gland were seen as decisive for altered food intake and eating behavior by Bumke, Bostroem, Hoff and Huber (21, 32, 33, 35).

Currently, three main neurocircuits are held to be principally involved in food intake, appetite, body weight regulation and the pathophysiology of EDs: These are the self-regulation, hedonic and homeostatic systems.

The self-regulation system embeds eating in the social context, creates individual values and performs self-regulatory control. Its main center lies in the prefrontal cortex (58). It has been debated whether the enhanced control of food intake in patients with AN might be an effect of augmented control in general (81). An fMRI study showed that patients with AN have deviant folding in the prefrontal cortex, persistent even after weight gain and possibly of pathophysiological significance (82). On the other hand, reduced self-regulatory control has been put forward as a neurocognitive feature of BN and BED. In particular, the uncontrolld binge eating that occurs in these disorders suggests reduced control over behavior. Recent findings of an fMRI study underline the possible impact of the self-regulatory system in BN: Reduced thickness in parts of the prefrontal cortex (orbitofrontal cortex, inferior frontal cortex) was associated with more frequent manifestation of BN symptoms in patients (83).

The function of the hedonic system is to elicit the desire to eat and to evoke pleasure during food consumption. Its neurons and synapses are found mainly in the prefrontal cortex, basal ganglia and thalamus (58). In AN, an altered response to reward stimuli is proposed, affecting eating behavior. For patients with AN, food seems to be less rewarding than for the general population. Patients with AN might be able to ignore food-related rewards (84). Alterations in the reward system do not seem to be confined to eating behavior and persist even after convalescence: A fMRI study showed deviant activity in the reward system when patients were confronted with monetary stimuli (85). In BED, on the other hand, patients show an increased reward from food intake and hedonic eating behavior, which could explain the increased food intake (86). For BN, there have been no consistent findings, and studies have found both increased and decreased reward responses to food stimuli (87).

The homeostatic system integrates peripheral signals of food consumption and energy storages and regulates appetite. The hypothalamus and the pituitary gland play a prominent role in this system (58).

The historical assumption that AN could be a consequence of hypofunction of the hypophysis is considered obsolete today. Although there have been observed alterations in hypothalamic-hypophysis-axis in patients with AN, this phenomenon is not considered to have a pathophysiological impact. It is rather considered as an non-specific consequence of starvation in patients with AN (88), a bodily adaptation to decreased food intake and energy deficit, explaining some of the typical somatic complications of AN. Elevated CRH and ACTH levels lead to hypercortisolism, resulting in lowered bone density. Alterations in the pulsatility of LH-secretion contribute to amenorrhea (89).

From today's point of view, the pathophysiological contributions made by Bostroem and Hoff stand out. In the middle of the 20th century, both authors elucidated brain areas that are still considered to play an important role in food regulation. Bostroem identified frontal brain damage as a possible cause of food cravings [(32), p. 23]. As noted above the prefrontal cortex, as a part of frontal cortex, influences food behavior substantially and is considered to play a role in the pathophysiology of EDs. Hoff, on the other hand, considered lesions of the diencephalon as a possible cause of food cravings [(35), p. 199]. Distinct areas of the diencephalon, namely the hypothalamus and the pituitary gland, are still considered to regulate food intake. This emphasizes the early adoption by Hoff and Bumke of the study of circumscribed brain areas as possible causes or loci of disordered eating. This contrasts with the dominant approach in the 20th century to frame the causality of EDs in terms of social, environmental or cultural issues. Today's research seeks to understand both aspects of this equation in relation to EDs, whereby it is postulated that such social factors, together with increased vulnerability due to altered brain functions, could lead to the manifestation of eating disorders (90).

Limitations

A systematic literature review according to modern standards is currently not possible for a longitudinal study with historical literature: Historical sources are not included in today's literature databases, the quality standards for scientific work common today did not exist in the past. As a result, the selection of literature using PRISMA guidelines or similar criteria was not possible.

Nonetheless, we have made use of the structured and predefined PRISMA methodical approach as outlined in the PRISMA checklist (91) by describing the rationale for the review, providing an explicit statement of questions being addressed, defining eligibility criteria of the psychiatric textbooks as information sources and describing the selection and data extraction process. We also summarized the evidence in a structured way, addressed the limitations and drew comprehensible conclusions that are justified by the applied methods and the obtained results. Overall, we applied the PRISMA approach and its philosophy as far as possible to adhere to contemporary scientific quality standards and to provide evidence-based scientific work. But due to the nature of the historic material, a methodological compromise had to be attained. Whilst his may be seen as a limitation it could also be perceived as the result of successful interdisciplinary cooperation.

Historical textbooks are difficult to compare with each other, especially due to the substantially changed terminology over the course of time. For the selection of literature, we decided on the following strategy: We intentionally chose psychiatric textbooks because we wanted to present the knowledge that was considered valid at the time, representing the most common and generally accepted views of medical doctors and psychiatrists on disordered eating in the past 200 years. The resulting inclusion criteria are noted in the methods section. Articles in journals were not taken into consideration, as they did not necessarily represent valid and widespread knowledge. The main intention was not to compare the sources with each other, but rather to chart how disturbed eating behavior has been viewed over the course of the study period, 1803–2017. This allows a representation of progressions, continuities and breaks over time that would not be possible with a cross-sectional study. A further limitation is the small number of publications considered. This makes it impossible to obtain an all-encompassing overview of all the concepts discussed regarding disordered eating behavior. However, by limiting the literature selection to relevant textbooks from acknowledged authors, it is possible to obtain an overview of the predominant and widespread concepts on disordered eating behavior and eating disorders, gaining an impression how patients suffering from those disorders have been diagnosed and treated in psychiatric clinics.

In this article, we have contrasted the content of important German textbooks with the DSM classification even though we are aware that this comparison may be misleading. It would have been more adequate to compare English language textbooks of psychiatry over the same period with their German counterparts, covering the same breadth of perspectives. Similarly, with the French literature, which also has some historical alignment. Such an approach would be highly informative, but it was well-beyond the scope of the current study. The emphasis on the DSM classification was chosen largely to emphasize two points, firstly the convergence of illness concepts in German with those in the English-speaking world and, secondly, to illustrate how much the illness concepts and disease categories of disordered eating are in flux. This may be seen as supporting the need for a detailed historical analysis to illustrate areas of firm agreement over two centuries vs. areas which have only consolidated in the past decades.

CONCLUSION

Although AN was first described in the late 19th century and received broad attention in France and the United Kingdom, it took a long time until AN was recognized as a distinct mental disorder in German-speaking psychiatry. We found the first mention in Huber's textbook of 1974, a full century after its first description in France and England. BN and BED appeared only recently in German textbooks. However, throughout the past two centuries, disordered eating has been recognized as a symptom of various mental disorders, including those classified today as depressive disorders, schizophrenia and bipolar disorder. Interestingly, there are numerous overlaps between those mental disorders and EDs, and DSM-5 features some of them as possible differential diagnoses. Similarities can be found in their genetics, pathophysiology, symptoms and therapy, possibly leading to promising new therapeutic approaches for EDs in the future.

DATA AVAILABILITY STATEMENT

The datasets generated for this study are available on request to the corresponding author.

AUTHOR CONTRIBUTIONS

HS and LB conceptualized the study. HS provided methodological advice for literature review, provided information regarding the history of psychiatry, and the selected psychiatrists. HH provided professional support and made additional remarks regarding the current state of scientific knowledge of eating disorders. KK revised language style of the article and provided professional remarks. LB examined the selected textbooks, undertook a literature search, and wrote the first manuscript draft. All authors contributed and have approved the final manuscript.

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