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Community Series in Extreme Eating Behaviors Volume II

Edited by
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Community series in extreme eating behaviors - volume II

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Editorial: Community series in extreme eating behaviors—Volume II

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KEYWORDS

eating disorders, anorexia nervosa, bulimia nervosa, eating, physical health, obesity

Editorial on the Research Topic
Community series in extreme eating behaviors—Volume II

Introduction: recent developments in eating disorders and obesity

Currently, a significant and multi-dimensional shift in how we perceive eating disorders (EDs) and obesity is taking place.

Firstly, the perception of the spectrum of disorders associated with disordered eating has widened, leading to the addition of avoidant restrictive food intake disorder, pica and rumination disorder to the 5th edition of the Diagnostic and Statistical Manual of Mental Disorders (1), to an increased clinical and scientific interest in disordered eating in physical health problems such as cancer (2) and type 1 diabetes mellitus (3) and to a better understanding of the transdiagnostic features of body dysmorphic disorder, muscle dysmorphia and eating disorders (4).

Secondly, new genetic discoveries have opened our eyes for the metabo-psychiatric nature of eating disorders and their brain-related biological pathogeneses (5). This new perception of EDs is driving novel discoveries and developments regarding psychopharmacological treatments (6), nutritional interventions including pre- and pro-biotics (7), brain stimulation and targeted psychotherapeutic interventions to train specific brain functions such as attention (8) and impulsiveness (9). These new perspectives also help to generate an integrated view of the diagnosis and treatment of EDs and their psychological and physical co-morbidities (10). Additionally, researchers are making progress in understanding the psychological and behavioral underpinnings of obesity such as loss of control eating (11) and grazing (12).

Thirdly, the awareness of the importance of inclusiveness in EDs and obesity research is rising. For example, sexual minority groups have been identified as presenting an elevated risk for eating disorder symptoms and behaviors (13), and it has been noticed that people from ethnic minority backgrounds often experience greater difficulties in accessing support for an ED or other mental health problems (14).

Finally, there is a growing body of evidence that indicates the potential benefit of creative and receptive arts therapies in EDs and related mental health problems. For example, the therapeutic application of music such as listening to classical music, singing in a group and songwriting have been reported to be helpful in EDs (15) and in their most frequent co-morbidities like personality disorders (16) and obsessive-compulsive disorder (17).

Content of the second volume of "Extreme Eating Behaviors"

Because of these exciting developments in the field of EDs and obesity and the success of our initial Research Topic on "Extreme Eating Behaviors" (18) published in 2019, we were encouraged to issue a second volume on this Research Topic which covers brain research, psychological and physical aspects of eating behaviors, EDs and obesity, eating-related traits of specific population groups, and novel treatments for EDs.

Armon et al. investigated differences in brain activation in response to sweet and sour tastes in female study participants with and without bulimia nervosa and found differences in several brain regions which may be central to perception and processing of taste, including the operculum, the anterior cingulate cortex, the midbrain, and the cerebellum.

Munguía et al., Hussenoeder et al., Staníková et al., and Saure et al. investigated the relationship between physical and psychological risk factors of EDs and obesity such as thyroid hormone levels, food addiction, anxiety, food preferences, sensory processing, and autistic traits. Interesting findings from their studies include the association between sensory sensitivity and food addiction on the one hand and anxious symptoms and problems with specific food groups on the other hand as well as the potential involvement of thyroid hormone signaling in food preferences and the development of obesity.

Two articles addressed the connections between EDs and physical health problems: Riedlinger et al. examined gastrointestinal complaints in patients with anorexia nervosa, and Paszynska et al. analyzed that there is a high risk of dental caries and erosive tooth wear in children and adolescents with anorexia nervosa.

The articles by Gulec et al. and Stein et al. cover eating-related psychopathological and behavioral aspects in specific minority groups, namely a lesbian, gay, bisexual, transgender, intersexual, and queer (LGBTIQ) sample in Turkey and a sample of Jewish ultra-orthodox religious men. Stein et al. found that Jewish ultra-orthodox religious males with obsessive-compulsive disorder might be at risk for severe undernutrition because their rigid observance of Jewish everyday laws might interfere with their eating. As in this group of patients, the loss of weight did not result from body image concerns, Stein et al. argue that these patients should rather be diagnosed with restricting type ED than with anorexia nervosa. However, the authors themselves indicate that their diagnostic opinion is debatable. For clarity, we would like to inform the readers that body image disturbance is not mandatory for the diagnosis of anorexia nervosa according to DSM-5 (1). A lack of insight into the seriousness of the disease together with a significantly low body weight and the fear of weight gain, for example, would suffice (1).

From a historic point of view, we would like to mention that the role of religion or religiousness has been discussed as a pathophysiological, maintaining, protective, diagnostic, or therapeutic factor of EDs from the beginning of academic psychiatry (19–21) until today (22).

Regarding novel treatments, Flynn et al. published a protocol for an innovative study that allows to test whether concurrent self-administered transcranial direct current stimulation (tDCS) and attention bias modification training might be suitable to improve symptoms of binge eating disorder.

Expression of gratitude and good wishes

We are thankful to all the authors mentioned above who submitted excellent manuscripts for this Research Topic. We also thank our reviewers who gave useful feedback and thus helped to improve the manuscripts and the second volume in its entirety.

Even though a single Research Topic cannot cover all the facets of EDs and of obesity research, we hope that this article Research Topic is making a decent contribution to the field. In this sense, we wish to attract attention to some so far underestimated disease aspects with this second volume of "Extreme Eating Behaviors".

Author contributions

All authors listed have made a substantial, direct, and intellectual contribution to the work and approved it for publication.

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.

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ORIGINAL RESEARCH
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Atypical Sensory Processing Is Associated With Lower Body Mass Index and Increased Eating Disturbance in Individuals With Anorexia Nervosa

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Background: Elevated autism spectrum disorder (ASD) traits are associated with anorexia nervosa (AN). Conversely, eating disturbances, which are core characteristics of AN, are common in ASD. Among individuals with ASD, atypical sensory processing is associated with eating disturbance. Because AN and ASD appear to overlap, it would be crucial to understand whether sensory processing atypicality exist also in AN. Further, it would be essential to find if atypical sensory processing is associated with eating disturbances in individuals with AN, since treatment modifications may be needed. We therefore aimed to examine whether atypical sensory processing is associated with AN and its core characteristics.

Methods: Participants of the current study included 42 individuals with AN and 40 healthy controls (HCs). All participants were adult women. Sensory processing, other ASD traits, and eating disorder symptoms were assessed with self-report questionnaires.

Results: Individuals with AN reported lower registration, decreased sensation seeking, increased sensory sensitivity, and increased sensation avoiding compared to HCs. When analyzing groups with restrictive AN (AN-R) and binge-purge type AN (AN-BP) separately, only individuals with AN-R exhibited decreased sensation seeking, and only those with AN-BP exhibited lower registration. After controlling for body mass index as a covariate, group differences remained significant only in sensory sensitivity between individuals with AN and HCs. Increased atypical sensory processing predicted lower body mass index and increased disordered eating.

Conclusion: Results suggest that sensory processing appears to differ between AN and HC women, and AN subtypes may exhibit distinct sensory processing atypicality. Sensory sensitivity may be stable traits whereas other aspects of atypical sensory processing may be related to acute AN. Atypical sensory processing may contribute to the severity of AN, and thus it is crucial to recognize sensory processing differences when treating individuals with AN.

Keywords: anorexia nervosa, feeding and eating disorders, autism spectrum disorder, sensory processing, selective eating

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INTRODUCTION

Anorexia nervosa (AN) is a potentially severe mental health disorder which core characteristics are restriction of energy intake leading to low body weight, intense fear of gaining weight, or persistent behavior that interferes with weight gain and a disturbance in the way in which one's body weight/shape is experienced (1). Elevated autism spectrum disorder (ASD) traits and diagnosed ASD are overrepresented among individuals with AN (2–5). ASD is a developmental condition characterized by deficits in social interaction and communication, as well as repetitive, stereotyped behavior and interests (1). Atypical sensory processing, for instance, atypical responses to touch, pain, smell, taste, or bodily-related perception, is a common feature and a diagnostic criterion of ASD (1). In individuals with ASD, atypical sensory processing is strongly associated with eating disturbances, which most commonly include selective eating, food aversion due to specific texture or color, and food neophobia (6–9). Because disordered eating is a core feature in AN, and ASD and AN appear to somewhat overlap in their disordered eating symptoms, it would be essential to understand whether disordered eating in AN is also associated with the level of atypical sensory processing. However, only a few previous studies have investigated atypical sensory processing among individuals with AN, and the possible joint effect of high ASD traits for different sensory processing dimensions has not been taken into account (10–12).

Sensory processing refers to the ability to register and modulate sensory information and to organize and use this information to respond to environmental stimuli. It consists of two constructs: neurological threshold to sensory stimuli and response strategy to these stimuli (13). Response strategies for sensory stimuli refer to ways of regulating perceived sensory input. For example, individual may stay away from noisy places, leave to another place when smelling a strong odor, eat only bland food or avoid some food textures in order to minimize sensory input. Two constructs combine into four basic dimensions of sensory processing: low registration, which is characterized by a low threshold and passive regulation; sensation seeking that is characterized by a high threshold and active regulation; sensation sensitivity that is characterized by a low threshold and passive regulation, and sensation avoiding that is characterized by a low threshold and active regulation.

Some studies have shown that individuals with AN with high ASD traits self-report increased sensory sensitivity and sensation avoiding (11, 12, 14), whereas one study did not found association between ASD traits and taste or smell processing in individuals with AN (15). The two subtypes of AN may differ from each other in ASD traits and exhibit a different pattern of sensory processing. Restrictive anorexia nervosa (AN-R) symptoms include food restriction without binge-eating and/or purging behavior; and binge-purge type anorexia nervosa (AN-BP) symptoms include both food restriction and binge-eating and/or purging (1). Individuals with AN-R have been reported to exhibit higher self-reported ASD traits and more ASD-related neuropsychological characteristics than individuals with AN-BP (16, 17). In addition, a recent study found that only individuals with the AN-R subtype reported more hyper-hyporeactivity to sensory input than HCs, whereas those with AN-BP were comparable to HCs (16). Unfortunately, the study did not investigate specific dimensions of sensory processing or specify if AN-R participants exhibited more hyper- or hyporeactivity than HCs; instead these were combined under the same scale. In summary, it is likely that specifically individuals with AN-R have elevated ASD traits and difficulties in sensory processing. However, we are not aware of any previous studies delineating the specific dimensions of sensory processing difficulties by the two subtypes of AN or characteristics of AN.

Sensory processing may be associated with the core symptoms of AN, that is, food restriction and body image distortion, that are shared with both its subtypes. One study found that atypical sensory processing among individuals with AN positively correlated with the severity of overall eating disorder symptoms (10). However, the possible joint effect of other ASD traits and atypical sensory processing was not investigated nor the role of the subtypes of AN. In another recent study including participants with both AN and ASD, the participants described that they had food-specific sensory sensitivities, and that food restriction was often related to the sensory properties of food (18). However, since this study was based on qualitative interviews, it did not investigate the possible association of sensory sensitivity and eating disorder symptoms with quantitative methods. In addition to eating problems, sensory processing may be involved in another core symptom of AN, that is, body image disturbances. Body image (i.e., subjective representation of one's own body) is partly based on sensations arising within the body, for example, sensing body position and body boundaries (19). To sum up, atypical sensory processing may have a central role in understanding the symptoms of AN.

In conclusion, subtypes of AN may exhibit different patterns of sensory processing, but studies investigating this are lacking. Further, sensory processing difficulties may relate to the core eating disorder symptoms, but the evidence is scarce. High ASD traits in AN are associated with illness prolongation and poorer treatment outcomes (20–23). Treatment adaptations could therefore be beneficial for individuals with AN with high ASD traits. Further, if the AN subtypes exhibit different sensory processing patterns, treatment modifications according to subtypes may also be necessary. The present study aimed to examine: (1) whether sensory processing dimensions differ among individuals with AN and healthy controls (HCs); and further, whether there are differences in sensory processing between individuals with two subtypes of AN (AN-R and AN-BP), and (2) whether atypical sensory processing predicts core characteristics of AN [eating disorder symptoms, body mass index (BMI)] or duration of illness when the group (AN or HC) and other ASD traits are also included in the analysis.

MATERIALS AND METHODS

Participants

Participants with AN were recruited via The Eating Disorder Association of Finland and via Turku University Hospital.

All individuals with AN had been diagnosed by professionals and fulfilled the diagnostic criteria of AN or atypical AN (F50.0 and F50.1 in ICD-10 World Health Organization), (24), both of which are included in DSM-5 AN [307.1, (1)]. Participants with AN were asked to report in the background questionnaire whether their symptoms included binge and/or purge behavior. Those who reported binge and/or purge behavior were included AN-BP group, and those who did not report those behaviors were included AN-R group. These subtypes are not defined in ICD-10, which is used in Finland, and therefore the subtypes were not defined by professionals. HCs were recruited via the University of Helsinki emailing lists. The participants participated voluntarily after providing informed written consent for the study. The Ethics committee of Helsinki Uusimaa Hospital District (HUS/1886/2017) approved the study and the study was conducted in accordance with the Declaration of Helsinki.

Exclusion criteria for all the participants were as follows: history of diagnosed psychosis or substance abuse, ASD, ADHD, neurological disorder, learning disability, head trauma with unconsciousness, or score of under 70 in full-scale intelligence quotient (FSIQ), verbal comprehension index (VCI), or perceptual reasoning index [PRI, (25)]. Additionally, for the HC participants, exclusion criteria included any current or past diagnosed mental disorder. All participants were adult females. The final sample comprised 82 participants: 40 HCs and 42 individuals with AN, of whom 20 had AN-R and 22 AN-BP. Three individuals were excluded from the original HC group ($n = 43$): one had a PRI score under 70, one reported having a diagnosed mental disorder, and one reported having a diagnosed neurological condition. The characteristics of participants are presented in **Table 1**.

Measures

Background Information

Participants filled in a background questionnaire, in which they were asked about their date of birth, education in years, existing psychiatric and neurological conditions, psychopharmacological medication, weight, and height. BMI was calculated using self-reported weight and height.

Adult Sensory Profile

The Sensory Profile is a widely used self-report questionnaire that measures sensory processing (25). It consists of 60 items that are self-rated for the frequency of a range of behaviors on a five-point scale. The scale has four subscales: low registration (questions about situations in which individuals do not notice some sensory stimulus, e.g., do not notice when someone touches them), sensory seeking (questions about behavior that lead to sensory stimulation, e.g., if individual likes to go places that have bright lights and loud music or if individual likes eat spicy food), sensory sensitivity (questions about how easily individual is distracted if there is a lot of sensory stimulation, e.g., loud noises or particular food textures) and sensory avoiding (questions about behavior that lead muting of sensory stimulation, e.g., using earplugs, staying away from noisy places, eating only familiar food). Higher scores indicate lower registration, sensory seeking, sensory sensitivity, and sensory avoiding.

Wechsler Abbreviated Scale of Intelligence

WASI was used to assess participants' cognitive ability. WASI consists of the following four subtests: vocabulary, similarities, block design, and matrix reasoning. The WASI produces verbal, performance, and full-scale intelligence quotient scores (VCI, PRI, FSIQ) (26). There is no official edition of the WASI in Finland, so these quotients were formed based on the same subtests from the Wechsler Adult Intelligence Scale-IV (WAIS-IV, Wechsler), (27).

Eating Disorder Examination Questionnaire

Eating Disorder Symptoms were assessed with EDE-Q (28, 29). EDE-Q is a self-report questionnaire consisting of four subscales measuring restraint, eating concerns, shape concerns, and weight concerns. Higher scores indicate more eating disorder symptoms.

Swedish Eating Assessment for Autism Spectrum Disorder

SWEAA is a self-report questionnaire designed to measure eating disturbances associated with ASD (30). SWEAA measures eating problems related to perception, motor control, purchase of food, eating behavior, mealtime surroundings, social situations at mealtime, and recognition of hunger and satiety. Higher scores indicate more eating problems.

Autism Quotient

ASD traits were measured using AQ that is a widely used scale containing 50 self-report items (31, 32). It measures the following ASD traits: social skills, attention switching, attention to details, communication, and imagination. Higher scores indicate increased ASD traits. AQ was used in the analysis to control for other ASD traits beyond atypical sensory processing.

Data Analysis

Power analysis revealed that the sample size was sufficient for sensation seeking, sensation sensitivity, and sensation avoiding (80% power with alpha set at $p < 0.05$) (33). In the context of low registration, our study was slightly unpowered as about 60 participants were required. The normality of variables in the two samples was assessed with histograms and with Shapiro-Wilk tests. ANOVA was used to calculate differences for those background variables that were normally distributed in all groups (FSIQ, VCI, illness duration, BMI). Kruskal-Wallis tests were used for calculating group differences in the other background variables (age, education, PRI, EDE-Q, SWEAA, AQ). For dichotomous variables, that is, psychopharmacological medications and comorbid conditions, group differences were calculated with the chi-square test.

Subscales of Sensory Profile were normally distributed in all three groups. All subscales were first analyzed together with multivariate analysis of variance (MANOVA), and secondly, separately with univariate analysis of variance (ANOVA). The scores of the sensory profile subscales were included in the analyses as dependent variables. The group (in the first analyses AN and HC groups, and in the second analyses

TABLE 1 | Characteristics of the AN and HC groups.

	AN ($n = 42$) mean (SD)	AN-R only ($n = 20$) mean (SD)	AN-BP only ($n = 22$) mean (SD)	HC ($n = 40$) mean (SD)
Age (years)	23.61 (3.69)	24.34 (3.59)	22.95 (3.74)	23.10 (3.03)
Education (years)	14.21 (2.43)	14.55 (2.56)	13.91 (2.31)	14.15 (1.82)
Full-scale intelligence quotient (FSIQ, WASI)	108.31 (17.15)	110.95 (17.39)	105.91 (16.97)	109.68 (13.00)
Perceptual reasoning index (PRI, WASI)	105.33 (15.91)	107.65 (16.71)	103.23 (15.22)	106.10 (15.02)
Verbal comprehension index (VCI, WASI)	108.36 (14.37)	110.00 (14.70)	106.86 (14.25)	110.48 (13.91)
Autism spectrum traits (AQ)	21.57*** (9.29)	22.05*** (9.10)	21.14*** (9.65)	10.90 (6.32)
Body mass index	17.00*** (2.64)	16.68*** (2.88)	17.30*** (2.44)	21.61 (1.22)
Duration of illness	7.46 (3.65)	8.14 (3.83)	6.85 (3.45)	N/A
Eating disorder symptoms (EDE-Q)	85.86*** (33.08)	78.90*** (36.12)	92.18*** (29.46)	9.32 (7.11)
Eating disturbances associated with ASD (SWEAA)	91.38*** (35.51)	101.50*** (26.47)	82.18*** (27.03)	35.51 (11.75)
Psychopharmacological medication *n* (%)	16*** (38.1 %)	7*** (35.0)	9*** (40.9%)	0 (0 %)
Comorbid psychiatric conditions *n* (%)	25*** (59.5 %)	11 *** (55%)	14*** (63.6%)	0 (0 %)

*Means and standard deviations are presented in the table. Significant between-group differences when compared to HCs are marked with the following symbols: *** $p < 0.001$. Participants with AN-R and AN-BP did not differ from each other in any of the variables.*

WASI, Wechsler Abbreviated Scale of Intelligence; FSIQ, Full-Scale Intelligent Quotient; VCI, Verbal Comprehensive Index; PRI, Perceptual Reasoning Index; AQ, Autism Quotien; EDE-Q, Eating Disorder Examination Questionnaire; SWEAA, Swedish Eating Assessment for Autism spectrum disorders.

AN-R, AN-BP, and HC groups) was included in analyses as an independent variable. Bonferroni correction was used for multiple comparisons. BMI was included as a covariate since it differed significantly between the groups.

Linear regression analyses were used to investigate whether atypical sensory processing (composite score) predicts eating disorder characteristics (BMI, duration of illness, scores of EDE-Q, scores of SWEAA). The group (AN or HC) was entered at the first step, and in addition, ASD traits (AQ) were added to the model at the second step, in order to control for the more general prediction by them. Sensory processing (composite score) was entered at the third step as an independent variable. Dependent variables in separate analyses were BMI, duration of illness scores of SWEAA, and scores of EDE-Q. Before the regression analyses, scores of sensory processing dimensions (low registration, sensation seeking, sensory sensitivity, and sensation avoiding) were summed up and combined under one composite score representing overall atypical sensory processing. Results of sensation seeking were reversed (scores were subtracted from 75 that is the maximum score of the scales) because in the other dimensions, higher scores indicate higher atypicality, whereas, in the sensation seeking scale, lower scores indicate higher atypicality. The internal consistency of the sensory processing composite was adequate when investigated with an inter-item correlation matrix and Cronbach's Alpha of 0.789.

In the SWEAA, the data of five HC participants were missing because the questionnaire was included after these participants had already participated in the study. Weight information was missing from two participants' self-report questionnaires (one AN-R and one AN-BP). Missing information was not replaced, and thus these participants were not included in the analysis concerning the missing variables (SWEAA or BMI). The Statistical Package for the Social Sciences, version 26.0 (34), was used to analyze the data.

RESULTS

Group Differences in Sensory Processing

In the first analysis, we examined with MANOVA whether there were differences between the total AN and HC groups. There was a significant difference between the AN and HC groups in sensory processing [$F(4.77) = 17.812$, $p < 0.001$, Wilks' $\lambda = 0.519$, partial $\eta^2 = 0.481$]. Follow-up ANOVAs revealed significant group differences in all sensory processing variables: when compared to HCs, the AN group exhibited more low registration [$F(1.80) = 4.005$, $p = 0.049$, partial $\eta^2 = 0.048$], less sensation seeking [$F(1.80) = 9.958$, $p = 0.002$, partial $\eta^2 = 0.111$], more sensory sensitivity [$F(1.80) = 70.216$, $p < 0.001$, partial $\eta^2 = 0.467$], and more sensation avoiding [$F(1.80) = 39.555$ $p < 0.001$, partial $\eta^2 = 0.331$] (see **Table 2**). After controlling for BMI as a covariate in MANCOVA analysis, the significant group difference remained [$F(4.74) = 5.785$, $p < 0.001$, partial $\eta^2 = 0.238$]. Follow-up ANCOVAs revealed significant group difference only in sensation sensitivity [$F(1.77) = 16.168$, $p < 0.001$, partial $\eta^2 = 0.174$], whereas in other sensory processing dimensions, AN and HC groups did not differ significantly from each other. See **Supplementary Tables 1, 2** for summarized results of MANOVA, MANCOVA, ANOVAs and ANCOVAs.

In the second analysis, we examined with MANOVA whether there were differences between AN-R, AN-BP, and HC groups. There was a significant difference between the AN-R, AN-BP, and HC groups in sensory processing [$F(8.152) = 9.333$, $p < 0.001$, Wilks' $\lambda = 0.450$ partial $\eta^2 = 0.329$]. Follow-up ANOVAs revealed significant group differences in all sensory processing variables, that is, low registration [$F(2.79) = 4.550$, $p = 0.013$, partial $\eta^2 = 0.103$], sensation seeking [$F(2.79) = 5.809$, $p = 0.004$, partial $\eta^2 = 0.128$], sensory sensitivity [$F(2.79) = 35.043$, $p < 0.001$, partial $\eta^2 = 0.470$], and sensation avoiding [$F(2.79) = 20.330$, $p < 0.001$, partial $\eta^2 = 0.340$]. In Bonferroni corrected *post-hoc* analyses, the AN-R group

did not differ significantly from HCs in low registration but exhibited significantly less sensation seeking ($p = 0.004$) as well as significantly more sensation sensitivity ($p < 0.001$) and more sensation avoiding ($p < 0.001$) than HCs. The AN-BP group did not differ significantly from HCs in sensation seeking but exhibited significantly more low registration ($p = 0.013$), more sensation sensitivity ($p < 0.001$) and more sensation avoiding ($p < 0.001$) than HCs (see **Table 2**). The AN-R and AN-BP groups did not differ significantly from each other in any of the investigated sensory processing dimensions. After controlling for BMI as a covariate in MANCOVA analysis, the significant group difference remained [F (8.146) = 4.451, $p < 0.001$, partial $\eta^2 = 0.196$]. Follow-up ANCOVAs revealed significant group difference only in sensation sensitivity [F (2.76) = 8.641, $p < 0.001$, partial $\eta^2 = 0.185$] whereas AN-R, AN-BP and HC groups did not differ significantly from each other in other sensory processing dimensions. Further, pairwise comparisons revealed that both AN-R and AN-BP groups exhibited significantly more sensory sensitivity than HCs ($p = 0.004$ and $p < 0.001$, respectively). See **Supplementary Tables 1, 2** for summarized results of MANOVA, MANCOVA, ANOVAs and ANCOVAs.

Sensory Processing Atypicality as a Predictor for Eating Disorder Characteristics

Linear regression revealed that group at step 1 was a significant predictor for BMI [F (1.78) = 100.250, $p < 0.001$] and ASD traits at step 2 enhanced significancy of the prediction [F (2.77) = 56.525, $p < 0.001$; F change (1.77) = 6.164, p change = 0.015]. At step 3, when sensory processing atypicality was included as a third predictor, the accuracy of prediction was further significantly increased [F (3.76) = 41.314, $p < 0.001$; F change (1.76) = 5.007, p change = 0.028], indicating that higher sensory processing atypicality was associated with lower BMI after the prediction by group and other ASD traits were also included in the model. Only the group (AN or HC) predicted significantly the duration of illness [F (1.80) =166.921, $p < 0.001$], and adding ASD traits or sensory processing atypicality to the model did not significantly increase the accuracy of prediction [F (2.79) = 84.053, $p < 0.001$; F change (1.79) = 1.060, p change = 0.306; F (3.78) = 58.526, $p < 0.001$; F change (1.78) = 3.070, p change = 0.084., respectively]. Also, for the eating disorder symptoms measured by EDE-Q, only the group (AN or HC) was a significant predictor [F (1.80) =205.016, $p < 0.001$] while ASD traits and sensory processing atypicality did not significantly increase the accuracy of prediction [F (2.79) = 105.189, $p < 0.001$; F change (1.79) = 2.224, p change = 0.140; F (3.78) = 69.891, $p < 0.001$; F change (1.78) = 0.535, p change = 0.467, respectively]. For the eating disorder symptoms measured by SWEAA, the group at step 1 [F (1.75) = 119.941, $p < 0.001$], and ASD traits at step 2 enhanced significancy the prediction [F (2.74) = 83.698, $p < 0.001$; F change (1.74) = 18.873, p change < 0.001], and when sensory processing atypicality were included at step 3 the accuracy of interpretation was further significantly increased [F (3.73) = 65.178, $p < 0.001$; F change (1.73) = 9.319, p change = 0.010], indicating that higher sensory processing atypicality was associated with severity of eating disorder symptoms measured by SWEAA after the prediction by group and other ASD traits were also included in the model (see **Table 3** for total R^2 for every step and R^2 changes).

DISCUSSION

This study aimed to investigate sensory processing among individuals with AN. We found that women with AN had

TABLE 2 | Means and standard deviations of sensory processing dimensions are presented in the table.

	AN ($n = 42$) mean (SD)	AN-R only ($n = 20$) mean (SD)	AN-BP only ($n = 22$) mean (SD)	HC ($n = 40$) mean (SD)
Low registration	31.76* (7.75)	29.30 (7.82)	34.00* (7.13)	28.65 (6.20)
Sensation seeking	42.60** (8.38)	41.05** (6.82)	44.00 (9.52)	47.90 (6.71)
Sensation sensitivity	48.62*** (7.84)	47.90*** (8.22)	49.27*** (7.62)	35.63 (6.03)
Sensation avoiding	44.19*** (10.04)	45.55*** (9.23)	42.95*** (10.79)	32.90 (5.43)

Statistical significance in ANOVA post-hoc analyses when comparing the AN-R and AN-BP groups to HCs is marked with the following symbols: $^{*}p < 0.05$ $^{**}p < 0.01$ $^{***}p < 0.001$.

TABLE 3 | Coefficient of determination (R^2) for each step and changes in R^2 are presented in table.

	Predictors	BMI	Duration of illness	EDE-Q	SWEAA
First step: group	R^2 (only group)	0.562***	0.672***	0.719***	0.615***
Second step: group and ASD traits	R^2 change	0.032*	0.004	0.008	0.078***
	R^2 (group and ASD traits)	0.595***	0.672***	0.727***	0.693***
Third step: group, ASD traits, and sensory processing	R^2 change	0.025*	0.012	0.002	0.035**
	R^2 (group, ASD traits and sensory processing)	0.620***	0.681***	0.729***	0.728***

Statistical significance is marked with following symbols: $^{*}p < 0.05$ $^{**}p < 0.01$ $^{***}p < 0.001$.

significantly lower registration, less sensation seeking, and increased sensory sensitivity as well as sensation avoiding compared to healthy control individuals. Examination of the two subtypes of AN showed that only the participants with AN-R exhibited significantly less sensation seeking, and only the participants with AN-BP exhibited significantly lower registration, as compared to HCs. However, after controlling for BMI, significant group differences remained only in sensory sensitivity between individuals with AN and HCs. Both individuals with AN-R and AN-BP exhibited heightened sensory sensitivity when compared to HCs. Higher ASD traits and atypical sensory processing predicted lower BMI and higher eating disturbance after the group was also included as a predictor.

In line with the previous studies (11, 12), we found that individuals with AN had high sensation sensitivity. These difficulties could underlie decreased eating among individuals with AN, since eating often includes plenty of sensory stimuli, including the texture, smell, taste, and temperature of food, sounds of eating, and visceral sensations caused by food (e.g., stomach fullness). Individuals with sensory sensitivities may perceive eating as unpleasant because of its sensory load, and in order to avoid unpleasant sensory experiences, they may refrain from eating (35). Further, we found that AN-R and AN-BP differed in sensory processing when compared to HCs. Both subgroups exhibited more sensation sensitivity and sensation avoiding than HCs, whereas only the AN-R subgroup exhibited less sensation seeking than HCs. Low sensation seeking among AN-R could reflect the same phenomena discussed above that sensory input is perceived as unpleasant. Binge-purge episodes seen in AN-BP are accompanied by sensory stimulation and can be seen as a way to seek sensory experiences. Therefore, it is possible that low sensation seeking acts as a protective factor from these episodes for those with AN-R, whereas those with AN-BP tend to seek sensations. Additionally, only the AN-BP group exhibited lower registration, implying a lower threshold for noticing sensory stimulation, as compared to HCs. Low registration is associated with hyporesponsiveness to sensory stimulation among individuals with ASD (36). Therefore, low registration could also contribute to binge-purge episodes among AN-BP individuals as these episodes include high sensory stimulation.

After controlling for BMI, significant group differences remained only in sensory sensitivity between individuals with AN and HCs. This may indicate that some aspects of atypical sensory processing relate to acute AN. In the context of other ASD traits, many studies have reported that these traits both precede the onset of AN and remain after recovery from it (37–39). Some studies have found elevated ASD traits only during acute AN (40). It is suggested that starvation or other issues related to acute AN may strengthen ASD traits, which may also be true in the context of sensory processing (22). It has been suggested as well that low BMI may heighten the vigilance for sensations (12) that may be one acute AN related factor contributing to sensory processing atypicality. However, it has also been reported that sensory sensitivity and differences in sensory responses persist after weight recovery (10–12, 41). Therefore, sensory sensitivity seems to be a trait, whereas other dimensions of sensory processing may reflect some acute illness related processes.

In this study, we found that more atypical sensory processing predicted eating disturbances after group (AN or HC) and ASD traits were already considered, implying that sensory processing independently contributes to eating disturbances. Interestingly, we found this association only when eating disturbances were measured with SWEAA that includes questions of disordered eating typical to individuals with ASD, such as disturbed eating related to sensory issues, social situations, motor control, selective eating, as well as understanding hunger and satiety signals (30). In contrast, atypical sensory processing did not predict symptoms of eating disorders when measured with the widely used EDE-Q questionnaire, which includes questions about eating, weight, and body shape concerns. We suggest that this indicates that among individuals who exhibit sensory processing difficulties, eating disorder symptoms are qualitatively different from what has traditionally been regarded as eating disorder symptoms in AN, and which are measured by EDE-Q (such as weight and shape concerns). This can be a reason why these individuals have challenges in benefiting from traditional treatment methods (20, 21).

We also found that increased atypical sensory processing predicted lower BMI, indicating increased severity of AN. This is in line with a previous study showing that sensation sensitivity was positively correlated with lower minimum BMI during the eating disorder among those with AN (12). It is, therefore, possible that both high sensory sensitivity and low sensation seeking contribute to low weight. It has also been suggested that a low BMI may mute aversive sensory stimuli and therefore help cope with sensory overload (12). To summarize, sensory processing difficulties may contribute to the core symptoms of AN, including eating disturbance and low body weight, thus contributing to the illness severity.

Atypical sensory processing is likely to manifest specifically among those individuals with AN who have also high ASD traits (14). Our findings suggest that elevated traits of ASD, and particularly atypical sensory processing, predict the core symptoms of AN. Characteristics of ASD in individuals with AN manifesting either as a comorbid ASD diagnosis or increased ASD traits have been found to increase the risk for illness prolongation and poor prognosis (20, 21, 37). Sensory processing difficulties may be one ASD-related factor that contributes to poor prognosis in AN. Therefore, those with high ASD traits could benefit from treatment modifications that take aspects of sensory processing into account.

Limitations

ASD traits were measured with a self-report questionnaire that is dependent on the participants' ability to recognize and verbalize these traits. Additionally, weight and height were self-reported, and some reporting bias may occur. In addition, the subtyping of AN (AN-R or AN-BP) was based on self-reported symptoms, not on clinical interview or diagnoses made by professionals. Further, comorbid conditions were assessed with self-report questionnaire rather than clinical interview. It is also possible that some comorbid symptoms, especially anxiety and depressive

symptoms that are very common in individuals with AN and play an important role in AN symptoms, (42) may also explain some of the group differences in sensory processing. All the participants were women; it is known that both quantitative and qualitative sex/gender differences exist in ASD traits, e.g., females with ASD have less repetitive and restricted behavior than males with ASD, and therefore, males with AN and ASD traits may also exhibit a different pattern of sensory processing (43). Therefore, our results may not be generalizable to men with AN.

CONCLUSION

In this study, we found sensory processing differences in individuals with AN compared to healthy individuals. Participants with both subtypes of AN exhibited increased sensory sensitivity and sensory avoiding, whereas only those with AN-R subtype exhibited decreased sensory seeking, and only those with AN-BP subtype exhibited lower registration, as compared to HCs. After controlling for BMI, group differences remained only in sensory sensitivity between individuals with AN and HCs. This may indicate that sensory sensitivity is a stable trait, whereas other aspects of atypical sensory processing may be related to acute AN. Higher ASD traits and increased atypical sensory processing predicted higher ASD-related eating disturbance and lower BMI, implying that sensory processing differences may contribute to illness severity. In the future, it is crucial to recognize atypical sensory processing patterns when treating individuals with AN, especially among those with high ASD traits, and develop treatment modifications for those with AN and atypical sensory processing.

DATA AVAILABILITY STATEMENT

The datasets presented in this article are not readily available because the data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy. Requests to access the datasets should be directed to emma.saure@helsinki.fi.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Ethics Committee of Helsinki Uusimaa Hospital District. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

ES contributed to the conceptualization, conducting the research, data analysis, and writing the original manuscript. TL-P, AR, and ML contributed to the conceptualization and manuscript's editing and revision. All authors contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIAL

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Risk of Dental Caries and Erosive Tooth Wear in 117 Children and Adolescents' Anorexia Nervosa Population—A Case-Control Study

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Introduction: Restrictive type of *anorexia nervosa* (AN) is still one of the most severe eating disorders worldwide with an uncertain prognosis. Patients affected by AN should be encouraged to undertake psychiatric care and psychotherapy, but whether they should necessarily be included in careful dental care or not may still be questionable. Even though there is a constantly increasing number of AN studies, there are just a few data about the youngest group of AN children and adolescents aged < 18.

Methodology: This case-control study aimed to compare the dental health and gingival inflammation level in female adolescent inpatients affected by severe AN restrictive subtype vs. controls. Based on clinically confirmed 117 AN cases (hospitalized in years 2016–2020 in public Psychiatric Unit, BMI < 15 kg/m^2, mean age 14.9 ± 1.8), the dental status has been examined regarding the occurrence of caries lesions using *Decay Missing Filling Teeth* (DMFT), erosive wear as *Basic Erosive Wear Examination* (BEWE), gingival condition as *Bleeding on Probing* (BOP) and plaque deposition as *Plaque Control Record* (PCR). The results were compared with age-matched 103 female dental patients (BMI 19.8 ± 2.3 kg/m^2, age 15.0 ± 1.8, $p = 0.746$) treated in a public University dental clinic.

Results: AN patients were found to present a higher incidence of oral-related complications according to dental status (DMFT 3.8 ± 4.5 vs. 1.9 ± 2.1, $p = 0.005$), erosive tooth wear (BEWE 18.9 vs. 2.9%, $p < 0.001$), less efficient in controlling plaque (PCR 43.8 vs. 13.7%, $p < 0.001$) and gingival inflammation (BOP 20.0 vs. 3.9%, $p < 0.001$) compared with female adolescents. In the AN group, a significant correlation between BOP, BEWE, and duration of AN disease ($p < 0.05$), similarly to the number of decayed teeth D, filled teeth F and PCR were detected ($p < 0.05$).

Conclusions: Although the obtained results did not reveal any severe oral status, our findings indicated impaired dental and gingival conditions in young anorexics.

Considering AN's potential role in oral health, it is essential to monitor dental treatment needs and oral hygiene levels in their present status to prevent forward complications in the future.

Keywords: anorexia nervosa, adolescence, oral health, caries, erosion, dental plaque, gingival inflammation

INTRODUCTION

Restrictive type of *anorexia nervosa* (AN) is still one of the most severe eating diseases worldwide with an uncertain prognosis as 1.2–2.2% of girls/women are suffering from full-blown anorexia nervosa (AN) during their lifetime; even more, than 4% are considered as an atypical form (1–3). Unfortunately, some of the cases are not included in statistics due to a lack of insight into the disease or reluctance to start therapy (2). Anorexic type of eating disorder (ED) often begins quite early, even at 12-years-old or younger (1). A reason why oral status is vital at this age may be explained by their developmental period when the permanent teeth mineralization and periodontal tissue are formulated (4). Any case of oral imbalance may provide long-lasting consequences in their future oral health. Severely ill adolescents with AN are at risk of extremely low body weight, macro/micronutrient deficiencies (5), and combined with diminished salivation and neglecting of hygiene habits, protection for dental or periodontal tissues may be lost at an older age (6–8). Significant dental caries, erosive tooth wear, and loss of periodontal health were observed in other studies considering adult AN subjects (8, 9). However, in the available literature, few scientific reports focused on the oral status among AN individuals under the age of 18 and affected by disease < 5 years, i.e., during the first acute stage of ED (10, 11). It is proven that AN patients should be encouraged to undertake psychiatric/psychotherapy (11). However, whether they should be included in careful dental care may still be considered in an open discussion. Therefore, each oral health assessment among young AN patients may provide important directions for dental care and answer questions about what type of oral care elements should be considered in adolescent AN patients.

The study aimed to establish the oral status regarding caries incidence, tooth wear, gingival inflammation, and oral hygiene levels among severely ill adolescent inpatients diagnosed with AN.

The null hypothesis assumed no significant difference in the oral disease symptoms between patients with AN and healthy individuals matched in early adolescence.

METHODS

Participants

The case-control study was conducted according to the Good Clinical Practice guidelines and the pattern of the Declaration of Helsinki after approval by the Bioethics Committee of the Poznan University of Medical Sciences (Resolution No. 66/12). The content of the study was explained to all 220 participants, who gave their informed written consent to participate in it. Additionally, a parent or legal guardian's approval was needed for inclusion in the project. A lack of acceptance from patients, parents, or legal guardians excluded such subjects from the study. The subjects were assigned to two groups: the anorexic (AN) group and the control (Ctrl) group (**Table 1**).

The AN group consisted of one-hundred-seventeen consecutive adolescent patients from the mid-west part of the country admitted in the acute phase of AN to one public Psychiatric Unit for Child and Adolescents from 2015 to 2020. Patients admitted to the hospital were primarily female because, during the survey, only one boy was hospitalized and suspected to be affected with AN. Still, he was excluded from the study group due to statistical reasons. Diagnosis of the restrictive subtype of AN was confirmed after a semistructured interview conducted by a child and adolescent psychiatrist based on ICD-10 (code F50.1) and DSM-5 (code 307.1) criteria (12, 13). The study group had similar clinical characteristics (restrictive type) concerning their menstrual status (secondary amenorrhea). Other inclusion criteria assumed that the symptoms of the AN disease lasted < 12 months, and only patients who suffered from the main type of AN were enrolled. All patients were hospitalized in the same public Psychiatric Unit for Children and Adolescents for the first time. The medical examination was taken during the acute stage of the symptoms (BMI < 15 kg/m^2) within the patients' 1st week after admission. The participants did not suffer from any other somatic disorder. A bulimic type of anorexia was excluded from the study to achieve homogeneity among the participants. Other exclusion criteria were: chronic somatic diseases or other mental/neurodevelopmental disorders (a primary disease in relation to eating disorders), hereditary disorders (first-degree relatives), pharmacotherapy, hormonotherapy, pregnancy, contraception, dietary supplements, smoking. Inclusion and exclusion criteria are described particularly in **Table 1**.

The control group (Ctrl group) consisted of one-hundred-three female teenagers recruited among one-hundred-thirty dental patients attending routine dental care in the public University dental clinic matched in terms of age (12–18 years) and sex (female) in respect to the studied AN group in the same period. The control group consisted of eumenorrheic and generally healthy girls who agreed to participate in the study. Patients attending for urgent or non-routine treatment were excluded from the control group. Notably, no control subject reported any eating disorders in the past. Other exclusion criteria in the Ctrl group related to general health were: chronic somatic diseases, mental or neurodevelopmental disorders, hereditary disorders (first-degree relatives), pregnancy or breastfeeding, pharmacotherapy, hormonotherapy, dietary supplements, or contraception (**Table 1**). We found the following potential confounders: social status, uncontrolled diet, number of meals,

TABLE 1 | Inclusion and exclusion criteria for both groups.

Criteria for inclusion into the study group (AN)	Criteria for inclusion into the control group (Ctrl)	Criteria for exclusion from study and control groups
Children of female sex aged 12–18	Children of female sex aged 12–18	Adolescents aged > 18 Male sex
Children with diagnosed AN restrictive subtype in accordance with ICD-10 and DSM-V diagnostic criteria (diagnosis confirmed by two independent psychiatrists)	Lack of mental disorders—assessment with the use of ICD-10 and DSM-V diagnostic criteria (confirmed by two independent psychiatrists). Children without hereditary mental disorders (first-degree relatives)	Children with disorders of the central nervous system (e.g., epilepsy, serious injuries, and CNS infections) Coexisting: schizophrenia, bipolar affective disorder, any serious somatic disorders
Clinically significant AN symptoms lasting over six months	No ED symptoms in present and past times	Chronic somatic diseases Persistent pharmacotherapy Hormonotherapy Contraception Pregnancy Dietary supplements
BMI < 15 kg/m^2	BMI 17–24 kg/m^2	BMI > 25 kg/m^2
A patient, parent or legal guardian approval	A patient, parent or legal guardian approval	Lack of acceptance from patients, parents or legal guardians
N smokers	No smokers	Smoking
	No urgent dental recall visit	Professional scaling Orthodontic treatment Antibiotic therapy Anti-inflammatory drugs 3 months before dental examination

AN, anorexia nervosa; ED, eating disorders; ICD-10, International Statistical Classification of Diseases and Related Health Problems (10th edition); DSM-V, Diagnostic and statistical manual of mental disorders (5th ed.); CNS, Central Nervous System; BMI, Body Mass Index.

mineral composition of teeth, the buffer capacity of saliva, oral pH, the frequency of tooth brushing, and using different oral hygiene products. Additionally, eligible volunteers were excluded if they were children of dental professionals/dental students and had received any general or oral care that could bias their gingival status (**Table 1**). The flow chart of the study is described in **Figure 1**.

Anthropometric measurements (height, weight) and an assessment of oral condition were taken within the patients' 1st week after admission of malnourished AN patients. Body height was measured with a SECA 216 wall stadiometer with an accuracy of 0.1 cm while the child was standing (14, 15). Bodyweight was recorded in light clothing on a digital scale with an accuracy of 0.1 kg (14, 15). Body mass index (BMI) as ratio of body weight (kg) to (height)^2 and percentage of ideal body weight (% IBW) as ratio of actual to ideal weight (IBW) × 100% where IBW (kg) = height (cm) – 100 – {[(height (cm) – 150)]/2} according to the Lorentz formula (14–16).

Clinical Dental Examination

The clinical dental examination included such elements as oral hygiene and gingival status regarding inflammation, evaluation of dental tissues using standardized indicators of dental caries, and erosive tooth wear (see description below). Before the study, two qualified dentists were trained and calibrated to a gold standard (EP, AH). Examiner reliability was acceptable for the oral examination parameters because the ICC values and Cohen's Kappa coefficient were ≥0.9 ($p < 0.001$).

Dental plaque and gingival conditions were recorded using a manual graded periodontal WHO probe (LM-instruments, LM8 5050 probe, Osakeyhtiö, Parainen, Finland). The probe consisted of a 0.5 mm ball at the tip and had mm markings at 3.5, 8.5, 11.5 mm and color-coding from 3.5 to 5.5 mm. The probing was performed using only gentle probing forces with a periodontal probe of suitable dimensions (force 0.25–0.30 N). Plaque control was evaluated using the dichotomized Plaque Control Record index (PCR) (17). Gingival inflammation was determined using the Bleeding on Probing index (BOP) (18), measured in six points of the gingival sulcus of all teeth (excluding the third molars) by the same WHO probe. The proportion of surfaces (%) with dental plaque or bleeding-on-probing gums was calculated as % of sites (17–19).

After cleaning and drying (excluding the third molars), the teeth surfaces were scored under good dental lighting, without magnification (20). Dental examination records included the number of carious teeth, the number of restored teeth by fillings, and the number of missed teeth due to caries, using the Decayed, Missing, Filled teeth (DMFT) score evaluating dental caries (20).

The dental examination also included erosive tooth wear by Basic Erosive Wear Examination (BEWE) score (21). The BEWE is a partial scoring system that recorded the most acutely affected accessible dental surfaces (buccal, lingual, occlusal) in a sextant. Criteria for erosive wear estimation were in the following grades:

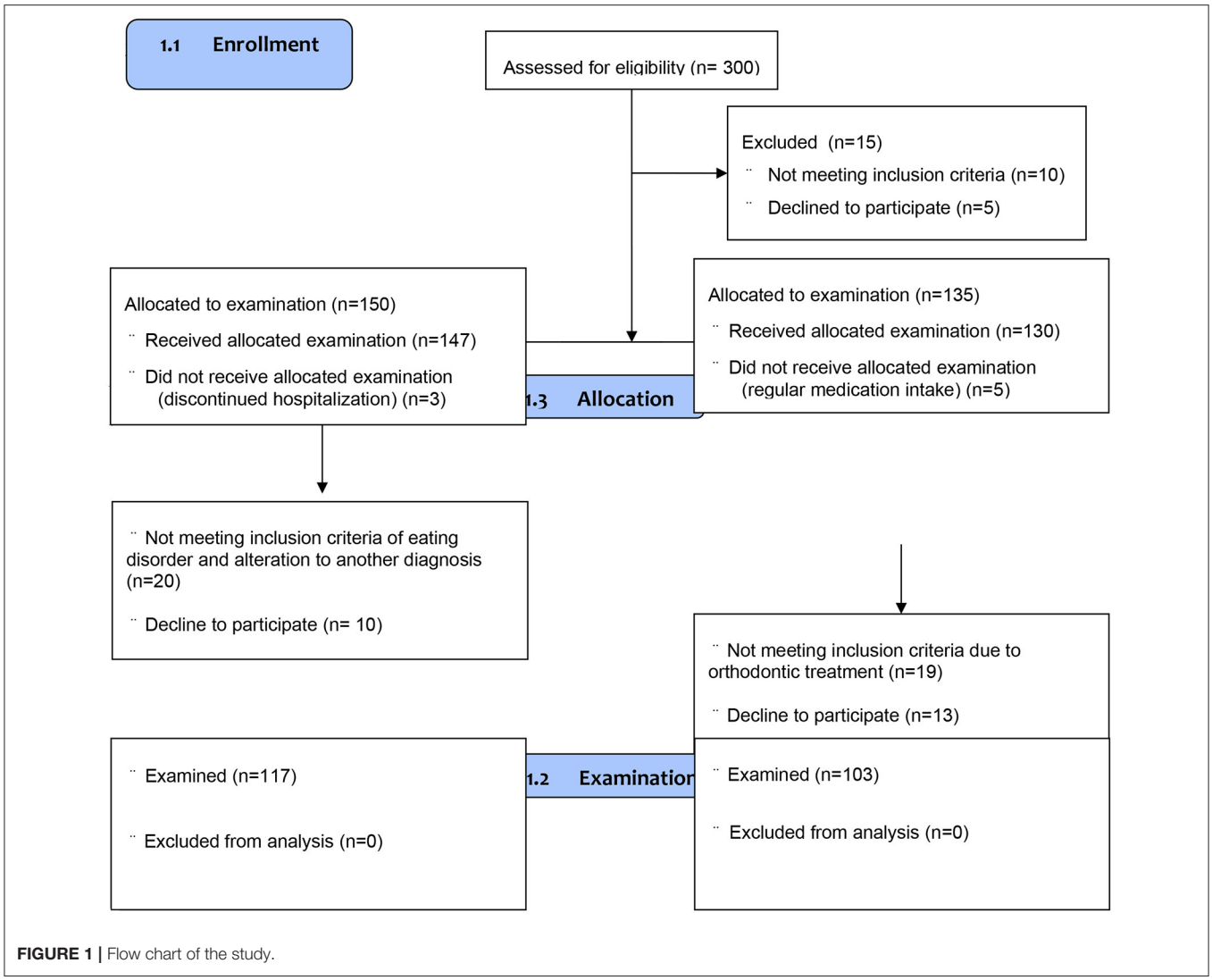

FIGURE 1 | Flow chart of the study.

0—erosive tooth wear absent; 1—initial loss of dental structure (dentine not involved); 2—significant hard tissue loss < 50% of the surface area (dentine involved); 3—significant hard tissue loss higher than 50% of the surface area (dentine involved) (22).

Statistical Analysis

As appropriate, the analyzed data were expressed as mean ± standard deviation, median, minimum and maximum values, interquartile range, or percentage. Normality of distribution was tested using the Shapiro–Wilk test (interval scale). Two unpaired groups were compared using the Mann–Whitney U-test (data were not normally distributed or ordinal data). The relationship between variables was analyzed with Spearman's rank correlation coefficient (when data were not normally distributed or ordinal data). Categorical data were analyzed with the χ^2 test or the Fisher-Freeman-Halton test (for contingency table larger than 2 × 2 with any expected values was less or equal to 5). Statistical analyses were performed with STATISTICA 13.0 (StatSoft Inc., Tulsa, USA) or StatXact 11.0 (Cytel Inc., Waltham, Massachusetts, USA). Multivariate analysis as logistic regression (backward, forward) was also carried out to determine the AN group's risk factors. The odds ratio and 95% confidence intervals were set for the indicated variables. This way, the answer to the question was which of the independent variables significantly influences the AN group. Therefore, a relationship was sought between the probability of disease occurrence and the group of independent variables. The parameters taken for analysis were selected following previous research and the observations found in the literature. The variables included in the logistic regression were: BMI, duration of AN illness, DMFT, PCR, BOP, and BEWE. Logistic regression calculations and intra-examiner calibration results (ICC) and Cohen's Kappa coefficient were performed in a statistical package MedCalc v. 19.5.1 (MedCalc Software, Ostend, Belgium). All results were considered significant at $p < 0.05$.

Considering the size of the target AN population, the sample size was based on European data between 8 and 13 AN cases on 100,000 adolescent females. Similarly, in Poland, AN's frequency is estimated between 0.8 and 1.8% of girls under 18 y.o. (23, 24).

TABLE 2A | Comparison of anthropometric and oral parameters between AN patients and controls.

Group variables	All $n = 220$	AN $n = 117$	Ctrl $n = 103$	*p*-value
Age	15.1 ± 1.8	14.9 ± 1.8	15.0 ± 1.8	0.746 (ns)
Weight (kg)	44.9 ± 11.1	37.0 ± 5.5	53.9 ± 8.7	<0.001
Height (cm)	162.5 ± 7.3	161.1 ± 7.6	164.1 ± 6.6	<0.001
BMI (kg/m^2)	16.8 ± 3.6	14.2 ± 1.5	19.8 ± 2.3	<0.001
IBW (%)	65.6 ± 13.1	56.2 ± 7.5	76.1 ± 9.7	<0.001
Duration of AN disease	–	11.1 ± 7.2	–	–
Number of teeth	27.7 ± 1.3	27.6 ± 1.8	27.8 ± 0.5	0.837 (ns)
D	0.7 ± 2.0	1.2 ± 2.6	0.1 ± 0.4	<0.001
	0 (0–21)	**0** (0–21)	**0** (0–2)	
M	0.1 ± 0.3	0.1 ± 0.5	0.0 ± 0.0	0.017
	0 (0–3)	**0** (0–3)	**0** (0–1)	
F	2.2 ± 3.0	2.5 ± 3.6	1.8 ± 2.0	0.914 (ns)
	1 (0–16)	**1** (0–16)	**1** (0–10)	
DMFT	2.9 ± 3.7	3.8 ± 4.5	1.9 ± 2.1	0.005
	2 (0–21)	**2** (0–21)	**2** (0–10)	
PCR (% of sites)	29.7 ± 25.0	43.8 ± 23.4	13.7 ± 15.4	<0.001
	25 (0–100)	**40** (10–100)	**10** (0–54)	
BOP (% of sites)	12.5 ± 17.6	20.0 ± 20.1	3.9 ± 8.1	<0.001
	5 (0–90)	**15** (0–90)	**0** (0–35)	
BEWE *n* (%)	25 (21.7)	22 (18.9)	3 (2.9)	<0.001
≤2	4 (3.9)	1 (1.0)	3 (2.9)	
3–8	19 (16.2)	19 (16.2)	0 (0)	
9–13	2 (1.7)	2 (1.7)	0 (0)	
≥14	0 (0)	0 (0)	0 (0)	

Description of the abbreviations: mean ± standard deviation SD; Median (Minimum–Maximum); ns – not significant; duration of AN disease is expressed in the number of months.

TABLE 2B | Socio-economic status, education, blood parameters among AN group.

Group variables		AN $n = 117$	
Duration of school education (y.)	8.7 ± 1.6 **9** (6–11)	First menstruation (age)	12.12 ± 1.12 **12** (11–15)
Mother graduated education	**3** (1–4)	WBC	5.34 ± 1.76 **5.1** (2.4–11.1)
Father graduated education	**3** (1–4)	NEU	↓1.96 ± 1.14 **1.89** (0.57–5.36)

Description of the abbreviations: mean ± standard deviation SD; Median (Minimum–Maximum); y.-years; parents graduated education division (1) Primary, (2) Vocational, (3) Secondary, (4) Higher; WBC- white blood cells were the reference level (reference values 4–10,000/ul; NEU-blood neutrophils level was decreased (reference values 2,500–5,000/ul).

It was calculated using Cochran's formula (25) that at least 36–59% of the target AN eligible population individuals should be surveyed to reach a margin level of 2% at the confidence level of 95%.

The reporting of the study was made according to the Strengthening the Reporting of the Observational Studies in Epidemiology (STROBE) guidelines (**Supplementary Material**).

RESULTS

Demographic and Clinical Characteristics

All details of socio-demographic data, height, weight, BMI, and IBW% are presented in **Table 2A**. The mean age of all participants was 15.1 ± 1.8. No significant differences were found in age between all groups ($p = 0.746$). BMI was in the normal weight range for the Ctrl group (19.8 ± 2.3), while it was under the threshold of 15 kg/m^2 (severe underweight) for the AN group (14.2 ± 1.5, $p < 0.001$). Participants in the AN group were 32% lighter in weight than those in the healthy Ctrl group ($p < 0.001$). AN individuals suffered from eating disorder symptoms for at least < 12 months; the mean duration time was 11.1 ± 7.2 months.

Although cell blood tests still showed a satisfactory WBC level in AN groups, neutrophiles maintained under a lower reference level (**Table 2B**).

TABLE 2C | Comparison of duration of disease, BMI, PCR%, BOP%, BEWE in AN subgroups according to purging episodes.

Subgroup variable	AN without purging episodes $n = 99$	AN with purging episodes $n = 18$	*p*-value
BMI	14.1 ± 1.5	15.0 ± 0.9	<0.05
	14.2 (10.7–19.1)	**14.8** (13.7–16.6)	
Time duration of AN disease (months)	10.1 ± 5.9	15.1 ± 8.1	<0.004
	8 (2–36)	**12** (6–36)	
PCR (% of sites)	40.0 ± 22.2	59.8 ± 32.4	<0.05
	37.5 (10–90)	**50** (15–100)	
BOP (% of sites)	15.3 ± 18.0	41.1 ± 30.6	<0.005
	10 (0–60)	**35** (0–90)	
BEWE	0.3 ± 1.3	5.6 ± 2.5	<0.001
	0 (0–8)	**5** (3–12)	

Description of the abbreviations: mean ± standard deviation SD; Median (Minimum–Maximum); ns – not significant; duration of AN disease is expressed in the number of months.

In both groups (AN and controls), there was no presence of primary teeth. We performed an oral examination for gingival bleeding and dental parameters recording on permanent teeth. The most relevant findings of the present study were the tendencies for dental caries, and poor oral hygiene connected with gingival bleeding detected in the oral cavities of anorexic patients compared with those in the Ctrl group. Dental examination indicated that 37.6% of AN patients vs. 11.7% of the controls were affected by dental caries. Continuously there was a significantly higher DMFT score than in the controls (3.8 ± 4.5 vs. 1.9 ± 2.1, $p < 0.005$), as well as the number of decayed teeth (1.2 ± 2.6 vs. 0.1 ± 0.4, $p < 0.001$), the number of missing teeth (0.1 ± 0.5 vs. 0, $p < 0.02$) (**Table 2A**).

There was a significant difference in prevalence and severity of erosive tooth wear. A BEWE score ≤ 2 was detected in 18.9% of AN patients as compared with 2.9% Ctrl subjects ($p < 0.001$) but no present any higher score ≥ 3 (0% among Ctrl group) (**Table 2A**).

Regarding periodontal parameters, the mean percentages of sites with dental plaque and bleeding on probing were significantly higher among AN patients than in controls (43.8 ± 23.4 and 20.0 ± 20.1 vs. 13.7 ± 15.4 and 3.9 ± 8.1, $p < 0.001$, twice respectively) (**Table 2A**).

Comparison of PCR, BOP and BEWE in AN subgroups divided according to vomiting incidents showed significant differences in worse results for AN subgroups with purging episodes ($p < 0.05$; $p < 0.005$; $p < 0.001$, respectively). However, AN patients from the purging subgroup presented a higher BMI index and more extended AN disease history (15.0 ± 0.9, $p < 0.05$; 15.1 ± 8.1, $p < 0.004$, respectively) (**Table 2C**).

Correlations Between Analyzed Variables

In the AN group, Spearman analysis showed correlation between anthropometric measurements as percentage of ideal body weight (% IBW) and blood tests as WBC ($r_s = 0.39$; $p = 0.009$), neutrophile level ($r_s = 0.38$; $p = 0.011$). As to neutrophile level there was correlation found to PCR ($r_s = 0.32$; $p = 0.031$) and BOP ($r_s = 0.30$; $p = 0.047$). Other associations evidenced a significant relationship between duration of AN disease and BOP ($r_s = 0.19$; $p = 0.036$), BEWE ($r_s = 0.28$; $p = 0.002$). Moreover, PCR was correlated to the number of decayed teeth ($r_s = 0.41$; $p = 0.0001$), the number of restorations F ($r_s = 0.29$; $p = 0.002$), DMFT ($r_s = 0.49$; $p = 0.0001$) and BOP showed significant association with the number of decayed teeth D ($r_s = 0.42$; $p = 0.0001$), number of restorations F ($r_s = 0.29$; $p = 0.001$), DMFT ($r_s = 0.49$; $p = 0.0001$), PCR ($r_s = 0.92$; $p = 0.0001$). The correlation was also observed in tooth wear score BEWE and PCR ($r_s = 0.21$; $p = 0.033$) and BOP ($r_s = 0.24$; $p = 0.010$).

In the AN group, regarding the socio-economic relationship Spearman analysis showed a significant association between mother's education level and DMFT index ($r_s = 0.39$; $p = 0.022$). Father's education level was correlated to the number of missing teeth M ($r_s = -0.38$; $p = 0.027$), PCR ($r_s = 0.35$; $p = 0.041$) and BOP ($r_s = 0.39$; $p = 0.024$).

The AN group's main correlations are shown in **Figures 2A–C**.

In the Ctrl group statistical analysis showed significant correlations between anthropometric and oral parameters such as age and DMFT ($r_s = 0.37$; $p = 0.0002$) and BEWE score ($r_s = 0.24$; $p = 0.016$). The BMI was correlated to the number of decayed teeth ($r_s = 0.21$; $p = 0.042$), filled teeth ($r_s = 0.32$; $p = 0.001$), DMFT ($r_s = 0.35$; $p = 0.0003$), BOP ($r_s = 0.21$; $p = 0.037$). There was also a relationship between the number of carious teeth and dental plaque as PCR ($r_s = 0.25$; $p = 0.012$), BOP ($r_s = 0.33$; $p = 0.014$). Dental plaque as PCR% and BOP% revealed a distinct association ($r_s = 0.67$; $p = 0.0001$).

From the group of variables included in the logistic regression: BMI, duration of AN illness, DMFT, PCR, BOP, BEWE, the multivariate analysis model indicated three variables: BMI, DMFT, PCR, as they turned out to be statistically significant at the level of $p < 0.05$. The odds ratio (OR) of the BMI parameter was 0.07, which means that as the BMI increases, the chance of getting ill (being in a group

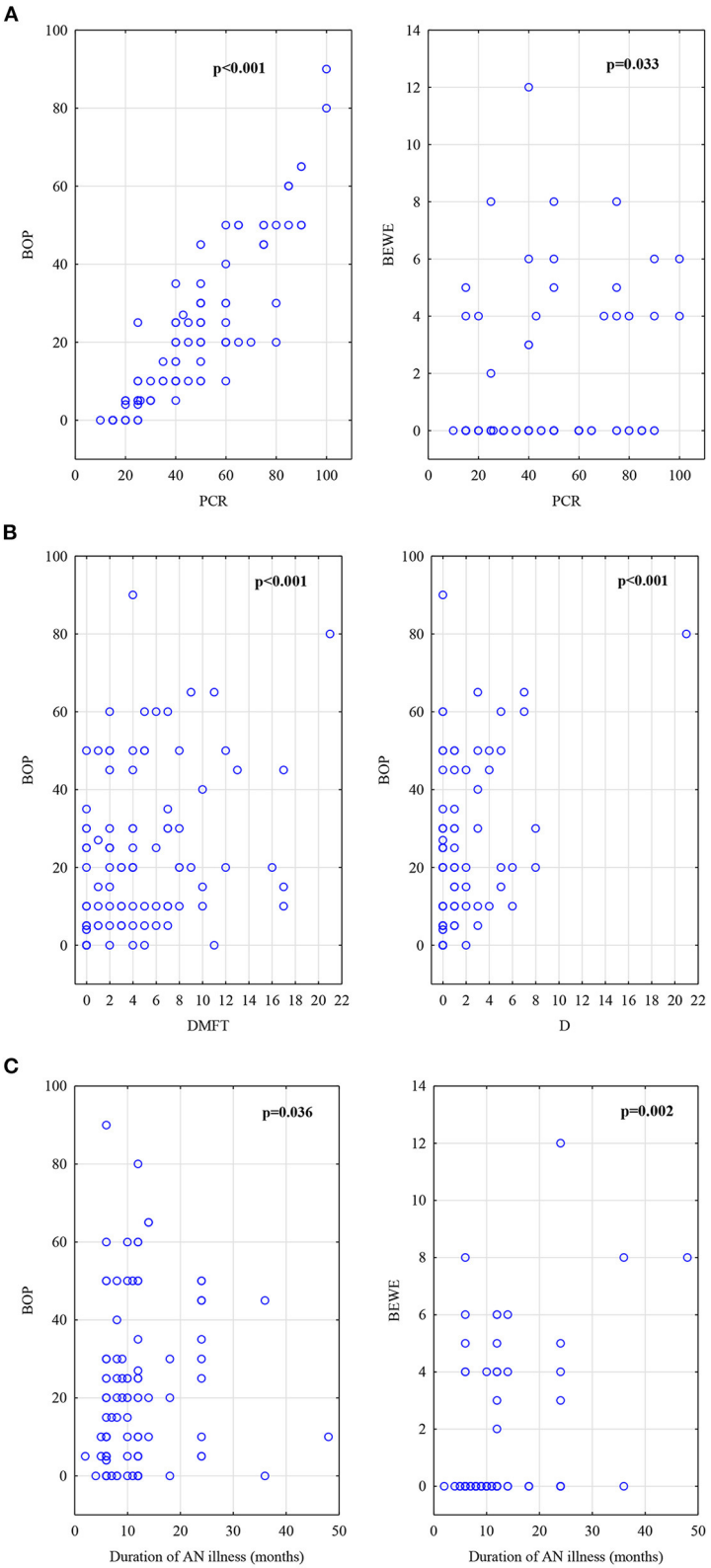

FIGURE 2 | (A) Correlations in AN group, BOP index and BEWE index to PCR index. **(B)** Correlations in AN group, DMFT score and D number to BOP index. **(C)** Correlations in AN group, BOP index and BEWE index to duration of AN illness (counted in months).

TABLES 3A and B | The logistic regression results indicated three variables: BMI, DMFT, and PCR. They turned out to be statistically significant at $p < 0.05$.

(A) Coefficients and standard errors

Variable	Coefficient	Std. error	Wald	*p*
PCR	0.08	0.03	7.02	0.008
DMFT	0.59	0.29	4.21	0.041
BMI	−2.62	0.67	15.51	0.0001
Constant	40.21	10.52	14.61	0.0001

Variables not included in the model

BEWE
BOP%

(B) Odds ratios and 95% confidence intervals.

Variable	Odds ratio	95% CI
PCR	1.08	1.02 to 1.15
DMFT	1.81	1.03 to 3.15
BMI	0.07	0.02 to 0.27

PCR, Plaque Index Record; DMFT-Decay, Missing and Filling Teeth index; BMI, Body Mass Index; BOP%, Bleeding on Probe index.

of AN) decreases. For DMFT, PCR the odds ratio was 1.81 and 1.08 (OR > 1), i.e., an increase by a DMFT index, PCR causes almost two times and 1.1 times higher a chance of being in the AN group, compared to the control subjects (**Tables 3A,B**).

DISCUSSION

In our study, patients from the AN group presented a higher incidence of oral-related complications regarding dental status and erosive tooth wear, less efficient control of plaque, and gingival inflammation than healthy subjects. A novel of our report is a collection of AN subjects in the youngest age under 18-years-old. After reviewing the literature on EDs, it should be noted that most oral clinical trials involved adult female patients (over 20 years of age) with a longer duration of AN than 5 years. Eating disorders are thus chronic diseases and are often associated with taking antidepressants and psychotropic drugs (26). Few dental analyses were based on a younger population of patients; the majority were limited in the number of cases and included a wide age range from 18 to 60-years-old (9, 27–40). Based on the analysis of the scientific literature, we found only nine studies separately involving young AN patients aged 18-years-old, as shown in **Table 4** (8, 27–34). The rest of the published studies related to the symptoms in the oral cavity of various types of EDs or AN patients represented <10% study group (9, 35–40). Selected results from 9 original studies indicated a significantly worse dental status in AN patients, which increased with their age and disease duration (8, 27–34). This is also in line with the literature reviews on the ED and oral implications (9, 41, 42).

Our subjects from the study group were young female AN patients up to 18 years of age in whom the disease only first developed. A dentist's support could counteract side effects and thus prevent permanent changes in oral homeostasis, which is also crucial for their health in the future (43–51). In the case of ED, including AN, the disease symptoms at an early age give an uncertain prognosis and reduce the chances of success in psychiatric therapy (3). The same thesis seems to apply to oral health. While in the case of the non-physiological destruction of teeth such as dental attrition or abrasion, implementation of changes in the patient's dental habits may stop tooth wearing. Unfortunately, the protection of teeth against caries or erosion is more multivariate, as it is often not conducive to the patient's general condition (44–52), selective low pH diet (52, 53), the insufficient activity of the salivary glands (6–8), salivary buffering capacity (54). Moreover, the dentist's commitment to dental patients affected by AN may motivate them to undertake general treatment and combat the disease (41, 42). Multidisciplinary support in the case of patients' severe psychosomatic conditions seems to be not only an empathetic or ethical but definitely a therapeutic indication (55, 56). Nevertheless, the multidisciplinary assessment of the AN adolescent population in longitudinal studies may be suggested for future research.

The mean DMFT score among AN subjects was significantly higher than the control group in the presented study. Other studies conducted on adult AN patients are similar (8, 33, 48). However, DMFT values usually reported higher numbers due to the older age of enrolled patients (>20-years-old), the chronic character of the disease (>5 years earlier AN diagnosis before oral examination), and psychotropic pharmacotherapy, which may limit salivary flow and make easier dental plaque colonization (8, 32, 48). Compared to a nationwide epidemiological oral health survey conducted in Poland among healthy age groups (15-year-olds, $n = 2{,}000$), the DMFT index among girls was estimated at the same level or higher than the obtained results (57–59). However, it may be commented that additional factors could influence the DMFT results as the different countryside living locations, mineral composition, the buffer capacity of saliva secretion, the frequency of tooth brushing, and the number of consumed meals, including carbohydrates (57–59).

The assessment of the BEWE index showed a low risk of dental erosion. It is worth noting that AN young patients (symptoms of ED had been observed for an average of 12 months) reported rare vomiting inducing. We suspect that the purging episodes had to occur much less frequently than in patients with bulimia nervosa (BN), in whom the severity of erosion is reported in the literature from 30 to 70% (49, 50, 52, 60–62). Pallier et al. (8) found a high risk of erosion in 16.7% of AN patients, but they studied much older adult female patients with long-term, chronic disease. However, the AN subgroups with purging episodes showed worse results concerning dental erosion. Apart from vomiting, more factors influence the BEWE score. The role of an acid diet may be crucial; foods and drinks predispose to decrease the pH of the oral cavity, especially in persons with

TABLE 4 | A synthesis of data obtained from the electronic research organized in PubMed database and Web of Science.

Clinical study (publishing year)	**Number of AN patients** (subtype)	**Age** range min-max or mean ± SD (years)	**Control group** +yes –no	**Oral examination**	**Significant results**
Hellström (27)	12 (restricting) 27 (purging)	rr 14–42 24.5 ± 1.3 26.2 ± 1.2	–	Caries, plaque, gingivitis, erosion, saliva analyses (secretion,pH, buffering)	More frequent erosion in purging type
Touyz et al. (28)	15	20.1 ± 8.3	+	DMFT, plaque, CPITN, erosion, recessions, salivary secretion, pH	Less plaque (51%) but more frequent gingivitis (16.9%) and recessions (10.2%), lower saliva pH (7.1 ± 0.4)
Daszkowska et al. (29)	15 (restricting) 35 (purging)	11.3–21.6	+	DMFT, caries frequency, erosion	94.3% caries frequency in restricting subgroup, vomiting was associated with greater erosion
Shaughnessy et al. (30)	23	rr 14.4–7.2	–	DMFT, OHI-S, erosion, recessions, MCW	DMFT (8.6), OHI-S: very good to excellent oral hygiene, recessions in 43% of AN subjects, no erosion detected (ns), MCW (4.8 mm)
Back-Brito et al. (31)	11 (restricting) 21 (purging)	rr 19–58 mean 26	+	Fungal flora	Common results calculated together with 27 BN subjects observed greater percentage for Candida species (74.6%)
Johansson et al. (32)	14	rr 10–50	+	DMFT, VPI, GBI, erosion, salivary secretion, soft tissue lesions	Common results calculated together with 8 BN and 32 EDNOS subjects as eating disorders (ED): lower VPI (7.1%) and GBI (1%), higher erosion, incidence of soft tissue lesions
Lourenço et al. (33)	18	rr 18–50	+	DMFT, gingivitis, periodontitis, erosion, salivary secretion, soft tissue lesions	Common results calculated together with 15 BN as ED: higher DMFT (8.8 ± 7.0), periodontitis, erosion, self-reported dentin hypersensitivity, incidence of soft tissue lesions, lower salivary flow rate
Garrido-Martínez et al. (34)	1 (restricting) 15 (purging)	rr 19–44 mean 27.6	+	DMFT, PI, erosion, salivary secretion, soft tissue lesions	Common results calculated together with other 43 ED patients: lower salivary flow rate, higher erosion and incidence of soft tissue lesions
Pallier et al. (8)	36	32.1 ± 9.1	+	DMFT, PI, BOP, BEWE.	Higher PI (78.8 ± 19.7%), BOP (41.3 ± 27.2%) and BEWE > 3 (41.7%)

Description of the abbreviations: mean ± standard deviation SD; rr, range of age as min-max; ns, not significant; BEWE, Basic Erosive Wear Examination; BN, bulimia nervosa; BOP, Bleeding on Probing; CPITN, Community Periodontal Index of Treatment Needs; DMFT, Decayed, Missing, and Filled Teeth; EDNOS, eating disorder not otherwise specified; GBI, Gingival Bleeding Index; GI, Gingival Index; MCW, mandibular cortical width; OHI-S, Simplified Oral Hygiene Index; PI, Plaque Index; VPI, Visual Plaque Index.

The following MeSH and non-MeSH search terms were used: ("Feeding" [MeSH terms] OR "Eating Disorders" [All fields] OR "Oral Health" [All fields]). "Feeding" and "Eating disorders" include the following terms: Anorexia Nervosa, Avoidant Restrictive Food Intake Disorder, Binge-Eating Disorder, Bulimia Nervosa, Diabulimia, Feeding and Eating Disorders of Childhood, Food Addiction, Night Eating Syndrome, Pica, Relative Energy Deficiency in Sport, Female Athlete Triad Syndrome, Rumination Syndrome. The search selected publications only with an anorectic group of patients published in English (9, 27–34).

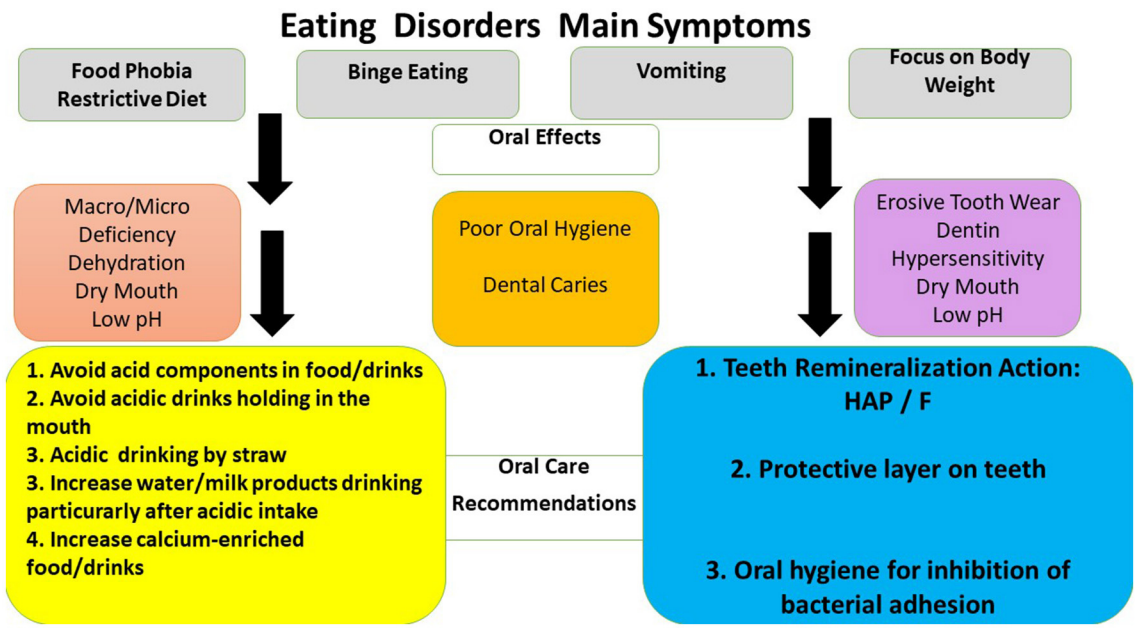

FIGURE 3 | Oral effects of eating disorders and oral care recommendations to health professionals and patients. HAP- oral care products containing synthetic hydroxyapatites, CPP-ACP- oral care products containing calcium-phosphate agents, F - oral care products containing fluoride products (73, 74, 76, 79).

severe ED when unstimulated saliva secretion is diminished (52, 53, 60, 61). Finally, it may also be connected with loss of hard tissues due to accompanying attrition or abrasion (62, 63). Shellis and Addy (63) pointed out that these processes coexist and have strong relationships. Comparing the findings on erosive changes among healthy 15-year-olds from southern Poland ($n = 181$), Kaczmarek et al. (62) observed only initial enamel erosion and more often observed it in boys than in girls. It is suggested that a low pH diet, especially drinks, and excessive physical activity may limit salivary buffer capacity at this age and stimulate non-carious dental tissue loss (64, 65).

It should be noted that AN subjects often perform excessive physical activities and prefer acid beverages, but they limit the amount of food consumption (32). The abovementioned data showed that dental erosion might occur among adolescents in various degrees of tooth wear with age. It is vital to adopt the hypothesis about the potential incidence of erosion among children (65).

In the AN group, poor dental hygiene and gingival inflammation are in line with other ED reports (11, 28, 32, 37, 40). In comparing our research with a national survey among healthy adolescents aged 16–18 years, Pietrzak et al. reached better dental hygiene results (66). We may explain our worse results; those dental examinations carried out in the first week after admission to the hospital ward might impact the worse oral hygiene conditions. The beginning of the hospital treatment seems to be a challenging period for AN patients, as they are mainly weakened and, at the same time, subjected to additional stress related to the hospital stay. All inpatients were enrolled in a behaviorally oriented nutritional rehabilitation program. They ate meals under the supervision of nursing personnel for 1-h observation. Thus, they could not perform hygienic procedures immediately after eating. Due to the nature of the therapy, meals contained a lot of simple sugars with a sticky consistency (e.g., jams, sweetened tea, white bread). Based on our observation and literature data, poor motivation to maintain good oral hygiene may also be influenced by a difficult life situation and the related apathy, depressed mood, psychomotor drive, and suicidal tendencies (67, 68). Other investigations indicated that a diet low in protein, vitamins, and unsaturated fatty acids contributes to metabolic and biochemical disturbances that cause an imbalance between oxidants and antioxidants (5–7, 53, 69). We agree with other authors that the pervasive state of malnutrition, especially in highly severe AN, influenced medical complications and a risk of rapid gingival inflammation (8, 9, 34). Obtained correlations to PCR and BOP indexes with lower neutrophile count results may suggest a relationship to the risk of gingival inflammation. It is worth quoting from other laboratory studies that about 80% of AN patients are affected by anemia, leukopenia 29%, neutropenia 79%, thrombocytopenia 25%, and 17% develop thrombocytosis (70). In our study, severe malnutrition and the laboratory-tested neutrophiles may explain the relationship between nutritional deficiencies and body defense and susceptibility to gingival complications (71, 72).

Consensus Report of the European Federation of Conservative Dentistry on eating disorders concluded that dental caries and erosion prevention objectives reduce or arrest the progression of these two processes, screening and

monitoring recall dental sessions (73). Our dental data indicated that the main tasks should include three directions: oral hygiene, remineralization, and diet advice (73–78). **Figure 3** shows that all preventive approaches may be applied (73, 79).

The present study's authors are aware of its limitations and recall most of them. The participants were not checked whether gastroesophageal reflux (GERD) or any other condition could have exposed their teeth to intrinsic sources of acid other than purging behavior. However, a qualified physician excluded any somatic diseases during a diagnostic interview. All patients were asked to express any digestive system ailments and did not report any symptoms. It is worth noting that all patients were hospitalized the first time after the onset of the AN disease. At this phase, a crucial hospitalization role was making the correct diagnosis but detecting any additional symptoms. The final diagnosis of all patients was the restrictive subtype of AN.

In addition, we can assume that the subjects had no comparable diet habits due to AN disease. It would be worth analyzing nutritional intake according to quantity and quality important from the point of view of oral health safety. According to diet behaviors in early disease development, anorexics do not have the same opinion on diet preferences. They often claim that they eat larger meals than before and start a selective diet. However, it is not easy to rely on such data. Studies have shown that their diet is low in carbohydrates (eliminated as the first ingredient). At the same time, protein and fat intake are maintained at an acceptable level, especially at the beginning of the disease (71, 80, 81). Besides protein-energy malnutrition (PEM), any deficiencies related to counts may raise the risk of bacterial infection.

It seems essential to consider a significant risk factor for erosive tooth wear among adolescents with purging/bulimic symptoms. Professional food and drink advice may have a preventive role to avoid erosive tooth wear (79). A significant limitation was a lack of data according to earlier oral status in both AN and Ctrl groups. This comparison could give additional conclusions for all children suffering from ED. Longer follow-up periods may be suggested to evaluate the clinical approach to oral health among AN patients.

Nevertheless, one may argue that we examined a small cohort of young AN patients under real-life conditions. Besides, family members were not included in the dental examination because living a long distance from the hospital clinic. Moreover, our project was also refined by the case-control design, and the assessment of oral clinical markers was based on visual criteria when examining the oral cavity. In detecting and assessing caries, digital devices could be implemented, e.g., DIAGNOdent Pen, DIAGNOcam and CarieScan PRO, but the visual DMFT index makes the results comparable to previously performed studies that focused on ED and AN. To our knowledge, this is the first clinical trial that compared such a group of AN patients in terms of homogeneity of subtype symptoms, adolescent age, sex, living area, nutritional status, and duration of disease, fewer than 5 years.

Even if our results are not enough to prove oral conditions among anorexic subjects, our limitations do not undermine the representativeness of the examined group.

CONCLUSIONS

Determination of AN restrictive subtype in adolescence may indicate numerous oral-related complications from dental caries, the beginning of erosive tooth wear, gingival inflammation development, and failure to cope with dental hygiene. Although the obtained results did not reveal any severe oral condition, there is a need for adequate oral hygiene/diet instructions combined with regular oral care to prevent forward complications in the patients' future.

Dental problems need to be tackled together with medical insight and interaction with physicians in the future. These disturbances to oral health should be routinely investigated, monitored, and treated during the perception of the primary disease. Multidisciplinary management of AN is essential to prevent the chronicity of the disorder and the potential severity of negligence.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Bioethics Committee of the Poznan University of Medical Sciences (Resolution No. 66/12). Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

AUTHOR CONTRIBUTIONS

EP, MT-N, and AS contributed to the conception and design of the study. AH, MR, KJ, and EP organized the database. MR performed the statistical analysis. EP performed clinical examinations. All authors contributed to manuscript revision and read and approved the submitted version.

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SUPPLEMENTARY MATERIAL

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Anxiety and Food Addiction in Men and Women: Results From the Longitudinal LIFE-Adult-Study

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Background: Anxiety is a widespread phenomenon, and it is connected to disordered eating and obesity. We want to analyze the connection between anxiety and food addiction (FA) over two points in time to better understand the directionality of the association. Since there are gender differences with regard to anxiety and eating, we are also interested in differences between men and women.

Methods: We used data from the population-based LIFE-Adult-Study (N = 1,474) at time 1 (baseline) and time 2 (first follow-up) to analyze the connections between anxiety (GAD-7) and FA (YFAS) using a multiple group latent cross-lagged panel model with female and male participants as groups. We controlled for age, marital status, socioeconomic status and social support.

Results: Anxiety (women: $\beta = 0.50$, $p \leq 0.001$; men: $\beta = 0.59$, $p \leq 0.001$) as well as FA (women: $\beta = 0.37$, $p \leq 0.001$; men: $\beta = 0.58$, $p \leq 0.001$) exhibited stability over time for both genders. We found a significant association between anxiety at time 1 and FA at time 2 for women ($\beta = 0.25$, $p \leq 0.001$) but not for men ($\beta = 0.04$, $p = 0.10$), and significant associations between FA at time 1 and anxiety at time 2 for women ($\beta = 0.23$, $p \leq 0.001$) as well as men ($\beta = 0.21$, $p \leq 0.001$).

Conclusion: Food addiction longitudinally affects anxiety, independent of gender and other sociodemographic variables. In addition, anxiety affects subsequent FA as well, but only in women. Interventions that address FA could reduce anxiety in men and women, while interventions that mitigate anxiety could help prevent FA in women.

Keywords: gender, GAD-7, YFAS, anxiety, longitudinal, food addiction

INTRODUCTION

Anxiety and anxiety symptoms are a widespread phenomenon (1, 2). For example, studies report a lifetime prevalence of generalized anxiety disorder (GAD) of around 3.7% (3), and of sub-threshold GAD of around 12.4% (4).

Anxiety is associated with eating-related health outcomes, as research links it to disordered, emotional, uncontrolled, and binge eating behaviors (5–8). In addition, studies show associations with obesity (9, 10) as well as bulimia, binge eating disorder and night eating syndrome that all involve excessive forms of eating behavior and food consumption (8, 11, 12).

While cross-sectional studies suggest an empirical connection between anxiety and eating, the direction of the connection is not clear to date, due to the lack of longitudinal studies in the field. Do increased levels of anxiety contribute to problematic eating behaviors, e.g., as a way of coping, or do problematic forms of eating longitudinally increase anxiety, e.g., *via* disturbing physiological homeostasis? It may also be that both phenomena are mutually dependent on each other in a longitudinal perspective.

In our study, we want to add to the literature by applying a cross-lagged design with two time points in order to evaluate the direction of the effects of the associations between anxiety and food addiction (FA). We chose FA for our analysis since, compared to eating disorders and obesity, it is more common in the general population and more accessible in terms of prevention measures. A current review shows a clear empirical connection between FA and binge eating disorder, bulimia nervosa, and obesity (13). FA has been validated in multiple international studies (14–16), and it is associated with typical addiction phenomena, i.e., brain reward dysfunction, preoccupation, risky use, impaired control, tolerance/withdrawal, social impairment, chronicity, and relapse (17). FA has already been connected to anxiety in cross-sectional research (18–20).

Since the literature shows that women are more likely than men to exhibit anxiety (21, 22) and FA (23, 24) and that the connection between anxiety and disordered eating could be moderated by gender (25, 26), we will further analyze whether the cross-lagged effects between anxiety and FA differ by gender.

MATERIALS AND METHODS

Study Design and Participants

The Adult Study of the Leipzig Research Centre for Civilization Diseases (LIFE) is a population-based cohort study in the city of Leipzig, Germany. It is a collaboration of several clinical and epidemiological research teams, for which 10,000 participants between 18 and 80 years were recruited through age- and gender-stratified random selection by the local residents' registry office. The only exclusion criterion was being pregnant. The majority of participants (84.9%) were above 40 years of age. The LIFE-Adult baseline examination was carried out between 2011 and 2014, when every participant provided written informed consent prior to participation. Participants underwent a set of assessments, including interviews, questionnaires, and medical examinations. Details on study design, methods and assessments can be found elsewhere (27). The follow up examination took place between 2017 and 2021 with a total of 5,665 individuals completing the postal questionnaires.

For our analyses we included those 1,934 participants that were asked for their eating behaviors and took part in the baseline assessment (time 1) as well as in the follow-up (time 2). We excluded participants who were living in retirement/nursing homes, with relatives or in some form of supported living because we assumed that this would affect their eating behaviors ($N = 60$). In addition, we excluded individuals with diabetes, and those that stated they were treated for a disease, when treatment or disease were likely to have an impact on eating behavior, like ulcer or cancer ($N = 361$). In addition, another 39 individuals had to be excluded due to missing information on covariates, resulting in a final analytical sample size of $N = 1{,}474$. There was no significant age difference between our sample and the other participants from the LIFE study at baseline, but our sample contained slightly less female participants (53.0% vs. 48.2%).

Ethics

The LIFE-Adult-Study complies with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008. The study was approved by the ethics committee of the University of Leipzig.

Measures

Anxiety

In order to measure anxiety, we used the Generalized Anxiety Disorder Scale-7 (GAD-7), (28, 29) which contains seven items that can be answered on a scale from "0" (=never) to "3" (=almost every day). The items refer to typical anxiety symptoms, like worrying, nervousness, and irritability, and higher scores represent higher levels of anxiety.

Food Addiction

We used the Yale Food Addiction Scale (YFAS); (30, 31) to assess FA. The scale contains 25 items with mixed response categories (dichotomous and Likert-type). The seven subscales of the YFAS represent the criteria for an eating addiction in line with the guidelines for substance dependence according to DSM-IV, like control over consumption and withdrawal. They were computed using the algorithm proposed in Gearhardt et al. (30). The eighth item (clinical significance) was excluded, so that the YFAS measurement resembles a symptom count without diagnosis at both times. Scores range from 0 to 7 with higher scores representing higher levels of FA.

Sociodemographic Variables and Covariates

Participants were asked for information on age, gender, marital status, and medical history in standardized interviews by trained study personnel. They also provided information on education, equivalent household income, and occupational status that was used to compute socioeconomic status (low, medium, and high); (32). We assessed social support *via* the 5-item ENRICHD Social Support Scale (33). We decided to include social support as a

covariate based on our own theoretical considerations as well as on the literature (34).

Statistical Analyses

Descriptive statistics of the analytical sample were estimated using Stata version 16 SE (Stata Corp., College Station, TX, United States). In particular, gender-stratified means with SDs and numbers of cases with percentages were reported for quantitative and qualitative measures, respectively.

The bidirectional relationships between FA and anxiety were examined using a latent autoregressive cross-lagged panel model with multiple groups, estimated in Mplus 8.6 (35). The model consists of three parts: the autoregressive paths a_1 and a_2 indicate the intraindividual stability of FA and anxiety over time (**Figure 1**). The two cross-lagged paths b_1 and b_2 represent the reciprocal effect of FA at time 1 on anxiety at time 2 and vice versa. Finally, the cross-sectional paths c_1 and c_2 model the covariance between FA and anxiety within each wave of assessment. The multiple-group option in Mplus allows estimating and comparing the depicted cross-lagged path model between men and women simultaneously.

Individual items of the GAD-7 and the subscale scores of the YFAS were entered as ordered categorical in Mplus and the constructs were modeled as latent variables. First, both constructs were evaluated separately using confirmatory factor analysis (CFA). With regard to the YFAS, the subscale "attempts" did not significantly predict the latent variable at time 1 ($\beta = 0.197$, $p = 0.056$) and time 2 ($\beta = 0.010$, $p = 0.937$) and was subsequently excluded from the analyses. Second, measurement invariance across time (i.e., time 1 and time 2) and across groups (i.e., men and women) was evaluated by introducing equality constraints on model parameters (e.g., factor loadings, intercepts, and variances) in a series of models with increasingly restrictive hypotheses. Parameters that proved not invariant, as indicated by model fit indices and chi-square difference tests in Mplus, were allowed to vary across time and groups. Error terms of the GAD-7 items and the YFAS subscales were set to be pairwise correlated over time, and factor means of the latent variables were allowed to vary by gender. Next, the partially invariant measurement models for FA and anxiety were combined to estimate the cross-lagged panel model shown in **Figure 1**. The model was finally adjusted for age, marital status, SES and social support at time 1. Results are presented as fully standardized (STDYX) regression coefficients with 95% confidence intervals for the paths a_1 to c_2 in the final cross-lagged model.

Since items of the GAD-7 and the computed subscale scores of the YFAS were ordered categorical, the WLSMV estimator in Mplus was used for the estimation of effects. Missingness on single indicators of the GAD-7 and the YFAS were handled using Full Information Maximum Likelihood (FIML) estimation, as implemented in Mplus. As indices of goodness-of-fit, the Tucker-Lewis fit index (TLI), the comparative fit index (CLI) and the root mean square error of approximation (RSMEA) were computed, with values below 0.06 for the RMSEA, and values above 0.95 for the TLI and CFI indicating a good model fit (36). All tests were two-tailed with $p < 0.05$ indicating statistical significance.

RESULTS

Our sample included 711 (48.2%) female and 763 (51.8%) male participants with an average age of 57.6 (female) and 58.4 (male) years. **Table 1** gives an overview of the general characteristics of our sample.

Table 2 depicts the correlations between key variables of our analysis, and shows that all of them are significantly correlated.

Model Fit

After adjustment for covariates, the final multiple-group cross-lagged panel model with partial measurement invariance yielded an excellent fit of the data ($\chi^2(988) = 1{,}372.07$, $p > 0.001$; CFI = 0.971; TLI = 0.970; RMSEA = 0.023). This model with

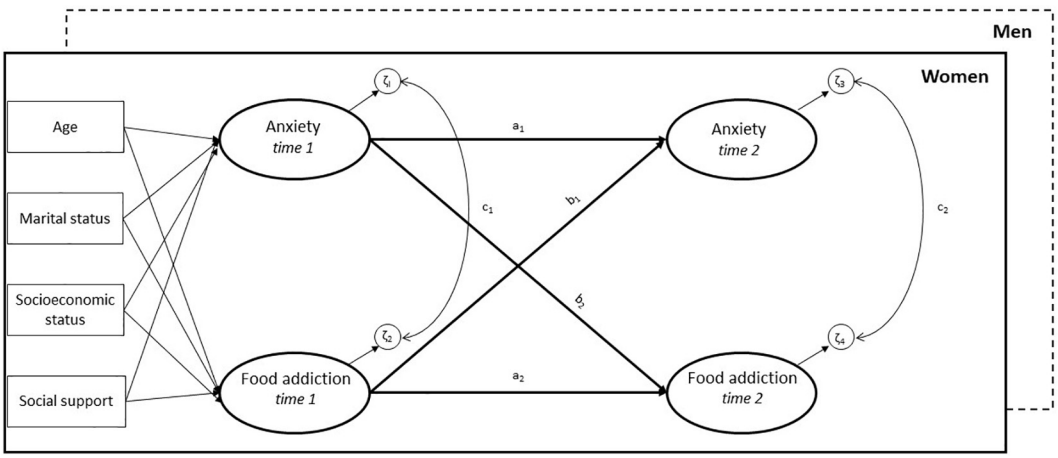

FIGURE 1 | Multiple-group latent autoregressive cross-lagged panel model of the association between anxiety and food addiction. a_1, a_2: autoregressive paths, b_1, b_2: cross-lagged paths; c_1, c_2: cross-sectional paths. The measurement models for the latent variables with pairwise correlated errors over time are not shown. Model adjusted for age, marital status, socioeconomic status and social support at time 1.

TABLE 1 | General characteristics of the study population.

	Women (*N* = 711)	Men (*N* = 763)	Total (*N* = 1,474)
Age *n.s.*	57.6 (14.5)	58.4 (14.9)	58.0 (14.7)
Marital status* **			
Married	431 (60.6%)	515 (67.5%)	946 (64.2%)
Single	148 (20.8%)	160 (21.0%)	308 (20.9%)
Divorced	80 (11.3%)	65 (8.5%)	145 (9.8%)
Widowed	52 (7.3%)	23 (3.0%)	75 (5.1%)
Socioeconomic status[1]**			
Low	119 (16.7%)	100 (13.1%)	219 (14.9%)
Medium	436 (61.3%)	443 (58.1%)	879 (59.6%)
High	156 (21.9%)	220 (28.8%)	376 (25.5%)
Social Support (ESSI; 5 – 25) *n.s.*	22.5 (3.2)	22.3 (3.4)	22.4 (3.3)
Anxiety (GAD-7; 0 – 21)			
Time 1***	3.5 (3.2)	2.5 (2.5)	3.0 (2.9)
Time 2***	3.7 (3.5)	2.7 (2.8)	3.2 (3.2)
Food addiction (YFAS; 0 – 7)			
Time 1 *n.s.*	1.4 (0.9)	1.3 (0.7)	1.3 (0.8)
Time 2*	1.4 (0.9)	1.3 (0.7)	1.3 (0.8)

*$p \leq 0.05$; **$p \leq 0.01$; ***$p \leq 0.001$; n.s., not significant (referring to differences between female and male participants). Continuous variables are given as mean (standard deviation), and p-values refer to independent t-tests; categorical variables are displayed as numbers (percentages), and p-values refer to Chi 2 –tests.
[1]Socioeconomic status was computed based on education, occupational status, and equivalent household income (32).

TABLE 2 | Correlations of key variables for women and men.

	1	2	3	4
Women				
1. Anxiety time 1	–			
2. Anxiety time 2	0.52***	–		
3. Food addiction time 1	0.23***	0.27***	–	
4. Food addiction time 2	0.24***	0.20***	0.28***	–
Men				
1. Anxiety time 1	–			
2. Anxiety time 2	0.52***	–		
3. Food addiction time 1	0.16***	0.16***	–	
4. Food addiction time 2	0.09*	0.10*	0.23***	–
Total				
1. Anxiety time 1	–			
2. Anxiety time 2	0.53***	–		
3. Food addiction time 1	0.21***	0.23***	–	
4. Food addiction time 2	0.19***	0.17***	0.26***	–

*Pearson's correlation, two-tailed. *$p \leq 0.05$; **$p \leq 0.01$; ***$p \leq 0.001$.*

gender-specific paths for the autoregressive, cross-sectional and cross-lagged effects fitted the data statistically better than a model with each of the effects constrained across gender ($\chi^2(4) = 17.33$, $p = 0.002$). Standardized coefficients and standard errors of the significant paths obtained from the final model are shown for both genders in **Figure 2**.

Autoregressive Paths

Autoregressive paths (a_1, a_2) represent the stability of a concept over time. Both autoregressive effects for anxiety (women: $\beta = 0.50$, $p \leq 0.001$; men: $\beta = 0.59$, $p \leq 0.001$) as well as for FA (women: $\beta = 0.37$, $p \leq 0.001$; men: $\beta = 0.58$, $p \leq 0.001$) were statistically significant for both genders.

Cross-Sectional Paths

Cross-sectional paths (c_1, c_2) represent correlations between concepts at either time 1 or time 2. Female participants showed a significant correlation between anxiety and FA at time 1 ($r = 0.37$, $p \leq 0.001$) but no significant correlation at time 2 ($r = -0.02$, $p = 0.78$), while male participants exhibited significant correlations at time 1 ($r = 0.28$, $p \leq 0.001$) and time 2 ($r = 0.25$, $p \leq 0.05$).

Cross-Lagged Paths

Cross-lagged paths (b_1, b_2) represent prospective bidirectional associations between one concept and the other over the two points of time. We found an association between anxiety at time 1 and FA at time 2 for women ($\beta = 0.25$, $p \leq 0.001$) but not for men ($\beta = 0.04$, $p = 0.69$). In addition, there were significant associations between FA at time 1 and anxiety at time 2 for women ($\beta = 0.23$, $p \leq 0.001$) as well as men ($\beta = 0.21$, $p \leq 0.001$).

DISCUSSION

Our study addressed the associations between anxiety and FA in a longitudinal design, showing the significant stability of both constructs over time. There was a significant effect of FA at time 1 on anxiety at time 2 for both genders. Vice versa, only women showed a significant effect of anxiety at time 1 on FA at time 2.

The stability of anxiety (37, 38) and FA (39, 40) over time that we have obtained from our data is also reflected in the literature. In addition, the higher levels of anxiety in women at both times of measurement resonate with other international studies (41, 42). With regard to FA, we found no gender difference at time 1 but a significantly yet only slightly higher score for women at time 2. These results are in line with the literature that suggest either no gender effects (43, 44) or higher values for women (24, 45).

We found a cross-sectional association between anxiety and FA for women as well as men at time 1 and for men at time 2, which matches with other studies that suggest associations between FA and a higher prevalence of anxiety disorders in obese patients seeking bariatric surgery (46) and between FA and anxiety in general (19). The results indicate that both concepts are interrelated, and the lack of a significant association for women at time 2 that is not reflected in the correlational analysis (**Table 2**) can be seen as a consequence of the inclusion of control variables.

We also found evidence for cross-lagged effects. There is a significant effect of anxiety at time 1 on FA at time 2 for women, indicating that anxiety has different implications depending on gender. This gender-specific effect could be explained by rumination, a cognitive process and maladaptive strategy for emotion regulation that involves repetitive thoughts about

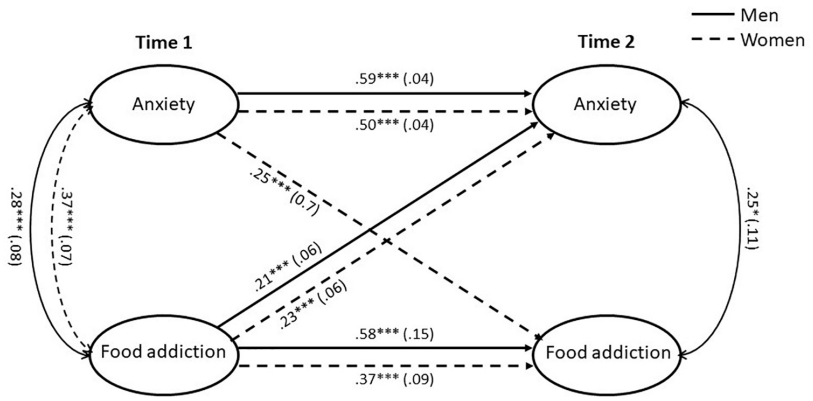

FIGURE 2 | Multiple-group latent autoregressive cross-lagged panel model with standardized beta coefficients and standard errors in parentheses. The model only displays the significant paths for men and women. The effects of control variables (age, marital status, socioeconomic status, social support) on anxiety and food addiction at time 1 were included in the estimation but not shown for ease of presentation. Sample size: 1,474 (48.2% female). $^{*}p \leq 0.05$; $^{***}p \leq 0.001$.

negative experiences and emotions. Rumination is empirically associated with both, anxiety and pathological forms of eating (47–49), and it has been connected to a variety of addictive behaviors, e.g., related to alcohol, work, or social media use (50–52). Furthermore, a current study suggests that targeting rumination could be important for reducing disinhibited eating patterns in women with normal body weight (53). Since women are more likely to ruminate than men (54), when men and women experience the same level of anxiety, women will be much more affected by rumination that then contributes to FA. This interpretation is in line with research that suggests that rumination mediated the connection between gender and food craving, binge eating, and eating pathology (55), that rumination can increase problematic alcohol and substance abuse, especially in women (56), and that women are more likely to exhibit emotional eating as a reaction to negative emotions (5, 57). Rumination has repeatedly been associated with exacerbating and maintaining psychopathology and physiological stress responses, prolonging negative emotional states, increasing negative emotional reactivity, interfering with problem solving, and acting as a transdiagnostic mental vulnerability (56). In that way, rumination that is associated with anxiety at time 1 could, in addition to maintaining anxiety over time as it is reflected in significant and substantial autocorrelations, set the stage for FA at time 2. On an applied level, our results indicate that interventions that mitigate anxiety could help prevent FA in women, who are more often affected by anxiety than men (58, 59). Meta-analyses show that measures based on cognitive behavioral therapy, delivered both online and offline (60, 61), are effective against anxiety, and a current study suggests that irrational beliefs could be a source of anxiety and a potential target for treatment in FA (62). By addressing anxiety, mental health professionals could not only mitigate FA in women, but they could also reduce the likelihood of a variety of negative health behaviors and outcomes that are related to FA, from unhealthy lifestyle habits (63) to eating disorders, mental illnesses, and obesity (19, 45, 64). Overweight and obesity are major risk factors for a variety of disorders, and they bear enormous costs for societies worldwide (65).

Our results further indicate a cross-lagged effect of FA at time 1 on anxiety at time 2 in both men and women. This could be a consequence of the fact that the overconsumption of food that is a central element of FA alters brain functioning and physiology, which then affects anxiety. Accordingly, there is a plethora of neurobiological studies that link the consumption of food that is high in calories, sugar, or fat to anxiety-like behaviors in rats and that emphasize the roles of certain brain circuits, neurobiological processes, and the immune system (66–68). In addition, research with human participants links disordered eating to subsequent increased anxiety and anxiety disorders (69, 70). Hence, interventions that address FA behaviors and food consumption could mitigate anxiety in men and women. Studies that address overeating and binge eating behaviors suggest that cognitive interventions that address internal food-related biases and response inhibition training, mindfulness-based interventions, and increasing physical activity could be promising avenues to address FA (71–73). A current study suggests that the treatment of FA could also benefit weight-related self-stigma and binge eating (74).

Limitations

While this study has several advantages, e.g., the large dataset and a longitudinal design, there are also certain limitations. First, FA was assessed *via* self-report, therefore we cannot rule out that there is a certain bias. Second, while we included established control variables in our model, there could be other variables that affect both anxiety and FA, e.g., specific personality traits, and future research may benefit from including them.

CONCLUSION

Our results show that FA longitudinally affected anxiety in both men and women, and that anxiety affected subsequent FA only in women. Hence, interventions that address FA could reduce

anxiety in both genders, while interventions that mitigate anxiety could help prevent FA in women.

DATA AVAILABILITY STATEMENT

The data analyzed in this study is subject to the following licenses/restrictions: The data that support the findings of this study are available from the corresponding author upon reasonable request. Requests to access these datasets should be directed to FH, Felix.Hussenoeder@medizin.uni-leipzig.de.

ETHICS STATEMENT

The LIFE-Adult-Study complies with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008. The study was approved by the Ethics Committee of the University of Leipzig. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

FH, AP, IC, and SR-H designed the study. FH and AP conducted the statistical analysis and literature searches. FH wrote the first draft of the manuscript. MGL, CE, SZ, NR, HG, AH, VW, MS, KW, TK, MKL, and AV contributed to the data and/or expertise. All authors contributed to and have approved the final manuscript.

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Food preferences and thyroid hormones in children and adolescents with obesity

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Background: Thyroid hormones profoundly affect energy metabolism but their interrelation with food preference, which might contribute to childhood obesity development, are much less understood. In this study, we investigated if thyroid hormone levels are associated with specific modulation of food preference and potentially linked to the level of obesity in children and adolescents.

Methods: Interrelations between food preference and peripheral thyroid activity were examined in a population of 99 non-obese and 101 obese children and adolescents (12.8 ± 3.6 years of age, 111/89 F/M) randomly selected from the patients of the Obesity and Metabolic Disease Out-patient Research Unit at National Institute for Children's Diseases in Bratislava in a period between December 2017 and March 2020.

Results: Children and adolescents with obesity had a lower preference for food rich in high sucrose and high-complex carbohydrates, while the preference for protein and fat-containing food and that for dietary fibers did not differ between obese and nonobese. In adolescents with obesity, free thyroxine (FT4) correlated positively with the preference for a high protein and high fat-rich diet, irrespective of the fatty acid unsaturation level. Moreover, FT4 correlated negatively with the preference for dietary fibers, which has been also exclusively found in obese adolescents. Individuals with obesity with higher FT4 levels had higher systemic levels of AST and ALT than the population with lower FT4. Multiple regression analysis with age, sex, BMI-SDS, and FT4 as covariates revealed that FT4 and male gender are the major predictors of variability in the preference for a diet high in protein, fat, and monounsaturated fatty acids. FT4 was the sole predictor of the preference for a diet containing saturated and polyunsaturated fatty acids as well as for a diet low in fiber.

Conclusion: The link between free thyroxin levels and dietary preference for food rich in fat and protein is present exclusively in individuals with obesity. Higher serum FT4 was linked with elevated AST and ALT in children and

adolescents with obesity, and FT4 was the best predictor for preference for food rich in fat and low in fiber. This may indicate that FT4 could contribute to the development of childhood obesity and its complications by modulating food preference.

KEYWORDS

food preference, children, obesity, thyroid hormones, FT4, high protein diet, high-fat diet, adolescents

Introduction

Food preferences represent choices of most satisfying and favored food components based on an individual's sensory and energy needs, which could significantly influence eating behavior and contribute thus to the development of obesity. Food preferences are modulated by many different food-related and internal psychological and physiological factors and signals aimed at securing the proper food choices necessary for individual health and survival (1). Food preferences begin taking shape during fetal development and continue changing throughout life, influenced by biological, social, and environmental factors. Early childhood seems to be a critical period to establish food preferences persisting in later life (2). Parents play a crucial role in shaping food preferences (3). Their choices of what to serve to exert influence on their children's food preferences because children's familiarity with food may be as influential as any particular taste. The social and emotional context of food also influences preferences (4). Thus, food preferences result from interactions between learned behavior and genetic and environmental factors and could be modulated by hormonal signaling (5).

Hormonal modulation plays an important role in food choices as it may change the sense of taste and specifically modify food intake (5). Hormones known to directly or indirectly regulate food intake and perception include leptin, ghrelin, glucagon-like peptide 1 (GLP1), cholecystokinin, insulin, vasoactive intestinal peptide (VIP), or peptide YY (5, 6). Ghrelin and leptin play an important role in appetite control and respond promptly to changes in energy availability (fasting/refeeding), as besides the brain, both peptides have receptors in metabolically relevant peripheral tissues, and recent research shows that they are also present in olfactory mucosa (7). Leptin targets peripheral taste organs in lean but not db/db obese mice, by selectively suppressing gustatory neural and behavioral responses to sweet compounds without affecting responses to other taste stimuli (8). Synchronization of diurnal variation in leptin levels and sweet taste recognition thresholds provides indirect evidence that leptin also modulates sweet taste recognition in humans (5, 8). Leptin is an adipocyte-secreted hormone that regulates food intake and whole-body energy expenditure and modulates thus body weight in humans. Leptin also contributes to thyrotropin-releasing hormone regulation in the hypothalamus (9). However, obesity is associated with hyperleptinemia due to leptin resistance (10). Glucagon-like peptide 1 (GLP-1) is a hormone produced in the small intestine in response to food intake, endowed with the capacity to enhance satiety (11). GLP-1 was shown to be produced in two distinct subsets of mammalian taste cells, while the GLP-1 receptor is expressed on adjacent intragemmal afferent nerve fibers. Dramatically reduced taste responses to sweet taste were found in *glp1-/-* mice, indicating that GLP-1 signaling might be critical for the maintenance of sweet taste sensitivity (12) and has a potential role in signaling sour or umami taste (13). Moreover, cholecystokinin (CCK) and peptide YY seem to have a role in processing perception of bitter compounds (14, 15). The above-mentioned capacity of hormones to modulate taste perception provides clear evidence for their involvement in food preference and macronutrient intake (5).

Hormones could also have an important role in the hedonic mechanisms of food intake influencing the dopaminergic system. Similarly to addictive drugs, palatable foods, which are rich in fat and sugar content, can significantly activate the dopamine reward system (16). Based on the role of the dopamine reward system in food-seeking behavior, considerable evidence has revealed that there is an interplay between the homeostatic regulator and dopamine system, such that homeostatic regulators of food intake interact with the dopamine reward system to exert an inhibitory or enhancing effect on food intake (17). It has been shown that leptin and insulin inhibit dopamine neurons, while ghrelin activates them. Hommel et al. established that ventral tegmental area dopamine neurons express the leptin receptor, and in response to leptin, these ventral tegmental area leptin receptors are activated and suppress the activity of dopamine neurons (18). Administration of leptin to the ventral tegmental area was found to decrease food consumption, while knockdown of leptin receptors in the ventral tegmental area resulted in an increase in food intake, locomotor activity, and hedonic feeding (17).

Thyroid hormones are important determinants of energy expenditure and appetite regulation as they are involved in the regulation of resting metabolic rate, *de novo* gluconeogenesis, and liver and adipose tissue lipolysis and lipogenesis (19). It is plausible to think that the regulation of these metabolic

processes might be tightly related to the regulation of taste perception and food preferences. To date, only a few studies in adults with hypothyroidism provided conflicting results on the effects of thyroid hormone replacement therapy on olfaction, taste, and food preferences (20, 21). Thyroid hormone secretion in children and adolescents is regulated similarly to that in adults, mainly through the hypothalamic-pituitary-thyroid axis (22). However, thyroid hormones in children and adolescents additionally have multiple functions affecting growth and development, including the development of the brain (23). Therefore, dysregulation of thyroid hormone secretion at young age can have serious developmental consequences.

Obesity is a serious condition, and already childhood obesity could have some serious consequences in later life. It was shown that almost 90% of the children who were obese at 3 years of age were overweight or obese in adolescence (24), around 80% of obese adolescents will still be obese in adulthood, and around 70% will be obese over the age of 30 years (25). Obesity is often associated with altered thyroid hormone levels, and their change could predict change in body weight. Among nonobese individuals in the Pizarra study ($n = 937$), those with higher levels of free triiodothyronine (FT3) or free thyroxine (FT4) had 3 times higher risk of becoming obese during the 6-year follow-up as compared with their counterparts with low thyroid hormone levels. Moreover, thyrotropin (TSH) and FT4 correlated with leptin, and FT3 correlated negatively with adiponectin (26, 27). A recent study has shown that obesity is associated with altered gene expression in human taste buds (28). It is widely accepted that metabolic surgery affecting the digestive as well as the hormonal milieu of the human body clearly modulates food preference, which might be linked with taste and odor sensing (29, 30). In this study, we hypothesized that thyroid hormones could be related to the modulation of food preferences and contribute thus to childhood obesity. Therefore, we investigated if thyroid hormone levels across different age groups are paralleled by specific modulation of food preference and, thus, could be potentially linked to the level of obesity in children and adolescents.

Materials and methods

Study population

In this study, we examined interrelations between food preference and peripheral thyroid activity in a population of 99 non-obese and 101 obese adolescents selected from the patients of obesity and metabolic disease out-patient research unit at the National Institute for Children's Diseases in Bratislava examined between December 2017 and March 2020. All children and adolescents with obesity, thyroid disorder, or healthy children aged >4 years referred to a pediatric endocrinologist with suspicion of thyroid disease were included. Individuals with any other chronic or acute metabolic disorder including diabetes mellitus and individuals with genetic syndromes were excluded. A total of 11 participants (5.2%) with incomplete food preference questionnaires were also excluded. There was no additional dropout. Participants did not have any specific medical-based dietary recommendations. At the time of the examination, anthropometric data were recorded, and blood was sampled for biochemical analyses while children and adolescents with or without the assistance of their parents/guardians filled out the food preference questionnaire.

Anthropometry

Anthropometric measurements were taken by trained nurses according to standardized protocols. Body mass index (BMI) was calculated as weight divided by the square of body height. The standard deviation score (SDS) for BMI was calculated using local reference values (31). Categories for the BMI SDS score were defined as follows: non-obese children and adolescents with a BMI SDS <1.88 and obese with BMI SDS ≥ 1.88. Both non-obese and obese patients were further stratified to low and high FT4 subpopulations according to the median level of free thyroxine.

Assessing food preferences

Food preferences were assessed using the validated food preference questionnaire (32). The food preference questionnaire requires patients to rate 72 food items on a 9-point scale ranging from "dislike a lot" (1), neutral feelings about the food (5) to "like a lot" (9). If patients did not have a memory of trying the particular food item or if they have never tested it, "I don't know" was selected. Food items were classified into 12 groups according to the nutrient composition; eight of them were used in this study (high sugar score, high complex carbohydrate score, high protein score, high-fat score, high saturated fatty acid score, high monounsaturated fatty acid score, high polyunsaturated fatty acid score, and low dietary fiber score).

Biochemical analyses

Blood for biochemical and hormonal analyses was collected from the serum tubes between 7.30 and 10.00 a.m. The samples were processed and analyzed as routine fresh samples by the clinical service laboratory at the National Institute for Children's Diseases. Thyroid hormone levels and biochemical markers describing the metabolic health in obese individuals were selected for the analyses.

TABLE 1 Basic characteristics of the study population.

	All	Non-obese	Obese	p
Age (years)	12.95 ± 3.29 (200)	12.48 ± 3.25 (99)	13.41 ± 3.28 (101)	**0.047**
Sex (% of girls)	55.5 (200)	67.7 (99)	43.6 (101)	**<0.001**
Height (cm)	158.14 ± 17.74 (200)	154.29 ± 18.25 (99)	161.91 ± 16.47 (101)	**0.002**
Height SDS	2.16 ± 2.68 (200)	0.07 ± 1.41 (99)	0.42 ± 1.17 (101)	0.052
Body weight (kg)	65.1 ± 29.11 (200)	47.56 ± 15.91 (99)	82.29 ± 28.9 (101)	**<0.001**
BMI (kg/m^2)	24.95 ± 7.85 (200)	19.3 ± 3.19 (99)	30.48 ± 7.08 (101)	**<0.001**
BMI SDS	0.25 ± 1.3 (200)	0.16 ± 0.99 (99)	4.12 ± 2.35 (101)	**<0.001**
TSH (mU/l)	3.01 ± 1.83 (200)	2.72 ± 1.53 (99)	3.31 ± 2.06 (101)	**0.023**
FT4 (pmol/l)	15.53 ± 2.6 (200)	16.03 ± 2.88 (99)	15.04 ± 2.21 (101)	**0.007**
FT3 (pmol/l)	6.96 ± 1.1 (142)	6.94 ± 1.11 (68)	6.97 ± 1.09 (74)	0.835
High sugar score	5.69 ± 1.36 (200)	5.99 ± 1.33 (99)	5.4 ± 1.35 (101)	**0.002**
High complex carbohydrate score	5.85 ± 1.25 (200)	6.04 ± 1.23 (99)	5.68 ± 1.24 (101)	**0.041**
High protein score	5.54 ± 1.52 (200)	5.57 ± 1.54 (99)	5.52 ± 1.51 (101)	0.820
High fat score	5.71 ± 1.38 (200)	5.86 ± 1.34 (99)	5.56 ± 1.41 (101)	0.122
Low fiber score	5.94 ± 1.38 (133)	6.11 ± 1.23 (69)	5.75 ± 1.51 (64)	0.131
Foods cotaining ≥1.5 g of saturated FA per 100 g	5.71 ± 1.32 (133)	5.93 ± 1.22 (69)	5.47 ± 1.38 (64)	**0.041**
Foods cotaining ≥1.5 g of polyunsaturated FA per 100 g	5.76 ± 1.3 (133)	5.97 ± 1.22 (69)	5.54 ± 1.35 (64)	0.057
Foods cotaining ≥1.5 g of monounsaturated FA per 100 g	5.73 ± 1.28 (133)	5.95 ± 1.21 (69)	5.49 ± 1.33 (64)	**0.040**

Data are expressed as the mean ± standard deviation. TSH, thyroid-stimulating hormone; FT4, free thyroxine; FT3, free triiodothyronine; BMI, body mass index; SDS, standard deviation score; FA, fatty acids. The p-value for the difference between populations of lean and obese children and adolescents, value in parentheses (number of participants). All significant values ($p < 0.005$) are in bold.

Statistics

Variables were checked for normality using the Shapiro–Wilk test. Normally distributed data are expressed as the mean ± SD. Non-normally distributed data (aspartate aminotransferase (AST), alanine aminotransferase (ALT), and ALT/AST ratio) are presented as the median and interquartile range. Differences between the two groups were tested using the two-sided Student's *t*-test or with Mann–Whitney *U* test and by Fisher's test for binary data. Univariate associations of food preferences with the other clinical variables were calculated using Pearson's correlation and linear regression. Multivariate associations between selected variables were determined using forward linear multiple regression analyses. Food preferences were used as dependent variables, and age sex, BMI-SDS, and FT4 were used as covariates. $p < 0.05$ was considered statistically significant. Statistical analyses were performed using the SPSS version 27 (IBM, USA), JMP (USA), and GraphPad Prism 7 (GraphPad, USA) software.

Results

Study population

This study included 200 children and adolescents; 99 were non-obese, and 101 had obesity. Characteristics of the study population are presented in Table 1.

Food preference in nonobese and obese children and adolescents

Obese participants (57 boys and 44 girls) indicated a lower preference for food rich in high sucrose and high complex carbohydrate, while the preference for protein and fat-containing food and for dietary fibers was not different in obese and non-obese groups. Participants with obesity had also a lower preference for food rich in high saturated and monounsaturated fatty acids, and the trend was found for a lower preference to eat a diet rich in polyunsaturated fatty acids (Table 1, Figure 1).

Thyroid hormones and food preferences

Interrelations between food preference parameters and serum levels of FT4, FT3, and TSH were examined in both, obese and non-obese children and adolescent populations. Children and adolescents with obesity had lower serum FT4 levels compared with non-obese participants (Table 1).

Serum FT4 levels in children and adolescents with obesity correlated positively with their preference for food containing high protein, high-fat diet, as well as with preference for a diet rich in saturated, monounsaturated, and polyunsaturated fatty acids, and with a diet low in dietary fibers (Figure 2). It is important to note that no significant

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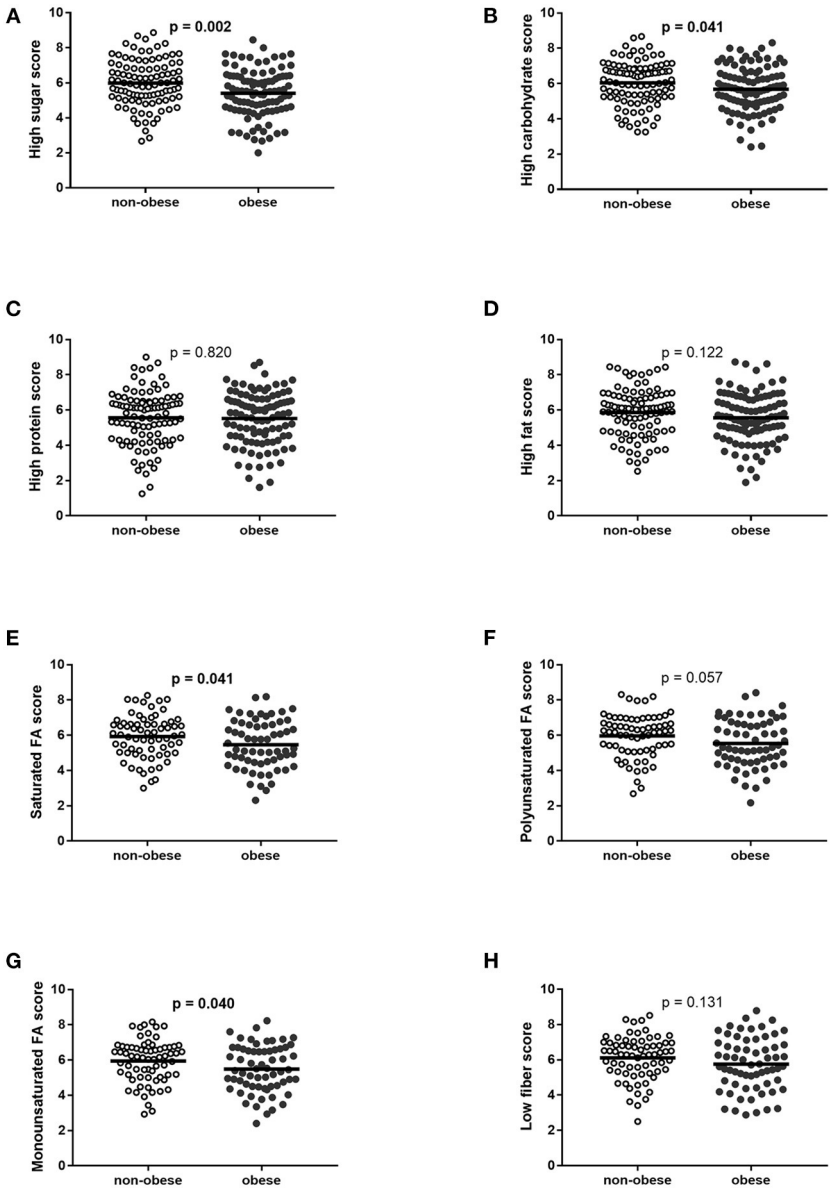

FIGURE 1
Food preferences in non-obese and obese children and adolescents. **(A)** High sugar score, **(B)** high carbohydrate score, **(C)** high protein score, **(D)** high-fat score, **(E)** high saturated fatty acid score, **(F)** high polyunsaturated fatty acid score, **(G)** high monounsaturated fatty acid score, and **(H)** low fiber score. Displayed as mean and confidential intervals for the mean. Differences were calculated using the *t*-test. FA, fatty acids.

correlations were found between FT4 and food preferences in the non-obese population of children and adolescents (data not shown).

Serum FT3 levels in the obese group correlated positively with dietary preference for food rich in carbohydrates ($r = 0.239$, $p = 0.040$), saturated ($r = 0.356$, $p = 0.019$), monounsaturated ($r = 0.322$, $p = 0.035$), and polyunsaturated fatty acids ($r = 0.345$, $p = 0.024$), as well as for food with low fiber content ($r = 0.336$, $p = 0.028$). In the non-obese population, FT3 levels correlated negatively with the preference for high carbohydrate food ($r = -0.307$, $p = 0.011$).

Serum levels of TSH did not correlate with any of the examined food preferences in neither obese nor non-obese populations.

Stratification of the patient population by the levels of FT4 reveals distinct patients' characteristics

Stratification of the patient population into low FT4 and high FT4 subgroups revealed no additional FT4-related

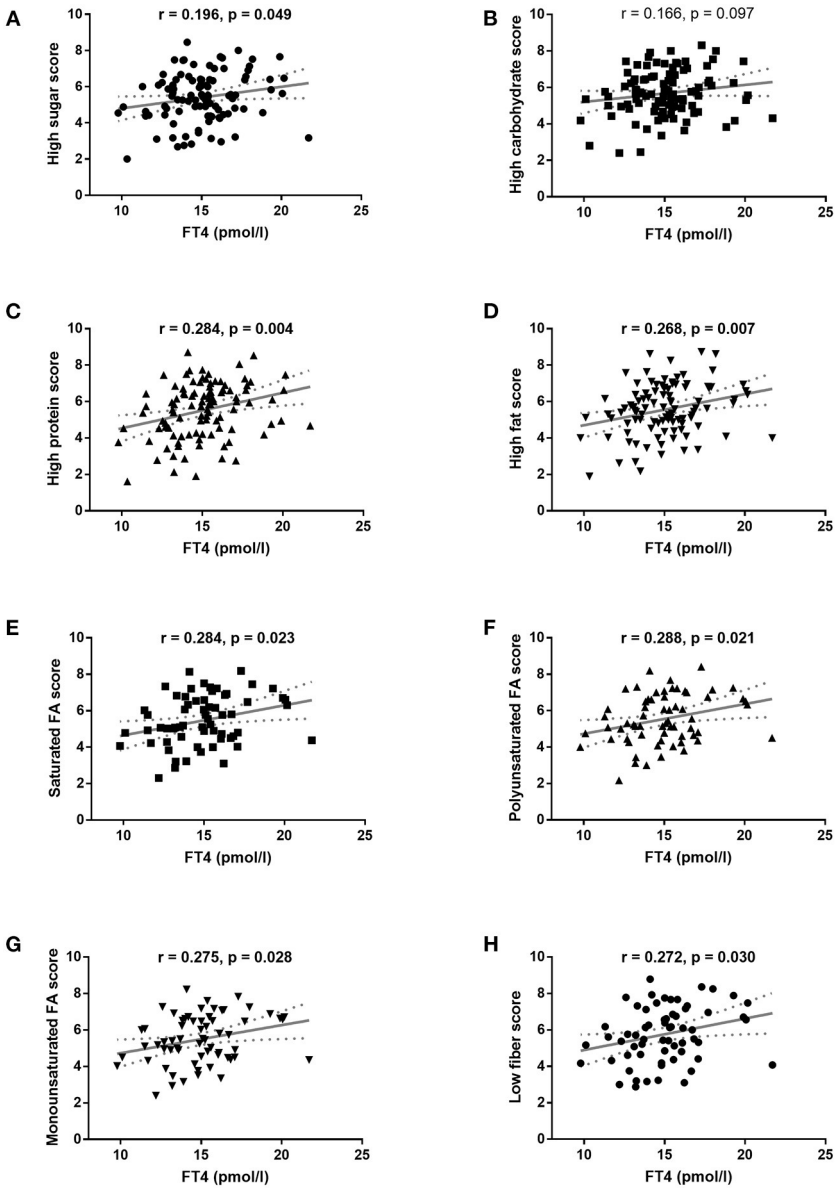

FIGURE 2
Pearson's correlation of food preferences with FT4 serum levels in obese children and adolescents. **(A)** High sugar score, **(B)** high carbohydrate score, **(C)** high protein score, **(D)** high-fat score, **(E)** high saturated fatty acid score, **(F)** high polyunsaturated fatty acid score, **(G)** high monounsaturated fatty acid score, and **(H)** low fiber score. Associations were calculated with Pearson's correlation. The regression line with 95% confidence intervals was calculated in linear regression analysis.

regulation of the dietary preference for food rich in simple and complex carbohydrates. However, participants with obesity and high FT4 levels showed a higher preference for food high in protein and fat. More detailed analysis revealed that higher FT4 levels were linked to an increased dietary preference for food items containing more than 1.5 g of fat per 100 g serving. This held true for food containing saturated, monounsaturated, and polyunsaturated fatty acids. Moreover, children and adolescents with obesity who had high FT4 levels preferred a diet with low fiber contents (Table 2).

Children and adolescents with obesity and high circulating FT4 were characterized by higher AST and ALT serum levels as compared with their counterparts with low FT4 levels. No significant differences in obesity level (BMI-SDS), fasting glycemia, urea, creatinine, uric acid, gamma-glutamyl transferase, alkaline phosphatase, and serum lipids were found in obese children and

TABLE 2 Selected phenotypes in children and adolescents stratified according to FT4 serum levels.

	Non-obese			Obese		
	Low FT4	High FT4	p	Low FT4	High FT4	p
Age (years)	12.19 ± 2.81 (50)	12.77 ± 3.65 (49)	0.378	13.54 ± 3.28 (49)	13.27 ± 3.31 (52)	0.680
Sex (% of girls)	70.0 (50)	65.3 (49)	0.671	51.0 (49)	36.5 (52)	0.164
BMI SDS	0.26 ± 1.03 (50)	0.07 ± 0.95 (49)	0.341	4.11 ± 1.99 (49)	4.12 ± 2.66 (52)	0.98
TSH (mU/l)	2.87 ± 1.64 (50)	2.56 ± 1.4 (49)	0.306	3.58 ± 2.33 (49)	3.05 ± 1.75 (52)	0.198
FT4 (pmol/l)	13.83 ± 1.56 (50)	18.28 ± 2.05 (49)	**<0.001**	13.33 ± 1.28 (49)	16.66 ± 1.58 (52)	**<0.001**
FT3 (pmol/l)	7.13 ± 1.01 (34)	6.74 ± 1.19 (34)	0.144	7.02 ± 0.94 (34)	6.93 ± 1.22 (40)	0.728
Fasting serum glucose (mmol/l)	4.89 ± 0.35 (27)	4.86 ± 0.45 (20)	0.748	4.88 ± 0.39 (32)	4.81 ± 0.42 (30)	0.494
Urea (mmol/l)	3.71 ± 1 (13)	3.98 ± 1.27 (9)	0.582	3.81 ± 0.84 (22)	4.15 ± 0.83 (25)	0.166
Creatinine (mmol/l)	48.53 ± 9.19 (30)	52.81 ± 10.79 (26)	0.157	51.08 ± 12.98 (36)	53.76 ± 14.32 (33)	0.419
Uric acid (μmol/l)	249.19 ± 68.94 (26)	261.62 ± 69.06 (21)	0.542	312.65 ± 78.3 (34)	325.21 ± 69.4 (34)	0.486
AST (μkat/l)	0.39 (0.32–0.45) (30)	0.36 (0.31–0.47) (27)	0.614*	0.39 (0.35–0.44) (35)	0.46 (0.37–0.53) (33)	**0.013***
ALT (μkat/l)	0.24 (0.21–0.35) (31)	0.25 (0.22–0.31) (27)	0.857*	0.35 (0.27–0.45) (35)	0.44 (0.37–0.77) (33)	**0.006***
ALT/AST ratio	0.866 (0.56–0.86) (30)	0.68 (0.58–0.81) (27)	0.955*	0.89 (0.74–1.19) (35)	1.07 (0.82–1.65) (33)	0.111*
GGT (μkat/l)	0.24 ± 0.13 (9)	0.17 ± 0.03 (4)	0.313	0.33 ± 0.18 (17)	0.38 ± 0.24 (21)	0.492
ALP (μkat/l)	3.75 ± 1.2 (14)	2.95 ± 1.52 (10)	0.162	3.9 ± 1.84 (19)	3.58 ± 1.5 (24)	0.532
Total-cholesterol (mmol/l)	3.88 ± 0.6 (28)	4.34 ± 0.94 (24)	**0.037**	4.15 ± 0.53 (34)	4.25 ± 0.71 (32)	0.493
HDL-cholesterol (mmol/l)	1.38 ± 0.25 (16)	1.52 ± 0.35 (14)	0.206	1.24 ± 0.27 (34)	1.27 ± 0.28 (30)	0.688
LDL-cholesterol (mmol/l)	2.36 ± 0.59 (15)	2.73 ± 0.6 (14)	0.104	2.62 ± 0.53 (34)	2.71 ± 0.71 (30)	0.582
Triglycerides (mmol/l	0.97 ± 0.5 (24)	0.9 ± 0.45 (23)	0.596	1.2 ± 0.62 (34)	1.09 ± 0.46 (32)	0.400
Insulin (mU/l)	14.78 ± 9.3 (10)	9.36 ± 3.17 (7)	0.162	22.81 ± 15.06 (30)	16.41 ± 9.72 (28)	0.062
High sugar score	5.98 ± 1.3 (50)	6 ± 1.36 (49)	0.939	5.25 ± 1.43 (49)	5.55 ± 1.25 (52)	0.259
High complex carbohydrate score	5.98 ± 1.29 (50)	6.1 ± 1.18 (49)	0.637	5.47 ± 1.28 (49)	5.88 ± 1.19 (52)	0.098
High protein score	5.64 ± 1.62 (50)	5.49 ± 1.47 (49)	0.64	5.08 ± 1.6 (49)	5.93 ± 1.3 (52)	**0.004**
High fat score	5.93 ± 1.42 (50)	5.8 ± 1.27 (49)	0.636	5.26 ± 1.47 (49)	5.85 ± 1.3 (52)	**0.033**
Low fiber score	6.22 ± 1.29 (35)	6 ± 1.18 (34)	0.462	5.35 ± 1.55 (32)	6.15 ± 1.37 (32)	**0.034**
Score for foods cotaining ≥1.5g of saturated FA per 100g	6.06 ± 1.28 (35)	5.8 ± 1.17 (34)	0.395	5.08 ± 1.4 (32)	5.85 ± 1.26 (32)	**0.023**
Score for foods cotaining ≥1.5g of polyunsaturated FA per 100g	6.09 ± 1.27 (35)	5.84 ± 1.17 (34)	0.402	5.17 ± 1.39 (32)	5.9 ± 1.22 (32)	**0.029**
Score for foods cotaining ≥1.5g of monounsaturated FA per 100g	6.07 ± 1.24 (35)	5.82 ± 1.18 (34)	0.409	5.15 ± 1.37 (32)	5.83 ± 1.21 (32)	**0.039**

Normally distributed data are expressed as the mean ± standard deviation. Non-normally distributed data* (AST, ALT, and ALT/AST ratio) are presented as the median and interquartile range. TSH, thyroid-stimulating hormone; FT4, free thyroxine; FT3, free triiodothyronine; BMI, body mass index; SDS, standard deviation score; AST, aspartate aminotransferase; ALT, alanine aminotransferase; GGT, gamma-glutamyl transferase; ALP, alkaline phosphatase; FA, fatty acids. Value in parentheses (number of participants). All significant values ($p < 0.005$) are in bold.

adolescents in association with low or high levels of FT4 (Table 2).

It is important to note that no significant differences in food preference were found in non-obese children and adolescents in relation to low and/or high FT4 serum levels.

The best predictors of dietary preference

Multiple regression analysis aimed at identifying the best predictors of variability in dietary preference in children and adolescents with obesity encompassed age, sex, BMI-SDS, and FT4 as covariates. The results revealed that FT4 and sex are the major predictors of variability in the preference for a diet high in protein, fat in general, and monounsaturated fatty acids in particular. High levels of FT4 were the sole predictor of the higher preference for a diet containing saturated and polyunsaturated fat as well as for a diet low in fiber (Table 3).

Discussion

This study clearly shows that higher levels of FT4 are associated with a higher preference for protein and a fat-rich

TABLE 3 Multiple regression analysis of food preferences in obese children and adolescents.

Model summary	Dependent	Independent	ΔR^2	$\beta \pm$ SEM	*p*-Value
$R^2 = 0.186$; $p < 0.001$; $n = 101$	High protein score	Sex	0.105	0.32 ± 0.10	**0.001**
		FT4	0.081	0.28 ± 0.10	**0.002**
$R^2 = 0.180$; $p < 0.001$; $n = 101$	High fat score	Age	0.087	-0.27 ± 0.12	**0.005**
		FT4	0.048	0.22 ± 0.11	**0.020**
		Sex	0.045	0.21 ± 0.11	**0.023**
$R^2 = 0.074$; $p = 0.030$; $n = 64$	Low fiber	FT4	0.074	0.23 ± 0.12	**0.030**
$R^2 = 0.081$; $p = 0.023$; $n = 64$	Foods containing ≥1.5g of saturated FA per 100g	FT4	0.081	0.25 ± 0.12	**0.023**
$R^2 = 0.083$; $p = 0.021$; $n = 64$	Foods containing ≥1.5g of polyunsaturated FA per 100g	FT4	0.083	0.26 ± 0.12	**0.021**
$R^2 = 0.135$; $p = 0.012$; $n = 64$	Foods containing ≥1.5g of monounsaturated FA per 100g	FT4	0.075	0.25 ± 0.12	**0.024**
		Sex	0.059	0.24 ± 0.12	**0.045**

Analyzed in forward linear multiple regression analyses. Covariates: age, sex, BMI-SDS, and FT4. FT4, free thyroxine; BMI, body mass index; SDS, standard deviation score; FA, fatty acids. All significant values ($p < 0.005$) are in bold.

diet, regardless of the level of fatty acid unsaturation, and with a lower preference for dietary fibers in children and adolescents with obesity. Children and adolescents with obesity and higher FT4 levels (stratified by median value) had higher systemic levels of AST and ALT. Multiple regression analysis revealed that higher FT4 is an independent predictor of preference to consume a diet low in fiber and high in protein and fat content and irrespective of the fatty acid unsaturation level among children and adolescents with obesity. No significant associations between thyroid hormones and food preference scores were found in non-obese children and adolescents.

To the best of our knowledge, this is the first study bringing evidence indicating that the thyroid hormones might modulate food preference in children and adolescents with obesity. Several studies have already pointed out links between thyroid hormones and dietary fat intake. Kalicanin et al. used a food frequency questionnaire to examine dietary habits in 491 patients with Hashimoto's thyroiditis (HT) and 433 controls. They found that the consumption of the plant oils correlated positively with triiodothyronine levels in the entire cohort of HT patients, as well as in those on LT4 therapy (33). Matana et al. used logistic regression analysis to evaluate associations between dietary factors and plasma thyroid peroxidase antibodies (TPO-Ab) and/or thyroglobulin antibodies (Tg-Ab) in 462 TPO-Ab and/or Tg-Ab positive antibodies and 1,425 were negative individuals. A food frequency questionnaire was used to evaluate dietary habits, and logistic regression analysis showed that the consumption of animal fat and butter was associated with the presence of plasma antithyroid peroxidase (TPO-Ab) and/or thyroglobulin (Tg-Ab) antibodies (34). The fact that the high-fat diet induces ectopic lipid deposition in the thyroid gland of young adult Sprague-Dawley rats, resulting in decreased thyroid function and manifested by a decline of thyroxine, FT4, and increased thyrotropin allows us to speculate that lower levels of FT4 in some children and adolescents with obesity might indicate obesity-related impairment of thyroid function and counter-regulatory inhibition of dietary fat intake (35, 36). The link between thyroid hormones and food preference/taste perception has also been documented in a study examining interrelations between type 2 taste receptors (TAS2R), activated by bitter-tasting compounds with thyroid function. TAS2Rs were shown to play an important role in the modulation of thyroid hormone (T3/T4) production (37).

The fact that the associations of thyroid hormones and food preferences were, in our study, exclusive to children and adolescents with obesity supports the hypothesis that obesity alters the regulation of thyroid hormones and modulates thus the food preferences in order to limit the intake of high fat-containing diet. A recent Australian study provided clear evidence of the mutual interrelationship between obesity and taste perception. Authors have shown specific obesity-related differences in the gene expression profile of human fungiform papillae. Very distinct was also the taste bud cellular microenvironment, which could alter taste bud function and therefore modulate taste perception and food intake (28). The alterations of thyroid hormone levels in common obesity are believed to be rather a consequence than a cause of obesity (26), and we explored the hypothesis that the modulation of food preference could also be a part of the regulatory circuit. It is also known that thyroid hormones modulate resting energy expenditure and might therefore be involved in modulating energy allostasis and body weight control (38). However, the pathophysiological mechanisms by which thyroid hormones regulate the balance between energy intake and expenditure are not fully explained, and one of the possibilities could be *via* modulating food preferences. We could also speculate that the positive association of serum FT4 levels with food preferences in obese children and adolescents might be one of the reasons why patients with obesity and subclinical hypothyroidism mostly do not lose weight on the L-thyroxin

treatment. Higher serum levels of FT4 caused by substitution therapy should increase energy expenditure. However, this effect could be balanced with the increased preferences for a diet rich in fat and protein while containing only a limited amount of dietary fiber. Therefore, our results support recommendations that thyroxine treatment should be carefully considered in children and adolescents with obesity. In people who do require thyroxine replacement therapy, it would be beneficial to use not only serum TSH but also FT4 concentrations to monitor the treatment. A further potential application of our results in clinical practice may also be in the identification of individuals with obesity and higher FT4 concentrations that may be at risk for the development of obesity-related hepatopathy. The clinical utility of our results could be further supported by the prospective follow-up of this patient population as well as by including patients with abnormal or extreme levels of thyroid hormones.

Limitations

Several factors that were not evaluated in this study, including social and cultural influences, could have an impact on food preferences. There was also a significant gender imbalance in the non-obese and obese participants which could influence the comparisons between these two groups. Moreover, associations between thyroid hormones and food preferences in obese individuals were found in a specific age group of children and adolescents. Therefore, further studies in other age groups will be needed to generalize our presumptions.

Conclusion

Food preference could be an important predictor of weight changes and certainly should be considered in the management of childhood obesity. Association with serum levels of thyroid hormones provides an interesting link, with the potential clinical utility of FT4 concentrations in monitoring thyroxine replacement therapy in people with obesity or in identifying persons at higher risk of developing specific complications of obesity.

It is important to note that the lower food preference for protein and fat that we observed in children and adolescents with obesity and low FT4 levels could provide specific protection from obesity-related lipotoxicity as evidenced by lower AST and ALT. Collectively, it is possible to speculate that lower FT4 might signal the need for protection against metabolic disease in children and adolescents with obesity, which might be exemplified by a lower preference for protein and fat-rich food.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving human participants were reviewed and approved by Ethics Committee of the National Institute for Children's Diseases in Bratislava. Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

Author contributions

DS, BU, JU, and JS: original idea development. DS, LD, PF-P, LS, EV, LT, and JS: data collection. DS, JU, and JS: analysis. DS and LK: manuscript preparation. JU, BU, and JS: critical reading and editing of the manuscript. All authors contributed to the study design, reviewed the manuscript critically, and approved the final version.

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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.

Publisher's note

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Does concurrent self-administered transcranial direct current stimulation and attention bias modification training improve symptoms of binge eating disorder? Protocol for the TANDEM feasibility randomized controlled trial

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Background: Binge eating disorder (BED) is a common and disabling problem associated with impaired cognitive control. Preliminary studies show that brain-directed treatments, including transcranial direct current stimulation (tDCS) and attention bias modification training (ABMT), improve cognitive control and alleviate symptoms of BED. When combined, tDCS may enhance the effects of ABMT, and vice versa, thereby improving treatment outcomes.

Methods: This protocol describes a feasibility single-blind randomized sham-controlled trial of concurrent self-administered tDCS and ABMT in adults with BED (The TANDEM Trial). Eighty adults with BED will be randomly assigned to one of four groups: ABMT with real or sham self-administered tDCS, ABMT only, or waiting list control. In the treatment arms, participants will complete 10-sessions of their allocated intervention over 2–3 weeks. Outcomes will be assessed at baseline (T0), immediately post treatment (T1), and 6 weeks after end of treatment (T2), and at comparable timepoints for participants in the waitlist control group. Feasibility will be evaluated by assessing recruitment/retention rates and blinding success. Acceptability will be assessed quantitatively *via* participant ratings and qualitatively *via* semi-structured interviews. Episodes of binge eating at follow-up will be the primary clinical outcome and rate ratios from Poisson regression will be reported. Secondary outcomes will assess changes in ED and general psychopathology, attention bias toward high calorie foods, and executive function.

Discussion: It is hoped that data from the trial will contribute to the development of neurobiologically informed treatments for BED, provide insights into the potential use of at-home variants of tDCS, and inform the design of future large scale trials.

KEYWORDS

eating disorders, binge eating disorder, transcranial direct current stimulation (tDCS), attention bias, neuromodulation

Introduction

Binge eating disorder (BED) is a common and disabling eating disorder (ED) affecting 1–3% of the global population (1). It is characterized by recurrent episodes of binge eating accompanied by feelings of loss of control and subsequent distress. Episodes occur in the absence of compensatory behaviors intended to prevent weight gain (2). Among individuals with BED, psychiatric and physical health comorbidities are common; nearly 80% of those diagnosed with BED will suffer from another psychiatric disorder during their lifetime (3), and up to 88% live with overweight or obesity, increasing individual risk for obesity related physical health problems (4). Consequently, the economic and quality of life burden associated with BED is substantial (5–7).

Psychotherapy [particularly cognitive behavior therapy (CBT)] and self-help interventions are recommended first-line treatments for BED (1). However, only about half of those who complete treatment report a significant reduction in, or abstinence from, binge eating in the 12-months following the end of treatment: moreover, neither treatment yields a significant or sustained reduction in weight (8). With respect to pharmacotherapy, second-generation antidepressants, anticonvulsants, and central nervous system stimulants produce short-term reductions in episodes of binge eating and are routinely used when treating BED. However, drug-driven reductions in binge eating episodes are not sustained beyond 3–6 months. Lisdexamphetamine, a central nervous system stimulant, is the only drug approved for use in the treatment of moderate-severe BED. However, the effect of the drug on ED psychopathology and mood remains unclear, and data on the long-term maintenance of effects are lacking. There are also significant risks associated with the drug's use; little is known about the effects of long-term administration, and rates of adverse events and premature discontinuation of the drug were elevated in RCTs (4, 8). It is possible that combining psychotherapy with pharmacotherapy may produce superior outcomes from treatment, however, findings from a recent meta-analysis yielded minimal support for this hypothesis; of the 12 included trials, only two reported that combined treatment enhanced binge eating and weight outcomes, both of which used anticonvulsant medications, and only two reported modest improvements in weight loss, but not binge eating, outcomes, both of which used the weight-loss medication, Orlistat (9).

It is widely agreed that novel treatments informed by neurobiological models of illness are needed (10). Current models propose that emotion dysregulation, elevated food cue reactivity, and executive dysfunction, are central to the etiology and maintenance of BED (11–16). These difficulties may indicate a broad impairment in cognitive control, and therefore aberrant functioning of the brain's cognitive control network. Cognitive control is the ability to orchestrate thought and action in accordance with internal goals and relies on prefrontal brain regions (e.g., the dorsolateral prefrontal cortex [dlPFC]) and associated neural networks (17). In this framework, the affective reactivity (i.e., craving and emotional reactivity) and poor self-regulatory abilities reported in BED may be a consequence of impairments in cognitive control, and interventions which improve cognitive control may facilitate remission from BED.

Cognitive bias modification (CBM) is one tool which may be used to improve cognitive control. CBM refers to a class of interventions that use experimental paradigms to change biased cognitive processes which perpetuate maladaptive behavior (18). Attention bias modification training (ABMT) is a form of CBM which aims to alter the automatic allocation of attention toward salient cues. Food-specific variants of ABMT, which were developed for use in binge-type EDs and obesity, train individuals to avoid salient high-calorie food cues and attend to neutral and low-calorie food cues (19). Meta-analyses of RCTs in healthy volunteers have revealed that a single session of food-specific ABMT is associated with a significant short-term reduction in high-calorie food consumption (medium effect size) (20) and a significant short-term reduction in bias toward high-calorie foods (medium effect size) (21). Though few studies

Abbreviations: ABMT, Attention bias modification training; BED, Binge eating disorder; dlPFC, Dorsolateral prefrontal cortex; DSM-5, Diagnostic and Statistical Manual of Mental Disorders, 5th Edition; ED: Eating Disorder; NIBS, Non-invasive brain stimulation; TDCS, Transcranial direct current stimulation.

have used food-specific ABMT in BED, those that have report promising outcomes from treatment. One study reported that a single session of ABMT was associated with a significant short-term reduction in subjective food craving (22). Another open feasibility trial delivered 8 weekly sessions of ABMT and reported significant post-treatment reductions in weight, ED symptoms, episodes of binge eating, and attention bias toward food, and these were sustained to 3-month follow-up (23). Thus, although data on the long-term effects of ABMT are lacking, the available evidence suggests that ABMT may improve affective regulation in the context of food (i.e., cognitive control), and may have clinical utility in BED.

Non-invasive brain stimulation (NIBS) may also be used to modify functioning of cortical regions or networks implicated in BED (24, 25). Transcranial direct current stimulation (tDCS) is a NIBS technique which may be particularly well-suited to the treatment of BED: it is a safe and well-tolerated technique which is inexpensive, portable, easy to use, and suitable for remote self-administration (26, 27). In tDCS, a constant weak direct current is applied *via* electrodes placed on the scalp to increase (anodal tDCS) or decrease (cathodal tDCS) cortical excitability. Specifically, tDCS modulates network dynamics within functionally connected areas beyond the cortical regions located beneath the electrodes. As a result, tDCS has the potential to modulate task- or symptom-specific neural networks. These changes in cortical excitability outlast the stimulation period (up to 60 min after a single-session) and, with repeated administration, may lead to lasting changes in brain function (26). In light of this, tDCS is being applied to the treatment of psychiatric disorders with moderate success, particularly in major depression (26). However, questions remain about optimal participant/patient selection, parameters for stimulation, mechanisms of action and the effects of long-term use.

Proof-of-concept studies suggest that tDCS may be effective for the treatment of binge-type EDs. In bulimia nervosa, a proof-of-concept RCT with 24-h follow-up, indicated that a single-session of right dlPFC anodal tDCS improves ED psychopathology, reduces craving for food, reduces urge to binge, and improves self-regulatory control during reward related decision making (28). In BED, a single-session RCT using right dlPFC anodal tDCS reported a short term reduction in craving for food and desire to binge eat in participants who received real tDCS (29). This finding was replicated in a sham-controlled crossover trial: following a single-session of right dlPFC anodal tDCS, short-term improvements in food-related response inhibition and craving for food were observed in participants who received real 2mA tDCS stimulation, as opposed to real-1mA or sham stimulation (30).

Two studies have examined the effect of multiple sessions of tDCS on BED symptoms. A randomized sham-controlled trial involving 32 adults examined the effect of 10 sessions of tDCS on attention bias toward food, craving for food, and cognitive flexibility (31). In this trial, tDCS was given with the anode over the left dlPFC and the cathode over the right dlPFC (2mA/20 min). Sessions were 3/week until 10 sessions had been completed. At post-treatment and 45 day follow up, real tDCS treatment was associated with a greater reduction in attention bias toward food, a greater reduction in craving for food, and an improvement in cognitive flexibility. However, effect sizes were small, and the authors acknowledged several study limitations, including a small sample ($n = 32$) and concerns about the effect of poor eye-tracker calibration on the reliability of attention bias outcomes.

Our group has also recently completed an RCT of six sessions of right-anodal tDCS targeting the dlPFC delivered over 3 weeks in adults with BED [$n = 65$, (32) for protocol]. In this trial, we examined whether symptoms of BED were improved by an intervention involving the concurrent delivery of tDCS and approach bias modification training, a form of CBM which targets approach bias toward high-calorie foods. Participants were randomly allocated to one of three study groups (approach bias modification training with real tDCS, approach bias modification training with sham tDCS, or wait-list control) and outcomes were assessed at baseline, 3-weeks post-randomization, and 7-weeks post randomization. Clinical and neurocognitive outcomes are yet to be published; however, findings from a qualitative study of the treatment experience indicate that this combined approach to treatment is tolerable and acceptable (33).

It has been suggested that the efficacy of tDCS may depend on the functional state of the brain at the time of stimulation. If this is true, then greater and longer-lasting neuroplastic effects might be achieved when tDCS and CBM co-activate a disorder-related neural network (34). This may be because, by altering the relationship between excitatory (glutamatergic) and inhibitory (GABAergic) systems in the brain (35), tDCS creates optimal conditions for memory reconsolidation, a process which may re-enforce the new learning which takes place during CBM. Similarly, CBM promotes the activation of disorder relevant brain areas, and this might enhance the effectiveness of stimulation. Consistent with this, several studies in anxiety, depression, and substance abuse disorders have reported superior outcomes from treatment when tDCS was combined with interventions which activate cognitive control regions (27, 36–38).

In summary, concurrent tDCS and food-specific CBM may be a promising treatment, or adjunct to treatment, for BED. This is because of (a) evidence suggesting that tDCS and food-specific CBM may independently produce therapeutic effects in BED, and (b) the neurobiological rationale for combining these two treatments. Moreover, with the recent arrival of tDCS devices intended for supervised self-administration, both interventions can now be safely provided in the home, thereby increasing their accessibility and scalability. Accordingly, we present the protocol for a feasibility randomized controlled trial

of concurrent at-home self-administered tDCS and food-specific ABMT in BED (The TANDEM trial).

Study aims

The primary aim of the TANDEM trial is to assess the feasibility of using 10 sessions of concurrent food-specific ABMT (henceforth, ABMT) and self-administered right-dlPFC anodal tDCS as a treatment for BED. This intervention will be compared to training in combination with sham stimulation, stand-alone training, and a "no treatment" waiting control condition. In doing so, we aim to acquire key information to inform the design of a large-scale RCT.

Specifically, we aim to:

1. estimate the rate ratio for the proposed primary outcome, change in the number of monthly episodes of binge eating from baseline to follow up. This will inform the sample size calculation for a large-scale RCT.
2. explore the feasibility of conducting a large-scale RCT of at-home self-administered concurrent tDCS and ABMT in adults with BED by assessing recruitment, attendance, and retention rates;
3. assess acceptability by examining participant ratings of treatment acceptability and tolerance, and by evaluating feedback provided during semi-structured interviews;
4. determine the best instruments for measuring primary and secondary outcomes in a full trial by examining the quality, completeness, and variability in the data.

The primary clinical endpoint will be the change in monthly episodes of binge eating from baseline to follow-up. Secondary aims will focus on evaluating changes in overall ED pathology and general psychopathology, changes in attention bias toward high-calorie foods, and changes in executive functioning from baseline to 6-weeks post treatment completion.

Methods

Reporting of this protocol is guided by the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) checklist (39) and the Consolidated Standards of Reporting Trials (CONSORT) statement extension for feasibility randomized controlled trials (40). The TANDEM trial has also been registered with the U.S. National Institute for Health (NIH) Clinical Trials database (ClinicalTrials.gov; trial identifier: NCT04424745).

Study design

TANDEM is a randomized single-blind sham-controlled feasibility trial with four parallel arms: [ABMT + real tDCS], [ABMT + sham tDCS], [ABMT only], and 8-week wait-list control. After baseline assessment (T0), participants will be randomly allocated to a study group. Those allocated to treatment groups will then complete 10 sessions of their allocated treatment over 2 weeks. Outcome measures will be completed first at baseline (T0), then again immediately after completing treatment or after 2-weeks waiting (T1), and finally 6-weeks after completing treatment, or after 8-weeks of waiting (T2). Process outcomes will also be assessed at each treatment session.

Participants

Recruitment

Recruitment for this trial began in March 2021 and ran for 12 months. Participants will be recruited from the community (*via* advertisements on social media, research participant recruitment websites, and university-managed webpages), and from the South London and Maudsley outpatient ED service.

People interested in the study will receive verbal and written information about the study rationale, aims, and methodology. Specifically, participants are told that there is tentative evidence to suggest both tDCS and ABMT may reduce craving for food and episodes of loss of control eating, and that the present study will be the first to examine whether combining these two interventions may alleviate symptoms of BED. After providing written consent, participants will be screened against inclusion and exclusion criteria.

Inclusion criteria

Participants eligible for the trial must comply with all of the following criteria at randomization:

1. Aged 18–70 years.
2. Right handed
3. Overweight or obese (body mass index (BMI) $\geq$25 kg/m^2).
4. Meet diagnostic criteria for full-syndrome BED diagnosis according to the Diagnostic and Statistical Manual 5th Edition (2013).
5. Normal or corrected to normal vision.
6. Access to a laptop or desktop computer with a webcam.

Exclusion criteria

1. Insufficient knowledge of the English language.
2. Pregnancy or suspected pregnancy.
3. Current significant or unstable medical or psychiatric disorder needing acute treatment in its own right.
4. A lifetime diagnosis of substance dependence, psychosis, bipolar disorder, or borderline personality disorder.

5. Developmental or neurological disorder (e.g., dementia, attention deficit hyperactivity disorder, autism spectrum disorder).
6. Psychotropic medication other than a stable dosage of an antidepressant (e.g., selective serotonin reuptake inhibitor) for at least 14 days prior to study enrolment.
7. Non-removable metal parts in the area of the head (excluding dental work).
8. History of epilepsy or migraine.
9. Use of a pacemaker.

We will report the number of participants excluded, with reasons, and the number who decline consent or withdraw from the study, with reasons where provided.

Sample size

As TANDEM aims to establish feasibility rather than between-group differences, an a priori sample size calculation is not necessary. Guidance suggests that, where available, sample size should be based on previous feasibility or pilot studies of a similar intervention, or with a similar primary outcome measure or trial design. Where this information is lacking, it is argued that a total sample between $n = 12$ and $n = 50$ is sufficient for robust assessment of feasibility outcomes (39). Previous comparable trials in BED included 20 participants in each trial arm [e.g., (31, 41)]. As this trial includes four arms, we have chosen a target end study sample size of $n = 80$. Assuming the attrition to follow-up rate is ∼10% [as found in previous recent BED treatment trials, e.g., (42)], we will recruit an actual sample size of 88 (22 participants/group).

Randomization

The study will use a randomized controlled design, stratified by age, gender and BMI. Participants will be randomly allocated to a study group in a 1:1:1:1 ratio. Randomization will be completed using the Sealed Envelope Simple+ randomization service (https://www.sealedenvelope.com/). After completing the T2 assessment, participants in the waiting control arm will be offered ABMT.

Blinding and protection against bias

For pragmatic reasons, single-blinding will be implemented for [ABMT + real tDCS] and [ABMT + sham tDCS] groups. As such, participants in tDCS treatment groups will be blinded to real/sham allocation, but the researcher who leads treatment and conducts assessments will be unblinded. A validated protocol for sham stimulation will be used to deliver sham treatment; in the sham condition, tDCS electrodes will be properly mounted over the right and left dlPFC, and a 2mA current will be applied for 60 s at the beginning and end of each session. During the first and final 60 s of each session, no ABMT will be completed. Therefore, participants who receive sham will perceive typical sensations of tDCS (e.g., tingling), but will be unaffected by the stimulation. To assess if blinding was successful, participants will be asked to guess which condition they believe they have received and indicate how certain they feel about this. Once T2 and, where relevant the optional semi-structured interview about the treatment experience, are complete, participants will be unblinded. Those who receive sham treatment will not be offered any additional treatment. Blinding will not be implemented for ABMT only and waiting conditions.

The single-blind study design increases risk for experimenter bias. To protect against bias, self-report questionnaires (as opposed to interviews) will be used to assess clinical outcomes, including episodes of binge eating. All outcome measures will be collected online using either Qualtrics^{XM} for questionnaire measures, or Gorilla^{TM} or Inquisit Millisecond for neurocognitive task measures. As such, the experimenter will have no influence on participant responding or task performance. Semi-structured interviews about the treatment experience will be conducted before participants are unblinded and by independent investigators who are naïve to real/sham allocation.

Intervention

Participants will complete 10 sessions of tele-supervised treatment over 2–3 weeks (i.e., week daily sessions until 10 sessions have been completed). Sessions will involve either concurrent ABMT and real/sham tDCS, or ABMT only. Participants in the waiting control arm will receive ABMT after completion of the T2 assessment.

Attention bias modification training

ABMT aims to train participants to "look toward" low-calorie food and "look away" from high-calorie food using a modified version of the anti-saccade task by Werthmann et al. (43). Training is completed on a personal laptop or desktop computer and lasts 10–15 min with breaks. Participants completing concurrent treatment (i.e., ABMT + real/sham tDCS) will begin ABMT 5 min after starting the stimulation. They will also be instructed to rest while waiting to begin and after completing the training.

ABMT paradigm

The modified task consists of 360 trials. Of these, 180 require participants to look toward low calorie foods, and 180 trials require participants to look away from high calorie foods. At the beginning of each trial, a black fixation point appears for 100 ms, followed by a red or blue fixation point (500 ms). A blue point

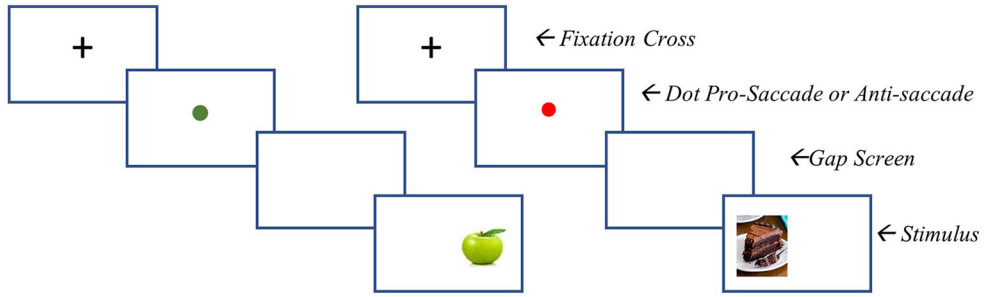

FIGURE 1
ABMT stimulus presentation. Left = pro-saccade stimulus presentation (i,e., participant is to look toward the food image presented). Right = anti-saccade stimulus presentation (i,e., participant is to move their gaze away from the stimulus).

indicates that a pro-saccadic eye movement is required (i.e., look toward the food picture which appears after the fixation point), whereas a red point requires an anti-saccadic eye movement (i.e., direct the gaze away from the food picture which appears after the fixation point). Low-calorie cues are always preceded by a blue dot and high calorie food cues are always preceded by a red dot. A blank screen is inserted for 200 ms between the fixation point and the stimulus presentation. The pictorial stimulus (a high- or low-calorie food picture) then appears on either the left or the right side of the screen for 500 ms. Inter-trial interval is 1,300 ms. Trials will be presented in a random order across three blocks, each including 120 trials. See Figure 1 for an example of a pro-saccade and anti-saccade stimulus presentation.

Stimuli

Pictorial stimuli are 30 low calorie food and 30 high calorie food pictures, which are visually matched for brightness, color, and complexity, taken from Werthmann et al. (43). Each image is presented twice in each block, once on the left side of the screen and once on the right side of the screen (in a counterbalanced order), resulting in a total of 360 training trials (30 food stimuli + 30 non-food stimuli × 2 positions × 3 blocks).

Response and feedback

In addition to directing their gaze toward or away from the stimulus presented, participants will be instructed to press the arrow key which corresponds with the direction of their gaze. Response latencies will be recorded to monitor accuracy and provide participants with feedback. For each block, the number correct responses will be summed up and presented as percentage score of correct performance to the participant.

Self-administered transcranial direct current stimulation

Participant administered tDCS will be delivered using the Newronika HDC system (Figure 2). The Newronika system

FIGURE 2
Equipment for TDCS self-administration.

consists of an easy to use, lay friendly stimulator, a programming device used by the researcher to securely set stimulation parameters, and a customisable MindCap electrode placement system which ensures simple, safe, and reliable placement of the anode and cathode over the right and left dlPFC. Stimulation will be delivered at a constant current of 2 mA (with a 30 second fade in/fade out) for 20 min. This tDCS montage has been used in studies of food craving, bulimia nervosa, and BED (28, 32, 41, 44). As with real tDCS, sham stimulation will run for 20 min however, participants will not receive active stimulation for the full 20-min period. Instead, sham participants will receive 60 s of stimulation at the start ("ramping up") and the end ("ramping down") of the stimulation period.

Rationale for session number and frequency

Although consensus around the optimal number of ABMT sessions is lacking, a review of meta-analyses of CBM concluded that the number of sessions appears to moderate outcomes, with higher session numbers being associated with greater change in cognitive bias (18). In line with this, Beard, Sawyer et al. (45) found that as session number increased, so did the potency of

the effect of CBM on symptoms in depression, anxiety, and addiction disorders. However, this effect appeared to stabilize after 10 sessions. Therefore, 10 sessions may be the optimal dose for ABMT.

With regards to tDCS, although there is a similar lack of consensus about the optimal treatment parameters, it is broadly accepted that multiple sessions are needed to achieve lasting therapeutic effects (27, 44). The vast majority of multisession studies in psychiatric disorders have applied 10-sessions of tDCS once daily over 2–3 weeks (27). Thus, the choice of 10 sessions is also supported by the literature on tDCS use in psychiatric disorders.

Safety procedures

Published guidance for ensuring participant safety during self-administration of tDCS will be adhered to Knotkova et al. (46). This guidance is as follows: First, training and supervision should be provided to those self-administering tDCS. In TANDEM, all participants will be trained in safe tDCS self-administration, and all treatment sessions will be supervised *via* video-call. Second, the tDCS equipment used must be intended for home use by the lay community. We will use the Newronika HDC stimulator and MindCap electrode placement system which is CE marked for supervised home use in the UK and Europe. This equipment is pre-programmed by the researcher, simple to use, and includes features which prevent misuse (e.g., the researcher can set a minimum time between treatment sessions, and/or set a maximum number of sessions before re-calibration by the researcher). Third, care must be given to the participant's capacity for self-administration. Prior to beginning treatment, the TANDEM researcher will assess each participant's ability to self-administer tDCS safely. Where necessary, additional training will be provided. Participants who cannot safely self-administer tDCS after training will be withdrawn from the study, and the reason for their withdrawal will be reported. Fourth, tDCS tolerance and adverse events must be assessed at each session. Consistently, process outcomes will monitor tDCS tolerance and adverse events at each treatment session (see "Outcome Assessment" for more details), In addition, during or near to the final (T2) assessment, tDCS tolerance and adverse events will be assessed in an optional semi-structured interview about the treatment experience.

Concomitant care

As the trial focusses on feasibility rather than efficacy, participants will be allowed to receive other parallel treatments for their ED. Concurrent use of psychoactive medications (excluding neuroleptics or benzodiazepines) will be allowed, providing the dose has been stable for at least 14 days prior to baseline assessment.

Trial procedure

The individual participant timeline is illustrated in Figure 3. Study duration for each participant is 8 weeks. All participants will partake in assessments at each of the three time points; baseline (T0), post-treatment (T1) and follow-up (T2). Each assessment will be completed *via* videoconferencing (i.e., participants complete both assessments and treatment at home using a laptop or desktop computer with a webcam). Questionnaire measures will be completed online using Qualtrics^{XM} and neurocognitive tasks will be completed online using either Gorilla^{TM} or Millisecond by Inquisit^{TM}.

Informed consent will be provided *via* an online consent form (Qualtrics^{XM}). Once completed, potential participants will be screened over the phone for inclusion in the study. At screening, BED diagnosis is confirmed using a standardized interview [Eating Disorders Diagnostic Screen; (47)]. Physical and psychiatric comorbidities, current medications, and tDCS safety are assessed using a general health questionnaire developed for the purpose of screening. Eligible participants then complete the baseline (T0) assessment. After baseline assessment, participants are randomized to one of four groups: (1) ABMT + real tDCS, (2) ABMT + sham tDCS, (3) ABMT only, or (4) wait-list control group. Intervention groups will then complete 10 sessions of treatment, up to 5 sessions/week, across 2–3 weeks. The waitlist control group will receive no experimental treatment during this time. All participants will complete the post-treatment assessment (T1) after the 10th (final) session of treatment or 2-weeks of waiting, and the follow-up assessment (T2) 6-weeks after completing treatment, or after 8-weeks of waiting. After completing the final (T2) follow-up, waiting control participants will receive ABMT.

Outcome assessment

Primary outcomes

The primary clinical outcome will be monthly episodes of binge eating, as measured by the Eating Disorders Examination Questionnaire [EDE-Q; i.e., change in the number of monthly episodes of binge eating from baseline (T0) to follow-up (T2)]. Medians and rate ratios (with confidence intervals) will be reported, and these will inform the minimum sample size required for a fully powered large-scale RCT. Rates for recruitment and retention to 8-week follow up will also be reported to provide insight into the time and resources needed for a larger trial.

Intervention acceptability will be assessed in two ways. First, by asking participants the following two questions at post treatment (T1) and follow-up (T2) assessments: (1) "If you could continue with this treatment, would you?" (Yes/No) and "Would you recommend this treatment to a friend who was struggling with binge eating?" (Yes/No). The intervention

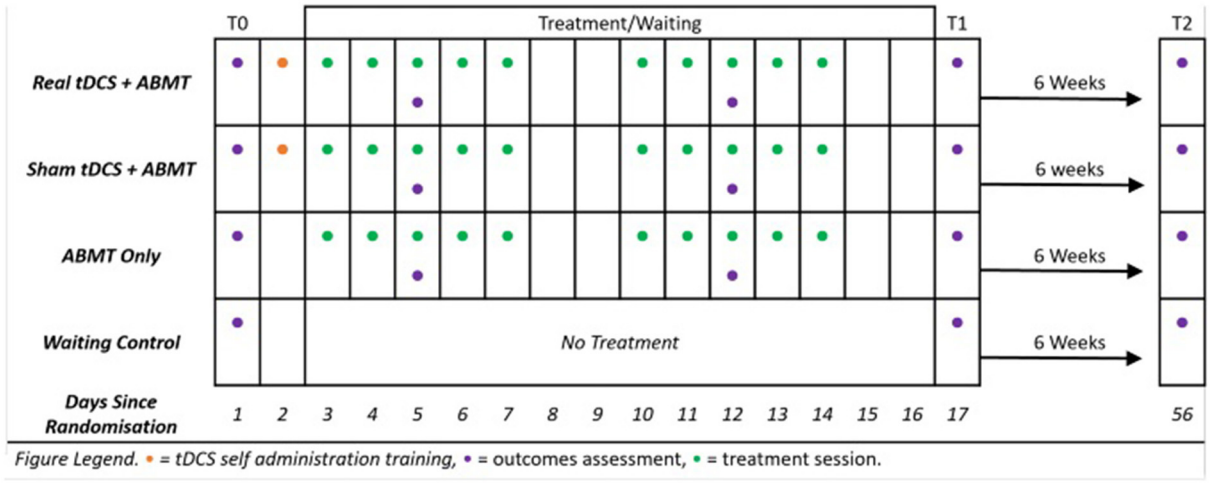

FIGURE 3
TANDEM participant timeline.

will be viewed as acceptable if at least 75% of those who receive the real concurrent treatment indicate that they would continue the intervention if given the opportunity and/or if 75% would recommend the treatment to a friend. Second, at or near-to the final (T2) assessment, participants will be invited to complete an optional semi-structured interview about the treatment experience. This will provide qualitative data which will give insight into (a) whether participants viewed the treatment as acceptable and (b) why/why not. Interviews will be recorded, transcribed, and analyzed using thematic analysis.

Feasibility will also be assessed by looking at participant ratings of tDCS tolerability. Participants who receive tDCS will complete a 10-point visual analog scale (VAS) of tDCS discomfort after each session. We will then take the average of ratings across the ten sessions for each participant and use this to assess the average rating for tDCS related discomfort for the real tDCS + ABMT group. The intervention will be considered well-tolerated if this number is ≤ 4 (i.e., mild discomfort). Prior to beginning each tDCS session, participants will also report any side effects they have experienced since their previous session. The type and frequency of side effects will be reported for consideration.

Secondary outcomes

Secondary outcomes will be assessed using validated self-report instruments and neuropsychological tasks. Change in score/performance from baseline (T0), to post treatment (T1) and follow up (T2) will be examined by looking at within and between group effect sizes and standard deviations. These data will inform outcome measure selection for a future large-scale RCT.

Outcome measures

See Table 1 for a summary of the measures collected at each timepoint.

Questionnaires measures

Participants will complete a battery of questionnaire measures at each assessment (T0, T1 and T2). These will assess ED psychopathology [Eating Disorder Examination Questionnaire (48)], general psychopathology [Depression, Anxiety and Stress Scale – 21 item version (49)], craving for food [Food Craving Questionnaire – trait version (50)], ED related clinical impairment [Clinical Impairment Assessment (51)], emotion regulation [Difficulties with Emotion Regulation Scale – 16 item version (52)], and impulsivity [Barratt Impulsiveness Scale (53)]. Self-reported weight and height will be used to calculate BMI.

Task measures of neurocognition

Attention bias toward high calorie foods will be assessed using the visual probe task described in Mercado et al. (54). In TANDEM, as participants will be taking part from home, webcam based eye-tracking technology (as opposed to specialist

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TABLE 1 Summary of outcome assessment by visit.

	Screening	T0	During treatment	T1	T2
Eating disorder diagnostic screen	X				
TDCS safety screen	X				
General health and lifestyle questionnaire	X				
Demographics		X			
Eating disorder examination questionnaire (EDE-Q)		X		X	X
Depression, anxiety, stress scale (DASS-21)		X		X	X
Food craving questionnaire—trait version		X		X	X
Clinical impairment assessment (CIA)		X		X	X
Difficulties in emotion regulation scale (DERS)		X		X	X
Barrett impulsiveness scale (BIS-11)		X		X	X
Visual probe task		X		X	X
Food attention network task		X		X	X
N-back task		X		X	
Wisconsin card sorting task		X		X	
Delay discounting task		X		X	
Affective go/no go task		X		X	
VAS measures		X	X	X	X
Assessment of tDCS discomfort/Side effects			X		
Semi-structured interview about treatment (optional)					X

lab-based eye-tracking equipment) will be used to record eye movements.

Food-related attention will be assessed using the food-specific attention network task described in Heve, Stingl et al. (55) and in Mercado et al. (54). This task examines three components of attention (alerting, orienting, and executive function) using food (low- and high-calorie) and non-food picture stimuli.

Working memory will be assessed using the n-back task described in Meiron and Lavirdor (56). Accuracy (% correct responses) and reaction time for correct responses (ms) will be reported.

Affective inhibitory control will be assessed using the Face Affective Go/No Go task from the EMOTICOM neuropsychological test battery (57). Error rate and latency will be used to estimate inhibitory control, and reaction times will be used to calculate affective bias scores.

Cognitive flexibility will be assessed using the Wisconsin Card Sorting Test (58). Difficulties with set-shifting will be reflected in perseverative errors, thus, higher scores on this test indicate poorer performance.

Preference for immediate vs. delayed rewards will be assessed using the delay discounting task described by Kirby and Maraković (59). Modeling techniques are used to fit participant responses to the function that relates time to discounting. This produces a temporal discounting curve. The rate at which delayed rewards are discounted will be derived by calculating the area under the curve, and steeper discounting will be reflected by a smaller area under the curve (60).

Optional semi-structured interview

All participants (i.e., including those who received ABMT only) will be invited to complete a semi-structured interview about the treatment experience. This interview, developed for the TANDEM trial, was based on previous semi-structured interviews about tDCS treatment by Gordon et al. (33) and Smits et al. (61). Questions examined seven domains of acceptability: affective attitudes, burden, ethicality, intervention coherence, opportunity costs, perceived effectiveness, and self-efficacy. Interview prompts are included in the Supplementary material.

Within session measures

At each treatment session, participants will complete measures of current symptoms and, where relevant, tDCS related discomfort. Before each treatment begins, participants will complete an online "check in" questionnaire which asks about episodes of binge eating since their previous session and, where relevant, adverse events/side effects that may be related to tDCS. They then complete 10-point visual analog scales (VAS) assessing current hunger, feeling of fullness, craving for food, urge to binge, level of tension, level of stress, level of discomfort, and feeling of low mood. At the end of each session, participants complete a "check-out" questionnaire which repeats

VAS measures and, where relevant, asks about tDCS related discomfort during the session.

Data analysis

The primary analysis will use the number of episodes of binge eating in a Poisson regression model with baseline adjustment. Descriptive statistics will be used to assess recruitment and retention rates, intervention adherence, and the quality and completeness of the data. In secondary analyses, a mixed model approach will be used to analyse the effect of treatment on primary (PO) and secondary outcomes (SOs), with baseline adjustment. To examine the whether the effect of treatment is different for different levels of overweight or obesity, BMI will be included in the model as an interaction effect. Effect sizes will be analyzed and reported for PO and SOs. For the Poisson regression, rate ratios will be reported. For binary outcomes, odds ratios will be reported. For quantitative outcomes, standardized differences will be reported. Primary parameters will be time vs. treatment interactions at both timepoints after baseline. *P*-values will be reported but for exploratory purposes only (i.e., they will not be interpreted to accept or reject the null hypothesis). The analyses will be done in the intent to treat population, which is defined by including all patients with baseline assessment. Outcome data already obtained for participants who discontinue or deviate from the intervention protocol will be kept and analyzed. Analyses will be conducted using RStudio (62).

Patient and public involvement

In our previous trial of tDCS enhanced CBM in BED, a subset of participants completed a semi-structured interview about their treatment experience (33). These interviews included a question about participant views about future directions for tDCS in BED. While these responses did not refer directly to at-home treatment, participants described practical barriers to accessing treatment (e.g., caring responsibilities, time pressures, and travel burden). From these responses, we inferred that participants would welcome investigation into at-home treatment. Prior to submitting the study protocol for review by the research ethics committee, 10 randomly selected participants from our previous trial were invited to provide feedback about the proposed intervention procedures, and the objectives for the research. Eight participants responded with constructive feedback which was incorporated into the study before ethics approval was awarded.

Participant facing forms were also reviewed by people with lived experience of mental health problems and their carers *via* the South London and Maudsley's Feasibility and Acceptability Support Team for Researchers (FAST-R).

Ethical considerations

The TANDEM trial was awarded favorable opinion by the London-Fulham NHS Research Ethics Committee on the 6th of August 2020 (REC Reference 20/LO/0936). Approval to begin the trial was granted by the Health Research Authority (HRA) on the 6th of August 2020. All trial participants will provide written informed consent prior to inclusion into the study and may withdraw from the trial at any point, without consequence or giving a reason.

Discussion

The TANDEM trial will be among the first feasibility studies of concurrent tDCS with cognitive training in BED [see also (33, 41)]. As such, we expect it will contribute new information and will inform the continued development of neurobiologically informed approaches to BED treatment. Indeed, should this trial evidence that concurrent tDCS and ABMT is feasible and acceptable, a large-scale trial with long-term follow up will be needed to evaluate treatment effectiveness.

The design has several strengths. While most studies of tDCS use convenience samples from healthy populations, TANDEM will use a clinical sample who meet DSM-5 criteria for BED. Second, by bringing brain-based treatment into the home, TANDEM overcomes a number of barriers to treatment cited by participants in previous studies (33, 63). Moreover, we will increase access to treatment during a time of elevated uncertainty and compromised access to conventional care (i.e., during the coronavirus pandemic). In fact, in a letter to Brain Stimulation, Caulfield and George (2020) called for this type of approach, saying that the time is ripe for investigating at home neurotherapeutics, and that tDCS is a prime candidate (64). Third, we have tested our CBM intervention (ABMT) in trials involving adults with obesity (54) and anorexia nervosa: in this latter case, training focused on altering avoidance of food, as opposed to bias toward high-calorie foods (65). As such, we have a useful preliminary understanding of the therapeutic effects of ABMT in populations with EDs and disordered eating behaviors, and a good understanding of how participants view the treatment (i.e., acceptable, accessible, and credible). Fourth, we have chosen a primary outcome with high clinical relevance (i.e., monthly episodes of binge eating), and, unlike many studies which examine short-term intervention effects, we have incorporated a comparatively long follow up period (6-weeks post treatment end). This will allow us to examine the maintenance of any therapeutic effects observed immediately post treatment and allow time for more gradual changes to emerge.

There are some challenges for the TANDEM trial. TANDEM is/has been conducted during the coronavirus pandemic (COVID-19) and it is possible that there may be a negative

COVID-related impact on recruitment and retention. In response, TANDEM has adopted a fully remote design (i.e., participants complete all components of treatment and research participation from home). We expect that this may mitigate the negative impact of COVID on recruitment however, by adopting a fully remote design, TANDEM has sacrificed some of the advantages of conducting research in the lab (e.g., access to state-of-the art eye tracking equipment, controlled testing environments, and reduced reliance on self-report data). In publications arising from this trial, we will comment on the quality and completeness of the data collected to assist with future decisions about trial design. Finally, to minimize attrition, we have chosen to collect only a subset of outcome measures at 8-week follow up. As such, we will not be able to comment on change from baseline to follow up for some secondary neurocognitive outcomes.

We expect that the TANDEM trial will provide a valuable contribution to the literature on concurrent tDCS and CBM treatments for EDs, and that the data collected will provide a foundation for future related trials. Moreover, we hope that TANDEM will shed light on the potential for bringing NIBS treatments into the home so that we can continue increasing access to novel treatments for psychiatric disorders.

Trial progress

Recruitment commenced in March 2021 and ended in February 2022. Data collection will be completed by June 2022. Amendments to the study protocol will be reported in publications of study outcomes.

Author contributions

MF, IC, and US conceived the idea for the trial. MF led trial design and obtained ethical approvals. The manuscript was written by MF with input/feedback from IC and US. All authors contributed to the article and approved the submitted version.

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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.

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The views expressed in this publication are those of the authors and not necessarily those of the National Health Service, the NIHR or the UK Department of Health.

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyt.2022.949246/full#supplementary-material

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Gastrointestinal complaints in patients with anorexia nervosa in the timecourse of inpatient treatment

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Background: In patients with anorexia nervosa (AN), gastrointestinal (GI) symptoms are common and usually improve during or after nutritional rehabilitation. It is unclear when exactly GI symptoms change in the timecourse of treatment and to which extent. In this study, we analyzed the timecourse of GI symptoms and their relation to disease-specific, demographic, anthropometric, and psychological factors in inpatients with AN.

Methods: In weekly intervals, the Gastrointestinal Symptom Rating Scale (GSRS) was completed, and body weight was measured over a mean of 9.5 weeks in inpatients with AN. A total of four self-report questionnaires assessing psychological factors were completed before and after inpatient treatment. Data from 38 inpatients with AN were analyzed using mixed linear models.

Results: Abdominal pain and constipation improved significantly in the timecourse with 0.085 (p = 0.002) and 0.101 (p = 0.004) points per week on the GSRS and were predicted to normalize after 13 (p = 0.002) and 17 (p = 0.004) weeks, respectively. Total GI symptoms tended to normalize after 25 weeks (p = 0.079). Indigestion (borborygmus, abdominal distension, eructation, flatulence) was the most severely pathological symptom at admission and did not improve significantly (p = 0.197). Diarrhea and reflux were, on average, not pathological at admission and remained stable during treatment. In addition to treatment time, the strongest predictors were ED pathology at admission for the development of abdominal pain, constipation,

reflux, and total GI symptoms; stress for the development of constipation and total GI symptoms; and depression for constipation.

Conclusions: Informing patients with AN about the course of GI symptoms and their improvement during weight rehabilitation may help support compliance during treatment.

KEYWORDS

abdominal pain, anorexia nervosa, constipation, eating disorders, gastrointestinal complaints, indigestion

Introduction

Eating disorders (EDs) such as anorexia nervosa (AN) are characterized by aberrant patterns of eating behavior. AN is characterized by a restriction in food intake, which can sometimes be combined with binge-purging behavior, high levels of physical activity, and body image disturbances (1–3). Aside from that, gastrointestinal (GI) complaints are not only common in patients with AN (4) but also play an important role in the maintenance of eating disorder pathology (5) as patients often report GI symptoms as a justification for not being able to eat. Patients with AN show a wide range of GI symptoms, such as abdominal pain, constipation, or heartburn (6, 7). These GI symptoms are thought to be of functional or somatic origin or a combination of both (8–11).

Many of the GI symptoms found in patients with AN overlap with symptoms typical for functional gastrointestinal disorders (FGIDs) (12–14), which is why many authors estimate the functional origin of GI problems in EDs more probable than indicating an underlying somatic GI disease (15, 16). Several studies on FGIDs in patients with ED found a prevalence of more than 90% according to Rome criteria (17, 18). Moreover, disordered eating attitudes are high in patients with irritable bowel syndrome (IBS) (19) and correlate with current IBS symptoms (10). However, some somatic GI disorders can be misleadingly held for an ED, such as inflammatory bowel diseases, achalasia, or celiac disease (20–22), while contrariwise, serious somatic complications requiring a surgical approach or with a possibly lethal outcome can develop by the end of an ED, for example, gastric rupture after a binge-eating episode (6). The microbiota–gut–brain axis is presumed to be an important underlying mechanism for the intensification of GI disturbances such as intestinal microbiota, which have been proven to be altered in patients with AN (23, 24) as well as with FGIDs (25), and play a key role in the bidirectional communication between gut and brain (26, 27).

Overall, many studies report a change in GI disturbances during treatment—some remain the same, some improve or even disappear, and others newly occur—which appears to be particularly dependent on a specific GI symptom (6). Examining studies that analyzed the development of FGIDs, especially AN, evidence can be found that FGIDs persist even after recovery from an ED (28). Nevertheless, other studies show that improvement in overall GI disturbances is possible (29). The key to GI improvement in AN appears to be long-term rehabilitation concerning both weight and psychological condition as symptoms tend to relapse after a short-term weight gain (30).

Predictors of the prevalence of GI problems and development during treatment in patients with AN were analyzed by several studies. Psychopathological features in patients with AN were found to be associated with both functional and somatic GI disorders (31, 32). Starvation, somatization, state–trait anxiety, binge-eating behavior, and laxative abuse were identified as more specific predictors for prevalence of individual FGID subgroups in patients with AN and other EDs (18, 33, 34). In general, frequently examined predictors of worsening of FGIDs or FGID-like symptoms in patients with AN are overall disordered psychological features and diagnosed mental comorbidities like affective (e.g., depression), anxiety, or personality disorders (e.g., obsessive-compulsive, avoidant, and schizoid personalities) (33, 35). Even after recovery from an ED, FGID symptoms more probably persist in patients who are psychologically distressed (28), which underlines the importance of psychotherapy in ED treatment. Moreover, only long-term weight rehabilitation was found to improve both psychological features and GI problems (30). Normal scores of somatization, neuroticism, and anxiety (33), as well as hypochondriasis and depression (36), could be identified as specific psychopathological traits that predict long-term improvement of GI symptoms. Thus far, this has only been shown in patients with bulimia nervosa, but not in patients with AN. Chami et al. reported that GI symptoms only improved in patients with AN who also showed an improvement in depressive symptoms during treatment (37). Depression as predictor of GI development in patients with AN was, to our knowledge, only reported by Salvioli et al. who analyzed GI disturbances at 1- and 6-month follow-ups

(36). Nevertheless, Boyd et al. could not identify depression as a significant predictor of the presence of FGID in patients with AN and other EDs (33). Another possible predictive factor of GI symptoms in patients with AN is serum amylase. Several previous studies have found increased serum amylase levels in patients with AN, particularly in binge-purging-type AN (38). However, the relationship between serum amylase and GI symptoms, particularly symptom complexes including reflux and heartburn, which are frequent in patients with binge-purging behavior, has not yet been examined.

Giving patients a deeper understanding of the development of their GI symptoms in the timecourse of nutritional rehabilitation may support the recovery process by helping to motivate and reassure patients with AN to continue to eat normal amounts of food, despite having severe GI complaints at the beginning of treatment. A more closely monitored longitudinal observation of GI symptoms, which is lacking in the current literature, might contribute to this understanding. The aims of the study were to prospectively analyze (i) the timecourse of various GI symptoms in inpatients with AN and (ii) the relationship of the development of GI symptoms during inpatient treatment with anthropometric, demographic, disease-specific, and psychological factors.

Materials and methods

Study design and participants

Participants with AN were recruited within the context of an inpatient treatment program at the Eating Disorders Unit of the Department of Psychosomatic Medicine and Psychotherapy at the University Medical Hospital in Tübingen, Germany, in the periods from 2016/01 to 2017/01 and 2018/01 to 2019/02. The main inclusion criterion was a diagnosis of AN according to the Diagnostic and Statistical Manual of Mental Disorders 5 (DSM-5) (1) and the International Classification of Diseases 11 (ICD-11) criteria (2). At admission, all patients were assessed for possible somatic GI diseases that can mimic an ED by using clinical evaluation, blood tests, and GI-specific instrumental investigations, if deemed necessary by the psychologists and physicians in charge. The treatment was conducted by a multidisciplinary team and aimed at increasing body weight and normalizing eating behavior in accordance with the latest developments in medicine as documented in the national German S3-guideline for the assessment and therapy of EDs. This includes a nutritional rehabilitation program and a multimodal psychotherapeutic approach. At admission, the patients were given normal nutritionally balanced food. Meals were eaten in groups under supervision and with the support from specialized nurses and therapists. The caloric intake was then increased step by step to hypercaloric ranges in order to ensure weight gain. The patients agreed to sign a "weight contract" declaring that they aim to gain a certain amount of weight per week, usually between 500 and 700 grams. Nutritional rehabilitation was further supported by different forms of psychotherapy, for example, individual and group therapy, also complemented by music and art therapy. Time of inpatient treatment usually was planned for 8–10 weeks but sometimes was extended, if considered necessary.

Within the 1st week after admission, patients with AN with a body mass index (BMI) $\leq$ 18.5 kg/m^2 were recruited for the study. BMI was calculated using the common formula: BMI = weight/height^2 (in kg/m^2). The participants had to be old enough to be treated in the ED unit for adults, which usually requires the age of 18 years. However, patients who would soon be turning 18 years were also admitted in some cases and were not excluded from analysis for reasons of age. Both sexes were included in order to capture the spectrum of patients with AN. Patients with severe somatic diseases, which are likely to induce GI symptoms like Crohn's disease, or those with limited knowledge of the German language were excluded from analysis.

Procedures

At admission, body height, age, sex, age at the first diagnosis, duration of illness, vomiting behavior, and laxative misuse were assessed. A total of four questionnaires were distributed at admission and at discharge, assessing patients' mental condition (psychometric variables): the Eating Disorder Inventory 2 (EDI-2), the Generalized Anxiety Disorder 7 (GAD-7), the 9-item depression scale of the Patient Health Questionnaire (PHQ-9), and the Perceived Stress Questionnaire (PSQ). Only the sum scores of these questionnaires were applied, but no subscales. Body weight and the Gastrointestinal Symptom Rating Scale (GSRS) questionnaire were assessed once weekly from the 1st week after admission until discharge. In case of the GSRS, the subscales were also of interest on top of the total score for better differentiation and analysis of GI symptoms. Serum amylase levels were retrieved from the standard laboratory blood measurements. Finally, the length of inpatient stay was recorded.

The Gastrointestinal Symptom Rating Scale (GSRS) is a self-report questionnaire evaluating common GI symptoms (39). The GSRS questionnaire, which has been used in many studies examining patients with FGIDs, is valid and reliable (40) but also brief and therefore useful as an instrument for repeated measures (28). It inquires after patients' complaints with 15 different items grouped into five subscales on a 7-point Likert scale with scores from 1 denoting "no discomfort at all" to 7 indicating "very severe discomfort." The conventional total GSRS score is the mean of these 15 symptoms. The five subscales, each constructed of two to four different GI symptoms which are assessed in the questionnaire (with individual symptoms

in brackets also serving as a definition for the symptom complexes), are abdominal pain (abdominal pain, hunger pains, nausea), constipation (constipation, hard stools, feeling of incomplete evacuation), diarrhea (diarrhea, loose stools, urgent need for defecation), indigestion (borborygmus, abdominal distension, eructation, flatulence), and reflux (heartburn, acid regurgitation). According to previous studies, a value of ≥ 2 in GSRS scores is defined as pathological (40–42). An AN-typical total score was calculated in addition to the conventional GSRS total score and subscales. This score consisted of the mean of the three GSRS subscales, which had been pathological in the majority of patients at the beginning of treatment (abdominal pain, constipation, and indigestion) and were therefore the most relevant GI symptoms in the examined patients with AN.

The Eating Disorder Inventory 2 (EDI-2) examines behaviors and attitudes typical for EDs (43). It consists of 91 items divided into the following 11 subscales: asceticism, body dissatisfaction, bulimia, drive for thinness, impulse regulation, ineffectiveness, interoceptive awareness, interpersonal distrust, maturity fears, perfectionism, and social insecurity and has been applied in patients with AN before (44). The six-point response format ranges from 1 denoting "never" to 6 denoting "always." Answers from all items are summed up to a total score. Only the EDI-2 total scores were used for further analysis as ED pathology in general was of interest.

The Generalized Anxiety Disorder 7 (GAD-7) is a seven-item anxiety scale of the Patient Health Questionnaire, which was developed and initially validated as a brief self-report screening tool for generalized anxiety disorder (GAD) in clinical practice (45). Answers are scored from 0 to 3, indicating increasing symptoms with increasing values, and are summed up to a total score. Apart from that, it is also commonly applied as a reliable and valid tool in order to measure general anxiety symptoms in different populations and settings (46).

The Patient Health Questionnaire 9 (PHQ-9) is a 9-item depression scale based on the Patient Health Questionnaire (47). Answers are scored from 0 to 3, with the latter indicating difficulties nearly on a daily basis. The questions inquire about the patients' interest or joy in doing things, feeling down or hopeless, difficulty with sleeping, tiredness or feeling of low energy levels, change in appetite, self-perception, ability to concentrate, de-/accelerated functioning, and suicidal thoughts (48). Answers from all items are summed up to a total score.

The Perceived Stress Questionnaire (PSQ) is a 30-item stress questionnaire constructed to measure subjective perception, evaluation, and processing of stress (49). The original version of the PSQ contains 30 items. To increase the feasibility of completing the questionnaires, we applied a 20-item short version that evaluates the four subscales worries, tension, demands, and joy. It applies five items each on a four-item Likert scale, with 1 denoting "almost never" and 4 denoting "most of the time" within the last 6 weeks (49). The polarity of the items (e.g., feeling calm versus feeling frustrated) was taken into account by respective poling. PSQ values range between 0 and 1 according to common calculation. The PSQ is widely considered to be a reliable and valid tool in the assessment of subjectively experienced stress (50).

Data analysis

Data were analyzed using IBM SPSS Statistics, version 27.0 (51) and R statistics (52). Data sets of participants were included if GSRS questionnaires were completed at least three times of the seven measurements during the first 6 weeks of their inpatient stay so that a development would be detectable. For all variables, mean, standard deviation (SD), median, and interquartile range (IQR) at the beginning of treatment were calculated. The percentage of patients with pathological GSRS scores at admission was also recorded.

Because of the repeated measures design of the study with measures at different timepoints (level 1) nested within patients (level 2), a mixed linear model (MLM) approach, also called hierarchical linear model, was considered appropriate to analyze the data. The MLM takes into account that the repeated observations in one patient are dependent. If calculated otherwise, estimators could be biased, and standard errors (SE) could be underestimated. In case of missing data, imputation is not necessary as cases are not excluded listwise, and parameters are estimated with the available data. Within- and between-person predictors were handled following common recommendations (53). Because of meeting the linearity of relationships, data transformation was not required.

MLM can be used with different covariance types depending on the structure of the data. The data showed different variance at each timepoint and constant covariance between the measurements; thus, a diagonal covariance structure was applied. Several different models were built in order to analyze the data step by step. (1) A so-called "empty model" without any explanatory variables was calculated to estimate the extent to which the GSRS scores differed between patients. (2) Next, the random intercept model was conducted with the number of treatment weeks, which is the central explanatory predictor at level 1, as the fixed effect. (3) A random slope model was calculated to assess for varying time slopes across patients. The latter two steps were also tested with a quadratic slope by squaring the amount of treatment weeks to test for increasing or decreasing influence of treatment time on the GI development. (4) BMI and amylase, the remaining predictors of level 1 with measures at each timepoint, were applied as fixed effects in separate models. (5) All predictors of level 2 (those which were only measured at the beginning of treatment) were modeled as fixed effects in separate models. Interactions of all predictors with the treatment time in weeks were tested consecutively to examine if the influence of a predictor on GI symptom development changes during treatment time.

Model fits calculated as -2 log-likelihood and Akaike information criterion were taken into account in order to

compare the fit of different models. MLM was used for the total GSRS score and each subscale separately using repeated measures until week 10. Week 10 was chosen as the last timepoint to be included into analysis as this was the upper limit of the planned treatment time and also matched with the approximate average time of the actual inpatient stay.

MLM calculations were not adjusted for multiple testing, but only strong p values of < 0.005 were considered as statistically significant. Results with p values < 0.05 were, however, also reported and can be considered putative effects.

Results

Characteristics of participants

Of the 38 patients with diagnosis of AN included in the study, 17 patients were categorized as restrictive, 16 as binge-purging, and five as unspecified subtype. The average age was 27.9 [SD = 10.3, median = 23.5, IQR = (20.0–35.0)] years, ranging from 17 to 53 years. Only two male patients fulfilled the inclusion criteria (5.3% of patients); 19 patients were categorized as having extreme AN with a BMI of < 15.0 kg/m^2 according to the DSM-5 criteria, nine as severe (BMI 15.0–15.9 kg/m^2), three as moderate (BMI 16.0–16.9 kg/m^2), and six as mild AN (BMI > 17.0 kg/m^2) (1). The average length of inpatient stay was 9.5 [SD = 3.3, median = 9.0, IQR = (7.0–12.0)] weeks, ranging from 5 to 17 weeks. On average, the mean age at first diagnosis was 20.9 [SD = 9.1, median = 18.0, IQR = (15.0–22.0)] years, and duration of the disease was 7.5 [SD = 8.5, median = 4.0, IQR = (2.5–10.0)] years. Vomiting behavior was reported by 11 (29.0%) and laxative misuse by seven patients (18.4%). Most patients had several somatic and mental comorbidities; depressive disorder was the most frequent mental disorder, found in 32 patients. Other comorbidities were posttraumatic stress disorder in four patients and obsessive-compulsive disorders in three patients; one patient had attempted suicide twice, and another had surgically treated ulcerative colitis.

Gastrointestinal development over the timecourse

The pre- and post-treatment characteristics of the study population are summarized in **Table 1**. A more detailed descriptive overview on the longitudinal GI data is given in **Supplementary Table 1**. In the median, 31.0 [IQR = (20.0–34.5)] measurements were available per timepoint. The prevalence of GI symptoms at admission varied widely with diarrhea being quite rare (26.3%), while relevant symptoms in the field of indigestion were reported by almost every patient (94.7%). Abdominal pain and constipation were similarly highly prevalent (76.3% and 84.2%, respectively), whereas reflux was a serious problem in approximately half of the participants (42.1%). Overall GI symptoms scored pathological in 86.8% of the patients. As described earlier, we constructed an additional AN-typical GSRS total score summarizing the means of abdominal pain, constipation, and indigestion as these were, on average, pathological at the beginning of treatment and thus the most relevant GI symptoms in the examined AN population, being pathological in 86.8% of patients at the beginning of treatment.

As the GI development over the timecourse was modeled using the MLM, random intercepts (which are estimates at admission), linear and quadratic fixed and random slopes could be tested in addition to the analysis of weekly development. First of all, models with random intercepts and fixed slopes had good model fits, and random intercepts were significant with $p < 0.001$ in all models calculating random intercepts, irrespective of the GSRS score of the dependent variable, as presented in **Table 2**. The estimates of the random intercepts in the final models range from 1.6 ($p < 0.001$, SE = 0.132) on the GSRS score for diarrhea (not pathological) to a highly pathological value of 3.8 ($p < 0.001$, SE = 0.205) for indigestion. These estimates are also similar to the means at admission, which are presented in **Figure 1**. Testing of a quadratic development of GI symptoms was not found to be significant for any GSRS score. Temporal development can therefore not be thought to take a quadratic course but is most likely linear among all patients and GSRS scores. In the next step, models allowing for GI development differing between the patients over the timecourse in addition to random intercepts (random slope models) were tested. This further improved the model fits of the models examining the GSRS total and AN-typical scores as well as the subscales abdominal pain, constipation, and indigestion, but not diarrhea and reflux, which are therefore the only subscales reported as models with fixed slopes in **Table 2**. Indigestion and overall GI symptoms (including diarrhea and reflux, which were overall not pathological in the first place) did not change significantly, as can be seen in **Table 2**. However, abdominal pain, constipation, and AN-typical GI symptoms improved significantly during treatment with estimated weekly improvements of 0.085, 0.101, and 0.076 on the GSRS score. The estimated improvements after 10 weeks of treatment are shown in **Figure 1**, for example, in the case of constipation, one point on the GSRS score is estimated to be improved after 10 weeks of treatment. Reaching normal values is still estimated by the models to take several weeks longer depending on the symptom. As presented in **Figure 1**, at the end of the treatment, more patients range within GSRS scores considered healthy than at the beginning for all total and subscales, except diarrhea. Applying the functions given in **Figure 1**, the week in which GSRS scores are estimated to reach normal values can also be estimated. For the GSRS scores which improve significantly, namely, AN-typical, abdominal pain, and constipation, 20.3,

TABLE 1 Description of body mass index, serum amylase levels, gastrointestinal symptom rating scale scores, and psychometric variables at admission and discharge.

	Admission			Discharge			Difference	
	Mean (SD)	Median [IQR]	[Min-Max]	Mean (SD)	Median (IQR)	[Min-Max]	Mean	Delta Mean in %
BMI	14.73 (1.79)	14.92 [13.22–14.92]	[11.42–18.14]	16.55 (1.81)	17.06 (2.67)	[13.02–19.84]	1.81	12.27
Amylase	108.21 (68.16)	92.00 [71.00–113.25]	[32.00–330.00)	108.73 (51.02)	89.00 (54.50)	[53.00–264.00]	0.53	0.49
GSRS								
Total	3.06 (1.12)	2.73 [2.14–4.10]	[1.60–5.60]	2.58 (1.14)	2.07 (1.77)	[1.20–4.80]	0.49	15.85
AN-typical	3.49 (1.29)	2.99 [2.56–4.33]	[1.64–6.42]	2.97 (1.37)	2.57 [1.83–3,95]	[1.25–6.55]	0.52	14.89
Abdominal Pain	3.07 (1.57)	2.67 [1.67–4.17]	[1.00–6.67]	2.40 (1.12)	2.00 (2.17)	[1.00–4.67]	0.66	21.58
Constipation	3.61 (1.88)	3.00 [2.17–5.17]	[1.00–7.00]	3.01 (1.82)	2.67 (3.25)	[1.00–7.00]	0.60	16.64
Diarrhea	2.09 (1.60)	1.33 [1.00–3.00]	[1.00–7.00]	1.89 (1.27)	1.33 (1.58)	[1.00–6.00]	0.20	9.60
Indigestion	3.93 (1.34)	3.75 [2.75–4.75]	[2.00–7.00]	3.38 (1.52)	3.00 (2.38)	[1.50–6.75]	0.55	13.89
Reflux	1.94 (1.29)	1.00 [1.00–3.00]	[1.00–6.00]	1.59 (0.94)	1.00 (1.00)	[1.00–4.50]	0.35	18.08
Psychometric variables								
EDI-2	288.59 (70.20)	276.50 [230.26–348.75]	[173.00–416.00]	282.28 (70.93)	296.00 (131.50)	[144.00–389.00]	6.31	2.19
GAD-7	15.29 (6.51)	14.00 [9.75–20.00]	[4.00–27.00]	10.97 (6.33)	10.00 (10.00)	[1.00–25.00]	4.33	28.30
PHQ-9	10.76 (5.29)	9.50 [6.00–15.25]	[3.00–21.00]	8.21 (5.27)	6.00 (10.00)	[2.00–17.00]	2.56	23.76
PSQ	0.63 (0.20)	0.68 [0.47–0.77]	[0.23–0.93]	0.51 (0.20)	0.50 (0.28)	[0.03–0.82]	0.11	17.84

AN, Anorexia nervosa; BMI, Body Mass Index (BMI); EDI-2, Eating-Disorder-Inventory-2; GAD-7, Generalized-Anxiety-Disorder-7; GSRS, Gastrointestinal Symptom Rating Scale; IQR, interquartile range; Max, Maximum; Min, Minimum; PHQ-9, Patient-Health-Questionnaire-9; PSQ, Perceived Stress Questionnaire; SD, standard deviation.

12.8, and 16.6 treatment weeks are estimated to be necessary in order to reach normal values for the average patient population. However, this is no longer included in our observation period and should therefore be considered with caution. Diarrhea and reflux remained stable over the timecourse, with the median of values being already below pathological threshold at admission. Still, especially in reflux, many outliers showing much higher values than both the median and the mean account for a more diverse picture.

Predictors of gastrointestinal symptom improvement

An overview on the assessed predictors of GI symptom improvement is presented in Table 2. The predictors were analyzed applying the same models as explained before (MLM with random intercepts and fixed slopes for diarrhea and reflux and MLM with random intercepts and random slopes for abdominal pain, constipation, indigestion, and overall AN-typical GI symptoms). Strong predictors with $p < 0.005$ were ED pathology for abdominal pain, constipation, reflux, overall AN-typical GI symptoms, stress for constipation, and AN-typical GI symptoms, as well as depression for constipation. The estimates reported are not effect sizes and not standardized and can therefore not be compared between the different predictors. Instead, they are interpreted in relation with the respective GSRS scores and the average values of the respective predictor. For example, for constipation and ED pathology, this implies that the GSRS score is estimated to be 0.016 GSRS points lower for every full point less on the EDI-2. Given that the average EDI-2 score of our study population is 288.6, substantial differences between the patients in constipation outcomes associated with higher or lower EDI-2 scores appear reasonable.

More factors with $p < 0.05$, but not > 0.005, are reported in Table 2 but not discussed further as they cannot safely be considered significant predictors due to multiple testing. Interactions between tested predictors and treatment week, which are supposed to indicate if an effect of a predictor changes during treatment, are not reported in Table 2 because no interaction was found to be significant with $p < 0.005$. Other tested predictors (BMI, serum amylase, age, age at first diagnosis, duration of disease, length of inpatient stay, vomiting behavior, laxative misuse, anxiety, and depression) did not significantly contribute to weekly GI development. Altogether, the most important contributing predictor was treatment time, as reported in the previous section.

Discussion

GI symptoms are common in patients with AN (6). In line with other studies, we found that such symptoms improved in patients with AN during or after inpatient treatment (11, 54, 55). However, this study analyzed the dynamics of GI symptom development in patients with AN during treatment for the first time—knowledge that can be helpful in supporting patients with AN during nutritional rehabilitation. In addition, this study extends the knowledge about predictors for GI outcome in patients with AN.

Abdominal pain, constipation, and indigestion (borborygmus, abdominal distension, eructation, flatulence) are typical GI symptoms in patients with AN and develop differently in the timecourse of treatment. Abdominal pain and constipation, as well as AN-typical symptoms,

TABLE 2 Key findings of mixed linear models for gastrointestinal symptoms rating scale total and subscores.

	Total GSRS		AN-typical		Abdominal pain		Constipation		Diarrhea		Indigestion		Reflux	
	Estimate (SE) CI	*p* value	Estimate (SE) CI	*p* value	Estimate (SE) CI	*p* value	Estimate (SE) CI	*p* value	Estimate (SE) CI	*p* value	Estimate (SE) CI	*p* value	Estimate (SE) CI	*p* value
Estimate at admission	2.955*** (0.153) [2.644–3.265]	< 0.001	3.544*** (0.193) [3.153–3.936]	< 0.001	3.089*** (0.174) [2.740–3.440]	< 0.001	3.678*** (0.293) [3.086–4.271]	< 0.001	1.779*** (0.159) [1.460–2.098]	< 0.001	3.821*** (0.205) [3.406–4.237]	< 0.001	1.801*** (0.158) [1.484–2.119]	< 0.001
Weekly GI change	−0.038 (0.021) [−0.081–0.005]	0.079	−0.076** (0.025) [−0.127–−0.024]	0.005	−0.085** (0.024) [−0.134–−0.035]	0.002	−0.101** (0.032) [−0.167–−0.035]	0.004	0.011 (0.015) [−0.020–0.042]	0.479	−0.036 (0.028) [−0.093–0.020]	0.197	−0.008 (0.014) [−0.036–0.019]	0.561
Predictor														
Weekly BMI	−0.011 (0.065) [−0.141–0.118]	0.863	0.012 (0.081) [−0.150–0.174]	0.882	0.034 (0.083) [−0.131–0.198]	0.684	0.088 (0.126) [−0.163–0.338]	0.489	0.009 (0.077) [−0.144–0.163]	0.904	−0.000 (0.089) [−0.178–0.177]	0.996	0.134 (0.076) [−0.018–0.286]	0.083
Weekly Amylase	0.003 (0.002) [−0.001–0.008]	0.159	0.006* (0.003) [0.000–0.011]	0.043	0.002 (0.003) [−0.005–0.008]	0.557	0.008 (0.004) [−0.001–0.017]	0.066	0.002 (0.003) [−0.004–0.008]	0.493	0.000 (0.003) [−0.006–0.006]	0.975	−0.001 (0.003) [−0.006–0.005]	0.843
Age	−0.012 (0.015) [−0.043–0.019]	0.427	−0.012 (0.019) [−0.051–0.027]	0.540	−0.021 (0.017) [−0.055–0.014]	0.232	0.010 (0.029) [−0.049–0.070]	0.725	−0.002 (0.016) [−0.034–0.030]	0.908	−0.019 (0.021) [−0.060–0.023]	0.373	−0.026 (0.016) [−0.058–0.006]	0.107
Duration of illness	0.002 (0.020) [−0.039–0.044]	0.907	0.014 (0.026) [−0.038–0.067]	0.576	−0.004 (0.024) [−0.053–0.046]	0.877	0.050 (0.037) [−0.025–0.125]	0.185	−0.021 (0.023) [−0.066–0.025]	0.371	−0.001 (0.028) [−0.056–0.059]	0.958	−0.022 (0.022) [−0.067–0.0236]	0.341
Age at first diagnosis	−0.007 (0.019) [−0.045–0.031]	0.695	−0.011 (0.023) [−0.059–0.036]	0.631	−0.010 (0.022) [−0.054–0.035]	0.662	−0.011 (0.034) [−0.080–0.058]	0.750	0.009 (0.020) [−0.030–0.049]	0.634	−0.001 (0.026) [−0.053–0.051]	0.955	−0.025 (0.020) [−0.065–0.015]	0.216
Length of inpatient stay	0.006 (0.049) [−0.093–0.105]	0.905	0.013 (0.062) [−0.112–0.137]	0.840	−0.043 (0.055) [−0.154–0.068]	0.435	0.042 (0.093) [−0.146–0.231]	0.653	−0.006 (0.050) [−0.107–0.095]	0.901	0.038 (0.065) [−0.095–0.170]	0.566	−0.057 (0.050) [−0.159–0.044]	0.262
Laxative misuse	−0.406 (0.349) [−1.120–0.307]	0.254	−0.399 (0.451) [−1.321–0.523]	0.384	−0.312 (0.421) [−1.166–0.542]	0.463	0.165 (0.735) [−1.335–1.665]	0.824	−0.190 (0.308) [−0.812–0.432]	0.541	−1.022 (0.534) [−2.114–0.069]	0.065	0.029 (0.368) [−0.717–0.775]	0.937
Vomiting behavior	0.376 (0.333) [−0.300–1.051]	0.267	0.297 (0.424) [−0.563–1.158]	0.488	0.360 (0.385) [−0.416–1.136]	0.354	0.330 (0.647) [−0.980–1.640]	0.613	0.588 (0.330) [−0.074–1.250]	0.081	0.239 (0.454) [−0.681–1.159]	0.602	0.082 (0.355) [−0.631–0.795]	0.818
Eating behavior (EDI-2)	0.007** (0.002) [0.003–0.012]	0.001	0.010*** (0.003) [0.005–0.015]	< 0.001	0.009** (0.003) [−0.003–0.014]	0.002	0.016*** (0.004) [0.008–0.023]	< 0.001	0.002 (0.003) [−0.003–0.007]	0.519	0.005 (0.003) [−0.001–0.011]	0.121	0.007** (0.002) [0.002–0.011]	0.004
Depression (PHQ-9)	0.059* (0.024) [0.010–0.109]	0.020	0.086* (0.030) [0.025–0.147]	0.007	0.080* (0.029) [0.022–0.137]	0.008	0.156*** (0.041) [0.071–0.241]	< 0.001	0.003 (0.028) [−0.052–0.059]	–0.906	0.021 (0.035) [−0.050–0.093]	0.551	0.024 (0.026) [−0.029–0.077]	0.368
Anxiety (GAD-7)	0.048 (0.031) [−0.015–0.111]	0.133	0.059 (0.039) [−0.021–0.139]	0.144	0.055 (0.037) [−0.019–0.130]	0.139	0.145* (0.055) [0.033–0.257]	0.013	0.025 (0.033) [−0.042–0.093]	0.450	−0.013 (0.043) [−0.101–0.075]	0.760	0.048 (0.032) [−0.016–0.112]	0.137
Stress (PSQ)	2.048* (0.775) [0.470–3.626]	0.013	3.103** (0.933) [1.202–5.004]	0.002	2.200* (0.931) [0.309–4.090]	0.024	5.825*** (1.252) [3.276–8.374]	< 0.001	−0.145 (0.894) [−1.952–1.661]	0.872	1.684 (1.105) [−0.567–3.935]	0.137	0.494 (0.838) [−1.194–2.182]	0.558

The main results of the basic mixed linear models (MLM) analyzing all Gastrointestinal Symptom Rating Scale (GSRS) scales as a dependent variable are presented in the upper part. The estimates at admission and the estimated weekly gastrointestinal (GI) change for all GI symptoms as calculated in the best fitting models are reported. As best fitting models MLM with random slopes were identified for total GSRS score, AN-typical GSRS score and the subscales abdominal pain, constipation and indigestion. MLM with fixed slopes produced the best model fits for the GSRS subscales diarrhea and indigestion. Furthermore, variables tested as predictors for development of GI symptoms calculated with the same MLM as explained above are presented in this table. Standard errors (SE), confidence intervals (CI) and *p* values are reported for all calculated estimates. Significant *p* values were indicated with stars: *$p < 0.05$; **$p < 0.005$; ***$p < 0.001$. Due to multiple testing, we only considered *p* values with $p < 0.005$ as statistically significant. The predictor's estimates specify how many points the examined GSRS score changes if the respective predictor changes a full point on its scale. Therefore, taking into account the mean values of the predictors as reported in Table 1 and in the main text is recommended. Interactions between predictor and treatment week were also calculated but not reported here as no interaction was statistically significant with $p < 0.005$.

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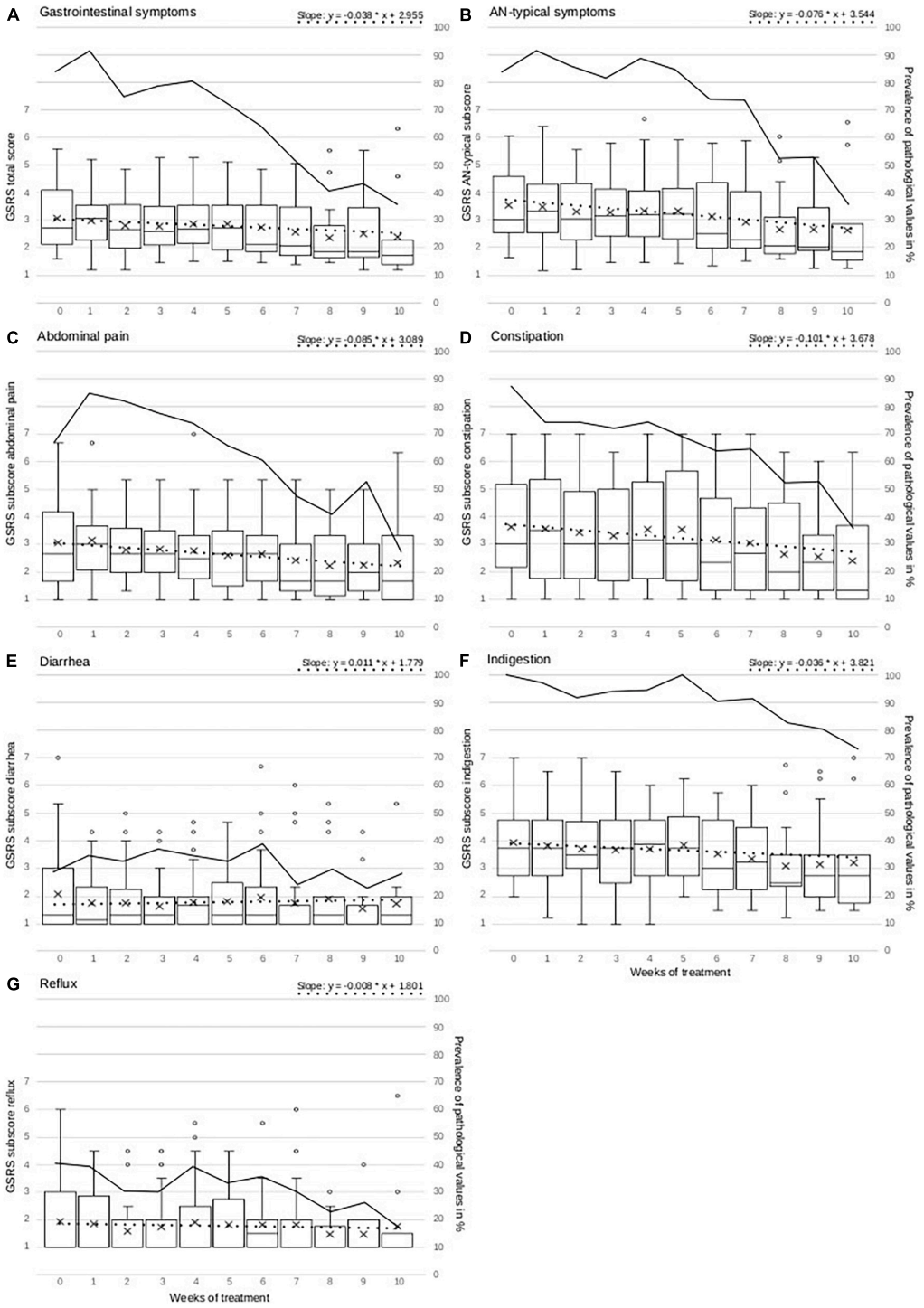

FIGURE 1

Figure presents weekly measurements of overall GI symptoms, AN-typical GSRS score and GSRS subscales abdominal pain, constipation, diarrhea, indigestion, and reflux as boxplots with mean (+), median (–), interquartile range (IQR = box), whiskers (1.5 × IQR), and outliers (o > 1.5 IQR). The y-axis for all GSRS scores is located on the left of each graph. The dotted line represents the development estimated by mixed linear models for each GSRS score. The mathematical function for this development estimated by mixed linear models is given in the upper right of each separate graph and is constructed with the estimate at admission and the weekly GI change (also see **Table 2**). In this formula, the *x* value can be replaced by the treatment week in order to calculate the corresponding estimated GSRS score, which is represented by the *y* value, for this specific treatment week. The formula is derived from the mixed linear model results, which are presented in **Table 2**. The continuous line represents the development of the prevalence of pathological GSRS values in % within the examined population. The y-axis of the prevalence is located on the right side of each graph.

altogether improved significantly within the observation period. Constipation appeared to improve at a higher rate than abdominal pain, with about 0.1 points on the GSRS score per treatment week. Both symptom complexes did, on average, not normalize during treatment, but due to significant weekly improvement, the normalization of the average GSRS scores of abdominal pain and constipation can be assumed. However, a longer observation period would be required for certainty. These results can be helpful in encouraging patients to continue eating despite GI symptoms troubling the patients particularly at the beginning of treatment.

Symptoms of indigestion were very high at the beginning of treatment and neither normalized throughout treatment in more than 80% of the patients nor improved significantly. The persistence of these symptoms is consistent with a previous study (54). Apparently, indigestion is the most persistent symptom complex concerning GI discomfort in patients with AN. The question is when, and if at all, indigestion symptoms would normalize and whether this would require a longer observation period since symptoms might persist for years after recovery, as shown in a retrospective study (28). Generally, many studies drew the conclusion that long-term disordered eating behavior can lead to prolonged medical problems and physiological adaptations that may appear as FGIDs (10, 11, 34).

Diarrhea and reflux symptoms played a minor role in the investigated population with AN as the majority of patients showed normal values from admission onward. In the first week of treatment, diarrhea symptoms appeared to worsen in some patients, but not significantly and not to pathological levels on the GSRS. Reflux symptoms were of particular interest as they might be a consequence of binge-purging behavior, more specifically vomiting. Interestingly, neither serum amylase nor vomiting behavior, factors that can be hypothesized to be connected with reflux symptoms, was found to be associated with the latter for the complete AN group. An analysis within the different AN subgroups—restrictive and binge-purging—would have been necessary but would have resulted in insufficient subgroup sample sizes in this study.

A key finding of this study was that disordered ED pathology at admission appeared to be an important predictor for the development of abdominal pain, constipation, reflux, and overall AN-typical GI symptoms. Overall, this suggested that GI symptoms might rather be of functional origin in patients with AN. Although ED pathology appeared to be a predictor for several GI symptoms in this study, the EDI-2 score remained high despite treatment. In line with the high mortality rate of patients with AN due to the difficult course the disease can take, ED pathology was found to be persistent, on average, even after inpatient treatment (56). Surprisingly, weekly measured BMI did not predict the development of GI symptoms. As weight gain is a main objective in the treatment of patients with AN and treatment of AN has been shown to improve GI symptoms, it was expected that a BMI increase would contribute to a better GI outcome and vice versa, although information about BMI as a predictor was not found in the literature beforehand. However, this finding overall implied that GI symptoms might improve equally in patients with different starting positions or suboptimal weight development. Overall, nutritional rehabilitation with normalized food intake and functioning of the GI tract appeared to support a favorable GI outcome with a higher likelihood than mere weight gain in this study. Despite these findings, it might also be possible that the length of observation and thus the degree of weight restoration was not sufficient to find a positive influence of weight gain on GI symptoms as many patients in this study remained on low BMI levels until discharge. However, applying EDI-2 at admission might be useful in order to estimate GI development before treatment and particularly support patients with more severely disordered ED pathology.

In addition, the outcome of constipation was also predicted by stress and depression, and AN-typical GI symptoms could be predicted by stress. Anxiety was the only psychological factor that showed no association with any GI symptom complex—a finding which is coherent with an earlier study (36). Considering depression as a predictor of GI symptom development in AN, we found studies with conflicting results, as presented in Introduction (33, 36). An explanation for this discrepancy of depression as a predictor might be the observation period. It is possible that depression can be considered as a predictor of long-term GI symptom improvement, whereas depression may not be a considerable predictor when GI symptoms are examined for a short term. Our finding is also consistent with a that of a previous study that reported GI symptoms to improve in patients with AN only if depressive symptoms improved coherently (37). This supports the hypothesis expressed by several authors that GI symptoms and EDs like AN might be mediated by an underlying psychiatric disorder and therefore regularly occur together (28), while others also interpret the coherent appearance of disordered ED pathology, GI disturbances, and psychiatric disorders as an overlapping psychopathophysiologic syndrome (57). Specifically in cases of severe constipation, the assessment of the prevalence of stress and depression could be helpful for the treatment of an affected patient.

This study has strengths and limitations. First, it is possible that patients with ED report more severe GI symptoms than they actually have; hence, using this as a means to justify why eating is not possible. Thus, the reliance on self-report data may bias the results. Of course, complaints about GI symptoms should be taken seriously in patients with AN, but there still might be a certain degree of overestimation additionally because of psychomental

distress like depression, which is prevalent in many patients with AN. Second, replicating the analyses of this study with a larger sample size would be necessary in order to strengthen the results. This would be helpful for the analyses conducted in general but also because an addition of separate analyses comprising the different subtypes of AN would be feasible. Such subgroup analyses have been left out in this study because this would have resulted in insufficient subgroup sample sizes. However, they could support the understanding of, for instance, the relationship between binge-purging behavior, reflux symptoms, and increased serum amylase levels in future studies. Third, some of the patients included received medications like antidepressants because of depressive symptoms. However, some antidepressants, among them serotonin reuptake inhibitors, can influence gut motility and thus GI symptoms directly and not only *via* improving depression (58). Fourth, this study did not include a healthy control group. Finally, there are also special strengths of this study. One of these is the measurement of GI symptoms in regular periods over 10 weeks and under controlled conditions in inpatients with AN which was conducted as such for the first time. This provided the possibility of a close monitoring of the GI symptom development over the timecourse. Another strength is the MLM approach as a rather complex method of analysis, which enabled analyzing data with repeated measures design and also including predictors.

In summary, abdominal pain, and constipation-related and AN-typical GI symptoms improved significantly and stabilized in most patients to a normal range during the treatment period. Diarrhea- and reflux-related symptoms overall played a less important role in patients with AN with normal values on average throughout treatment and therefore did not improve significantly during the timecourse. Disordered ED pathology at admission predicted the outcome of abdominal pain, constipation, and reflux, as well as AN-typical and overall GI symptoms; depression predicted the outcome of constipation symptoms; and stress predicted the outcome of constipation and AN-typical symptoms. Weekly measured BMI, serum amylase, anxiety, current age, age at first diagnosis, duration of illness, length of inpatient stay, vomiting behavior, or laxative misuse were not found to predict any GI outcomes. Further research comprising larger sample sizes in order to strengthen the results and enable analyses of different AN subgroups would be a necessary contribution to the field.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving human participants were reviewed and approved by Ethics Committee of the University of Tübingen (ethic protocol number: 392/2019BO2). Written informed consent to participate in this study was provided by the participants or the participants' legal guardian/next of kin in case of underage participants.

Author contributions

CR was responsible for data analysis and interpretation, drafted the manuscript, and acquired data. IM was responsible for conception, design, and preparation of the study, data interpretation, and manuscript writing. NM was responsible for data interpretation. NS was involved in data management. SZ and PE were responsible for conception and design of the study and data interpretation. KG and AS were involved in data interpretation. All authors revised the manuscript and approved the final version of 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.

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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.2022.962837/full#supplementary-material

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An Erratum on

Gastrointestinal complaints in patients with anorexia nervosa in the timecourse of inpatient treatment

by Riedlinger, C., Mazurak, N., Schäffeler, N., Stengel, A., Giel, K. E., Zipfel, S., Enck, P., and Mack, I. (2022). *Front. Psychiatry* 13:962837. doi: 10.3389/fpsyt.2022.962837

Due to a production error, an author's comment was added to the article in error.

A correction has been made to the section **Discussion**, Paragraph Number 8:

"In summary, abdominal pain, and constipation-related and AN-typical GI symptoms improved significantly and stabilized in most patients to a normal range during the treatment period. Diarrhea- and reflux-related symptoms overall played a less important role in patients with AN with normal values on average throughout treatment and therefore did not improve significantly during the timecourse. Disordered ED pathology at admission predicted the outcome of abdominal pain, constipation, and reflux, as well as AN-typical and overall GI symptoms; depression predicted the outcome of constipation symptoms; and stress predicted the outcome of constipation and AN-typical symptoms. Weekly measured BMI, serum amylase, anxiety, current age, age at first diagnosis, duration of illness, length of inpatient stay, vomiting behavior, or laxative misuse were not found to predict any GI outcomes. Further research comprising larger sample sizes in order to strengthen the results and enable analyses of different AN subgroups would be a necessary contribution to the field."

The publisher apologizes for this mistake. The original article has been updated.

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Food addiction in Bulimia Nervosa: Analysis of body composition, psychological and problematic foods profile

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Introduction: Food Addiction (FA) has been related with eating disorders (ED), especially Bulimia Nervosa (BN). BN + FA may have different physical characteristics than patients with BN without the comorbidity, such as body mass index (BMI) or body composition, and psychological as emotion regulation. However, the relationship between psychological and physical aspects, connected by problematic food and its influence on body composition, has been barely studied. Therefore, the aims of the present study are:

Aims: (a) To explore the differences in body composition between FA positive (FA+) and negative (FA−) in women with BN; (b) to identify problematic relationship with certain food types, according with the foods mentioned in the YFAS scale questionnaire, between FA+ and FA− patients; (c) to know the psychological characteristic differences between FA+ and FA− patients, considering emotion regulation, personality traits and general psychopathological state; (d) to identify the relationship between physical and psychological traits, and the identified problematic foods, in patients with BN and FA.

Methodology: *N* = 81 BN women patients, with a mean age of 29.73 years ± 9.80 SD, who completed the questionnaires: Yale Food Addiction Scale V 1.0 (YFAS 1.0), Eating Disorder Inventory-2 (EDI-2), Symptom Checklist-90 Items-Revised (SCL-90-R), and Difficulties in Emotion Regulation Strategies (DERS). YFAS problematic foods were

grouped considering their principal nutrients sources. Body composition and difference in metabolic age was determined using bioimpedance analyzer.

Results: The 88% of patients with BN presented FA+. Patients with BN who were FA+ self-reported more problematic relationships with sweets and starches. Also presented higher emotion regulation difficulties, general psychopathology and eating symptomatology severity, than those without FA. Finally, emotional regulation difficulties were positively associated with higher eating disorder symptomatology and more types of foods self-reported as problematic, which increased indirectly fat mass.

Conclusion: The results suggest that BN + FA presented more eating and psychopathology symptomatology and higher problems with specific food types. As well, the path analysis emphasized that emotion regulation difficulties might be related with problematic food relationship in BN, impacting over the ED severity.

Implications: The results may impact the development of precise therapies for patients with BN + FA.

KEYWORDS

food addiction, Bulimia Nervosa, emotion regulation, problematic foods, body composition

Introduction

Food addiction (FA) has been described as the presence of maladaptive eating behaviors consistent with addictive processes, mainly characterized by excessive consumption of ultra-processed foods. While several studies have reported FA in non-clinical samples (general adult population and student samples), the prevalence of FA is higher in populations with obesity, and in Eating Disorders (ED) patients, especially the ones in the binge spectrum disorders, as Bulimia Nervosa (BN) (86–96%) (1–3).

Frequently, in BN higher FA scores have been positively associated with greater ED severity (4, 5), more general psychopathology (5, 6) and greater dysfunctional personality traits (6, 7). Furthermore, Emotion Regulation (ER) difficulties and greater impulsivity seem to be an important characteristic in this population with absence of FA (FA–). Negative urgency has been found in the presence of FA (FA+) and binge spectrum disorders patients (8, 9). Negative urgency represents the emotional-related aspect of impulsivity, indicating the tendency to act rashly and engage in problematic behavior (in the case of FA, the disorder eating patterns, and excessive food intake) as a response to a negative emotional state (10).

It is important to mention that recent studies have identified different subgroups of patients with ED and FA. Considering a cross-sectional and a longitudinal approach, Cluster-based analyses have found that FA is most commonly associated with BN (relative to other types of disordered eating) (7, 11), which predicts poorer treatment response, as higher rates of dropouts (11). These results are consistent with other studies that have found that patients with BN + FA had worse prognosis than patients with BN without FA (2).

In BN, abnormal eating patterns and excessive compensatory behaviors may result in alterations in body composition. It has been previously reported that patients with bulimia had significantly higher total daily energy intake compared with control subjects (12). Further, certain groups of women with BN consumed large meals primarily of desserts and snack foods (13), which may contribute to higher BMI and greater accumulation of adipose tissue. However, other study on body composition has found that normal weight patients with BN display no significant differences in body composition when compared to healthy normal weight controls (14).

Regarding the influence of FA on body composition, the evidence suggests that individuals with FA and obesity present higher weight and had greater total body fat and trunk fat than non-FA individuals (15), however, it has not been previously reported whether the presence of FA may play a role in the body composition of patients with BN. Even though people with BN might present a normal weight in the majority of cases (16), the presence of comorbid FA could be affecting total body fat percentage. Previous studies have associated the excess accumulation of body fat in normal weight individuals with adverse metabolic profiles, including dyslipidemias and cardiometabolic dysregulations (17–19). A more comprehensive clinical profile of BN + FA patients, including psychological, nutritional and body composition

features, might be needed in order to establish a more personalized treatment approach for this group.

In order to explore this, is important to consider certain foods as potentially addictive. Regarding FA model, this matter is still under debate. Studies of non-ED patients have found that ultra-processed foods, high in refined carbohydrates and/or added fats are typically endorsed as the most addictive, but investigations into this topic in ED samples are limited (20, 21).

Therefore, the present study has as aims: (a) to explore the differences in body composition between BN + FA and BN-FA patients; (b) to identify problematic food relationships, according to the foods identified as most addictive on the YFAS, between BN + FA and BN-FA; (c) to determine the clinical differences in both groups, considering emotion regulation, personality traits and general psychopathological state; (d) to identify the relationship between physical and psychological traits, and the considered problematic foods, in BN with FA patients, in order to determine a complete clinical profile in this population.

We hypothesize that those BN + FA patients, when compared to BN-FA, will present higher BMI and higher total body fat percentage, as well as worst general psychopathological state, higher severity of the disorder, and more emotional regulation difficulties. We also expect that the food referred with a problematic relationship will be different between BN + FA and BN-FA, where those patients with comorbid FA will report higher problematic associations to high fats and refined carbohydrates food groups. Finally, that FA will not only be related with the psychological variables, contributing to a general worst profile, as mentioned above, but will also have more problematic food relationships, as well as differences in the body composition.

Materials and methods

Sample and procedure

The present cross-sectional study was conducted in a sample composed of female outpatients diagnosed with BN (n = 81), with a mean age of 29.22 years ± 9.80 SD. Participants were recruited from the Eating Disorders Unit of the University Hospital of Bellvitge – Barcelona, who attended to request treatment or were already linked to it, from 2013 to 2016. Diagnosis of BN was made by senior clinicians through a DSM-5 diagnostic criteria semi-structured clinical interview (SCID-5) (22). Participants were evaluated trough a psychometric battery that included different questionnaires (see section "Psychometric measures"). All evaluations were performed by experienced psychologists and psychiatrists.

In accordance with the Declaration of Helsinki, the present study was approved by the Clinical Research Ethics Committee of the University Hospital of Bellvitge. During the first evaluation session, participants are informed that several research studies are carried out in the ED unit, and thought informed consent, they accepted the data of their evaluations to be used with clinical and research purpose. Only participants that singed an informed consent were included in the study.

Assessment

Psychometric measures

Yale Food Addiction Scale V 1.0 (YFAS 1.0), (23)*;* validated in Spanish population (5). The YFAS questionnaire was validated for a clinical population in 2009 and was subsequently validated in Spanish. YFAS is based on the criteria of the Diagnostic and Statistical Manual of Mental Disorders, that measures levels of substance dependence, where the term "substances" is replaced by "certain food" and is used for the quantification of the severity of FA during the previous 12 months. This questionnaire assesses seven diagnostic criteria for dependence in case of excessive consumption of high-fat and/or high-sugar foods. It uses two scoring systems: a count of FA symptoms (from 0 to 7, according to DSM-IV-TR diagnostic criteria) and for the assessment of the diagnosis of FA (3 or more symptoms plus clinically significant impairment/distress). The measures consisted of 25 items answered on an 8-point Likert scale. The internal consistency of the total scale for our sample was 0.820 (coefficient alpha).

Eating Disorders Inventory 2 (EDI-2) (24). Is reliable and valid self-report questionnaire that assesses different cognitive and behavioral characteristics typical of ED in eleven subscales: drive for thinness, bulimia, body dissatisfaction, inefficacy, perfectionism, interpersonal distrust, interoceptive awareness, fear of maturity, asceticism, impulse regulation, and social insecurity. The measures consist of 91 items, answered on a 6-point Likert scale. The internal consistency of the total scale for our sample was 0.955 (coefficient alpha).

Symptom Checklist-90-Revised (SCL-90-R) (25). The SCL-90-R questionnaire is used to assess a wide range of psychological problems and symptoms of psychopathology considering nine primary symptom dimensions: somatization, obsessive-compulsive, interpersonal sensitivity, depression, anxiety, hostility, phobic anxiety, paranoid ideation, and psychoticism; and includes three global indices: global severity index (general psychological distress), positive symptom distress index (the intensity of symptoms), and a positive symptom total (self-reported symptoms). The global severity index was used as a test summary. The measure consists of 90 items answered on a 5-point Likert scale. The internal consistency of the subscales for our sample was 0.969 (coefficient alpha).

Difficulties in Emotion Regulation Scale (DERS) (26), validated in Spanish population (27).The DERS questionnaire assesses emotion dysregulation in six subscales: non-acceptance of emotional responses, difficulties in pursuing goals when

experiencing strong emotions, difficulties in controlling impulsive behaviors when experiencing negative emotions, lack of emotional awareness, limited access to emotional regulation strategies and lack of emotional clarity. The measure consists of 36 items and is answered on a 5-point Likert scale. The internal consistency of the subscales for our sample ranges between 0.796 and 0.924, and the one for the total score was 0.950 (coefficient alpha).

Anthropometric parameters and body composition

Both height and weight were measured by trained personnel and used to determine the body mass index (BMI), calculated as weight (Kg)/[height(m)]^2. Body composition was determined using the bioimpedance analysis, a practical, inexpensive, and non-invasive method, utilizing a Multifrequency TANITA MC-80 body impedance device (TANITA, Japan). Values of total fat, non-fat, muscle and bone mass, as body water percentage was analyzed. Basal metabolic rate and metabolic age (Met-age) were determined by the device. Met-age was used to calculate difference in age (participants' chronological age *minus* participants Met-age). Metabolic age has been previously proposed as an indicator of inflammation and cardiovascular risk (28).

Problematic food groups

To identify the problematic relationships generated by certain food groups, the last item of the YFAS questionnaire was considered. This item presents a list of different foods so that the participants can indicate those that him/her recognizes as problematic. These foods were then grouped into five categories according to the possible addicting nutritional content of their chemical composition: high in fat and simple sugars, high in fat and sodium, high in starch, high in simple sugars, and control foods (low in fat, sodium, starch, and simple sugars) (**Table 1**).

Statistical analysis

Statistical analysis was done with Stata17 for Windows (29). The comparison between the groups defined for the screening score in the YFAS (FA− versus FA+) was done with chi-square (χ^2) tests for categorical measures and *t*-tests for quantitative measures (exact p-values were obtained for proportion comparisons with expected counts lower than 5 and for mean comparisons with non-normal distribution). In addition, these analyses included the calculation of the effect size through the standardized Cohen coefficient (*h*-value for proportion comparisons and *d*-value for mean comparisons, considering the thresholds 0.50 and 0.80 for moderate and large effect size) (30). The association between the FA severity level (YFAS total score) with body composition and other clinical measures was estimated with the correlation coefficients. Due the solid association between the significance level for the *R*-coefficients and the sample size, effect size was considered low-poor $|R| > 0.10$, moderate-medium for $|R| > 0.24$ and large-high for $|R| > 0.37$ (31).

Path analysis was implemented through Structural Equation Modeling (SEM). All the parameters were free-estimated, and a latent variable measuring the problematic foods profile was defined based on the different foods analyzed in this work. With the aim to obtain a final parsimonious model (with the highest statistical power), parameters with not significant tests were deleted and the model was re-specified and re-adjusted (only non-significant coefficients were retained for the measurement parameters related to the latent variable). Goodness-of-fit was evaluated using standard statistical measures, and it was considered adequate for (32): non-significant result in the χ^2 test, root mean square error of approximation RMSEA < 0.08, Bentler's Comparative Fit Index CFI > 0.90, Tucker-Lewis Index TLI > 0.90, and standardized root mean square residual SRMR < 0.10The global predictive capacity of the model was measured by the coefficient of determination (CD).

TABLE 1 Distribution of the problematic foods included in YFAS.

Food groups	Foods included in YFAS
High fat/High sugars	ice cream, chocolate, cookies, cake, donuts
High fat/High sodium	bacon, burgers, pizza, French fries, steak, cheeseburgers
High starches	white bread, pasta, rice, rolls
High in sugars	candies, soft drinks
Controls	apples, broccoli, lettuce, strawberries, carrots, bananas

Results

Association of food addiction with problematic food groups, body composition and clinical profile

The first block of **Table 2** contains the distribution of all the variables of the study among the total sample. The mean for BMI was 24.2 kg/m2 (SD = 4.9). The problematic relationship with high fat/high sugars food was reported by 93.8% of the patients, high fat/high sodium foods by 88.9%, high starches by 82.7% and high sugars by 61.7%. Control foods were endorsed by 22.2%.

Figure 1 displays the bar-charts with the distribution of the problematic food groups, for patients with and without FA, according to the YFAS screening tool. Overall, patients with a positive FA score increase the likelihood of recognize as problematic all types of food, although only significant differences were obtained for sweets with high fat content ($p = 0.034$, $|h| = 0.57$) and starches ($p = 0.022$, $|h| = 0.70$). However, the control foods were endorsed the least of all food

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TABLE 2 Association between food addiction (FA) screening scores and clinical profile.

	Total (*n* = 81)		FA − (*n* = 9)		FA + (*n* = 72)			
	Mean	*SD*	*Mean*	*SD*	*Mean*	*SD*	*p*	|*d*|
Fat mass	26.88	7.60	25.03	4.08	27.11	7.92	0.441	0.33
Non-fat mas	44.64	3.65	44.50	2.30	44.66	3.80	0.901	0.05
Muscle mass	42.62	3.50	42.45	2.25	42.64	3.64	0.880	0.06
Body water%	51.13	4.79	52.48	2.61	50.96	4.99	0.372	0.38
Bone mass	2.27	0.18	2.27	0.12	2.27	0.19	0.993	0.00
Basal metabolic rate	1369	123.0	1370	61.0	1369	128.9	0.975	0.01
Metabolic age	27.16	12.86	21.04	7.60	27.93	13.20	0.130	**0.64**†
Difference in age	2.06	10.18	1.52	6.22	2.13	10.60	0.867	0.07
BMI (kg/m^2)	24.18	4.88	23.16	1.63	24.30	5.13	0.513	0.30
EDI Drive thinness	15.21	4.51	11.56	4.45	15.67	4.33	**0.009***	**0.94**†
EDI Body dissatisfaction	17.27	7.38	14.56	6.35	17.61	7.47	0.244	0.44
EDI Interoceptive awareness	12.69	6.25	7.78	5.72	13.31	6.07	**0.011***	**0.94**†
EDI Bulimia	10.36	4.35	6.44	3.57	10.85	4.20	**0.004***	**1.13**†
EDI Interpersonal distrust	5.60	4.52	2.67	2.40	5.97	4.60	**0.038***	**0.90**†
EDI Ineffectiveness	12.06	6.69	9.56	4.98	12.38	6.84	0.236	0.47
EDI Maturity fears	7.94	4.59	8.00	2.92	7.93	4.78	0.966	0.02
EDI Perfectionism	6.38	4.56	3.78	2.28	6.71	4.68	0.069	**0.80**†
EDI Impulse reg.	6.79	5.17	4.78	5.65	7.04	5.10	0.218	0.42
EDI Ascetic	7.94	4.04	5.00	2.60	8.31	4.05	**0.020***	**0.97**†
EDI Social insecurity	8.10	5.09	5.67	2.96	8.40	5.23	0.129	**0.64**†
EDI Total	110.35	39.14	79.78	28.00	114.17	38.79	**0.012***	**1.02**†
SCL-90R Somatic	1.83	0.76	1.29	0.92	1.89	0.72	**0.023***	**0.73**†
SCL-90R Obs.-com	1.97	0.72	1.44	1.01	2.04	0.66	**0.017***	**0.71**†
SCL-90R Sensitivity	2.16	0.69	1.68	0.75	2.22	0.66	**0.026***	**0.76**†
SCL-90R Depress.	2.40	0.74	1.84	0.91	2.47	0.69	**0.016***	**0.77**†
SCL-90R Anxiety	1.62	0.69	1.16	0.83	1.67	0.66	**0.034***	**0.69**†
SCL-90R Hostility	1.22	0.78	0.72	0.52	1.28	0.79	**0.041***	**0.84**†
SCL-90R Phobic	0.97	0.66	0.80	0.72	0.99	0.66	0.433	0.27
SCL-90R Paranoia	1.45	0.72	1.23	0.92	1.48	0.69	0.328	0.31
SCL-90R Psychotic	1.34	0.55	1.20	0.68	1.36	0.54	0.408	0.27
SCL-90R GSI	1.79	0.56	1.37	0.78	1.84	0.52	**0.017***	**0.72**†
SCL-90R PST	65.16	12.73	57.78	21.12	66.08	11.16	0.065	**0.51**†
SCL-90R PSDI	2.41	0.50	1.97	0.56	2.46	0.47	**0.005***	**0.94**†
DERS Non-acceptance	19.83	6.06	17.44	4.80	20.13	6.16	0.213	**0.51**†
DERS Directed goals	17.30	4.69	16.67	4.06	17.38	4.78	0.672	0.16
DERS Impulse	18.15	4.81	15.56	2.96	18.47	4.92	0.087	**0.72**†
DERS Awareness	17.23	4.05	18.44	2.01	17.08	4.22	0.345	0.41
DERS Strategy	26.37	6.65	23.44	5.22	26.74	6.74	0.163	**0.55**†
DERS Lack of clarity	14.60	4.34	13.44	3.71	14.75	4.41	0.398	0.32
DERS Total	113.48	23.40	105.00	17.33	114.54	23.94	0.251	0.46

*Bold: significant comparison. † Bold: effect size into the mild to large range.

groups and there were no differences between the FA+ and FA– groups (22.2% of individuals in both groups endorsed a problem with a control food).

Table 2 contains the comparison of the body composition and clinical profile for women with BN and with FA+ versus FA–. Due the low sample size for the FA− group (11.25% of the sample), relevant differences were considered for significant differences ($p < 0.05$) or effect size within the ranges moderate to large ($|d| > 0.50$). No significant differences were observed in the body composition profile between the FA+ and FA– groups. Women within the FA+ group had a higher mean metabolic age, though no significant

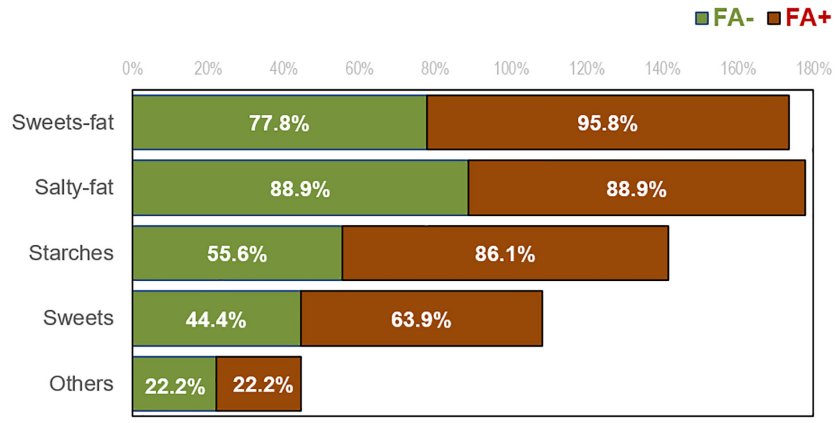

FIGURE 1
Distribution of the self-reported problematic type of foods in patients with FA negative and positive score.

differences were observed in the difference with chronological age. The FA+ group also reported higher ED severity levels (EDI-2 drive for thinness, interoceptive awareness, bulimia, interpersonal distrust, perfectionism, ascetic, social insecurity and total scales), worse psychology state (higher means in all the SCL-90R scales, except for phobic anxiety, paranoid ideation and psychotic ideation), and worse performance in the emotion regulation (higher means in the DERS non-acceptance of emotional responses, impulse control difficulties, and limited access to emotion regulation strategies).

Table 3 includes the correlation matrix to assess the relationship between the YFAS-total score (as a dimensional measure for the FA severity level) with body composition and clinical profile. The YFAS-total was positively related with the total fat mass, metabolic age, the ED symptom severity levels as measured with the EDI-2 (except for ineffectiveness, maturity fears, perfectionism, impulse regulation, and social insecurity), the psychological distress as measured by the SCL-90R (sensitivity, depression, and the global indexes), and the difficulties in the emotional regulation (controlling impulsive behaviors when experiencing negative emotions and limit access to emotional regulation strategies). A negative correlation was also found between the YFAS-total and the percentage of body water.

TABLE 3 Correlation matrix.

	YFAS total		YFAS total
Fat mass	**0.289**†	SCL-90R Somatic	0.223
Non-fat mas	0.135	SCL-90R Obsessive-compulsive	0.217
Muscle mass	0.121	SCL-90R Sensitivity	**0.365**†
Body water%	**−0.299**†	SCL-90R Depression	**0.338**†
Bone mass	0.126	SCL-90R Anxiety	0.205
Basal metabolic rate	0.158	SCL-90R Hostility	0.215
Metabolic age	**0.304**†	SCL-90R Phobic	0.136
Difference in age	−0.107	SCL-90R Paranoia	0.096
BMI (kg/m^2)	0.226	SCL-90R Psychotic	0.134
EDI Drive thinness	**0.357**†	SCL-90R GSI	**0.289**†
EDI Body dissatisfaction	**0.261**†	SCL-90R PST	**0.258**†
EDI Interoceptive awareness	**0.323**†	SCL-90R PSDI	**0.292**†
EDI Bulimia	**0.377**†	DERS Non-acceptance	0.204
EDI Interpersonal distrust	**0.274**†	DERS Directed goals	0.171
EDI Ineffectiveness	0.135	DERS Impulse	**0.246**†
EDI Maturity fears	0.120	DERS Awareness	− 0.056
EDI Perfectionism	−0.030	DERS Strategy	**0.244**†
EDI Impulse reg.	0.086	DERS Lack of clarity	0.115
EDI Ascetic	**0.312**†	DERS Total	0.219
EDI Social insecurity	0.189		
EDI Total	**0.317**†		

† Bold: effect size into the mild to large range.

Path analysis

Figure 2 shows the path-diagram with the standardized coefficients. Adequate goodness-of-fit was achieved [$\chi^2 = 28.98$ ($p = 0.413$), *RMSEA* = 0.021 (95% confidence interval: 0.001 to 0.080), *CFI* = 0.993, *TLI* = 0.989, and *SRMR* = 0.080]. The global predictive capacity was around 31% (*CD* = 0.306). Supplementary Table 1 (Supplementary material) contains the complete results for the SEM (tests for the total, direct and indirect effects).

In this study, the latent variable measuring the foods profile was significantly defined by the observed variables sweets high fat, starches, and sweets (the coefficients for salty high fat and control foods obtained $p < 0.05$ values). Patients

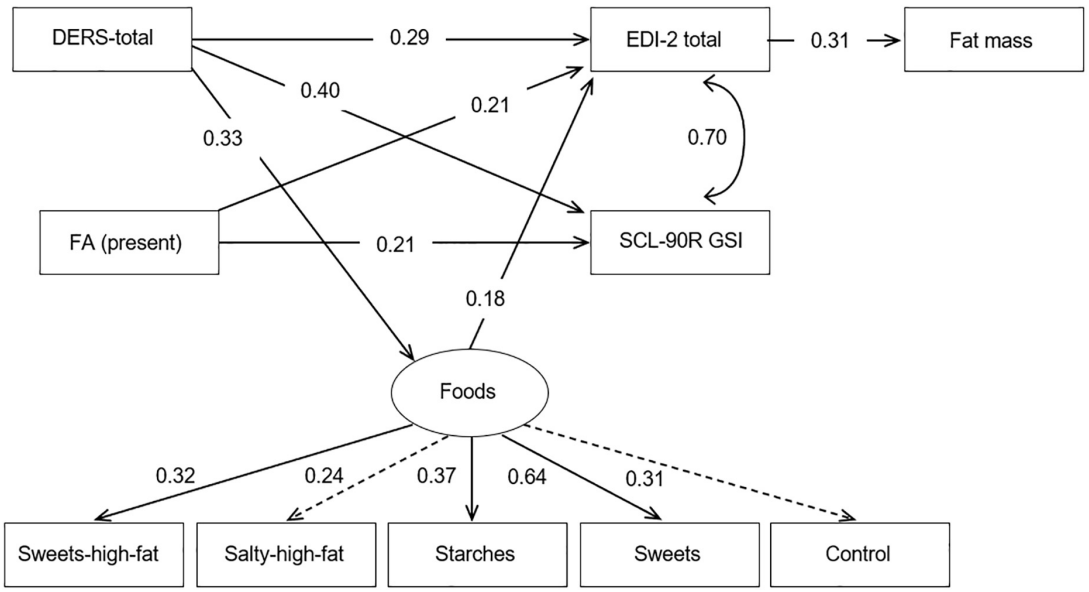

FIGURE 2
Standardized coefficients in the path-analysis. FA: food addiction (0 = absent; 1 = present). Fit statistics: χ^2 = 28.98 (p = 0.413); RMSEA = 0.021 (95%CI: 0.001 to 0.080); CFI = 0.993; TLI = 0.989; SRMR = 0.080; CD = 0.306.

with more difficulties in the emotion dysregulation functions obtained higher ED severity levels, worse psychopathology state, and higher scores in the latent variable measuring the foods consumption profile. Women with FA + screening score also greater ED severity level and higher psychological distress. The higher fat mass levels were directly predicted by higher scores in the EDI-2 total. The ED severity level was also implied in some indirect relationships: (a) higher scores in the DERS total and being in the FA+ group impacted in the EDI-2 total score, which next contributed to the increase in the fat mass; and (b) higher scores in the latent variable measuring the foods consumption profile were associated with increased levels in the EDI-2 total, which next contributed on the fat mass.

Discussion

The aims of the present study were to explore differences in body composition and psychological characteristics between BN with and without FA, whether there were differences in the self-reported problematic relationship with the different food types evaluated with the YFAS; and finally, in BN + FA patients, to identify the relationship between physical and psychological traits, and the food type considered problematic.

The majority of patients with BN endorsed FA (88.75%), which highlights the importance of investigating addictive mechanisms in this population (1, 6, 7). Despite the relatively small number of patients with BN who did not endorse FA, differences between those with and without FA still emerged.

Our results, regarding the association of FA with specific problematic food groups, showed that those patients with BN and FA+ significantly recognize high sugars foods, high fat content foods and starches as problematic. These findings are consistent with data obtained in a study that aimed to explored the differences in dietary preferences, through the dietary intake, among an adult population with and without FA (33). Their results regarding dietary behavior showed that a significantly higher proportion of people with FA+ reported higher intakes of high fat foods, such as snacks, fast food and chips, as well as greater intake of soft drinks, rich in sugars (33). This is also consistent with studies in non-clinical samples that find that foods with high levels of refined carbohydrates and/or added fats are indicated as the most addictive (20, 21). This is relevant to the current debate about whether the attributes of the food are an important factor in triggering addictive processes or whether the act of eating (regardless of food type) is more important (34). The current findings are consistent with the hypothesis that certain foods are more likely to be implicated in addictive patterns of intake, specifically processed foods with high levels of reinforcing ingredients (e.g., sugar, starches, fat).

Regarding the psychological characteristics, the present results were coincident with the literature in reference to a worst psychopathological general state, and, specially, more difficulties in ER, in BN + FA, when compared to BN-FA [T. (7–9, 11, 35)]. As well, the FA + groups presented higher ED severity; current literature have reported that FA was associated with

more craving and binge episodes in BN (36). According to the FA model, this could be related with the type of foods that are consumed. In both, animals and human based studies, the consumption of high palatable foods and with a high glycemic load generate changes in the hunger and reward circuits (37–39). Current reviews have gone deeper into the study of how the addictive process can be activated by certain types of food in similar ways as in other addictive substances. They concluded that high palatable food could induced changes in the hedonic system resulting in craving for the substance (positive reinforcement), while tolerance is developed, and the desire of further activation increases as well, in order to avoid the negative effect of the non-consumption of the substance (negative reinforcement) (40).

Considering body composition, although BN + FA showed quasi-significant greater levels of fat mass and mean BMI, contrary to our hypothesis, those results were not statistically significant, when compared with BN-FA. Even though we expected to find dissimilarities when compared the FA+ and FA– groups, these results are consistent with that of Probst et al. (14) who concluded that BN women patients did not display differences in the body composition profile when compared to healthy controls (14). These may be due to our study small sample size, and further studies with a bigger cohort are needed to confirm them.

Finally, the path analysis that explores the associations of FA, psychological traits, and fat mass, show interesting results. The presence of FA, and the higher scores in the DERS total, both had an impact in the EDI-2 total score, which then contributed indirectly to the increased fat mass. This result could support the multicausality and multifunctionality of eating disorders, and the justification of biopsychosocial explanatory models, as has been suggested in previous studies (41). As well, these results open an important research line. We found that ER state was possible associated with the type of food considered problematic, which may be an introductory aspect to determine a different BN + FA profile, highly influenced by ER difficulties, due to only indirect results have been explored in this field (2).

Previous studies have found that the mood influences in the body idealization and dissatisfaction, besides the presence of high caloric food cues (42), and that the negative emotions triggered the desire to eat and the selection of high caloric foods (43, 44). Other authors have found, in laboratory controlled situations, that patients with FA increases their attention to food images after sad mood was induced (45). Therefore, future studies, from a broader neurobiological perspective, may analyze the underlying interaction of abnormal eating patterns and emotional regulation difficulties (46, 47) in BN, in order to confirm whether BN + FA patients, who have higher ER difficulties, may be a different BN subtype. In addition, measurement of specific neurobiological biomarkers could improve the identification of specific subset of patients.

Limitations and future research lines

This study has a few limitations. Firstly, due to the cross-sectional design of the study causality cannot be conferred. Secondly, our cohort consisted of young women adults with BN, further studies would be required focusing on both sexes and wider age range including postmenopausal women and, finally, the low sample size of the BN-FA group that may compromise the generalization of the results.

However, an interesting research line could be open based on the current results. To our knowledge, there are few studies exploring the relationship between BN, FA, and body composition parameters that suggest the important relevance of ER processes. Empirically supported treatments for addiction commonly focus on helping individuals develop ER strategies (48), therefore, investigating whether targeted interventions for ER could also improve treatment outcomes for BN + FA individuals is an important next step to explore. Further, the high endorsement rate of problems with foods types that are hypothesized to be more addictive (e.g., high fat sweets) suggests that future research is needed to understand the role of the food triggering addictive eating and foresee treatment outcome for individuals with eating disorders.

Data availability statement

The datasets presented in this article are not readily available because of the protection law for the anonymized data of public hospital patients in Spain. Requests to access the datasets should be directed to FF-A, ffernandez@bellvitgehospital.cat.

Ethics statement

The studies involving human participants were reviewed and approved by Clinical Research Ethics Committee of the University Hospital of Bellvitge. The patients/participants provided their written informed consent to participate in this study.

Author contributions

LM, LC-B, SJ-M, and FF-A: conceptualization. RG: methodology, formal analysis, and data curation. LM, LC-B, and AG-P: investigation. SJ-M and FF-A: resources. LM, LC-B, AG-P, SJ-M, RG, and FF-A: writing – original draft preparation. LM, SJ-M, AG, and FF-A: writing – review and editing. LM, SJ-M, CD, AG, and FF-A: supervision. SJ-M and FF-A: funding acquisition. All authors have read and agreed to the published version of 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.

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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.2022.1032150/full#supplementary-material

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Eating attitudes and depressive symptoms in a LGBTIQ sample in Turkey

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Background: Lesbian, gay, bisexual, transgender, intersexual and queer (LGBTIQ) individuals are often stigmatized due to their minority status. Sexual-minority stress is often discussed as a risk factor for the increased mental health problems reported in this population.

Objective: The current study (1) investigated eating attitudes and depressive symptoms in a sexual minority sample from Turkey who identify themselves as LGBTIQ and (2) explored the role of sexual minority stressors beyond the potential predictors of eating attitudes and depressive symptoms in this population.

Methods: Recruitment was supported and streamlined by several Turkish NGOs and LGBTIQ community networks. Sociodemographic measures, eating attitudes, depressive symptoms, sexual minority stressors (e.g., heterosexist experiences, internalized homophobia), and the potential predictors of eating attitudes and depressive symptoms were assessed with an anonymous online survey between February 2022 and June 2022. The sample consisted of 440 participants. The mean age was 31.92 (SD = 11.82). The majority of the participants reported their current gender identity as male (64.3%; $n = 440$) and their sexual orientation as attracted to men (62.8%; $n = 439$). For 79.7% of the participants, the assigned sex at birth was man ($n = 439$).

Results: Two separate three-stage multiple hierarchical regression analyses were conducted, controlling for sociodemographic characteristics and the risk and protective factors of eating attitudes and depressive symptoms. Disturbed eating attitudes were predicted by assigned female sex at birth, higher scores for depression, social isolation, and the total number of heterosexist experiences, and lower distress related to heterosexist experiences. Depressive symptoms were predicted by assigned female sex at birth, lesbian sexual orientation, disturbance in eating attitudes, increases in generalized anxiety, and distress related to daily heterosexist experiences.

Conclusion: The current study demonstrated the significant role of sexual minority stressors in the prediction of disturbed eating attitudes and depressive symptomatology beyond the general psychosocial vulnerability factors. These findings emphasize the need for developing strategies to reduce prejudicial attitudes at the societal level and to enhance the skills of LGBTIQ individuals in coping with sexual minority stressors in Turkey.

KEYWORDS

eating attitudes, depressive symptoms, sexual minority, LGBT, LGBTIQ

Introduction

Lesbian, gay, bisexual, transgender, intersexual, and queer (LGBTIQ) individuals are often stigmatized as a sexual minority (1). Negative experiences, such as disapproval, exclusion, rejection by their families and close social circles, and discrimination in education, employment, housing, and access to social services, are not uncommon (2, 3). Accordingly, previous studies have shown a heightened risk for mental health conditions, including disordered eating behaviors and depressive symptoms in LGBTIQ individuals compared to heterosexual individuals (4, 5).

Minority stress theory is one of the major theoretical frameworks that explains the increased rates of mental health problems in sexual-minority individuals (6). It connects mental health problems in LGBTIQ individuals to stressors related to their sexual-minority status. The minority stressors may be distal (i.e., external) and proximal (i.e., internal). Distal minority stressors are negative experiences due to prejudicial attitudes in the environment, such as victimization, blaming, and harassment. Proximal minority stressors include the internalization of these prejudicial attitudes by the individual and result in self-stigma, such as the internalization of homophobic attitudes and the concealment of sexual identity. The current study examined the roles of psychosocial vulnerability factors and minority-related stressors in order to explain disturbed eating attitudes and depressive symptomatology in a sample of LGBTIQ individuals in Turkey.

Most previous research on eating disorders focused on female, cisgender, and heterosexual populations (7). Few studies that focused on sexual minorities and gender-diverse populations showed clear associations between sexual identity or orientation and eating disorders (8–12). For example, gay and bisexual secondary school boys and girls were more likely to report purging behavior and the use of diet pills than their heterosexual counterparts, who more often reported a positive body image and no indications of eating concerns (13). Another study with a large sample of adolescents in the United Kingdom found that sexual-minority girls had twice the likelihood of purging and binge eating than heterosexual girls (14).

Given that sexual-minority and gender-diverse populations are prone to experiencing negative social evaluations, interpersonal theories seem to be applicable to them. One model that incorporates interpersonal and psychological difficulties into the development of eating disorder symptoms is the "interpersonal theory of eating disorders" (15). This model highlights inadequate social situations that involve real or perceived negative evaluations by others, such as a hindered feeling of social belongingness, to explain eating disorders (16). It suggests that such interactions lead to conflicts with oneself, lower self-esteem, and cause negative affect, which trigger or maintain eating disorder symptoms, such as dieting, in order to enhance self-esteem or binge eating for emotional regulation. Another model is the "tripartite influence model" (17), which postulates that exposure to idealized appearances through media, parents, or peers causes adolescent girls to develop body dissatisfaction through the processes of internalizing ideal appearances and social appearance comparisons. Recently, this model, alongside the minority stress theory, was included in a theoretical consideration to generate a new model specific to sexual-minority women (18). The examination of the model showed similar correlates for disordered eating behaviors among heterosexual and sexual-minority women in terms of the internalization of sociocultural norms, social resources, emotion regulation, negative affect, and body surveillance. Overall, the model emphasized the intersection of the psychosocial experiences of eating disorders in general populations, with identity-related experiences, such as harassment, heterosexism, and internalized minority stress.

Studies report the significant role of general psychosocial factors in disordered eating and the overall wellbeing of LGBTIQ individuals. For example, one study found significant associations between weight-based victimization by family members and poorer self-rated health, less self-esteem, and depressive symptoms among LGBTQ adolescents (19). Adolescents who experienced weight-based victimization in their families also reported lower positive attitudes from family members toward their LGBTQ status and lower family connectedness (19). In another study, weight-based victimization from family members was related to dysfunctional

eating behaviors (e.g., binge eating), dieting, or poorer weight-related health (e.g., exercise avoidance, less physical activity, higher stress levels) (20). The significant relationships remained after accounting for participants' age, BMI, sexual and/or gender identity, and race (20). These findings were supported by another study, which showed that parents could influence their daughters' disordered eating behaviors *via* body esteem, but regardless of their body-esteem LGBTQ+ girls were engaged in caloric restriction if they experienced general victimization (11).

There is evidence to indicate sexual orientation disparities in disordered eating, weight-related behaviors, and their predictors among LGBTIQ individuals. For instance, a recent study found that bisexual women and gay men reported significantly higher body weight dissatisfaction than lesbian women, bisexual men and their cisgender counterparts and the highest body weight misperception was present in gay men (21). In another study, lesbian women showed higher rates of being prone to eating disorders than gay men did (9). Also, lesbian women were more likely to report a heightened weight-based self-worth than gay men. However, a recent systematic review found that disordered eating behaviors were more pronounced during adolescence than in young adulthood for LGBTIQ females (22). Furthermore, it concluded that disordered eating and weight-related behaviors were more consistent among males than females in this population. The highest rates in dissatisfaction with eating patterns were reported for transgender and non-conforming adults. The general proneness for eating disorders was predicted by depression, perceived stigma, and self-compassion in gay men; depression in lesbian women; and self-compassion in transgender and non-conforming adults (9).

Similar to disturbed eating attitudes, sexual-minority individuals reported heightened rates of depressive symptomatology compared to heterosexual people (23). Studies demonstrated that stressors related to sexual-minority status, including victimization (24), perceived discrimination (25), and harassment (26), were associated with depression. Also, general psychosocial determinants, such as perceived social support (27), and psychological resources, such as self-esteem (28), significantly mediated the association between sexual-minority status and depressive symptomatology. Studies also found sexual orientation disparities in depressive symptomatology within LGBTIQ subgroups and indicated a substantial burden for bisexual individuals due to the higher prevalence of major depressive disorders as compared to gay and lesbian individuals (29).

Mood disorders are related to changes in metabolism and eating attitudes (30). Accordingly, studies indicate an association between depressive symptoms and unhealthier eating styles and body weight dissatisfaction (21, 31–33). Also, there is evidence to indicate gender-specific differences and similarities between men and women regarding the associations between depression, anxiety and disordered eating behaviors (34). During the COVID-19 pandemic, changes in eating attitudes have been reported by university students and also depressive symptoms were found to be associated with bulimia nervosa (35). Furthermore, reporting a gender-diverse identity as a university student was associated with depressive symptoms (36), which indicates the need to examine the prevalence and potential relation between eating attitudes and depressive symptomatology in sexual minorities during this period.

Taken together, available research supports the assumption that general psychosocial vulnerability and sexual-minority status are important for the understanding of disturbed eating attitudes and depressive symptomatology in LGBTIQ individuals. Yet, the current evidence relies mostly on research conducted in Europe and the United States and needs to be expanded to contexts with different cultural and religious backgrounds. Furthermore, most previous studies focused on the factors that increase the risk for mental health conditions in LGBTIQ individuals, and neglected the roles of potentially protective factors. Studies that take general risk and protective factors into account could provide valuable information about the unique role of sexual-minority stressors in the LGBTIQ population and enhance the theoretical conceptualizations that intend to explain mental health disparities in LGBTIQ individuals. Therefore, the current study aims to understand whether sexual-minority-related stressors explain the disturbance in eating attitudes and depressive symptomatology beyond the general psychosocial risk and protective factors in a sample of LGBTIQ individuals in Turkey.

Research demonstrated that LGBTIQ individuals perceive substantial direct and indirect discrimination in areas related to education, employment, and health care in Turkey (37). Furthermore, due to the lack of legislation related to LGBTIQ rights, most report a reluctance to pursue a legal complaint about these negative experiences and do not believe that the justice system can solve their problems (37). LGBTIQ individuals reported a significantly higher number of minority stressors that involved physical, psychological, and economical violence, and forced sexual relationships in adulthood compared to heterosexual controls in Turkey (38). They were also more likely to experience physical and sexual abuse during childhood (38). Homosexual men reported a significantly higher disturbance in eating attitudes as compared to heterosexual men (39). Identifying as homosexual or bisexual was associated with an increased risk for suicidal ideation than for heterosexual sexual identity (40). Furthermore, internalized homophobia predicted worse general health status and depressive symptomatology among the LGBTIQ individuals (41, 42).

LGBTIQ individuals experienced worse mental health regarding depression and anxiety symptoms during the COVID-19 pandemic and reported increased problem drinking behaviors in comparison to their cisgender counterparts (43). Recent studies demonstrated that pandemic-related stress aggravated eating concerns and disorders among LGBTIQ individuals (12, 44). It was found that constraints

to physical exercise, challenging eating patterns, and weight concerns were related to LGBTIQ individuals' pandemic experiences. Moreover, social support, which was hindered because of the pandemic-related restrictions, was found to be protective against increased eating disorder symptoms (12). Therefore, the interpersonal relationships that already play a negative impact on these people's mental health, might have worsened during the pandemic. By evaluating eating attitudes and depressive symptoms of this Turkish sexual minority sample, which identifies as LGBTIQ, during the pandemic, this study intends to identify disorder-specific risk factors that might be useful to address and tailor mental health promotion strategies for this population.

The current study (1) investigated eating attitudes and depressive symptoms in a Turkish sexual minority who identify as LGBTIQ and (2) explored potential predictors for eating attitudes and depressive symptoms (e.g., minority stressors, appearance anxiety, appearance perfectionism, body perception, body dissatisfaction, generalized anxiety, social support, social isolation, self-efficacy, resilience). We examined whether minority stressors (e.g., heterosexist experiences, internalized homophobia) explained eating attitudes and depressive symptoms after controlling for selected psychosocial risks and protective factors. The present study provides data from a large sample of LGBTIQ individuals in Turkey and aims to disentangle the factors that heighten the risk for disturbed eating attitudes and depressive symptomatology in this population.

Materials and methods

Participants and procedure

Recruitment took place between February 2022 and June 2022. Multiple recruitment strategies were utilized to reach the participants of the study. LGBTIQ associations and solidarity groups in Turkey were contacted and informed about the purpose of the study. They shared the information about the research on their social media sites and accounts, and sent recruitment e-mails through their listservs. In addition, a popular online dating website for LGBTIQ individuals advertised the study. We also conducted online presentations on websites that LGBTIQ individuals frequent. Participants received a link to an online questionnaire. They had to consent to participate before they could access the questionnaires. In the consent form, participants received comprehensive information about the purpose of the study, and about the survey's anonymity and the possibility of refusing to participate. The survey took approximately 35 min to complete. The Research Ethics Committee of Bursa Uludag University approved the study.

Measures

Sociodemographic characteristics

The participants were asked to indicate their age and assigned sex at birth: "Woman" (1) and "Man" (2). They responded to a question that inquired about their gender identity. The response options included: Male (1), Female (2), Trans male (3), Trans female (4), and Non-binary (e.g., diverse, genderqueer, gender nonconforming, agender, gender fluid, trans-non-binary, intersex) (5). To indicate their sexual orientation, the participants chose whether they were "Attracted to men" (1), "Attracted to women" (2), "Attracted to both men and women" (3), or "Attracted to neither men nor women" (4). They could also respond to this question with the "I don't want to respond" (5) option. Finally, we asked them to indicate whether they considered themselves part of the LGBTIQ community ("Yes" or "No"). This question was added to ensure that only the participants who identified themselves as part of the LGBTIQ community were included in the sample. Therefore, we classified participants attracted to men as "gay men" and those attracted to women as "lesbians." Participants attracted to both men and women were classified as "bisexuals." "Asexual" individuals were attracted to neither men nor women. Participants were also asked questions about their occupation, educational level, relationship status, whether they experience any chronic physical conditions ("Yes" or "No"), and had a history of mental disorder diagnoses ("Yes" or "No"). The participants with a history of mental disorder diagnoses were also assessed on the type of diagnoses they received. The response options involved depression, bipolar disorder, anxiety disorder, obsessive-compulsive disorder, personality disorder, eating disorder, attention deficit hyperactivity disorder, and any other mental disorder diagnoses. The participants could also respond with "I don't know" option. Multiple responses were allowed.

Outcome measures

Eating Attitudes Test-26

The Eating Attitudes Test-26 (EAT-26) (45) is the shortened version of the 40-item form of the same scale (i.e., EAT-40) (46). It is one of the most widely used scales to detect disturbances in eating patterns in both clinical and non-clinical samples. The EAT-26 consists of three parts (A, B, and C). Part A contains demographic information about the participants and their weight, height, and their lowest and highest weight; Part B contains 26 items related to eating attitudes; and Part C includes five items related to eating behaviors. The scoring for the first 25 questions that make up Part B is 3 = Always, 2 = Very often, 1 = Often, and 0 = Other answers (i.e., sometimes, rarely, never). For the last question (i.e., Question 26), reverse scoring is used. Scores of 20 and above indicate deterioration in eating patterns. Parts A and C of the scale are not included in the scoring. However, the information obtained from these sections is used

to evaluate the current eating pathology. The scale consists of three factors: "diet," "bulimia and food preoccupation," and "oral control."

The psychometric properties of the Turkish adaptation of the EAT-26 were examined in a sample of university students (N = 1,500) (47). The exploratory factor analysis revealed a three-factor structure called "Preoccupation with Eating," "Restriction," and "Social Pressure," which explained 38.5% of the total variance. The confirmatory factor analysis showed that the three-factor structure was close to the acceptable fit. Significant positive correlations were found between the EAT-26 and EAT-40 and the Brief Symptom Inventory (48). In addition, the Eating Disorder Examination Questionnaire (49) and the Brief Symptom Inventory scores of those who scored above or below the cut-off score of EAT-26, differed significantly. The Cronbach's alpha internal consistency coefficient of the scale was 0.84, and the test-retest reliability coefficient was 0.78. These findings indicated that the scale could be used as a valid and reliable measurement tool to evaluate eating attitudes in Turkey. In the current study, the total scale score was used and the internal consistency was acceptable (Cronbach's $\alpha = 0.88$). We also calculated the body mass index (BMI) based on the reported weight and height.

Patient Health Questionnaire-9

The Patient Health Questionnaire-9 (PHQ-9) is the nine-item depression module of the Patient Health Questionnaire (50). The PHQ-9 evaluates the criteria outlined in the Diagnostic and Statistical Manual of Mental Disorders-IV (DSM-IV) (51) to diagnose depression. It provides information on the frequency and severity of depressive symptoms. It is one of the most widely used scales for depressive symptoms and their severity. The response scale ranges from "0" (not at all) to "3" (almost daily). Total scores between 1 and 4 indicate normal or minimal depression, scores between 5 and 9 indicate mild depression, scores between 10 and 14 indicate moderate depression, scores between 15 and 19 indicate moderately severe depression, and scores between 20 and 27 indicate severe depression.

Turkish adaptation of the PHQ-9 was conducted on 96 patients who applied to family medicine clinics in Turkey (52). Three researchers translated the scale, and then an independent professional translator back-translated it into English. The meaning and intelligibility between the English text obtained by the back translation and the Turkish text were compared. The internal consistency coefficient calculated for the final translation of the scale was determined as 0.84. The internal consistency of the scale was acceptable in the current study (Cronbach's $\alpha = 0.91$).

Sexual-minority stress

Daily Heterosexist Experiences Scale

The Daily Heterosexist Experiences Scale is a self-report measure that assesses the minority stress of lesbian, gay, bisexual, and transgender individuals (53). The scale consists of 50 items, including nine factors. Participants indicate to what extent the experiences expressed in each item disturbed or bothered them during the preceding 12 months. The items are evaluated on a 6-point Likert-type scale: 0 = Didn't happen/not applicable to me; 1 = It happened, and it bothered me not at all; 2 = It happened, and it bothered me a little bit, 3 = It happened, and it bothered me moderately; 4 = It happened and it bothered me quite a bit; 5 = It happened and it bothered me extremely. The scoring can be done in two ways. First, after re-coding the answers as 0 = 0 and all other answers (i.e., 1, 2, 3, 4, 5) = 1, a total score is obtained to determine how many heterosexist experiences have occurred. After re-coding the answers with 0, 1 = 0, and all the other answers remaining the same, the results show the average level of distress experienced by the participants in the face of heterosexist experiences. The nine factors of the scale were "Gender Expression," "Vigilance," "Parenting," "Discrimination/Harassment," "Vicarious Trauma," "Family of Origin," "HIV/AIDS," "Victimization," and "Isolation." The Cronbach's alpha internal consistency coefficient of the total scale score was calculated as 0.92. The Cronbach's alpha internal consistency coefficients calculated for the subscales ranged between 0.76 and 0.87. The score obtained from the scale was moderately associated with psycho-social distress (i.e., depression, anxiety, post-traumatic stress disorder, perceived stress level).

Since the adaption of the scale into Turkish has not yet taken place, we translated and back-translated it before administering it in the current study. Most LGBT individuals who are parents keep their gender identities and sexual orientation secret in Turkey. Therefore, we excluded the six items under the "Parenting" factor that assess the perceived anti-LGBT discrimination related to LGBT individuals' children and parenting. The scale developers also recommended determining the subscales to administer based on the study's objectives (53). We calculated both the number of and the distress related to daily heterosexist experiences in the current study. The internal consistency for the number of daily heterosexist experiences was 0.97. The internal consistency for the distress related to heterosexist experiences was 0.96.

Internalized Homophobia Scale

The Internalized Homophobia Scale is a nine-item scale developed to determine the internalization of homophobic attitudes among gay men (6). Later, separate forms for lesbian women and bisexual women and men were developed (54–56). Each item is scored on a 5-point Likert-type scale (1 = strongly disagree, 5 = strongly agree). Higher scores indicate increased internalized sexual stigma and negative attitudes toward the self. Individuals with higher scores had low self-esteem and less openness to heterosexual people about their sexual orientation. They were less satisfied with homosexual friends

and communities and more likely to associate personal failures with homophobic prejudices (57). The Turkish adaptation of the scale was carried out on a sample of 112 gay men and 20 bisexual male university students (58). The internal consistency (0.82) and split-half reliability (0.82) of the scale were good, and it had a single-factor structure similar to the original study. The scores obtained from the scale were associated with psychological problems, especially depression and anxiety symptoms. In addition, the scale scores were positively related to negative affect and negatively associated with self-esteem.

In the current study, participants who were "attracted to men" and "attracted to women" received the forms for gay men and lesbian women, respectively. Those who indicated their sexual orientation as "attracted to both men and women" received bisexual forms of the questionnaire, depending on their reported gender identity. Participants who identified as "female" received the bisexual female form. In contrast, participants who identified as "male" received the bisexual male form. Individuals who identified their gender identity as non-binary and responded to the sexual-orientation question as "attracted to both men and women" received the scale based on their sex at birth. Participants whose assigned sex was "woman" received the bisexual female form, whereas participants whose assigned sex was "man" received the bisexual male form. Participants who responded to the sexual-orientation question with "attracted to neither men nor women" and "I don't want to respond" did not receive the questionnaire. The scale's internal consistency was acceptable for gay men (0.88), lesbian women (0.75), bisexual female (0.89), and bisexual male (0.84) forms. A composite score was used as the measure for internalized homophobia in the current study.

Potential predictors of eating attitudes and depressive symptomatology

Social Appearance Anxiety Scale

The Social Appearance Anxiety Scale is a self-report measure that assesses the cognitive, emotional, and behavioral anxiety related to social appearance (59). The scale consists of 16 items that are evaluated on a 5-point Likert scale (1 = never; 5 = extremely). Higher scores indicate increased anxiety about social appearance. Higher scores were also found to be associated with the fears of negative evaluation and depression. The Turkish adaptation of the scale was conducted with 340 university students (60). The scale had a single-factor structure similar to its original form. The Cronbach's alpha internal consistency coefficient was 0.93, the test-retest reliability coefficient was 0.85, and the split-half reliability coefficient was 0.88. In the current sample, the scale had acceptable internal consistency: 0.95.

Physical Appearance Perfectionism Scale

The Physical Appearance Perfectionism Scale is a self-report scale developed to capture both the positive and negative aspects of physical appearance perfectionism (61). It consists of 12 items that are evaluated on a 5-point Likert scale (1 = strongly disagree; 5 = strongly agree). As the score obtained from the scale increases, perfectionism about physical appearance increases. The exploratory and confirmatory factor analyses indicated a two-factor structure for the scale. The two factors were "Worry About Imperfection" and "Hope for Perfection." The "Worry About Imperfection" factor was associated with a negative-appearance evaluation and concerns about body image and weight. The "Hope for Perfection" factor, on the other hand, was positively associated with the striving dimension of perfectionism and better self-image. The Turkish adaptation of the scale was conducted on 320 volunteers (62). The findings showed that the scale had a two-factor structure similar to its original form. Cronbach's alpha coefficients were 0.90 and 0.93 for the "Worry About Imperfection" and "Hope for Perfection" factors. In the current sample, the scale had acceptable internal consistency: 0.89.

Figure Rating Scale

The Figure Rating Scale consists of 18 schematic silhouettes (nine women and nine men) that range from very thin to obese (63). The scale is widely used to measure body perception and dissatisfaction. The respondents indicate which of the nine silhouettes best reflects their own body. Then they are asked to choose the figure that reflects their ideal body size. The discrepancy between the figure that reflects the respondents' own body (i.e., perceived body mass index) and the figure that reflects their ideal body (i.e., ideal body mass index) provides the measurement for body dissatisfaction. In addition, the body perception index is calculated by multiplying the ratio of the body mass index perceived to the actual body mass index by 100. The body perception index determines whether the individual evaluates their perceived body mass index realistically. The test-retest reliabilities for the perceived body mass index and ideal body mass index ranged between 0.81–0.92 and 0.71–0.82, respectively (64). In the current study, the participants were presented with women's and men's silhouettes and instructed to indicate their ideal and perceived body mass index based on the gender with which they identified. We calculated body dissatisfaction based on the discrepancy between perceived and ideal body mass index.

Generalized Anxiety Disorder-7

The Generalized Anxiety Disorder-7 (GAD-7) is a short self-report test that evaluates generalized anxiety disorder criteria according to the DSM-IV classification (65). The scale consists of seven items that inquire about common anxiety symptoms experienced in the preceding 2 weeks. The items are evaluated on a 4-point Likert-type scale (0 = never, 1 = some days,

2 = more than half of the days, 3 = almost every day). Total scores of 5, 10, and 15 are determined to be the cut-off points for mild, moderate, and severe anxiety, respectively. Higher scores were strongly associated with multiple domains of functional impairment (i.e., general health scales and disability days). Although generalized anxiety disorder and depression symptoms are often together, it was shown that generalized anxiety disorder and depression symptoms had independent effects on functional impairment and disability. The Turkish adaptation of the GAD-7 was conducted with 110 patients who had been diagnosed with generalized anxiety and 112 healthy control group participants (66). The findings indicated that the scale had a single factor structure similar to the original test. The most acceptable cut-off value for the GAD-7 test was found to be 8. The Cronbach's alpha internal consistency coefficient for the total scale score was calculated as 0.85. In the current sample, the scale had acceptable internal consistency: 0.94.

ENRICHD Social Support Inventory

The ENRICHD Social Support Inventory is a self-report measure developed within the Enhancing Recovery in Coronary Heart Disease (ENRICHD) project (67). It determines the amount of social support in the lives of patients with coronary heart disease. The scale consists of seven items and it is evaluated on a 5-point Likert scale (1 = never, 5 = always). The "Yes" answer to the last question (i.e., "Are you married or living with a partner?") is calculated as 4 points, and the "No" answer as 2 points. The higher the score on the scale, the higher the perceived social support. The scores obtained from the scale were correlated with other scales that measure perceived emotional support. Since it is a short scale with good psychometric properties, it is often used for screening purposes to measure the amount of perceived emotional and functional social support in different samples (68). A Turkish adaption of the scale has not been conducted. Therefore, we translated and back-translated it for the current study. The internal consistency of the scale was acceptable: 0.90.

UCLA Three-item Loneliness Scale

The UCLA Three-item Loneliness Scale (69) was developed from the Revised UCLA Loneliness Scale (70). This shortened screening tool demonstrated similar psychometric properties to the 20-item Revised UCLA Loneliness Scale. It addresses the lack of friendship, feeling excluded, and feelings of isolation from others. Each item is rated on a 3-point Likert-type scale (1 = Almost never, 2 = Sometimes, 3 = Often). All items are summed to give the total score. The Three-item Loneliness Scale provides a quick and concise method to collect information about social isolation. Total scores range from 3 to 9, and scores above 6 indicate that individuals feel lonely. A Turkish adaption of the scale has not been conducted. Therefore, we translated and back-translated it for the current study. The internal consistency of the scale was acceptable: 0.86.

General Self-efficacy Scale

The General Self-efficacy Scale is designed to assess the positive self-beliefs that capture an individual's capacity to cope with various challenges and demands in life (71). It has 10 items that are evaluated on a 4-point Likert scale (1 = Totally false, 4 = Totally true), where higher scores indicate increased self-efficacy beliefs. The scale's psychometric properties were examined in 25 countries and showed a single-factor structure (72). The Turkish adaptation of the scale was conducted with 693 university students aged 17–39 (73). The Turkish version of the scale was found to have a two-factor structure with "Effort and Resistance" and "Ability and Confidence" categories. The total scale score's internal consistency and test-retest reliability coefficients were calculated as 0.83 and 0.80, respectively. The internal consistency of the scale was acceptable in the current sample: 0.93.

Brief Resilience Scale

The Brief Resilience Inventory is a six-item scale developed to measure the ability to overcome stress and self-recovery (74). Each item is rated on a 5-point Likert scale (1 = strongly disagree, 5 = strongly agree). The total score varies between 6 and 30. Higher scores indicate psychological resilience. The scores obtained from the scale indicated a single factor structure and they were negatively related to anxiety, depression, negative emotions, and perceived stress. The Turkish adaptation of the scale was conducted on a university sample with acceptable fit indices for the single-factor structure similar to the original study (75). The internal consistency of the scale was low in the current study: 0.14.

Statistical analysis

Descriptive statistics were run for the sociodemographic characteristics on the whole sample and the sample of completers. Participants were considered completers if they provided data on at least one of the outcome measures (i.e., PHQ-9 or EAT-26). Subgroup analyses were conducted with chi-square-tests or Fisher's exact test (when more than 20% of the cells had expected frequencies < 5) to identify differences between the completers and the drop-outs regarding sociodemographic characteristics. Subgroup analyses were also conducted on the sample of completers regarding the differences in sociodemographic characteristics by sexual orientation (i.e., lesbian, gay, bisexual, asexual). The Standardized Pearson Residuals were used to decompose the effect of significant test statistics (76). To gauge the effect size, the ϕ-coefficient was calculated, while Cramér's V (ϕ_c) was used when the contingency table was larger than 2×2, with ϕ, $\phi_c = 0.10$ indicating a small effect, ϕ, $\phi_c = 0.30$ an average effect, and ϕ, $\phi_c = 0.50$ a large effect (77).

A three-stage multiple hierarchical regression analysis was conducted with eating attitudes (EAT-26) as the dependent variable. Age, assigned sex at birth, and sexual orientation were entered in the first step to control for sociodemographic characteristics. To examine the unique contribution of minority stress on eating attitudes, variables related to depression (i.e., Patient Health Questionnaire-9), anxiety symptoms (i.e., Generalized Anxiety Disorder-7), body image (i.e., Figure Rating Scale, Social Appearance Anxiety Scale, Physical Appearance Perfectionism Scale), social support (i.e., ENRICHD Social Support Inventory), social isolation (i.e., UCLA Three-item Loneliness Scale), self-efficacy (i.e., General Self-efficacy Scale), and resilience (i.e., Brief Resilience Scale) were entered in the second step. In the third step, both the number of and the distress related to heterosexist experiences from the Daily Heterosexist Experiences Scale and the scores of the Internalized Homophobia Scale were entered. The same procedure was followed to predict depressive symptomatology. The sociodemographic characteristics were entered in the first step, disorder-specific risk factors were entered in the second step, and variables related to sexual minority stress were entered in the final step.

Prior to the analyses, collinearity and multivariate outliers were examined. The collinearity statistics revealed that tolerance and variance inflation factor (VIF) statistics were within the acceptable limits for the independent variables (tolerance values were above 0.2 and VIF values were <4). An examination of the Mahalanobis distance scores indicated no multivariate outliers and the inspection of residual and scatter plots for both dependent variables confirmed that the normality, linearity, and homoscedascity assumptions were met. The analyses were run using the Statistical Package for Social Sciences (SPSS) version 28 (78). A two-tailed $\alpha = 0.05$ was applied to statistical testing.

Results

Sociodemographic characteristics

Overall, 477 participants started the online questionnaire. Thirty-seven participants gave online consent to participate but did not provide further data. Thus, the total sample size consisted of 440 participants. The mean age of the participants was 31.92 ($SD = 11.82$). The majority of the participants (64.3%) reported that their current gender identity was male. This was followed by non-binary (14.1%), female (13.9%), trans female (4.1%), and trans male (3.6%) gender identities. For 79.7% of the participants, assigned sex at birth was man ($n = 439$). The data on sexual orientation were available for 433 participants. Of these, 62.8% ($n = 272$) reported being attracted to men, 23.6% ($n = 102$) were attracted to both men and women, 7.2% ($n = 31$) were attracted to women, and 3% ($n = 13$) were attracted to neither men nor women. Fifteen participants (3.5%) did not want to respond to this question. More than half of the participants were single (58.9%, $n = 259$). For the remaining, 111 (25.2%) reported being in a relationship, 27 (6.1%) were divorced, 27 (6.1%) were widowed, and 16 (3.1%) were married. The information on occupational and educational status were provided by 434 and 426 participants, respectively. The majority of the sample were workers and civil servants (37.6%), students (24.4%), and unemployed (17.3%). The percentage of participants who had at least a high school education was 86.9, indicating reasonably high educational status. The majority of the participants had not received a mental disorder diagnosis in the past (87.6%; total $n = 434$) and they were not suffering from a chronic physical condition (86.1%; total $n = 433$). Of the received mental disorder diagnoses, depression was the most frequently reported mental disorder diagnoses (57.4%). This was followed by anxiety disorder (31.5%), bipolar disorder (27.4%), obsessive-compulsive disorder (20.4%), attention deficit hyperactivity disorder (20.4%), personality disorder (7.4%) and eating disorder (7.4%). Also, 7.4% mentioned that they had received another mental disorder diagnoses and 3.5% responded with "I don't know" option.

Of the 440 participants, $N = 237$ participants provided data on at least one of the outcome measures (i.e., PHQ-9 or EAT-26) and they were considered completers. There were significant differences between the completers ($N = 237$) and non-completers ($N = 240$) regarding age ($t(437) = 2.206$, $p = 0.028$), gender identity [$\chi^2(4) = 46.554$, $p < 0.001$; $\phi_c = 0.325$], assigned sex at birth [$\chi^2(1) = 38.493$, $p < 0.001$; $\phi = 0.296$], and sexual orientation [$\chi^2(4) = 52.558$, $p < 0.001$; $\phi_c = 0.348$]. The completers were younger and more likely to report their gender identity as male and their assigned sex at birth as man. They were also more likely to report their sexual orientation as gay. On the other hand, female, trans male, trans female, and non-binary gender identities were more frequently mentioned by the non-completers. Their assigned sex at birth was more likely woman and they more often reported their sexual orientation as lesbian, bisexual, and asexual. The groups also differed in their educational level [$\chi^2(2) = 31.713$, $p < 0.001$; $\phi_c = 0.273$], relationship status [$\chi^2(4) = 18.204$, $p = 0.001$, $\phi_c = 0.203$], history of mental disorder [$\chi^2(1) = 13.357$, $p < 0.001$; $\phi = -0.175$], and the presence of a chronic physical condition [$\chi^2(1) = 5.199$, $p = 0.025$; $\phi = -0.110$]. No education and less than a high school education was more frequently reported by non-completers. In contrast, completers more frequently reported at least high school and higher educational degrees. Being single was more commonly reported among the completers, whereas widows were more common among the non-completers. Finally, the completers were more likely to have received a mental disorder diagnosis in the past and to suffer from a chronic physical condition.

The remaining analyses were conducted on the completers ($N = 237$). Most reported their sexual orientation as attracted

to men ($N = 181$). It was followed by those attracted to men and women ($N = 43$) and those attracted to only women ($N = 11$). None of the completers reported being asexual. Two participants did not want to answer the question about their sexual orientation. Table 1 represents the sociodemographic characteristics of the completers and the differences by sexual orientation.

The Fisher's exact test statistics indicated that the participants' gender identity ($p < 0.001$; $\phi_c = 0.367$) and assigned sex at birth ($p < 0.001$; $\phi_c = 0.490$) differed significantly by sexual orientation. For the participants attracted to men, the assigned sex at birth was more likely to be man. They were also more likely to report their gender identity as male. By comparison, participants attracted to women more frequently had their assigned sex at birth as woman. They were also more likely to identify as female than as male. Thus, the participants attracted to men and those attracted to women more frequently indicated their gender identities aligned with their assigned sex at birth. Participants attracted to both men and women were more likely to report their assigned sex at birth as women than participants who were attracted to men. Overall, four participants reported their gender identity as trans female, and all indicated their sexual orientation as attracted to men. Another four identified as trans males. Of these, two reported their sexual orientation as attracted to both men and women, one as attracted to men, and one to women.

There were significant differences between the groups regarding their relationship ($p < 0.001$; $\phi_c = 0.243$) and educational ($p = 0.002$; $\phi_c = 0.233$) status. Participants attracted to men were more likely to be single and less likely to be in a relationship than both participants attracted to women and participants attracted to both men and women. They were also more likely to report university or higher academic degrees. Lastly, the presence of chronic physical conditions differed significantly by sexual orientation ($p = 0.030$; $\phi = 177$). Participants who were attracted to women suffered significantly more from chronic physical conditions.

Predictors of eating attitudes

The hierarchical multiple regression analysis to predict eating attitudes at Stage 1 revealed that sociodemographic characteristics contributed significantly to the model [$R^2 = 0.18$, $F_{(4,174)} = 9.88$, $p < 0.001$]. Introducing variables related to depression, anxiety, body image, social support, social isolation, self-efficacy, and resilience was associated with a significant additional 13% variation in Stage 2 [$F_{(9,165)} = 3.41$, $p = 0.001$]. The model was also statistically significant [$R^2 = 0.31$, $F_{(13,165)} = 5.78$, $p < 0.001$)]. In Stage 3, variables related to sexual-minority stress accounted for a significant additional 12% variation in eating attitudes [$F_{(3,162)} = 11.24$, $p < 0.001$]. The final model was statistically significant [$R^2 = 0.43$, $F_{(16,162)} = 7.68$, $p < 0.001$]. The summary of the findings for the prediction of eating attitudes is shown in Table 2.

The results demonstrated that participants whose assigned sex at birth was woman and participants who were attracted to men were more likely to report deterioration in their eating attitudes in Stage 1 of the analyses. In Stage 2, only sexual orientation and social isolation were significant predictors of eating attitudes. Participants who were attracted to men and participants who reported increased social isolation were more likely to experience deterioration in their eating attitudes. When all of the variables were entered in the final stage, disturbance in eating attitudes was predicted by assigned sex at birth, depression, social isolation, and daily heterosexist experiences. Participants whose assigned sex at birth was woman and who reported higher depression, social isolation, and daily heterosexist experiences and lower distress related to heterosexist experiences were more likely to report disturbance in eating attitudes.

Predictors of depressive symptomatology

The hierarchical multiple regression analysis to predict depressive symptomatology at Stage 1 revealed that sociodemographic characteristics contributed significantly to the model [$R^2 = 0.19$, $F_{(4,174)} = 10$, $p < 0.001$)]. Introducing variables related to eating attitudes, anxiety, body image, social support, social isolation, self-efficacy, and resilience was associated with a significant additional 49% variation in Stage 2 [$F_{(4,165)} = 28,51$, $p < 0.001$]. The model was statistically significant [$R^2 = 0.68$, $F_{(13,165)} = 27.2$, $p < 0.001$]. In the final stage, variables related to sexual-minority stress accounted for an additional 2% variation. The final model was statistically significant [$R^2 = 0.70$, $F_{(16,162)} = 23.42$, $p < 0.001$] and indicated that the inclusion of variables related to sexual-minority stress improved the model prediction [$F_{(3,162)} = 2.93$, $p = 0.035$]. The summary of the findings for the prediction of symptoms is represented in Table 3.

The findings demonstrated that assigned female sex at birth was associated with depressive symptoms at all stages of the analyses. Although younger age was associated with depressive symptomatology at Stage 1, it was not a significant predictor after the inclusion of variables at the second and third steps of the analyses. In Stage 2, higher generalized anxiety and physical appearance perfectionism predicted depression symptoms. Also, participants attracted to women were more likely to experience depressive symptoms. When all of the variables were entered in the final stage, depression symptoms were predicted by assigned sex at birth, sexual orientation, eating attitudes, generalized anxiety, and distress related to daily heterosexist experiences. Participants whose assigned sex at birth was woman and who reported being attracted to women were more likely to experience depressive symptoms.

TABLE 1 Sociodemographic characteristics of the whole sample and differences by sexual orientation ($N = 237$).

	Completers ($N = 237$) Mean (SD)	Attracted to men ($N = 181$) Mean (SD)	Attracted to women ($N = 11$) Mean (SD)	Attracted to both ($N = 43$) Mean (SD)	p
Age	30.77 (9.31)	31.04 (8.53)	29.55 (14.89)	30.37 (10.86)	0.819
Gender identity					**<0.001**
Female	8.4%	3.3%	63.6%	14%	
Male	78.5%	84%	18.2%	74.4%	
Trans male	1.7%	0.6%	9.1%	4.7%	
Trans female	1.7%	2.2%	0%	0%	
Non-binary	9.7%	9.9%	9.1%	7%	
Assigned sex at birth					**<0.001**
Woman	9.3%	2.8%	63.6%	20.9%	
Man	90.7%	97.2%	36.4%	79.1%	
BMI	24.65 (4.38)	24.60 (4.32)	23.21 (5.64)	24.98 (4.37)	0.553
Relationship status					**<0.001**
Married	4.6%	5%	9.1%	2.3%	
In relationship	21.9%	17.1%	54.5%	34.9%	
Widowed	3%	2.2%	18.2%	2.3%	
Single	65.8%	71.3%	9.1%	55.8%	
Divorced	4.6%	4.4%	9.1%	4.7%	
Occupation					0.728
Student	21.9%	20.4%	27.3%	27.9%	
Unemployed	16.9%	17.7%	18.2%	11.6%	
Worker/Civil servant	36.7%	38.1%	27.3%	32.6%	
Self-employed	21.1%	19.9%	27.3%	25.6%	
Housewife	0.8%	0.6%	0%	2.3%	
Retired	2.5%	3.3%	0%	0%	
Education					**0.002**
No education/Primary school	1.7%	0.6%	18.2%	2.4%	
Middle/High school	3%	30.7%	36.4%	50%	
University or higher	95.2%	68.8%	72.7%	88.1%	
History of mental disorder	17.7% (Yes)	18.8% (Yes)	18.2% (Yes)	11.6% (Yes)	0.565
Chronic physical condition	17.3% (Yes)	14.4% (Yes)	45.5% (Yes)	18.6% (Yes)	**0.030**

BMI, body mass index. History of mental disorder diagnosis and chronic physical condition were assessed with "Yes"/"No" answers. Significant p values are shown in boldface, $p < 0.05$.

Higher disturbance in eating attitudes and increased generalized anxiety was associated with depressive symptomatology. In addition, participants who experienced higher distress related to daily heterosexist experiences were more likely to report depression symptoms.

Discussion

This study presents the first comprehensive information about eating attitudes and depressive symptoms during the COVID-19 pandemic in a Turkish LGBTIQ sample.

A heterogeneous and large sample was recruited *via* community networks in Turkey and the participants filled out an online survey. There were differences between the completers and participants who dropped-out and did not finish the online survey. Completers were mostly younger, had male as their gender identity, assigned sex as man at birth, were attracted to men, and single. Considering that none of the completers reported being asexual, the recruitment procedures, which included ads on a Turkish dating website, could have been flawed. In addition, completers had higher education levels, they were more likely to have received a mental disorder diagnosis in the past, and more likely to suffer from a chronic physical condition, which could indicate that the participants who completed the survey probably tend to value the importance of this research and research topic. To sum up, there were

TABLE 2 Summary of the multiple hierarchical regression analysis predicting eating attitudes ($N = 237$).

Variables	*b*	95% CI[a]	β	t	*p*
Block 1					
Age	−0.04	−0.21; 0.13	−0.03	−0.47	0.638
Assigned sex at birth	−10.85	−18.18; −3.52	−0.24	−2.92	**0.004**
Sexual orientation					
Attracted to women vs. men	13.52	3.91; 23.13	0.23	2.78	**0.006**
Attracted to both vs. men	3.46	−0.98; 7.89	0.11	1.54	0.126
Block 2					
Age	0.14	−0.04; 0.33	0.113	1.56	0.121
Assigned sex at birth	−6.64	−13.96; 0.69	−0.15	−1.79	0.075
Sexual orientation					
Attracted to women vs. men	15.91	6.38; 25.44	0.27	3.3	**0.001**
Attracted to both vs. men	2.68	−1.55; 6.92	0.09	1.25	0.213
Depressive symptomatology (PHQ-9)	0.32	−0.07; 0.71	0.18	1.61	0.108
Anxiety (GAD-7)	−0.14	−0.6; 0.32	−0.07	−0.60	0.548
Social appearance anxiety (SAAS)	0.07	−0.1; 0.24	0.09	0.85	0.398
Physical appearance perfectionism (PPS)	0.01	−0.20; 0.23	0.01	0.13	0.895
Body dissatisfaction (FRS)	0.33	−0.59; 1.26	0.05	0.71	0.476
Social Support (ENRCHD)	0.00	−0.24; 0.24	0.00	0.03	0.977
Self-efficacy (GSE)	0.16	−0.09; 0.42	0.1	1.26	0.211
Resilience (BRS)	−0.31	−0.85; 0.24	−0.08	−1.11	0.267
Social isolation (UCLA)	1.48	0.32; 2.63	0.26	2.52	**0.013**
Block 3					
Age	0.10	−0.06; 0.27	0.08	1.22	0.223
Assigned sex at birth	−9.18	−15.99; −2.37	−0.20	−2.66	**0.009**
Sexual orientation					
Attracted to women vs. men	4.69	−4.86; 14.24	0.08	0.97	0.333
Attracted to both vs. men	0.35	−3.72; 4.42	0.01	0.17	0.864
Depressive symptomatology (PHQ-9)	0.38	0.01; 0.74	0.22	2.04	**0.043**
Anxiety (GAD-7)	−0.14	−0.56; 0.28	−0.07	−0.66	0.508
Social appearance anxiety (SAAS)	0.06	−0.1; 0.23	0.08	0.8	0.424
Physical appearance perfectionism (PPS)	0.05	−0.15; 0.25	0.04	0.46	0.644
Body dissatisfaction (FRS)	0.57	−0.29; 1.42	0.08	1.3	0.196
Social support (ENRCHD)	−0.03	−0.25; 0.19	−0.02	−0.26	0.791
Self-efficacy (GSE)	0.23	−0.02; 0.47	0.14	1.83	0.069
Resilience (BRS)	−0.35	−0.85; 0.15	−0.09	−1.37	0.171
Social Isolation (UCLA)	1.38	0.31; 2.45	0.24	2.55	**0.012**
Number of heterosexist experiences (DHES)	0.73	0.47; 0.99	0.57	5.56	**<0.001**
Distress related to heterosexist experiences (DHES)	−0.14	−0.20; −0.09	−0.52	−4.98	**<0.001**
Internalized homophobia (IHS)	0.04	−0.11; 0.2	0.03	0.54	0.588

PHQ-9, Patient Health Questionnaire-9; GAD-7, Generalized Anxiety Disorder-7; SAAS, Social Appearance Anxiety Scale; PPS, Physical Appearance Perfectionism Scale; ENRCHD, ENRICHD Social Support Inventory; GSE, General Self-Efficacy Scale; BRS, Brief Resilience Scale; UCLA, UCLA 3-item Loneliness Scale; DHES, Daily Heterosexist Experiences Scale; IHS, Internalized Homophobia Scale.
Significant *p* values are shown in boldface.
[a]95% confidence interval for b.

differences between the completers and the people who did not complete the survey. Nevertheless, a fairly large and heterogeneous sample was recruited in the Turkish LGBTIQ community.

Predictors of eating attitudes

Participants who reported female sex at birth and higher scores for depression and social isolation were more likely

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TABLE 3 Summary of the multiple hierarchical regression analysis predicting depressive symptomatology ($N = 237$).

Variables	*b*	95% CI[a]	β	t	*p*
Block 1					
Age	−0.26	−0.36; −0.16	−0.36	−5.21	**<0.001**
Assigned sex at birth	−6.61	−10.81; −2.41	−0.26	−3.11	**0.002**
Sexual orientation					
Attracted to women vs. men	−4.37	−9.88; 1.13	−0.13	−1.57	0.119
Attracted to both vs. men	1.05	−1.49; 3.59	0.06	0.81	0.417
Block 2					
Age	−0.06	−0.12; 0.01	−0.08	−1.58	0.117
Assigned sex at birth	−3.86	−6.69; −1.03	−0.15	−2.7	**0.008**
Sexual orientation					
Attracted to women vs. men	−5.73	−9.47; −1.99	−0.17	−3.03	**0.003**
Attracted to both vs. men	0.33	−1.33; 1.99	0.02	0.39	0.695
Eating attitudes (EAT-26)	0.05	−0.01; 0.11	0.08	1.61	0.108
Anxiety (GAD-7)	0.73	0.59; 0.87	0.61	10.21	**<0.001**
Social appearance anxiety (SAAS)	0.03	−0.03; 0.10	0.08	1	0.317
Physical appearance perfectionism (PPS)	0.09	0.01; 0.17	0.13	2.15	**0.033**
Body dissatisfaction (FRS)	−0.22	−0.58; 0.14	−0.05	−1.19	0.234
Social Support (ENRCHD)	−0.08	−0.17; 0.01	−0.09	−1.74	0.083
Self-efficacy (GSE)	−0.01	−0.12; 0.09	−0.02	−0.3	0.765
Resilience (BRS)	−0.12	−0.34; 0.09	−0.06	−1.15	0.252
Social Isolation (UCLA)	−0.14	−0.60; 0.31	−0.04	−0.62	0.533
Block 3					
Age	−0.06	−0.13; 0.01	−0.08	−1.62	0.107
Assigned sex at birth	−3.50	−6.36; −0.65	−0.14	−2.42	**0.017**
Sexual orientation					
Attracted to women vs. men	−4.57	−8.51; −0.63	−0.13	−2.29	**0.023**
Attracted to both vs. men	0.09	−1.61; 1.8	0.00	0.11	0.913
Eating attitudes (EAT-26)	0.07	0.00; 0.13	0.11	2.04	**0.043**
Anxiety (GAD-7)	0.69	0.55; 0.83	0.58	9.72	**<0.001**
Social appearance anxiety (SAAS)	0.02	−0.04; 0.09	0.05	0.71	0.480
Physical appearance perfectionism (PPS)	0.07	−0.01; 0.16	0.11	1.78	0.076
Body dissatisfaction (FRS)	−0.18	−0.54; 0.18	−0.04	−0.99	0.325
Social Support (ENRCHD)	−0.08	−0.17; 0.01	−0.08	−1.67	0.097
Self-efficacy (GSE)	−0.00	−0.11; 0.1	−0.00	−0.07	0.943
Resilience (BRS)	−0.12	−0.33; 0.09	−0.06	−1.16	0.249
Social Isolation (UCLA)	−0.18	−0.64; 0.27	−0.06	−0.8	0.428
Number of heterosexist experiences (DHES)	−0.08	−0.20; 0.03	−0.11	−1.39	0.167
Distress related to heterosexist experiences (DHES)	0.03	0.00; 0.05	0.18	2.24	**0.027**
Internalized homophobia (IHS)	0.06	−0.00; 0.13	0.09	1.95	0.053

EAT-26, Eating Attitudes Test-26; GAD-7, Generalized Anxiety Disorder-7; SAAS, Social Appearance Anxiety Scale; PPS, Physical Appearance Perfectionism Scale; ENRCHD, ENRICHD Social Support Inventory; GSE, General Self-efficacy Scale; BRS, Brief Resilience Scale; UCLA, UCLA 3-item Loneliness Scale; DHES, Daily Heterosexist Experiences Scale; IHS, Internalized Homophobia Scale. Significant *p* values are shown in boldface.

[a]95% confidence interval for b.

to experience a disturbance in their eating attitudes. There was a significant association between the number of heterosexist experiences and eating attitudes. Participants who reported a higher number of heterosexist experiences were more likely to report deterioration in their eating attitudes. By comparison, the distress related to heterosexist experiences was negatively associated with eating attitudes. Participants with higher distress related to heterosexist experiences were less likely to report a disturbance in their eating attitudes.

Although there were more participants assigned at birth as man, in line with previous findings, this study highlighted the female sex at birth and its proneness to eating disorders (9, 14). The intersection among the psychosocial experiences of eating disorders in populations with identity-related experiences, such as harassment, heterosexism, and internalized minority stress, as posed by the "tripartite influence model" (17), could clarify the significant association found between the number of heterosexist experiences and the deterioration in eating attitudes. Furthermore, the findings that showed social isolation and depressive symptoms as significant predictors of disturbance in eating attitudes align with the interpersonal theory of eating disorders (15), which highlights the inadequacy of social interactions that lead to negative affect to trigger or maintain eating disorders. Previous studies found that isolation and depression are significant risk factors for disordered eating behaviors in LGBTIQ individuals (5). Our findings also align with a previous study which showed that social support which was hindered because of the pandemic-related restrictions, was protective against increased eating disorder symptoms among the LGBTQ+ (12).

On the other hand, it was surprising that participants with higher distress related to heterosexist experiences were less likely to report disturbances in their eating attitudes. In the current study, the data were collected through LGBTIQ associations, solidarity groups, and a popular online dating website for LGBTIQ individuals. The participants were highly educated and most probably more accepting of their sexual-minority status. The distress related to heterosexist experiences was revealed by how bothered participants felt when faced with these experiences. It might be possible that the acknowledgment of negative feelings about heterosexist experiences in our highly educated sample was protective against disordered eating attitudes as it might have facilitated the utilization of effective coping strategies. A previous study showed coping *via* internalization as a significant intrapsychic risk factor for disordered eating behaviors (79).

Overall, current findings are in line with previous research regarding the significant role of depressive symptoms and social belongingness in eating attitudes among the LGBTIQ (9, 12) and highlights the vulnerability of female sex at birth to eating disorders even amidst a sample mostly comprised by male sex in our sample of LGBTIQ individuals. It also highlights that the number of heterosexist experiences is crucial in understanding maladaptive eating attitudes beyond the psychosocial risk and protective factors in this population.

Predictors of depressive symptomatology

Results indicated that previously reported risk factors in heterosexual samples, such as female sex (80), generalized anxiety (81), and disturbed eating attitudes (82), were significant predictors of depressive symptomatology in this Turkish LGBTIQ sample. As compared to being attracted to men, participants who were attracted to women were more likely to report depression symptoms. In addition, higher distress related to daily heterosexist experiences was associated with depressive symptomatology, as would be expected for people who internalize prejudicial attitudes and, thus, present self-stigma as posed by the minority stress theory (6).

A previous study that stratified sexual orientation by sex reported higher rates of depression for bisexual females (29). Our findings supported female assigned sex but not bisexual orientation, as a significant predictor for depression symptoms. The comorbidity between eating disturbance and depressive symptomology and the higher prevalence of both conditions among women is attributed to the cultural ideal of thinness (83). Thin idealization occurs more frequently among women and sets the stage for increased body dissatisfaction and depressive symptomatology. In turn, disordered eating behaviors are viewed as ineffective coping strategies for depressed women in response to unattainable beauty ideals. Our findings showed disturbed eating attitudes, assigned female sex and lesbian sexual orientation as risk factors for depressive symptomatology in our sample of LGBTIQ individuals. These findings might suggest that thin idealization is a mechanism to explain why the increased depression symptoms and eating disturbances in heterosexual women might apply similarly to LGBTIQ individuals of female sex and lesbian sexual orientation.

Weight bias is a crucial concept to understand negative emotions and judgmental evaluations relating to one's body image, shape and weight. It refers to the negative weight-related evaluations of overweight and obese individuals (84). Previous research demonstrated an association between sexual minority status and the internalization of weight biases (85, 86). In a recent study, the connections between weight bias, eating concerns and depression symptoms were more pronounced in sexual minority individuals as compared to their cisgender counterparts (87). Furthermore, bisexual and lesbian women reported worst psychological wellbeing concerning eating attitudes and depressive symptoms (87). These previous findings highlight that weight bias could be an important factor in understanding eating attitudes and depressive symptoms in LGBTIQ individuals. Also, our findings might stimulate further research to examine whether LGBTIQ individuals of female sex and lesbian sexual orientation could be more prone to internalize weight biases.

Similar to the findings reported for heterosexual adults (81), generalized anxiety was a risk factor for depressive symptoms among LGBTIQ individuals in the current study. In a qualitative study, LGBT individuals with self-injurious and suicidal behaviors stated increased tension between the way that they learned how to present themselves and the impression they made on others (88). Considering the issues of discrimination toward the LGBTIQ community in Turkey

(37, 89), we believe that a proportion of the increase in the generalized anxiety scores might be attributed to the minority stressors in the current sample. This interpretation is supported by the finding that demonstrated that higher distress related to heterosexist experiences was predictive of depressive symptomatology beyond the psychosocial risk factors. It is possible that, for LGBTIQ individuals who are prone to developing depression symptoms, managing the distress related to daily heterosexist experiences was counteracted by ineffective emotional coping strategies. These findings might point to the need for interventions in the mental field that empowers LGBTIQ individuals' skills in coping with unpleasant emotions related to heterosexist experiences.

The psychosocial impacts of the COVID-19 pandemic have been reported along with various mental health issues in the recent research (90). Although face-to-face interactions were diminished, the exposure to social media and, considering the recruitment procedure of the current study, the use of dating apps increased in this period (91). In a context of social distancing during the pandemic, the evaluation by others could have had an even bigger impact on body image. Additionally, the context could also contribute to increased body surveillance and trigger or aggravate conflicts with oneself regarding body image and lead to negative affect. Thus, it is possible that maladaptive eating attitudes to cope with negative affect might have been intensified during this period. This interpretation is consistent with the interpersonal theory of eating disorders, which views eating disorders as maladaptive coping strategies to regulate emotion in response to negative social interactions (15). Nevertheless, the effects of the pandemic on individuals, especially individuals with sexual minority background, seem not to be fully understood and need further research over the next years.

Strengths and limitations

The findings of the current study should be interpreted with acknowledgment of its limitations. Since the data collection was online, the sample comprises only of participants with internet access. Considering that one of the recruitment procedures was a dating website, it could shape some of the sociodemographic characteristics of the sample. Not all of the assessments were adequately validated (e.g., Daily Heterosexist Experiences Scale) and the internal consistency of the Brief Resilience Scale was low. In addition, the response characteristics of the participants could not be controlled due to self-report assessments. The majority of the current sample consisted of gay men. It is notable that the other subgroups represent a minority that is still difficult to reach, especially in countries where sexual minorities experience substantial discrimination in the public sphere (89). We understand that social stigma may play an important role when it comes to sexual-minority and gender-diverse populations. There was a certain number of participants who did not complete the survey. We also found differences between the completers and the people who did not complete the online survey. Thus, the characteristics of the sample should be considered when interpreting the findings of the current study. Also, the lack of information on the distribution of sexual minority individuals in Turkey limits the generalizability of the findings. Finally, our ability to infer causal associations between the studied variables was limited due to the cross-sectional study design. Nevertheless, the results of this study are valuable for its input about the LGBTIQ population in Turkey and its ability to stimulate and streamline further research in this field. To our knowledge, the present study was the first to examine eating attitudes, depressive symptoms, and their predictors in a large sample of the LGBTIQ Turkish community. It contributed by identifying disorder-specific psychosocial vulnerability factors and minority stressors, which might inform mental health promotion strategies for this population.

Future directions

The current findings provide evidence that the minority stressors are significant risk factors beyond the psychosocial vulnerability for eating disorders and depressive symptomatology in this population. Further investigation of direct and indirect relations between the vulnerability factors and the minority stressors could reveal the specific pathways that lead to disturbed eating behaviors. For instance, a previous study showed that an unmet need to belong and perceived stigma predicted increased depression and decreased self-compassion, which in turn were associated with higher levels of disordered eating behaviors among gay men (9). Moreover, longitudinal studies with sexual-minority and gender-diverse populations could investigate the long-lasting impact of the pandemic on their mental health which would show causal associations and risk and protective factors involved. Additionally, further research could focus on sexual minority subgroups about whom there is little literature available.

Conclusion

The findings demonstrated the significant role of sexual minority stressors in the prediction of disturbed eating attitudes and depression symptoms beyond general psychosocial risk and protective factors. These results emphasize the need to develop strategies to reduce prejudicial attitudes at the societal level and to enhance the skills of LGBTIQ individuals in coping with minority stressors in Turkey.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving human participants were reviewed and approved by the Research Ethics Committee of Bursa Uludag University. The patients/participants provided their written informed consent to participate in this study.

Author contributions

HG, TT, and EK designed the study. HG performed the statistical analysis. EK, HG, and ASP drafted the article. ASP implemented the survey. HG, TT, SB, CR-K, and EK discussed the results and contributed to the final manuscript. All authors have approved the final manuscript.

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Conflict of interest

Author CR-K received lecture honoraria from Recordati and Servier, which was outside and independent of the submitted work.

The remaining 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.

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Brain activation in individuals suffering from bulimia nervosa and control subjects during sweet and sour taste stimuli

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Introduction: Episodes of eating great quantities of extremely sweet and often aversive tasting food are a hallmark of bulimia nervosa. This unique eating pattern led researchers to seek and find differences in taste perception between patients and healthy control subjects. However, it is currently not known if these originate from central or peripheral impairment in the taste perception system. In this cross sectional study, we compare brain response to sweet and sour stimuli in 5 bulimic and 8 healthy women using functional magnetic resonance imaging (fMRI).

Materials and methods: Sweet, sour and neutral (colorless and odorless) taste solutions were presented to subjects while undergoing fMRI scanning. Data were analyzed using a block design paradigm.

Results: Between-group differences in brain activation in response to both sweet and sour tastes were found in 11 brain regions, including operculum, anterior cingulate cortex, midbrain, and cerebellum. These are all considered central to perception and processing of taste.

Conclusion: Our data propose that sweet and sour tastes may have reward or aversion eliciting attributes in patients suffering from bulimia nervosa not found in healthy subjects, suggesting that alteration in taste processing may be a core dysfunction in bulimia nervosa (BN).

KEYWORDS

bulimia nervosa, neuroimaging, taste, sweet, sour, eating disorders

Introduction

Symptoms of bulimia nervosa (BN) include repeated events of ingesting enormous quantities of food (termed "binge") followed by inappropriate compensatory behaviors to avoid weight gain. During binges there is a feeling of uncontrol regarding quantity or nature of food ingested (1).

Taste perception is complex since it combines appearance, familiarity, odor, texture, and temperature of food and, for human beings, also the social, emotional and cognitive contexts under which it is eaten. Therefore, taste is considered a multimodal sense. Researchers to this date have not succeeded in revealing its anatomical pathways or functional circuitry (2).

Patients with BN exhibit preference for sweet taste (3–5), and do not show a decrease in craving (6) or pleasantness (7) after repeated ingestion of sweet food constituents. The ingested foodstuffs

may also be aversive, and include frozen food, food picked up from garbage, spoiled food, etc (4). These anomalous eating patterns led researchers to seek an aberration in peripheral taste perception and cerebral representation and processing of taste stimuli in patients with BN.

Only a few functional imaging studies examined brain response to taste stimuli in patients with active BN. Women with (largely sub-threshold) BN showed trends for less activation than healthy controls in the left middle frontal gyrus, right posterior and mid dorsal insula, right precentral gyrus and left thalamus in response to consumption of chocolate milkshake compared to a tasteless solution (8). Data obtained from the same cohort (9) suggest that negative affect may increase the reward value of food for individuals with BN. Functional imaging studies conducted on recovered BN patients show (10) that individuals recovered from a bulimic-type eating disorders (ED) had significantly lower activation than controls in the right anterior cingulate cortex (ACC). A more recent study from the same group (11) found that women recovered from BN had a significantly elevated hemodynamic response to the taste of sucrose in the right anterior insula. Khalsa et al. (12) suggested that adults remitted from BN may have elevated reward-related brain activation in response to taste after having eaten, and this may underlie the tendency to eat beyond satiety. Studies looking at brain response to visual food presentation in BN reported that patients, compared with healthy controls, displayed increased activation in the medial orbitofrontal cortex (OFC) and the anterior cingulate and decreased activation in the inferior parietal lobe and the left cerebellum in response to food perceived as aversive (13).

The purpose of this study was to compare brain response to sugar, a pleasant taste, to sour, an aversive taste, in contrast to water, a neutral taste, between patients with BN and matched healthy controls. We believe patients with BN are impaired in brain processing and assignment of reward value to sweet taste. We hypothesized we will see reduced activation in BN patients in secondary associative taste areas such as the OFC and ACC in response to exposure to unpredictable sweet stimuli. We presented participants in the study with an aversive (sour) taste in an attempt to determine whether impairment in brain activation in BN is limited to sweet taste or may generalize to other tastes as well.

Materials and methods

Participants

Five women suffering from bulimia nervosa (bulimia group, BG) and 8 matched healthy women (control group, CG) participated in the study. Inclusion criteria were age 18–40, Body Mass Index (BMI) within normal range. Diagnosis of BN according to DSM-IV criteria. All participants were outpatients, with no current or past substance abuse, no systemic or neurological illnesses, and no history of head trauma. No psychiatric diagnosis, other than bulimia nervosa in the experimental group was accepted. Subjects were not on any medication other than oral contraceptives and smoked up to 10 cigarettes a day. Study was approved by our institutional review board and all participants signed an informed consent form.

Subjects were assessed using the Structured Clinical Interview for DSM-IV (SCID) (14) Eating Disorder Inventory 2 (EDI2) (15) and the Yale – Brown Obsessive compulsive scale (Y-BOCS) (16).

Subjects were instructed to fast from 24:00 on the night prior to the experiment. They were given a standard breakfast at 8 AM, consisting of one 3% plain yoghourt, one red apple, and one cup of tea/coffee with one teaspoon of sugar. Blood sugar levels were measured using an Elite© instant glucose meter. Subjects with readings out of normal range were excluded. Experiments commenced at 9 AM.

Stimuli

Taste stimuli consisted of three flavors: sweet (0.3 M sucrose, 10%), sour (0.05 M citric acid, 1%), and mineral water. Taste stimuli were given to subjects first outside the scanner: Nine cups (3 per taste), each containing 5cc of colorless and odorless solution, were presented to subjects. Each cup was rated for pleasantness (most repulsive to most enjoyable) and for intensity (weakest to strongest) on a 100 mm visual analog scale. Inside the scanner stimuli were delivered into the subject's mouth *via* sterile tubes (tubes consisted of 3.6 meters of BioMetrix© infusion line). Stimuli were administered manually, 0.5 cc of solution drip onto the subject's tongue. Between taste conditions a wash of mineral water was used to prevent flavor mixing and diluting. "Taste" blocks lasted 24 s in which a bolus of stimulus was administered every 3 s. (8 boluses). "Wash" block took 12 s in which 4 boluses were given. Each functional imaging session consisted of two runs, each 10 min long. Stimuli presentation was pseudorandomly ordered to ensure that all stimuli appeared in equal number over both sessions.

Magnetic resonance imaging acquisition

Scans were performed on a whole-body 3 T MRI scanner, General Electrics Medical Systems G3, with resonant gradient echoplanar imaging system. Before the experimental run anatomical images were acquired through T1-weighted 3D spoiled gradient echo (SPGR) sequence, with high resolution. SPGR scanning protocol consisted of FOV of 240, with a matrix of 256×256, voxel size 1 mm × 1 mm × 1 mm. No evidence of structural abnormalities were found in any of the participants.

The functional T2*-weighted scans were obtained in an oblique plane, according to a line determined anatomically from under the frontal lobe all the way under the fourth ventricle, including the whole of the pons (being a primary taste area). Functional scanning parameters were: TR = 2 s, TE = 30 ms, FA = 90°, imaging matrix = 64 × 64, FOV = 20 cm. 33 slices were obtained with slice thickness 3 mm and no slice gap. A functional run consisted of 300 scans (10 min). At the end of each scan a short anatomical scan was performed in order to help with future alignment of functional and anatomical data.

Data analysis

Data preprocessing and co-registration were performed using the Brain Voyager 2000, 4.96, software package, while statistical analysis was performed using Brain Voyager QX 1.8 (Brain Innovation, Maastricht, Netherlands). First 6 volumes were removed to allow signal stabilization. Head motion and slice scan time corrections and high-pass temporal filtering in the frequency domain were applied in order to remove drifts and to improve signal to noise ratio. For all subjects head motion was <1 mm. Co-registration of individual anatomical and functional data,

and normalization with respect to one common reference data set (17) were performed for all subjects. Spatial smoothing of 4 mm was applied for group comparisons.

Analysis was performed in two steps: In the first, whole brain analysis was performed to find regions sensitive to taste. As the aim was to assemble all regions that may be of interest a lenient approach was used and we included all regions showing an effect of taste in any of the groups and in any of the contrasts (sweet > neutral; sour> neutral). In the next step we extracted the data from these regions to identify between group differences.

A multi-study general linear model (GLM) was used to generate statistical parametric maps of both runs together. Group comparisons were calculated using random effects GLM. A minimum cluster size of 10 functional voxels was applied to all data. Thresholds used were corrected ($p < 0.001$) for cluster size. As regions involved in taste processing may be small, and this analysis is merely aimed in identifying regions involved in processing taste to be used in the following between group analysis a lenient cluster size was selected. For proof of concept, we first generated a statistical map of "taste" (both sweet>neutral and sour>neutral) for all subjects. Then, we used random effect GLM to detect brain regions significantly positively or negatively activated by either taste (sweet>neutral; sour>neutral) within each group (CG and BG). This was preferred over the between group whole brain analysis because we wanted to make sure that areas that are significantly different between groups are significantly activated in response to taste in at least one group. Regions found to be sensitive to taste in either group were used as regions of interest (ROIs) to evaluate the effect of bulimia on taste related regions. This allowed us to ensure that between groups effects were indeed in regions involved in processing taste. Activation from these regions was extracted for between group analysis using *t*-test. The averaged signal change during stimulus presentation was also calculated (Figure 1B).

Results

Participants were 19–25 years old, female, with a BMI of 19–25, The two groups did not differ in age, height, weight, BMI and handedness, but significantly differed on most EDI (15) and Y-BOCS scales and sub-scales (16). The mean duration of BN was 6 years (SD = 4).

When solutions were presented outside the scanner (Table 1), a statistically non-significant trend (Mann–Whitney two group comparison) was seen in which the BG rated pleasure for sweet higher and for sour lower than the CG. BG seemed to enjoy sweet more and dislike sour more than CG. Both groups found the three different taste stimuli significantly distinct from one another, both in intensity and in pleasure ratings (a parametric Friedman test of ranks, $p < 0.002$ for CG, $p < 0.015$ for BG, data available on request).

Inside the scanner, taste (sweet and sour) vs. neutral analysis for all subjects revealed activation in the thalamus, midbrain and cerebellum in the right hemisphere (RH) and in the operculum, basal ganglia (BaGa), somatosensory cortex (SSC) and cerebellar regions in the left hemisphere (LH). Sour vs. neutral gave almost the same results as taste (sweet and sour) did. Sweet vs. neutral gave less areas of activation (data available on request). Group (BG/CG) and taste (sweet/sour) were then analyzed separately. All regions (except for the thalamus) found active in the "all subjects" analysis, were found active in at least one group/taste condition, as well as several additional regions (see Table 2). All were used as ROIs in a group by taste random effect analysis. Table 3 presents the 11 regions that significantly differed between the groups. In eight of these the BG had higher activation than the CG. In three regions activation was lower in the BG. Figure 1 shows significantly lower sweet vs. neutral response pattern in the left anterior cingulate of bulimic subjects compared to controls.

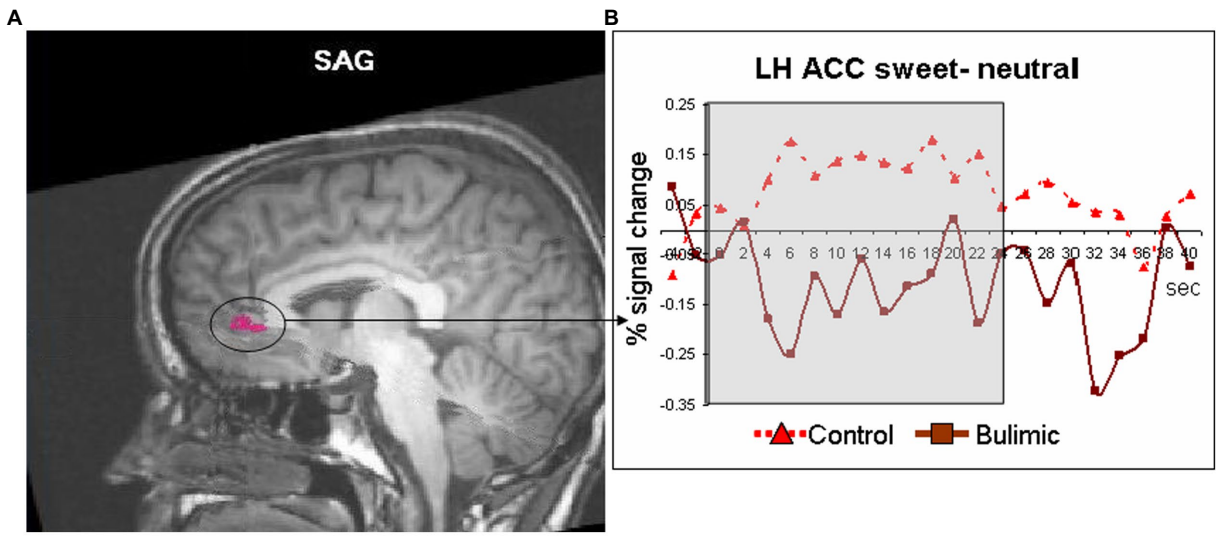

FIGURE 1
Significantly lower activation in the left anterior cingulate of bulimic subjects in response to sweet taste stimulation compared to controls. **(A)** Response to sweet compared to neutral taste in the anterior cingulate cortex (circled and marked in pink, displayed of T1 sagittal image) significantly differed between groups [$t(11)=3.066$, $p<0.01$]. **(B)** Averaged time courses for each group.

TABLE 1 Mean values of intensity and pleasure for each flavor by group after tasting stimuli in cups outside the scanner, and Mann–Whitney two group comparison between groups.

	Sweet				Sour				Neutral			
	Intensity		Pleasure		Intensity		Pleasure		Intensity		Pleasure	
	BG	CG	BG	CG	BG	CG	BG	CG	BG	CG	BG	CG
Mean Value	51	52	74	60	78	77	8	22	21	9	57	50
Mann–Whitney U	18		10.5		16		10.5		13		13.5	
Significance	0.769		0.163		0.558		0.163		0.304		0.163	

No significant difference was found but a trend for higher pleasure for sweet taste and lower pleasure for sour in BG compered to CG was observed. Comparison of intensity and pleasure ratings given after tasting stimuli in cups. Mann Whitney U-two group comparison. BG, bulimic group; CG, control group.

Discussion

All regions activated by "taste" *per se* in this study were identified as such in previous studies (18, 19). Sour and sweet tastes activated both similar and different brain regions. This response pattern is not likely to be due to peripheral nervous system differences such as taste receptor damage following purging behavior, in which case the perceived differences would be the same for all flavors, but rather to impairment in central nervous system sensory and/or emotional processing circuitry.

Yeung et al. (20) performed connectivity meta-analysis of taste processing fMRI studies in healthy adults. Results revealed nine clusters activated by the effect of taste. Four involved the insula and the rest included the thalamus, pre and post central gyrus, hippocampus and caudate. Sweet taste contributed to all clusters while other tastes contributed to only some of the nine clusters (16). A systematic review of Chao et al. (5) found 15 studies that preformed fMRI to examine taste brain activation in ED. The vast majority of studies included only sweet stimuli. Due to differences in methodology and populations, strong conclusions could not be drawn. Neural responses differed when sweet taste stimuli were predictable compered to unpredictable stimuli. A general trend for reduced responsiveness during random application of taste but not during predictable applications was observed (5). In our study the application of taste was random. In eight regions the BG had higher activation than the CG. In three regions (such as the ACC, see Figure 1), activation was lower in the BG. In the same review, of nine taste preference studies, three compered BN to controls and found higher preference to sweet taste compered to controls (5), we found the same trend (non-significant) in our results.

Our finding of reduced activity in the ACC in the bulimic group replicates that of (10), who found reduced ACC activity in recovered BN in response to glucose, although reduced ACC activation in our study was found in the left hemisphere while (10) found a reduction on the right. Other imaging studies found altered serotonergic activity in cingulate regions in BN subjects (18). Moreover, (13) reported that presentation of pictures of food increased activity in the ACC and other regions in BN compared with CG subjects (13). Likewise, (19) report greater ACC activation in bulimic compared with healthy patients in response to visual presentation of high caloric food (19). This difference in ACC response between studies may reflect a difference in brain response to an actual perceptual sensation of taste versus response to a visual stimulus (and/or anticipation), or whether subjects were actively ill or recovered.

The ACC plays an important role in anticipation of reward (20). Regional cerebral blood flow in the ACC wsa reported to be inversely proportional to the desirability of chocolate (21), and cingulate activation was reported to be associated with cue-induced cocaine craving (22). Addiction-like cue reactivity has been described in bulimia nervosa (23). Thus, altered ACC activity may reflect a disturbance of taste reward expectancy in individuals with BN.

Brain activation in the inferior parietal region was higher in the BG relative to CG in response to sour taste and in the occipital cortex in response to sweet taste. (13, 15) found that patients with ED (Anorexia Nervosa and BN) showed decreased activation in inferior parietal lobe (IPL) and increased (13) or decreased (15) occipital activation after exposure to visual food stimuli relative to healthy control subjects. Activation of the IPL has previously been associated with appetitive and food-related behavior and satiation (24). Part of the IPL contains secondary and tertiary somatosensory areas (25) and the IPL is closely interconnected with the insula, the primary taste cortex, and receives both somatosensory and gustatory projections (26). Our findings indicate that posterior brain regions may be involved in the pathophysiology of eating disorders.

We found a region within the left operculum to be more active in the BG in reaction to sweet stimulus. In contrast, another region within the operculum and the insula was similarly activated in both groups. The operculum and insula are accepted as primary taste regions (26). Small et al. (14) found that the insula and operculum responded to pleasantness but not to intensity (14, 27) found opercular activation to be in correlation with pleasantness ratings of sweet stimuli (28). This is consistent with our finding showing higher activation in the left operculum in the BN group, as previous studies found that BN subjects prefer sweeter stimuli compared with CG (4). In these studies, intensity of taste did not differ between the groups, which could explain the lack of OFC and amygdala differences between the groups (14). An increased attribution of pleasantness to sweet stimuli, in combination with decreased ability to regulate affective behavior may be the beginning of a mechanism explaining binge eating, represented in, or stemming from brain alterations.

Cerebellar activation was elicited by both sour and sweet tastes. A significantly higher activation in a cerebellar sub-region was observed in the CG in response to the sweet stimulus. Not much has been reported on cerebellar activity in taste. Activity in the cerebellum has been found when showing pictures of food and pictures of emotional stimuli to bulimic subjects (13). The cerebellum has also been implicated in sending satiety signals (27). Small et al. (14) found the cerebellum responsive to intensity, irrespective of valence of taste stimuli. These last two findings offer an explanation for why in controls the cerebellum reacts more strongly to sweet taste than in bulimics,

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TABLE 2 Brain regions showing significant activation for taste (sweet/sour) vs. neutral, analyzed separately for each group.

	Sweet				Sour			
	RH		LH		RH		LH	
	BG	CG	BG	CG	BG	CG	BG	CG
Insula	33, 11, 8		−25, −7, 13	−31, 25, 3	34, 10, 7		−27, 21, −1	
Operculum*			**−39, 35, 6****	−46, 17, 9				
ACC				**−10, 42, 8**				
SSC*					**47, −52, 41****	57, −12, 30		−45, −17, 34
BaGa*	23, 10, 10	20, 7, 17	−24, 8, 9	−4, 2, 11	19, 4, 12	13, 3, 20	−18, −5, 15	
	10, 17, 7	11, 12, 12					−13, −24, −2	
Cuneus					**1, −79, 3****		**−4, −69, 30**	
Midbrain*				**−9, −5, −9**	0, −12, 1			
MFG							**−45, 19, 34**	
IFG							**−52, 12, 23**	
IPG							**−49, −51, 32**	
POC		22–5,617						
Occipital				**−26, -76, 24**				
Cerebellum*		**19, -62, -30**				30, −55, −30	−25, −50, −25	−15, −45, −24
						9, −52, −31		

Bolded and underlined regions were significantly different between-groups in a random effect, region of interest analysis. Marked with * are Regions significantly activated in the taste vs. neutral comparison, all subjects analyzed together. Marked with ** are regions with higher activation in BG. Brain regions showing significant activation for taste (sweet/sour) vs. neutral, analyzed separately for each group. $p < 0.005$, corrected for cluster size. RH, right hemisphere; LH, left hemisphere; ACC, anterior cingulate cortex; SSC, somato sensory cortex; BaGa, basal ganglia; MFG, middle frontal gyrus; IFG, inferior frontal gyrus; IPG, inferior parietal gyrus; POC, posterior occipital cortex; Occipital, occipital cortex; BG, bulimia group; CG, control group. Bolded and underlined regions significantly different between-groups in a random effect, region of interest analysis.*Regions significantly activated in the taste vs. neutral comparison, all subjects analyzed together.
**Higher activation in the BG.

enabling bingeing of high intensity sweet foods which would have otherwise been aversive.

The striatum has been shown to receive inputs from the insula (29) and is hypothesized to mediate behaviors involving eating, particularly of highly palatable, high energy foods (30). Almost all imaging taste studies report findings in striatum and sometimes other regions of the basal ganglia, but most chose not to comment on these. We found activation in these regions in most subjects but did not find significant differences between groups.

Strengths and limitations

This study is one of few studies comparing taste perception between subjects with active BN and healthy controls, and their brain response to sweet and sour stimuli. The small sample size (especially of the BG) is the major limitation of our study. Patients with BN were reluctant to undergo brain imaging of all sorts or take part in our taste evaluation paradigm.

Oral health complications associated with self-induced purging include symptoms such as hyposalivation, xerostomia, burning mouth syndrome and dysgeusia. These can all affect taste perception (31–33). Since oral status evaluation of BN subjects wasn't performed in our study, this potential influence on taste perception wasn't included in our analysis, and should be considered a limitation of our study.

A further limitation in our study may be that the neurological changes reported in our manuscript may be, at least in part, reflective of an underlying subclinical depressive condition (34). The oral burning sensation often reported by ED patients, secondary to oral mucosa atrophy, induced by deleterious nutritional choices and repeated self-vomiting episodes, could contribute to the evolution of depressed mood in this patient population (31).

Defining the ROIs separately in each group, while ensuring that all relevant regions will be included in analysis, may induce a bias towards "between group differences". Indeed, in regions identified in the BG, activation was higher than controls, while in regions identified in CG, a mixed pattern was found. We recognize this is a limitation of the analysis we chose.

Swallowing during fMRI was shown to influence brain activity (35). While it was suggested to control for swallowing, this is not a standard practice and was not done in this study. As subjects were instructed to swallow at need we assume this was distributed randomly between conditions and therefore considered random noise. However swallowing may be influenced by taste (36) and may be influenced by BN as well. Further research is necessary to entangle the response to swallowing and taste and their interaction with Eating Disorders.

Conclusion

Our findings imply that people with BN have aberrant sensitivity to the reward or aversion-inducing properties of sweet and sour tastes compared to healthy individuals. These appear to be associated with differences in brain activation, suggesting that impaired taste processing may represent a fundamental pathophysiology of BN. Further research with a larger number of

TABLE 3 All brain regions showing preferences for taste in any of the groups.

	Whole brain within group analysis				ROI between group analysis	
Brain region	Group, flavor found in	Tal X,Y,Z	size	Average *p* value	Average statistic**	Average *p* value
LH Oper.	BG, sweet	39, 35, 6	979	0.003	−2.396	0.035
RH cuneus	BG, sour	1, −73, 3	548	0.003	−2.99	0.012
LH cuneus	BG, sour	−4, −69, 30	346	0.0025	−2.939	0.01
RH SSC	BG, sour	47, −52, 41	303	0.003	−3.22	0.008
LH MFG	BG, sour	−45, 19, 34	450	0.0035	−3.3	0.007
LH IFG	BG, sour	−52, 12, 23	339	0.003	−2.9	0.016
LH IPL	BG, sour	−49, 51, 32	402	0.003	−4.5	0.0009
RH cerebellum	CG, sweet	19, −62, −30	397	0.004	2.8	0.017
LH, ACC	CG, sweet	−10, 42, 8	288	0.0048	3.066	0.01
LH Occ' c	CG, sweet	−26, −76, 24	487	0.004*	−3.2	0.008
LH midbrain	CG, sweet	−9, −5, −9	353	0.004	2.5	0.029

*Neutral > sweet.

**Negative numbers: BG > CG.

Table lists their location, size, the contrast they were found to be significant and the statistical value of the effect. For each region the results of the between groups analysis (statistical analysis and average *t*-value) are included. Regions found significant in ROI analysis between groups. RH, right hemisphere; LH, left hemisphere; Oper, operculum; SSC, somato sensory cortex; MFG, middle frontal gyrus; IFG, inferior frontal gyrus; IPG, inferior parietal gyrus; ACC, anterior cingulate cortex; Occ' c, occipital cortex; Tal X,Y,Z, Talairach coordinate system; BG, bulimia group; CG, control group.

subjects is needed to establish or refute these findings and reveal more subtle processes.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving human participants were reviewed and approved by Haddasah Hebrew University Medical Center Ethics Committee. The patients/participants provided their written informed consent to participate in this study.

Author contributions

GB and OB performed the SCID to participants. DA, AB, and TH performed the experiments and contributed to data acquisition. EB contributed to the experimental design. OB, SK, and SF wrote the manuscript. SL and AB contributed to the interpretation of the results. All authors contributed to manuscript revision, read, and approved the submitted version.

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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.

Publisher's note

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Case report: Anorexia nervosa and unspecified restricting-type eating disorder in Jewish ultra-orthodox religious males, leading to severe physical and psychological morbidity

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Background: Young Jewish Ultra-Orthodox women usually show less disturbances in body image and eating in comparison to less religious communities. By contrast, problems with eating are highly unknown and unrecognized in Jewish Ultra-Orthodox males.

Aim: To investigate whether in Ultra-Orthodox males, restricting-type AN (AN-R) with highly obsessional physical activity and unspecified restricting eating disorder (ED) in the context of obsessive–compulsive disorder (OCD) would lead to severe physical and emotional morbidity.

Results: The study included two groups: the first, 3 adolescents with AN-R developing severely increased ritualized obsessional physical activity in addition to restricting eating, requiring inpatient treatment because of severe bradycardia. These youngsters ignored the severity of their obsessional physical activity, continuing with it in hospital despite their grave medical condition. One student began extensive training for triathlon, whereas another student, upon remitting from AN, developed severe muscle dysmorphia. These findings suggest that young Ultra-Orthodox males with AN may develop obsessional physical activity to increase their muscle mass rather than to lose weight Another four Jewish Ultra-Orthodox males developed malnutrition in the context of severe OCD, with no evidence of dieting or body-image disturbances. These individuals developed highly obsessional adherence to different Jewish religious rules, including prolonged praying, asceticism, and overvalued strict adherence to Jewish Kashrut rules of eating, leading in all cases to severe food restriction. They were highly unaware of their severe weight loss and required hospitalization because of severe physical disturbances associated with malnutrition. Moreover, most did not cooperate with their treatment, and their ED-related obsessionality was mostly resistant to psychopharmacotherapy.

Conclusion: Owing to their highly ritualistic rigid way of life, combined with the need for excellency in studying, Jewish Ultra-Orthodox adolescent males with AN might be at a specific risk of developing severe physical disturbances if their illness is associated with highly perfectionistic obsessional physical activity. Second, Jewish Ultra-Orthodox religious males with OCD might be at a specific risk for severe undernutrition, as their rigid relentless observance of Jewish everyday laws might highly interfere with their eating.

KEYWORDS

anorexia nervosa, Jewish, obsessive compulsive disorder, orthodox, religion

Introduction

Currently, anorexia nervosa (AN) is considered a genetic-related psychobiological neurodevelopmental disorder (1, 2). Nonetheless, on this biological basis, socio-cultural parameters may exert an impact on the outcome and prognosis of AN (3).

One such relevant socio-cultural aspect is religion (4). In Judaism, Ultra-Orthodox people represent the most religiously observant group, followed by Modern-Orthodox Jews, other subgroups of religious Jews (e.g., Conservative and Reform Jews), partially observant Traditional Jews, and non-religious secular Jews. Studies show that young Ultra-Orthodox women have usually (5–10), but not always (11) the most positive body image, are the least dissatisfied with their body, and show less disordered eating symptoms, followed by Modern-Orthodox women, with secular women being at the worst end of the continuum.

Considering the findings about the complex association between discorded eating and religion in Jewish religious female subgroups, the aim of the present manuscript was to describe severe restrictive eating with severe medical and emotional complications in a specific population that to the best of our knowledge has not been studied yet, i.e., Jewish Ultra-Orthodox males.

Whereas many clinical core AN-related symptoms are similar in female and male patients, several important differences do exist. Specifically, the body ideal typically presented in males centers on muscularity rather than on thinness (12, 13) or overvaluation of body weight and shape (14). Thus, in comparison to restriction which is significantly more prevalent in females, the presence of compulsive exercise is similar in male and female AN adolescents (15).

This manuscript relates to two groups of Jewish Ultra-Orthodox males with severe restricting eating disorders (EDs). The first includes adolescents with restricting-type AN (AN-R). Ultra-Orthodox adolescents leave their home around the age of 14 to study in a special boarding-school system termed Yeshiva, where they are highly invested in Holy studying. They come home only in some weekends. This may reduce eating in some vulnerable youngsters, even if unintentionally at first. As EDs are less known and suspected in Ultra-Orthodox populations, specifically in males, it might take a prolonged period before they are diagnosed.

The second group includes mostly older Ultra-Orthodox males with severe obsessive–compulsive disorder (OCD), centered around Jewish religious issues. Judaism demands strict exactness in keeping the required rules, inculcates the performance of rituals supporting it from childhood, and views their non-performance as wrong or sinful (16, 17). Rituals concerning exactness are common in Ultra-Orthodox Jews with OCD (17), but also in people with AN (18).

Research about the association between OCD and food restriction in Ultra-Orthodox males is scarce. In one of the few existing surveys (17), in a sample of 34 psychiatric outpatients with OCD from Jerusalem, Israel, religious OC symptoms were found in 13 of the 19 Ultra-Orthodox patients in this cohort, compared to only one of the 15 non-Ultra-Orthodox patients. The main religious topics identified in the Ultra-Orthodox cohort included OC symptoms related to prayer (prolonged periods of praying), dietary practices (too many food types that are not allowed to eat because of too strict religious Kashrut regulations—i.e. what is not allowed to eat in Judaism), menstrual practices, and cleanliness before praying.

Materials and methods

Case series

The present article describes three male patients with AN-R and four male patients with atypical restricting ED (19) resulting from severe OCD (19), all developing severe physical deterioration requiring hospitalization. Their names are not provided, and all their demographic data have been changed, to preclude their identification. Ethical review and approval is not required for this type of study in human participants in accordance with the local legislation and institutional requirement. Written informed consent to publish the manuscript has been provided by the participants and their legal guardians as required.

The first group included two Jewish Ultra-Orthodox male adolescents and one Jewish Modern-Religious male adolescent. All were diagnosed with AN-R according to the DSM 5-TR (19) criteria, with highly excessive obsessional ritualistic physical activity, exceeding their intentional food restriction. Their pre-hospitalization data is summarized in Table 1, and their admission, hospitalization, and post-hospitalization data in Table 2. Both tables include specific data for each patient.

Several important conclusions can be drawn from these tables. The three adolescents had no evidence of psychiatric family history; the developmental history before the onset of eating-related problems was normal in two cases (#1 and #3). All showed significant increase in their weight before developing intentional restriction and weight reduction. Socio-cultural triggers to weight reduction were related to normal developmental processes the Bar-Mitzva celebration occurring

TABLE 1 Three adolescents with DSM 5-TR AN: pre-hospitalization data.

Age and school year at admission (years)	Family background/early development/problems before AN (including weight history)	Onset of AN	Symptoms
1. 13.5, 9th grade	4/6 children; no[1]; no[2]; ⇑ weight since age 8; at age 12 BMI > 95th centile*	6–12 months before hospitalization (around age 13-Bar-Mitzva)	Restricting, intentional weight loss; mainly ⇑ obsessional physical activity – 1.5 h daily 400 lift-ups, 200 pushups
2. 17.4, 11th grade	10/10 children; no[1]; congenital ptosis of right eyelid, stuttering, school problems; ⇑ weight since age 9–10; at age 16 BMI > 95th centile*	8 months before hospitalization	School refusal since 9th grade; severe conflicts with parents about religiosity; restricting, intentional weight loss; mainly ⇑ 3 h daily physical activity; 50 kg ⇓
3. 15, 10th grade	1/3 children; no[1]; no[2]; sharp weight ⇑ in previous year; 6 months before hospitalization, after leaving home for 1st time to Yeshiva, ⇓ in weight	6 months before hospitalization	Restricting, intentional weight loss; mainly ⇑ obsessional daily physical activity—triathlon; self-prepared protein diet 800–1,000 kcal/24 h; ED-related obsessions; lost 8 kg; blackouts

DSM 5-TR: Diagnostic and Statistical Manual for the Diagnosis of Mental Disorders, fifth edition text revised (19); AN-anorexia nervosa; BMI-body mass index; no[1]: no problems in family; no[2]: no problems in early development; *according to the National Center for Health Statistics [see Centers for Disease Control and Prevention's Year 2000 Growth Charts, adapted for Israeli children and adolescents (20)].

at age 13 for every Jewish boy (case #1) and leaving home to study in a Yeshiva (case #3).

In all cases, the highly obsessional ritualistic characteristics of the physical activity exceeded that of intentional restriction (see Table 2). They were not only for weight reduction, but also for increasing muscle mass (case #1), semi-professional sports fitness (triathlon, case #3), and to reduce stress and increase self-control in the face of severe conflicts with parents (case #2).

All three adolescents were hospitalized because of severe bradycardia. Two did not cooperate with the requirement to reduce physical activity in the hospital (cases #1,#3). Upon discharge from inpatient treatment, none had evidence of AN symptoms. In case #2, the reduction of AN symptoms, specifically of the compulsive physical activity, occurred within a relatively brief period, when his parents accepted his wish to become non-religious (he later joined the Israeli army, which is forbidden in Ultra-Orthodox communities).

For the next years, a repeated pattern was observed for case #3. Whenever returning to the Yeshiva, he started again with restriction and excessive obsessional physical activity, requiring again hospitalization because of severe bradycardia. Finally, at the age of 18, he went to a Yeshiva near his home, where the demand for excellency in studying was as perfectionistic as elsewhere, but where he could sleep at home each night and take care of his food menu. His eating stabilized, his physical activity decreased, and he had no longer interest in triathlon.

For case #1, at follow-up 1 year after discharge, his BMI was >95th percentile (see Table 2). He continued with daily strict obsessive physical activity for the sole purpose of increasing his muscle mass and planned for himself a daily diet of over 3,500 calories with mostly dense proteins. He had no core symptoms of AN, transitioning to DSM 5-TR (19) diagnosis of body dysmorphic disorder (specifier muscle dysmorphia), and functioning well in his daily living.

The second group includes one adolescent and three adult Ultra-Orthodox males with DSM 5-TR (19) OCD, with no symptoms indicative of AN, whose severe malnutrition is directly related to their OCD. Their pre-hospitalization data is summarized in Table 3, and their admission, hospitalization, and post-hospitalization data in Table 4. Several important conclusions can be drawn from these tables.

First, none had a psychiatric family history. Two had evidence of OCD from childhood. All three adults had a history of weight reduction for several years before hospitalization, likely indicating denial of the severity of their developing malnutrition.

The development of severe malnutrition in these four patients was primarily associated with the highly religious content of their obsessions, interfering with normal eating, e.g., excessive time devoted to praying, and faulty interpretation of the Jewish food Kashrut laws. This led to the consideration of the food cooked in the Ultra-Orthodox medical center where they were hospitalized as not Kosher enough. All demonstrated elevated OC characteristics interfering with an adaptive handling of their overvalued religious-related behaviors, including elevated rigidity, preservation, and perfectionism (21, 22). All were hospitalized with severe bradycardia, and their medical condition at admission and during hospitalization was highly compromised (see Table 4).

The greater religious observance in the adolescent patient (case #4) was related to his high aspirations and perfectionistic studying when leaving to the Yeshiva, alongside a wish to suppress almost all earthly pleasures to purify his body from urges. This led him to keep strict rituals in his praying and eating behavior, as well as to tightening of his belt to separate his upper spiritual part from his lower "lust" part, all leading, unintentionally, to severe food restriction.

During hospitalization, the patient said that he did not eat mostly to suppress all evil lust to become an outstanding Torah scholar. Later, while his weight and eating stabilized, he still adhered to strict obsessive religious observance in general and in his eating in particular, and his ascetic behaviors did not decline.

All three adult patients were in their 30th-40th when hospitalized, with severe weight reduction over a period of several years (36 kg in case #5, 25 kg in case #6, 20 kg in case #7); this indicate denial of the patients and their families of their grave physical deterioration.

Case #5 suffered from early childhood from rituals related to eating and praying. At the age of 18, he stared to considerably increase his praying, and avoided certain food types as means to identify with a famous Rabbi, known for his asceticism. Toward the birth of his third child, he decided to be stricter religiously and to abstain from any physical pleasure. Thus, he started walking instead of taking the

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TABLE 2 Three adolescents with DSM 5-TR AN: admission, hospitalization and post-hospitalization data.

Admission	Hospitalization	Medications	Follow-up	Diagnosis/outcome
1. Weight < 5th centile Height > 95th centile BMI < 5th centile*; HR 35 BPM ⇑ cholesterol ⇓ T3	8 months; nasogastric tube feeding; continuing ⇑ obsessional physical activity	Fluoxetine 50 mg/day Risperidone 0.75 mg/day	Quick dropout post-hospitalization; after 1 year: weight 90%; height 50–75%; BMI > 95%*; obsessional physical activity to build muscles; self-imposed diet of 3,500 kcal (dense proteins)	AN-R ⇒ muscular dysmorphia (body building disorder)
2. Weight < 50th centile Height > 95th centile BMI < 5 centile*; hypoglycemia, ⇓ phosphor (i.e., mild refeeding syndrome), ⇓ T3; HR 40 BPM	7 months; continued ⇑ physical activity in hospital, stood for hours	No medications because of parents' refusal	Became secular (non-religious); at discharge and follow-up: no AN preoccupations and no ⇑ physical activity	AN-R; at discharge and follow-up no ED
3. Weight 5–10th centile, height 10th centile, BMI 17.5th centile*; HR 32–35 BPM	1st hospitalization in pediatric department full cooperation, weight ⇑; 2nd hospitalization in pediatric department after 4 months because of quick relapse (800 kcal/24 h, ⇑ physical activity); HR 40 BPM, laboratory examinations OK.	Sertraline 100 mg/day Risperidone 1.5 mg/day	after 2nd hospitalization Yeshiva, continuation of ambulatory treatment for 1.5 years: supervised physical activity; at the end of school new Yeshiva far away ⇒ relapse; returned home to university studies; no AN symptoms, no ⇑ physical activity; lost interest in triathlon	AN-R; after 2–3 years no ED

DSM 5-TR: Diagnostic and Statistical Manual for the Diagnosis of Mental Disorders, fifth edition text revised (19); AN-anorexia nervosa; AN-R-anorexia nervosa restricting type; BMI-body mass index; BPM-beats per minutes; ED-eating disorder; HR-heart rate; T3-Triiodothyronine; *according to the National Center for Health Statistics [see Centers for Disease Control and Prevention's Year 2000 Growth Charts, adapted for Israeli children and adolescents (20)].

bus, to avoid eye contact with women, and avoided sweets "to control his desire."

The food restriction of case #6 was evident from the onset of the COVID-19 pandemic, related to financial problems. Regarding case #7, he repeatedly washed his hands for prolonged periods before eating whenever he returned from being outside. Gradually he stopped leaving his home completely. Finally, he stopped eating at all and refused to move outside his bed.

The three adult patients (and their families) were seemingly not fully aware of their grave medical condition before and during hospitalization. Case #5 often disappeared from the department against medical advice to pray at the hospital's synagogue, leading to missing his meals. Finally, he discharged himself against medical advice, claiming that he never had any psychiatric disturbance, and all his problems were physical. When re-hospitalized 1 month later, he agreed to take medications (Sertraline 200 mg/day and Olanzapine 5 mg/day). His physical condition and eating gradually improved. His weight at his final checkup was 84.4 kg (BMI of 26.9 kg/m^2), which was his average weight before starting with restriction.

Case #6 was diagnosed for the first time with severe OCD related to prolonged praying to atone for everyday sins only during inpatient treatment. After 4 months, when his physical condition somewhat stabilized, he discharged himself against medical advice.

For case #7, it was not clear whether he avoided food to reduce his prolonged hand washing because of regarding food as dirty and contaminated, and/or because of the requirement of Jewish religious codes of meticulous hand washing before every meal. After 3 weeks of inpatient treatment, in which he was mostly fed with a nasogastric tube (he did not need to wash his hands with nasogastric feeding), he discharged himself against medical advice.

Last, the response of the three adult to pharmacotherapy with adequate doses of SSRIs (Sertraline and Fluoxetine) and 2nd-generation antipsychotics (Olanzapine) was unfavorable (except for case #5 during his second hospitalization; see Table 4).

Discussion

The aim of the present case series was to describe the development of AN-R and of atypical restricting-type ED (19), with severe resultant physical deterioration, requiring hospitalization, in Jewish Ultra-Orthodox males. The first group included 3 adolescents with AN-R, where one of the leading symptoms was a highly excessive obsessional physical activity. The second group included one adolescent and three adult males, whose ED resulted from severe OCD. In this group, the reduction in food intake and the subsequent deterioration of the physical state were related to highly excessive praying, overly strict food-related Kashrut keeping, and spiritual asceticism, with no evidence of AN-related stigmata.

Regarding the first group, it is of note that in contrast to secular non-religious Jewish Israeli adolescents, where diverse forms of physical activities are part of their daily routine, physical activity is not supported, and even discouraged in Ultra-Orthodox youngsters,

TABLE 3 One adolescent and three adults with DSM 5-TR unspecified restricting-type eating disorder resulting from OCD; pre-hospitalization data.

Age at admission (years)	Family background/early development; problems before ED	Onset of ED	Symptoms
4. 16; 11th grade	1/7 children; no[1]; no[2]; outstanding student, ⇑ expectations; tendency for ⇑ weight since childhood.	1 year before hospitalization	⇓ weight because of ⇑ in religious studying,⇑ observance of Jewish Kashrut food laws, prolonged praying; ⇓eating as did great model Torah scholars, freezing showers (⇑ asceticism); tightening belt to separate ⇓ body "lust" part, from ⇑ spiritual part; no AN symptoms
5. 31, married +4	No[1]; from early childhood rituals about food and prayers	In past 3 years ⇓ from 84 kg to 48 kg	After 18, ⇑ rituals about food and prayers, with ⇑ food restriction; from 28 ⇓ in any physical pleasure (walking to control lust and no bus to avoid contact with women); no AN symptoms
6. 39, married +6	No[1]; no[2]	During COVID-19 financial problems ⇒ ⇑ anxiety ⇒ ⇓ eating, weight, sleep and concentration	⇓ 25 kg in 3 months; no AN symptoms
7. 48, married +8	No[1]; from early age OCD, treated with Fluoxetine, Risperidone; gradually did not leave home and stopped eating because of compulsive handwashing when out/eating	Several years	⇓ 20 kg; ⇓ in eating and weight because of compulsive handwashing for hours before eating

DSM 5-TR: Diagnostic and Statistical Manual for the Diagnosis of Mental Disorders, fifth edition text revised (19); AN-anorexia nervosa; ED-eating disorder; OCD-obsessive–compulsive disorder; no[1]: no problems in family; no[2]: no problems in early development.

where excellence in learning (of religious material), is not only required, but highly praised.

The question then arises as to why these three Ultra-Orthodox male adolescents arrived at a point where their "excellence" in physical activity endangered their lives. First, all experienced a considerable earlier increase in weight, when premorbid overweight is a significant risk factor for the development of AN in male adolescents (23).

Second, all were characterized with psychological traits associated with AN, including rigidity, perfectionism. Obsessionality, and perseverance (18, 24, 25), that have the potential to induce, and maintain, excessiveness, in the present case of physical activity.

Third, all left home to study in the Yeshiva, within a short period before the appearance of disturbed eating. Leaving home, in the context of severe social and academic pressure for excellency, might have been overly stressful for these youngsters.

Fourth, these adolescents developed a highly perfectionistic, ritualistic, almost "professional" physical activity plan: exercising for muscularity in case (1), highly excessive physical training in case (2), and triathlon training in case (3). It is as if the atmosphere of excellency in the Yeshiva met in these vulnerable youngsters with an unrecognized need for perfectionistic, obsessional sports activity. This became even more clear when considering that once the emotional conflicts were solved for case (2), and the living conditions were settled for case (3), their overvalued sports activity subsided. Case (1) was the only youngster continuing with obsessional physical activity, but for him, muscle development was from the beginning, the main goal.

Last, the development of restricting and excessive physical activity have ben likely unnoticed in the Yeshiva, where the focus is on studying. This when bearing in mind that AN is usually revealed much later in male vs. female adolescents (26), particularly in Ultra-Orthodox communities, where the whole problem of EDs is still largely unrecognized.

The 2nd subset comprised four Jewish Israeli Ultra-Orthodox patients with severe restriction of eating in the context of severe OCD. The resultant weight loss was severe enough to require hospitalization.

In cases #4, # 5, and #6, weight reduction resulted from prolonged obsessional praying (eating is not allowed in Judaism during praying) and from excessive observance of the Jewish Kashrut laws of eating. In case #7, it was not entirely clear whether his compulsive handwashing and resultant avoidance of food was related to regarding food as dirty and contaminated, and/or to excessive fulfillment of Jewish religious requirements.

Alongside the issues of praying and Kashrut, cases #4 and #5 reduced their eating also as an ascetic wish of control over the pleasures of life, including eating to purify their bodies from earthly pleasures and urges. The adolescent patient also took for this purpose frequent freezing showers and tightened his belt to separate his lower "lust" part, from the spiritual upper part, and case #5, stopped taking the bus to avoid eye contact with women. Reduction of eating to reduce sexual desires (fighting against the sexually invested "evil nature" in Judaism) is highly relevant in the development of disturbed eating in young males (12), specifically in Ultra-Orthodox communities. Where issues of masturbation, sex before marriage, sexual orientation and gender dysphoria are unspoken forbidden topics.

It is of note that whereas Christianity may support appetitive control and asceticism [including self-starvation for atonement (27, 28)], in Judaism, people are considered to have sinned if they willfully abstain from essential physical needs, including food (16, 29). Despite this clear requirement, case #6 has specifically reduced his eating to atone for his everyday sins. Along this line, past prominent Jewish religious figures have fasted to abolish any physical pleasure as an act of atonement for the sins of the entire community (4, 30). Some Ultra-Orthodox people nowadays, including case #4 here, may still admire these figures, identify with them, and incorporate their behaviors.

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TABLE 4 One adolescent and three adults with DSM 5-TR unspecified restricting-type eating disorder resulting from OCD: admission, hospitalization, and post-hospitalization data.

Admission	Hospitalization	Medications	Follow-up	Diagnosis/outcome
4. weight < 6th centile; height > 85th centile; BMI < 6th centile; * HR 41 BPM day, 33 BPM night	4 months; ICU ⇒ pediatric department; in the beginning refused to eat because of Kashrut (the hospital is Jewish Ultra-Orthodox) and to suppress evil lust.	No; ⇑ in eating and weight ⇒ ⇓ in religion-related obsessions	At discharge weight 10–25 centile; height 25–50 centile; BMI 10 centile*	OCD ⇒ unspecified restricting ED (no AN symptoms); still adheres to strict religious observance in general and in eating in particular; no ⇓ in ascetic behaviors despite ⇑ in weight; still fighting with lust; no AN symptoms
5. Psychiatric department; weight 48 kg, height 1.77 m, BMI 15.4 kg/m^2; HR 40 BPM; transferred to internal medicine department; laboratory examination: ⇑ liver enzymes, ⇓ phosphor (i.e., refeeding syndrome)	⇓ cooperation (disappeared to pray) ⇒ HR 44 BPM ⇒ ICU: ⇑ praying and physical activity and ⇓ eating to control "lust"; no AN symptoms	2nd hospitalization: Sertraline 200 mg/day Olanzapine 5 mg/day.	Discharged himself from hospital when medically stabilized against medical advice; rehospitalization after 1 month: weight 48 kg, BMI 15.3 kg/m^2; HR 60 BPM; discharged after 3 months: weight 67.6 kg, BMI 21.5 kg/m^2; 6 months day center: discharge weight 84 kg, BMI = 26.9 kg/m^2 (similar to pre-illness)	Severe OCD ⇒ unspecified restricting ED (no AN symptoms); good remission of ED, partial remission of OCD
6. weight 40 kg, height 1.66 m, BMI 14.5 kg/m^2; ⇓ glucose, phosphor (i.e., refeeding syndrome)	⇓ eating to atone for everyday sins (disclosed only during hospitalization) and because of ⇑ keeping of Kashrut laws (the hospital is Jewish Ultra-Orthodox); later in psychiatric department hid food, complained of "fullness"	Sertraline 200 mg/day, Olanzapine 7.5 mg.	After 4 months weight 45.7 kg BMI 16 kg/m^2 again weight ⇓ when going home for weekends; discharged himself against medical advice	OCD ⇒ ⇓ eating and weight because of religious issues; allegedly some AN behaviors (food hiding, "fullness, denial of medical severity of ⇓ weight), but no AN-related obsessions
7. Weight 38 kg, height 1.70 m, BMI 13.1 kg/m^2: ⇓ Natrium = 132 mmol/l; ⇓ albumin = 2.4 g/dl ⇓; ⇑ liver enzymes, rhabdomyolysis (⇑creatine phosphokinase (CPK) 600 u/L)	Hospitalized in internal medicine department for 3 weeks; refeeding syndrome (⇓ phosphor); nasogastric tube feeding; patient and family refusing psychiatric consultation and psychiatric hospitalization: 1. would intervene with children's marriage prospects; 2. because problem is considered physical	Fluoxetine 60 mg/day, Olanzapine 7.5 mg/day	Discharged himself against medical advice; at discharge ⇓ Natrium, normal urea and CPK; lost to follow-up	OCD; avoiding food because of 1. "classical" handwashing compulsions—food is dirty, contaminated; 2. religious-related handwashing required in Judaism before meals, but here overly prolonged and compulsive

DSM 5-TR: Diagnostic and Statistical Manual for the Diagnosis of Mental Disorders, fifth edition text revised (19); AN, anorexia nervosa; BMI, body mass index; BPM, beats per minutes; ED, eating disorder; HR, heart rate; ICU, intensive care unit, OCD, obsessive–compulsive disorder; *according to the National Center for Health Statistics [see Centers for Disease Control and Prevention's Year 2000 Growth Charts, adapted for Israeli children and adolescents (20)].

Religious Jews adhere every day to the strict codes of observance, here to those related to the manner of praying and allowed/forbidden food, but with no disturbance in their daily life. By contrast, in the individuals with OCD in the present case series, the interpretation of the Jewish regulations has been highly overvalued, leading to frank misperception of reality (e.g., you cannot stop praying to eat, and no food is Kosher enough), leading to severe deterioration in functioning and health.

To perform their payer with what they consider the required devotion, our OCD patients have prayed for many more hours than required, in some cases to metaphorically "clean their head" from forbidden thoughts. Similarly, an earlier case series described weight loss resulting from religious zeal in three young Jewish Ultra-Orthodox males. These individuals "indicated that they had restricted their diet in a misguided attempt not to "indulge" themselves, as a misinterpretation of what they had been taught in their studies in the Yeshivas" (30).

Three other factors seem of importance. Similar to the 3 adolescents with AN-R, there was no evidence of psychiatric family history also in the patients with OCD (although this could have been hidden because of stigma-related issues, specifically relevant in Ultra-Orthodox communities). Second, the three adults with OCD did not

acknowledge the psychiatric origin of their weight loss or the severity of their medical condition, did not cooperate with their treatment, and actually discharged themselves against medical advice, while mostly still being underweight. Third, they did not respond well to a combination of SSRIs and 2nd-gereration antipsychotic medications.

Summary

The present case series described the occurrence of psychologically related food restriction leading to severe weight loss with physical deterioration requiring hospitalization in Jewish Israeli Ultra-Orthodox males. Two subsets of this population were described, 3 adolescents with AN-R and one adolescent and three adults with atypical restricting-type ED (19), resulting from severe OCD, laden with highly religious content. Although the lack of psychiatric family history, the presenting ED symptoms, and the severity of the physical state were similar, the two groups were highly different. In the adolescent group, the severity of the AN symptoms was related to severe, ritualistic, highly structured and exaggerated sports activity, geared for muscularity. The message to bring home here is the need to increase the knowledge about the possible, although rare, occurrence of AN in young Ultra-Orthodox males, who leave their home to a Yeshiva for the first time.

In the mostly adult male group with severe OCD, the loss of weight has not resulted from core AN-related concerns. Rather, their ritualistic, dysfunctional religion-laden obsessionality has been embedded in their life for a prolonged period. This might explain their lack of awareness and acknowledgment of the psychiatric origin of their weight loss, and their resistance to change and to treatment. Nonetheless, it can be argued that the lack of insight of these patients into the seriousness of their illness, alongside their inability to gain weight before inpatient treatment can be potentially associated with a DSM 5 (19) diagnosis of AN.

The message to bring home here is that severe OCD should be considered in prolonged food restriction and weight loss in Ultra-Orthodox adult males. Last, this study suggests that, similarly to findings elsewhere (12, 13), the influence of religiosity on eating-related issues in Ultra-Orthodox Jewish Israeli men is highly multifaceted, contradicting the premise that greater religiosity is necessarily associated with less eating-related pathology.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed 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 publish the manuscript was provided by the participants and their legal guardians/next of kin as required.

Author contributions

SL, EH, DSe, YL, and DSt contributed the different case reports. RA, OA, SO, MS, MU, and AE-L provided important data about the different cases. DSt and EW were responsible for the organization and writing of the article. All authors contributed to the conception and design of the study, read all drafts, provided useful comments, and approved the final draft of this article.

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.

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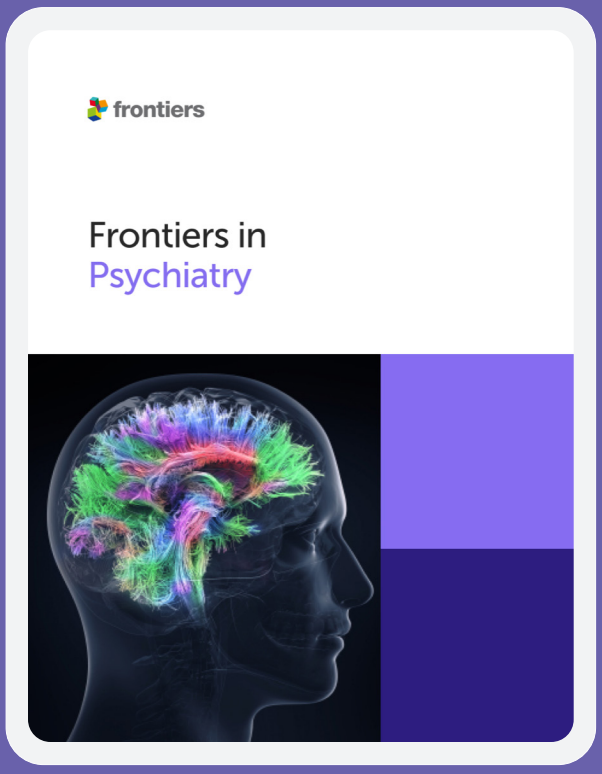

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