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Addictions and eating behavior

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Addictions and eating behavior

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Editorial: Addictions and eating behavior

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dopamine, food addiction, feeding, reward, eating behavior

Editorial on the Research Topic
Addictions and eating behavior

Feeding is a complex process that involves multiple brain regions responsible for homeostasis, learning, memory, emotion, and reward (1, 2). Consequently, dysregulation of these areas can lead to hyperphagia, an increased preference for obesogenic foods, and, in the short or medium term, the development of overweight and obesity.

In this Research Topic of *Frontiers in Nutrition*, "*Addictions and Eating Behavior*", we have published nine original articles authored by 59 researchers from Chile, China, Spain, Finland, Israel, Italy, and the United States, with more than 14,000 views and downloads. These articles provide novel insights into neurobiological mechanisms, genetic polymorphisms, and environmental factors that contribute to changes in eating behaviors, such as increased preference for obesogenic foods.

A primary focus of the published articles is the relationship between stress, anxiety, and eating behavior, ranging from appetite suppression to overeating. In this context, Peleg et al. demonstrate that emotional regulation, stress management, and the development of healthy coping mechanisms reduce the risk of binge eating, which otherwise leads to compulsive food consumption and, in the long term, increases the likelihood of developing overweight and obesity. The study by Marchena-Giráldez et al. highlights how emotional eating—the tendency to eat in response to both negative and positive emotions—is associated with excessive Internet use and the development of anxiety and stress-related traits, which may further promote overweight and obesity. Additionally, the work of Tan et al. identifies a positive correlation between social support and healthy eating behaviors in children and adolescents, independent of body mass index (BMI). This suggests that social support plays a crucial role in mitigating the risk of obesity and unhealthy eating behaviors.

A second key topic explored in this Research Topic concerns food addiction and its association with the compulsive consumption of high-fat, high-sugar foods, which activate the brain's reward system in a manner similar to drugs of abuse. In this context, Mastrobattista et al. investigate the relationship between food addiction and psychological risk factors such as impulsivity, social anxiety, and depressive disorder. Their findings suggest that public health initiatives should consider food addiction as a contributing factor to the development of chronic non-communicable diseases. Furthermore, Palacio et al. demonstrate that patients undergoing weight loss treatment exhibit a positive correlation between food addiction and higher body weight, waist circumference, and BMI. Friling et al. report that dietary supplementation with wild green oat extract reduces stress levels associated with smoking cessation, potentially mitigating the hyperphagia commonly observed during tobacco withdrawal.

A third key area covered in the accepted articles focuses on genetics, specifically how genetic variants influence obesity risk by affecting the regulation of hunger-satiety cycles, preference for obesogenic foods, and macronutrient metabolism. In this context, Dabin Yeum et al. show that the risk allele of the FTO gene (associated with fat mass and obesity) at locus 16q12.2 predisposes individuals to a heightened hedonic response to food, which is linked to dysfunction in homeostatic feeding regulation areas such as the lateral hypothalamus. The work of Luengo et al. provides evidence that genotypes associated with reduced dopaminergic signaling are linked to uncontrolled emotional eating, potentially leading to overweight and obesity. Finally, Sayers et al. demonstrate at a fundamental level that Pituitary Adenylate Cyclase-Activating Polypeptide (PACAP) neurons in the ventromedial hypothalamus can inhibit dopaminergic neurons in the ventral tegmental area, thereby reducing impulsive food intake. These findings offer new perspectives for the treatment of obesity and food addiction.

This Research Topic has significantly contributed to advancing scientific knowledge on the pathophysiological mechanisms underlying dysregulated eating behaviors and their role in the development of chronic non-communicable diseases associated with high BMI. We look forward to further exploring both pathophysiological and therapeutic aspects of addictions and eating behavior in future research endeavors.

Author contributions

RS-Z: Writing – original draft, Writing – review & editing.

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Psychosocial risk and protective factors for youth problem behavior are associated with food addiction in the Generation Z

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Objective: Food Addiction (FA) and other well-known risk behavior as substance misuse tend to co-occur and may share similar risk and protective factors. The aim of this study was to assess the association between the diagnosis/severity of FA and psychosocial domains typically related to risk behavior syndrome in a large, nationally representative community sample of Generation Z underage Italian students.

Method: The sample consisted of 8,755 students (3,623 from middle schools, 5,132 from high schools). A short version of the Yale Food Addiction Scale 2.0 was administered to evaluate FA. Risk and protective factors related to demographic, personality, behavior, and family variables were examined. Stepwise multivariate logistic and linear regressions were conducted.

Results: The prevalence of FA was 30.8%. Female gender, social anxiety and depression symptoms, social withdrawal risk, Internet gaming disorder, social media addiction, current substance use, social challenge engagement and experienced doxing boosted the chance of FA diagnosis, whereas eating fruit and vegetables, playing competitive sports and an average sleep duration of 7–8 h per night reduced these odds. FA severity was significantly and positively associated with trait impulsiveness, social anxiety and depressive symptoms, risk of social withdrawal, recent substance use, social media, and gaming addiction, doxing suffered and risky social challenges participation. Negative associations between the severity of FA and fruit and vegetable diet habits were found.

Conclusion: Our findings confirm that FA is widespread among Italian adolescents. The associations between the diagnosis and severity of FA and psychosocial risk factors for health, including, addictive and deviant behaviors related to digital misuse, suggest its belonging to the risk behavior constellation. Health promotion schemes based on a multicomponent strategy of intervention should consider the inclusion of FA and its psychosocial correlates.

KEYWORDS

food addiction, psychosocial risk and protective factors, behavioral addiction, adolescence, Generation Z

1 Introduction

The increased availability and intake of hyper-palatable foods in the last decades (1) has raised important concerns since it is considered a relevant contributor to the spreading risk of obesity and overweight in both children and adults (2, 3). Indeed, large cohort longitudinal studies have found high daily consumption of ultra-processed foods to be associated with greater boosts overtime on indicators of child and adolescent adiposity (4).

Growing evidence has consistently related this escalation in consumption with the potential addictive role of these foods (5, 6), suggesting that food reward-related ability could promote not only this raising trend but also trigger addiction symptoms in a similar manner to substance use disorders (SUD) (7–9). For instance, one of the most frequently referred antecedents of binge eating episodes is craving for sweets (10) or carbohydrates (11). Craving is a SUD core feature considered a strong predictor of drug use (12). Interestingly, recent neuroimaging studies have revealed common neural underpinnings for craving induced by food and drug cues (13).

The Yale Food Addiction Scale (YFAS) (14) is a self-reported scale developed to assess addiction signs to ultra-processed foods by adapting the Diagnostic and Statistical Manual of Mental Disorders IV (DSM-IV) criteria for substance dependence to "Food Addiction" (FA). Lately, this version has been updated into the YFAS 2.0 (15), which reflects the oncological changes for SUDs underwent in the DSM-5. Systematic reviews of the YFAS studies on adults have reported estimated prevalence of FA ranging from 0 to 25.7% in nonclinical samples and from 6.7% up to 100% in some eating disorder clinical cohorts (16).

This phenomenon also seems to be widespread among children and adolescents. In fact, a recent meta-analysis of the studies assessing FA in this populations reported an average prevalence rate of 12% for community samples and 19% for overweight and obese individuals (17). These rates on adolescence may be particularly troubling since, in this neurodevelopmental phase, the strong influence of motivational substrates is coupled with the immature and not yet fully effective inhibitory control system (18). This could thus determine a heightened vulnerability among youths toward the emergence of psychosocial problems and health risky behaviors as addictive substance use (19) or delinquency (20). Substantial evidence supports the key notion of the adolescent problem behavior model (21) that youth risk behaviors tend to co-occur (22). It is well-known that the juvenile involvement of risk behaviors like aggression is strongly associated with the engagement in other risk behaviors as substance use or crime (23). Moreover, high levels of co-occurrence between risky behaviors in adolescence have been shown to predict negative outcomes in terms of social adjustment in the adulthood (24). Results indicate that problematic food and substance consumption often occur together (25) and symptoms of FA are positively correlated with smoking, alcohol, and cannabis use among adolescents (26). This suggests that underage FA could be part of the constellation or syndrome of risk behavior (27), and therefore, shares similar risk and protective factors. Within this framework, several psychosocial domains are relevant to the prediction of adolescents problematic life-styles (28, 29): among others, sociodemographic, family, personality and behavioral risk factors. Sociodemographic factors as lower socioeconomic status (SES) have been shown to be associated with externalizing problems (withdrawn and aggressive behavior) (30). Family variables as the quality of the father-child relationship have been found to be a predictor of the risk of engagement in multiple teen risky behaviors (31). Key personality features as impulsivity, negative emotionality, avoidant tendencies, and other personality risk factors reflecting psychosocial unconventionality as low academic achievement have been linked to a higher likelihood of involvement in multiple adolescent problem behaviors (32, 33). Regarding the behavioral domain, recently, the adolescent risk behaviors related to the overuse of the Information and communication technologies (ICTs) are being a matter of growing concern because of the particularly increasing usage, especially among adolescent of Generation Z (born from 1997 through 2012), since the beginning of the COVID-19 pandemic (34, 35). In this generation, also known as "digital natives" because of their early immersion in socio-digital technologies (36), ICTs misuse and online deviant behaviors have been found to be associated with offline teen risky behaviors as drug use or sexual risk behaviors (37–40).

Alongside with behavioral risk factor, the social-psychological framework has considered the involvement in conventional and healthy behavior as serving to attenuate the impact and effects of risk factors (41). Indeed, health behaviors as balanced diet or regular sleep habits and conventional activities as the participation in sports have been shown to be protective against multiple risk-taking behavior in Generation Z adolescents (42, 43). Therefore, this risk and protective factors approach provides an explanatory schema for studying changes in multiple risk behavior among youth and vulnerable groups (27) that could be useful to develop effective prevention and treatment strategies. Furthermore, this idea underlies the application of this psychosocial approach to the study of new variants of adolescent risk behaviors among digital natives, such as problematic cell phone use (44), social networking site usage (37) or excessive videogaming (45).

Hence, given the association of FA with other well-known risk behaviors such as substance abuse among youth and the commonalities from a clinical and neurobiological standpoint, it could be helpful to test whether and to what extent, these problematic behaviors share similar risk and protective factors. Thus, the aim of the present research was to assess the association between the diagnosis/severity of FA and psychosocial domains widely evinced as related to behavioral health risk factors (29) in a large and nationally representative community sample of Italian underage students. An additional purpose was to determine the prevalence of this phenomenon (i.e., FA) among adolescents from Italy. Our hypothesis is that typical psychosocial risk and protective factors of the risk behavior syndrome will fulfill the same function in predicting the prevalence and severity of FA.

2 Materials and methods

2.1 Participants

A national survey called "Generation Z" and aimed to assess behavioral addiction and other mental health problems among 11–17-year-old Italian students was conducted by the Italian National

Institute of Health during the 2022 academic year at middle and high schools allocated throughout the Italian territory.

A 3-stage probability-proportional-to-size (PPS) sampling procedure was adopted to ensure the best possible representativeness of the population under study (i.e., 11–17-year-old Italian students). For stratification, the municipalities were considered as the first stage unit, the schools as the second stage unit and the school classes as the third stage unit. At the first stage, the municipalities (45 for middle schools and 55 for high schools) were selected according to a stratification level by geographic macro-area (North West, North East, Central Italy, South and Islands) and by municipality size (200,000 inhabitants and more, between 100,000 and 199,999 inhabitants and less than 100,000 inhabitants). Within each first-stage stratum, at the second stage middle schools (71) were selected with a probability proportional to the number of students enrolled; high schools (82) were stratified by type of school (high schools, vocational schools, technical institutes and art institutes) and selected with a probability proportional to the number of students enrolled. At the third stage, classes were selected with probability proportional to the number of students enrolled in the class.

To warrant a sample size of at least 4,000 questionnaires for each age range (i.e., 11–13 and 14–17-year-old) and hypothesizing a participation rate of between 15 and 20%, 676 middle and high schools across the national territory were invited to take part on a voluntary basis. The participation in the study was 22.7% on the part of middle schools (21.1% in North West, 23.9% in North East, 26.2% in Central Italy, 21.4% in the South, and 20.0% in the Islands) and 22.6% on the part of high schools (23.3% in North West, 26.8% in North East, 18.5% in Central Italy, 21.1% in the South, and 22.6% in the Islands). A total of 10,181 questionnaires were collected (4,140 and 6,041 in middle and high schools respectively), of which 1,426 (14.0%) were discarded due to respondents outside the target age (under 11 years or over 17 years), incomplete responses, and questionnaires filled out twice due to technical connection problems.

The final sample was therefore composed of 8,755 students (mean age = 14.03 years, SD = 1.98), 3,623 (41.4%) of which were attending middle school (mean age = 11.99 years, SD = 0.81) and 5,132 (58.6%) were high school pupils (mean age = 15.48 years, SD = 1.08).

Females (4,187, 47.8%) and males (4,291, 49.0%) were equally distributed throughout the sample. A small proportion of students preferred not to report their gender (277, 3.2%). Most of the participants (7,535, 86.1%) reported being of Italian nationality.

Written informed consent was required from all enrolled students and their parents. The collection and processing of the data was carried out in accordance with the national privacy regulations to ensure anonymity. The study was approved by the National Ethical Committee of the Italian National Institute of Health (prot. PRE BIO CE 0010655 of 22/03/2022). All procedures were in accordance with the 1964 Helsinki declaration and its later amendments.

2.2 Instruments

All students were presented with a questionnaire which assessed FA and the main domains of risk factors associated with the most common health risk behaviors in adolescents (29). The survey was administered electronically, in the classroom during class time, and in the presence of a trained experimenter who was instructed to assist students if necessary.

2.2.1 Food addiction assessment: the short form of Yale food addiction scale 2.0 (S-YFAS 2.0)

The S-YFAS 2.0[1] is short form of the Italian version of the YFAS 2.0 (46) validated on large sample of middle and high school Italian students, proving to be an efficient and sensitive measurement of FA. The scale consists of 24 items, scored on an 8-point Likert scale (i.e., from 0 = "*never*" to 7 = "*every day*"), accounting for 11 symptoms of addiction-like eating behavior plus the perceived level of distress derived from them, reported over 1-year period. No sum score is calculated from the single items but each criteria (i.e., symptom and distress criteria) is considered present when at least one of the two questions concerning it reaches its own specific threshold [established by Receiver Operator Characteristic (ROC) curves; (15)]. Like the long version, the S-YFAS 2.0 allows two scoring modalities: a symptom score reflecting the number of symptom criteria that are met and ranging from 0 to 11; and a dichotomous diagnosis which is defined as the endorsement of two or more symptom criteria in addition to the criterion of clinically significant distress.

2.2.2 Sociodemographic risk factors

Demographic variables comprised age, gender, nationality, and region of residence, which was employed to compute the Subnational Human Development Index [SHDI; (47)] according to the data retrieved from the Subnational HDI Database.[2] The SHDI, used here as socioeconomic status proxy, is an average measure at the subnational level of the education, health, and standard of living indexes whose score ranges from 0 to 1. Higher values indicate greater human development (48). To facilitate data interpretation, the SHDI value was categorized based on the percentile distribution provided by the aforementioned database as follows: ≤ 85th percentile/90th percentile/ 95th percentile.

2.2.3 Family risk factors

The quality of the familiar relationship was assessed by means of the following question with dichotomous response: *How easy is it for you to talk to your mother and/or father about things that really worry you?* ("Easy"; "Difficult or Do not have or see them"). We focused on the assessment of the parent-adolescent communication easiness because it has been associated with high parent–child relationship satisfaction (49), which is deemed to fulfill the role of protective factors from problem behaviors in the Jessor et al.'s theoretical framework (27).

2.2.4 Personality risk factors

As a measure of trait impulsiveness, the Italian version of the Barratt Impulsiveness Scale (BIS-15) (50), was administered. This 15-item self-report scale is an abbreviated version of the Italian BIS–11 (51). This brief variant has not been specifically validated in the Italian adolescent population, although the 30-item version from which it is derived has been adapted to this population (52). As recommended

1 Anselmi P, Colledani D, Monacis L, Gómez Pérez LJ, Genetti B, Andreotti A, et al. Development and Validation of a Short Form of the Yale Food Addiction Scale 2.0. Manuscript Submitted publication. 2023.

2 https://globaldatalab.org/shdi/, version v7.0.

(53), we considered the BIS-15 score as continuous with higher scores indicating higher impulsivity.

The negative emotionality and avoidance factors were assessed throughout the following questionnaires:

- Severity Measure for Social Anxiety Disorder (Social Phobia)— Child Age 11–17 (SAD-D; 54): A 10-item measure evaluating the DSM-5 criteria for social anxiety disorder (54) during the past 7 days and providing a 5-point severity level (i.e., 0 = None/1 = Mild/2 = Moderate/ 3 = Severe/ 4 = Very severe).
- Severity Measure for Depression, Child Age 11 to 17 (PHQ-9 modified for Adolescents [PHQ-A], Adapted) (55): A 9-item measure (score range: 0–27) assessing the severity of clinically significant depressive symptoms during the past week as follows: 0–4 = None, 5–9 = Mild, 10–14 = Moderate, 15–19 = Moderately severe, and 20–27 = Severe.
  Although these two emerging APA measures (i.e., the SAD-D and the PHQ-A) have been proposed as useful tools for research and clinical evaluation (54), and some evidence of validity has emerged in adolescent samples (56, 57), they have not been specifically validated in Italian youths.

- Hikikomori Risk Inventory-15 [HRI-15; (58)]: This is a short version of the HRI-24 (59), measuring the typical feelings and behaviors related to social withdrawal on adolescents. A total score (range: 15–75) representing the Hikikomori risk score can be computed and an empirical cut-off score of 37 has been defined for identifying at-risk individuals.

For the analytical and clinical purposes of simplifying as much as possible the interpretation and classification of risk factors (60), the above variables were dichotomized as follows: Social Anxiety Disorder (i.e., SAD-D: None vs. Mild/Moderate/Severe/Very Severe) and Depression Disorder (i.e., PHQ-A: None vs. Mild/Moderate/Moderately severe /Severe). Moreover, a participant with a score of 37 or more in the HRI-15 was considered as at-risk of social withdrawal (58).

Psychosocial unconventionality [i.e., Non-compliance to conventional behavior standards; (58)] was captured in relation to the school institution by assessing the last year academic performance throughout the following question: *How was your academic performance last year?* The following three response options were available: Failed or lower than the class average, on average or higher than the class average, I do not remember.

2.2.5 Behavioral risk factors

Factors associated with teen unhealthy lifestyles (28), such as substance use and other addictions or forms of deviant behavior associated with ICTs use, were considered within the behavioral risk factor domain. Likewise, measures related to more conventional activities, as potential protective factors of risk-taking behaviors (61), were included.

Substance consumption was ascertained by asking participants whether they had consumed alcohol, tobacco, or energy drinks in the last month.

Addictive behaviors related to digital technology were investigated through the following self-reported scales:

- Italian version of Bergen Social Media Addiction Scale [BSMAS; (62)]: A 6-item scale (score range: 6–30) assessing core addiction symptoms related to past year social media use. Recent research suggests a total score of 24 as the optimal clinical cut-off score (63). Therefore, this score was considered as discriminant of Social Media Addiction (SMA) in our study.
- Internet Gaming Disorder scale–short-form [IGDS9-SF; (64)]: A 9-item scale (score range: 9–45) corresponding to the nine core criteria of DSM-5 for Internet Gaming Disorder (IGD) (54) assessed over a 12-month period. In this study, the empirical cut-off point of 21 defined by Monacis et al. (64) was used to establish this diagnosis in our sample.

The main forms of ICTs related deviant behavior contemplated in this survey were:

- Doxing [i.e., internet dissemination without consent of other's personal and sensitive data; (62)] was checked by asking participants the following queries: *Have you ever shared photos, images, personal data of someone without their consent to make fun of them?* (Yes/No) and *Has anyone ever shared photos, images, or personal data without your consent to make fun of you (excluding your family members)?* (Yes/No).
- Online Self-Harm Challenge engagement [i.e., risk-taking practices mediated by digital sociability; (63)] was investigated through an *ad hoc* dichotomous question about respondents lifetime participation in this kind of challenges (i.e., *Have you ever participated in dangerous online social challenges like "the Skullbreaker challenge" or similar?* Yes/No).

The assessment of conventional lifestyle was based on the following question:

- Dietary habits: *How many times a week do you usually eat fruit or vegetables?* (Never /Not every week/Weekly).
- Sports habits: *Do you play competitive sports?* (Yes/No).
- Volunteering: *Do you often go to parish/ volunteering/ scouting groups?* (Yes/No)
- Sleep habits:
  - Sleep duration: *How many hours did you sleep on average at night during the last month?* (6 h or less/7–8 h/9–10 h/More than 10 h).
  - Sleep latency: *During the last month, how long did it usually take you to fall asleep each night?* (Less than 15 min/15–45 min/ More than 45 min).

2.3 Data analysis

The FA diagnosis, the S-YFAS 2.0 individual symptoms prevalence, and the mean symptom score were calculated for the total sample.

The primary outcomes of the present study were (1) the FA diagnosis and (2) the symptom score as defined above. The latter dependent variable was selected for being considered as a sensitive indicator of FA severity in non-clinical adolescent populations (65).

Regarding the first primary outcome, a preliminary bivariate analysis was conducted between the FA diagnosis variable and each exposure of the above-described domains. Specifically, concerning the symptom score, the Kolmogorov–Smirnov normality test was performed (for each exposure factors), and the Skewness and Kurtosis indices were verified (|Skewness|, |Kurtosis| > 1). The differences among groups were analyzed via nonparametric tests, namely Mann–Whitney test (2 groups) and Kruskal-Wallis test (3 groups or more). Then, a multivariate logistic regression was used to analyze the association between the outcome variable (i.e., FA diagnosis) and the independent variables which were found to be associated with it in the bivariate model. All these variables were entered as covariates one at a time using a forward stepwise approach. Variables were retained in the model if the *p*-value of the regression coefficient was less than 0.05. Subsequently, all variables were entered as covariates using a backward stepwise approach and removed from the model if the *p* value of the regression coefficient was greater than 0.10. The model with the best goodness of fit (i.e., Cox and Snell pseudo R2) between the two was selected. Odds Ratio (OR) was calculated as an effect size (ES) index of the association between every exposure and the outcome. For the ORs larger than 1, values of 1.22, 1.86, and 3.00 were considered small, medium, and large effect sizes; for the ORs lower than 1, values 0.82, 0.54, and 0.33 were pondered small, medium, and large effect sizes (66).

Thereafter, for examining the psychosocial factors associated with the severity of FA, two multivariate linear regressions, one with the total sample and the other with the subsample of participants with FA diagnosis, were applied with the symptom score as dependent variable and all the variables covering the psychosocial domain mentioned before as covariates. The same back and forward stepwise procedure as described for the multivariate logistic regression model was adopted, except for the model selection method which was based on the higher coefficient of determination (R^2). Cohen's f^2 was calculated for each independent variable in each model as a local ES measure. In line with Cohen's (67) guidelines, $f^2 \geq 0.02$, $f^2 \geq 0.15$, and $f^2 \geq 0.35$ were considered small, medium, and large effect sizes, respectively.

The statistical analyses were performed using IBM SPSS Statistics 20.

3 Results

3.1 Descriptive statistics

Prevalence rates of each FA symptoms, of the FA diagnosis, the total sample mean symptom score and the results of the bivariate analysis are depicted in Supplementary Table 1. It is worth noting that the prevalence of FA was 30.8%, with a mean symptom score of 1.5 (SD = 2.4) for the total sample and of 4.3 (SD = 2.6) for the FA diagnosed subsample. Concerning the individual symptoms of FA, "Great deal of time spent" was the most frequent (16.9%). In relation to sociodemographic domain, female gender (40.0% vs. 21.3% of male gender) was more often associated with the FA diagnosis. Regarding family domain, participants who reported difficulties in talking with parents (40.4% vs. 22.3% of those referring parent's easy talking) more frequently met the FA diagnostic criteria. Within the personality domain, individuals at risk of social withdrawal (76.9%) were much more classified as food addicts than those who were not at risk (29.9%), also reporting high mean symptom scores (mean = 4.5, SD = 3.5). In the behavioral domain, the covariate most associated with increased prevalence of FA was SMA, with a FA diagnosis percentage more than double among participants with SMA (74.6%) compared to those not affected (29.5%). Furthermore, the mean symptom score was more than three times higher in the former (mean = 4.7, SD = 3.7) than in the latter (mean = 1.4, SD = 2.3).

3.2 Associations between FA diagnosis and psychosocial risk factors

Figure 1 shows the results of the multivariate logistic regression model. As regard to sociodemographic factors, female gender (OR = 2.03, 95% CI [1.80, 2.29]) and preference of not reporting gender (OR = 1.46, 95% CI [1.09, 1.95]) raised the odds of FA diagnosis, whereas a 95th SHDI percentile (OR 0.79, 95% CI [0.68, 0.92]) and a 90th SHDI percentile (OR = 0.82, 95% CI [0.73, 0.93]) lowered this likelihood. ESs were medium for female gender, small to medium for the preference of not reporting gender, and small for SHDI categories. As to familiar relationship quality, child's difficult talking with parents (OR = 1.12, 95% CI [1.00, 1.25]) increased the probability of meeting the diagnostic criteria for FA, although the ES for this significant association was small. Respecting to personality features, the presence of social anxiety (OR 1.75, 95% CI [1.52, 2.01]) and depression symptomatology (OR = 2.48, 95% CI [2.14, 2.87]), the risk of social withdrawal (OR = 2.83, 95% CI [1.91, 4.20]), a higher score in a trait impulsiveness indicator (OR = 1.05, 95% CI [1.04, 1.06]) and a last year academic performance below the average (OR = 1.23, 95% CI [1.05, 1.45]) or not remembered (OR = 1.36, 95% CI [1.10, 1.67]) incremented the odds of FA. The ESs of all these associations were small except for social anxiety, depression, and social withdrawal, which were respectively, small to medium, and medium to large. In reference to the behavioral domain, suffering from IGD (OR = 2.59, 95% CI [2.22, 3.03]) and from SMA (OR = 1.96, 95% CI [1.42, 2.72]), last month substance consuming (OR = 1.43, 95% CI [1.27, 1.61]), online self-harm challenge engagement (OR = 1.51, 95% CI [1.22, 1.86]), and being victim of doxing (OR = 1.34, 95% CI [1.19, 1.50]) boost the chance of FA. Instead, eating fruit and vegetables weekly (OR = 0.57, 95% CI [0.45, 0.72]) or even not every week (OR = 0.60, 95% CI [0.46, 0.78]), playing competitive sports (OR = 0.87, 95% CI [0.78, 0.97]), and a monthly average sleep duration of 7–8 h per night (OR = 0.87, 95% CI [0.77, 0.97]) reduced the odds of being classified as addicted to food. The ESs were small for the variables of doxing, competitive sports playing and sleep duration, small to medium for last month substance use, online self-harm challenge engagement and for the frequency of eating fruit/vegetables, and medium to large for the IGD and SMA exposures.

3.3 Associations between S-YFAS 2.0 symptom score and psychosocial risk factors in the total sample

The stepwise multivariate linear regression analysis revealed that S-YFAS 2.0 symptom count was significantly and positively associated with female and the preference of not reporting gender ($\beta = 0.51$, 95% CI [0.42, 0.59]), social anxiety ($\beta = 0.41$, 95% CI [0.30, 0.52]) and

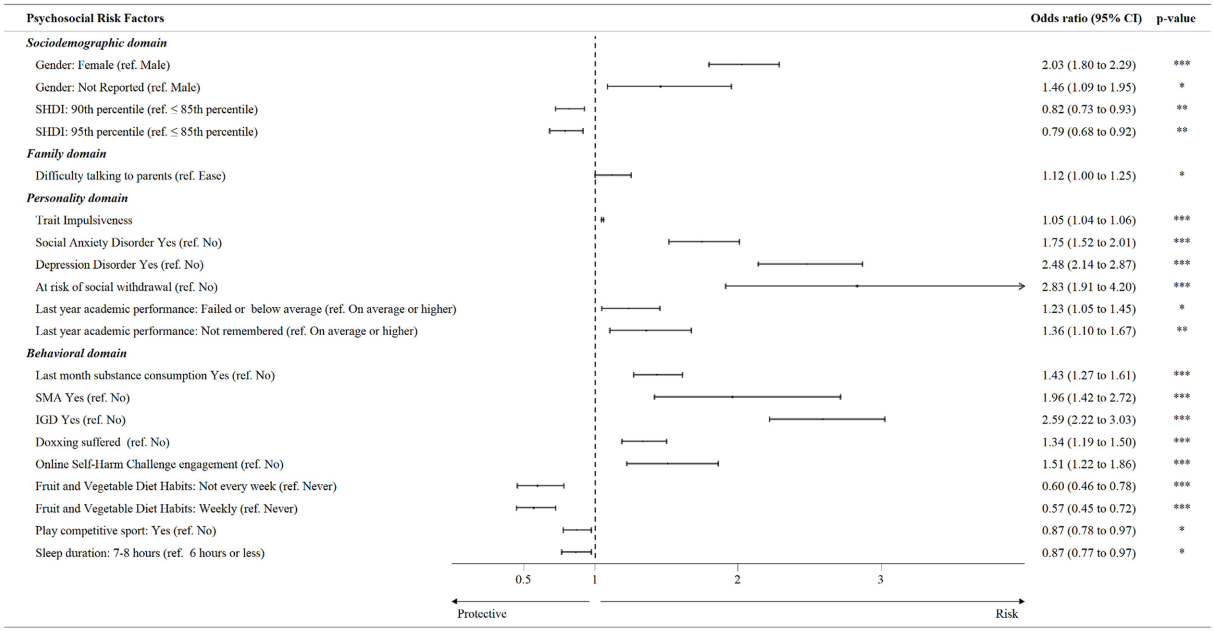

FIGURE 1
Multivariate logistic regression analysis of associations between Food Addiction diagnosis and psychosocial risk factors.

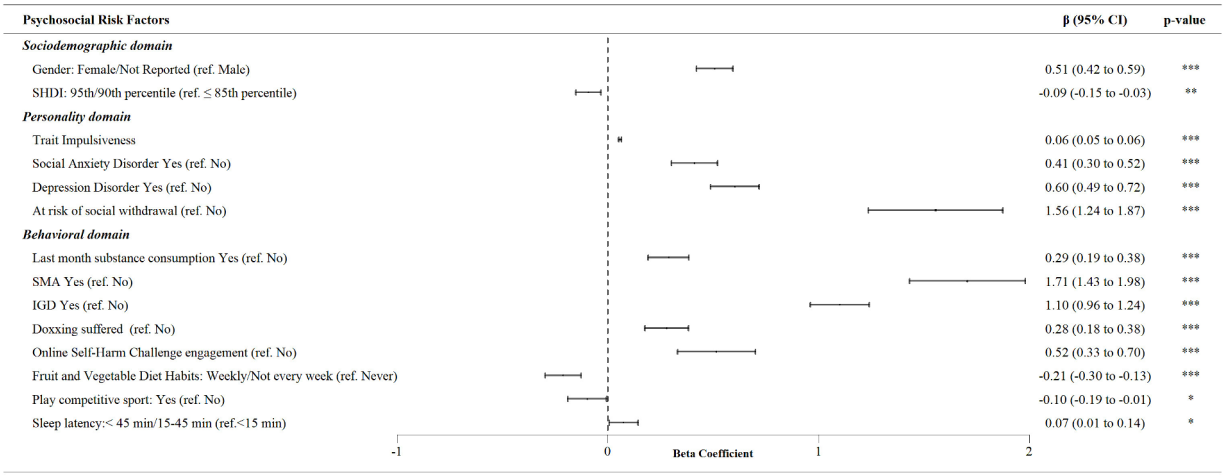

FIGURE 2
Multivariate linear regression analysis of associations between S-YFAS 2.0 symptom score and psychosocial risk factors in the total sample.

depression disorder symptoms ($\beta = 0.60$, 95% CI [0.49, 0.72]), risk of social withdrawal ($\beta = 1.56$, 95% CI [1.24, 1.87]), trait impulsiveness index higher scores ($\beta = 0.06$, 95% CI = 0.05–0.06), last month substance use ($\beta = 0.29$, 95% CI [0.19, 0.38]), presence of SMA ($\beta = 1.71$, 95% CI [1.43, 1.98]) and IGD ($\beta = 1.10$, 95% CI [0.96, 1.24]), doxing suffered ($\beta = 0.28$, 95% CI [0.18, 0.38]), participation in an online self-harm challenge ($\beta = 0.52$, 95% CI [0.33, 0.70]), and an elevated night sleep latency in the last month ($\beta = 0.07$, 95% CI [0.01, 0.14]; Figure 2). Negative and significant associations were found, instead, between FA symptom score and high SHDI level ($\beta = -0.09$, 95% CI [−0.15, −0.52]), weekly or quasi-weekly fruit and vegetables intake ($\beta = -0.21$, 95% CI [−0.30, −0.13]), and the practice of competitive sports ($\beta = -0.10$, 95% CI [−0.19, −0.01]; Figure 2). However, the ESs for these associations were small ($f^2 \geq 0.02$).

3.4 Associations between S-YFAS 2.0 symptom score and psychosocial risk factors in the FA diagnosed subsample

When the psychosocial factors associated with the count of FA symptoms in the subsample of participants with a FA diagnosis were considered, the stepwise multivariate linear regression (Figure 3) found gender (i.e., female and the preference of not reporting gender

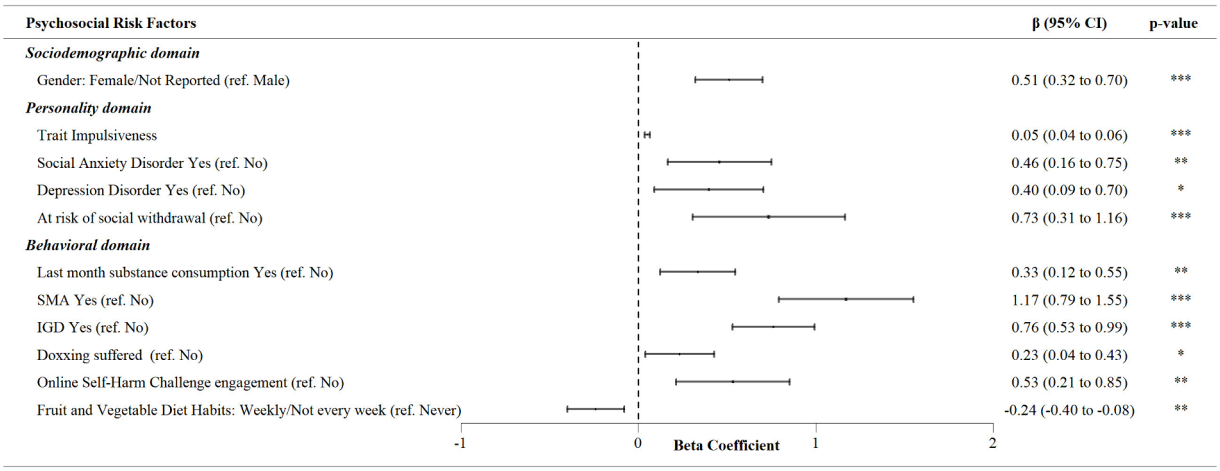

FIGURE 3
Multivariate linear regression analysis of associations between S-YFAS 2.0 symptom score and psychosocial risk factors in the subsample with Food Addiction diagnosis.

versus male gender; $\beta = 0.51$, 95% CI [0.32, 0.70]), the trait impulsiveness index score ($\beta = 0.05$, 95% CI [0.04, 0.06]), social anxiety ($\beta = 0.46$, 95% CI [0.16, 0.75]) and depressive symptoms ($\beta = 0.40$, 95% CI [0.09, 0.70]), risk of social withdrawal ($\beta = 0.73$, 95% CI [0.31, 1.16]), substance use in the previous month ($\beta = 0.33$, 95% CI [0.12, 0.55]), SMA ($\beta = 1.17$, 95% CI [0.79, 1.55]) and IGD diagnosis ($\beta = 0.76$, 95% CI [0.53, 0.99]), being a doxing victim ($\beta = 0.23$, 95% CI [0.04, 0.43]) and self-harm social challenge participation ($\beta = 0.53$, 95% CI [0.21, 0.85]) as significant and positive associated factors of FA disorder severity. Only the fruit and vegetable diet habits (i.e., weekly, or quasi-weekly versus never; $\beta = -0.24$, 95% CI [−0.40, −0.08]) were observed to be negatively and significantly associated with the severity of this addiction (i.e., higher symptom count on S-YFAS 2.0). It is important to note that the ESs calculated for these associations were small ($f^2 \geq 0.02$).

4 Discussion

The study results provide critical information on the prevalence of FA in the largest and nationally representative sample, to our knowledge, of underage students from a European country. Similarly, this research assessed the association between the diagnosis and severity of FA and psychosocial domains related to the risk behavior syndrome (28), considering among these, those particularly raised among Generation Z adolescents during the COVID-19 pandemic period such as addictive and deviant behaviors associated with ICTs (34, 35).

The prevalence of FA in our sample was particularly high (30.8%). As far as we know, this prevalence ranks among the highest reported on children and adolescent samples (17). In a recent meta-analysis (17) analyzing 22 studies and involving a total of 6,996 adolescents, the estimated prevalence of FA was 15% (95% CI [11, 19]) for all samples, 12% (95% CI [8, 17]) for community samples, and 19% (95% CI [14, 26]) for overweight/obese samples. In Italy, in particular, prevalence studies have recently been carried out only in small clinical samples of adolescents with eating disorders yielding rates between 49.4% (68) and 51.9% (69). Our results suggest prevalence rates higher than those above reported on average for the clinical population, which might be due to differences in diagnostic threshold criteria. The studies analyzed in this systematic review used the YFAS, which has a more restrictive diagnostic boundary than the YFAS 2.0 used in our study (70). However, in our study, 17% of food-addicted individuals exhibit moderate (meeting at least 4 criteria) or severe symptoms (meeting at least 6 criteria). Furthermore, among those diagnosed, the symptom count average was higher than 3, which is the diagnostic threshold adopted by the YFAS.

A possible explanation for the high prevalence rate of FA found in our study could be related to the reported increase in habitual consumption of ultra-processed food and physical inactivity among Italian adolescents during the SARS-CoV-2-pandemic period (71–73). Since extant literature has consistently conceived FA as an addiction to this kind of hyper-palatable foods (74), it would not be surprising to suppose that the aforementioned increase in consumption has led to higher rates of addiction. Interestingly, the rise in the intake of these groceries has been strongly linked to boosted boredom and emotional overeating (75). Boredom has had a reinforcing effect of the perceived emotional distress during the pandemic outbreak (76) and emotional overeating, a firmly-related feature of FA (77), could have been an important strategy to cope with it.

Be that as it may, this FA rates, which are specific for population in the adolescent life stage, should raise concerns because of their deleterious impact on youth quality of life dimensions such as physical, emotional, social, and school functioning (78). Furthermore, the early onset of these risk behaviors during adolescence could lead to more severe mental health pathology during adulthood, as it has been demonstrated in the case of substance abuse (79, 80), behavioral addictions (81) and eating disorders (82).

Various associations with FA diagnosis/severity emerged in the psychosocial domains typically related with risk-taking behavior among youth people. Regarding sociodemographic variables, our analysis revealed that higher SHDI values were associated with lower prevalence rates and symptom count of FA. SHDI is a statistical

composite index that considers SES indicators as the income *per capita* level. These data seem to be in line with a large body of literature indicating a connection during adolescence between low SES and health risk behaviors as poorer diets, less physical activity, and greater cigarette smoking (83). Interestingly, among adolescents, socio-economic position has been shown to be inversely associated with two closely phenomena for FA (84) as obesity (85) and a high frequency of consumption of fast food (86).

In our study, other demographic variables, such as gender, have shown to be related with FA. Specifically, female gender showed a significantly higher probability of FA diagnosis and greater severity compared to males, drawing attention to previous research [i.e., (87, 88)] highlighting gender differences in addiction tendencies. This result is also supported by Leary et al. (89), who found an association between symptom count and female gender.

Several biological, psychological, and social mechanisms could account for the higher probability of FA in females. For example, it has been suggested that the effects of pubertal ovarian hormones may lead to increased binge eating (90), which has been found to be strongly correlated with FA (91). Moreover, women have shown more brain reactivity to external food-related stimuli in craving-related cerebral regions (92). From a psychosocial perspective, gender differences in FA rates may be connected to gender differences in mental health and body perception (93). Indeed, adolescent girls tend to report higher levels of body dissatisfaction and depression than their male counterparts (94). The negative evaluation of one's own body and depression symptoms are known risk factors for FA (95, 96).

Concerning the family domain, communication difficulties with parents were significantly associated with FA diagnosis, foregrounding the potential impact of family relationships not only on conventional risk behaviors among youth (31) but also on adolescent eating behaviors as reported in other recent studies (97).

Personality traits such as social anxiety, depressive symptoms, and a tendency for social withdrawal were strongly linked to a higher probability of meeting FA diagnostic criteria. These findings are consistent with the reported associations between anxious-depressive symptoms and FA diagnosis/severity among adolescents (98). This, in turn, appears to be coherent with the evidence showing the interconnectedness of this negative affect symptomatology and multiple domains of teen risk-taking behavior including drug and alcohol use, worse perception of health, computer overuse, academic failure, or overweight (99, 100). Regarding the association between FA and social withdrawal, as far as we are aware, this is first research in reporting it. There is no literature confirming this, but it could reflect a trend toward emotional dysregulation and avoidance as reported in previous studies on FA (101) and other risky behavior samples (32).

In the behavioral domain, several factors related to youth problematic lifestyle increase the risk of diagnosis and are associated with greater FA symptomatology, including IGD, SMA, recent substance use, involvement in risky online challenges, and being a victim of doxing. Indeed, in the literature, FA seems to be associated with substance use (26) or other behavioral addictions (102). This could partly have to do with the online exposure to risky behavior content and its relationship with drug use, excessive alcohol use, disordered eating, self-harm, violence to others, and dangerous pranks, as demonstrated in young adult samples (103). Intriguingly, a significant association between exposure to social media content and disordered eating was only found for female gender, which in our data was a strong predictor of FA (103). In this sense, systematic reviews of the evidence from the field of eating disorders and health psychology hint that mass media are a key source of information and reinforcement regarding the relevance of the thin beauty ideal, and the way to achieve it, determining therefore a media-mediated pressure to be slim that may be a risk factor for body dissatisfaction, weight concerns, and disordered eating behaviors in adolescent girls (104).

On the other hand, our research found that habits such as regular consumption of fruits and vegetables, participation in competitive sports, and adequate sleep duration seemed to have a protective effect against FA similar to that reported in large samples of Generation Z adolescents in the case of other more conventional risk behaviors such as substance use, risky sexual behavior or deviant behavior (42, 43). This suggests that health promotion approaches focusing on these healthy habits could be a potentially effective primary prevention strategy for this type of problematic eating.

In the subgroup diagnosed with FA, similar trends persisted, reinforcing the impact of gender, impulsive tendencies, mental health problems, addictive behaviors, and negative online experiences on the severity of FA. However, the consumption of fruits and vegetables showed an inverse relationship, albeit with a small ES, suggesting a potential pathway to manage the severity of FA symptoms.

The present study has some limitations that should be considered when interpreting our results. First, the cross-sectional nature of the research limits establishing causal relationships between FA and identified correlates. Longitudinal studies could provide a more comprehensive understanding of the temporal relationship between risk factors and the development of FA over time. Second, our study primarily relies on self-reported data, which might be subjected to recall or social desirability bias. Participants might under or over report their eating habits or behavioral tendencies due to perceived societal norms. However, to mitigate this potential bias, we guaranteed that respondents would remain anonymous. Another study limitation lies in the absence of some measures or factors that could contribute to the FA phenomenon such as anthropometric parameters (i.e., BMI, height, weight), genetic and cultural influences, comorbidities, or environmental influences like marketing strategies for hyper-palatable foods. Finally, some of the instruments measuring personality risk factors (i.e., the BIS-15, the SAD-D and the PHQ-A) have not been specifically validated for the target population of our study (i.e., Italian adolescents), although they have shown evidence of validity in adolescent samples from other countries (56, 57) or have been drawn from longer measures actually validated in Italian adolescents (52). This lack of specific validation has been suggested as a possible restraint to cross-cultural comparisons (105).

In any case, these results collectively underline the multifaceted nature of FA, highlighting the importance of considering various psychosocial factors to understand its prevalence and severity among adolescents. Addressing these complex interactions between behavior, environment, and individual characteristics is crucial in developing targeted interventions aimed at preventing and managing FA in this vulnerable demographic group.

In conclusion, as expected, FA is related with conventional psychosocial risk and protective factors of the risk behavior syndrome. Particularly, the association between FA and indicators of deviant and/or dangerous behaviors (i.e., current substance consumption, IGD, SMA, social challenge, doxing) might suggest that FA is part of a cluster of problematic and risky behaviors for health (drug use,

academic failure, crime, etc.) in adolescence that prevention interventions should consider.

Data availability statement

The datasets presented in this article are not readily available because of the sensitive nature of the information included, in compliance with national legislation. Requests to access the datasets should be directed to CM, claudia.mortali@iss.it.

Ethics statement

The studies involving humans were approved by National Ethical Committee of the Italian National Institute of Health (prot. PRE BIO CE 0010655 of 22/03/2022). The studies were conducted in accordance with the local legislation and institutional requirements. Written informed consent for participation in this study was provided by the participants' legal guardians/next of kin.

Author contributions

LM: Conceptualization, Methodology, Writing – original draft, Writing – review & editing, Supervision, Validation. LP: Conceptualization, Methodology, Supervision, Writing – original draft, Writing – review & editing. LG: Supervision, Writing – original draft, Writing – review & editing. BG: Data curation, Formal analysis, Supervision, Writing – original draft, Writing – review & editing. AA: Data curation, Formal analysis, Writing – original draft, Writing – review & editing. DF: Data curation, Formal analysis, Writing – original draft, Writing – review & editing. LM: Supervision, Writing – original draft, Writing – review & editing. PA: Supervision, Writing – original draft, Writing – review & editing. DC: Supervision, Writing – original draft, Writing – review & editing. AM: Conceptualization, Supervision, Writing – original draft, Writing – review & editing. CM: Funding acquisition, Project administration, Supervision, Writing – original draft, Writing – review & editing.

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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

Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpubh.2024.1414110/full#supplementary-material

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Emotional eating, internet overuse, and alcohol intake among college students: a pilot study with virtual reality

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Introduction: The term emotional eating (EE) describes the tendency to eat as an automatic response to negative emotions and has been linked to anxiety and depression, common symptoms among the university population. The EE tendencies have also been associated with excessive internet use and an increase in alcohol intake among young university students.

Methods: The aim of this study is to examine the relationship between the tendency towards EE and other health-compromising behaviors, such as excessive internet use or high alcohol intake. Additionally, it aims to investigate the association of these risky behaviors with the participants' performance level in a virtual reality (VR) task that assesses their executive functioning, and to assess impulsivity and levels of anxiety and depression.

Results: The results associate EE with excessive internet ($r = 0.332$; $p < 0.01$). use but not with alcohol consumption. Alcohol consumption was not associated with anxiety, depression, or impulsivity, but it was related to altered executive functions in the VR task: flexibility and working memory explained 24.5% of the variance. By contrast, EE and internet overuse were not related to executive function but were associated with impulsivity, depression, and anxiety. Impulsivity and depressive symptoms accounted for 45% of the variance in EE. Depression, trait anxiety and impulsivity explained 40.6% of the variance in internet overuse.

Discussion: The results reveal distinct patterns of psychological and neuropsychological alterations associated with alcohol consumption compared to emotional eating (EE) and excessive internet use. These findings underscore significant differences in the contributing factors between addictions and other substance-free addictive behaviors. For a deeper understanding of the various contributing factors to EE in college students, further research is recommended.

KEYWORDS

emotional eating, alcohol intake, internet addiction, executive functions, virtual reality, impulsivity, depression

1 Introduction

Eating behavior is a multifaceted phenomenon influenced not only by biological or genetic factors, but also by environmental and psychological factors (1). For more than 30 years, studies have consistently highlighted the significance of self-regulation and emotion in shaping the emergence of unhealthy eating habits (2, 3). Stress and negative emotions are frequently linked to increased food intake (4). One of the most dysfunctional eating habits is emotional

eating. The term *emotional eating* (EE) describes the propensity to eat as an instinctual reaction to unpleasant feelings (5) and implies a disproportionate intake of food, regardless of whether or not the individual is actually hungry, but in a nonpathological way. It differs from *binge eating disorder* (BED), which was officially recognized in 2013 in the DSM-5 as a separate eating disorder characterized by recurrent episodes of binge eating accompanied by a feeling of loss of control over eating, along with marked distress regarding binge eating, but without the compensatory mechanisms observed in anorexia or bulimia nervosa such as self-induced vomiting or excessive laxative use (6).

EE has been linked to symptoms of anxiety and depression in the general (non-clinical) population (7, 8). Episodes of emotional eating (EE) are typically accompanied by high-calorie, sugary, and/or high-fat food consumption. This eating pattern has been described as one behavioral mechanism linking depression to the development of obesity and abdominal fat (9). Individuals who are obese or overweight frequently experience this eating behavior pattern (10). Emotional eating was also strongly associated with psychological distress (11) and feelings of guilt or shame (12, 13).

University students exhibit elevated anxiety levels compared to the broader population with concerns about academic performance being a primary contributor to this distress (14, 15), and they also grapple with issues such as gaining autonomy from parents, financial constraints, and social competition or isolation, among various other concerns (16). Stress, anxiety, and depression emerge as prevalent psychological challenges faced during university education globally. Studies consistently indicate that university students tend to experience lower mental well-being compared to the general population (17, 18). When they fail to adapt adequately, they may exhibit maladaptive coping behaviors. Recent studies indicate a broad spectrum of risky behaviors among college students, such as heavy alcohol consumption and unhealthy eating patterns (19, 20). A considerable level of EE (29%) has been also found among the university population (8). Lack of effective stress management strategies can lead to resorting to unsuitable or harmful coping mechanisms like increased alcohol intake or EE. In a recent study, the frequency, and patterns of EE over the past 28 days were assessed among 335 female university students. The findings revealed that 51.3% of these episodes were associated with emotional states, notably anxiety (21), and it has been suggested that the intake of alcohol might serve as a substitute coping mechanism for managing negative emotions, particularly anxiety, replacing EE. A study employing person-centered longitudinal analysis over three years found that undergraduates tend to resort to excessive drinking as a means of relieving stress and managing social anxiety (22).

The existence of eating disorders, such as anorexia, bulimia, and binge-eating disorder, has also been associated with problematic internet use among university populations (23), suggesting that the duration of students' internet usage influences eating behavior disorders (24). At a subclinical level, problematic internet and smartphone abuse has been linked to problems with self-control over eating and a greater propensity to consume automatically in reaction to negative emotions or sentiments in teenagers and young adults, as shown by a study involving 209 adolescents as part of a school-based mental health promotion program (25), consumption pattern previously described and known as EE (26). Since both EE and excessive internet use are probable products of a lack of emotional regulation, there is undoubtedly a connection between the two (27). Additionally, a recent study conducted with 551 adolescents aged 15–17 suggests that social pressure and anxiety may act as mediating factors in the association between EE and internet addiction (IA), particularly social media addiction via smartphones (28).

College students experience a phase of transition into adulthood where they have attained physical maturity but might not have achieved similar levels of psycho-social development (29). The onset of the college experience often brings about substantial lifestyle shifts, notably in dietary habits characterized by skipping meals, insufficient nutrition, and frequent consumption of fast food. Moreover, during this stage, the brain is highly susceptible to external influences, particularly in the final phases of neuromaturation, which represent a critical period for neurodevelopment (30). In associative areas, especially the prefrontal cortex, there is a notable increase in white matter between the ages of 18 and 22, which correspond to the first years of university (31). Additionally, throughout the first half of the first year of university, there have been changes found in the volume of grey matter (32). These changes have been linked to the executive function's end of maturation, which occurs between the end of adolescence and the beginning of adulthood (33). The prolonged developmental phase explains the specific vulnerability of executive functions compared to other cognitive processes influenced by external factors, risky behaviors, or addictions. Executive functions (EF) are higher-level cognitive mechanisms that regulate lower-level cognitive processes and also impact behavioral control (34), and have an important role in the development of emotional regulation strategies: a heightened level of executive functions is somewhat connected to the effective implementation of emotion regulation strategies (35), and deficiencies in executive functions (working memory, planning, flexibility) are widespread among adolescents experiencing challenges in emotional regulation (36). Various studies have found alterations in the executive functions of university students associated with alcohol consumption (20, 30), abusive internet use (37), and EE (38). Regarding this, a systematic review demonstrates that proper functioning of executive functions is associated with adequate and correct self-regulation of eating behavior (2), and a longitudinal study conducted with 169 teens with type 1 diabetes shows that high levels of disordered eating practices in teenagers are associated with difficulties in EF (39).

In the evaluation of EF, discrepancies sometimes emerge between the scores obtained in traditional pen-and-paper tests and the performance of tasks in daily life. The utilization of virtual reality (VR) technology increasingly influences the process of neuropsychological assessment. By facilitating dynamic interaction and replicating three-dimensional environments, VR provides participants with an immersive experience that closely simulates real-life settings (40). VR also allows for the reproduction of multitasking environments, necessary to increase the ecological validity and predictive value of the functional performance of the individuals being evaluated (41).

Another relevant factor to consider in the increasing prevalence of these unhealthy and risky abusive behaviors among college students is impulsivity. Impulsivity results from a lack of inhibitory control, and it is defined as the tendency to act swiftly in response to any stimulus, whether internal or external, without prior evaluation of all available information and regardless of the potential consequences of the action. Numerous studies corroborate the pivotal role impulsivity plays in substance addictions (42), alcohol consumption (43), and it

also appears to be a relevant factor in internet addiction (37, 44). Impulsivity has been directly linked to overeating (45), food addiction (46), and BED (47), serving as a mediating factor between EE and overweight (48).

The objectives of this study include:

1 To assess the levels of EE in a sample of college students and their relationship with other abusive behaviors, such as excessive internet usage and alcohol consumption.
2 To verify the relationship between these behaviors, impulsivity and executive functioning assessed through a virtual reality (VR) task.
3 To evaluate the distinct roles that depression and anxiety may play in EE, excessive internet usage and alcohol consumption.

2 Method

2.1 Participants

The sample consisted of 56 undergraduate students (age > 18), of whom 30.4% were men and 69.6% were women. The age range was between 18 and 26 years. The mean age of participants was 20.62 (SD = 2.4). All the participants were university students from Francisco de Vitoria University in Madrid, Spain. The students were selected through non-probabilistic and accidental sampling. Table 1 shows more details about sample characteristics. Inclusion criteria were not having any psychiatric diagnosis, not being receiving psychological treatment at the time of the study and not consuming psychoactive substances. The study protocol and design were approved by the Ethics Committee of the University Francisco de Vitoria, and it fully complied with the Helsinki Declaration.

2.2 Variables and instruments

Sociodemographic information. Participants provided information about their age, gender, and educational level through a questionnaire created *ad hoc*.

TABLE 1 Description of the sample.

Variable	Variables	%
Study level	Graduate	12.3%
	Undergraduate	87.7%
Emancipated	No	78.9%
	Yes	21.1%
Sentimental state	Single	50.9%
	In a relationship	49.1%
Current on diet	Yes	10.5%
	No	89.5%
Eating disorder diagnosis	Yes	0%
	No	100%

Emotional eating was measured using the Emotional Eater Questionnaire (EEQ) (49). The EEQ consists of 10 items on a 4-category Likert scale ranging from 0 to 3. The test provides a global score to distinguish between non-emotional eaters (score between 0–5), slightly emotional eaters (score between 6–10), emotional eaters (score between 11–20), and highly emotional eater (score between 21–30). The temporal stability shows a medium to high correlation in the test–retest average ($r = 0.702$; $p < 0.001$), and the internal consistency of the subscales ranges from $\alpha = 0.61$ to $\alpha = 0.77$. In our study, the internal consistency was $\alpha = 0.86$.

Internet addiction was assessed using the Internet Addiction Test (IAT). This instrument was originally created in 1998 (50). For our study we used the Spanish version validated by Puerta-Cortés et al. (51). The IAT consists of 20 items with a Likert-type response format with 5 levels. The cutting point for identifying internet overuse is 40. The diagnostic validity showed 81% sensibility and 82.6% of specificity. Internal consistence values obtained in the validation study was good ($\alpha = 0.82$). In the present study, internal consistence was also good ($\alpha = 0.88$).

Alcohol consumption was measured using the Alcohol Use Disorders Identification Test (AUDIT) (52). This questionnaire was composed of 10 items with a five-point (0–4) Likert scale as a response format, except for the last two items, which have three answer options (0–2). Problematic alcohol consumption is considered from 8 points. AUDIT showed high sensibility and specificity (0.90 and 0.80 respectively). The validation of the test on a Spanish university population (53) found the internal consistency of the AUDIT test to be $\alpha = 0.75$. In the present study, the internal consistency for the AUDIT was also good ($\alpha = 0.83$).

Depression was measured with the Beck Depression Inventory (BDI), revised and updated in 1996 (54) and validated in a Spanish sample (55). The BDI consists of 21 items on a 4-category Likert scale (0–3). The test score allows for classification into minimal depression (0–13), mild depression (14–19), moderate depression (20–28) and severe depression (29–63). The internal consistence of the BDI in previous studies was $\alpha = 0.83$. In the present study, the internal consistence was good ($\alpha = 0.90$).

Anxiety was assessed by using the State–Trait Anxiety Inventory (STAI), adapted to the Spanish population (56). This questionnaire consists of a 40-items scale divided into two parts: the first 20 items measure anxiety as state; and the las 20 items measure anxiety as trait. Each of the 20 items in each subsection uses a 4-category Likert scale ranging from 0 to 3. A reliability study showed high internal consistency ($\alpha = 0.93$). In the present study, the internal consistency was also good ($\alpha = 0.81$)."

Impulsivity was measured using the Barratt Impulsiveness Scale, a questionnaire that was originally created in 1987 and adapted to the Spanish population in 2001 (57). The scale consists of 30 items with 4 response options, from 1 (always) to 4 (never). Reliability analysis showed good values of internal consistency (α =0 0.81). In our study the internal consistency was adequate ($\alpha = 0.70$).

Processing speed, planification, working memory and flexibility were measured with the Ice Cream Test (ICT), created by Giunti Psycometrics®, within Nesplora® package through virtual reality. This test has shown validity and reliability to measure executive functions (40). The task allows to measure attention, working

TABLE 2 Descriptive analysis of participants' values for evaluated variables.

Measures	Variables	*M* [Range]	*SD*
EEQ	Emotional eating	9.8 [2–29]	5.83
IAT	Internet overuse	30.71 [4–63]	13.06
AUDIT	Alcohol consumption	5.64 [0–21]	4.8
BDI	Depression	12.41 [1–36]	9.57
STAI	Anxiety state	24.93 [11–36]	4.88
	Anxiety trait	28.57 [17–38]	4.42
BIS	Impulsivity	23.14 [8–37]	6.95
ICT	Processing speed 1	5.24 [3.24–5.74]	1.09
	Processing speed 2	5.62 [3.53–5.94]	1.28
	Planification	45.53 [39–72]	7.24
	Working memory	27.03 [17–28]	1.87
	Flexibility	−2.71 [−7–0]	1.35

AUDIT, Alcohol Use Disorders Identification Test; BDI, Beck Depression Inventory; BIS, Barratt Impulsiveness Scale; EEQ, Emotional Eater Questionnaire; IAT, Internet Addiction Test; ICT, Ice Cream Test; STAI, State–Trait Anxiety Inventory.

memory, planification, flexibility and processing speed at the same time (58).

The participants were immersed in a VR experience where they had to assume the role of an ice cream vendor, following the instructions given at the beginning of the task. All task instructions are delivered audibly: "*you'll be working at the ice cream shop for a while. Customers come in groups of four, and you must serve them according to your boss's instructions. Call your boss, and he'll provide you with his priorities for serving customers. Click on the phone to give him a call.*" The boss's instructions outlined the order of attending to customers based on various criteria and the preparation of ice creams, which differed for each customer. Participants were provided with a recipe book, which they could consult whenever they deemed it necessary.

The test consists of 20 sequences divided into two rounds, A and B. Prior to the start of the task, all participants underwent a series of practice trials to ensure that the instructions were properly understood and that the task was manageable for each subject. In both parts A and B, the test operates with the same structure, environment, and task. Midway through the test, the initially learned series of ice creams changes, and a new set of ice cream variants must be learned to perform correctly in the second half of the test. The task requires to attend to customer requests and orders, utilize working memory to remember orders and manage inventory, plan, and organize tasks efficiently to serve customers. In round 2, participants must adapt to changing customer demands, demonstrating flexibility, and process orders quickly to serve customers effectively, thus measuring processing speed. In this way, upon finishing the test, four indices can be obtained for each participant: planning (correct assignments, assignment time, cognitive load), working memory (correct services without consultation), flexibility (interference between instructions, switching) and processing speed (duration of task completion).

The immersive and interactive nature of this VR experience can enhance the engagement of the assessment and potentially offer a more accurate representation of an individual's executive functioning abilities in a real-world context.

2.3 Procedure

The study was conducted in two steps: first, using the Qualtrics platform,[1] where participants completed the questionnaires. The second step took place in person, individually, in a calm and quiet environment. In the second step, participants completed the VR task (ICT). Participation was voluntary and required prior informed consent. Participants did not receive any rewards. This study received approval from the University Francisco de Vitoria Ethics Committee and was conducted in accordance with the principles of the Declaration of Helsinki.

2.4 Data analysis

Firstly, we obtained descriptive statistics for all the measures. To analyze the association between psychological and neuropsychological variables and emotional eating, internet overuse, and alcohol consumption, we calculated Pearson correlation coefficients. Finally, we conducted a series of stepwise linear regression models, introducing the significantly associated variables along with age and gender as explanatory variables. The data obtained in the study was analyzed using the Statistical Package for the Social Sciences 25.0 (SPSS) for Windows.

3 Results

3.1 Descriptive analysis and linear correlation among the studied variables

Table 2 displays the descriptive analysis of each measure. Scores exhibit moderate variability based on the range values, typical of a subclinical sample.

1 https://www.qualtrics.com

TABLE 3 Correlation analysis: Pearson correlation coefficient between the measures.

Measures	1	2	3	4	5	6	7	8	9	10	11
1. EEQ											
2. IAT	0.332*										
3. AUDIT	0.216	−0.002									
4. BDI	0.548**	0.466**	0.155								
5. STAI (trait)	0.370*	0.448**	0.186	0.275*							
6. STAI (state)	0.249	0.050	0.111	−0.053	0.095						
7. BIS	0.449**	0.376**	0.212	0.075	0.270*	0.338*					
8. ICT Processing speed 1	0.002	0.168	0.149	0.023	0.219	0.040	0.239				
9. ICT Processing speed 2	0.058	0.129*	0.318*	0.173	0.139	0.068	0.073	0.638**			
10. ICT Planification	0.183	0.225	−0.052	0.164	0.191	−0.005	0.050	0.344*	0.307*		
11. ICT Working memory	−0.084	−0.045	−0.410**	−0.017	−0.044	−0.055	−0.303	−0.635**	−0.453**	−0.092	
12. ICT Flexibility	−0.223	0.062	−0.296*	−0.171	0.036	−0.082	0.000	−0.154	−0.547**	−0.084	0.153

AUDIT, Alcohol Use Disorders Identification Test; BDI, Beck Depression Inventory; BIS, Barratt Impulsiveness Scale; EEQ, Emotional Eater Questionnaire; IAT, Internet Addiction Test; ICT, Ice Cream Test; STAI, State–Trait Anxiety Inventory. *$p < 0.05$; **$p < 0.01$.

TABLE 4 Regression analysis: explanatory model of emotional eating.

Model	Variables	*b*	*t*	R adjusted
1	Depression	0.519	5.021**	31%
2	Depression	0.519	5.021**	31%
	Impulsivity	0.402	3.895**	16%

*$p > 0.05$; **$p > 0.001$.

The Pearson correlation coefficients between each of the measures are presented in Table 3. Considering the main study variables, EE and the propensity for internet addiction are related. Trait anxiety and depression, along with increased impulsivity are associated with EE. These same variables and additionally the processing speed (measure round 2) were positively associated to the internet overuse score. Concerning alcohol consumption, processing speed (measured in round 2) also exhibited a positive association with AUDIT scores, albeit in a different context; meanwhile, working memory and flexibility demonstrated an inverse correlation with this variable. However, alcohol intake is not linked to higher levels of anxiety and depression.

3.2 Explanatory models of emotional eating, internet overuse, and alcohol consumption

Considering the psychological and neuropsychological variables associated with the main study variables, a series of stepwise regressions were conducted. In these regressions EE, internet overuse and alcohol consumption were introduced as dependent variables and the previous variables with significant correlations were introduced as independent variables. In the same way, gender and age were also included as independent variables in the explanatory models. Table 4 shows the explanatory model of emotional eating that was obtained.

For EE, depression and impulsivity resulted as explanatory variables. The combined model, comprising both variables, accounted for 45% of the variance in EE ($F = 22.293$; $p > 0.001$). Trait anxiety, gender, and age did not emerge as significant explanatory variables. For this model, the assumptions of linear regression were met. The Durbin-Watson statistic for residual independence was 2.047, and the collinearity criteria displayed appropriate values: tolerance level > 0.1 (1.00) and FIV < 10 (1.004).

Regarding internet overuse scores, Table 5 shows the explanatory model obtained. Levels of depression, trait anxiety, and impulsivity were significant explanatory variables. The complete model explained 40.6% of the variance in internet overuse ($F = 11.412$; $p > 0.001$). However, processing speed (round 2), gender, and age did not result as significant explanatory variables of internet overuse. Conditions for linear regression were also met. The Durbin-Watson test value was 1.711, and values for no collinearity were appropriate: tolerance level > 0.1 (0.85–0.932) and FIV < 10 (1.00–1.176).

Lastly, Table 6 shows results of explanatory model of alcohol consumption. We identified working memory and flexibility as significant explanatory variables. However, processing speed (round 2), gender, and age were not significant. The complete model explained 24.5% of the variance in alcohol consumption ($F = 8.428$; $p = 0.001$). Similarly, the requirements for linear regressions were satisfactorily met. The Durbin-Watson test value was 2.057, and for no collinearity, we obtained tolerance levels >0.1 (0.978–1.000) and FIV < 10 (1.000–1.023).

4 Discussion

Our findings uncover specific patterns of psychological and neuropsychological changes linked to EE and excessive internet

TABLE 5 Regression analysis: explanatory model of internet overuse.

Model	Variables	*b*	*t*	R adjusted
1	Depression	0.377	3.339**	22%
2	Depression	0.377	4.339*	22%
	Trait anxiety	0.292	2.469*	12%
3	Depression	0.377	4.339*	22%
	Trait anxiety	0.292	2.469*	12%
	Impulsivity	0.245	2.137*	5%

*$p > 0.05$; **$p > 0.001$.

TABLE 6 Regression analysis: explanatory model of alcohol consumption.

Model	Variables	*b*	*t*	R adjusted
1	Working memory	−0.389	−3.189*	18%
2	Working memory	0.389	−3.189*	18%
	Flexibility	−0.257	−2.083*	6%

*$p > 0.05$; **$p > 0.001$.

use when contrasted with alcohol consumption. These differences suggest that in university students, there are diverse underlying mechanisms and behavioral pathways, shedding light on the unique impacts of each behavior on cognition and mental health.

Regarding the first objective (to assess the levels of EE and their relationship with excessive internet usage and alcohol consumption): the average level of EE in the sample of students studied falls within the upper range of slightly emotional eaters (score between 6–10), very close to the range corresponding to emotional eaters (score between 11–20), according to the validation of the instrument conducted with a Spanish clinical population (participants in a weight-reduction program) (49). Although individuals with excess weight score higher on measures of EE than those within the "normal" weight category (59), our result is consistent with the estimated prevalence of EE found in earlier research, whereby 20–45% of adult non-clinical samples self-identify as emotional eaters (8, 60). According to accounts, these episodes frequently appear to be an attempt to prevent, manage, or deal with unpleasant feelings like sadness or anxiety (61). Approximately 44.7% of Spanish university students had mental distress suggestive of anxiety, while 13.5% showed indicators of depression, according to a survey involving approximately 706 individuals (62) and this would be in line with the prevalence data of EE found in this study. Additionally, it has been established that the EE propensity is linked to the tendency toward excessive internet use, but not to an increase in alcohol consumption. Consistently, it has been found that addictive internet use via smartphones in adolescents and young adults is associated with issues of control over eating, particularly with a greater tendency to eat automatically as a reaction to unpleasant feelings or emotions (25). Both excessive internet use and EE have been linked to symptoms of anxiety and depression in the general (non-clinical) population (7), and the likely connection between EE and excessive internet use is probably due to both being consequences of a lack of emotional regulation (27). There's a proposal suggesting that alcohol consumption among university students could be influenced more by contextual factors, such as increased independence, reduced parental supervision, heightened social homogeneity, and the presence of alcohol-related social activities, rather than being primarily linked to psychological distress or difficulties in emotional regulation (63), and this would account for the absence of a correlation between alcohol consumption and excessive eating (EE) or internet overuse. On the other hand, if both EE and alcohol consumption can be understood as two different inadequate coping strategies for negative emotions, it may be that this stress response varies depending on variables such as gender (21), which, due to limitations related to sample size, we have not been able to consider in this pilot study.

Regarding objective 2 (verify the relationship between these behaviors, impulsivity and executive functioning assessed through a VR task). It is found that alcohol consumption is related to flexibility and working memory: lower cognitive flexibility and poorer performance in working memory during the VR task predict a higher tendency for alcohol intake. The relationship between alcohol consumption and executive issues in young population has been described in previous studies (20, 30), although other studies have not found this connection (64). These differences could suggest that self-report questionnaires or conventional neuropsychological tests do not accurately capture the complexity and dynamic character of real-life circumstances. To address these limitations, in our study is that the executive functioning of students has been assessed using an ecological VR task: the Ice Cream Test (ICT). Tools for neuropsychological assessments based on VR may provide improved validity and accuracy for evaluating a variety of cognitive skills, including executive functions (40, 58, 65, 66). There has not been any observed change in executive functions associated with the inclination toward EE or excessive internet use, in contrast to the effects seen with alcohol consumption. In line with the findings outlined in relation to objective 1, alcohol consumption seems to be linked to factors separate from those driving EE and internet overuse. However, both patterns of behavior, EE and excessive internet use, have been associated with increased impulsivity,

which serves as a predictor in both instances. Previous studies have shown that decreased inhibitory control or impulsivity are linked to EE through a variety of different processes (67, 68). Impulsivity is defined as the tendency to act quickly in response to any stimulus (external or internal) without prior evaluation of all available information, hence, without considering the potential consequences of the action. From a neuropsychological perspective, impulsivity stems from a lack of inhibitory control, and response inhibition (which allows for the interruption or non-execution of inappropriate behavior) is a skill related to the integrity of the dorsolateral prefrontal cortex (69), an area still undergoing maturation in university students. Impulsivity plays a fundamental role in addictive behaviors, including non-substance addictions (44, 70). Impulsive behavior is maintained through positive reinforcement and is geared toward seeking pleasure and fulfilling individual needs. Impulsivity seems to underlie the onset of these behaviors, EE, and excessive/problematic internet use. In relation to eating behavior, there's a proposed concept of an 'eating continuum' ranging from EE (considered non-pathological) to binge eating disorder (BED), suggesting an escalation in the severity of overeating behaviors coupled with a rise in deficits in emotion control and inhibition (47), and it would be important to take these factors, impulsivity and lack of inhibitory control, into account for preventive treatments for obesity or eating disorders.

Regarding objective three (to evaluate the role that depression and anxiety may have on these behaviors), trait depression and anxiety are related to excessive internet use and EE, but not to alcohol consumption. Depression emerges as a predictive variable for EE and internet addiction, but trait anxiety only predicts internet overuse, but not EE. A recent study finds that, of all the emotions described as triggers for episodes of loss of control over food intake (anxiety, depression, boredom, or happiness), depression was the factor most clearly associated with these episodes (3). Our results align with that conclusion, and from a clinical perspective, it appears that, in order to develop successful programs to prevent EE and obesity, sadness and depressive tendencies must be taken into consideration.

In our sample of university students, alcohol consumption is not associated with higher levels of anxiety or depression, reiterating that alcohol consumption among Spanish university students is driven by different factors compared to excessive eating (EE) and internet abuse. Emotional needs are not at all the sole motivator for university students to drink. Alcohol consumption is very common in this stage as most young people include alcohol in their leisure activities, and it forms a part of their recreational culture (71, 72).

Despite the phenomenological parallels between addictions and certain abusive acts (substance-free addictions by certain authors) (73, 74), our findings suggest that there are significant distinctions between alcohol intake and other substance-free addictive behaviors in terms of the components involved. Cognitive assessment via the VR task revealed neuropsychological impairment among individuals who consumed alcohol, but not among emotional eaters or those prone to excessive internet use. However, in the latter groups, other psychological factors such as impulsivity, anxiety, and depression appear to be significant contributors. Given the severe detrimental effects of internet overuse (behavior of growing prevalence) (75), both on personal and socio-familial aspects, it is important to consider these results for the implementation of prevention and intervention programs.

Further research is advised to better understand the various causal factors that lead to EE among college students. The study of the prevalence and frequency of EE during the formative years at university, as well as the exploration of the associated risk factors, is necessary. This knowledge will be necessary to support intervention techniques and programs run by public health and policy experts, and college students represent an important demographic for interventions aimed at preventing obesity. The use of VR as an assessment tool can evaluate participants' performance in more ecological scenarios and provide more reliable results. But it is necessary to develop a more appropriate VR environment in the future for the assessment of cognitive functions, one that incorporates contexts relevant to participants' concerns, such as EE, internet overuse, and alcohol consumption. This pilot study is the first step toward a more extensive study using this methodology.

This study has several limitations. Firstly, as we have already mentioned at the beginning of this introduction, the small sample size, largely due to the time and resources required to conduct the VR Tasks. A larger sample would allow us to include sociodemographic variables in the analysis, resulting in more broadly generalizable findings. Additionally, all participants were university students from Francisco de Vitoria University in Madrid. It would be desirable to compare the results obtained in this study with those obtained from students in other institutions and with non-student youth of the same age range. Moreover, longitudinal research is required. In reference to impulsivity, it would have also been desirable to assess it through a VR task rather than solely relying on a self-report questionnaire, although the Barratt Impulsiveness Scale shows good values of internal consistency in our study (α =0 0.70).

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 humans were approved by Universidad Francisco de Vitoria. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

Author contributions

CM-G: Writing – original draft, Writing – review & editing. MC-C: Writing – original draft, Writing – review & editing. EB-B: Conceptualization, Writing – original draft, Writing – review & editing.

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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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Dietary supplementation with a wild green oat extract (*Avena sativa* L.) to improve wellness and wellbeing during smoking reduction or cessation: a randomized double-blind controlled study

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Objective: Smoking reduction or cessation are critical public health goals, given the well-documented risks of tobacco use to health. Reducing smoking frequency and cessation entirely are challenging due to nicotine addiction and withdrawal symptoms, which can significantly affect mental wellness and overall wellbeing. Previous research has suggested that certain dietary supplements may support smoking cessation and reduction efforts by mitigating these adverse effects. The objective of this study was to assess the effect of supplementation with 900 mg/day of Neuravena®, a green oat extract (GOE) of *Avena sativa* L., in enhancing wellness and wellbeing during a smoking reduction or cessation experience.

Methods: This was an 8-week randomized, double-blind, placebo-controlled study, ClinicalTrials Identifier: NCT04749017 (https://classic.clinicaltrials.gov/ct2/show/NCT04749017). Participants were assigned to one of the study groups, 72 participants were assigned to GOE and 73 to placebo. The subjects were followed for 8-weeks intervention period as well as an additional 4-week follow-up period. At subsequent visits, they underwent clinical assessments including assessments of quality of life, perceived stress, depression, nicotine dependence, anxiety, cognitive performance, and specific assessments of craving intensity.

Results: GOE was associated with greater improvements in elements of the abbreviated World Health Organization Quality of Life (WHOQOL-BREF) questionnaire as compared with placebo. Similar results were obtained from the SF-36 questionnaire and a visual QoL analogue scale (VAS). Perceived stress levels showed greater decline from baseline among the GOE supplemented participants as compared to placebo. Sleep quality parameters improved with

GOE supplementation and worsened in the placebo group. At the end of the intervention period, the percentage of successful reducers (defined as >20% reduction in daily cigarettes) was higher in the GOE group as compared to placebo (66.7% vs. 49.3%, $p = 0.034$). The improvements from baseline in QoL measures in the GOE group persisted at 4 weeks after termination of the intervention.

Conclusion: GOE supplementation demonstrated greater improvements in quality of life measures, stress and sleep related parameters during a smoking reduction or cessation experience and the product was shown to be safe and well tolerated.

KEYWORDS

tobacco, dietary supplement, Neuravena®, quality of life, *Avena sativa*

1 Introduction

Cigarette smoking is a major public health concern and is a leading cause of disability and premature death (1, 2). Therefore, smoking cessation is recommended due to the many associated advantages for the individual and society, including increasing life expectancy and reduction of health care costs associated with the treatment of smoking related conditions (3). The risk for serious disease is reduced rapidly after smoking cessation regardless of the duration and intensity of previous smoking habit, existing comorbidities, or age of the individual (4, 5).

Despite the clear benefits of smoking reduction, smoking is a very difficult addiction to break (5). Most smokers want to quit, but less than 10% of those who attempt cessation remain abstinent for at least 6 months (6). The mechanism responsible for the addiction has largely been attributed to the pharmacodynamics of nicotine. Nicotine stimulates nicotine acetylcholine receptors (nAChRs) in the brain, which elevate the release of neurotransmitters, mainly dopamine, promoting reward circuits and thus perpetuating consumption (7). Following repeated exposure to nicotine, cessation can also lead to a well characterized withdrawal syndrome that typically includes irritability, anxiety, increased appetite, insomnia, and impaired cognitive performance (8, 9). All these manifestations are temporary, reaching the greatest intensity in the first week and then decreasing over the course of the following 2–4 weeks. More than 40% of smokers report symptoms that persist for longer periods (4, 10).

One of the reasons why people fail to quit smoking is due to the complex interplay between physiological, psychological, and behavioral factors (11–13). Often, smokers report smoking cigarettes to alleviate emotional problems, such as stress relief (14). This is all part of the tobacco withdrawal cycle, misleading the smoker to believe that smoking offers psychological benefits (15). Usually, the level of functional beliefs, such as weight and stress control, associated with smoking correlate with smokers attempt to quit and whether they are successful (14, 16). Moreover, the physiologic effects associated with nicotine withdrawal symptoms may affect one's overall perception of their quality of life (17). According to the World Health Organization (WHO), health is defined as not merely the absence of disease or infirmity, but a state of complete physical, mental and social wellbeing (18). Indeed, several studies showed that symptoms related to the smoking cessation cause negative alterations in the perceived quality of life (13, 19–21).Therefore, understanding the relationship between one's perception of overall life satisfaction, may help to improve the individual's motivation to quit, and enhance relapse prevention strategies (17, 22).

Novel interventions supporting subjects' wellbeing and quality of life during smoking reduction or cessation experience are necessary. *Avena sativa* (oats) is considered as a nervine herb, supporting the nervous system. It has been used for its physical and psychological effects for centuries, mostly as stress and anxiety reducer, mild anti-depressant, and improving cognitive functions, and is considered to be safe with no known safety concerns at various dosages (23–26). Although some of the oats believed benefits are lacking scientific evidence, studies have showed impact of green oat herb extract (Neuravena®, IFF) on mental functions, and maintenance of cardiovascular health (23, 27, 28). Furthermore, Neuravena® has demonstrated an ability to inhibit monoamine oxidase-B (MAO-B) (28, 29). Inhibition of this enzyme increases the dopaminergic availability, and therefore it is hypothesized that it may be beneficial during smoking reduction or cessation by alleviating nicotine withdrawal symptoms and promoting pleasure and a sense of wellbeing (30–33).

Considering the proposed the traditional usage of green oat extract (GOE) and it's suggested mechanism of action, this study aimed to evaluate the potential effect of supplementing Neuravena® on the wellbeing of smokers during their smoking reduction or cessation experience.

2 Materials and methods

2.1 Study design and participants

This was a single-center, randomized, double-blind, two-arm parallel-group, placebo-controlled study conducted at the Health Sciences Department of Universidad Católica San Antonio de Murcia (UCAM), in Murcia, Spain between 26th January and 27th July 2021.

Participants were recruited by advertising the study through media, social networks, and e-mail lists of the UCAM University community. Eligible participants were healthy subjects between 18

and 65 years of age, regular smokers of 10 or more cigarettes per day (CPD) at least for the last 6 months, who were willing to reduce/quit daily cigarettes as assessed by the Richmond test (34), who had exhaled carbon monoxide (CO) levels of 10 ppm or more, had a negative urine drug test, and were able to provide informed consent and fully participate in all aspects of the study.

The exclusion criteria were the following: smokers of other nicotine-containing products, such as hookahs, smokeless tobacco or e-cigarettes; use of other smoking cessation aids within the previous 30 days; use of any mineral/vitamin/drug or other supplements within the previous 30 days; presence of any active or chronic disease or chronic medication except for stable antihypertensive and/or antihyperlipidemic agents; presence of depression, anxiety or stress as assessed by psychological evaluation and DASS-21 questionnaire; history of alcohol or drug abuse or dependence within the past year; diagnosis and treatment for mental illness within the past year; known allergy to any of the study components; pregnant or breast-feeding women; and any other laboratory test abnormality, medical condition, or psychiatric disorder that may adversely affect the subjects ability to complete the study according to the investigator's opinion.

Participants were randomly assigned into the intervention or placebo groups using a computer-generated randomization list with Epidat 4.1 software program (Xunta de Galicia, Santiago de Compostela, Spain) by an independent center. All participants were stratified according to number of daily smoked cigarettes, categorized as below 16 CPD or equal to or greater than 16 CPD, and the willingness to reduce smoking categorized as greater than or equal to a score of 6 and less than a score of 6 (moderate motivation) of the Richmond test (34). A stratified randomization was performed based on two factors (the number of daily smoked cigarettes and the willingness to reduce tobacco smoking). A simple randomization procedure was applied for each of the 4 groups generated, leading to unequal number of subjects between study groups. Restrictive or balanced randomization which requires that the two groups have the same number of subjects, could not be implemented in this study.

The study was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice (GCP) standards (35, 36). The study protocol was approved by the Ethics Committee of Universidad Católica San Antonio de Murcia (code CE102004 approval date October 30, 2020; Murcia, Spain) and registered in ClinicalTrials.gov (NCT04749017). Written informed consent was obtained from all participants.

2.2 Intervention and study products

The investigational product consisted of a wild green oat herb extract (Neuravena®, IFF España, Sant Cugat del Vallés, Barcelona, Spain). The daily dosage consisted of two capsules each containing 450 mg of Neuravena®, or 519 mg maltodextrin as placebo. Both GOE and placebo products were encapsulated by an independent company (Laboratorios Admira, Murcia, Spain), providing an identical hard gelatin capsule format. All participants were instructed to take two capsules daily (one in the morning and one in the afternoon) for 8 consecutive weeks (60 days). The GOE dose of 900 mg/day was selected as it was shown to be safe in previous clinical studies (20, 21, 30).

2.3 Study procedures and data collection

The study design and procedures taken during the trial are visualized in Figure 1. Each subject participated in an 8-week intervention period and an additional 4 week follow up period. This 12-week study period included a baseline visit (Visit 2), mid-study visit at 4 weeks (Visit 3), end of intervention visit at 8 weeks (Visit 4), and last visit at 12 weeks (Visit 5).

The screening visit (Visit 1) took place 15 days prior to the baseline visit, where the inclusion and exclusion criteria were evaluated, and the written informed consent was obtained. Once consent was obtained, participants completed a medical history and physical examination. Vital signs, height, weight, blood, and urine samples (including pregnancy test for women), as well as exhaled carbon monoxide (CO) were collected. Participants were evaluated for their psychological eligibility (depression, anxiety, and stress levels) by completing the DASS-21 questionnaire and a psychologist's evaluation. Participants' willingness to reduce daily cigarette number was assessed by the Richmond test. Furthermore, personal, demographic and life habitual information was collected: Age, ethnicity, familiar status, education, social habits, smoking habits (past/current), etc. Eligible participants were randomized and allocated into one of the groups at the baseline visit (Visit 2). Thereafter, the clinical assessments started and were similar on all intervention visits (Visit 2–Visit 4).

At Visits 2–4, participants were instructed to consume a light lunch 2 h before the visit and were requested to abstain from smoking once entering the clinic. The timeline and sequence of assessments is provided in Table 1. All questionnaires and scales were adapted and validated for Spanish. On each visit, eligibility criteria were checked, and vital signs and body weight were recorded. Participants completed the following efficacy assessments: the abbreviated World Health Organization Quality of Life (WHOQOL-BREF)[1] (37); the Short-Form Health Survey (SF-36) (38); the Perceived Stress Scale (PSS) (39); the Beck Depression Inventory-II (BDI-II) (40); the Minnesota Nicotine Withdrawal Scale (MNWS) (41); the Fagerström Test for Nicotine Dependence (FTND) (42); the State–Trait Anxiety Inventory (STAI) (43); a cognitive battery using the Computerized Mental Performance Assessment System (COMPASS, Northumbria University, UK, instruction screens adapted for Spanish); and a 100 mm visual analogue scale (VAS) symptoms panel developed for this study. Craving intensity was assessed twice, before and after a provocation procedure. After participants abstained smoking for ~150 min, craving assessment was conducted in a cue induced test. Craving was provoked by participants' exposure to smoking related cues which included visual stimuli of seven categories (social celebration, study environment, smokers, coffee and cigarette, cigarette and pack, free time, ashtray, and cigarettes) and presence of tobacco as a tactile and olfactory stimulus. The level of craving was assessed before and after the provocation by (1) Brief Questionnaire on Smoking Urge questionnaire (QSU-Brief) (44). (2) A 100 mm VAS craving question developed for this study.

Perceived QoL was evaluated by a 100 mm VAS QoL panel developed for this study and recorded by participants in their diary every 2 weeks (from the night before Visit 2 to the night before Visit 5). In

1 https://www.who.int/tools/whoqol

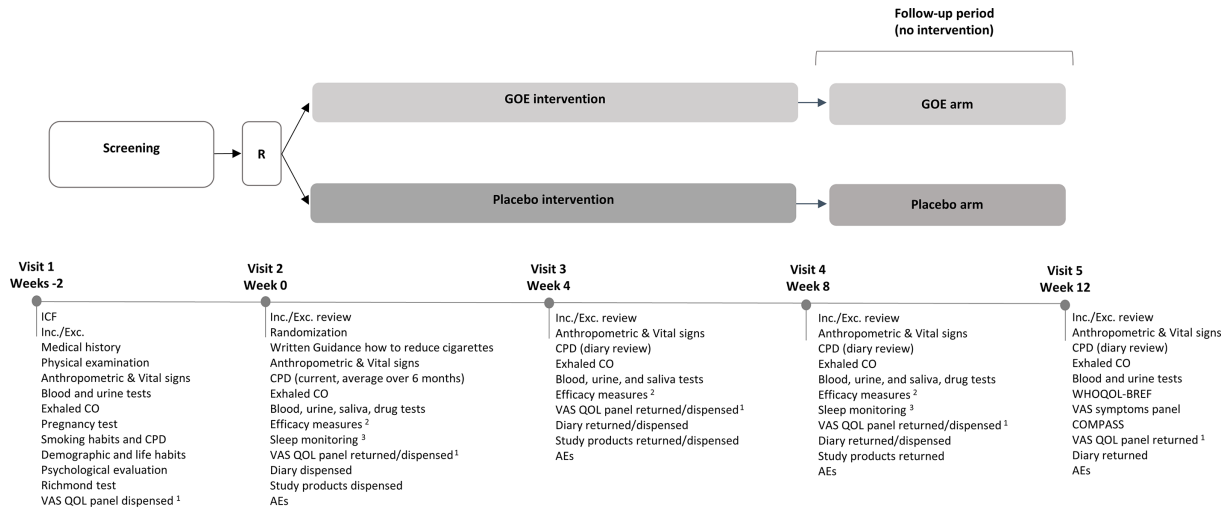

FIGURE 1
Study design. [1]VAS QOL panel was completed every 2 weeks the night prior to the next visit or during weeks between visits; [2]Efficacy measures: WHOQOL-BREF, SF-36, VAS symptoms panel, PSS, STAI, BDI-II, MNWS, FTND, COMPASS, Cue induced craving test (QSU + VAS); [3]Sleep was monitored over 3 working days +1 weekend before visit 2 and visit 4 (8 weeks); R, Randomization; ICF, Informed Consent Form; Inc./Exc., Inclusion/Exclusion; CPD, Cigarettes Per Day; CO, Carbon Monoxide; VAS, Visual Analogue Scale; QOL, Quality of Life; AEs, Adverse Events.

addition, sleep quality was assessed in all participants by using a wrist-worn accelerometer during 3 consecutive weekdays and 1 weekend day before Visit 2 and Visit 4. A more detailed explanation of all assessments, scores and necessity of use can be found in Supplementary Table S1.

Biochemical measurements related to smoking were exhaled CO level (9 ppm was defined as a cutoff point to identify current smokers) (7) and blood and urine cotinine. Urinary and saliva cortisol levels were analyzed for stress related biochemical measurements. Urinary drug test was performed (on Visit 2 and Visit 4 only) for tetrahydrocannabinol (THC), amphetamines, methamphetamines, cocaine, and opioids. More details on biochemical measurements can be found in Supplementary Table S2.

After the 8-week intervention, participants were followed for an additional 4 weeks. At the end of the follow-up period (Visit 5), participants completed the WHOQOL-BREF questionnaire and the COMPASS tests, exhaled CO was measured, blood and urine samples for cotinine levels were collected, and VAS symptoms panel was completed.

At the end of Visits 2 and 3, participants received the exact number of capsules required for the next 4 weeks of intervention, a diary for daily record of CPD and completion of VAS QoL panel was provided. Subjects were requested to return all blisters they have received in the previous visit, and compliance was monitored at visits 3 and 4 by counting the number of capsules remaining in the blisters pack. Dose compliance was defined as the number of capsules taken by a participant during 4 weeks of the study period divided by the number of capsules expected to be taken during these 4 weeks multiplied by 100. Compliance was assessed for consumption during the first and second 4 weeks period, and during the overall study period (throughout 8 weeks). In addition, the sleep accelerometer was dispensed to participants a few days before Visits 2 and 4 to evaluate the quality of sleep. A diary to record CPD was dispensed at the end of Visit 4. Adverse Events (AE) were recorded on Visits 2–5 for safety evaluation.

2.4 Study endpoints

The primary end points of the study were significant differences between the GOE and placebo group in the change in WHOQOL-BREF from baseline to the end of the trial (8 weeks).

The secondary endpoints were the following: differences between the groups in changes from baseline of QoL as measured by WHOQOL-BREF at 4 weeks and to the end of the follow-up period (Visit 5); differences between the groups in changes from baseline to weeks 4 and 8, and during the follow-up period in the collected questionnaires: perceived QoL (measured by VAS QoL panel); severity of physical symptoms related to the smoking reduction or cessation experience and impact on ability to function (measured by VAS symptom panel); frequency of physical symptoms related to the smoking reduction or cessation experience; extent of smoking reduction (averaged CPD across 7 days prior to the respective visit and biochemical markers: exhaled CO, cotinine level in both blood and urine); proportion of participants reporting 7-day smoking abstinence (verified by exhaled CO readings of <9 ppm); and cognitive performance (measured by COMPASS). Additionally, differences between the groups in changes from baseline to weeks 4 and 8 were evaluated in: general health aspects (assessed by SF-36); perceived stress (assessed by PSS); stress level (measured by salivary cortisol and urinary biopyrrin); anxiety level (assessed by STAI); depression level (assessed by BDI-II); withdrawal symptoms appearance (assessed by MNWS); nicotine dependency levels (assessed by FTND); urge for smoking following cue-induced craving test (assessed by QSU-brief questionnaire and VAS); stress levels following cue-induced craving test (measured by salivary cortisol); and sleep quality (measured by sleep accelerometer; change from baseline to week 8 only). Safety endpoints were anthropometric variables, vital signs, and AEs.

Exploratory endpoints included within group changes in the measured variables from baseline to weeks 4 and 8 and during follow-up.

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TABLE 1 Timeline and sequence of assessments.

Time from visit start	Procedure and assessment
Evening before	VAS QoL panel (diary)
−120 min	Consumed light lunch (at home)
−60 min	Product consumption (at home)[1]
0–45 min	Abstinence from smoking started when attending the clinic
	Inclusion/exclusion criteria and diary review
	Vital signs (heart rate, blood pressure, and temperature), and weight
	WHOQOL-BREF
	SF-36[2], PSS[2], BDI-II[2]
	Exhaled CO (20–30 min post abstinence)
	Blood (cotinine), urine (cotinine, biopyrrin[2], drug test[3]), and saliva (cortisol[2]) samples collection
	VAS symptoms panel
45–90 min	Break
90–150 min	COMPASS cognitive test panel[4]
	MNWS[2], FTND[2], STAI[2]
	Pre exposure to cue assessment (QSU-Brief, VAS craving level)[2]
	Exposure to cues provoking craving[2]
	Post exposure to cue assessment (QSU-Brief, VAS craving level)[2]
	Saliva (cortisol) sample collection[2]

[1]Product consumption applies only for visits 3 and 4. [2]Assessments apply only for visits 2–4, not performed at follow-up. [3]Drug test applies to visits 2 and 4 only, including THC, amphetamines, methamphetamines, cocaine, and opioids. [4]On visit 5, performed within 50–75 min; Min, minutes.

2.5 Statistical analysis

A sample size of 140 participants, with a total of 160 participants when assuming a dropout rate of 12.5%, was estimated to reflect a difference between the groups with an effect size of 0.48 and 80% power using an independent *t*-test with 0.05 two-sided statistically significant level. The intent-to-treat (ITT) dataset included all randomized participants for whom any post-randomization efficacy evaluation was available. The per-protocol population (PP) included all subjects in the ITT population who completed post-randomization evaluations at all study visits and did not have any major protocol violations. The main evaluations of the efficacy parameters were based on the ITT population. Linear mixed model for repeated measures (MMRM) was fitted for the primary endpoint analyzing the change from baseline to week 8 between the study groups. The model included fixed effects for baseline (week 0), week number (week 8), and product group (GOE and placebo). Study subjects were considered as random effects. For secondary and exploratory endpoints, an independent *t*-test was used for continuous variables. For continues variables with a frequency of occurrence of less than 30 subjects with non-normal distribution, the non-parametric Mann–Whitney U test was used to compare the mean rank of two not related samples and determine differences. For categorical variables, the chi-square test was used. In addition, comparison was conducted within each group between respective time points. Paired *t*-test was used for continuous variables, and McNemar's test was used for categorical variables. Analysis was corrected for baseline values as appropriate. Statistical significance was set at $p < 0.05$. Statistical analyses were performed with SPSS 25.0 (or higher) for Windows.

3 Results

3.1 Study population

A total of 192 participants were assessed for eligibility and 162 were randomized, 80 were assigned to the GOE group and 82 to the placebo group. One participant randomized to the GOE group discontinued the study during the initial visits and, therefore, was not included in the further analysis. Finally, 71 participants from the GOE group and 72 from the placebo group completed the five study visits. The flow chart distribution of participants is shown in Figure 2.

There were 74 men and 87 women (54%) with a mean age of 29.59 (±10.76) years participating in the study. The participants demographics are shown in Table 2. The mean age when participants started smoking was 16.12 (±3.32) years. Participants smoked 13.47 (±10.63) years on average. The mean CPD number was 16.24 (±5.46), and the motivation to quit was assessed to be moderate (Richmond score 6.29 ± 1.7). No significant differences were found between the participants assigned to the GOE group and placebo group, except for participants going out more frequently in the GOE group.

3.2 Primary outcome- changes in quality of life from baseline to the end of the intervention assessed by WHOQOL-BREF

The primary endpoint of the study was differences between study groups in the changes in QoL scores assessed by WHOQOL-BREF from baseline to 8 weeks. There was a statistically significant improvement from baseline to week 8 in physical health and psychological domains for the GOE group as compared to placebo ($p = 0.006$ and $p = 0.008$, respectively; Table 3; Figure 3). There were no significant differences in the other measured points of the questionnaire.

3.3 Secondary outcomes and exploratory analysis

3.3.1 Quality of life and general health aspects

Changes in the QoL parameters measured by the WHOQOL-BREFF from baseline to the mid-point of the intervention (week 4), showed significant improvements for the GOE group in overall QoL, physical health, psychological, and environmental as compared to placebo (Table 4; Figure 3). Over time, significant improvements within the GOE group were observed in all parameters except social relationship (Supplementary Table S3).

The VAS QoL panel showed significant improvement for the GOE group in the perceived confidence level as compared to placebo following 4 and 8 weeks of intervention (Table 4). Significant improvements in the GOE group over time as compared to the baseline occurred in most of the measured variables as shown in Supplementary Table S4. The placebo group showed a significant

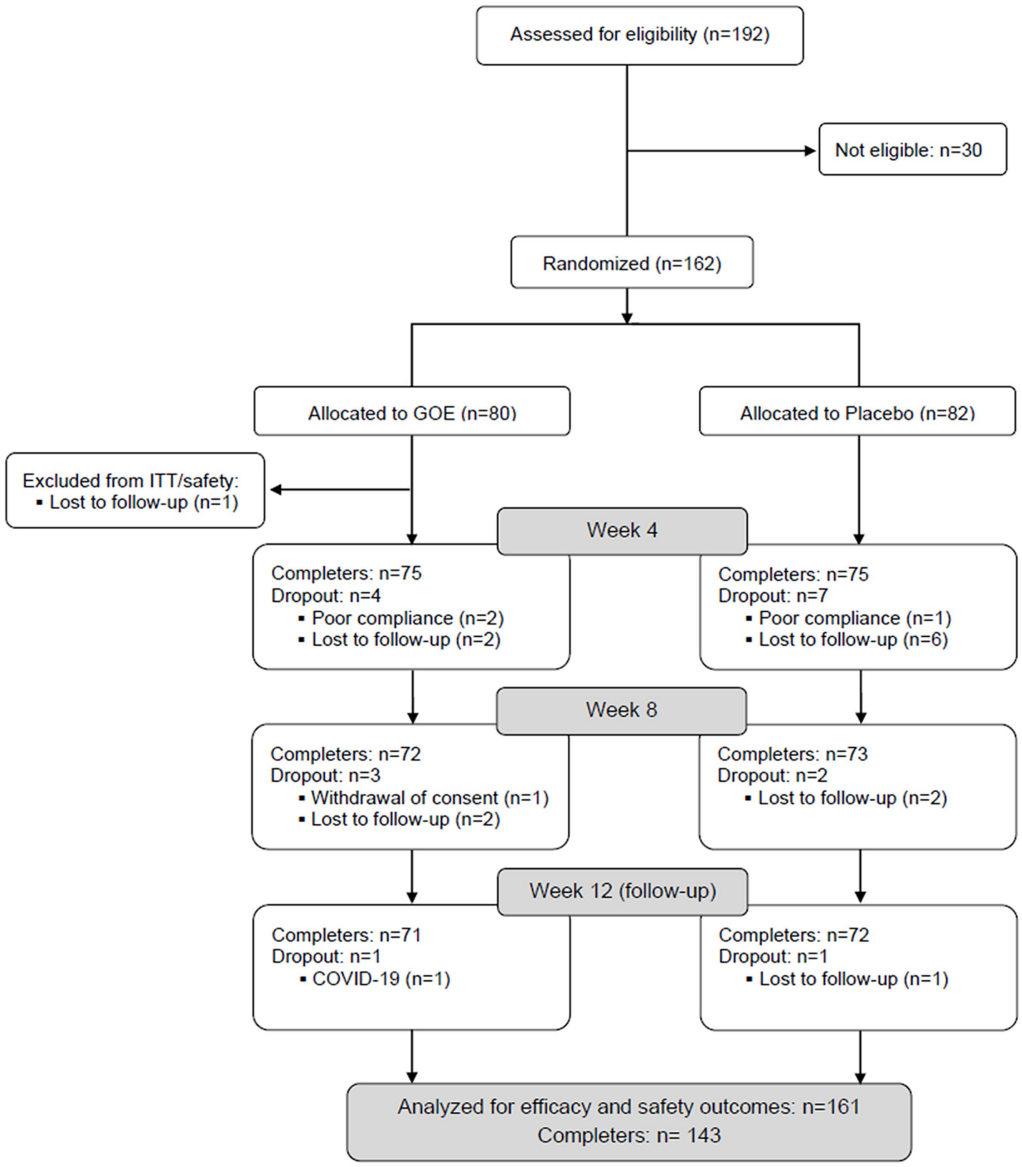

FIGURE 2
Flow chart of the study population (GOE: green oat extract).

improvement in sleep quality, decrease in the urge to smoke, and a decline in confidence level as compared to baseline (Supplementary Table S4).

Assessment of general health with the SF-36 questionnaire showed a significant improvement in the vitality and mental health domains following 8 weeks of GOE intervention as compared to placebo. A significant improvement in the change in bodily pain domain was shown following 4 weeks intervention of GOE as compared to placebo (Table 4). In addition, the change in the physical component summary score showed a significant increase for the GOE group compared to placebo. Overtime, a significant improvement from baseline was observed within the GOE group in physical functioning, physical role limitations, bodily pain, vitality, mental health, physical health component summary, and mental component summary. On the other hand, the placebo group showed significant improvement in bodily pain only as compared to the baseline (Supplementary Table S5).

3.3.2 Smoking behavior

Both groups showed a significant reduction in daily cigarette consumption (CPD) over time from baseline throughout the study period. However, significant differences in CPD between the treatment groups was not observed following 4 and 8 weeks of intervention (Supplementary Table S6). Following 8 weeks of intervention, a significantly higher proportion of participants were considered successful reducers (CPD reduction of >20%) in the GOE group as compared to placebo (66.7% vs. 49.3%; Table 4; Figure 4A). As an objective measurement of cigarette consumption reduction, we found that the exhaled CO levels were significantly decreased after 8 weeks as compared to baseline only in the GOE group (Table 4; Figure 4B). With respect to blood or urinary cotinine levels, significant differences were not found between study groups, nor in each group relative to baseline values (Supplementary Table S6). Analysis of participants who abstained from cigarettes did not show

TABLE 2 Demographic and clinical characteristics of participants randomized into the study.

Variables	Total (n = 161)	Study arm		P-value[1]
		GOE (n = 79)	Placebo (n = 82)	
Age, years	29.6 (10.8)	28.3 (10.4)	30.8 (11.1)	0.133
Sex, n (%)				
Male	74 (46.9)	41 (51.9)	33 (40.2)	0.138[2]
Female	87 (54.0)	38 (48.1)	49 (59.8)	
Body mass index, kg/m^2	25 (4.8)	24.8 (4.9)	25.1 (4.7)	0.703
Ethnicity, n (%)				
Caucasian	159 (98.8)	79 (100.0)	80 (97.6)	0.377[2]
Arab	1 (0.6)	0	1 (1.2)	
White Hispanic	1 (0.6)	0	1 (1.2)	
Marital status, n (%)				
Married/living with partner	42 (26.1)	20 (25.3)	22 (26.8)	0.089[2]
Single	108 (67.1)	57 (72.2)	51 (62.2)	
Divorced/separated	11 (6.8)	2 (2.5)	9 (11.0)	
Social habits, n (%)				
Going out <3 times a week	118 (73.3)	50 (63.3)	68 (82.9)	0.005[2]
Going out >3 times a week	43 (26.7)	29 (36.7)	14 (17.1)	
Age started daily smoking, years	16.1 (3.3)	16.4 (3.4)	15.9 (3.3)	0.351
Total smoking period, years	13.5 (10.6)	11.9 (10.3)	15 (10.8)	0.070
Smokers with quitting attempts, n (%)	83 (51.6)	36 (45.6)	47 (57.3)	0.136 [2]
Cessation period, months	9.8 (15.3)	6.5 (8.0)	12.3 (18.9)	0.080
Smokers with attempts to reduce smoking, n (%)	85 (52.8)	39 (49.4)	46 (56.1)	0.392 [2]
Reduced number of cigarettes	5.8 (3.6)	5.3 (3.5)	6.3 (3.7)	0.236
DASS-21 total score	10.1 (5.9)	10.5 (5.9)	9.8 (6.0)	0.448
Cigarettes per day	16.2 (5.5)	15.7 (5.0)	16.7 (5.9)	0.231
Richmond test score	6.3 (1.7)	6.1 (1.6)	6.5 (1.8)	0.179

Data expressed as means (standard deviation) unless otherwise stated. DASS-21: Depression Anxiety and Stress Scale 21. [1]p-values were derived from an independent t-test. [2]p-values were derived from a Chi-square test.

TABLE 3 Quality of life parameters at baseline and change following 8 weeks.

WHOQOL-BREF Item/domain	GOE group		Placebo group		p-value
	Baseline (n = 79)	Change from baseline to week 8 (n = 72)	Baseline (n = 83)	Change from baseline to week 8 (n = 73)	
Overall QoL	3.6 (0.9)	0.2 (0.8)*	3.8 (0.7)	0.1 (0.8)	0.282
Overall health	3.2 (0.9)	0.3 (1.0)*	3.2 (0.9)	0.2 (0.9)*	0.512
Physical health[1]	72.5 (13.4)	4.2 (11.0)*	74.8 (12.8)	−1.2 (11.8)	**0.006**
Psychological[1]	64.5 (15.4)	3.9 (10.9)*	69.6 (14.5)	−1.2 (8.9)	**0.008**[†]
Social relationships[1]	70.3 (18.7)	−1.3 (16.4)	69.2 (19.3)	1.3 (16.4)	0.341
Environmental[1]	68.0 (11.5)	1.0 (10.3)	69.7 (14.2)	−0.9 (12.8)	0.339

WHOQOL-BREF: abbreviated World Health Organization Quality of Life. A higher score indicated better outcome. [1]Domains raw score were transformed on a scale from 0 to 100; Data is expressed as mean (standard deviation); P-values are based on MMRM analysis for the change from baseline to week 8 between the groups; [†]Based on analysis of covariance controlled for baseline; *Significance based on paired t-test between baseline to a respective time point; Bold indicates significant differences at $p < 0.05$.

any significant results as only one participant in each group successfully abstained from cigarettes at 8 weeks (Supplementary Table S6).

3.3.3 Stress levels

The perceived stress levels as measured with the PSS scale declined in both groups over the 8 weeks of intervention, with a significantly

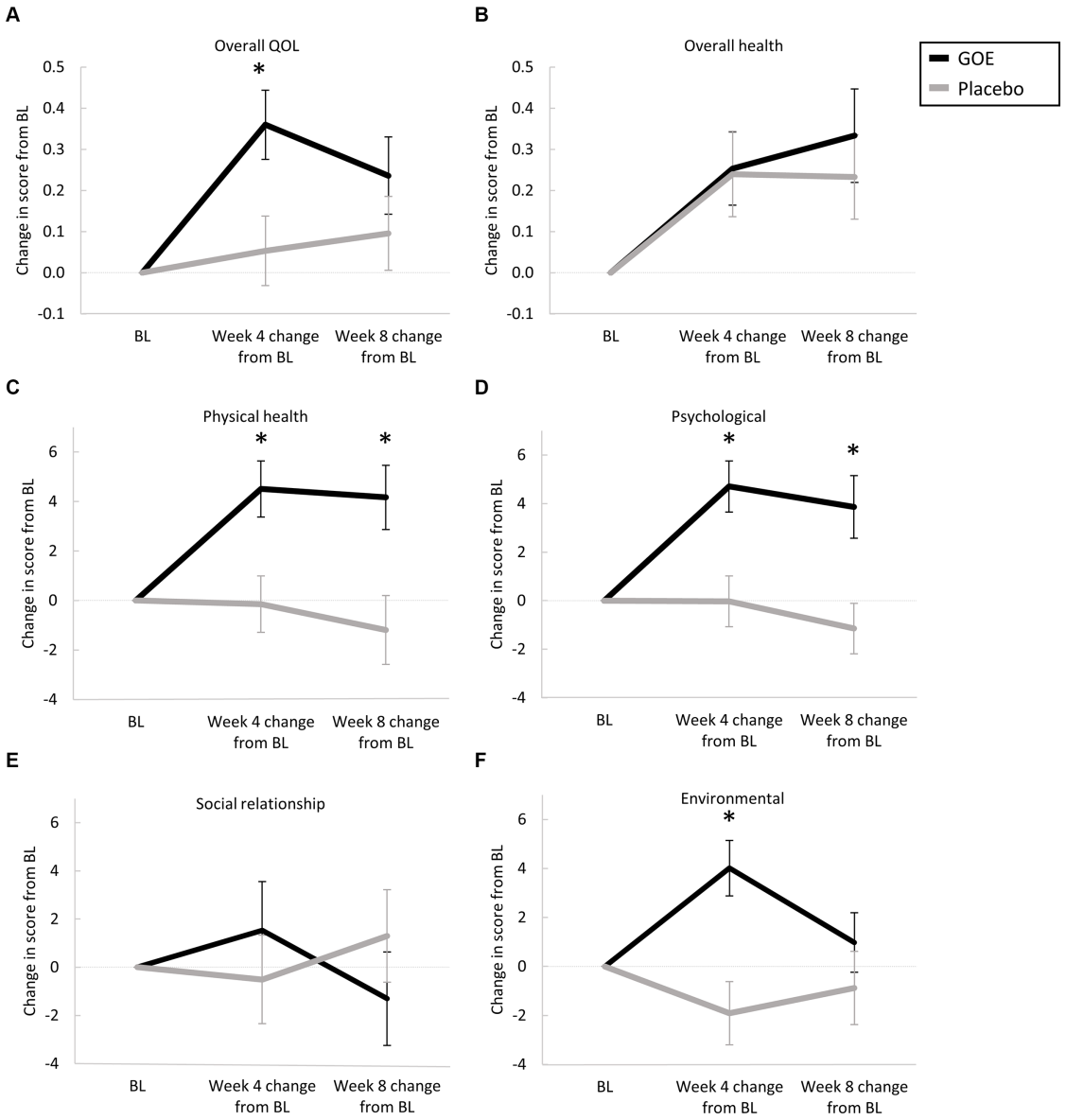

FIGURE 3
Changes in QoL parameters at baseline and following 8 weeks. **(A)** Overall QoL. **(B)** Overall health. **(C)** Physical health. **(D)** Psychological. **(E)** Social relationships. **(F)** Environmental. *$p < 0.05$ for between-group comparisons.

greater decrease in the GOE group as compared to placebo (Table 4). Moreover, the perceived stress score significantly reduced overtime (week 4 and 8) as compared to baseline only in the GOE group (Supplementary Table S7). No significant reduction of stress levels was observed with in the placebo group.

Stress-related biomarkers (urinary biopyrrin and salivary cortisol) did not differ between the study groups and a similar significant increase in urinary biopyrrin was observed in both study groups compared to baseline values (within-group differences, $p < 0.05$).

3.3.4 Physical and psychological symptoms related to the smoking reduction or cessation experience

As measured with the VAS symptom panel at the initial visit, a higher percentage of participants reported headaches in the GOE group vs. placebo, but the difference was not statistically significant ($p = 0.187$) (Supplementary Table S8). However, there was a significant decrease in reported headache in both groups after 8 weeks of treatment as compared to baseline. The percentage of participants who reported to experience any symptom at baseline was 74.7 and 62.2% within the GOE and placebo groups, respectively (Supplementary Table S8). Following the 8 weeks of intervention, the percentage of participants experiencing any symptom significantly decreased within both study groups to 55.6 and 39.7%, respectively. The percentage of participants who experienced any symptom, and participants who reported an impact on the ability to function were comparable between study groups at both time points. Following 8 weeks of intervention (within group comparison), both products resulted in significantly fewer participants reporting any symptoms, coughing, sore throat, and headache. Additionally, the placebo group

TABLE 4 Descriptive parameters of the variables studied with statistically significant differences.

Measurement	Item	GOE			Placebo			*p*-value		
		Baseline	Change from baseline		Baseline	Change from baseline		P1	P2	P3
			Week 4	Week 8		Week 4	Week 8			
		N = 79	*N* = 75	*N* = 72	*N* = 82	*N* = 75	*N* = 73			
WHOQOL-BREF (quality of life)	Overall QoL	3.6 (0.9)	0.4 (0.7)	0.2 (0.8)	3.8 (0.7)	0.05 (0.7)	0.1 (0.8)	0.077	**0.011**	**0.282**
	Physical health	72.5 (13.4)	4.5 (9.9)	4.2 (11.0)	74.8 (12.8)	−0.2 (9.8)	−1.2 (11.8)	0.258	**0.004**	**0.006**
	Psychological	64.5 (15.4)	4.7 (9.1)	3.9 (10.9)	69.6 (14.5)	−0.0 (9.1)	−1.2 (8.9)	**0.033**	**0.009**†	**0.008**†
	Environmental	67.9 (11.5)	4.0 (9.8)	1.0 (10.3)	69.7 (14.2)	−1.9 (11.2)	−0.9 (12.8)	0.387	**0.001**	0.339
VAS QoL panel (perceived quality of life)	Confidence level (cm)	6.7 (2.1)	0.5 (2.1)	0.4 (2.3)	7.3 (2.0)	−0.4 (1.7)	−0.2 (1.6)	0.061	**0.006**	**0.047**
SF-36 (general health aspects)	Bodily pain	76.6 (20.2)	4.8 (21.0)	5.6 (25.0)	79.3 (20.6)	−2.9 (22.9)	5.1 (19.0)	0.405	**0.032**	0.892
	Vitality	61.6 (15.3)	3.6 (15.2)	7.8 (15.8)	65.2 (13.9)	0.4 (13.6)	1.0 (15.3)	0.118	0.179	**0.009**
	Mental health	70.4 (15.2)	2.7 (12.7)	5.5 (13.2)	74.8 (15.1)	0.1 (13.7)	0.8 (15.2)	0.069	0.229	**0.048**
PSS (perceived stress)	PSS score	21.0 (8.2)	−2.1 (5.7)	−3.2 (6.5)	19.1 (7.6)	−0.6 (6.3)	−0.6 (7.5)	0.124	0.111	**0.028**
Sleep quality	WASO (min)	38.0 (18.1)	–	−0.7 (16.9)	35.7 (16.5)	–	5.4 (19.0)	0.403	–	**0.047**
Successfully reduced smoking, n (%)		–	42 (54.5%)	48 (66.7%)	–	33 (43.4%)	36 (49.3%)	–	0.169*	**0.034***

GOE, Green Oat Extract; WHOQOL-BREF, abbreviated World Health Organization Quality of Life; VAS, Visual Analogue Scale; F-36, Short Form-36 Health Survey; PSS, Perceived Stress; COMPASS, Computerized Mental Performance Assessment System; Data is expressed as mean (standard deviation); Data is expressed as mean (standard deviation) unless otherwise stated; P1, Comparison between baseline values; P2, Comparison between GOE and placebo for change from baseline to week 4; P3, Comparison between GOE and placebo for change from baseline to week 8; *P*-values are based on an independent *t*-test; †Based on analysis of covariance controlled for baseline; **P*-values are based on the Chi-squared test; Bold indicates significant differences at $p < 0.05$.

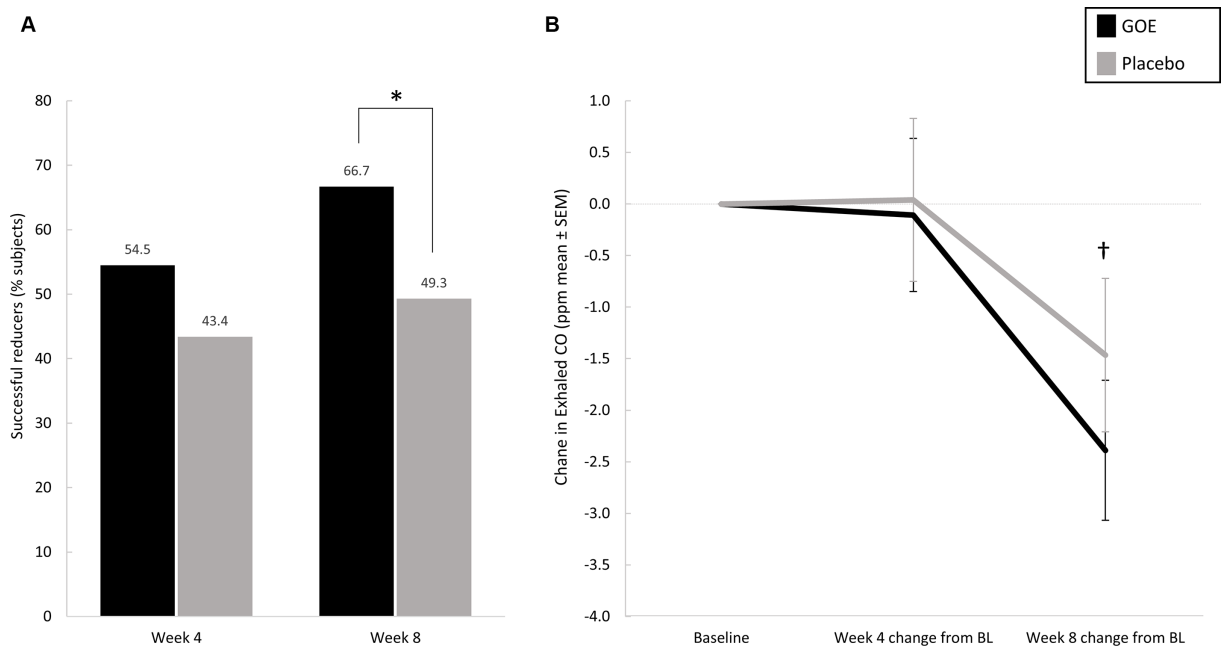

FIGURE 4
(A) Percentages of successful reducers (20% or more reduction in CPD) in the two study groups, with significant differences in favor of the GOE group at week 8. **(B)** Exhaled CO measurements (ppm) in the two study groups. *$p < 0.05$ for between-group comparisons. †$p < 0.05$ for change at week 8 compared to baseline in the GOE group. BL, baseline.

resulted in less participants who reported tingling in hands and feet, sweating, and dizziness/vertigo over time. In comparison of symptoms severity, no significant differences were observed between the groups or overtime in any of the symptoms following 4 and 8 weeks of consumption (Supplementary Table S8).

3.3.5 Depression and anxiety levels

There were no significant differences between study groups in reported anxiety levels (STAI questionnaire) or depression (BDI-II) levels. Study groups presented a decrease in subscales scores overtime, however only the STAI-Trait (general anxiety feeling) score was found to be significantly different compared to baseline in both groups (Supplementary Table S9). BDI-II scores within the GOE group decreased significantly following 4 and 8 weeks as compared to baseline. In the placebo group, a significant decrease was observed only following 4 weeks of consumption (Supplementary Table S9).

3.3.6 Craving level, nicotine dependency, and withdrawal symptoms

No significant differences were observed between the study groups in craving parameters, nicotine dependency and withdrawal symptoms. Within both study groups, there was a significant decline in some of the craving parameters, cigarette dependency and withdrawal test measures at weeks 4 and 8 when compared to baseline values (Supplementary Table S10).

3.3.7 Sleep quality

At 8 weeks, a significant improvement in the wakefulness after sleep onset (WASO) was recorded in the GOE group as compared to the placebo group (Table 4). Furthermore, sleep efficiency, WASO, and time of mean wake episode were also deteriorated in the placebo group overtime, while there were no significant changes in the GOE group (Supplementary Table S11).

3.3.8 Cognitive performance

We did not observe significant differences in the cognitive performance between the study groups. The results of cognitive performances using the COMPASS platform are summarized in Supplementary Table S12. Both groups showed significant improvements in some parameters, and worsening in others as shown in Supplementary Table S12, therefore the cognitive results were considered inconclusive and not clinically meaningful.

3.3.9 Follow-up period

After the 8-weeks intervention period, participants went through an additional 4 weeks of follow-up (no intervention) to obtain information on differences in their QoL parameters, physical symptoms, cognitive performance, and smoking behavior. After the 4-week follow-up period the GOE group showed a significant improvement as compared to placebo in the overall QoL and social relationship domains of the WHOQOL-BREF (Supplementary Table S3). The GOE group also showed improvement in social relationship overtime. Furthermore, significant differences were found in the level of concentration/focus as measured by the VAS QoL panel, where the GOE group showed improvement as compared to placebo. Significant differences overtime were observed at week 12 in the concentration/focus level records for the GOE group, and an increase in physical health, happiness, satisfaction with leisure time activity and mood level in the placebo group (Supplementary Table S4).

No significant changes in CPD, exhaled CO, urinary or blood cotinine levels between the two study groups were found from weeks 8 to 12. Abstinence after the follow-up period was achieved in 2 participants in the GOE group and 3 participants in the placebo group (Supplementary Table S6). Results of cognitive performance after the follow up period are shown in Supplementary Table S12. Like the cognitive outcomes in the intervention period, both groups showed significant improvements in some parameters, and worsening in others and the results are inconclusive.

3.3.10 Adverse events and compliance

A total of 35 AEs occurred among the 79 participants in the GOE group, and 48 AEs were reported among 82 participants in the placebo group. A majority of the complaints were related to musculoskeletal and gastrointestinal AEs, particularly muscle pain, back pain, and abdominal discomfort. All AEs were of mild intensity and unrelated to the study products, except for two cases of loss of appetite (GOE and placebo groups, one participant in each) and one case of gastroenteritis in the placebo group, which were considered possibly related with the study product (data not shown).

The overall mean compliance with the study products was 97.5% (± 3.1) with no significant difference between the study groups (detailed in Supplementary Table S10).

4 Discussion

This study evaluated the potential effects of GOE on wellness and wellbeing of healthy individuals during their smoking reduction or cessation experience. GOE has been shown to act as MAO-B inhibitor and could potentially increase dopaminergic availability. This is the hypothesized mechanism contributing to reduction of physical and psychological symptoms associated with smoking reduction or cessation. This study demonstrated that 8-week consumption of GOE during smoking reduction or cessation experience was associated with greater improvements from baseline in physical health and psychological domains (WHOQOL-BREF, primary outcome). Similarly, additional measured aspects of quality of life, physical and mental subscales of general health, perceived stress and the quality of sleep have also showed improvement with GOE supplementation as compared to placebo and across the intervention period, when compared to baseline.

Participants in this study could be classified as moderate nicotine dependents based on their reported CPD and FTND scores, this classification also stands in regard to the measured QOL scores in WHOQOL-BREF domains which are considered appropriate for mild to moderate dependence, as was observed in other studies (45, 46). In general terms, quality of life is associated with person's total wellbeing, psychological, social, and physical health status and the interrelations between these aspects (18, 46, 47). The physical aspects of quality of life are likely related to a subjects' general functioning, disabilities or impairments which distress the perception of their health, while the psychological and mental parameters are commonly associated with depression, anxiety, and stress, which are common among smokers (22, 48). This study demonstrated that GOE supported the participants' physical and psychological aspects of quality of life,

therefore enabling a more successful reduction experience. This was observed by the significant difference of those subjects who successfully reduced smoking.

Many smokers are under the impression that smoking aids in their ability to manage stress, and they fear that quitting smoking would lead to the loss of an efficacious stress-coping mechanism. However, there is strong evidence that the act of quitting smoking is linked to a reduction in stress levels (49, 50). Others suggest that the interplay between smoking and stress is bidirectional, wherein unsuccessful cessation or relapse could heighten an individual's stress levels, while conversely, stress might interfere with smoking cessation success (51). In light of this conceptual framework, the consumption of GOE has demonstrated the ability to reduce stress levels among individuals trying to reduce or cease smoking. Consequently, this intervention holds the potential to foster a more constructive and positive experience.

An additional factor that impacts the health and wellbeing of any individual, particularly smokers, is sleep quality. Inadequate sleep can lead to a wide range of disorders (52). In our study, sleep quality among placebo consumers was significantly worsened across study period with poorer sleep efficiency and more wakefulness time, while GOE consumers maintained their sleep quality and experienced significantly less minutes of wakefulness after sleep onset. In light of other studies suggesting that targeting sleep quality could be a potential treatment for relapse prevention (53), GOE is potentially supporting smokers experience to reduce and quit smoking also by maintaining their sleep quality.

We showed that subjects consuming GOE for 8 weeks included significantly more successful reducers (>20% reduction in CPD) as compared to the placebo group. This finding reinforces the suggested association between improvement in subjects' wellness and wellbeing to successful reduction experience. The negative relationship between smoking and quality of life and the association with number of cigarettes smoked is well known and demonstrated in several previous studies (22, 47, 54). Smoking reduction is often suggested as a step toward quitting for individuals who are unable or not willing to quit smoking abruptly. Studies have shown that smoking reduction increases the probability of cessation in the long term, as gradual and controlled reduction is related with less withdrawal symptoms and a success feeling that may motivate smokers to quit (55–57). Therefore, improvement in an individual's wellness and wellbeing during the experience of reduction could also play an important role contributing to cessation success. Although the exhaled CO levels were significantly reduced from baseline values in the GOE group, there were no significant differences between the groups for the change in exhaled CO level. This could be related to the relatively small decrease and accuracy of the method or to the relatively high variance between the participants in both groups.

In relation to physical and physiological symptoms, the consumption of GOE did not seem to have any impact on the severity or frequency of symptoms related to the smoking reduction or cessation experience, impact on general functioning, nicotine withdrawal symptoms, nicotine dependence level, anxiety, depression, urge to smoke, as well as the related biomarkers. Although there was a significant difference in proportion of participants reporting headache, which appeared to be higher in the GOE group as compared to placebo, this difference was not considered a clinically meaningful in terms of tolerability outcome, as both groups showed significant reduction overtime in the reported frequency. Similarly, reward craving score and momentary urge to smoke following cue exposure test were significantly different at week 4 only with better outcome for placebo, but this was also not considered clinically meaningful. It was previously demonstrated that GOE had improved cognitive performance (28), however, cognitive performance results of the present study were inconclusive. This may be associated with the smoking abstinence time before participants conducted the test (>1.5 h). It was suggested in other studies, that nicotine has a temporary effect in enhancing cognitive performance. Therefore, during smoking deprivation, cognitive deficits are observed in participants who are deprived smoking than those who actively smoked immediately before the test or nonsmokers. Research also showed that smoking is significantly associated with cognitive deficits regardless of depravation time, and more smoking tend to show larger deficits (58–61).

During the follow-up period, smoking behavior remained consistent with the end of intervention period. Participants in the GOE arm reported significant improvement in several quality-of-life parameters including overall QoL, social relationship, and concentration/focus level as compared to placebo. These differences may be attributed to the higher numbers of successful smoking reducers that were observed at the end of the intervention period following GOE consumption and were consistent during the follow up period. Coughing was improved in favor of the placebo group, but this difference is not considered clinically relevant. In relation to cognitive performance, tests results remained inconclusive, similar to the intervention period. In terms of safety, GOE was well tolerated by the study participants, all AEs were mild and only one was considered possibly related to study product.

4.1 Limitations and strengths

Despite the asset of this randomized, double-blind, placebo-controlled design there were limitations to the study, one of which being the relatively short intervention period not showing a long-term effect of the product. Additionally, the studied population mostly consisted of mild to moderate tobacco dependent participants, therefore not showing efficacy to those with high tobacco dependency. Nevertheless, this study is considered clinically relevant and showed adequacy in assessing QoL during smoking reduction or cessation experience while demonstrating outcome measures in line with other studies in the specific research area (46, 49, 62, 63). This study showed the practical clinical applicability of GOE as an ingredient that can effectively support the first weeks in smoking reduction or cessation attempts, which are considered to be a critical period for a successful quitting in the long term (64, 65). Further studies should be planned to confirm the benefits of GOE supplementation during smoking reduction or cessation experience, particularly including population of heavy smokers.

5 Conclusion

GOE (Neuravena®) supplementation provided greater improvements in quality of life measures as well as parameters

quantifying stress and sleep during smoking reduction or cessation as compared to those consuming placebo. The beneficial effects were also demonstrated by the higher prevalence of successful smoking reducers at the end of the intervention period in the GEO group. Therefore, Neuravena® may be useful to support subjects in the process of reducing their smoking consumption.

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 authors.

Ethics statement

The studies involving humans were approved by the Ethics Committee of Universidad Católica San Antonio (protocol code CE102004). The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

Author contributions

MF: Conceptualization, Writing – original draft, Writing – review & editing, Data curation. AG-M: Investigation, Writing – original draft, Writing – review & editing, Data curation. AL: Conceptualization, Writing – review & editing. SP-P: Investigation, Writing – review & editing. DV-M: Investigation, Writing – review & editing. FL-R: Conceptualization, Formal analysis, Writing – review & editing. AG-G: Investigation, Writing – review & editing. JM-M: Investigation, Writing – review & editing. FC: Conceptualization, Investigation, Writing – original draft, Writing – review & editing. EI: Conceptualization, Writing – original draft, Writing – review & editing. JJ: Writing – original draft, Writing – review & editing.

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Conflict of interest

MF, EI, AL, and JJ were employees of IFF Health, which commercializes the Neuravena®. FL-R, FC, AG-M, DV-M, SP-P, and AG-G were part of the Physiology Laboratory staff at Catholic University of Murcia, Murcia, Spain, and were hired by IFF Health to conduct the study.

The remaining author declares 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/fnut.2024.1405156/full#supplementary-material

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Unraveling the role of social support in eating behavior among children and adolescents in Shanghai, China: exploring the mediating role of self-efficacy and the moderating influence of BMI and weight concern

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Objective: This study explores the intricate relationship between social support and eating behaviors in children and adolescents, considering the mediating role of eating self-efficacy and the moderating effects of body mass index (BMI) and weight concern.

Methods: Data from 1986 primary and secondary school students aged 8 to 17 in Shanghai, China, were analyzed using moderated mediation analysis.

Results: The results demonstrate a robust positive association between social support and eating self-efficacy, particularly prominent among individuals with low BMI (effect = 0.506, 95% CI [0.376, 0.636]). Moreover, the study highlights that eating behavior is influenced not only by eating self-control (β = −0.054, 95% CI [−0.062, −0.046]) but also by the interaction term between individuals' perceptions of their body weight (β = −0.0008, 95% CI [−0.0015, −0.0001]).

Conclusion: Eating self-efficacy serves as a mediator in the relationship between social support and eating behavior, modulated by BMI and weight concern. Importantly, high weight concern significantly strengthens the mediating effect of eating self-efficacy on the relationship between social support and eating behavior, regardless of BMI.

KEYWORDS

eating behavior, self-efficacy, social support, weight concern, obesity

1 Introduction

In recent decades, obesity among children and adolescents has surged, with the prevalence rate increasing approximately eightfold (1). This escalation is closely tied to unhealthy eating behaviors, including the consumption of high-energy-dense foods and beverages (2). A study involving Bangladeshi adolescents aged 13–19 revealed that the likelihood of obesity among those with unhealthy eating behaviors was 1.634 (95% CI 1.495–1.786) compared to those with healthy eating behaviors (3). Despite numerous intervention studies targeting eating behaviors, treatments often fail shortly after initiation. This failure is largely attributed to our limited understanding of the psychological factors behind unhealthy eating behaviors and a flawed assumption that teenagers will readily modify their unhealthy behaviors solely in response to persuasion from teachers, parents, and other sources (4).

Eating behaviors have been shown to be associated with individual characteristics (e.g., body mass index) (5), interpersonal interactions (e.g., social support) (6), and an individual's perceived confidence (i.e., self-efficacy) (7). Recent studies have suggested that social support serves as a positive impetus for healthy eating (8, 9). Furthermore, social support and self-efficacy are significantly correlated and play crucial predictive roles in healthy eating behaviors, as validated in populations such as pregnant women (2), athletes (10) and middle-aged and elderly individuals (11). Previous studies consistently indicate that higher levels of social support can enhance health dietary habits through self-efficacy, resulting in reduced fat intake and increased consumption of fruits and vegetables. However, there is limited understanding regarding the association between social support and healthy eating behaviors among children and adolescents in middle-income countries.

Building upon the Theory of Planned Behavior and the Health Action Process Approach, this study posits that social support fosters intentions and subsequently impacts eating behavior through the mediation of self-efficacy. Social support is defined as individuals' perception of the care, support, and assistance received from family members, friends, and others (9, 12).

Demonstrated as a protective factor, social support has consistently shown a positive association with eating self-efficacy. Eating self-efficacy, also known as self-efficacy in weight management, reflects one's confidence in self-regulation to achieve healthy eating behaviors despite temptations (13). Higher levels of eating self-efficacy indicate stronger self-regulation, leading to healthier eating behaviors.

BMI can significantly influence the psychological well-being of adolescents. For example, a study has found that obese adolescents often experience higher levels of self-consciousness and inner sensitivity (14). Groshon demonstrated that individuals with high BMI may internalize stereotypes of lacking self-control, leading to a reduction in eating self-efficacy (15). To better explore the psychological states of youths with different BMIs and their potential impact on eating behaviors, this study incorporates BMI as a moderating variable between social support and eating self-efficacy. It hypothesizes that high BMI may weaken the effect of social support on eating self-efficacy.

It is further hypothesized that the influence of eating self-efficacy on eating behavior is moderated by weight concern, which refers to an individual's perception of their body weight. The hypothesis is grounded in the concept that "people will have greater self-efficacy if they perceive stronger motivation and severity" (16), and is supported by research confirming the interrelationships among weight concern, self-efficacy, and eating behavior (17, 18). Eating self-efficacy may be significantly correlated with increased adoption of diet-promoting behaviors, particularly notable when individuals express heightened concern about their weight.

In this study, we present a structural equation model aimed at uncovering the intricate pathways connecting social support with healthy eating behavior, utilizing eating self-efficacy as a mediator and BMI and weight concern as moderators (see Figure 1). Our aim is to enhance comprehension of the psychological mechanisms through which social support influences changes in eating behavior among children and adolescents. By addressing current research disparities, our study provides crucial insights for the development of effective weight loss interventions in the future.

2 Materials and methods

2.1 Participants and procedures

The cross-sectional study, employing cluster random sampling, was conducted in Shanghai, China, from October to December 2023. Jing'an District was specifically chosen as the study site due to its central location within Shanghai and its representation of the city's average economic status. Within this district, a neighborhood administrative office (street office) was randomly selected. Subsequently, all public primary and secondary schools with four or more enrollment classes within the jurisdiction of this selected neighborhood administrative office were identified and enlisted. Random numbers were then assigned to each eligible school, and using a randomized selection process, two middle schools and two primary schools were chosen from this pool of eligible institutions. To accommodate the cognitive levels of younger students, data collection in primary schools covered grades 3 to 5. Additionally, in recognition of the transition pressures associated with higher education, junior high schools encompassed grades 6 through 8, while senior high schools included grades 10 and 11. The study questionnaire consisted of 166-items. Following the principle of sample size determination, which dictates that the sample size should statistically cover ten times the number of items (19), a minimum sample size of 1660 was determined. Factoring in a 20% non-response rate, the target sample size was set at 2075.

Based on the research objectives, we developed a web-based information system comprising of six modules encompassing demographic information, physical activity, eating behavior, sleep patterns, psychological aspects and social support. After consent was obtained from the participants and legal guardians, all eligible students accessed the system with the assistance of the researchers to complete the questionnaire autonomously. Furthermore, a professional team conducted physical examinations on students, including measurements of height, weight, visual acuity, and other relevant indicators.

A total of 2106 students completed the questionnaire, yielding 1986 (94.30%) valid responses. Among these, 1056 (53.18%) were

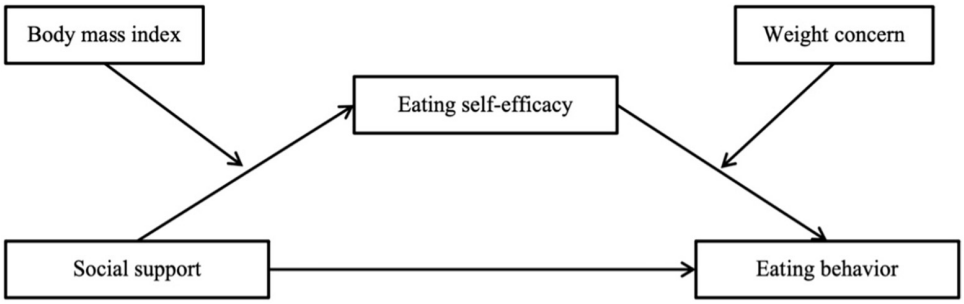

FIGURE 1
Conceptual framework of this study.

male, and 930 (46.83%) were female. The surveyed population comprised 670 primary school students, 660 junior high school students, and 656 senior high school students, with ages predominantly falling between 8 and 17 years.

2.2 Measures

2.2.1 Anthropometric measures

Body weight (recorded to the nearest 0.1kg) and height (recorded to the nearest 0.5cm) were obtained during the physical examination. BMI values were then calculated using the formula: weight (kg)/height (m^2).

2.2.2 Social support

Social support was measured by the Social Support Appraisals (SS-A) scale (20), consisting of three subscales: support from family, friends, and others outside of family and friends. This scale, comprising 20 items rated on a 5-point Likert scale, has been extensively utilized in Chinese adolescents (21). A total score was calculated by summing these items, with higher scores indicating greater perceived social support. In the present study, the Cronbach's α coefficient for the entire scale was 0.849.

2.2.3 Eating self-efficacy

Participants' eating self-efficacy was evaluated using the Weight Efficacy Lifestyle Questionnaire Short-Form (WEL-SF), originally developed by Matthew M. Clark (22) and revised by G. E. Ames (23). This 8-item questionnaire has been validated to assess self-efficacy judgments regarding eating behavior (24), with a higher total summed score indicating stronger eating self-efficacy. The questionnaire demonstrated strong psychometric properties in the current sample (Cronbach's α = 0.937).

2.2.4 Weight concern

Body weight concern was assessed using The Weight Concerns Scale (WCS) (25), a valid measure consisting of five items rated on a Likert-type scale ranging from 4 to 7 points (26). This scale was developed based on the observed strong association between eating disorder symptoms and concerns related to body weight, with higher scores indicating greater weight concerns. In our study, the Cronbach's α coefficient for this scale was computed at 0.788.

2.2.5 Eating behavior

The eating behavior questionnaire was adapted from the Chinese Adolescent Health-Related Behavior Survey (27). It comprises 10 items assessing the frequency of consumption of fruits, vegetables, dairy products, and unhealthy foods (snacks, sugar-sweetened beverages, desserts, and fried foods). Additionally, it calculates the frequency of breakfast consumption, dining at Western-style fast food restaurants and street vendors, and identifies whether there is selective eating behavior. Unhealthy eating behavior was indicated by a higher total score, the internal consistency of this data was α = 0.628.

2.3 Data analyses

Social support, eating self-efficacy, eating behavior, BMI, and weight concern were included in the analyses, with social support serving as the independent variable and eating behavior as the dependent variable. Spearman correlations were utilized to explore both the intra- and inter-relationships among the variables. We examined the distribution of variables and standardized weight concern, social support, eating self-efficacy, and BMI. SPSS Statistics Version 27.0, incorporating the PROCESS macro-instructional software Model 21 (28) with 5000 bootstrapped resamples, was employed to investigate whether eating self-efficacy mediates the relationship between social support and eating behavior, and whether this mediation is moderated by BMI and weight concern when adding gender as a covariate. A simple slope test was then used to examine the moderator effect (29).

3. Results

3.1 Descriptive analysis results

Table 1 presents the descriptive analysis and bivariate analysis of the variables under investigation. Participants exhibited a moderate to high level of social support (Mean = 50.030) and relatively high eating self-efficacy (Mean = 55.390), indicating a strong confidence in overcoming challenges associated with excessive eating. Additionally, a significant positive correlation was observed between social support and eating self-efficacy ($r = 0.218$, $p < 0.001$), suggesting that higher levels of social support were

TABLE 1 Descriptive statistics and correlation analysis.

Variables	*M*	SD	Correlations				
			1	2	3	4	5
1. Social support	50.030	10.414	1.000	0.218***	−0.222***	−0.064**	−0.142***
2. Eating self-efficacy	55.390	22.334		1.000	−0.033***	−0.123***	−0.175***
3. Eating behavior	18.570	4.206			1.000	0.091***	0.025
4. Body mass index	20.417	5.752				1.000	0.276***
5. Weight concern	13.523	11.592					1.000

$N = 1986$; $^{**}p < 0.01$, $^{***}p < 0.001$.

TABLE 2 Moderated mediation analysis results.

Direct effects	Eating self-efficacy (SE)			Eating behavior (EB)		
	β (SE)	β 95% CI	*T*-value	β (SE)	β 95% CI	*T*-value
Social support (SS)	0.385 (0.047)***	(0.292, 0.478)	8.125	−0.067 (0.009)***	(−0.085, −0.050)	−7.736
Body mass index (BMI)	−0.369 (0.103)***	(−0.571, −0.168)	−3.590			
SS × BMI	−0.021 (0.008)**	(−0.036, −0.006)	−2.674			
Eating self-efficacy (SE)				−0.054 (0.004)***	(−0.062, −0.046)	−13.159
Weight concern (WC)				−0.040 (0.008)	(−0.020, 0.110)	−0.484
SE × WC				−0.0008 (0.0003)*	(−0.0015, −0.0001)	−2.283
Conditional indirect effects				**Effect**	**95% CI**	
SS → SE → EB: low BMI, low WC				−0.023	(−0.031, −0.009)	
SS → SE → EB: low BMI, medium WC				−0.027	(−0.036, −0.011)	
SS → SE → EB: low BMI, high WC				−0.032	(−0.043, −0.013)	
SS → SE → EB: medium BMI, low WC				−0.017	(−0.024, −0.011)	
SS → SE → EB: medium BMI, medium WC				−0.021	(−0.027, −0.015)	
SS → SE → EB: medium BMI, high WC				−0.024	(−0.033, −0.016)	
SS → SE → EB: high BMI, low WC				−0.012	(−0.025, −0.006)	
SS → SE → EB: high BMI, medium WC				−0.014	(−0.031, −0.007)	
SS → SE → EB: high BMI, high WC				−0.017	(−0.035, −0.008)	

SE, standard error; 95% CI = 95% confidence interval. $^{*}p < 0.05$, $^{**}p < 0.01$, $^{***}p < 0.001$.

associated with greater eating self-efficacy. Furthermore, both social support ($r = -0.222$, $p < 0.001$) and eating self-efficacy ($r = -0.033$, $p < 0.001$) demonstrated significant negative correlations with eating behavior, indicating that higher scores in social support and perceived eating self-efficacy were associated with lower scores on eating behavior questionnaires and fewer unhealthy eating behaviors.

3.2 Moderated mediation analysis results

Table 2 displays the direct relations between social support, eating self-efficacy and eating behavior, as well as the indirect effects of social support on eating behavior mediated by eating self-efficacy, as moderated by BMI and weight concern. Figure 2 illustrates the results of the model testing, highlighting statistically significant paths ($p < 0.05$). The model significantly predicted eating behavior, R-squared = 0.13, $F = 69.90$, $p < 0.001$.

Social support exhibited a significant negative relationship with eating behavior (β = −0.067, $p < 0.001$), supporting the hypothesis that higher levels of social support are associated with healthier dietary patterns. Furthermore, increased social support was significantly linked to higher eating self-efficacy, moderated by BMI (β = 0.385, $p < 0.001$), while eating self-efficacy was significantly associated with healthy eating behavior moderated by weight concern (β = −0.054, $p < 0.001$). This suggests that social support indirectly promotes healthy eating behavior by enhancing eating self-efficacy. To be more specific, through eating self-efficacy, the impact of social support is particularly robust when BMI is low and weight concern is high (conditional indirect: −0.032, 95% CI from −0.043 to −0.013). Conversely, the indirect effect is minimal among adolescents with high BMI and low weight concern (conditional indirect: −0.012, 95% CI from −0.025 to −0.006). Moreover, high weight concern can mitigate the impact of high BMI, with the effect being amplified when both BMI and weight concern are high (conditional indirect: −0.017, 95% CI from −0.035 to −0.008).

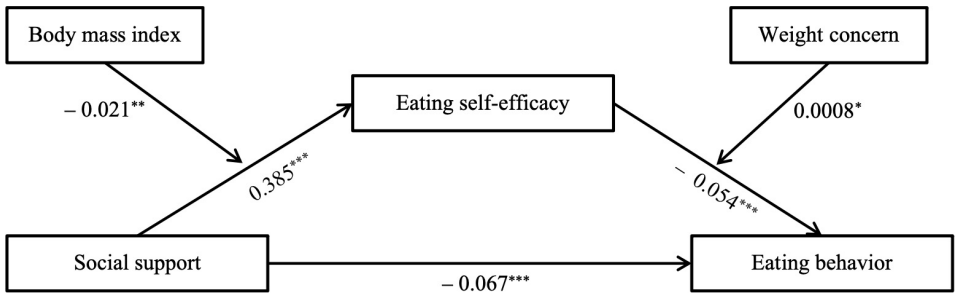

FIGURE 2
Moderated mediation model with indirect and direct effects of eating self-efficacy and social support on eating behavior. *Indicates significant paths: *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$.

TABLE 3 Moderation analysis results.

Variables	Moderator	Values	Effect	95% CI	
				Lower limit	Upper limit
Social Support	Body mass index	Low (-1SD)	0.506***	0.376	0.636
		Medium (the mean)	0.385***	0.292	0.478
		High (+ 1SD)	0.265***	0.138	0.391
Eating self-efficacy	Weight concern	Low (-1SD)	−0.045***	−0.055	−0.035
		Medium (the mean)	−0.054***	−0.062	−0.046
		High (+ 1SD)	−0.063***	−0.075	−0.051

95% CI = 95% confidence interval. ***$p < 0.001$.

3.3 Simple slope analysis results

To further elucidate the moderation effects, moderators were categorized by addition or subtraction of one standard deviation from the mean, and simple slope tests were carried out to explore the relationships (see Table 3). As depicted in Figure 3, with increasing BMI, the effect diminishes, suggesting that social support has a stronger influence on eating self-efficacy among adolescents with lower BMI. Specifically, when BMI is low (−1 SD), the effect is 0.506 ($p < 0.001$). When the value reaches the mean, the influence decreases to 0.385 ($p < 0.001$). Further increasing the moderator value to high (1 SD) results in a decreased influence of 0.265 ($p < 0.001$).

The simple slope test examines the interaction between eating self-efficacy and weight concern on eating behavior (see Figure 4). Eating self-efficacy significantly contributes to healthy eating behavior to a greater extent when weight concern is high (effect = −0.063, $p < 0.001$) compared to when it is low (effect = −0.045, $p < 0.001$). Notably, individuals with high weight concern and low levels of eating self-efficacy exhibit elevated scores on the eating behavior questionnaire, indicating unhealthy eating behavior. These findings underscore the importance of a positive combination of eating self-efficacy and weight concern for fostering healthy eating behavior.

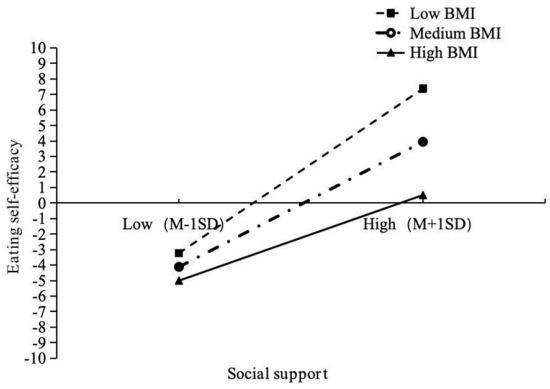

FIGURE 3
Simple slope analysis: relationship between social support and eating self-efficacy moderate by BMI.

4 Discussion

To our knowledge, this study represents a pioneering attempt to introduce a conceptual model examining whether self-efficacy mediates the relationship between social support and eating behavior among children and adolescents in China. The findings from a substantial dataset support our hypothesis that self-efficacy mediates the association between social support and eating behavior, with BMI and weight concern moderating these effects.

The results revealed strong associations between social support, eating self-efficacy, and healthy eating behavior. Consistent with prior research (2, 13), individuals experiencing greater social support showed increased eating self-efficacy, leading to enhanced healthy eating behaviors. Furthermore, compared to adolescents with high BMI, those with low BMI exhibited stronger indirect

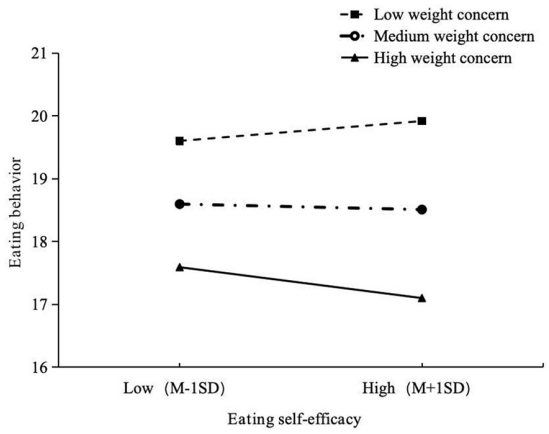

FIGURE 4
Simple slope analysis: relationship between eating self-efficacy and eating behavior moderate by weight concern.

effects. In other words, high social support brings about stronger eating self-efficacy among adolescents with low BMI, thereby improving their healthy eating behavior. A cross-sectional study in Finnish adults also found that a weak healthy self-efficacy was associated with increasing BMI, and perceived healthy self-efficacy correlated with a healthy food pattern (30). Additionally, the study revealed that regardless of BMI, social support significantly influenced healthy eating behavior through eating self-efficacy, particularly when weight concern was high. However, low eating self-efficacy in adolescents coupled with high weight concern paradoxically increased unhealthy eating behaviors. Previous research has underscored the link between weight concern and eating disorders, where heightened weight concern heightened the risk of binge eating (31). A plausible explanation is that heightened weight concern elevates the risk of binge eating, coupled with low eating self-efficacy, resulting in inadequate self-control and increased unhealthy eating behaviors. Overall, these findings highlight a combination of positive social support, eating self-efficacy, and weight concern in improving healthy eating behaviors and facilitating weight loss.

This article not only holds theoretical significance by addressing a research gap concerning the mechanisms of social support and dietary behavior among children and adolescents but also offers practical implications. It urges policymakers to integrate support from various sectors of society to develop specialized solutions for addressing the increasingly serious issue of childhood and adolescent obesity. Social support is consistently believed to contribute to the development of healthy eating behaviors, including the establishment of supportive environments and the provision of public weight-loss programs (32). Additionally, study by Gitta et al. emphasize that it is not solely the provision of social investment that matters, but also the enhancement of the public's subjective perception of the usefulness of social resources and support mechanisms, which further aids in the development of healthy eating behaviors (8). Research indicates that self-efficacy plays a crucial role in fostering healthy dietary behaviors (33). Moreover, parental dietary practices, feeding methods, and communication styles with their children can influence their children' s autonomy regarding eating behaviors and food choices (34, 35). Hence, collaborative efforts among families, schools, and community health centers are essential to conduct dietary self-regulation training for obese and overweight students, imparting knowledge on healthy eating, enhancing awareness, establishing correct self-image perceptions and weight perceptions. While improving eating self-efficacy, it is important to recognize the potential health risks associated with high BMI, increase weight concern, and promptly assist overweight adolescents in achieving weight loss goals.

While this study advances our understanding of the associations between social support and eating behavior, it is important to recognize several limitations. Firstly, the study data are cross-sectional, which restricts the ability to establish definitive directional relationships among the variables. Variables in the model, particularly BMI, weight concern, and social support, are subject to change over time. Therefore, longitudinal studies are essential to accurately monitor these fluctuations and their impact on eating behavior. Secondly, due to cost considerations, self-reported eating behavior questionnaires were used, assessing the frequency of consumption of various food items rather than quantifying absolute amounts. This approach may introduce biases, and ideally, more comprehensive questionnaires or 24-h dietary recalls should be employed. Thirdly, this study did not account for the influence of parental food practices, which may introduce bias into the data. This underscores the importance of considering confounding variables in future research to ensure the accuracy of results. Finally, the limited generalizability of the study findings may be attributed to specific sample characteristics, as the study only included primary and secondary school students from Shanghai. Future research should include data from more economically disadvantaged areas to confirm the external validity of the results.

In conclusion, the present study suggests that eating self-efficacy serves as a valid mediator of the influence of social support on eating behavior among Chinese children and adolescents. This mediation effect varied depending on BMI and weight concern; individuals with a lower BMI exhibited stronger eating self-efficacy, while high weight concern facilitated the transformation of social support into healthier eating behaviors through eating self-efficacy.

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 humans were approved by the Public Health and Nursing Research Ethics Committees affiliated to Shanghai Jiao Tong University School of Medicine (ref: SJUPN-20211). The studies were conducted in accordance with the local legislation and institutional requirements. Written informed

consent for participation in this study was provided by the participants' legal guardians/next of kin.

Author contributions

ST: Data curation, Formal analysis, Writing – original draft. RY: Data curation, Writing – original draft. GA: Data curation, Writing – review and editing. YX: Resources, Writing – review and editing. LZ: Resources, Writing – review and editing. BX: Resources, Writing – review and editing. WS: Resources, Writing – review and editing. LS: Investigation, Writing – review and editing. BJ: Investigation, Writing – review and editing. ZW: Project administration, Writing – review and editing. CC: Investigation, Project administration, Resources, Writing – review and editing. JS: Funding acquisition, Investigation, Project administration, Resources, Writing – review and editing.

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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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Exploring the relationship between binge eating and differentiation of self: the mediating role of emotional distress and work stress

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Binge Eating Disorder (BED) is a prevalent eating disorder outlined in the DSM-5. Emotional distress (including stress, anxiety, and depression) stands out as a critical risk factor for developing eating disorders, and specifically BED. Recent studies have identified differentiation of self- a family pattern involving the ability to balance emotions and cognitions, as well as intimacy and autonomy—as a factor that exacerbates emotional distress. This relationship highlights the importance of addressing both emotional distress and family dynamics in understanding BED. While associations have been found between work-related factors and family dynamics with emotional distress, there has been limited investigation into the specific risk factors that are uniquely linked to BED. It was hypothesized that differentiation of self would relate to BED symptoms through the mediation of emotional distress and work stress. A systematic sampling method was applied to select a total of 275 participants for this study, with 60% women and 40% men (aged 20–45, M=32.71, SD=7.50). The findings suggest that low differentiation of self may increase vulnerability to BED symptoms by increasing susceptibility to emotional distress, including stress in the workplace. In addition, the analyses indicated that women reported higher levels of BED symptoms, while men reported higher levels of differentiation of self. The study sheds light on the contribution of unregulated family and emotional patterns to BED, providing valuable insights for organizations seeking to promote healthier work environments.

KEYWORDS

binge eating, differentiation of self, emotional distress, work stress, anxiety, gender differences

Introduction

The prevalence of eating disorders is steadily increasing among women and men worldwide (1, 2). Among the various eating disorders outlined in the DSM-5 (3), binge eating disorder (BED) is particularly common, with a higher prevalence than anorexia nervosa and bulimia nervosa (4). BED has significant consequences for physical health (5, 6), and is often displayed with mental health disorders, such as anxiety, depression, and suicidal tendencies (7–9).

Research has found emotional distress to be a foremost catalyst of eating disorders (1, 2, 10, 11), particularly with regard to BED. There is also evidence that family dynamics play a crucial role in exacerbating, or conversely alleviating, emotional distress. An essential family

pattern associated with both mental and physical health is differentiation of self (DoS). This family pattern entails balancing intimacy and autonomy in interpersonal relationships with significant others. Moreover, within the intrapersonal realm, it involves managing cognitions and emotions during stressful situations (1, 2). A low level of DoS has been associated with emotional distress (1, 2), depressive symptoms (12), somatic symptoms (13), an increased risk of eating disorders (1, 2), work stress, and workplace dysfunction, including diminished job satisfaction (14) and heightened burnout (15).

Despite the extensive evidence, theoretical and empirical literature on the symptoms of BED remains limited (4). Furthermore, only a small number of studies have investigated the factors that may contribute to its escalation (16, 17). Hence, the primary aim of the current study was to elucidate the intricate interplay between these dimensions and to explore whether a low level of DoS would contribute to the amplification of emotional distress and work stress, contributing in turn to the intensification of BED symptoms. In addition to this, considering the gender differences reported in studies on DoS, emotional distress, and, notably, some studies on BED, further investigation is imperative. Hence, another goal is to explore gender differences to ascertain whether, akin to other eating disorders, BED exhibits a higher prevalence among women. Additionally, examining gender differences aims to discern variations in the relationships among the research variables and BED. Exploring variations in the relationships between BED and associated risk factors, such as DoS and emotional distress, is crucial for several reasons. Firstly, understanding how these factors interact differently in individuals with BED can provide insights into the underlying mechanisms and pathways contributing to the development and maintenance of the disorder. Secondly, identifying specific patterns of association between BED and risk factors across genders can help tailor interventions more effectively, considering the unique needs and vulnerabilities of men and women.

BED symptoms

Individuals with BED engage in episodes of extreme food consumption, eating significantly larger amounts of food than the average person under similar circumstances. These episodes involve rapid and secretive eating, a lack of hunger, and a perceived loss of control (18). Feelings of self-disgust, depression, and discomfort due to excessive fullness are common during these episodes (17). BED is not associated with compensatory behaviors like vomiting or excessive exercise (3), though efforts are made to maintain weight and diet (19). Individuals diagnosed with BED are often prone to various health problems, including high cholesterol levels, high blood pressure, and type 2 diabetes. These conditions further elevate the risk of more serious diseases, such as heart disease and stroke (6, 20).

BED has been recognized as a distinct eating disorder in the DSM-5 (3) and is now acknowledged as one of the most prevalent ones. It is estimated to occur among 3.5% of women and 2.0% of men (19), compared to 0.9 and 0.3%, respectively, for anorexia nervosa and 1.5 and 0.5%, respectively, for bulimia nervosa (16). BED typically develops during emerging adulthood, specifically between ages 18 and 26, whereas anorexia nervosa often manifests at an earlier age (18). Indeed, BED is particularly prevalent among young adults (5, 21).

BED is a complex condition influenced by genetic, environmental, and psychological factors. Studies have linked BED to such factors as BMI, metabolic issues, and disrupted hunger and satiety mechanisms (22). Obesity has also been associated with BED (9, 23).

Recent research has highlighted the significant contribution of emotional factors to BED. Emotional distress is considered crucial to the development and persistence of BED (7, 24). Individuals with BED may be at increased risk of suicide attempts (8), and more than half (58%) the individuals diagnosed with BED seek therapy (6).

Emotional distress

Emotional distress encompasses symptoms of depression, anxiety, and stress, reflecting a state of emotional suffering. It arises from perceived difficulties in meeting daily demands and coping with stressful factors, often resulting in chronic somatic symptoms (25–27). Emotional distress serves as a crucial indicator of various mental disorders, such as depression and anxiety (3). High emotional distress has been associated with weight-related stigmatization reactions (28), food addiction (29), and excessive preoccupation with weight demonstrated through dietary restraint and dieting behaviors (30, 31). It has also been shown to be a primary risk factor for eating disorders, with individuals who experience stress, anxiety, and depression being particularly susceptible. Those exhibiting elevated levels of disordered eating attitudes and behaviors often display a heightened avoidance of emotions, and increased sensitivity. Consequently, adolescents and adults grappling with anxiety or depression may develop problematic or pathological eating patterns and thoughts (1, 2). Additionally, individuals with eating disorders and a history of childhood maltreatment exhibit heightened emotional overwhelming and increased post-stress body dissatisfaction, indicating altered emotional responses to stressors [e.g., (32)].

There is evidence of gender differences in emotional distress: elevated levels of persistent stress tend to be more prevalent among women (22, 24). Moreover, the work environment, including factors such as high workloads and time pressure, has been associated with elevated levels of emotional distress among employees, leading to various emotional responses, such as anxiety, depression, irritability, and burnout (33, 34).

Work stress

Work stress has become increasingly prevalent in recent decades due to global, economic, and technological changes, as well as population growth and lifestyle modifications (35). It intensifies when there is a disparity between employees' skills and the demands of their jobs (36) leading to difficulties in coping with work-related tasks (37, 38). Over 50% of workers consider work-related stress as the primary factor influencing their job, family life, and overall well-being, given the significant time spent at work (35). Studies on work stress have shown that both women and men experience increased work stress and reduced satisfaction with family and overall life when faced with long work hours and limited family time (33, 39).

Work stress has detrimental effects on employees, including diminished self-esteem (38), compromised job security, and reduced social relationships with colleagues (40). In addition, work

stress has been found to be correlated with less satisfaction with work and in personal life (41), as well as increased anxiety and depression (33). Physiologically, work stress has been associated with imbalanced high-calorie eating habits, often perceived as comforting but leading to weight gain (42), increased body mass (BMI), and risk of BED (43). Furthermore, work stress has been identified as a risk factor for heart disease and cancer (35).

Work-related stress has been attributed to various factors, such as high workloads, long hours, excessive job demands (35, 37), and work–life imbalance (e.g., limited self-care or leisure time, fatigue) (39, 44). Moreover, unregulated family patterns may act as a risk factor: a low level of DoS can contribute to elevated stress levels and reduced job satisfaction among employees in organizations (44). Individuals with low DoS are indeed more prone to heightened work-related stress and may encounter greater challenges in managing stress within work environments (14).

Differentiation of self

Family systems theory (45, 46) highlights the influence of emotional dynamics within the nuclear family on individuals' self-perception and development. A key pattern in this theory is Differentiation of Self (DoS), which defines family members' levels of emotional maturity, and is passed down from one generation to the next. DoS reflects emotional maturity and a strong sense of identity. Kerr and Bowen (46) distinguished between two realms of DoS, the intrapersonal and the interpersonal. At the intrapersonal level, it involves maintaining a healthy balance between emotions and rational thinking and expresses the individual's ability to separate their instinctually driven emotional reaction from their goal-directed functioning. On an interpersonal level, high DoS entails establishing a harmonious equilibrium between intimacy and autonomy in meaningful relationships (2, 47).

Kerr and Bowen (46) argued that DoS is critical for mature development and the attainment of psychological health. Higher DoS allows one to experience strong affect or shift to calm, logical reasoning when circumstances dictate. Well differentiated individuals operate equally well on both emotional and rational levels while maintaining a measure of autonomy within their intimate relationships. In contrast, poorly differentiated persons tend to be more emotionally reactive (46) (p. 320), finding it difficult to remain relaxed when dealing with stressful situations. With intellect and emotions fused, they tend to make decisions based on what "feels right"; in short, they are trapped in an emotional world (45). The concept of DoS has been used to describe the way family patterns affect the trajectory of individual health and influence the extent to which individuals are able to take personal responsibility for age-appropriate tasks, and experience strong connections with significant others (48).

DoS encompasses four dimensions. Emotional reactivity relates to the intensity of emotions experienced and expressed in challenging circumstances. I-position reflects an individual's ability to assert their needs, thoughts, and emotions while maintaining a sense of self without excessive reliance on others for validation. Emotional cutoff involves emotional and behavioral disconnections arising from difficulties in direct communication during challenging situations. Finally, fusion with others refers to the tendency to form dependent relationships characterized by blurred boundaries (49, 50).

From a gender perspective, men tend to report higher levels of emotional cutoff, while women tend to report higher levels of emotional reactivity and fusion with others (13, 50). Well-differentiated individuals tend to exhibit better coping abilities in stressful situations, experience greater well-being, possess a positive self-concept, and align their lives with their own desires (50). Conversely, poorly differentiated people are more likely to report higher levels of anxiety (51), stress, and depression (2), and to be at higher risk for type 2 diabetes mellitus (52) and eating disorders (10, 53).

DoS, shaped by interactions within the family of origin, can impact relationships at work, where individuals spend a substantial amount of time. Limited research suggests that individuals with lower levels of DoS are more likely to experience lower job satisfaction and conflicts in the workplace. These challenges may stem from difficulties in adapting to job demands, regulating emotions effectively, and relying heavily on others for emotional support (14, 46). As far as we know, no studies have examined the contribution of DoS and work stress to BED.

Rationale and hypotheses

The literature highlights associations between BED symptoms, emotional distress (22), and work stress (43); between DoS and work stress (14); and between DoS and the risk of developing eating disorders (10). Yet, there is a lack of studies examining the combined contribution of these factors to the risk of BED among young adults, despite its high prevalence in this age group (18).

The goal of this study is to provide a framework that allows for an in-depth investigation of the complex relationships between BED symptoms, DoS (emotional reactivity, I-position, emotional cutoff, fusion with others) emotional distress (stress, anxiety, depression), and work stress, considering the potential mediating role of the latter two. Specifically, we examine how low DoS can heighten emotional distress and work stress, which in turn may exacerbate BED symptoms. This intricate interplay suggests that individuals with lower DoS are more vulnerable to stressors from work and family environments, which intensify emotional distress and may increase the risk of developing BED.

By incorporating all these variables and examining their associations, our research aims to provide a more nuanced understanding of the intricate pathway through which DoS, emotional distress, and work stress contribute to the development of BED. Moreover, we account for gender differences, acknowledging the observed distinctions in eating disorders (2) and specific symptoms of BED (7). Hence, we also investigate whether, in line with observations among young adults, BED tends to be more prevalent among women. This inquiry aims to deepen our comprehension of the risk factors associated with BED.

Accordingly, our research hypotheses were:

1 DoS (emotional reactivity, I-position, emotional cutoff, fusion with others) will be associated with BED symptoms (emotional/cognitive and behavioral), through the mediation of emotional distress (depression, anxiety, and stress) and work stress (Figure 1):

a Elevated levels of emotional reactivity, emotional cutoff, and fusion with others are expected to be associated with higher emotional distress and work stress, and consequently with heightened symptoms of BED.
b Conversely, a high level of I-position is anticipated to mitigate emotional distress and work stress, thereby being associated with a reduced likelihood of experiencing BED symptoms.

2 Gender differences are expected: women will be more likely to report higher levels of BED symptoms, emotional reactivity, fusion with others, and emotional distress than men, while men will be more likely to report higher levels of emotional cutoff than women.

3 Gender will moderate the associations between DoS and emotional distress and work stress, as well as between these study variables and BED symptoms. Specifically, these associations will be stronger for women than for men.

Methods

Sample

A systematic sampling method was applied, and a representative sample of the general Hebrew-speaking population of Israel was recruited. The sample includes a total of 275 Israeli participants, with 60% women and 40% men aged 20–45 ($M = 32.71$, $SD = 7.50$). Inclusion criteria required participants to be working individuals who were fluent in Hebrew, capable of understanding the questionnaire, and providing responses to the survey.

Instruments

The ***Binge Eating Scale*** (BES) (54) was used to assess the severity of BED symptoms. For the purpose of this research, the questionnaire was translated into Hebrew by an expert and then back-translated to English by another expert. The second author checked the congruency between the versions, and the final versions were reviewed by the three authors of the study. The questionnaire consists of 16 items divided into two scales: emotional/cognitive (sample item: "I do not feel self-conscious about my weight or body size when I'm with others"), and behavioral. Each item is rated on a Likert scale, with scores ranging from 0 to 2 or 0 to 4 (54). The scoring range for the questionnaire is 0–46, where 0–17 = no evidence of BED symptoms; 18–26 = a moderate degree; and 27 or higher = a severe degree. The cutoff point defining the presence of BED symptoms is set at 17 (55–58). The BED questionnaire demonstrated good internal consistency for the total score ($\alpha = 0.84$), and the feelings and thoughts scale ($\alpha = 0.81$), but low internal consistency for the behavior scale ($\alpha = 0.62$). Due to this latter low internal consistency and the high correlation between the two subscales, the total score was used in the present study.

The ***Short Depression, Anxiety and Stress Scale*** (DASS–21) (59), translated to Hebrew (1), was used to assess emotional distress. This 21-statement self-report questionnaire assesses symptoms in three areas (divided into three subscales): depression, anxiety, and stress. Sample item for stress: "I find it difficult to relax." Participants respond on a 4-point Likert scale (0 = strongly disagree, 3 = strongly agree). The questionnaire is suitable for both adults and youth aged 14 and above. In the current study, high internal consistency was found for the total score of the questionnaire ($\alpha = 0.94$), and good internal consistencies were observed for the three subscales: depression ($\alpha = 0.88$), anxiety ($\alpha = 0.82$), and stress ($\alpha = 0.88$).

The ***Job Stress Questionnaire*** (60), based on the Job-Related Tension Inventory (JRTI) (60), is a 15-item self-report tool used to assess employees' perceptions of work stress. We used the Hebrew version in the current study (Hebrew). Sample item: "How often are you bothered at work by not knowing what exactly the people you work with expect from you?" Participants respond on a Likert scale ranging from 1 (never) to 5 (almost all the time). Scores are averaged to calculate an overall score, ranging from 1 to 5. The questionnaire has demonstrated good internal consistency ($\alpha = 0.92$).

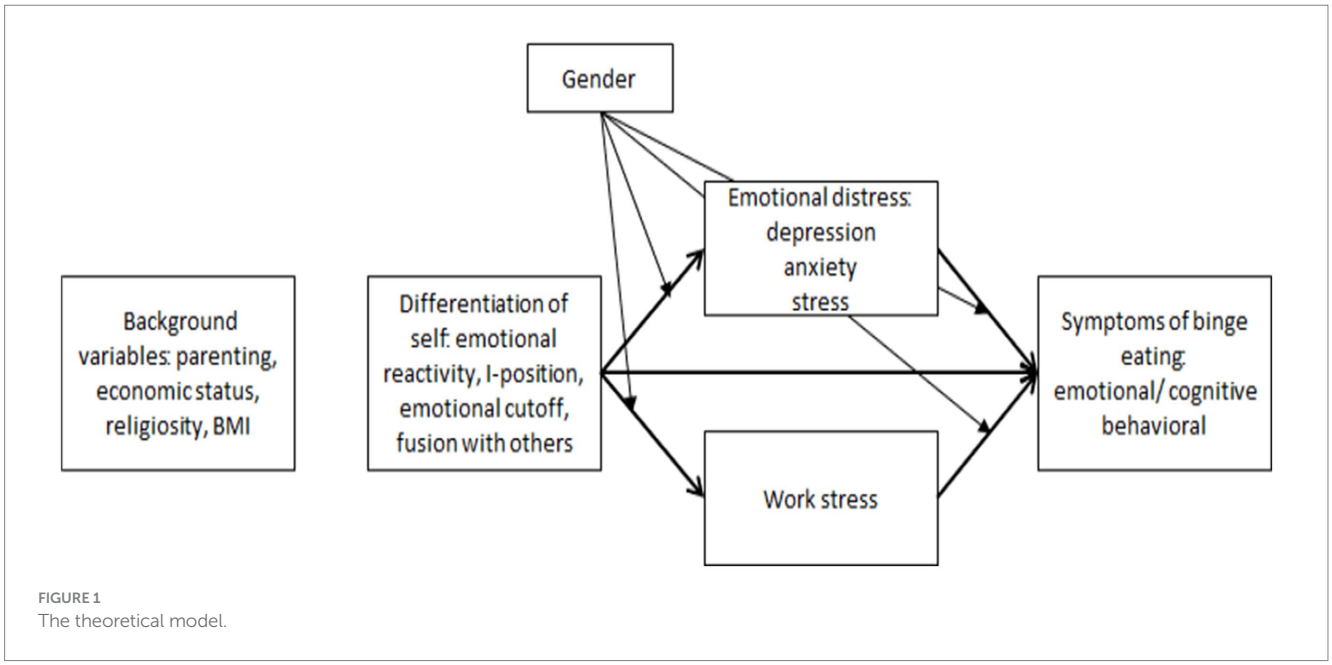

FIGURE 1
The theoretical model.

The *Differentiation of Self Inventory-Revised* (DSI-R) (48, 61) is a self-report questionnaire that has been translated to Hebrew by Peleg (62, 63). It assesses an individual's level of DoS and their relationships including with their family of origin. The 46 items are divided into four subscales: emotional reactivity, I-position, emotional cutoff, and fusion with others. Sample item: "I have difficulty expressing my feelings toward people who are important to me" (emotional cutoff). Participants respond on a Likert scale ranging from 1 (not at all true for me) to 6 (very true for me). The total score of the questionnaire is calculated by averaging the raw score of all the items in each of the four scales, with a higher score in the I-position scale, along with lower scores in emotional reactivity, emotional cutoff, and fusion with others scales, indicating a higher level of DoS. The questionnaire has demonstrated high internal consistency in the present study: for the total score ($\alpha = 0.90$), and for the four subscales, emotional reactivity ($\alpha = 0.89$), I-position ($\alpha = 0.81$), emotional cutoff ($\alpha = 0.82$), and fusion with others ($\alpha = 0.81$).

A ***demographic questionnaire*** was specifically developed for the present study. It included the following information: gender, age, marital status (married/in a relationship, single, divorced/widowed), parentage, number of children, education level, employment status (full-time salaried employee, part-time, self-employed), occupation, weekly work hours, economic status, religiosity (secular, traditional, religious, ultra-Orthodox), has a chronic illness, has learning disabilities, and weight and height (BMI). In assessing the economic status of participants, we used both a subjective assessment of their economic situation and an assessment based on the average income in Israel; the correlation between these two measures was $r = 0.53$ ($p < 0.001$). To provide a comprehensive representation of the participant's economic situation, an average between these two assessments was calculated.

Procedure

A survey company was contracted to assist with the distribution of the questionnaire to individuals who met the predetermined inclusion criteria using systematic sampling. The survey company uses a systematic sampling method (approacing every i^{th} person), using an on-line or direct communication with them. All participants were provided with a detailed explanation of the study's purpose and procedures. Participants were assured that their details would be kept anonymous and that their responses would be treated with utmost discretion. They were also informed of their right to withdraw from the study at any point without facing any consequences. Upon understanding the study's requirements and providing their voluntary consent, participants signed an informed consent form to signify their agreement to participate. They were then given access to the online questionnaire, which typically took 20–30 min to complete. Data collection took approximately 1 month. The study was approved by the University Ethics Committee (Approval No: 231/23).

Data analysis

Data analysis was done with SPSS software, version 28. Means and standard deviations were computed for continuous background variables; frequencies and percentages were calculated for categorical background variables. Means and standard deviations were calculated for the study variables, and Pearson correlations were calculated to examine their associations. Internal consistencies of the research variables were assessed by Cronbach's alpha (α). For BED symptoms and emotional distress, abnormality categories were determined based on the guidelines provided by the measurement tools. To explore the potential associations of background characteristics with the study variables, t-tests were performed comparing the study variables with dichotomous background variables (e.g., gender), and Pearson correlations were calculated between the study variables and the main continuous background variables (e.g., age). As the emotional distress variable and its dimensions were found to deviate from a normal distribution (skewness index = 1.09–1.68, SE = 0.15), a logarithmic transformation was applied to them. The two economic status variables (subjective assessment and assessment based on average income) were found to follow a normal distribution (skewness = −0.44, SE = 0.15, and skewness = −0.03, SE =0.15, respectively) and were thus treated as continuous variables.

The first hypothesis was evaluated through Pearson correlations between the independent (DoS), mediating (emotional distress, work stress), and dependent (BED symptoms) variables, as well as multiple linear regressions. For BED symptoms, background variables were entered in the first step, the independent variable (DoS) in the second step, and the mediating variables (emotional distress and work stress) in the third step. Regressions were also calculated for the mediating variables, with the background variables entered in the first step and the independent variable in the second.

To test the mediation model, structural equation modeling (SEM) was applied using AMOS software, version 28. The measurement model, which includes correlations between latent variables, was estimated first, followed by the mediation model. Fit indices were used to assess model fit, where a Cmin/df value of less than 3 was considered indicative of a good fit (64); NFI, NNFI, and CFI values greater than 0.90 represented a reasonable fit and values greater than 0.95 indicated a good fit (64, 65); and RMSEA values below 0.08 indicated a reasonable fit and values below 0.05 indicated a good fit (66). The mediation analysis was calculated using path analysis with 5,000 bootstrap samples and a bias-corrected confidence interval of 95%. Continuous variables were standardized. Control variables were gender, parentage, economic status, level of religiosity, and BMI.

The second research hypothesis, which focused on gender differences in the research variables, was examined with multivariate analyses of variance (MANCOVA), controlling for parentage, economic status, level of religiosity, and BMI.

Results

Descriptive findings

The distribution of the background variables is shown in Table 1. Approximately 10% of the study participants reported having chronic illnesses. The average body mass index (BMI) of participants was around 25, and about 56% of the participants reported normal weight or underweight.

Table 2 presents the distribution of the study variables and Pearson correlations between them. Significant moderate correlations were found between most of the variables. The three dimensions of DoS that point

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TABLE 1 Distribution of background variables ($N = 275$).

Variable		Values
Gender, n (%)	Male	110 (40.0%)
	Female	165 (60.0%)
Age, years M(SD)	Range: 20–45 years	32.71 (7.50)
Marital status, n (%)	Married, in a relationship	197 (71.7%)
	Single	71 (25.8%)
	Divorced/widowed	7 (2.5%)
Children, n (%)	Yes	161 (58.5%)
Number of children, M(SD)	Range: 1–9	2.48 (1.31)
Education level, n (%)	Less than high school	13 (4.7%)
	High school	48 (17.5%)
	Vocational	27 (9.8%)
	College student	34 (12.4%)
	Bachelor's degree	104 (37.8%)
	Graduate degree	49 (17.8%)
Years of education, M(SD)	Range: 8–22 years	14.75 (2.57)
Employment status, n (%)	Full-time salaried employee	220 (80.0%)
	Part-time salaried employee	45 (16.4%)
	Self-employed	10 (3.6%)
Occupation, n (%)	Manager	42 (15.3%)
	Academician	43 (15.6%)
	Technician, agent	24 (8.7%)
	Clerical/office worker	61 (22.2%)
	Sales and services	20 (7.3%)
	Skilled/unskilled worker in agriculture or industry	25 (9.1%)
	Other	60 (21.8%)
Weekly work hours, M(SD)	Range: 7–90 h	40.32 (11.56)
Economic status (subjective assessment), n (%)	Very bad	7 (2.5%)
	Bad	17 (6.2%)
	Moderate	123 (44.7%)
	Good	110 (40.0%)
	Very good	18 (6.5%)
Income relative to national average, n (%)	Much below average	34 (12.4%)
	Below average	74 (26.9%)
	Average	86 (31.2%)
	Above average	69 (25.1%)
	Much above average	12 (4.4%)
Religiosity, n (%)	Secular	129 (46.9%)
	Traditional	56 (20.4%)
	Religious	54 (19.6%)
	Ultra-Orthodox	36 (13.1%)
Chronic illnesses, n (%)	Yes	26 (9.5%)
Learning disability, n (%)	Yes	52 (18.9%)
BMI, M(SD)	Range: 17–55	25.46 (5.32)
BMI categories, n (%)	Underweight	11 (4.0%)
	Normal	143 (52.0%)
	Overweight	83 (30.2%)
	Obese	38 (13.8%)

TABLE 2 Distribution of the study variables and Pearson correlations between them ($N = 275$).

	M(SD)	1.	2.	3.	4.	5.	6.	7.	8.	9.	10.	11.
1. BED symptoms	9.37 (6.70)	1										
2. Emotional distress: total	21.68 (20.24)	0.40	1									
3. Depression	6.63 (7.36)	0.40	0.87	1								
4. Anxiety	5.37 (6.45)	0.31	0.80	0.68	1							
5. Stress	9.69 (8.42)	0.36	0.92	0.73	0.65	1						
6. Work stress	2.10 (0.67)	0.34	0.48	0.47	0.44	0.47	1					
7.DoS: total	3.86 (0.62)	−0.33	−0.61	−0.58	−0.48	−0.63	−0.53	1				
8. Emotional reactivity	3.39 (1.05)	0.29	0.57	0.50	0.47	0.63	0.46	−0.88	1			
9. I-position	4.07 (0.80)	−0.19*	−0.24	−0.30	−0.20*	−0.24	−0.25	0.45	−0.18*	1		
10. Emotional cutoff	2.58 (0.85)	0.18*	0.42	0.41	0.34	0.41	0.37	−0.67	0.43	$-.11^{ns}$	1	
11. Fusion with others	3.67 (0.81)	0.26	0.43	0.40	0.31	0.46	0.39	−0.77	0.75	$-.07^{ns}$	0.29	1

All r significant at $p < 0.001$, or $*p < 0.01$, and ns- non- significant.

to low differentiation (namely, emotional reactivity, emotional cutoff, and fusion with others) were positively correlated with BED symptoms, emotional distress, and work stress. Conversely, I-position and the total score of DoS (both of which indicate high differentiation) were negatively correlated with these same study variables. BED symptoms, emotional distress, and work stress were all positively correlated.

The categorization of BED scores revealed that approximately 88% of participants were classified as having no evidence of BED (a score of 0–17), while about 12% were classified as having a moderate (18–26) or severe (27+) degree of the disorder. In terms of gender differences, 21 women (12.7%) and 12 men (10.9%) were classified as suffering from moderate or severe BED, with no significant gender difference ($Z = 0.45$, $p = 0.649$). Similarly, the scores for the emotional distress dimension were also categorized.

Relationships between background and research variables

We examined relations between background and study variables to identify potential confounding factors that should be controlled for when analyzing the research hypotheses.

For BED symptoms, a significant gender difference was observed, with women reporting higher levels ($M = 10.13$, $SD = 6.68$) than men ($M = 8.23$, $SD = 6.59$) [$t(273) = 2.32$, $p = 0.021$]. Furthermore, there was a positive correlation between BMI and BED symptoms: the higher the BMI, the higher the level of BED symptoms ($r = 0.27$, $p < 0.001$).

With respect to emotional distress, significant differences in the total score were observed with regard to the parenting variable: non-parents reported higher levels of emotional distress ($M = 28.00$, $SD = 22.90$) than parents ($M = 17.20$, $SD = 16.81$) [$t(262.13) = 4.67$, $p < 0.001$]. Significant differences in the total score and all three dimensions (depression, anxiety, and stress) were also found for economic status: the better the financial situation, the lower the emotional distress ($r = -0.14$, $p = 0.026$). Significant differences in the total score were also found for degree of religiosity: traditional, and secular participants reported higher levels of emotional distress ($M = 24.69$, $SD = 21.55$) than religious and ultra-orthodox participants ($M = 15.49$, $SD = 15.58$) [$t(273) = 3.61$, $p < 0.001$]. Findings for the three dimensions were similar. In addition, a positive correlation was found between BMI and emotional distress (total score and all dimensions), indicating that the higher the BMI, the greater the emotional distress ($r = 0.19$, $p = 0.001$).

Finally, the total DoS score was found to be higher among men ($M = 4.04$, $SD = 0.57$) than women ($M = 3.74$, $SD = 0.62$), pointing to gender differences [$t(273) = 4.18$, $p < 0.001$]. Moreover, parents reported higher DoS ($M = 3.94$, $SD = 0.60$) than non-parents ($M = 3.75$, $SD = 0.62$) [$t(273) = 2.55$, $p = 0.011$]. Lastly, a positive correlation was found between participants' economic status and DoS: the better the financial situation, the higher the DoS ($r = 0.14$, $p = 0.018$). In light of these findings, the research hypotheses were examined controlling for gender, parentage, economic status, level of religiosity, and BMI. No significant relationships or differences were found between work stress and the background variables examined in the study.

Examination of research hypotheses

Relationships between the study variables

To further examine these relationships, multiple regression analyses were calculated controlling for gender, parentage, economic status, level of religiosity, and BMI. Owing to a high correlation between two dimensions of DoS, namely, emotional reactivity and fusion with others ($r = 0.75$), as well as between the three dimensions of emotional distress ($r = 0.65$ to $r = 0.73$), total scores were used for DoS and emotional distress to avoid collinearity. Regarding BED, in the first step the background variables were entered, followed by the total score of DoS in the second step, and finally the total scores of emotional distress and work stress in the third step.

The regression model for BED symptoms yielded significant results, explaining 23% of the variance. In the first step, 10% of the variance was significantly accounted for by the background variables, so that for women, and for higher BMI level, there were higher levels of BED symptoms. The addition of DoS in step 2 was significant, adding 8% to the explained variance (the lower the level of total DoS, the higher the level of BED symptoms). Levels of emotional distress and work stress in step 3 added 5% to the explained variance: the higher these levels, the higher the level of BED symptoms.

With respect to emotional distress (total and the three dimensions) and work stress, all five regression models were significant, explaining

28–44% of the variance in these two variables. Across all models, the inclusion of DoS in step 2 significantly increased the explained variance by 18–35%. Being a parent, level of religiosity, and BMI were identified as significant predictors of emotional distress. Moreover, the addition of the total DoS score was significant, suggesting that the lower the level of DoS, the higher the level of emotional distress. Similar findings were found for the dimensions of depression, anxiety, and stress. After controlling for background variables, negative associations were found between DoS and all three dimensions of emotional distress. With respect to work stress, a significant association was found with DoS: the lower the DoS, the higher the level of work stress.

Hypothesis 1: The mediation model

According to the first hypothesis, emotional distress and work stress will mediate the relationship between DoS and BED symptoms (Figure 1). Due to the abovementioned high correlation between emotional reactivity and fusion with others and between the three dimensions of emotional distress, the hypothesis was tested by structural equation modeling (SEM), with gender, parentage, economic status, level of religiosity, and BMI defined as control variables. DoS was defined as the independent variable (latent variable) when the four dimensions were defined in the positive direction (a higher score representing a better result). Emotional distress and work stress were defined as the mediating variables (latent variables), while the level of BED symptoms (emotional/cognitive and behavioral) was defined as the dependent variable (latent variable with both dimensions).

Examining the measurement model, results indicated a good fit to the data: Cmin/df = 2.292, NFI = 0.951, NNFI = 0.951, CFI = 0.971, RMSEA = 0.069. These fit indices suggest that the measurement model adequately represents the relationships between the observed indicators and the latent variables. Results for the mediation model also indicated a good fit: Cmin/df = 1.660, NFI = 0.935, NNFI = 0.959, CFI = 0.973, RMSEA = 0.049. This latter model is shown in Figure 2.

Results yielded significant associations between the research variables, such that the lower the level of DoS, the higher the levels of emotional distress and work stress; in turn, the greater the emotional distress and work stress, the higher the level of BED symptoms. Indeed, according to these direct relationships, the overall mediation effect was found to be significant: effect = −5.53, $SE = 3.10$, $p < 0.001$, 95%CI = −14.45, −2.89. The two specific effects were also significant; for the relationship of DoS → emotional distress→BED symptoms: effect = −0.91, $SE = 0.30$, $p < 0.001$, 95%CI = −1.57, −0.39; for DoS → work stress→BED symptoms: effect = −0.28, $SE = 0.13$, $p = 0.019$, 95%CI = −0.55, −0.04. These values suggest that the indirect pathways through emotional distress and work stress explain a significant portion of the relationship between DoS and BED symptoms, supporting the first research hypothesis.

Hypotheses 2 and 3: Gender differences and moderation effects

The second hypothesis suggested that women will report higher levels of emotional reactivity, fusion with others, emotional distress,

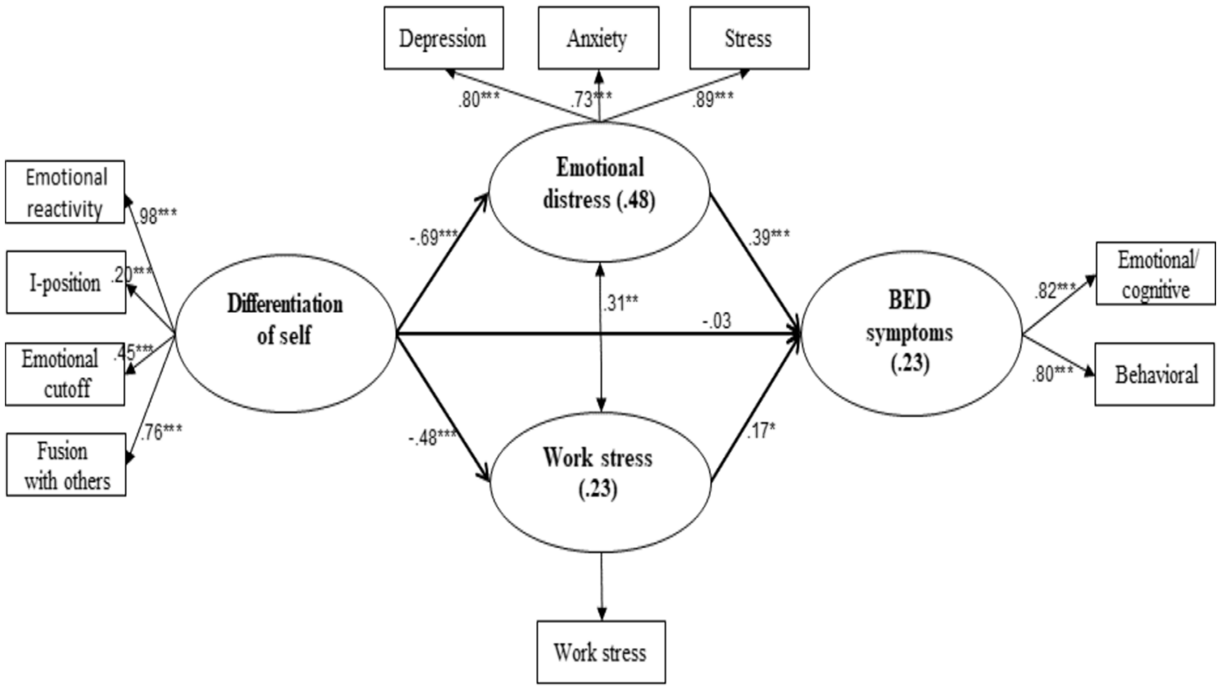

FIGURE 2
Structural equation modeling for emotional distress and work stress as mediating the association between Dos and BED symptoms. *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$. Observed variables are inside rectangles; latent variables, together with the percent of explained values (R^2), are in ellipses. Values next to unidirectional arrows are β values; the value next to the bidirectional arrow is a Pearson's r. Control variables are excluded for purposes of clarity.

and BED symptoms, while men will report higher levels of emotional cutoff. Multivariate analyses of variance (MANCOVA), controlling for parentage, economic status, level of religiosity, and BMI, indicated that women reported higher levels of BED symptoms and fusion with others, while men reported higher levels of DoS (total score; Table 3). Together, these findings partially support the second hypothesis.

In addition to examining direct gender differences, its moderating effect on the model associations was examined. As shown in Table 2, the correlation between two aspects of DoS (emotional reactivity and fusion with others) was $r = 0.75$ ($p < 0.001$), thus leading to collinearity in any model involving the DoS aspects separately (VIF = 3.23). Thus, the moderating effects were examined regarding the total DoS score. All moderating effects for gender were found to be non-significant: for the associations between DoS and emotional distress ($\beta = 0.01$, $p = 0.867$), DoS and work stress ($\beta = -0.02$, $p = 0.786$), DoS and BED symptoms ($\beta = 0.11$, $p = 0.220$), emotional distress and BED symptoms ($\beta = 0.03$, $p = 0.709$), and work stress and BED symptoms ($\beta = 0.11$, $p = 0.172$). Thus, despite significant gender differences observed in DoS and BED symptoms, the model associations were not moderated by gender, refuting the third hypothesis.

Discussion

The main study objective was to investigate the mechanism that activates BED symptoms, and the pathway through which family, work, and personality factors contribute to their development. Taken together, the findings suggest that low DoS (the predictor) may increase vulnerability to BED symptoms (the outcome) by increasing susceptibility to emotional distress, including stress in the workplace (mediators). In addition, the analyses pointed to certain gender differences: women reported higher levels of BED symptoms, while men reported higher levels of DoS.

Emotional distress and work stress mediate the relationship between DoS and the risk of BED symptoms

A major tenet of the current study was that low DoS might increase the likelihood of BED symptoms by increasing vulnerability to emotional distress and work stress. Indeed, the findings revealed that the severity of emotional distress and work stress mediated the relationship between BED and DoS. These results align with previous research that has linked DoS to emotional well-being and mental health outcomes. They reinforce the notion that emotional maturity and the ability to maintain a balance between emotional and intellectual functioning are crucial for psychological well-being in various domains of life (49, 50).

Apparently, well-differentiated individuals are more likely to navigate uncertain circumstances and emotionally charged events using calm, rational thinking (67). In contrast, poorly differentiated individuals may find it difficult to maintain a clear sense of self and have difficulty adhering to their personal convictions instead of

TABLE 3 Means, standard deviations, and f values for the study variables by gender ($n = 275$).

	Total M(SD) (skewness, kurtosis)	Females M(SD)	Males M(SD)	$F(1, 269)$, (p) (η^2)
BED symptoms	9.37 (6.70) (0.86, 0.64)	10.13 (6.68)	8.23 (6.59)	7.63 ($p = 0.006$) ($\eta^2 = 0.028$)
Emotional distress: total	21.68 (20.24) (1.44, 2.69)	22.55 (20.00)	20.38 (20.60)	1.59 ($p = 0.208$) ($\eta^2 = 0.006$)
Depression	6.63 (7.36) (1.68, 3.67)	6.70 (7.38)	6.51 (7.37)	0.21 ($p = 0.646$) ($\eta^2 = 0.001$)
Anxiety	5.37 (6.45) (1.53, 1.98)	5.53 (6.34)	5.13 (6.63)	1.25 ($p = 0.264$) ($\eta^2 = 0.005$)
Stress	9.69 (8.42) (1.09, 1.40)	10.32 (8.39)	8.75 (8.42)	3.21 ($p = 0.074$) ($\eta^2 = 0.012$)
Work stress	2.10 (0.67) (0.41, −0.25)	2.12 (0.68)	2.07 (0.66)	0.23 ($p = 0.631$) ($\eta^2 = 0.001$)
DoS: total	3.86 (0.62) (−0.28, 0.63)	3.74 (0.62)	4.04 (0.57)	15.64 ($p < 0.001$) ($\eta^2 = 0.055$)
Emotional reactivity	3.39 (1.05) (0.09, −0.38)	3.66 (1.03)	2.98 (0.94)	1.25 ($p = 0.264$) ($\eta^2 = 0.005$)
I-position	4.07 (0.80) (−0.22, 0.17)	4.03 (0.82)	4.12 (0.76)	0.09 ($p = 0.765$) ($\eta^2 = 0.001$)
Emotional cutoff	2.58 (0.85) (0.49, 0.42)	2.59 (0.88)	2.56 (0.81)	0.08 ($p = 0.774$) ($\eta^2 = 0.001$)
Fusion with others	3.67 (0.81) (−0.32, 0.27)	3.84 (0.79)	3.40 (0.77)	20.21 ($p < 0.001$) ($\eta^2 = 0.070$)

For skewness values: SE = 0.15, for Kurtosis values: SE = 0.29. For females: skewness values = −0.50 to 1.74, SE = 0.19; kurtosis values = −0.27 to 3.67, SE = 0.38. For males: skewness values = −0.22 to 1.61, SE = 0.23; kurtosis values = −0.57 to 3.90, SE = 0.46.

conforming to others' expectations. They also may tend to isolate themselves from others and their emotions when faced with intense interpersonal experiences, or conversely, create dependent relationships and lean on close people, finding it difficult to maintain healthy boundaries in relationships (51, 68). While these maladaptive coping patterns may provide temporary relief, in the long term they can increase emotional burden, a sense of being overwhelmed, which may further exacerbate emotional distress and consequently elevate the risk of BED. It is suggested that the risk of BED increases because individuals may use BED as a way to alleviate negative emotions (69). Furthermore, it is likely that emotional distress can disrupt normal appetite regulation mechanisms, leading to dysregulated eating patterns (70). It is possible that difficulties regulating their emotions and their relationships with significant others leads such individuals to eat in an effort to numb their emotions and maintain a sense of control (2, 69), turning to food as a mechanism for coping with emotional distress. Such reliance on food can hinder the use of healthier skills that can manage emotions effectively.

The current results indicate that not only personal distress, but also stress in the work environment, mediates the relationship between DoS and BED. The workplace can be seen as a social and emotional system that encompasses interpersonal interactions, rules, expectations, and roles. This environment acts as a platform where individuals express what they have learned from their family of origin as they mature (44, 45). Research suggests that even individuals who are well-differentiated may experience increased stress situations; however, they respond and react to these situations differently than poorly differentiated individuals (71). The present results thus partially support findings indicating that low DoS predicts high levels of work stress and low job satisfaction (14), as well as higher levels of conflicts (14). Moreover, poorly differentiated individuals tend to have decreased enthusiasm and increased stress and burnout (15), as well as a high dependency on others (25, 35). Another potential explanation is that poorly differentiated individuals may struggle to seek support in stressful situations, including the workplace (15, 71). As a result, they may find it challenging to cope with work-related stress and navigate workplace dynamics effectively (36). This can lead to decreased job satisfaction and increased conflicts in their professional lives. It is possible that the difficulty in regulating emotions in the workplace channels the emotional distress into unregulated eating patterns, and that increased work stress and burnout can lead to decreased awareness of eating, decreased intuitive eating, and a sense of lack of control overeating (31, 43, 72).

Gender differences

Consistent with prior research (6, 22), men in our study exhibited lower scores on BED symptoms than women. Women may be more influenced by societal pressure surrounding the ideal of thinness and beauty (2), potentially making them more susceptible to symptoms associated with BED. However, it is important to note the small difference in percentages between women and men diagnosed with moderate or severe BED in the current sample (12.7% vs. 10.9%, respectively). This emphasizes the significance of considering the experiences and challenges faced by both genders in relation to BED. In contrast, men exhibited higher DoS, suggesting a greater inclination toward emotional separateness from others. These gender differences may arise from a range of factors, such as societal expectations, cultural norms, coping mechanisms, and stress responses (2, 21, 31, 73).

Limitations and future research

Our results should be interpreted with caution due to several study limitations. Firstly, the sample size is relatively small, which may impact the generalizability of the findings. Furthermore, the sample was composed predominantly of individuals from middle and upper-class backgrounds, limiting the applicability of the findings to people of lower socioeconomic backgrounds. To address these limitations, future research should include larger and more diverse samples, particularly in terms of socioeconomic groups. This would facilitate a more comprehensive understanding of the relationships under investigation and allow for more accurate generalizations to be made.

Secondly, it is important to acknowledge other variables that might serve as moderators in the relationships between DoS and emotional distress; DoS and work stress; and emotional distress, work stress, and BED. It would be worthwhile to explore such socioeconomic demographic variables as cultural/ethnic affiliation and level of education; such workplace variables as workload and income level; such childhood family variables as parenting styles and family atmosphere; and such personality variables as assertiveness, agreeableness, and psychological flexibility. Indeed, several studies investigating the impact of psychological flexibility on eating-related concerns have indicated a heightened risk of eating disorders (74) and emotional eating (75) among individuals with extreme obesity, who often exhibit elevated emotional distress and low psychological flexibility. Further investigation is warranted to explore the specific mechanisms underlying these relationships for a more comprehensive understanding of the phenomenon.

Thirdly, the current study was conducted in a cross-sectional setting, capturing data at a single point in time. This limits the ability to measure the development and progression of BED symptoms over time. It is recommended to conduct a longitudinal study, allowing for the assessment of the development and trajectory of BED symptoms among young people over an extended period.

Theoretical conclusions and contributions

Notwithstanding the study's limitations, it offers significant contributions. From a theoretical perspective, previous research findings have shown that emotional distress mediated the relationship between DoS and the risk of eating disorders. The current study expands upon the existing literature by incorporating such novel variables as family, personality, and work-related factors in the investigation of BED. This enhances our understanding of the complex nature of BED beyond the traditional focus on personality measures (23, 24). Furthermore, the study sheds light on the contribution of unregulated family and emotional patterns to BED, providing valuable insights for organizations seeking to promote healthier work environments and improve employee well-being. The findings emphasize that unregulated family patterns and conflicts can add to stress levels and dissatisfaction, which can spill over into the workplace. Therefore, improving DoS within individuals

can help organizations mitigate the negative effects of family dynamics on workplace satisfaction and stress levels.

Relevance for clinical practice

In practical terms, increased knowledge of BED may contribute to the development of effective prevention strategies. By identifying risk factors and early signs, interventions can be designed to intervene and prevent the onset of BED before it becomes chronic. The study findings can thus contribute to evidence-based interventions for BED, encouraging healthier eating patterns by focusing on emotional triggers in individuals' lives, particularly within the family and the work environment. Organizations can support employees by addressing disordered eating symptoms, providing resources and interventions to improve overall well-being. This includes promoting healthy eating habits, offering counseling or employee assistance programs, and creating a supportive work environment that prioritizes work–life balance and stress management. By supporting individuals in the development of healthy coping mechanisms and interpersonal relationships, organizations can potentially reduce work stress and consequently the risk of BED. In addition, it is suggested that psychologists and family therapists who assist individuals suffering from Binge Eating Disorder (BED) should focus on improving DoS. This will lead to improved functioning both within their family and workplace environments.

Finally, from methodological and therapeutic perspectives, ongoing research can play a crucial role in refining the diagnostic criteria for BED, enabling better identification and monitoring of treatment outcomes. Advancements in understanding BED will pave the way for improved treatment outcomes.

In short, the research findings underline the importance of considering both personal and contextual factors in understanding, addressing, and treating BED. The study thus contributes to our understanding of the complex interplay between DoS, emotional distress, work stress, and BED.

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 humans were approved by the Ethics Committee of the University of Haifa, within the Department of Human Services. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

Author contributions

OP: Conceptualization, Data curation, Investigation, Methodology, Project administration, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. MI: Conceptualization, Data curation, Investigation, Project administration, Resources, Validation, Visualization, Writing – original draft, Writing – review & editing. RK: Conceptualization, Investigation, Project administration, Supervision, Validation, Visualization, Writing – review & editing.

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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 role of pituitary adenylate cyclase-activating polypeptide neurons in the hypothalamic ventromedial nucleus and the cognate PAC1 receptor in the regulation of hedonic feeding

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Obesity is a health malady that affects mental, physical, and social health. Pathology includes chronic imbalance between energy intake and expenditure, likely facilitated by dysregulation of the mesolimbic dopamine (DA) pathway. We explored the role of pituitary adenylate cyclase-activating polypeptide (PACAP) neurons in the hypothalamic ventromedial nucleus (VMN) and the PACAP-selective (PAC1) receptor in regulating hedonic feeding. We hypothesized that VMN PACAP neurons would inhibit reward-encoding mesolimbic (A10) dopamine neurons via PAC1 receptor activation and thereby suppress impulsive consumption brought on by intermittent exposure to highly palatable food. Visualized whole-*cell* patch clamp recordings coupled with *in vivo* behavioral experiments were utilized in wildtype, PACAP-*cre*, TH-*cre*, and TH-*cre*/PAC1 receptor-floxed mice. We found that bath application of PACAP directly inhibited preidentified A_{10} dopamine neurons in the ventral tegmental area (VTA) from TH-*cre* mice. This inhibitory action was abrogated by the selective knockdown of the PAC1 receptor in A_{10} dopamine neurons. PACAP delivered directly into the VTA decreases binge feeding accompanied by reduced meal size and duration in TH-*cre* mice. These effects are negated by PAC1 receptor knockdown in A_{10} dopamine neurons. Additionally, apoptotic ablation of VMN PACAP neurons increased binge consumption in both lean and obese, male and female PACAP-*cre* mice relative to wildtype controls. These findings demonstrate that VMN PACAP neurons blunt impulsive, binge feeding behavior by activating PAC1 receptors to inhibit A_{10} dopamine neurons. As such, they impart impactful insight into potential treatment strategies for conditions such as obesity and food addiction.

KEYWORDS

pituitary adenylate cyclase-activating polypeptide, hypothalamic ventromedial nucleus, ventral tegmental area, A_{10} dopamine neurons, food addiction, PAC1 receptor, hedonic feeding

1 Introduction

Obesity is a health malady that affects an individual's mental, physical, and social health (1). Furthermore, obesity promotes the development of metabolic and physiological comorbidities such as, but not limited to, type 2 diabetes, hypertension, cardiovascular disease, obstructive sleep apnea, and respiratory disease (2, 3). Pathology of obesity includes prolonged

imbalance between energy expenditure and energy intake (4). The cause of this imbalance is multifactorial, however, a main proponent may stem from the hedonic control of appetite and food intake. The hedonic pathway utilizes food reward cues to modulate energy intake and expenditure (5). Rodent studies investigating motivated behavior suggest that substance abuse and consumption of palatable foods converge at the same pathway within the limbic system (5–7). This pathway is comprised of dopaminergic (DA) signaling from A_{10} dopamine neurons originating at the ventral tegmental area (VTA) of the mesencephalon and terminating in the nucleus accumbens (NAc) (8). These neurons comprise the mesolimbic pathway (9) and are associated with regulation of behaviors motivated by reward (10). The release of DA in the NAc has been shown to facilitate goal directed motor behavior (11). In relation to obesity, an individual's consistent consumption of highly palatable foods over-activates this dopaminergic circuitry as it becomes habitually stimulated. This repeated activation of the mesolimbic pathway dampens the self-regulation of the mesolimbic circuitry, thereby rendering the subject susceptible to compulsive actions such as overeating or binge eating behaviors (12, 13).

Previous studies have depicted pituitary adenylate cyclase-activating polypeptide (PACAP) as a prominent regulator of feeding behavior (14–16). PACAP is abundantly expressed in the hypothalamic ventromedial (VMN), paraventricular (PVN), and arcuate (ARC) nuclei (17–19), which are implicated in homeostatic regulation of feeding. Administration of PACAP into the ARC, VMN, and PVN has been evidenced to decrease food intake and increase metabolic parameters such as locomotor activity, core body temperature, and O2 consumption (20–23). There are two populations of appetite-regulating PACAP neurons within the hypothalamus: one in the VMN and the other in the PVN. VMN PACAP neurons co-express steroidogenic factor-1 and glutamate, and are considered anorexigenic (18, 22, 24). PVN PACAP neurons co-express thyrotropin-releasing hormone and glutamate, and are considered orexigenic (19, 25). There are also two classes of receptors to which PACAP can bind. The PACAP-specific PAC1 receptor is highly selective for PACAP, whereas the VPAC1 and VPAC2 receptors have comparable affinity for both PACAP and vasoactive intestinal polypeptide (26). The PAC1R system is highly expressed within the dorsomedial nucleus (DMN), PVN, ARC, and VMN of the hypothalamus (15, 26, 27).

Activation of the PAC1R in anorexigenic proopiomelanocortin (POMC) neurons within the ARC elicits Gq-and phosphatidylinositol-3-kinase (PI3K)-mediated signaling that links this cognate receptor to transient receptor potential channel 5 (TRPC5) channels (22, 23). Opening of these channels upon PAC1R activation in POMC neurons leads to calcium and sodium influx and consequent depolarization of these cells, an effect that is potentiated by estradiol in females (22, 28). On the other hand, orexigenic ARC NPY/AgRP neurons express PAC1R and VPAC2R (29). PVN PACAP neurons provide excitatory input to ARC NPY/AgRP neurons, and are therefore able to modulate consumption via these orexigenic neurons (19). However, in keeping with their prominent anorexigenic role, optogenetic stimulation of VMN PACAP neurons, as well as bath application of exogenous PACAP powerfully hyperpolarizes NPY/AgRP neurons via Gq-coupled, PAC1R-mediated activation of K_{ATP} channels (23).

Investigation of the effects of PACAP in both the homeostatic and hedonic circuitries reveal PACAP exerts pleiotropic effects. While PACAP elicits excitation of ARC POMC neurons under *ad libitum*-fed conditions, deviations from homeostasis have been shown to either attenuate this response (in the case of diet-induced obesity), or reverse its polarity altogether (in the case of fasting) due to a switch in the PAC1R coupling from TRPC5 channels to K_{ATP} channels, which promote potassium efflux and hyperpolarization of the postsynaptic neuron (22, 30). We have also shown that the effect of PACAP on NPY/AgRP neurons reverses polarity from predominantly inhibitory to mostly excitatory under conditions of fasting (23). Injections of PACAP into the NAc reduces hedonic feeding and drive (31, 32). Additionally, PACAP and its cognate PAC1R are expressed in the NAc and VTA, which are evidenced to be involved in the hedonic regulation of feeding (33, 34). Similarly, intra-VTA PACAP administration suppresses the binge-like consumption of palatable food in lean mice due to activation of K_{ATP} channels and hyperpolarization of A_{10} DA neurons in the VTA (35), which is blocked by the PAC1/VPAC2R antagonist $PACAP_{6-38}$. A similar polarity switch occurs in A_{10} dopamine neurons from obese, high fat diet (HFD)-fed females, where the PACAP response flips from predominantly inhibitory to excitatory (5).

Seeing as the VMN PACAP neurons project to and synapse with VTA neurons, and with supporting evidence from previous studies depicting decreased drive for palatable food upon administration of PACAP to the VTA (35), it is hypothesized that selective knockdown of the PAC1R in A_{10} DA neurons will diminish the activation of K_{ATP} channels and subsequent inhibition of these cells; thereby blunting the PACAP-induced suppression of binge feeding. Furthermore, we postulate apoptotic ablation of VMN PACAP neurons will enhance the hedonic drive for highly palatable food evidenced by increased consumption during intermittent exposure to HFD. This research brings further clarity to the hedonic energy balance circuitry and the mechanisms driving food addiction and obesity, as well as potential therapeutic targets to alleviate hedonic drive and promote a return to homeostasis between energy intake and expenditure.

2 Materials and methods

2.1 Animal models

All animal care and procedures were compliant with Western University of Health Sciences' Institutional Animal Care and Use Committee, and the NIH Guide for the Care and Use of Laboratory Animals. The presented study utilizes PACAP-*cre* and tyrosine hydroxylase (TH-*cre*) transgenic mice populations purchased from Jackson Laboratories (Stock #030155, #008601 respectively, Bar Harbor, ME, United States). These strains were generated on a C57BL/6 background and bred in house. $PAC1R^{fl/fl}$ mice were obtained from Dr. Rachel Ross (Albert Einstein College of Medicine, Bronx, NY, United States), and bred with TH-*cre* mice to produce double transgenic TH-*cre*/$PAC1R^{fl/fl}$ mice (for experimentation lean mice: 16–25 g, 12–26 weeks; HFD mice: 18–35 g, 14–30 weeks). Additionally, wildtype mice bred in house on a C57BL/6 background were utilized. A total of 175 males and 41 ovariectomized females were utilized. Animals were provided food and water *ad libitum*, kept on a 12 h light–12 h dark schedule (light 06:00–18:00), and maintained under 25°C. At 21 days of age, pups were weaned and genotyped utilizing standard PCR protocols. Animals were subsequently assigned to either a standard chow diet (Teklad Rodent Diet, Teklad Diets,

Madison, WI, United States) with 18% of calories derived from fat, 24% from protein, and 58% from carbohydrates, or they were assigned to a high fat diet (HFD) group which derived 45% of calories from fat, 20% from protein, and 35% from carbohydrates 5–8 weeks prior to experimentation.

2.2 Surgical procedures

Approximately 5 days prior to experimentation, all female TH-*cre* and TH-*cre*/PAC1R$^{fl/fl}$ mice were ovariectomized (OVX) under 2% isoflurane anesthesia. Ovariectomies were utilized to control the estrous cycle and study sex differences. Surgical outfitting with a 26-gauge guide cannula (Plastics One, Roanoke, VA, United States) or stereotaxic injection of adeno-associated viral vector constructs (AAV) was performed in TH-*cre*, TH-*cre*/PAC1R$^{fl/fl}$, PACAP-*cre*, and wildtype mice. Animals were placed in a stereotaxic frame (Stoelting, Wood Dale, IL, United States), and anesthetized with 2% isoflurane. An incision was made to expose the skull, and either a unilateral or bilateral holes were drilled on one or both sides of the mid-sagittal suture to allow the guide cannula or injection needle to be lowered into the VTA (from bregma AP: −2.1 mm; ML: ±0.5 mm; DV: −4.0 mm from dura) or VMN (from bregma AP: −0.6 mm; ML: ±0.3 mm; D: −5.6 mm from dura). Injections of *cre-recombinase* dependent AAV1 containing either enhanced yellow fluorescent protein (eYFP) blank control (pAAV-Ef1a-DIO EYFP; 1.0×10^{13}, 300 nL total volume, Addgene, plasmid #27056, deposited by Karl Deisseroth), or caspase-3 (pAAV-flex-taCasp3-TEVp; 7×10^{12} genomic copies/mL); 300 nL total volume (gift from Nirao Shah and Jim Wells; Addgene plasmid #45580). Animals were used 2–4 weeks following AAV eYFP injection/surgical implantation with guide cannula for experimentation. Only animals with correct placement were included in experimentation data. Wildtype and PACAP-*cre* animals who received bilateral VMN injections with AAV caspase-3 were utilized for experimentation 4 weeks post injection to allow adequate time for viral transfection and subsequent VMN PACAP specific ablation to occur.

2.3 Drugs

All drugs were purchased from Tocris Bioscience/ R&D Systems (Minneapolis, MN, United States), unless stated otherwise. For electrophysiological experiments, the PAC1R agonist, $PACAP_{1\text{-}38}$ was prepared as a 100 μM stock solution in UltraPure H_2O and further diluted with artificial cerebrospinal fluid (aCSF) to a working concentration of 100 nM. For behavioral experiments, the PAC1/VPAC2 antagonist, $PACAP_{6\text{–}38}$ was prepared as a 200 mM stock solution, and $PACAP_{1\text{–}38}$ was prepared as a 150 μM stock, and these two stock solutions were further diluted to 1 nM and 30 pM solutions, respectively, by dissolving them in filtered saline.

2.4 Midbrain slice preparation

On experiment day, 32% isoflurane was utilized to briefly anesthetize the animal (TH-*cre* or TH-*cre*/PAC1R$^{fl/fl}$) prior to rapid decapitation. The brain was carefully and swiftly extracted from the skull and a coronal mesencephalic block was procured. The block was then mounted on a cutting platform and secured in a vibratome filled with ice-cold, oxygenated, sucrose-based cutting solution ($NaHCO_3$ 26; dextrose 10, HEPES 10; sucrose 208; KCl 2; NaH_2PO_4 1.25; $MgSO_4$ 22; $CaCl_2$ 1; in mM). Two to three slices at 250 um were obtained through the rostrocaudal aspect of the VTA. The slices were then transferred to an auxiliary chamber containing room temperature oxygenated aCSF containing the following (mM):

NaCl, 124; NaHCO3 26; dextrose 10, HEPES 10; KCl 5; NaH2PO4 2.6; MgSO4 2; CaCl2 1

2.5 Electrophysiology

Whole-cell patch clamp electrophysiological recordings from VTA neurons were performed utilizing biocytin-filled electrodes. During recordings, the slices were maintained in a chamber under continuous perfusion with oxygenated aCSF (35°C), with the $CaCl_2$ concentration raised to 2 mM. Artificial CSF and all drugs diluted with aCSF were perfused via a peristaltic pump at a rate of 1.5 mL/min. Borosilicate glass (World Precision Instruments, Sarasota, FL, United States; 1.5 mm OD) patch electrodes were pulled on a P-97 Flaming Brown Puller (Sutter Instrument Co., Novato, CA, United States), and filled with an internal solution containing the following: Potassium gluconate 128; NaCl 10; MgCl2 1; EGTA 11; HEPES 10; ATP 1; GTP 0.25; (in mM) and 0.5% biocytin. Internal solution was adjusted to a pH of 7.3 with KOH; osmolality: 286–320 mOsm. Recording electrode resistances ranged from 3 to 8 MΩ.

Recordings were visualized using an Olympus BX51 W1 fixed stage microscope outfitted with infrared differential interference contrast (DIC) video imaging. Multiclamp 700A or B preamplifiers (Molecular Devices) amplified potentials and passed current through the electrode. Analog-digital conversion of membrane current was carried out using Digidata 1550A or B interfaces (Molecular Devices) coupled to pClamp 10.6 or 11.0 software. Access resistance, resting membrane potential (RMP), and input resistance were monitored for the entirety of recordings. Recording was ended if access resistance deviated more than 10% of the original value. Low-pass filtering of the currents was conducted at a frequency of 2 kHz. Liquid junction potential was calculated as −10 mV, and corrected during data analysis with pClamp software. Recordings were performed at holding potential of −60 mV.

Initial baseline current–voltage (I/V) relationship was generated in slices from TH-*cre* or TH-*cre* PAC1R$^{fl/fl}$ mice injected 2–3 weeks prior with eYFP blank AAV into the VTA using a ramp protocol (75 mV/s; from −110 to −30 mV). Following baseline I/V, $PACAP_{1\text{-}38}$ [100 nM] was bath applied and the membrane current was continuously monitored until a new steady-state value was observed. Following this, a second I/V relationship was recorded. Membrane current was again continuously monitored as PACAP washed out and a final I/V relationship was recorded.

2.6 Behavioral studies

Behavioral studies were conducted utilizing a four station Comprehensive Lab Animal Monitoring System (CLAMS; Columbus Instruments, Columbus, Ohio, United States) as previously described and validated (36). Meal pattern and energy intake in intact male and OVX female wildtype, PACAP-*cre*, TH-*cre*, and TH-*cre*/PAC1R$^{fl/fl}$ mice were monitored. Prior to executing our binge feeding protocol, animals were allowed to acclimate in the CLAMS chambers for 3 days where they were handled, weighed, and returned to their cages every afternoon. Following acclimation, binge feeding was monitored over the course of 5 consecutive days as previously described (37, 38). Briefly, animals were exposed to HFD from 16:00 to 17:00, and at the end of each 1-h exposure, they were switched back to standard chow for the remaining 23 h. For the studies involving apoptotic ablation of VMN PACAP neurons, lean and obese male and OVX female wildtype and PACAP-*cre* animals were randomly assigned to either standard chow or HFD 5 weeks prior to experimentation. Subjects were injected with a caspase-3-containing AAV into the VMN 4 weeks prior to experimentation. Long term HFD-fed animals were switched back to standard chow a week before experimentation, then reintroduced to HFD for the binge hour as described above. For the studies involving TH-*cre* and TH-*cre*/PAC1R$^{fl/fl}$ animals, subjects were injected with PACAP$_{1-38}$ (30 pmol, 0.2 μL), PACAP$_{6-38}$ (1 nM, 0.2 μL), or its 0.9% saline vehicle (0.2 μL) directly into the VTA just prior to the HFD exposure hour.

2.7 Immunohistochemistry

Slices containing the VTA region from TH-*cre* and TH-*cre*/PAC1R$^{fl/fl}$ mice were fixed with 4% paraformaldehyde (PFM) in Sorenson's phosphate buffer (pH 7.4) overnight. Following the fixation period, slices were then immersed for 3 days in 20% sucrose dissolved in Sorenson's buffer which was changed daily. 2-methylbutane (EMD Millipore Corporation, Burlington, MA, United States) was utilized to snap freeze slices. Coronal sectioning (20 μM) through the VTA was conducted on a cryostat and mounted on chilled slides. Sections were then washed with 0.1 M sodium phosphate buffer (PBS; pH 7.4), and then processed overnight with a polyclonal antibody directed against PAC1R (ABCAM; Cambridge, MA, United States; AB28670; 1:500 dilution). The following day, two 15-min washes with PBS, and a 2 h incubation period with secondary biotinylated goat anti-rabbit antibody (Jackson ImmunoResearch Laboratories, Inc., West Grove, PA, United States; 1:300), then three 15 min washes with PBS and another 2 h overlay with streptavidin-Alexa Fluor 546 (Molecular Probes Inc., Eugene, OR, PA, United States 1:600) was conducted. This was followed by a final series of three 30-min washes. For TH immunolabeling, these same slides were washed in PBS as described above and processed overnight with a monoclonal antibody for TH (Immunostar, Inc., Hudson, WI, United States; 1:4,000 dilution). The following day, slides were washed with PBS twice for 15 min and secondary goat anti-mouse antibody conjugated with Alexa Fluor 488 (Life Technologies, Carlsbad, CA, United States, 1:300) was utilized for the 2 h overlay. Following the final series of three 30 min washes with PBS, slides were coverslipped and evaluated using fluorescence immunohistochemistry on a Zeiss Axioskop 2 Plus microscope (Carl Zeiss, Göttingen, Germany). Percent colocalization was calculated bia comparison of TH and PAC1R fluorescence. PAC1R positive and TH positive cells were divided by the total number of TH positive cells. Representative sections were evaluated in triplicate from three TH-*cre* mice and three TH-*cre*/PAC1R$^{fl/fl}$ mice. Cell counts were taken from 0.12 mm^2 area in the VTA and determined in triplicate (22, 23).

2.8 Statistical analysis

Student's *t*-test or Mann–Whitney U-test were utilized to draw comparisons between two groups. One-way or repeated measures, multifactorial ANOVA, followed by Least Significant Difference (LSD) test were utilized for comparisons made between more than two groups. An alpha probability of <0.05 was necessary for a difference to be considered statistically significant.

3 Results

3.1 The PAC1R is effectively knocked down in TH-*cre*/PAC1R$^{fl/fl}$ mice

Intra-VTA administration of PACAP$_{1-38}$ has been associated with decreased binge-like consumption of palatable food due to K_{ATP} channel activation and hyperpolarization of VTA A_{10} DA neurons (35). This effect is blocked by the PAC1/VPAC2R antagonist PACAP$_{6-38}$ (35). To confirm whether, indeed, the PAC1R is the mediator for the PACAP-induced hyperpolarization of A_{10} DA neurons, we utilized double transgenic TH-*cre*/PAC1R$^{fl/fl}$ mice to determine if inhibition persisted when the PAC1R was knocked down. We first wanted to validate the knockdown of the PAC1R expression in VTA neurons. We compared coronal VTA slices from TH-*cre* (Figures 1A–C) to TH-*cre*/PAC1R$^{fl/fl}$ mice (Figures 1D–F) that we immunostained with antibodies directed against TH and the PAC1R, and confirmed the PAC1R is appreciably knocked down in A_{10} DA neurons from TH-*cre*/PAC1R$^{fl/fl}$ animals (Figure 1G: Mann–Whitney U-test: $W = 0$, $p < 0.04$).

3.2 PAC1R is necessary for PACAP induced VTA A_{10} DA neuron hyperpolarization in TH-*cre* mice

Following establishment of the PAC1R knockdown in A_{10} DA neurons, we tested whether PACAP$_{1-38}$ would still induce hyperpolarization of these cells in the absence of the PAC1R. We conducted whole-cell patch clamp recordings of A_{10} DA neurons visualized with eYFP (Figures 2A–C) in both TH-*cre* and TH-*cre*/PAC1R$^{fl/fl}$ mice. The representative traces and I/V plots reveal that bath application of PACAP$_{1-38}$ (100 mM) induced a robust outward current in A_{10} DA neurons from TH-*cre* mice (Figure 2D), with a corresponding increase in slope conductance and reversal potential of −90 mV (Figure 2E). In contrast, bath application of PACAP$_{1-38}$ had no significant effect on membrane current from recorded A_{10} DA neurons nor a change in slope conductance in TH-*cre*/PAC1R$^{fl/fl}$ mice (Figures 2F,G). These are largely corroborated when looking at the composite data, with the slope conductance (ΔG) reduced by 69%

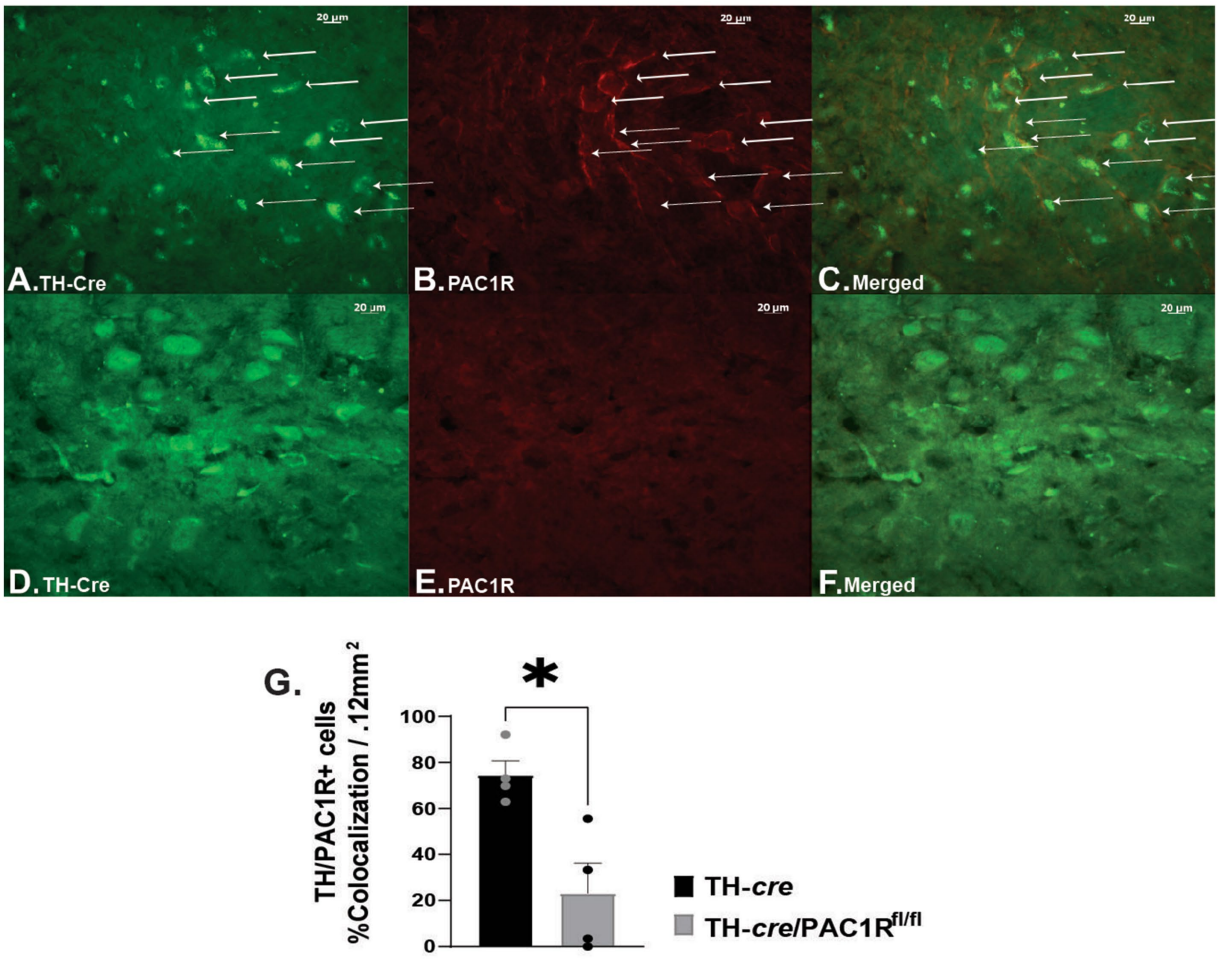

FIGURE 1
Validation of PAC1R knockdown in TH-*cre*/PAC1R$^{fl/fl}$ mice. Photomicrographs on the left represent TH immunostaining (visualized with Alexa Fluor 488) in sections from TH-*cre* **(A)** and TH-*cre*/PAC1R$^{fl/fl}$ **(D)** mice. Photomicrographs in the middle illustrate PAC1R immunostaining (visualized with Alexa Fluor 546) in the same sections from TH-*cre* **(B)** and TH-*cre*/ PAC1R$^{fl/fl}$ **(E)** mice. The photomicrographs in panels **(C,F)** denote merged images depicting retention of PAC1R in A_{10} DA neurons (denoted by the arrows) from TH-*cre* but not TH-*cre*/PAC1R$^{fl/fl}$ mice. **(G)** Percent of cells positive for colocalization of TH and PAC1R in TH-*cre* and TH-*cre*/PAC1R$^{fl/fl}$ mice. Mann–Whitney U-test, *$p < 0.05$, TH-*cre* $n = 4$, TH-*cre*/PAC1R$^{fl/fl}$ $n = 4$. Bars represent means and lines 1 SEM.

(Figure 2H: student's *t*-test, $t = 1.649$, DF: 16, $p < 0.12$) and the membrane current (Figure 2I: student's *t*-test, $t = 5.160$, DF: 16, $p < 0.0001$) negligible in TH-*cre*/PAC1R$^{fl/fl}$ compared to TH-*cre* mice with intact PAC1Rs. These data suggest the PAC1R is necessary to effectuate the inhibitory effect of PACAP on VTA A_{10} DA neurons (Figures 2J,K).

3.3 PAC1R knockdown abrogates the intra-VTA PACAP-induced decrease in binge intake, frequency, and bout duration in TH-*cre* mice

Seeing as how exogenous PACAP elicited no significant effect on recorded A_{10} DA neurons from TH-*cre*/PAC1R$^{fl/fl}$ mice, we therefore postulated that knockdown of the PAC1R would also negate the PACAP-induced inhibition of binge-like behavior. TH-*cre* and TH-*cre*/PAC1R$^{fl/fl}$ groups both were surgically outfitted with a guide cannula situated just above the VTA to allow for focal injection of $PACAP_{1-38}$ (30 pmol) or its saline vehicle (0.9%) and underwent intermittent 1-h exposure to HFD as previously described and validated (Figure 3A) (38). Pre-surgical weights were not significantly different between the two groups (TH-*cre*—23.8 ± 0.6 g, TH-*cre*/PAC1R$^{fl/fl}$—24.8 ± 1.6 g student's *t*-test, $t = 0.6705$, DF: 84, $p < 0.51$). Intra-VTA administration of $PACAP_{1-38}$ significantly just prior to this HFD exposure decreased binge intake in TH-*cre* mice (Figure 3B). This PACAP-induced decrement is associated with a reduction in both meal frequency (Figure 3C) and bout duration (Figure 3D) in TH-*cre* but not TH-*cre*/PAC1R$^{fl/fl}$ mice. The decreases in binge intake (Figure 3B) and meal frequency (Figure 3C) caused by PACAP were largely abolished in TH-*cre*/PAC1R$^{fl/fl}$ mice (Figure 3B: repeated measures multi-factorial ANOVA/LSD: $F_{PACAP1-38}$: 13.42, DF: 1, $p < 0.0006$; $F_{genotype}$: 5.86, DF: 1, $p < 0.02$; $F_{interaction:}$ 13.94, DF: 1, $p < 0.0005$, one-way ANOVA/LSD: $F = 8.12$, $p < 0.0002$; Figure 3C: repeated measures multi-factorial ANOVA/LSD: $F_{PACAP1-38}$: 19.19, DF: 1, $p < 0.0001$; $F_{genotype}$: 0.63, DF: 1, $p < 0.43$; $F_{interaction:}$ 6.79, DF: 1, $p < 0.02$, one-way ANOVA/LSD: $F = 6.74$, $p < 0.0005$). There was a significant main effect of both $PACAP_{1-38}$ and genotype on bout duration, but no interaction between the two factors, and we interpreted this to mean that the PACAP-induced

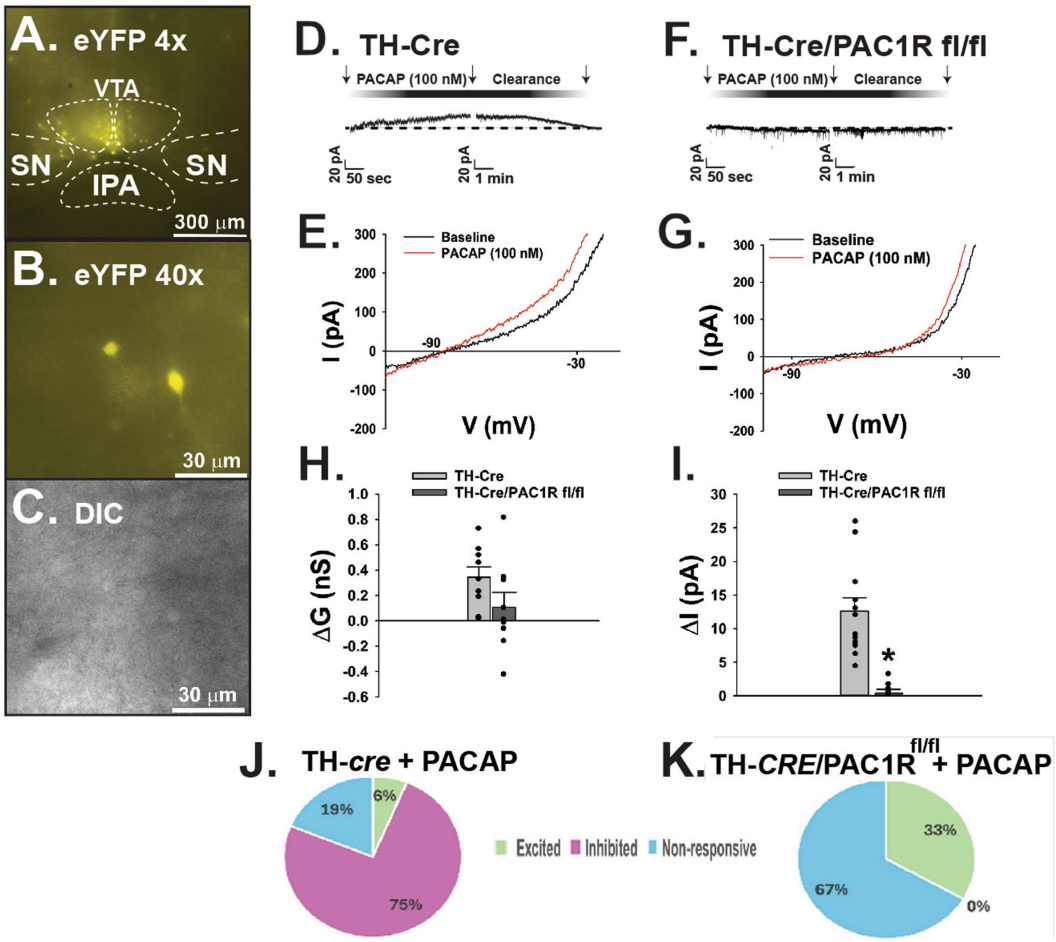

FIGURE 2
Lack of PAC1R attenuates PACAP induced outward current in VTA A_{10} DA neurons in TH-*cre*/PAC1R$^{fl/fl}$ mice. **(A)** Low powered (4X) photomicrograph of eYFP-fluorescing A_{10} DA neurons localized to the VTA. **(B)** High powered (40X) photomicrograph illustrating a representative A_{10} DA neuron about to undergo electrophysiologic recording. **(C)** Corresponding DIC image of the recorded TH neuron. **(D)** Representative outward current elicited in A_{10} DA neurons in TH-*cre* mice upon bath application of $PACAP_{1-38}$. **(E)** I/V plot showing a −90 mV reversal potential corresponding with the Nernst equilibrium potential for potassium conductance. **(F)** Representative voltage clamp trace depicting no significant change in membrane current in A_{10} DA neurons recorded from TH-*cre*/PAC1R$^{fl/fl}$ animals. **(G)** I/V relationship showing no significant change in slope conductance compared to baseline. **(H,I)** Composite data depicting slope conductance and membrane current are lower in TH-*cre*/PAC1R$^{fl/fl}$ animals following bath application of PACAP. Student's *t*-test, $*p < 0.05$, TH-*cre* $n = 6$ animals, 9 slices, 9 cells, TH-*cre*/PAC1R$^{fl/fl}$ $n = 5$ animals, 5 slices, 9 cells. Bars represent means and lines 1 SEM. **(J,K)** Pie charts reflecting the distribution of A_{10} dopamine neurons from TH-*cre* and TH-*cre*/PAC1Rfl/fl animals that are inhibited, excited or unresponsive to PACAP.

diminution of this meal pattern index was attenuated in TH-*cre*/PAC1R$^{fl/fl}$ mice (Figure 3D: repeated measures multi-factorial ANOVA/LSD: $F_{PACAP1\text{-}38}$: 4.38, DF: 1, $p < 0.04$; $F_{genotype}$: 7.58, DF: 1, $p < 0.008$; $F_{interaction:}$ 1.11, DF: 1, $p < 0.30$). Thus, the knockdown of the PAC1R in A_{10} DA neurons greatly compromises the inhibitory effect of intra-VTA PACAP on binge feeding behavior.

3.4 Apoptotic lesioning of VMN PACAP neurons enhances hedonic drive in PACAP-*cre* animals

Because VMN PACAP neurons project to and terminate in the VTA, and optogenetic stimulation of these cells inhibits A_{10} DA neurons (35), we tested the hypothesis that apoptotic ablation of VMN PACAP neurons would enhance hedonic drive. Lean, chowfed, and DIO HFD-fed male and female wildtype and PACAP-*cre* cohorts were injected with caspase-3 AAV in the VMN to apoptotically lesion VMN PACAP neurons 4 weeks prior to experimentation as described and validated previously (Figure 4A) (23). Caspase ablation promoted a significant increase in binge consumption in both lean and obese male (Figure 4B: repeated measures multi-factorial ANOVA/LSD: $F_{genotype}$: 23.88, DF: 1, $p < 0.0001$; F_{diet}: 0.38, DF: 1, $p < 0.55$; $F_{interaction}$: 2.15, DF: 1, $p < 0.15$) and female (Figure 4C: repeated measures multi-factorial ANOVA/LSD: $F_{genotype}$: 15.01, DF: 1, $p < 0.0005$; F_{diet}: 2.06, DF: 1, $p < 0.16$; $F_{interaction}$ genotype/diet: 0.07, DF: 1, $p < 0.80$) subjects. Thus, VMN PACAP neurons may tonically inhibit the hedonic consumption of palatable food irrespectively of sex or energy status. In comparing body weight of TH-*cre* and TH-*cre*/PAC1R$^{fl/fl}$ animals utilized for both feeding and electrophysiology studies, starting weight was not significantly different (student's *t*-test, $t = 0.6705$, DF: 84, $p > 0.05$).

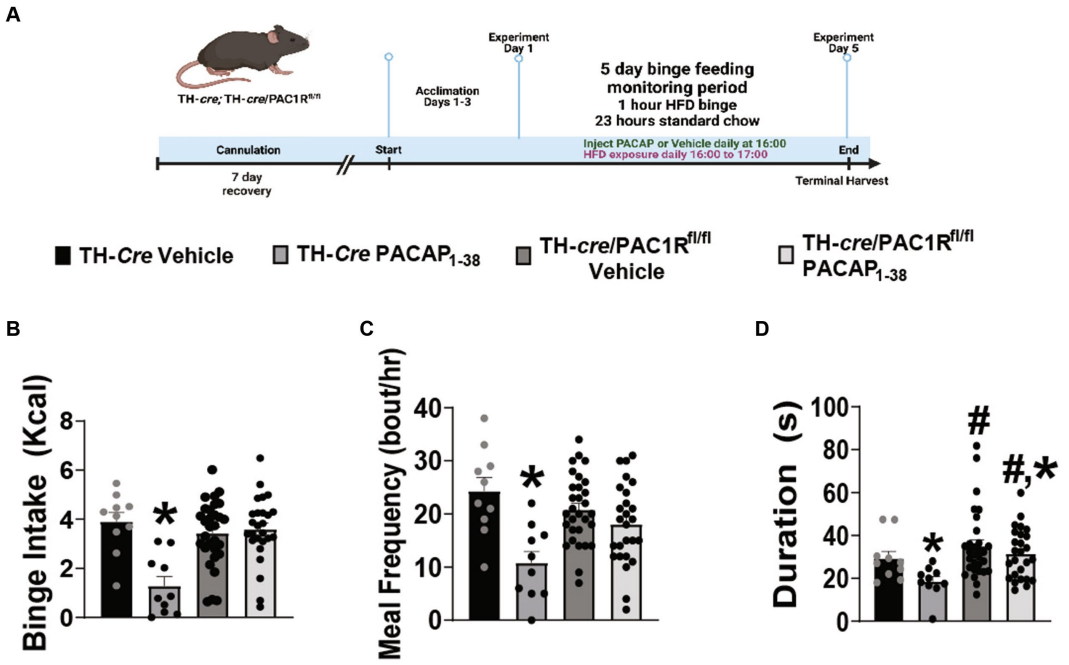

FIGURE 3
Intra-VTA $PACAP_{1-38}$ significantly reduces binge intake, meal frequency, and bout duration in TH-*cre* but not TH-*cre*/$PAC1R^{fl/fl}$ mice. **(A)** Schematic illustrating the procedural timeline for the execution of these experiments. **(B–D)** Composite data depicting $PACAP_{1-38}$ significantly decreases binge intake **(B)**, meal frequency **(C)**, and bout duration **(D)** in TH-*cre* mice, effects which are largely negated in the absence of PAC1R in VTA TH neurons. $^{*}p < 0.05$ relative to vehicle, $^{\#}p < 0.5$ relative to genotype. Repeated measures, multifactorial ANOVA/LSD, TH-*cre* vehicle $n = 10$, TH-*cre* $PACAP_{1-38}$ $n = 9$, TH-*cre*/$PAC1R^{fl/fl}$ vehicle $n = 30$, and TH-*cre*/$PAC1R^{fl/fl}$ $n = 26$. Bars represent means and lines 1 SEM.

4 Discussion

The data curated throughout this project indicate PACAP-induced inhibition of VTA A_{10} DA neurons is PAC1R-dependent. The PAC1R is necessary for PACAP's ability to exert its inhibitory effects on VTA A_{10} DA neurons, and attenuation of the PACAP mediated inhibition upon knockdown of the PAC1R in VTA A_{10} DA neurons increases hedonic drive. Additionally, VMN PACAP neurons tonically reduce hedonic drive independent of sex and diet. We have confirmed exogenous PACAP inhibits of VTA A_{10} DA neurons as evidenced by the robust and reversible outward current bath application of $PACAP_{1-38}$ promoted in recordings of VTA A_{10} DA neurons. Following knockdown of the PAC1R in these A_{10} DA neurons, bath application of $PACAP_{1-38}$ elicited no significant change in A_{10} DA membrane current. The reduced PACAP-mediated inhibition of A_{10} DA neurons greatly attenuates the decreased binge intake as well as meal frequency and bout duration during intermittent exposure to highly palatable food. Lastly, ablation of VMN PACAP neurons promoted increased drive for highly palatable food consumption, in both male and female groups, as well as lean and DIO sub-groups, confirming that VMN PACAP neurons tonically inhibit VTA A_{10} DA neurons.

4.1 Knockdown of PAC1R functionality in VTA A_{10} DA neurons diminishes PACAP induced inhibition

Retrograde tracing has indicated VMN PACAP neurons project to and terminate at VTA A_{10} DA neurons (35). Optogenetic stimulation of VMN PACAP neurons inhibits VTA neurons. This inhibitory effect was replicated with exogenous bath application of $PACAP_{1-38}$ in VTA A_{10} DA neurons and diminished in the presence of K_{ATP} channel blocker and PAC1R antagonist, tolbutamide and $PACAP_{6-38}$, respectively (35). PACAP selectively binds to PAC1R with high affinity, however, this neuropeptide also binds to VPAC1R and VPAC2R (39). It has been shown that the PAC1R/VPAC2R antagonist $PACAP_{6-38}$ abrogates the appetite-suppressing effects of PACAP in several different species, including goldfish and chicks; indicating PACAP's anorexic effects are PAC1R mediated (40, 41). In the present study, we show knockdown of the PAC1R in VTA A_{10} DA neurons renders the bath application of exogenous PACAP in mesencephalic slices ultimately ineffective. This was evidenced by the significant attenuation in change in A_{10} DA membrane current, as well as a lesser increase in slope conductance. These data confirm and extend PAC1R's role in mediating PACAP induced inhibition of A_{10} DA neurons.

4.2 Blunted PACAP-mediated inhibition of VTA A_{10} DA neurons increases tendencies toward binge feeding behavior during intermittent exposure to highly palatable food

The NAc has been strongly tied to appetitive motivation in both rodents and humans (42–44). The incentive-sensitization model of obesity suggests hyper-responsivity of the DA reward

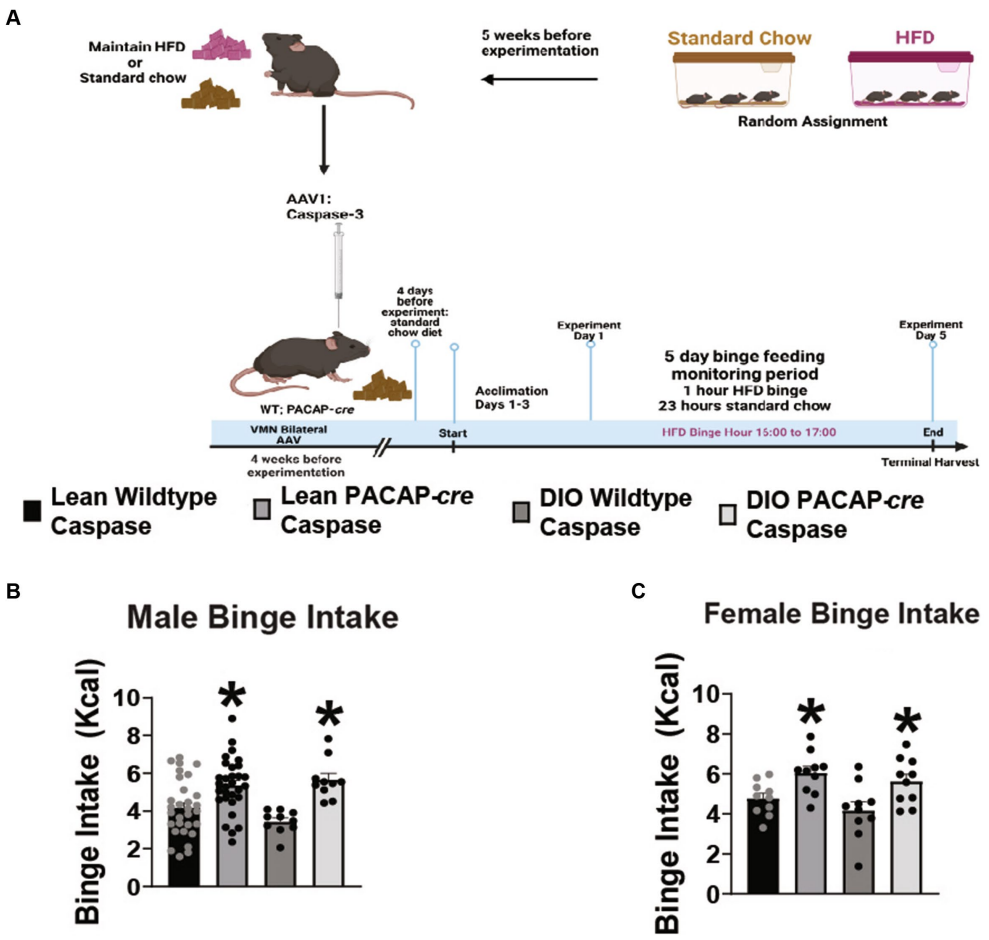

FIGURE 4
VMN PACAP neuron ablation in PACAP-*cre* mice increases binge consumption in males and females. **(A)** Schematic illustrating the procedural timeline for the execution of these experiments. **(B,C)** Composite data depicting caspase ablation of VMN PACAP neurons in PACAP-cre mice elicits a significant increase in binge consumption in both lean and obese male **(B)** as well as female **(C)** mice. *$p < 0.05$ relative to wildtype controls. Repeated measures, multifactorial ANOVA/LSD, **(B)** lean wildtype $n = 30$, lean PACAP-*cre* $n = 30$, DIO wildtype $n = 10$, DIO PACAP-*cre* $n = 10$; **(C)** lean wildtype $n = 10$, lean PACAP-*cre* $n = 10$, DIO wildtype $n = 10$, DIO PACAP-*cre* $n = 10$. Bars represent means and lines 1 SEM.

circuitry is due to repeated pairings of reward from food intake and food-intake associated cues (45). In accordance with this theory, the incentive-sensitization model of drug addiction asserts that hypersensitivity to motivational stimuli associated with high incentive salience promotes attentional processing bias toward reward-related cues (46). This bias toward reward-related cues is proposed to trigger the release of DA and drive consumption (47). The same underlying processes most likely extend to food addiction and eating disorders like bulimia. Indeed, our binge feeding paradigm results in a dramatic escalation in the ingestion of palatable food over the 5 days of the monitoring period; resulting in upwards of 40% of the daily caloric intake being consumed during the one-hour HFD exposure. This escalation is blunted by PACAP and other neuropeptides like nociceptin/orphanin FQ due to their ability to inhibit A_{10} dopamine neurons (35, 38).

Food cues act as stimuli, which promote the urge to eat. This is evidenced by rodent studies depicting increased cue-triggered motivation and a sensitized mesolimbic system following high fat diet (HFD) consumption resulted in increased activity of DA cells and increased expression of the rate limiting enzyme of DA synthesis, tyrosine hydroxylase (TH), within the NAc (48). Studies with clinically obese populations have reported stronger cue triggered food cravings coupled with larger portion consumption (47). Additionally, this study demonstrated that body mass index (BMI) is positively correlated with food-seeking behavioral responses, which implied food cues triggered a greater attention bias toward food in overweight versus lean individuals (47).

Pituitary adenylate cyclase-activating polypeptide and its cognate receptors are expressed in the NAc and VTA, which are evidenced to be involved in the hedonic regulation of feeding (5, 33, 34). In accordance with this, PACAP administered to the NAc reduced hedonic feeding without affecting homeostatic feeding (31, 32). Likewise, intra-VTA PACAP administration suppresses the binge-like consumption of palatable food in lean mice due to activation of K_{ATP} channels and hyperpolarization of A_{10} DA neurons in the VTA (35), which is blocked by the PAC1/VPAC2R antagonist $PACAP_{6-38}$. In the present study, intra-VTA administration of $PACAP_{1-38}$ significantly decreased binge intake,

meal frequency, and bout duration during intermittent exposure to HFD in TH-*cre*, but not TH-*cre*/PAC1R$^{fl/fl}$ animals. The most parsimonious explanation of this finding is that knockdown of the PAC1R attenuated the suppressive effect promoted by PACAP on hedonic feeding. TH-*cre*/PAC1R$^{fl/fl}$ animals exhibited binge feeding behavior virtually indistinguishable from their TH-*cre* saline vehicle-treated counterparts despite receiving intra-VTA administration of PACAP$_{1-38}$. Therefore, the reduced PACAP mediated inhibition of A_{10} DA neurons in TH-*cre*/PAC1R$^{fl/fl}$ animals exhibited in our electrophysiology studies translates behaviorally to decreased inhibition of the hedonic feeding behavior. Admittedly, we did not see an elevation in binge feeding *per se* in the vehicle treated, TH-*cre*/PAC1R$^{fl/fl}$ animals, which suggests that activation of PAC1Rs by PACAP do not tonically inhibit hedonic feeding. We also reported no significant difference in starting body weight for TH-*cre* and TH-*cre*/PAC1R$^{fl/fl}$ animals. While this data was solely from pre-surgical body weight, previous research followed body weight across an eight-week timespan and reported a significant increase in body weight gain in caspase induced ablation of VMN PACAP neurons (23). Additionally, this research depicted PACAP inhibits AgRP neurons resulting in decreased energy intake and expenditure, however, upon knockdown of the PAC1R in AgRP neurons, there was no significant difference in energy intake nor expenditure with application of PACAP. Nevertheless, our findings demonstrate the PAC1R can play a role in inhibition of the hedonic mesolimbic pathway. PACAP activation of the PAC1R, and subsequent activation of K_{ATP} channels (5), decreases A_{10} DA activity; desensitizing the mesolimbic system to food cues and decreasing hedonic drive toward highly palatable food.

4.3 VMN PACAP neurons are a key proponent for inhibition of the mesolimbic DA pathway and attenuation of hedonic behavior

The *cre*-dependent apoptotic ablation of VMN PACAP neurons promoted a significant increase in hedonic feeding behavior in both male and female, lean and obese cohorts. The significant increase in hedonic drive strongly indicates that VMN PACAP neurons are necessary for the tonic inhibition of VTA A_{10} DA neurons. In previous studies, we have demonstrated that optogenetic stimulation of VMN PACAP neurons effectively inhibit VTA neurons (35). VMN PACAP neurons contain other important phenotypic markers including glutamate steroidogenic factor-1 (24, 49–51). Considering that acute knockdown of PAC1R in A_{10} dopamine neurons *per se* did not affect binge feeding, it is entirely plausible that glutamate released from these neurons carry out this tonic inhibition via activation of metabotropic glutamate receptor, and future studies will determine if this is in fact the case. Nevertheless, it is apparent that VMN PACAP neurons play a key role in the inhibition of VTA A_{10} DA neurons and consequently the reduction in drive for hedonic feeding. On the other hand, the PACAP-induced diminution of binge feeding behavior is sex dependent in that intra-VTA PACAP decreases binge feeding in lean, otherwise chow-fed males but not in their female counterparts (35). Moreover, PACAP delivery into the VTA of obese females actually increases binge feeding behavior (5). Studies have shown that women have a greater risk of developing food addiction. This may be due, in part, to greater activation of the dorsolateral prefrontal cortex (dlPFC), medial orbitofrontal cortex, and the amygdala when presented with a food cue (52). Activation of the dlPFC is increased during reward anticipation, and this enhanced activity of the dlPFC stimulates A_{10} DA neurons (53). The medial orbitofrontal cortex and amygdala receive A_{10} DA input and are important for goal directed behavior and processing of emotional stimuli associated with food cues (54, 55). Additionally, binge studies in female rats depicted heightened tolerance to high levels of foot shock in acquiring Oreo cookies—indicating a food addiction defined as sustained desire for food consumption despite negative consequences (56, 57). Within the mesolimbic pathway, estradiol regulates dopamine neuron sensitization in females (58, 59), an effect that is not present in males (60). It follows then that estradiol's role in sensitization is a likely underlying factor in the sexually differentiated disparities in addiction and hedonic feeding behavior. However, in the present study we found that apoptotic ablation of VMN PACAP neurons increased binge feeding behavior in both lean and obese, male and female PACAP-*cre* animals. As mentioned above, VMN PACAP neurons are glutamatergic (24, 50, 51), and it bears repeating that glutamate acting at inhibitory metabotropic glutamate receptors may very well be responsible for the tonic suppression of binge feeding that is relieved upon apoptotic ablation of these cells. On the other hand, the actions of PACAP in the VTA with respect to hedonic feeding are clearly sexually differentiated; as PACAP decreases binge feeding in lean males but not females and increases it in obese females (5, 35). Thus, once sex and energy status have been factored in appropriately. The PACAP/PAC1R system may very well prove to be an effective target to curb excessive eating via inhibiting the hedonic feeding pathway.

In conclusion, we have demonstrated that the PACAP-induced inhibition of the mesolimbic pathway is reliant on PAC1R activation. Taken together, these data demonstrate the contribution of the PACAP/PAC1R system and VMN PACAP neurons in reducing excitability of the mesolimbic dopamine pathway via inhibition of VTA A_{10} DA neurons that in turn suppresses hedonic feeding. This knowledge renders the PAC1R a potential therapeutic target in managing excessive eating.

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 animal study was approved by Institutional Animal Care and Use Committee. The study was conducted in accordance with the local legislation and institutional requirements.

Author contributions

SS: Data curation, Formal analysis, Investigation, Methodology, Writing – original draft, Writing – review & editing. NL: Data curation, Formal analysis, Investigation, Methodology, Writing – review & editing. EW: Conceptualization, Funding acquisition, Methodology, Resources, Supervision, Writing – original draft.

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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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Association between dopamine genes, adiposity, food addiction, and eating behavior in Chilean adult

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Background: A frequent consumption of high sugar/fat foods can affect dopamine signaling in the brain and cause sustained stimulation of the reward system. It has been hypothesized that a hypodopaminergic trait results in an individual overeating in order to increase brain DA. Genetic variants in this route have been connected with addiction and eating behaviors. Most studies focus on a specific SNP, and few studies have used multilocus genetic scores, which quantify genetic risk on a continuum.

Aim: To assess the relationship between multilocus genetic scores based on multiple gene variants in the dopaminergic pathway and measurements of anthropometry, eating behavior, food reinforcement, and food addiction (FA) in Chilean adults.

Methods: We recruited 221 Chilean adults for a cross-sectional study. A standard anthropometric measurement procedure was followed and eating behavior was examined using the Three Factor Eating questionnaire (TFEQ), Food Reinforcement Value Questionnaire (FRVQ), Yale Food Addiction Scale (YFAS) and 24-h diet recall. Multilocus genetic scores were calculated using TaqMan assays (rs1800497-rs1799732-rs6277-rs4680).

Results: No differences were found in the entire sample for anthropometric measurements, by MLGS. We found that participants with a score ≥ 2.0 in the MLGS showed higher food choices on the RVFQ and lower energy intake in protein, lipids, SAFA, MUFA, PUFA, dietary cholesterol, omega-3 and Omega-6 fatty acids in the 24-h recall ($p < 0.05$). Stratified by nutritional condition, the group with obesity had inferior scores on cognitive restriction, greater scores on uncontrolled eating, emotional eating, and responding to palatable food in the RVFQ. Also, in subjects with obesity, there was more food addiction in the group scoring "MLGS ≥2.0 or low dopamine signaling" (53%), compared to the group scored "MLGS <2.0 or high dopamine signaling" (23%) (p-value; 0.05). Emotional Eating scores correlated positively with MLGS in subjects with obesity.

Conclusion: In adults with obesity, the MLGS of the dopamine pathway, reflecting hypodopaminergic signaling, was associated with greater scores on food addiction and altered eating behavior traits.

KEYWORDS

food addiction, polymorphism, eating behavior, dopamine, obesity

Introduction

Obesity is a worldwide problem (1). It could be due to interactions among environmental and genetic factor (2, 3). Considering the 2016 levels of childhood obesity in the USA, simulated growth trajectories suggest 57% of today's children will be obese by 35 (1). Like many other high-income and developing countries, Chile's overweight and obesity rate is rapidly increasing, most notably among preschool and school-aged children. The last National Health Survey inform that 74% of the adult population had excess. According to the research, 27.6% of adolescents (15–19 years) are overweight, 12.2% are obese, and 1% are severely obese (4). One of the question that scientists face in this field is related to eating behavior, overeating and food craving with addictive behavior (5, 6). Studies has established that frequent ingestion of high sugar/fat food can produce changes in brain dopamine signaling (7, 8). This can result in abnormally sustained reward system stimulation (9). Food is rewarding, in part, through activation of the mesolimbic dopamine (DA) pathway. A high sugar and fat content in some foods can act like drugs, causing compulsive eating and loss of control (7). There is an emerging literature investigating dopamine genes in relationship to addictive and compulsive appetitive behaviors (10, 11).

A recent 2016 genome-wide association study (GWAS) of 9,314 females of European ancestry who were identified as having food addiction by the modified YFAS (Yale Food Addiction Scale) did not identify a significant association with any single nucleotide polymorphisms (SNPs) or genes implicated in drug addiction (12). Nevertheless, a 2015 study of neurogenetic and neuroimaging evidence for a theoretical model of dopaminergic influences to obesity, found a collection of research involving an association between obesity and genetic variants in DA receptors genes for DA receptors 2, 3, 4 (DRD2, DRD3, and DRD4), dopamine transporter 1 (DAT1) and genes for enzymes implicated with dopamine degradation—catechol-o-methyltransferase (COMT) and monoamine oxidase isomers A and B (13). Although there are no evidences for the involvement of common variants near DRD2 gene from genome-wide association study, there are several association studies that have reported a possible involvement of DRD2 variants in eating behavior traits. In this field, we previously showed that rs1800497 was not associated with food addiction, but in obese female A1 carriers was associated with scores of emotional eating and snacking reinforcement (14). We then looked for the relation between the bilocus genetic profile (rs1799732 + rs1800497) and food addiction in the same sample, showing no association (15). Considering that only two variants account for a minimal percentage of phenotypical variation we decide to explore other methods.

In genetics, to predict an individual's risk of developing a particular trait or disease based on genetic data, certain tools are often used. Some studies use a Polygenic Risk Score (PRS) which is a numerical representation of the estimated effects of many genetic variants across the genome on an individual's phenotype, particularly complex traits. A PRS represents an individual's genetic predisposition to a trait or disease by integrating the cumulative impact of numerous small-effect variants, which are weighted based on their effect sizes in genome-wide association studies. An alternative approach, is the Multilocus Genetic Score (MLGS), which focuses on a specific set of genetic loci believed to contribute to a particular phenotype or disease. This method aggregates the effects of these loci, not necessarily derived from a genome-wide association studies. The MLGS can be seen as a more targeted approach, often reflecting the additive risk from a limited number of genes hypothesized to be involved in a specific biological pathway or trait.

Using the concept of candidate gene clustering, a multilocus genetic score was developed established on polymorphisms in multiple reward markers related to changes in dopamine transmission in the brain. Previously, Nikolova et al. (16) reported that MLGS was associated with higher DA signaling, predicting an increase in reward-related activity in the ventral striatum. According to this finding, a multilocus profiling method could capture the accumulative effect of genetic variants whose single effects might be undetected in small samples. After that, Davis et al. (17) showed that MLGP scores were higher in people with YFAS and that binge eating, cravings, and emotional overeating were positively correlated. In a similar manner, Yokum et al. found that participants with a greater number of alleles associated with DA signaling capacity, showed greater weight gain than those with fewer risk alleles (18).

Given this evidence, the aim if this study was to assess the relationship between multilocus genetic scores based on multiple gene variants in the dopaminergic pathway and measurements of anthropometry, eating behavior, food reinforcement, and food addiction (FA) in Chilean adults. We hypothesized that higher multilocus genetic score would exhibit higher adiposity, scores of unhealthy eating behavior and food addiction compared with lower scores.

Materials and methods

A cross- sectional study was developed between January 2016 and March 2017. The inclusion criteria were (i) subjects aged ≥18 years; without consumption of medications that affected body weight, and without treatment to lose weight. The exclusion criteria were (i) Patients with diseases such as genetic syndromes, pregnant women, individuals with associated diagnoses of cardiovascular, liver, kidney or cancer; and (ii) other pathologies that require dietary restrictions.

A convenience sample was recruited involving 221 adults (74% female, 18–54 years old), 43.8% with obesity, 11.3% overweight, and 44.8% normal weight. Participants were recruited through a variety of sources in the community, including posters, on campus at Universidad San Sebastian, recreational and community centers, as well as online advising on the website.[1] Informed consent was achieved from all subjects and laboratory tests occurred at San Sebastian University. The study was approved by the Research and Scientific

Abbreviations: DA, Dopamine; GWAS, Genome-wide association study; YFAS, Yale Food Addiction Scale; SNP, Single Nucleotide Polymorphisms; DRD2, Dopamine 2 receptor; DRD3, Dopamine 3 receptor; DRD4, Dopamine 4 receptor; DAT 1, Dopamine transporter 1; COMT, Catechol-o-methyltransferase; MLGS, Multilocus genetic scores; FA, Food addiction; BMI, Body Mass Index; TFEQ, Three Factor Eating Behavior Questionnaire; FRVQ, Food Reinforcement Value Questionnaire; ANKK1, Ankyrin repeat domain containing 1 gene; SAFA, Saturated Fatty Acids; MUFA, Monoinsaturated Fatty Acids; PUFA, Polinsaturated Fatty Acids; PCR-RFLP, Restriction Fragment Length Polymorphism.

1 http://www.uss.cl

Ethics Committee of San Sebastian University (#48–2021-20). The protocol was conducted in agreement with the Declaration of Helsinki research ethics guidelines.

Anthropometry

We measured height, weight and waist circumference without shoes, using a weight scale (Seca 700) with a stadiometer included (100 gr. and 0.5 cm sensitivity) (19).

Based on criteria established by the World Health Organization (20), BMI cut-offs were used to determine weight status. Subjects were classified as normal-weight, overweight or obese according to their BMI values ($\geq$ 24.9 Kg/m^2, $\geq$ 25.0–29.9 Kg/m^2, or $\geq$ 30.0 Kg/m^2, respectively). After an overnight fast, the body composition was assessed using bioelectrical impedance, based on the manufacturer's instructions using a Tanita TBF-300MA (Tanita Corporation, Tokyo, Japan).

Eating behavior: four questionnaires validated were used:

(1) *Three Factor Eating Behavior Questionnaire*: Using this instrument, 18 items are assessed and three components of eating behavior are evaluated. These components are: cognitive restraint (CR), emotional eating (EE), and uncontrolled eating (UE). Using a 4-point Likert scale, subjects rate their level of agreement on each item. Each subscale's score was calculated by summing individual raw scores and dividing them by the number of items in that subscale (21). A Cronbach-alpha value of 0.60–0.88 was found for all subscales in the present study, suggesting moderate-to-strong internal consistency (22).

(2) *Food Reinforcement Value Questionnaire (FRVQ)*: A 12-item questionnaire assesses the relative reinforcing value of food compared to an alternative reinforcer. Using this task, we assessed subjects' motivation to work toward obtaining either their most preferred snack food or their highest rated healthy alternative (fruits/vegetables). In this paradigm, work was defined as the number of button presses, with more button presses indicating a higher level of reinforcement. First, a fixed ratio schedule was applied, which required subjects to press the joystick button 20 times to access either snack food or fruit/vegetables. Among the remaining items, the reinforcement schedule for gaining access to preferred snack food increased by 20 button presses to a maximum of 240 button presses for item 12. In contrast, the reinforcement program for preferred fruits/vegetables remained the same. The amount of button presses associated with snack food choices denoted the relative reinforcing value of snack food. Based on the food choices made, it was expressed as a percentage. The validity of this tool has been established against a gold-standard in adults (23), and suggests good predictive validity since they predict weight gain over time (24).

(3) *24-h diet recall*: A staff of nutritionists evaluated each participant's total energy intake, macronutrient, fiber, saturated, monounsaturated, and polyunsaturated fat intake as well as total n-6 and n-3 fatty acids using 24-h dietary recalls on days randomly select. This survey estimate energy and nutrient intake based on exhaustive food descriptions, comprising ingredient names, preparations, portions, and brand (25). Using Food Processor w/PS 10.15, 24-h recalls were analyzed for each patient.

(4) *Yale Food Addiction Scale (YFAS) (First version)*: In accordance with the DSM-IV criteria for substance dependence, a 25-item questionnaire has been developed to assess symptoms of dependence on highly palatable foods (e.g., foods high in fats and/or carbohydrates). The YFAS requires the simultaneous existence of elevated clinically levels of distress for the food addiction diagnosis to be made. Additionally, food addiction symptoms were continuously assessed, with higher scores indicating increased susceptibility. According to Obregón et al., this instrument has been validated in Chilean adults (26), following the original validation (27).

Collection of biologic samples

A registered nurse obtain blood samples in an EDTA-coated tube of 4 mL for molecular analysis, after an overnight fast using a standard vacuum system protocol. We collected blood. After centrifuging the EDTA-coated tube at 3,300 rpm for 10 min at room temperature, plasma was separated from buffy coat and red blood cells. According to the manufacturer's instructions, DNA was extracted from each blood sample using the QIAGEN QIAamp DNA blood mini kit #51104 (28).

Molecular genotyping

We choose common genetic variants near DRD2 that have been previously associated in several studies with dopamine pathway and eating behavior (16–18).

Genetic variant rs1800497: PCR-RFLP was used previously to assess this variant (14). In order to determine if a given allele was present or absent, the expected sizes of the PCR products were determined: one band of 307 bp was observed for homozygous A1/A1, three bands were observed for heterozygotes of A1/A2, 307 bp, 177 bp, and 127 bp, and two bands were observed for homozygotes of A2/A2 with expected sizes of 177 base pairs and 127 base pairs.

Genetic variants rs1799732, rs4680, rs6277

These variants were identified using a predesigned Taqman assay ID C_33641686_10 (Applied Biosystems) using a QuantStudioTM 3 Real-Time PCR System. For rs1799732 (Homozygous G/G, heterozygous G/Del, and homozygous Del/Del genotype); for rs4680 (Homozygous AA, heterozygous A/G, and homozygous GG) and for rs6277 (Homozygous CC, heterozygous C/T, and homozygous TT) genotype groups were determine.

Multilocus genetic score

We estimated individually Multilocus genetic scores using 4 genetic variants of the dopaminergic system, using a similar approach as other groups (17). There was a score of 1 for genotypes associated with low DA signaling, a score of 0 for genotypes associated with high DA signaling, and a score of 0.5 for intermediate heterozygotes. A score of 1 ("low dopaminergic signaling") was assigned to TaqIA A1/A1, DRD2-141C Ins/Ins carriers, rs6277 (C957T; T-allele) and rs4680 COMT Met/Met genotypes. A score of 0 ("high dopaminergic signaling"), was assigned to TaqIA A2/A2, DRD2-141C Ins/Del and Del/Del carriers, rs6277 (C957T; C-allele), COMT Val/Val genotypes. Finally, a score of 0.5 ("intermediate dopaminergic signaling") was given to TaqIA A1/A2 and COMT Met/Val genotypes. The scores were added to build a multilocus genetic score. The global score at each locus will be 0–1, and for the total path a score of 0–4 (Table 1) (29).

Data analysis

We developed a descriptive analysis of the sample (mean or median and standard deviation). Genotype and allele frequencies were determined. Also the Hardy–Weinberg equilibrium was estimated using the goodness-of-fit X2 test. An examination of differences and associations between groups was conducted using non-parametric statistics (Mann–Whitney and Kruskal-Wallis tests), including a sex-specific analysis. Data were examined with STATA 14.0 software. In order to assess the association between the MLGS and anthropometrics and eating behavior variables, the MLGS was dichotomized into two groups (MLGS <2.0 and MLGS ≥2.0).

Results

Association between MLGS and anthropometric measurements

A total of 204 participants were completely genotypes in the sample. Table 1 presents the genotypic frequencies of genetic variants. All variants meet the Hardy–Weinberg equilibrium. Table 2 presents the frequency of multilocus genetic scores in our sample. The number of participants without risk alleles was only 2/204 (0.98%). 61% of the sample had a score of two or higher. 0.49% of the sample was homozygous for the four polymorphisms examined. To determine if any association existed between the MLGS and anthropometrics and eating behavior variables, the MLGS was dichotomized into two groups, MLGS <2.0 and MLGS ≥2.0. Table 3 shows that there were no differences in the entire sample for anthropometric measurements.

TABLE 1 Genotypic frequency of the SNPs studied and putatively functional association.

Gene	ID	Genotypic frequency	Functional association
ANKK1 (Taq1A C > T)	rs1800497	A1A1 21 (9.9%) A1A2 71 (33.6%) A2A2 119 (56.0%)	A1 allele or T-allele associated with reduced D2 receptor binding affinity
DRD2 -141C Ins/del	rs1799732	GG 155 (73.1%) G/del 54 (25.4%) Del/del 3 (1.42%)	The Del-allele has been associated with significantly less promoter activity and protein expression of DRD2
DRD2 C957T	rs6277 C > T	TT 76 (37.2%) CT 99 (48.5%) CC 29 (14.2%)	T allele associated with alteration in receptor binding affinity and thereby in stratial dopamine levels
COMT Val158Met	rs4680	Met/Met 35 (16.9%) Met/Val 95 (46.2%) Val/Val 76 (36.8%)	Met allele associated with a reduction in DA catabolism and therefore higher DA levels

Association between MLGS and eating behaviors measurements

Table 4 shows the results for eating behavior variables. In the entire sample subjects scoring MLGS ≥2.0 (*Low dopamine signaling*) showed no difference in the Eating behavior scores. We found higher % of food choice in the RVFQ and lower energy, protein, lipids, SAFA, MUFA, PUFA, dietary cholesterol, omega-3 and Omega-6 fatty acids in the 24-h recall ($p < 0.05$).

When we categorize by nutritional condition, we saw that in the Normal weight subjects the MLGS ≥2.0 group showed higher scores of cognitive restriction (ns), and lower intake of protein, SAFA, MUFA, PUFA, dietary cholesterol, omega-3 and Omega-6 fatty acids ($p < 0.05$). No differences were observed in the overweight group. Finally in the subjects with obesity we found lower scores of cognitive restriction and higher scores of Emotional eating, Uncontrolled eating ($p < 0.05$) and % of food choice in the RVFQ ($p = 0.05$). In the 24-h recall we found a lower omega-3 fatty acids intake ($p < 0.05$).

Relation between MLGS score and food addiction

No difference was observed in the frequency of diagnosis of food addiction by categories of MLGS (MLGS <2.0 and MLGS ≥2.0), in the total sample both genders, and by gender. Stratified by nutritional condition it was observed that in participants with obesity a greater % of food addiction was found in the group scored "MLGS ≥2.0 or low dopamine signaling" (53%), compared to the group scored "MLGS <2.0 or high dopamine signaling" (23%) (*p*-value; 0.05).

In the entire sample we did not find a significant correlation between MLGS, anthropometric and eating behavior variables. When the sample was categorized by nutritional condition, in the normal weight group we observed a positive and significant association between Emotional Eating and Uncontrolled Eating scores. A positive correlation was found between MLGS and Emotional Eating scores in the participants with obesity ($r = 0.21$; $p < 0.05$). In females there was a nearly significant positive association between MLGS and % food choice ($p = 0.05$).

TABLE 2 Frequency of multilocus genetic score in Chilean university students.

	Frequency multilocus genetic score								
	0 *n* = 2	0.5 *n* = 7	1 *n* = 31	1.5 *n* = 39	2 *n* = 53	2.5 *n* = 30	3.0 *n* = 23	3.5 *n* = 18	4.0 *n* = 1
Total	0.98%	3.45%	15.2%	19.2%	25.9%	14.7%	11.2%	8.8%	0.49%

Individual genetic profile scores represent the sum of "high" DA genotypes across two functional polymorphic loci. "High" genotypes received a score of 1, "low" genotypes a score of 0, and "intermediate" genotypes a score of 0.5. For example, the genetic profile score for an individual with the following 2 polymorphisms, DRD2-141C Ins/Ins and DRD2 Taq1A (0 + 0).

TABLE 3 Anthropometric measurements by Multilocus genetic score MLGS (rs1799732, rs6277, rs4680, rs1800497).

	Multilocus genetic score											
	All			Normal-weight			Over-weight			Obesity		
	<score 2 (*n* = 132)	≥score 2 (*n* = 72)	*p*-value	< score 2 (*n* = 56)	≥score 2 (*n* = 35)	*p*-value	< score 2 (*n* = 15)	≥score 2 (*n* = 9)	*p*-value	< score 2 (*n* = 61)	≥score 2 (*n* = 28)	*p*-value
Age (years)	24.9 ± 4.6	24.7 ± 5.9	0.67	23.6 ± 3.5	22.9 ± 4.6	0.64	22.5 ± 2.1	24.1 ± 2.9	0.17	26.6 ± 5.2	27.0 ± 7.3	0.98
Weight at Birth (gr)	3428.9 ± 594.6	3414.8 ± 656.2	0.80	3397.1 ± 486.0	3426.2 ± 551.7	0.22	3464.2 ± 589.0	2986.4 ± 672.7	0.08	3449.5 ± 687.5	3538.2 ± 733.4	0.69
Height at birth (cm)	50.9 ± 2.4	49.6 ± 3.3	0.48	50.3 ± 2.0	49.6 ± 2.3	0.16	49.1 ± 2.5	49.1 ± 3.2	0.58	50.1 ± 2.8	49.7 ± 4.3	0.90
Weight (kg)	75.8 ± 18.1	73.4 ± 16.4	0.40	59.9 ± 7.0	60.3 ± 5.9	0.69	72.0 ± 11.0	71.2 ± 8.9	0.65	91.3 ± 12.7	90.4 ± 10.9	0.60
Height (mts)	1.64 ± 0.08	1.63 ± 0.08	0.31	1.64 ± 0.07	1.62 ± 0.07	0.27	1.64 ± 0.10	1.62 ± 0.10	0.85	1.64 ± 0.08	1.63 ± 0.08	0.59
Body mass index (kg/mt^2)	28.1 ± 6.3	27.7 ± 5.7	0.85	22.2 ± 1.6	22.8 ± 1.3	0.07	26.8 ± 2.9	27.0 ± 1,2	0.74	33.8 ± 4.0	34.0 ± 3.5	0.98
Waist to height ratio	0.55 ± 0.1	0.55 ± 0.09	0.92	0.46 ± 0.04	0.48 ± 0.04	0.12	0.53 ± 0.07	0.54 ± 0.03	0.83	0.64 ± 0.08	0.64 ± 0.07	0.96
Abdominal circumference (cm)	90.4 ± 17.0	88.8 ± 14.6	0.58	75.7 ± 6.6	77.3 ± 6.3	0.30	87.2 ± 10.3	87.4 ± 5.5	0.92	104.9 ± 11.9	103.6 ± 10.2	0.68
Body fat %	32.0 ± 10.9	31.9 ± 10.0	0.99	23.7 ± 6.0	25.3 ± 6.3	0.13	27.5 ± 10.3	29.4 ± 8.2	0.83	40.8 ± 7.5	41.1 ± 6.8	0.91

*Significant differences were analyzed with the nonparametric Mann–Whitney by MLGP group.
*$p < 0.05$; **$p < 0.001$.

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TABLE 4 Eating behavior by multilocus genetic score MLGS (rs1799732, rs6277, rs4680, rs1800497).

	Multilocus genetic score											
	All			Normal-weight			Over-weight			Obesity		
	<score 2 (*n* = 132)	≥score 2 (*n* = 72)	*p*-value	< score 2 (*n* = 56)	≥score 2 (*n* = 35)	*p*-value	< score 2 (*n* = 15)	≥score 2 (*n* = 9)	*p*-value	< score 2 (*n* = 61)	≥score 2 (*n* = 28)	*p*-value
TFEQ												
Cognitive restraint	2.3 ± 0.58	2.3 ± 0.67	0.95	2.2 ± 0.65	2.5 ± 0.6	0.07	2.28 ± 0.53	2.22 ± 0.52	0.67	2.3 ± 0.54	2.0 ± 0.69	0.03*
Emotional eating	2.3 ± 0.8	2.57 ± 0.8	0.07	2.1 ± 0.78	2.3 ± 0.85	0.26	2.5 ± 0.92	2.1 ± 0.67	0.24	2.5 ± 0.76	2.9 ± 0.65	0.006*
Uncontrolled eating	2.43 ± 0.55	2.48 ± 0.61	0.33	2.42 ± 0.56	2.26 ± 0.6	0.28	2.4 ± 0.5	2.2 ± 0.57	0.33	2.4 ± 0.55	2.8 ± 0.46	0.006*
RVFQ												
Food choice (%)	16.4 ± 20.8	22.9 ± 24.7	0.02*	14.2 ± 17.2	20.4 ± 23.6	0.14	19.4 ± 29.3	16.6 ± 17.1	0.75*	17.6 ± 21.5	27.9 ± 27.8	0.05
24hours recall												
Energy intake (Kcal)	1665 ± 386	1512 ± 395	0.007*	1628 ± 354	1493 ± 366	0.1	1654 ± 400	1413 ± 252.3	0.1	1701 ± 414	1567 ± 466	0.26
Protein intake (g)	66.1 ± 20.5	58.1 ± 20.3	0.006*	62.7 ± 15.8	55.3 ± 17.7	0.03*	67.7 ± 27.4	60.9 ± 19.9	0.65	68.8 ± 22	60.8 ± 23.5	0.12
Carbohydrates (g)	218.1 ± 61.3	208.5 ± 56.6	0.25	213.5 ± 61.3	206.5 ± 56.5	0.52	240.7 ± 66.8	207 ± 45.0	0.27	216.7 ± 59.7	211.2 ± 61.7	0.68
Fiber (g)	19.7 ± 7.8	19.5 ± 7.6	0.95	19.3 ± 7.1	20.4 ± 8.43	0.46	20.9 ± 7.6	18.6 ± 7.2	0.61	19.9 ± 8.6	18.6 ± 6.9	0.59
Lipids (g)	58.5 ± 21.2	49.6 ± 20.5	0.004*	57.3 ± 18.7	49.6 ± 18.3	0.05	48.7 ± 24.3	38.7 ± 15.4	0.35	62.0 ± 22.1	53.2 ± 23.8	0.1
SAFA (g)	18.3 ± 7.7	15.0 ± 6.9	0.002*	18.0 ± 6.8	15.2 ± 6.6	0.03*	16.1 ± 10.1	13.1 ± 4.9	0.69	19.3 ± 7.7	15.6 ± 7.9	0.05
MUFA (g)	8.65 ± 5.52	6.41 ± 4.8	0.002*	9.3 ± 4.9	5.9 ± 4.5	0.01*	5.8 ± 4.6	4.8 ± 4.2	0.65	8.7 6 ± 6.0	7.4 ± 5.3	0.28
PUFA (g)	4.6 ± 3.7	2.99 ± 2.7	0.0001*	5.0 ± 3.3	2.8 ± 2.4	0.01*	2.8 ± 2.5	1.89 ± 2.5	0.35	4.72 ± 4.1	3.4 ± 3.1	0.21
Trans	0.75 ± 0.8	0.43 ± 0.49	0.001*	0.88 ± 0.88	0.38 ± 0.4	0.01*	0.58 ± 0.67	0.4 ± 0.65	0.24	0.67 ± 0.7	0.49 ± 0.55	0.19
Cholesterol (mg)	133.2 ± 67.9	106.2 ± 62.7	0.01*	125.9 ± 61.0	95.7 ± 49.6	0.02*	116.0 ± 80.3	95.1 ± 82.9	0.53	144.2 ± 69.9	122.9 ± 68.9	0.25
w3 (mg)	0.55 ± 0.54	0.35 ± 0.36	0.007*	0.58 ± 0.4	0.4 ± 0.3	0.06	0.26 ± 0.32	0.27 ± 0.38	0.8	0.6 ± 0.6	0.3 ± 0.3	0.04*
W6 (mg)	3.27 ± 3.3	2.0 ± 2.2	0.005*	3.44 ± 2.9	1.9 ± 1.9	0.01*	1.59 ± 2.2	1.1 ± 2.1	0.57	3.52 ± 3.7	2.4 ± 2.5	0.14
Iron (mg)	8.01 ± 4.1	7.38 ± 4.12	0.4	8.1 ± 4.1	8.0 ± 4.29	0.9	8.9 ± 5.7	8.9 ± 4.6	0.92	7.6 ± 3.7	6.0 ± 3.4	0.1
Food addiction criteria	2.3 ± 1.5	2.58 ± 2.01	0.9	1.91 ± 1.0	1.86 ± 1.7	0.33	2.0 ± 1.1	1.67 ± 1.2	0.39	2.9 ± 1.88	3.7 ± 2.0	0.06

*Significant differences were analyzed with the nonparametric Mann–Whitney by MLGP group.
*$p < 0.05$; **$p < 0.001$.

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Discussion

The present study evaluate the association between the multilocus genetic score, with anthropometric measurements, eating behavior, food reinforcement and food addiction (FA), in a population of adults from Chile. In our results we observed that 0.98% of the sample did not carrier the risk alleles and 61% had MLGS of two or higher.

According to MLGS, we did not find any differences in anthropometric measurements. These results are in agree with the study of Romer et al., who reported the BMI was not significantly associated with polygenic scores in adults (30), and also with the study conducted in Malaysian university students, which found that three SNPs (rs1800497, rs1079597, rs1800498) in DRD2 are not associated with obesity or adiposity (31). Nevertheless, this is in contrast to the results of Yokum et al. who reported an association with high DA signaling and future weight gain, reflecting that a high DA signaling promt increases in BMI, and with a longitudinal study that showed that the C- allele of the DRD2 rs6277 exhibits protective effects on weight gain (32).

In eating behavior, we observed that participants scoring MLGS ≥2.0 (*Low dopamine signaling*) had a higher % of food choice in the RVFQ, whereas subjects in the obesity group exhibited lower cognitive restriction scores and higher emotional eating, uncontrolled eating, and percentage of food choice.

In relation to eating behavior and obesity, an important theoretical background have related to the Reward Deficiency Syndrome, which emphasizes the neurofunctional parallels among pathological eating and drug addiction. The theory describes a hyposensitive reward system that motivates an individual to overeat to increase brain DA as a form of "self-medication" due to a hypodopaminergic trait (33, 34). Particularly, contrary to the idea of overfeeding to reestablish low concentrations of brain DA, an alternative thesis led to the Reward Surfeit Model. This indicates that persons with obesity are more reactive to food rewards, resulting in increased sensitivity to rewards (17, 35).

Based on our results, subjects scoring MLGS ≥2.0 (*Low dopamine signaling*) displayed no differences in their eating behavior scores on the TFEQ in the entire sample, but higher % of snack food choice on the RVFQ, reflecting a higher relative reinforcing value of snack food. Also we observed in subjects with obesity that scored in the MLGS ≥2.0, lower scores of Cognitive Restriction and higher scores of Emotional eating, Uncontrolled eating and % of snack food choice. Also the MLGS correlated positively with Emotional Eating scores ($r = 0.21$) and % food choice in female. This results are in accordance with Stice et al. who described that individuals with a higher number of these genotypes showed a lower level of activation in reward regions, such as the putamen, caudate, and insula, in response to monetary rewards, suggesting that individuals who have a greater number of variants associated with low DA signaling may perceive food rewards and monetary rewards as more important (29). And also with the results of Diekhof et al., who demonstrated that reward-related activation in the ventral striatum and ventral tegmental area (VTA) was significantly modulated by biologically informed MLGS profiles and sex (36). In relation to the overconsumption of drugs of abuse or palatable food, considering their reinforcing properties it has been described that the 7-repeat (7R) allele of a number of tandem repeats (VNTR) in DRD4, appears as a contributing factor in the neurobiological mechanisms underlying drug abuse, aberrant eating behaviors and related comorbidities (37). Also, the literature have report some longitudinal data. In this sense Fontana et al., developed a prospective cohort study in 359 children recruited at birth. They assessed the relation between genetic variants of dopamine genes such as the DRD4 (exon 3 VNTR) and weight observing that in the first year of life, DRD4.7R variant showed higher BMI Z-scores, and at 3–4 years of life a higher intake of palatable foods and a waist circumference, suggesting that carriers of these alleles can present an increased risk for obesity related to overeating.

In relation to addiction, we found no difference in the frequency of food addiction by categories of MLGS (MLGS <2.0 and MLGS ≥2.0) in the total sample, but in the group with obesity a greater percentage of food addiction was found "MLGS ≥2.0 or *low dopamine signaling*" (53%) vs. "MLGS <2.0 or *high dopamine signaling*" (23%). These results are somewhat in line with the results of Steiger et al., who studied the relation between dopamine genetic variations (DRD2 Taq1A, DRD4 7R, and COMT) and the risk of substance abuse in women with binge-purge eating syndromes. It was shown that women who carried high function COMT and low-function DRD4 7R alleles (higher risk) showed more substance abuse (cannabis) (38). Another study in a large cohort of Italian patients with eating disorders has suggested that the specific combination of variants in DRD2 and DRD4 genes are predisposing factors for EDs.

This contrast with previous research, examining the relationship between MLGS and food addiction, supporting that, high dopaminergic signaling genotypes are linked to obesity and higher food addiction scores, through the mechanism of higher responsiveness to eating (17, 30, 39).

Several genotypes isolated are associated with putatively low DA signaling. Individuals with an A1 allele instead of an A2/A2 allele of the TaqIA polymorphism and individuals with an Ins/Ins genotype instead of a Del-allele of the DRD2-141C Ins/Del polymorphism have fewer D2 receptors (40). In this sense, it has been suggest that altered availability of dopamine receptors specifically DA2/3R in extra-striatal and dopamine cell bodies may constitute biological vulnerability traits, for addictions (41).

Stice et al. showed that a lower caudate response predicted body fat gain in adolescents carrying TaqI A1 allele (less dopamine signaling) (42, 43). Cohen et al. showed that TaqIA A1 allele carriers have lower activation of the orbitofrontal cortex (OFC), amygdala, and hippocampal areas to monetary rewards (44) and lower activation in the midbrain, thalamus, and OFC to food rewards (45). Also the single nucleotide exchange in the Catechol-O-methyltransferase gene (COMT Val158Met), have shown fourfold less COMT activity in Met homozygotes compared to Val homozygotes (46) and according to Lachman et al. (47), the former have higher levels of tonic DA and less phasic release in the striatum.

Recently, Arrue et al. explored the relationship of cardiometabolic alterations with single genetic polymorphisms DRD2 in 285 psychiatric patients, they showed that a low dopaminergic activity was related to higher risk of suffering obesity, high diastolic blood pressure (DBP), and hypertriglyceridemia (HTG) (48). Also, Silveira et al. recently showed that variations in a MLGS reflecting DA signaling, was associated with differences in sugar intake in Children that had intrauterine growth restriction, suggesting that DA function is involved in this behavioral feature in these children (49).

This study has several limitations and strength. The fact that the data did not support our hypotheses about food addiction and MLGS could be explained in part by some methodological issues. (i) The small sample size of our study was obtained based on convenience and cannot generalized to all Chilean adults; (ii) Our results could be limited due to the small number of adults who met the criteria for food addiction; (iii) We evaluate dietary intake using

24-h recalls that have document several bias and could be responsible of some inconsistency in our results showing higher food choice, but lower energy and macronutrient intake by MLGS. Additionally, one limitation of our study was that we did not assess anxiety and depression levels in our sample, despite the fact that some studies have shown that anxiety, depression, and emotional eating are closely related (50, 51). This limitation could result in biases and misinterpretations of our results. Nevertheless, this study has the following strengths: (i) This is the first study in Chilean population that considers a multilocus approach, increasing the small contribution of individual polymorphisms to phenotypic variance; (ii) In order to measure eating behavior, we utilized a wide range of tools that were measured face-to-face by highly trained dietitians.

We conclude that, although we did not find any relationship between food addiction and MLGS, these results provide evidence for the involvement of genotypes associated with low dopaminergic signaling in eating behavior, specifically in snack food choice, emotional eating, and uncontrolled eating. These findings strongly encourage further investigations related to genetic susceptibility and the risk of chronic overeating, including the possibility to explore other pathways related to dopamine, such as physical activity. Dopamine is known to regulate physical activity, and in general studies reported in the literature as ours, do not consider this variable, open to the question of whether reduced D2R disrupts energy expenditure and activity. It is frequently suggest that reductions in D2R commonly create a reward deficit and altered appetitive motivation, which induce compulsive eating and obesity. Nevertheless, Beeler et al. developed a D2R knockdown (KD) mouse line and assessed energy expenditure and appetitive motivation under conditions of diet-induced obesity. Interestingly, the KD mice did not gain more weight or showed increased appetitive motivation and in an enriched environment with voluntary exercise opportunities, exhibited dramatically lower activity and became more obese than wild-type mice (52).

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors. Requests can be directed to the corresponding author.

Ethics statement

The studies involving humans were approved by Comite Ético Científico USS. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

Author contributions

NL: Conceptualization, Investigation, Methodology, Software, Resources, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. GG: Conceptualization, Writing – original draft, Writing – review & editing. AO: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing.

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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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Genetic associations with neural reward responsivity to food cues in children

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Objective: To test associations of candidate obesity-related single nucleotide polymorphisms (SNPs) and obesity polygenic risk scores (PRS) with neural reward reactivity to food cues.

Methods: After consuming a pre-load meal, 9–12-year-old children completed a functional magnetic resonance imaging (fMRI) paradigm with exposure to food and non-food commercials. Genetic exposures included *FTO* rs9939609, *MC4R* rs571312, and a pediatric-specific obesity PRS. A targeted region-of-interest (ROI) analysis for 7 bilateral reward regions and a whole-brain analysis were conducted. Independent associations between each genetic factor and reward responsivity to food cues in each ROI were evaluated using linear models.

Results: Analyses included 151 children ($M = 10.9$ years). Each *FTO* rs9939609 obesity risk allele was related to a higher food-cue-related response in the right lateral hypothalamus after controlling for covariates including the current BMI Z-score ($p < 0.01$), however, the association did not remain significant after applying the multiple testing correction. *MC4R* rs571312 and the PRS were not related to heightened food-cue-related reward responsivity in any examined regions. The whole-brain analysis did not identify additional regions of food-cue-related response related to the examined genetic factors.

Conclusion: Children genetically at risk for obesity, as indicated by the *FTO* genotype, may be predisposed to higher food-cue-related reward responsivity in the lateral hypothalamus in the sated state, which, in turn, could contribute to overconsumption.

Clinical trial registration: https://clinicaltrials.gov/study/NCT03766191, identifier NCT03766191.

KEYWORDS

food cues, fMRI, polygenic risk score, children, genotype, reward

1 Introduction

Obesity currently affects approximately 20% of children and adolescents aged 2–19 years in the United States according to the National Health Statistics Report (1). Obesity often continues from childhood into adulthood (2), and obesity in adulthood is a known risk factor for the development of multiple comorbidities including type 2 diabetes, cardiovascular diseases, and cancer (3). The etiology of obesity is multifactorial, affected by genes, environment, and gene-environment interactions (4, 5).

Environmental food cues include the smell, taste, and sight of highly palatable food or food-related situations and play a crucial role in obesity development through physiological and psychological responses (6–9). They are often presented through media in the form of advertisements for highly palatable, nutrient-poor, and energy-dense foods and beverages (10). Marketing of highly palatable foods and beverages is often directed toward younger children, and these exposures promote the development of unhealthy food preferences and eating behavior patterns that may ultimately lead to childhood obesity (10–15).

Exposure to highly palatable food and beverage cues may activate a response in dopaminergic reward regions of the brain that are associated with increased food consumption (16–18) and weight gain (19–21). Previous functional magnetic resonance imaging (fMRI) studies have identified the brain regions involved in the corticolimbic reward circuitries related to food cues: nucleus accumbens, orbitofrontal cortex, amygdala, insula, lateral hypothalamus (LH), substantia nigra, and ventral tegmental area (22–28). Further, these regions have been related to food cravings and appetitive motivation (29–33).

Several genes, including the fat mass and obesity-associated gene (*FTO*) and melanocortin 4 receptor gene (*MC4R*), have been implicated in obesity risk. Research has shown that divergent central nervous system (CNS) mechanisms may drive overconsumption in those with *FTO* risk alleles. A rodent study has shown that *FTO* is present primarily in the hypothalamus, a region related to hunger/satiation control (34). A common genetic variant within the first intron of the *FTO* gene, rs9939609, is known to be associated with higher energy intake (35–38) and BMI (39–41) in children. A previous study from our group also found that *FTO* rs9939609 was associated with children's food-cue-related neural reactivity in the left and right nucleus accumbens (42), a potential mediator of excess consumption and adiposity gain. Participants were only provided a light snack in that study to help control their hunger, so the association between *FTO* and food cue reactivity in the post-prandial state was not examined.

Melanocortin 4 receptors are also expressed in the hypothalamus as part of the leptin-melanocortin pathway and play a crucial role in regulating appetite, energy balance, and body weight (43–45). *MC4R* rs571312, a common near-*MC4R* variant, has been related to higher caloric intake (46) and greater BMI or obesity (47–49). Another study found a strong association between rs12970134 and obesogenic eating behaviors including greater food responsiveness and less satiety responsiveness in children (50). However, no studies to date have examined the effect of common *MC4R* polymorphisms on food-cue-related neural reward reactivity.

Though some individuals may have obesity due to a rare mutation in a single gene, most individuals with obesity have numerous polymorphisms that jointly affect their adiposity (51). A comprehensive genetic obesity risk can be summarized through an obesity polygenic risk score (PRS) that is constructed based on the effects of variants observed in genome-wide association studies (GWAS). Richardson et al. (52) created a 295 SNP PRS to predict adiposity in early life. Though previous studies in children have demonstrated an association between weight status and food-cue-related neural response to food cues (21, 53–55), the relationship between comprehensive genetic risk for obesity, characterized by a PRS, and food-cue-related neural responsivity has not yet been examined.

In this study, we aimed to test whether some children are genetically predisposed to heightened food-cue-related neural reward reactivity in the post-prandial period. We hypothesized that the genetic risk of obesity, defined by *FTO* rs9939609, *MC4R* rs571312, and a pediatric PRS, would relate to greater differential activation in brain reward regions in response to food advertisements. Additionally, we conducted a hypothesis-generating whole-brain exploratory analysis to identify additional regions that may be related to the associations between genetic exposures and post-prandial responsivity to food cues. This study builds upon previous work by examining a greater range of obesity-related factors and by examining how these genetic factors affect neural food cue reactivity when children are in the sated state.

2 Methods

2.1 Study participants

The data in this paper are from a larger study measuring the genetic associations with children's neural reward reactivity and eating in the absence of hunger in response to food cues. The study enrolled 189 pre-adolescent children from the Northern New England community. Seven participants were excluded after genotyping quality control, and 31 participants were excluded after MRI scanning quality control. Scan data from 31 participants were excluded due to: refusal to be scanned ($n = 12$); excessive movement in the scanner ($n = 9$); and technical issues ($n = 10$). The final analysis included 151 children (86 of whom were male) between the ages of 9 and 12 [mean (SD) = 10.9 (1.16) y]. Dartmouth College's Committee for the Protection of Human Subjects approved all study protocols.

2.2 Study overview

Participants attended a study visit alongside a parent or guardian. Visits were scheduled at either lunchtime (11:00 am–1:00 pm) or dinnertime (4:00 pm–6:00 pm). A trained research staff member collected children's saliva samples for genetic analysis, measured height and weight, and administered questionnaires to the parents. The parent-reported child's physical activity, date of birth, biological sex, race, ethnicity, annual household income, and parent education level. Participant height was measured to the nearest 0.1 cm using Seca 264 Stadiometer (Hamburg, Germany), and weight was measured to the nearest 0.01 kg using a Seca 703 Medical Scale (Hamburg,

Abbreviations: BMI, Body mass index; PRS, Polygenic risk score; SNP, Single nucleotide polymorphism; EER, Estimated daily energy requirement.

Germany). Children consumed a standardized pre-load meal consisting of macaroni and cheese, apple sauce, corn, milk, and water. Satiety level was measured prior to the scan using the Freddy Fullness scale (56), a validated visual analog scale for estimating fullness in children. The fullness scale was reported across a range of 0-150 mm and converted into percentages (out of 150 mm); higher scores indicated greater fullness.

2.3 Genotyping

DNA extracted from saliva samples was genotyped for >600,000 single nucleotide polymorphisms (SNPs) with the Illumina Global Screening Array 24 v1.0 or v3.0 (57). Pre-specified quality control thresholds were applied to generate genotype calls using GenomeStudio software (58) with downstream quality control steps and determination of European or non-European ancestry with principal components, as previously described (59, 60). Using the Michigan Imputation Server, haplotype-based imputation was performed with a quality score threshold of $R^2 > 0.8$ selected for SNPs with high-quality imputation (61, 62). Seven children were excluded for failing genotype quality control.

As primary exposures of genetic risk, two single SNPs were considered (*FTO* rs9939609 and *MC4R* rs571312), and a pediatric-specific PRS with 265 of 295 SNPs available in the data (52), the "Pediatric PRS." In additional exploratory analyses, we also analyzed three PRS previously associated with adult BMI. These included a 97 SNPs PRS (63), 557 SNP PRS (52), and a ~2 million SNP PRS (64), henceforth referred to as the "Adult 97 PRS," "Adult 557 PRS," and "Adult 2M PRS," respectively. Each PRS was computed as the product of the dosage of each risk allele (0, 1, or 2) and the published effect size, summed and standardized into *Z*-scores.

2.4 Scanning paradigm

Using E-Prime (65), children were presented with a series of videos that were designed to replicate a typical television show. The stimuli included three 5 min segments of a popular science show (MythBusters) interspersed with four 5 min commercial breaks.

Four functional runs were conducted in each scan. Additional functional runs were collected as part of the larger study after the experimental paradigm of this study, but are not relevant to this presented analysis. Each functional run began and ended with a 15 s presentation of a fixation cross. For each run, 5 food and 5 non-food TV commercials were presented which alternated in an AB pattern (66, 67). The block pattern for each run was randomized between participants (AB or BA) and which commercials were played during each block were also randomized between participants. Each commercial ran for approximately 15 s, and each functional run was approximately 5 min in length. The total duration of the scan was approximately 1 h.

2.5 Stimuli

Age-appropriate food and non-food commercials that were included in this study were rated by children for interest and excitement (42). There was no overall difference in interest and excitement between the food and non-food commercials.

2.6 Image acquisition

Scans were conducted using a 3.0 T Siemens MAGNETOM Prisma MRI scanner equipped with a 32-channel head coil. For T1-weighted structural scans (MPRAGE), the following parameters were employed: echo time (TE) of 2.32 ms, repetition time (TR) of 2,300 ms, flip angle of 8 degrees, matrix size of 256 × 256 mm, field of view of 240 × 240 mm, 192 slices with a slice thickness of 0.9 mm, and voxel size of 0.9 × 0.9 × 0.9 mm. Functional imaging utilized a T2*-weighted echo planar imaging (EPI) sequence with TE = 33 ms, TR = 1,250 ms, flip angle = 64 degrees, matrix size = 96 × 96, field of view = 240 × 240 mm, 56 slices with a slice thickness = 2.5 mm, and voxel dimensions of 2.5 × 2.5 × 2.5 mm. Four functional runs of 144 volumes were included in the analysis for each participant.

2.7 Model covariates

BMI was calculated based on participants' height and weight using the U.S. Center for Disease Control and Prevention (CDC) 2020 age-and sex-specific distributions (68). A missing value for physical activity ($N = 1$) was imputed with the most frequently reported value. A missing value for the fullness measure ($N = 1$) was imputed with the median value. One fullness value of 180 mm was imputed with the median due to researcher measurement error.

2.8 MRI pre-processing

Anatomical data preprocessing and functional data preprocessing were performed using *fMRIPrep* 1.2.5 (69, 70), which is based on *Nipype* 1.1.6 (71, 72). The pipeline and protocol used are described in detail as a template provided by *fMRIPrep* in a previously published article (73).

2.9 Statistical analysis

2.9.1 Subject-level analysis

Following pre-processing, participants' individual fMRI data were analyzed using the NLTools Python package (74). A general linear model (GLM) was conducted for subject-level analysis for each participant. This included constructing a design matrix, convolving with the hemodynamic response function (HRF), incorporating nuisance variables such as intercepts, linear and quadratic trends, motion covariates (comprising 24 parameters: six demeaned realignment parameters, their squares, derivatives, and squared derivatives), and identifying motion spikes (defined as spikes between successive TRs and global spikes exceeding an intensity change threshold of 2.5 standard deviations from the mean). The data underwent spatial smoothing using a Gaussian kernel with a full-width at half maximum (FWHM) of 6 mm. We conducted a standard visual inspection of scans with a frame-wise displacement of 1 or greater, and one of four functional runs was excluded for 17

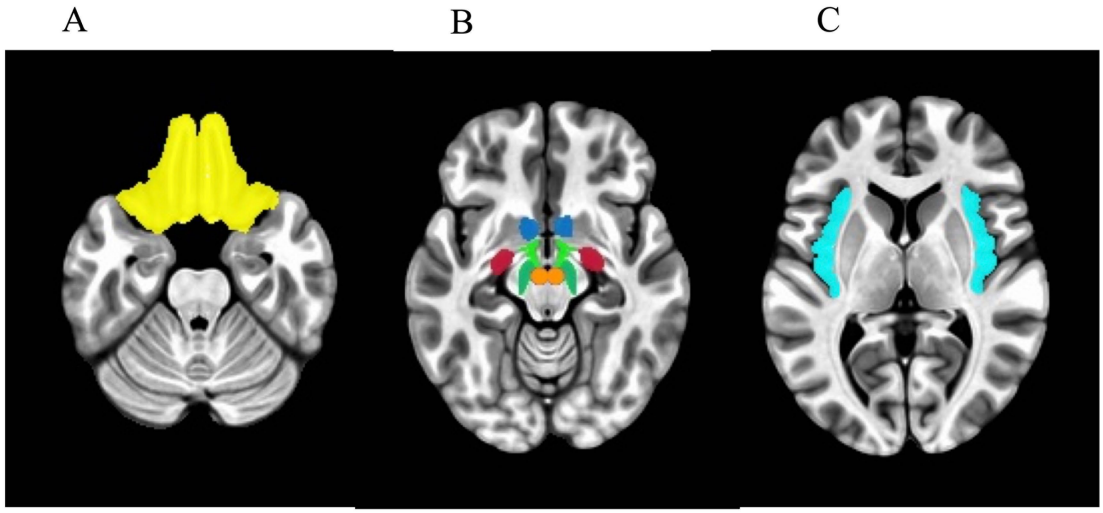

FIGURE 1
Axial view of masks used in the regions-of-interest (ROI) analysis. **(A)** Orbitofrontal cortex. **(B)** Blue: nucleus accumbens. Light green: lateral hypothalamus. Red: amygdala. Dark green: substantia nigra. Orange: ventral tegmental area. **(C)** Insula.

participants (~11%) due to such visual inspections (73). Additionally, we examined functional runs for extreme head motion defined as >25% motion spikes (> 36 spikes) of the scan volumes; however, no functional run was excluded from further analyses. To generate the food-specific regression coefficient maps for individuals, the coefficients in each voxel were averaged across functional runs for food and non-food ad conditions, separately, and then the within-subject difference between the two conditions was computed to create contrast maps. All individual-level contrast maps were used in the targeted region of interest (ROI) and whole brain analyses. Multiple comparison correction using the false discovery rate (FDR) was applied to the *p*-values across 7 bilateral ROIs with significance set at $q < 0.05$.

2.9.2 Region of interest analyses

For the *a priori* ROI analysis, seven bilateral ROIs were selected as candidate reward regions based on previous literature (25): the nucleus accumbens (NAcc), orbitofrontal cortex (OFC), amygdala, insula, lateral hypothalamus (LH), ventral tegmental area (VTA), and substantia nigra (SN). The masks of the bilateral NAcc, OFC, amygdala, and insula were extracted for each participant using FreeSurfer's autosegmentation.[1] The final group-level ROI masks were created by including those voxels that are counted in the individual-level masks for at least 75% of participants. As FreeSurfer does not include autosegmentation of the lateral hypothalamus and SN, masks of these regions were generated using the anatomical atlas of the human hypothalamic regions (75). The mask of the ventral tegmental area was defined by the sphere with a radius of 5 mm centered at the MNI coordinate [±4, −16, −10] (76). The ROI masks are shown in Figure 1. Beta values were then averaged across each mask and analyzed using R (77). We investigated the Pearson correlation between corresponding lateral reward ROIs as well as across reward ROIs.

Child age, biological sex, BMI *Z*-score, satiety level post preload-meal, and European ancestry were selected as covariates *a priori* for all adjusted models given potential relationships with genetic exposures and/or neural response to stimuli, for all adjusted models. After examining the bivariate relationships between the other potential covariates and the neural response in any ROIs using a threshold of $p < 0.1$, physical activity and annual household income were added into adjusted models. Linear models were used to test the independent associations between the genetic factors (*MC4R* rs571312, *FTO* rs9939609, Pediatric PRS) and the neural response in the bilateral ROIs. In an exploratory analysis, the linear models were repeated with the secondary genetic exposures of 3 adult obesity PRS. Given that the pediatric and adult obesity PRS measures were trained on individuals of European ancestry, the distribution of each genotype and PRS in participants with European and non-European ancestry was explored in Supplementary Table S1, and the regression models of the four PRS measures were repeated restricting the sample to participants with European ancestry in a sensitivity analysis.

2.9.3 Exploratory whole-brain analysis

A whole-brain analysis was conducted using the individual beta maps as input to a group-level analysis to test the unadjusted and adjusted linear relationships between food-cue-related response and genotypes. To determine significance at the group level, an initial voxel-wise significance threshold of *p*-value <0.001 was applied and was then cluster-corrected using a threshold of a cluster size of $k = 90$ for an overall *p*-value <0.05. Clustering parameters were based on 10,000 Monte-Carlo simulations determined using 3dClustSim from AFNI.

3 Results

Seven participants were excluded after genotype quality control, and 31 participants were excluded after MRI quality control, leaving 151 participants in the analysis (Table 1). Most participants

1 http://freesurfer.net

TABLE 1 Baseline characteristics of study participants ($N = 151$).

	Mean (SD) or *N* (%)
Age (years)	10.9 (1.16)
Child biological sex	
Male	86 (57.0%)
Female	65 (43.0%)
Ethnicity	
Non-Hispanic	141 (93.4%)
Hispanic	6 (4.0%)
Prefer not to answer	4 (2.6%)
Race	
White	143 (94.7%)
Non-White	8 (5.3%)
BMI *Z*-score	0.468 (0.953)
BMI category	
Underweight (<5th percentile)	1 (0.7%)
Healthy weight (5th to <85th percentile)	105 (79.5%)
Overweight (85th percentile to <95th percentile)	21 (13.9%)
Obese (≥95th percentile)	24 (15.9%)
Household annual income	
<$25,000	2 (1.3%)
$25,000–64,999	19 (12.6%)
$65,000–144,999	75 (49.7%)
$145,000–225,000	35 (23.2%)
>$225,000	16 (10.6%)
Prefer not to answer	4 (2.6%)
Parent's education level	
High school graduate or GED	5 (3.3%)
Some post-high school, no degree	11 (7.3%)
Associates degree	8 (5.3%)
Bachelor's degree	41 (27.2%)
Professional school or graduate school	85 (56.3%)
Missing	1 (0.7%)
Physical activity (active for at least 60 min per day in the past 7 days)	
No days	3 (2.0%)
1 day	4 (2.6%)
2–3 days	50 (33.1%)
4–5 days	61 (40.4%)
6–7 days	32 (21.2%)
Missing	1 (0.7%)
European ancestry	
European	136 (90.1%)
Non-European	15 (9.9%)
MC4R rs571312	
CC (0)	82 (54.3%)
AC (1)	62 (41.1%)
AA (2)	7 (4.6%)
FTO_rs9939609	
TT (0)	62 (41.1%)
AT (1)	73 (48.3%)
AA (2)	16 (10.6%)

were white (94.7%) and non-Hispanic (93.4%). The average (SD) BMI *Z*-score was 0.468 (0.95), and 30% of participants were categorized as either having overweight or obesity. The average (SD) caloric consumption of the standardized preload meal was 449 (171 kcal). Examining the distribution of *MC4R* rs571312 in our sample, 4.6% were highest-risk (AA) children ($N = 7$), 41.1% were heterozygotes (AC) children ($N = 62$), and 54.3% were homozygous low-risk (CC) participants ($N = 82$). Due to the limited number of participants in the highest-risk group, the *MC4R* AA and AC genotypes were collapsed into one category and analyzed with a dominant model (AA and AC vs. CC). In our sample, the distribution of *FTO* rs9939609 was 10.6% with the highest obesity risk (AA) ($N = 16$), 48.3% with moderate risk (AT) children ($N = 73$), and 41.1% with the lowest risk (TT) children ($N = 62$). The additive model of the *FTO* genotype (AA vs. AT vs. TT) was used in further analyses.

3.1 ROI analyses

The correlations between the responses of food > non-food contrast maps in 14 bilateral reward regions are shown in Figure 2. In general, all bilateral reward regions tested were positively and significantly correlated ranging from 0.93 for the OFC and 0.62 for the LH (Supplementary Figure S1). The right LH exhibited correlations with three other ROIs, and the bilateral VTA exhibited positive correlations with five ROIs. The ROI analysis examining the associations between each genetic exposure and neural response to food cues in the full cohort is presented in Table 2. Children with the *FTO* rs9939609 risk allele had a significantly higher food-related neural response in the right LH in models adjusted for covariates even after controlling for current adiposity ($t = 2.6$, $p = 0.01$) (Figure 3). However, the association did not remain significant after applying the FDR correction. The association between *FTO* rs9939609 risk alleles and food-related response in the left LH did not reach statistical significance ($t = 1.7$, $p = 0.08$). The *MC4R* genotype and Pediatric PRS were not significantly associated with the food-related reward reactivity in any of the explored ROIs (Table 2).

In the exploratory analysis that tested three additional adult obesity PRS associations, the 97 PRS with food cue-related activity in the left insula did not reach statistical significance ($t = 1.9$, $p = 0.06$) (Supplementary Table S2). In the sensitivity analyses of the PRS measures restricting the sample to participants with European ancestry ($N = 136$), the adult 97 and 557 PRS with food-related response in the LH did not reach statistical significance ($t = 1.8$, $p = 0.08$; $t = 1.7$, $p = 0.08$, respectively) (Supplementary Table S3).

No additional relationships between genetic factors and food-related responsivity in the whole brain analysis.

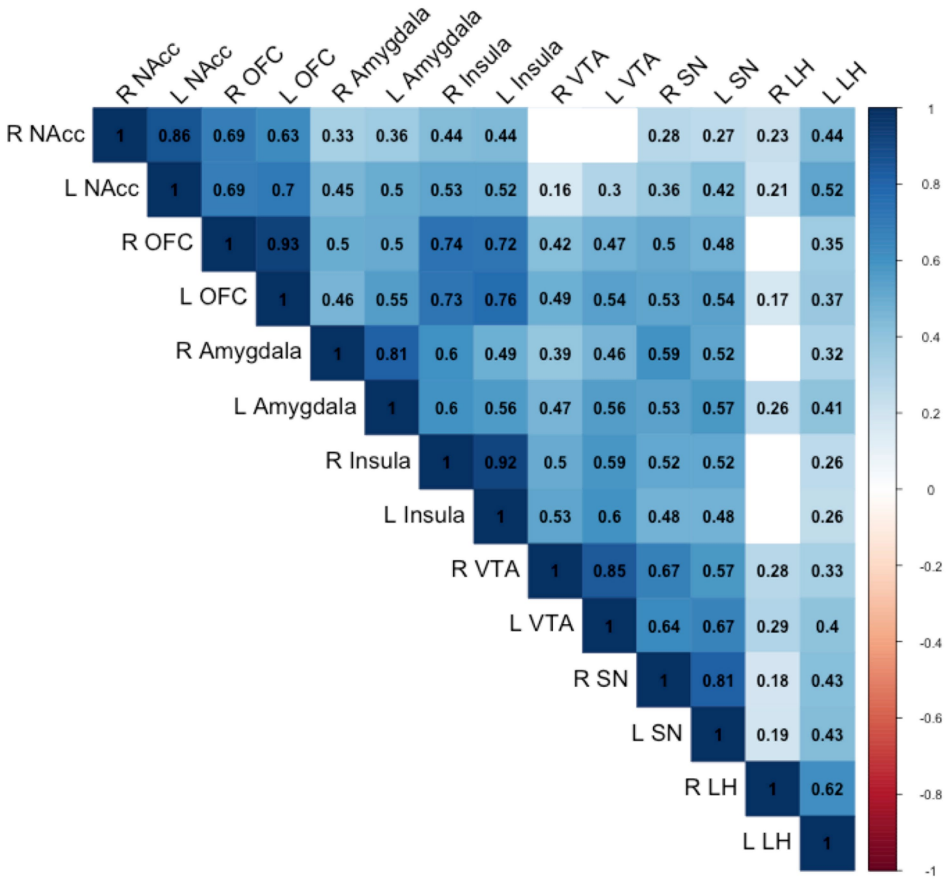

FIGURE 2
Pearson correlations between the reward regions are shown. Only correlations statistically significant at the $p < 0.05$ are numbered. NAcc, nucleus accumbens; OFC, orbitofrontal cortex; VTA, ventral tegmental area; SN, substantia nigra; LH, lateral hypothalamus.

4 Discussion

In this study of 151 children aged 9–12 years old, we found that the genetic risk of obesity was associated with greater brain activation in response to food advertisements in the lateral hypothalamus after eating a meal to satiety. Specifically, each risk allele of the *FTO* rs9939609 genotype was associated with heightened food-related responsivity in the right lateral hypothalamus.

In the brain, *FTO* is highly expressed in the hypothalamus, a region involved in the regulation of central energy homeostasis to control body energy balance, energy expenditure, and food intake (78). Many studies have reported the connection between *FTO* SNPs and obesity-related traits such as BMI, body fat mass, waist circumference, hip circumference, and energy intake (79–81). In addition, *FTO* risk alleles have been related to fat or carbohydrate intake, reduced satiety, overeating, and loss of control over eating (39, 82, 83). The lateral hypothalamus, as part of the hypothalamus, receives a high level of melanocortinergic inputs from the arcuate nucleus of the hypothalamus. Animal studies have identified that the LH is specifically involved in food-seeking behaviors, reward behaviors, and autonomic function (84–86). Our study finding that *FTO* is related to greater food-related reward activity in the lateral hypothalamus when children are in a sated state highlights a potential biological mechanism that may mediate the association between genetic obesity risk and excess weight gain. As the understanding of the LH's precise functions and mechanisms remains limited, further research is needed to understand if the higher food-related reward activity corresponds to cued non-homeostatic caloric intake in the post-prandial period.

In our previous study with an independent study cohort of the same age group, we observed a heightened reward response in the bilateral nucleus accumbens in response to food vs. non-food TV commercials among children with at least one *FTO* risk allele compared to those with no risk alleles (42). In that study, children were provided a light snack prior to imaging, rather than a full meal eaten to satiety. Together, these studies suggest that the *FTO* genotype is related to the heightened reward response to food cues in different brain regions at different states of satiety.

In our current study, we did not find significant neural reward reactivity to food cues associated with the *MC4R* genotype nor four PRS measures. Given the composite nature of PRS, they may have limited utility in clarifying the biological mechanisms underlying the genetic-reward activity relationship.

This study provides evidence that the *FTO* genotype is related to neural reward reactivity to food cues in children in the post-prandial period. Nevertheless, it is important to acknowledge the limitations of our study. Given the distinct role of the lateral hypothalamus in food-seeking and reward behaviors within the hypothalamus, we aimed to study this specific region. While we used a mask, future research could use manual segmentation of the lateral hypothalamus to potentially provide more accurate segmentation. Our sample

TABLE 2 Associations between genetic exposures and food-related response in the region-of-interest (ROI) after eating a meal to satiety ($N = 151$).

		Unadjusted models[a]		Adjusted model 2[a,b]	
	L/R	*t*-value	*p*-value	*t*-value	*p*-value
***FTO* rs9939609 (TT vs. AT vs. AA)**					
Nucleus accumbens	R	1.354	0.178	1.426	0.156
	L	1.081	0.281	1.017	0.311
Orbitofrontal cortex	R	0.035	0.972	−0.339	0.735
	L	0.076	0.940	−0.238	0.812
Amygdala	R	−0.892	0.374	−1.143	0.255
	L	−0.211	0.833	−0.291	0.772
Insula	R	0.368	0.713	−0.042	0.967
	L	0.669	0.505	0.340	0.734
Ventral tegmental area	R	−0.226	0.821	−0.116	0.908
	L	0.205	0.838	0.130	0.896
Substantia nigra	R	0.070	0.944	0.034	0.973
	L	0.036	0.971	−0.001	0.999
Lateral hypothalamus	R	1.958	0.052	**2.602**	**0.010**
	L	1.491	0.138	1.743	0.083
***MC4R* rs571312 (CC vs. AC + AA)**					
Nucleus accumbens	R	0.999	0.319	0.903	0.368
	L	0.260	0.795	−0.071	0.944
Orbitofrontal cortex	R	0.634	0.527	0.269	0.789
	L	0.731	0.466	0.265	0.792
Amygdala	R	−0.793	0.429	−0.837	0.404
	L	−0.221	0.825	−0.228	0.820
Insula	R	−0.614	0.540	−1.010	0.314
	L	0.045	0.964	−0.486	0.628
Ventral tegmental area	R	0.124	0.901	0.043	0.966
	L	0.119	0.905	−0.049	0.961
Substantia nigra	R	0.016	0.987	−0.126	0.900
	L	−0.247	0.806	−0.514	0.608
Lateral hypothalamus	R	1.201	0.232	1.120	0.265
	L	0.800	0.425	0.881	0.380
Pediatric PRS *Z*-score					
Nucleus accumbens	R	1.070	0.286	1.048	0.296
	L	1.057	0.292	1.051	0.295
Orbitofrontal cortex	R	1.088	0.278	1.005	0.317
	L	1.179	0.240	1.030	0.305
Amygdala	R	−0.392	0.696	−0.415	0.679
	L	−0.513	0.609	−0.475	0.636
Insula	R	0.748	0.456	0.558	0.577
	L	1.249	0.214	0.800	0.425
Ventral tegmental area	R	0.026	0.980	−0.267	0.790
	L	0.247	0.805	−0.106	0.916
Substantia nigra	R	0.523	0.602	0.250	0.803
	L	−0.277	0.782	−0.446	0.656
Lateral hypothalamus	R	0.450	0.654	0.187	0.852
	L	0.984	0.326	0.897	0.371

[a]Bold values represent the statistical significance at p-value < 0.05.
[b]Covariates include BMI *Z*-score, age, sex, physical activity, annual household income, European ancestry, and satiety post-meal (%).

predominantly consisted of individuals of a white, non-Hispanic population and relatively higher socioeconomic status. Additionally, the additive effect of the *MC4R* genotype was not explored due to the limited number the high-risk (AA) individuals. Due to limitations in sample size, the analysis did not extend to additional candidate genes associated with obesity. Future research should aim to explore the genetic effects on heightened neural reward responsivity in a larger and more diverse population, allowing for broader generalization of the findings.

5 Conclusion

Our findings indicate that some children possess a genetic predisposition towards heightened food-cue-related neural reward reactivity in the post-prandial period. Given the prevalence of extensive media exposure among children which often includes the promotion of a variety of unhealthy food products, it is crucial to understand the genetic influences on food-related neural responses in children and mitigate exposure that may contribute to excess consumption. Longitudinal studies are needed to understand whether this heightened reward response to food cues leads to greater cued consumption and, ultimately, to excess weight gain.

Data availability statement

The original contributions presented in the study are publicly available. This data can be found at: https://www.ncbi.nlm.nih.gov/gap/, phs003550.v1.

Ethics statement

The studies involving humans were approved by Institutional Review Board at Dartmouth College. The studies were conducted in accordance with the local legislation and institutional requirements. Written informed consent for participation in this study was provided by the participants' legal guardians/next of kin.

Author contributions

DY: Formal analysis, Writing – original draft, Writing – review & editing. TR: Writing – review & editing. DC: Data curation,

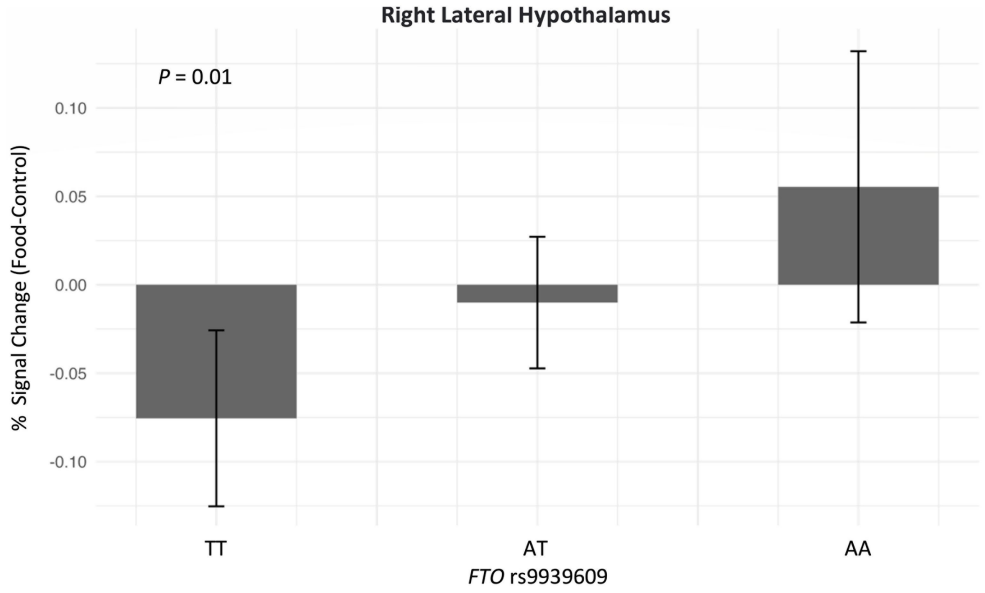

FIGURE 3
Adjusted association between *FTO* rs9939609 and neural response in the right lateral hypothalamus after eating a meal to satiety ($N = 151$). Adjusted linear regression model was conducted and adjusted for age, biological sex, BMI *Z*-score, satiety level post preload-meal, European ancestry, physical activity, and annual household income. The sample size of *FTO* rs9939609 for lowest-risk group (TT) is 62, heterozygotes (AT) is 73, and highest-risk group (AA) is 16. *FTO* rs9939609 was added as an additive model (TT vs. AT vs. AA).

Project administration, Writing – review & editing. GB: Data curation, Project administration, Writing – review & editing. RLa: Data curation, Project administration, Writing – review & editing. MM: Writing – review & editing, Validation. RLo: Conceptualization, Writing – review & editing. JE: Conceptualization, Formal analysis, Investigation, Validation, Writing – review & editing. TM: Conceptualization, Investigation, Methodology, Supervision, Writing – review & editing. DG-D: Conceptualization, Funding acquisition, Investigation, Methodology, Project administration, Supervision, Writing – review & editing.

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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/fnut.2024.1387514/full#supplementary-material

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Food addiction in patients on weight loss treatment

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Background: Food addiction (FA) is defined as hedonic eating behavior involving the consumption of highly palatable foods (i.e., ultra processed foods in quantities beyond homeostatic energy requirements). FA is present in a subset of patients with overweight or obesity and could contribute to the response to weight loss treatments.

Aim: Determine FA in individuals that fulfil the criteria of FA as measured by the YFAS 2.0, and its association with anthropometric and body composition variables in a clinical sample of patients undergoing weight loss treatment. Also, to determine the most prevalent FA criteria.

Methods: An observational, analytical, and cross-sectional study was conducted. Sampling was non-probabilistic, convenience based. A total of 158 participants were recruited from two clinical centers (private and public) focused on managing non-communicable chronic diseases. The Chilean version of YFAS 2.0 was administrated through the online REDCap platform. Anthropometric measurements were measured, and body mass index (BMI) was calculated.

Results: The mean age was 47.8 (SD 14.9) and BMI 28.7 (SD 5.3) kg/m^2. There were 12.7% patients who screened positive on the YFAS 2.0 Chilean version (3.2% for mild, 2.5% for moderate and 7.0% for severe), the mean symptom count was 2.2 (SD 2.6), with *withdrawal* being the most prevalent criterion (33.5%). FA patients had significantly higher body weight compared to non-FA subjects ($p = 0.045$). We observed a slight and significant correlation between FA symptom count and body weight ($p = 0.020$), waist circumference ($p = 0.005$), and BMI ($p = 0.023$).

Conclusion: This is the first study in Chile that showed that FA was present in patients undergoing weight loss treatment and was associated with anthropometric measurements. In addition, it showed that *withdrawal* was the most prevalent criterion. Future studies should investigate whether the presence of FA and the *withdrawal* criterion could contribute to suboptimal clinical response to weight loss treatment.

KEYWORDS

food addiction, YFAS 2.0, obesity, weight loss treatment, anthropometric measurements

1 Introduction

Chile is one of the Latin American countries with the highest rates of chronic non-communicable diseases associated with a sedentary lifestyle and the consumption of foods and beverages with a high contribution of critical nutrients like salt/sodium, sugar, saturated fats and trans fats (i.e., UPF) (1). The greatest concern lies in the high rates of overweight and obesity (74% of the population over 15 years of age) reported by the latest National Health Survey, which represents a public health problem (2).

In recent years, evidence has emerged that UPF consumption—one of the main causes of overweight and obesity—could be explained, in part, by addiction to these UPF (3–7). The construct of Food Addiction (FA) refers to the fact that, in vulnerable individuals, i.e., those who, due to certain circumstances, personal or situational characteristics, are at greater risk of suffering harm. The consumption of these UPF activates an addictive response, similar to the response to abuse of substances, which leads to overconsumption (8, 9).

In the last decade, FA has become a growing focus of research due to its plausible relationship with the rise in obesity and other metabolic disorders (10, 11). The neurobiological determinants underlying this addiction include the activation and alteration of brain reward circuits, specifically the dopaminergic system. Studies have shown that UPF consumption can induce excessive dopamine release in the nucleus accumbens, a key region of the reward system (12). This dopamine release is similar to that observed in addictions to substances such as cocaine and nicotine, suggesting a common mechanism in the compulsive pursuit of external rewards (13). Moreover, continuous exposure to these foods can lead to decreased dopamine sensitivity, resulting in the need to consume larger quantities to achieve the same level of satisfaction, a phenomenon known as tolerance (14). This neuroadaptive process, combined with the activation of other neurochemical systems such as the opioid and endocannabinoid systems, contributes to the perpetuation of addictive behavior and impairs individuals' ability to regulate their food consumption (15). Thus, for example, individuals with high body mass index (BMI) had the lowest D2 receptors values. Specifically, this reduction in striatal D2 receptors density correlates with reduced metabolism in cerebral areas (prefrontal and orbitofrontal cortex) that exert inhibitory control over consumption (16). Subjects with obesity show greater activation of reward and attention regions than normal-weight subjects do in response to hyper palatable food images versus control images (17). This observation suggests that a deficit in reward processing is an important risk factor for the addictive eating behaviors exhibited by individuals with obesity.

The conceptualization of FA has been based on theoretical models and assessment methods adapted from substance addiction. The Yale Food Addiction Scale (YFAS), developed by Gearhardt et al. (3), is a self-report scale designed to assess FA symptoms in the past 12 months, and has provided a validated tool to measure susceptibility to FA in the general population.

The most recent version, YFAS 2.0 (8), operationalizes the construct by applying the diagnostic criteria for substance use disorder from the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) (9) (e.g., loss of control over consumption, intense cravings, withdrawal, continuing to use despite negative consequences). A recent meta-analysis estimated that 14% of adults in nonclinical samples met criteria for FA, with a higher prevalence (31%) in samples of adults with obesity (18).

Likewise, the literature shows a strong association between the FA symptom counts measured by YFAS 2.0 and obesity (1, 2). A systematic review that included clinical and non-clinical samples indicates that a higher BMI is associated with a greater symptom count of FA (19). In patients who are in the preoperative period of bariatric surgery (BS), the most frequent diagnostic criteria are the inability to control consumption, persistent desire, continuous consumption despite negative consequences and tolerance (20). Furthermore, FA symptoms have been reported to correlate positively and significantly not only with BMI, but also with body weight, waist and hip circumferences, body fat, and trunk fat percentages, suggesting that FA contributes to the severity of excess weight (21).

Modification of lifestyles, mainly diet and exercise, are recognized as the pillars of obesity treatment; however, a low percentage of individuals can permanently reduce excess body weight. Individuals who have followed a program to reduce their weight, 36 weeks after completing the intervention, regain the lost weight, recovering it completely after 1 year (22). On the other hand, it has been observed that individuals with FA have less success in traditional weight loss programs (20). Considering the assessment of FA construct becomes relevant in weight loss treatments, since meeting or not meeting the FA criteria may influence the short- and long-term weight loss outcome of the treatment. The integration of FA assessment into weight loss programs -may provide a more complete overview of the difficulties faced by patients, considering that the literature supports the association of FA with overweight and obesity. By understanding how FA influences eating behaviors, healthcare professionals can design more effective and personalized treatment strategies, thereby improving outcomes and treatment adherence. Thus, the aim of the present study was to evaluate FA in individuals that fulfil the criteria of FA as measured by the YFAS 2.0, and its association with anthropometric and body composition variables in a clinical sample of patients undergoing weight loss treatment. Considering that this is the first YFAS 2.0 report in a clinical sample of Chilean population, it seems appropriate to take into account which are the most prevalent criteria. In our view, this will allow us to configure a more detailed description of the FA condition. Our hypothesis was to find in this clinical sample a FA prevalence similar to that reported in other clinical samples and we expected to find a significant correlation between FA symptom count and the anthropometric measures. On this basis, this study aims to provide new knowledge from a psycho-nutritional perspective for people who are undergoing weight loss treatment due to their excess weight.

2 Methods

2.1 Design, participants and procedure

A cross-sectional study was conducted in a non-probabilistic convenience sample during the months of August to October 2022. The clinical sample was composed of patients undergoing weight loss treatment due to some health condition. They were recruited from two health care centers, a private one from a high socioeconomic sector and a public one from a medium-low socioeconomic sector. Participants were invited to participate when they were in the waiting

room for a medical appointment corresponding to those included in the weight loss treatment program. They were told that this study was related to identifying different causes of overweight and obesity, and that participation was completely voluntary and without financial compensation; however, they would be given their anthropometric measurements. Those who were interested in participating were given informed consent. Participants who decided to participate, signed an informed consent. Once in the medical care room, they were asked to complete a questionnaire about demographic data; whether they were under psychological treatment; whether they had been diagnosed in the last 12 months with any of the following conditions: diabetes mellitus, insulin resistance, dyslipidemia, and/or hypertension; and whether they were taking any medication. After this questionnaire, they were given the Chilean version of YFAS 2.0 (23).

Once the scale was completed, anthropometric and body composition measurements were carried out by a nutritionist. A total of 158 individuals participated in this clinical sample (67.7% women; 15.2% diabetes mellitus; 20.3% insulin resistance; 32.9% hypertension; 25.3% hypercholesterolemia; 13.3% hypertriglyceridemia; 8.2% fatty liver; 8.2% polycystic ovary; 10.8% hypothyroidism; 84.8% taking medications).

The inclusion criteria were subjects over 18 years of age, who were in a weight loss treatment at the medical centers indicated above. Subjects who had any limitation, either in language or cognitive ability, that prevented self-administration of the questionnaire were excluded from the study. Additionally, pregnant, or lactating women were excluded.

2.2 Measurements

2.2.1 Demographic data

Participants were asked to provide information on basic demographic data, including gender, age, marital status, educational level, and employment status.

2.2.2 Anthropometric measurements and body composition

Weight and height were measured using a SECA® brand scale (precision of 0.1 kg) and a stadiometer (precision of 0.1 cm). Nutritional status was determined by calculating the BMI. It was classified according to the World Health Organization criteria as underweight (BMI ≤ 18.5), normal nutritional status (BMI 18.5–24.9 kg/m^2), overweight (BMI 25.0–29.9 kg/m2) or obesity (BMI ≥ 30 kg/m^2) (24). Waist circumference (WC) was measured using a flexible tape, measured at the midpoint between the iliac crest and the last rib. The participants remained standing with their arms next to their body and their trunk free of clothing, and the measurement was carried out with their abdomen relaxed at the end of expiration (25).

To measure body composition, an InBody® bioimpedance was used, determining the percentage of body fat mass and fat-free mass (i.e., muscle mass) (26). Nutritionists belonging to the weight loss treatment programs at each medical center performed the anthropometric and body composition measurements in the health care room, so that the privacy of the participants was protected during these measurements.

2.3 Chilean version of YFAS 2.0

The YFAS 2.0 is a 35-item self-report scale designed to assess FA symptoms over the previous 12 months based on the 11 diagnostic criteria for substance-related and addictive disorders proposed in DSM-5 and 1 clinical significance criterion (9). These FA criteria are *food consumed in larger quantities or over a longer period than intended*, *persistent desire or unsuccessful efforts to cut down or control consumption of certain foods*, *considerable time spent to obtain, consume, or recover from effects of food*, *giving up important social, occupational, or recreational activities because of food consumption*, *continuing to eat certain foods despite physical or psychological problems*, *tolerance*, *withdrawal*, *continued consumption despite social or interpersonal problems*, *failure to fulfill major role obligation*, *use in physically hazardous situations*, and *craving*, and *significant distress related to food*. This scale scored on an eight-level Likert scale (from 0 = never to 7 = every day). These scores produce two measurements: (a) a continuous symptom count score that reflects the number of diagnostic criteria met (ranging from 0 to 11); and (b) an FA threshold based on the number of symptoms (at least 2) and self-reported clinically significant impairment or distress. This final measurement allows for dichotomous classification of FA (FA vs. non-FA). Based on the DSM-5 taxonomy, the YFAS 2.0 also provides severity cutoffs for patients who exceed the FA threshold: mild (2 to 3 symptoms), moderate (4 to 5 symptoms), and severe (6 to 11 symptoms) (8). The Chilean version of the YFAS 2.0 has recently been validated, showing excellent psychometric properties (internal consistency KR20 0.85 and confirmatory factor analysis supported the unifactorial structure with fit indices of CFI = 0.975, TLI = 0.969, RMSEA = 0.056, with all factor loadings greater than 0.61) (23).

2.4 Statistical analysis

Stata version 16.0 (Stata Corp LLC, College Station, TX, United States) was used. The distribution of quantitative variables was evaluated using histograms and the Kolmogorov–Smirnov test. For statistical significance, a level of $p < 0.05$ was adopted.

The characteristics of the sample were represented in absolute values and percentages for qualitative variables and mean (SD: Standard Deviation) for continuous variables.

To detect differences between sociodemographic variables, anthropometric measurements, and body composition between subjects with and without FA, the Chi2, Fisher's Exact, Student's T or ANOVA test was used, depending on the type of variable. Spearman correlations between FA symptom counts and anthropometric and body composition measurements were assessed. As sensitivity analysis, we considered correlations without individuals with normal weight.

3 Results

Table 1 shows demographic and anthropometric characteristics of the sample. The largest proportion of participants were women (67.7%), employed (68.4%), married (56.3%) and with an educational level of completed university studies (51.2%). The mean age was 47.8 (SD 14.9) and BMI 28.7 (SD 5.3) kg/m^2.

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TABLE 1 Sociodemographic characteristics and anthropometric measurements in clinical sample ($n = 158$).

Variables		
Gender, % (n)	Female	67.7 (107)
	Male	32.3 (51)
Age, (M ± SD)	Years	47.8 (14.9)
Educational level, % (n)	Primary or less	14.6 (23)
	Secondary	34.2 (54)
	University	51.2 (81)
Employment situation, % (n)	Unemployed	29.7 (47)
	Employed	68.4 (108)
	University Students	1.9 (3)
Marital status, % (n)	Single	32.3 (51)
	Married	56.3 (89)
	Divorced	8.9 (14)
	Widower	2.5 (4)
Psychological treatment, % (n)	No	63.9 (101)
	Yes	36.1 (57)
Weight status, % (n)	Normal weight	20.9 (33)
	Overweight	37.3 (59)
	Obesity	41.8 (66)
Anthropometric measures, (M ± SD)	Weight (kg)	75.5 (15.2)
	BMI (kg/m2)	28.7 (5.3)
	WC (cm)	93.9 (10.8)
	Body fat (%)	36.2 (7.9)
	Lean mass (kg)	26.3 (5.7)

TABLE 2 Prevalence and symptom count of food addiction in clinical sample of adults ($n = 158$) according to the Chilean YFAS 2.0 scale.

Characteristics	% (n)
Prevalence FA	12.7 (20)
Mild	3.2 (5)
Moderate	2.5 (4)
Severe	7.0 (11)
Symptom count	2.2 (2.6)
Criteria	
Food consumed in larger quantities or over a longer period than intended	26.6 (42)
Persistent desire or unsuccessful efforts to cut down or control consumption of certain foods	31.0 (49)
Considerable time spent to obtain, consume, or recover from effects of food	22.2 (35)
Giving up important social, occupational, or recreational activities because of food consumption	10.1 (16)
Continuing to eat certain foods despite physical or psychological problems	21.5 (34)
Tolerance	15.2 (24)
Withdrawal	33.5 (53)
Continued consumption despite social or interpersonal problems	27.9 (44)
Failure to fulfill major role obligation	7.6 (12)
Use in physically hazardous situations	17.1 (27)
Craving	10.8 (17)
Significant distress in relation to food	16.5 (26)

Table 2 shows 12.7% FA prevalence and means symptom count 2.2 (SD 2.6). Regarding the severity of FA, the percentages were distributed as 3.2% for mild, 2.5% for moderate and 7.0% for severe. Regarding the number of symptoms reported, the most frequently reported were: 33.5% *withdrawal*, 31.0% *persistent desire or unsuccessful efforts to reduce or control the consumption of certain foods*, 27.9% *continuous consumption despite social or interpersonal problems*.

Table 3 shows the demographic and anthropometric characteristics according to fulfilment of criteria of FA (FA) or not fulfilment (non-FA). The patients with FA were significantly younger than the non-FA subjects ($p = 0.025$). Furthermore, FA patients had significantly higher body weight compared to non-FA subjects ($p = 0.045$).

The symptom count according to demographic and anthropometric characteristics is presented in Table 4, showing no significant differences between FA and Non-FA subjects.

We observed a slight and significant correlation ($p < 0.05$) between symptom count and body weight (rho = 0.19) (Figure 1), waist circumference (rho = 0.27) (Figure 2), and BMI (rho = 0.19) (Figure 3).

As a sensitivity analysis, we performed the correlations without considering normal-weight subjects. The result was that WC maintained a significant correlation (rho = 0.30; $p = 0.006$) (data not shown in figures).

4 Discussion

In this clinical sample of patients undergoing treatment for body weight loss, the prevalence of FA was 12.7%, with severe diagnosis being predominant severity. The most predominant diagnostic criterion was *withdrawal*. Furthermore, we found a relationship between FA symptom count, body weight, BMI, and WC. These results partially confirm our hypothesis, since the prevalence of FA was somewhat lower than expected and there was correlation between the FA symptom count and some anthropometric measures.

Depending on whether the samples are clinical or non-clinical, the literature reports FA prevalence of 31% vs. 14%, respectively (16). A recent meta-analysis that included Latin American countries shows FA prevalences of 5.9 to 95.3% in clinical samples (27). This wide range of prevalence can be attributed to the diverse characteristics of the included participants, since some were in treatments related to cardiovascular health (28), binge eating disorders (29) or evaluation for BS (30, 31). In our study, patients were undergoing treatment to reduce their body weight, for reasons of cardiovascular health or for management of metabolic syndrome. This could explain the lower prevalence compared to those reported for other clinical samples, mainly those that include candidates to BS (30, 31). Among the participants who met the diagnostic criteria for FA, 7% of them were found in the severe category, similar to what is reported in the literature (32).

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TABLE 3 Sociodemographic characteristics and anthropometric measurements according to no food addiction or food addiction in clinical sample ($n = 158$).

Variables		No food addiction $n = 138$	Food addiction $n = 20$	p value[a]
Gender, % (n)	Female	66.7 (92)	75.0 (15)	0.456
	Male	33.3 (46)	25.0 (5)	
Age, (M ± SD)	Years	48.8 ± 15.2	40.9 (10.7)	**0.025**
Educational level, % (n)	Primary or less	15.2 (21)	2.0 (10)	0.514
	Secondary	35.5 (49)	5.0 (25)	
	University	49.3 (68)	13.0 (65)	
Employment situation, % (n)	Unemployed	31.9 (44)	3.0 (15)	0.140
	Employed	66.7 (92)	16.0 (80)	
	University Students	1.4 (2)	1.0 (5)	
Marital status, % (n)	Single	31.9 (44)	35.0 (7)	0.650
	Married	57.2 (79)	50.0 (10)	
	Divorced	8.0 (11)	15.0 (3)	
	Widower	2.9 (4)	0.0 (0)	
Psychological treatment, % (n)	No	65.2 (90)	55.0 (11)	0.374
	Yes	34.8 (48)	45.0 (9)	
Weight Status, % (n)	Normal weight	21.7 (30)	15.0 (3)	0.678
	Overweight	37.7 (52)	35.0 (7)	
	Obesity	40.6 (56)	50.0 (10)	
Anthropometric measures, (M ± SD)	Weight (kg),	74.6 (14.0)	82.5 (21.4)	**0.045**
	BMI (kg/m2)	28.5 (4.6)	30.7 (9.0)	0.114
	WC (cm)	93.4 (10.4)	97.8 (12.8)	0.164
	Body fat (%)	35.9 (8.0)	38.6 (7.2)	0.290
	Lean mass (kg)	25.9 (5.5)	29.1 (7.1)	0.082

[a]Chi-square, Fisher Exact or T-Student test depending on the type of variable for the difference of sample; BMI: Body Mass Index. WC: Waist Circumference. In bold type, $p < 0.05$.

In the present study 2.2 (SD 2.6) symptom count were observed, lower than that reported by Pursey et al. in a meta-analysis in clinical samples a mean of 4.0 (SD 0.5) symptoms (33). This difference may be attributed to the lower BMI of our sample.

The FA diagnostic criterion that predominated in this clinical sample was *withdrawal* (33.5%), which refers to aversive physical, cognitive, and affective symptoms that arise after reduction or discontinuation of an addictive substance. This symptom was one of the most common in the original validation study (29.7%) and in a sample of the general Italian population (12.5%) (34). *Withdrawal* has great clinical relevance as a predictor of relapse and is a target for intervention in substance use disorders (35, 36). In the context of hyperpalatable foods, *withdrawal* has received less research than has been done with addictive drugs and may be an important area for future research with clinical relevance. The second criterion that occurred in the highest proportion (31.0%) was *persistent desire or unsuccessful efforts to reduce or control the consumption of certain foods*. This symptom has been reported in 91.7% in a sample of university students (7), and in 25.0% of the original validation study sample (8). Like consuming more than planned or losing control, this symptom frequently occurs in subjects with eating-related problems and could be triggered by the availability of hyperpalatable foods (37). The third criterion that predominated (27.9%) was *continued consumption despite social or interpersonal problems*. This shows the complexity of addiction, even when individuals are aware of how it can negatively impact their lives.

Our results showed no differences in the prevalence of FA between women and men. Scientific evidence shows diverse results depending on sex, some indicating that FA is more prevalent in women (8, 38, 39), while others have found no differences by sex (40). In the present study, the mean age of those who presented FA was 40.9 vs. 48.8 of those who did not present FA. The literature indicates that FA is more prevalent at younger ages (3).

Regarding nutritional status, no differences were found according to FA or non-FA. BMI also did not differ by FA diagnosis. The literature presents mixed results; some cross-sectional studies have reported that the probability of FA in participants with obesity is greater than in subjects with normal weight (40–42). However, other studies do not observe these differences according to nutritional status (43, 44). These mixed results could suggest that FA could be associated with other binge eating patterns beyond body weight. Minhas et al. indicate that FA appears to be associated with elevations in impulsivity, particularly deficits in emotional regulation (45).

Furthermore, the symptom count of FA was correlated with weight, BMI, and WC measurements. Cross-sectional design studies show a positive and significant correlation between symptom count of FA and BMI (31, 46, 47). It seems incongruent that in this sample

the symptom count of FA was associated with weight-related measures (such as BMI and WC), while FA (as a dichotomous measure) does not show differences by nutritional status. Well, the literature indicates that the symptom count of FA seems to be more sensitive to detect these associations, particularly in samples of participants where the prevalence of FA is not very high (between 10 and 15%) (46, 48, 49).

TABLE 4 Symptom count of food addiction according to demographics characteristics and anthropometric measurements in clinical sample ($n = 158$).

Variables		Symptom count (M ± SD)	*p* value
Gender	Female	2.47 (2.67)	0.086
	Male	1.72 (2.30)	
Educational level	Primary or less	2.13 (2.60)	0.056
	Secondary	1.67 (2.06)	
	University	2.64 (2.82)	
Employment situation	Unemployed	1.83 (2.18)	0.110
	Employed	2.38 (2.74)	
	University students	3.33 (1.15)	
Marital status	Single	1.96 (2.41)	0.151
	Married	2.31 (2.61)	
	Divorced	3.07 (3.08)	
	Widower	1.00 (0.81)	
Psychological treatment	No	2.13 (2.41)	0.752
	Yes	2.42 (2.84)	
Weight status	Normal weight	1.79 (2.47)	0.219
	Overweight	1.98 (2.27)	
	Obesity	2.68 (2.83)	

T-student test or ANOVA test.

On the other hand, we performed a sensitivity analysis eliminating subjects with normal weight from the statistical analyses. Correlations between FA symptom count, weight and BMI lose statistical significance, whereas WC maintains significance. This demonstrates that WC assessment ends up being relevant, given that it proved to be a robust indicator associated with FA. WC measurement could be a valuable tool for assessing FA due to its ease of collection and its relevance in the identification of cardiovascular risk. Although few studies have explored this relationship (45), our investigation has found a significant association between both variables. WC, as an indicator of metabolic health, not only reflects the physical state of the individual, but could also be a useful marker to identify eating behavior patterns. Therefore, we propose that its inclusion in clinical assessment could provide a comprehensive perspective in the management of cardiovascular risk and in FA treatment.

Besides, the study of FA may underlie behaviors that lead to cardiovascular risk factors, and is a possible psychological factor associated with cardiovascular diseases. Evidence suggests that individuals with FA often engage in overeating and poor dietary choices, contributing to obesity, hypertension, and dyslipidemia, all of which are established risk factors for cardiovascular diseases (7). Additionally, the compulsive eating behaviors seen in FA are linked to increased inflammatory markers, which play a crucial role in the development and progression of atherosclerosis. A recent review identified a positive relationship between C-reactive protein (CRP)/high-sensitivity CRP and loss of control eating which is one of the criteria for FA. Other inflammatory markers that potentially have a positive relationship with obesity-related eating behaviors include fractalkine and fibrinogen (50). On the other hand, research has shown a significant association between FA and increased risk of metabolic syndrome, a cluster of conditions that elevate the risk of

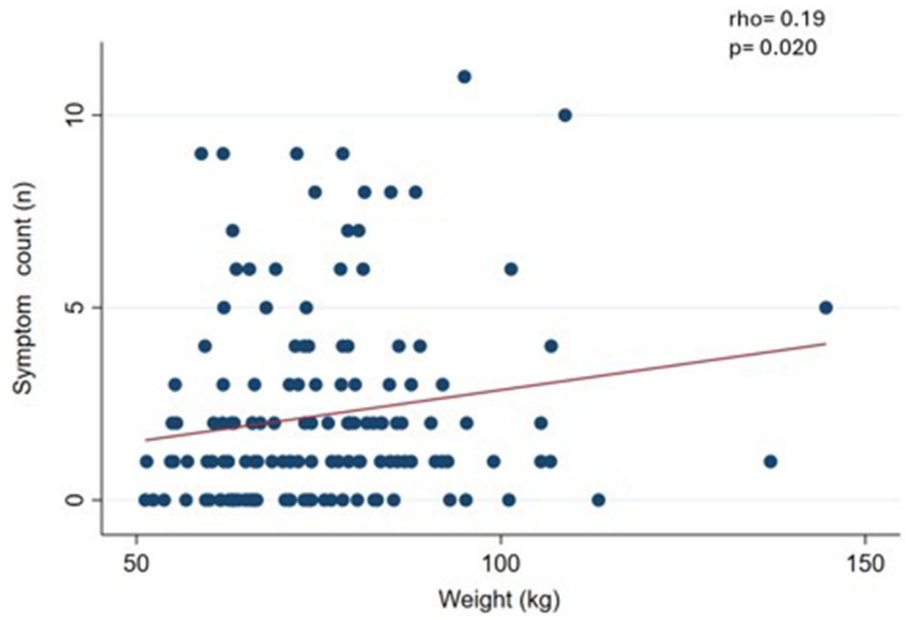

FIGURE 1
Correlation between food addiction symptom count and weight in clinical sample ($n = 146$).

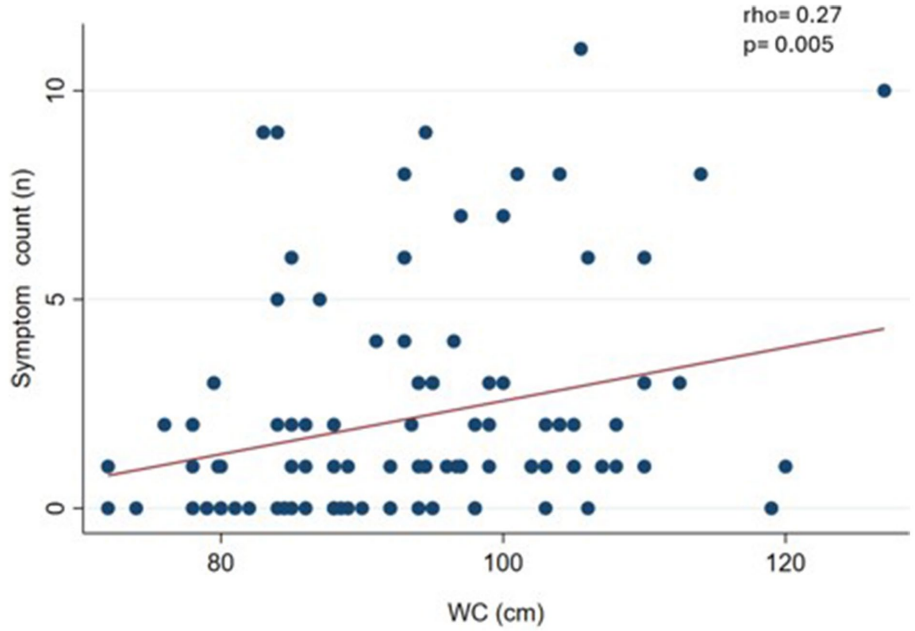

FIGURE 2
Correlation between food addiction symptom count and waist circumference (WC) in clinical sample (n = 108).

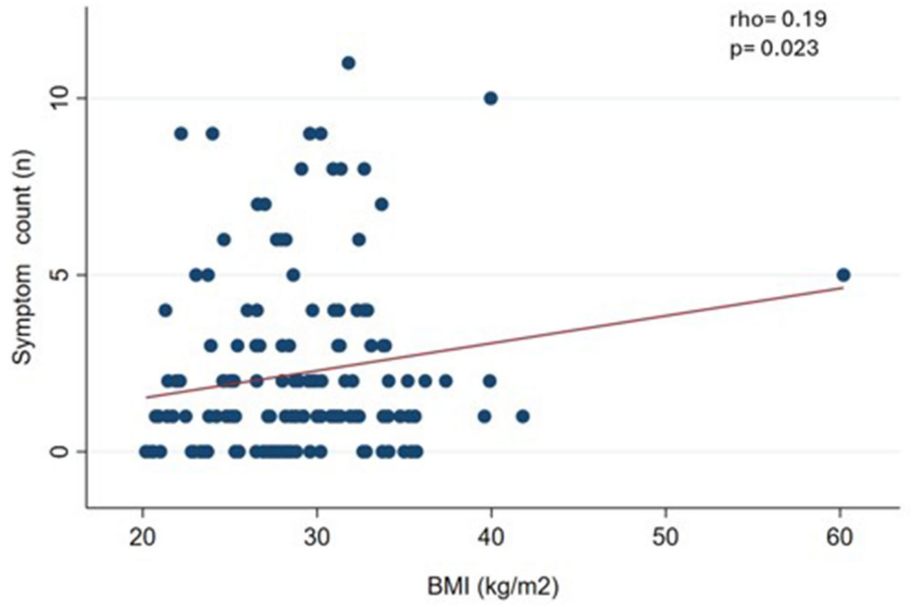

FIGURE 3
Correlation between food addiction symptom count and body mass index (BMI) in clinical sample (n = 144).

heart disease, stroke, and diabetes (21). Therefore, understanding FA and its impact on cardiovascular health is essential for developing comprehensive strategies to mitigate these risks.

The search for the ideal treatment for weight loss and its long-term maintenance have been the aim of numerous investigations. New causes and consequences of overweight and obesity are frequently revealed that must be treated to achieve success in this type of treatment. This is why the FA's role as a contributor must be investigated and addressed (42), considering that the diagnosis of FA could affect adherence to treatment and therefore its effectiveness in people seeking to lose weight (51).

Gearhardt and Hebebrand have conducted an interesting debate as to whether FA is a distinct construct. In this debate, data are provided on the activation of the reward system in the brain in response to certain foods (i.e., UPF), as well as the presence of addictive behaviors such as loss of control and compulsive seeking of certain foods, but disagreement remains as to the strength of the evidence that UPF are addictive (52). While we support the idea that

more evidence is needed regarding that UPF may have addictive effects, we believe that in a subset of the population these effects are significant enough to justify inclusion of the FA construct in obesity treatment.

Early recognition and selection of patients with greater barriers to controlling body weight is important to design strategies that contribute to improving treatment outcomes (53). On the other hand, it would be important to determine if FA predicts the probability of abandoning weight control programs, considering that the dropout rate of subjects who are in weight loss programs is generally high (30%) (53).

Our results must be interpreted considering certain limitations, typical of cross-sectional studies, which do not allow us to draw causal inferences. First, we do not have information regarding how long the subjects had been in the weight loss program, which could explain, in part, the presence of normal weight subjects in this clinical sample. Furthermore, no sample size calculation was performed due to time and cost considerations. Thus, our sample size may not have sufficient power to determine other potential expected associations, for example, the association between body fat percentage and FA.

As a strength we can mention that, to our knowledge, this is the first study to evaluate FA using YFAS 2.0 Chilean version in a clinical sample. This instrument has undergone rigorous psychometric testing and has strong internal consistency and inter-test reliability, as well as convergent, discriminant, and incremental validity (23). It has been translated into more than 12 languages, such as Spanish, Persian and Chinese, and these versions also show strong psychometric properties (54–56).

5 Conclusion

This is the first study in Chile that assessed in a clinical sample the association between FA and different anthropometric measurements, also showing the most prevalent FA criteria. We observed the presence of FA diagnostic criteria in this sample of patients undergoing weight loss treatment, with "*withdrawal*" being the most prevalent criterion. Moreover, FA symptom count was associated with key anthropometric measures such as weight, WC, and BMI. These findings highlight the clinical relevance of FA in individuals on a weight loss program, underscoring the need for tailored multidisciplinary interventions. It also highlights that "*withdrawal*" should be addressed in future studies. Addressing FA in this population may improve treatment outcomes, allowing for more personalized therapeutic strategies that take into account the presence of addictive eating behaviors. This approach could optimize resource allocation and facilitate the development of timely and effective interventions that support long-term weight control and improved health, aligning with the growing evidence linking FA to overweight and obesity.

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 humans were approved by Comité Ético Científico Facultad de Medicina—Clínica Alemana Universidad del Desarrollo. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

Author contributions

AP: Conceptualization, Data curation, Methodology, Writing – original draft, Writing – review & editing. CC: Data curation, Writing – original draft, Writing – review & editing. XD-T: Conceptualization, Data curation, Formal analysis, Funding acquisition, Methodology, Software, Supervision, Writing – original draft, Writing – review & editing.

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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.

The reviewer RLC declared a shared affiliation with the author XD-T to the handling editor at the time of review.

Publisher's note

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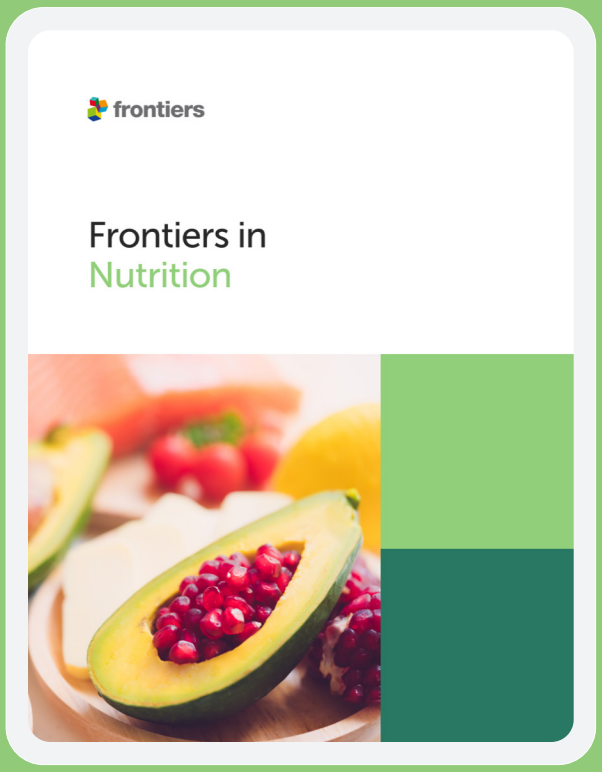

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