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# Gut Hormones, Adipokines, and Pro- and Anti-inflammatory Cytokines/Markers in Loss of Control Eating: A Scoping Review

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## Abstract

Loss of control (LOC) eating is the defining feature of binge-eating disorder, and it has particular relevance for bariatric patients. The biomarkers of LOC eating are unclear; however, gut hormones (i.e., ghrelin, cholecystokinin [CCK], peptide YY [PYY], glucagon-like peptide 1 [GLP-1], and pancreatic polypeptide [PP]), adipokines (i.e., leptin, adiponectin), and pro- and anti-inflammatory cytokines/markers (e.g., high-sensitivity C-reactive protein [hsCRP]) are candidates due to their involvement in the psychophysiological mechanisms of LOC eating. This review aimed to synthesize research that has investigated these biomarkers with LOC eating. Because LOC eating is commonly examined within the context of binge-eating disorder, is sometimes used interchangeably with subclinical binge-eating, and is the latent construct underlying disinhibition, uncontrolled eating, and food addiction, these eating behaviors were included in the search. Only studies among individuals with overweight or obesity were included. Among the identified 31 studies, 2 studies directly examined LOC eating and 4 studies were conducted among bariatric patients. Most studies were case-control in design (n=16) and comprised female-dominant (n=13) or female-only (n=13) samples. Studies generally excluded fasting total ghrelin, fasting CCK, fasting PYY, and fasting PP as correlates of the examined eating behaviors. However, there was evidence that the examined eating behaviors were associated with lower levels of fasting acyl ghrelin (the active form of ghrelin) and adiponectin, higher levels of leptin and hsCRP, and altered responses of postprandial ghrelin, CCK, and PYY. The use of GLP-1 analog was able to decrease binge-eating. In conclusion, this review identified potential biomarkers of LOC eating. Future studies would benefit from a direct focus on LOC eating (especially in the bariatric population),

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Author Contributions

Y.Y. designed the study, searched, screened, reviewed, and synthesized the studies, drafted the manuscript. I.F. and M.Y. critically reviewed and edited the manuscript. W.Z. verified the included studies and reviewed the manuscript. S.G. supervised the review process and critically reviewed the manuscript. All authors have read, reviewed and approved the manuscript and hold the responsibility for its final content.

Declarations of Interest

None.

using longitudinal designs, exploring potential mediators and moderators, and increased inclusion of the male population.

**Keywords**

Loss of control eating; binge-eating; gut hormones; adipokines; inflammation; cytokines

## 1. Introduction

Binge-eating disorder (BED), a mental illness that affects 2.8% of women and 1.0% of men worldwide[1], is characterized by recurrent binge-eating episodes in the absence of compensatory behaviors[2]. Binge-eating consists of two intercorrelated but dissociable features: loss of control (LOC) eating and overeating[2,3]. LOC eating is a subjective experience of being or feeling out of control when eating, no matter the amount of food consumed. As individuals who report LOC eating with or without overeating present similar psychosocial profiles[3,4], LOC eating has been widely recognized as the most salient feature of BED. Notably, emerging evidence has supported the validity of LOC eating as an independent construct[3]. For example, independent of overeating, LOC eating has unique cross-sectional and prospective associations with various physiological and psychosocial vulnerabilities, such as obesity[5], metabolic syndromes[6,7], general psychopathology (e.g., depression), and eating-related psychopathology (e.g., body dissatisfaction)[8,9].

The clinical relevance of LOC eating is particularly prominent in patients with severe obesity who seek or have undergone bariatric surgery. First, LOC eating is prevalent in this population, affecting 6.6%[10]-78.6%[11] of the preoperative and 5.4[12]-50.7%[13] of the postoperative patients. Second, LOC eating at post-surgery predicts adverse surgical outcomes, including less weight loss[14], weight regain[12,15], and more surgical complications (e.g., dumping, vomiting)[16,17]. Finally, and most importantly, as bariatric surgery dramatically reduces gastric volume, alters the gastrointestinal environment, and restricts eating capacity, overeating becomes physically difficult or impossible after surgery (at least in the short-term). Therefore, the overeating feature inherent in binge-eating may not apply to postoperative patients, making the importance of LOC eating stand out.

With increasing emphasis being placed on LOC eating, many efforts have been made to identify its physiological and psychosocial mechanisms. Physiologically, LOC eating involves a disruption in the homeostatic and hedonic eating regulation systems. The homeostatic system controls physiological appetite, hunger, and satiety through the hypothalamus, especially the hypothalamic arcuate nucleus[18]. Individuals with LOC eating have imbalanced expressions of orexigenic and anorexigenic neurons within the arcuate nucleus, reporting increased appetite, increased hunger, and decreased satiety compared to healthy controls[19]. The hedonic system regulates eating behavior mainly through the dopamine and opioid reward circuits, which modulates the “wanting” (food craving) and “liking” (food enjoyment) components of food reward, respectively. An accumulating body of behavioral and neuroimaging studies has shown that individuals with LOC eating self-report an elevated food craving/enjoyment and exhibit heightened brain reward responsivity

for high-energy foods (e.g., fats, sweets)[20,21]. Consequently, they are more likely to consume high-energy foods than those without LOC eating[22,23].

The psychosocial mechanisms of LOC eating have been widely studied both within and outside the bariatric population, and several types of risk factors have been identified. These psychosocial risk factors include negative emotions or affects (e.g., anxiety, depression, distress)[24,25], maladaptive emotion regulations strategies (e.g., rumination, suppression)[26,27], weight-related dysfunctional behaviors or perceptions (e.g., dietary restraint, weight suppression, and body dissatisfaction)[28,29], and deficits in cognitive control, especially inhibitory control[30,31].

While the physiological and psychosocial mechanisms of LOC eating have been somewhat uncovered, the biomarkers that are related to LOC eating are less studied in the general or bariatric population. Gut hormones, adipokines, and pro- and anti-inflammatory cytokines/markers are promising candidates because they are involved in homeostatic and hedonic eating regulation. As a result, the alterations of these biomarkers may increase or decrease individuals' appetite, hunger, satiety, and perceived food reward, thus ultimately influencing their motivations to initiate or stop consuming food and contributing to the experience of difficulty in stopping eating (LOC eating). Additionally, these biomarkers are closely related to the psychosocial risk factors of LOC eating[32–37].

Gut hormones include the "hunger" hormone, ghrelin, and "satiety" hormones such as cholecystokinin (CCK), peptide YY (PYY), glucagon-like peptide 1 (GLP-1), and pancreatic polypeptide (PP). Ghrelin activates the orexigenic and dopaminergic neurons, thus promoting appetite, hunger, food craving, and food-seeking behaviors[38,39]. Ghrelin exists in circulation in two major forms: acylated and des-acylated ghrelin. While the majority of circulating ghrelin is des-acylated, the acylated form is thought to be essential for ghrelin's biological activity in appetite stimulation[38]. In contrast, CCK, PYY, GLP-1, and PP inhibit orexigenic neurons, thus promoting satiety and eating termination. Additionally, there is evidence that GLP-1 also suppresses dopaminergic neurons[40]. Besides participating in hemostatic and hedonic eating regulations, gut hormones also regulate moods and cognitive functions that are related to LOC eating. For example, research has repeated demonstrated the anti-depressant effect of ghrelin[32] and the cognitive-enhancing effect of GLP-1[33].

Leptin and adiponectin are adipokines that are mostly secreted by white adipose tissue. Leptin acts as a negative feedback signal to control energy homeostasis at the hypothalamus[41,42], and it also suppresses dopamine signaling to reduce the craving or motivation to seek and consume food[42]. Although there is no consensus, it has been suggested that adiponectin regulates eating behavior in a glucose-dependent fashion. At low glucose conditions, adiponectin downregulates orexigenic and upregulates anorexigenic neurons to attenuate appetite; at high glucose levels, adiponectin downregulates both orexigenic and anorexigenic activities[43,44]. In addition to regulating eating behaviors, as the receptors of leptin and adiponectin are widely distributed in hippocampus and neocortex, they are likely to be involved in emotion regulation and cognitive control[34,36].

Pro-inflammatory cytokines, including interleukin-1α (IL-1α), interleukin-1β (IL-1β), interleukin-6 (IL-6), and tumor necrosis factor-α (TNF-α) are involved in eating regulation possibly through acting on hypothalamus[45,46] and dopaminergic neurocircuits[47,48], and through interacting with eating-regulation hormones (e.g., ghrelin, GLP-1, leptin)[49,50]. Despite inconclusive evidence, animal and human studies have shown that IL-1β, IL-6, and TNF-α suppress appetite[51,52] and eating motivation[53,54], hence reducing meal size and meal duration[55,56]. Furthermore, pro-inflammatory cytokines are intertwined with emotions and moods, such as depression, anxiety, and stress[37], which are all risk factors of LOC eating.

The pro-inflammatory cytokines are positively associated with inflammatory markers: C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR). In contrast, the synthesis of pro-inflammatory cytokines is inhibited by anti-inflammatory cytokines, such as interleukin-10 (IL-10) and interleukin-13 (IL-13). Therefore, these inflammatory markers and anti-inflammatory cytokines are potentially related to LOC eating, although their effect on eating regulation is unclear.

Recognizing the role of gut hormones, adipokines, and inflammatory cytokines/markers in eating regulation and psychosocial functioning, prior studies have reviewed their relationships with eating disorders[57–59]. However, these reviews predominantly focused on bulimia nervosa and anorexia nervosa, of which information cannot be readily applied to LOC eating due to the distinctive disease symptoms among these eating behaviors[57–59]. To address this gap, the aim of this review was to identify and synthesize quantitative research that has thus far investigated the associations of gut hormones, adipokines, or pro- and anti-inflammatory cytokines/markers with LOC eating in both children and adults. A greater understanding of the biomarkers related to LOC eating could advance the identification, prevention, and treatment of this disordered eating behavior. Additionally, as LOC eating is prevalent and negatively impacts weight loss and metabolic outcomes among bariatric patients, such knowledge could facilitate the development of interventions to promote optimal surgical outcomes.

## 2. Methods

### 2.1 Study design

A scoping review was conducted to examine the range and extent of existing evidence available on gut hormones, adipokines, and inflammatory cytokines/markers related to LOC eating. A scoping review instead of a systematic review was chosen because there are few publications on this topic, and the goal of a scoping review is to examine emerging and unclear evidence[60]. A standard five-stage process of scoping review was followed: (1) identifying the research question, (2) identifying relevant studies, (3) selecting studies, (4) charting the data, (5) collating, summarizing, and reporting the results[60].

### 2.2 Inclusion/exclusion criteria

Although LOC eating has been increasingly accepted as an independent construct and there is a growing call to study LOC eating and overeating separately[3,61,62], in most cases, it is examined within the context of BED. Additionally, subclinical binge-eating is

sometimes used interchangeably with LOC eating. Therefore, both BED and subclinical binge-eating were included in the search. Moreover, given studies have provided evidence that disinhibition, uncontrolled eating (a loss of control on food intake in response to emotional or external stimuli), and food addiction (a loss of control on food intake accompanied by other symptoms such as tolerance and withdraw) share the latent construct of "loss of control"[63,64], these eating behaviors were also included in the review. Studies that examined bulimia nervosa were excluded because although it has the defining feature of binge-eating, the levels of hormones, adipokines, and inflammatory cytokines/markers could be influenced by compensatory behaviors such as purging behaviors and vomiting.

It is known that the levels and functions of gut hormones, adipokines, and inflammatory cytokines/markers are influenced by body weight. For example, in individuals with obesity, levels of ghrelin and adiponectin are generally lower while levels of leptin and pro-inflammatory cytokines/markers are elevated[65,66]. To eliminate the confounding effect of body weight and increase the potential applicability to bariatric patients, only studies conducted among individuals with overweight or obesity (body mass index [BMI]>25 $kg/m^2$) were included.

In general, studies were included if they 1) reported associations of gut hormones, adipokines, or inflammatory cytokines/markers with LOC eating, subclinical binge-eating, BED, disinhibition, uncontrolled eating, or food addiction among individuals with overweight or obesity, or 2) compared the biomarkers between individuals with these eating behaviors and unaffected controls, where participants in both groups were overweight or obese, or 3) manipulated the biomarkers and reported an effect on these eating behaviors among individuals with overweight or obesity.

Studies published in non-English languages, and animal studies, abstracts, editorials, case studies, book chapters, dissertation work, review papers, or kin studies were excluded.

### 2.3 Search strategy

Three electronic databases, including PubMed (1947–March 5, 2021), PsycINFO (1967–March 5, 2021), and Embase (1974–March 5, 2021) were searched to obtain relevant studies. The search included the combination of the following keywords: gut hormones, ghrelin, CCK, PYY, GLP-1, PP, leptin, adiponectin, inflammation, IL-1α, IL-1β, IL-6, TNF-α, IL-10, IL-13, CRP, ESR, LOC eating, binge-eating, disinhibition, uncontrolled eating, and food addiction. The database search was complemented by a hand search of the reference lists obtained from the identified articles.

### 2.4 Study selection

A total of 31 studies were included in the final review. The study selection flow is presented in Figure 1. Author 1 (YY) screened titles and abstracts, both author 1 and author 2 (WZ) reviewed full-text articles.

### 2.5 Data extraction and synthesis

Key components extracted from each paper included: 1) study characteristics of title, first author, country, publication year, and study design; 2) participant characteristics of gender, age, race, BMI, sample size, and inclusion/exclusion criteria; 3) biomarkers assessed; 4) eating behaviors assessed; and 5) main study conclusion.

## 3. Results

### 3.1 Study and participant characteristics

The extracted data were organized according to individual biomarkers (Table 1). In terms of study characteristics, the 31 studies were conducted in 13 different countries with Italy (n=9) and US (n=8) accounted for the majority. Eleven studies were published in the last 5 years and 9 in the last 10 years. Most of the studies were case-control in design (n=16), followed by longitudinal (n=6), cohort (n=2), cross-sectional (n=4), randomized controlled trial (RCT, n=2), and randomized cross-over (n=1) designs. For the 16 case-control and 2 cohort studies, except for 1 study[67], BMI was either comparable between groups[68–80] or was adjusted as a covariate in analysis[81–84]. Regarding sample characteristics, 4 studies were conducted among pre- or post-bariatric patients[75,85–87], and participants from the remaining studies were patients who were seeking eating disorder (n=3) or behavioral weight loss treatment (n=6), were attending pediatric (n=3), endocrinology (n=3), or psychiatric clinics (n=1), non-treatment seeking (n=5), a mix of treatment-seeking and non-treatment seeking (n=2), and not specified (n=4). Six studies were conducted among children or adolescents[78,79,83,84,88,89], and the remaining 25 were among adults. Except for 1 study that did not report sex composition[90] and 4 studies that comprised comparable proportions of males and females[72,84,88,91], studies were female-dominant (n=13) or female-only (n=13). Two studies directly examined LOC eating[78,83] and 6 studies examined subclinical binge-eating[72–74,84,90,92] (none of these were conducted among bariatric population), others examined BED (n=13), disinhibition or uncontrolled eating (n=8), and food addiction (n=2).

### 3.2 Biomarkers Related to LOC Eating, Subclinical Binge-Eating, BED, Disinhibition, Uncontrolled Eating, or Food Addiction

**3.2.1 Fasting ghrelin—**Ghrelin is an appetite-stimulating peptide that increases food intake. In a healthy population, circulating levels of ghrelin increase during fasting to promote meal initiation and decrease shortly after meal consumption to terminate an eating episode[38]. Ghrelin has two major molecular forms (acylated and des-acylated ghrelin)—only the acyl ghrelin is able to bind to the ghrelin receptor and stimulate appetite[93].

Twelve studies have examined fasting ghrelin in relation to subclinical binge-eating, BED, disinhibition, uncontrolled eating, or food addiction. The majority (n=9) did not support a role of fasting total ghrelin in these eating behaviors. Specifically, 3 studies reported that fasting total ghrelin did not differ between individuals with subclinical binge-eating[84], BED[68], or food addiction[69] and unaffected controls. Next, 5 studies did not find significant cross-sectional or longitudinal associations between fasting total ghrelin and disinhibition[86,94,95] or uncontrolled eating[85,87] among patients who sought or had undergone surgical or behavioral weight loss treatment. Finally, 1 longitudinal study[70] assessed fasting

total ghrelin and BED before and after a cognitive-behavioral therapy (CBT). This study found that fasting total ghrelin did not respond to the intervention, and it failed to predict binge-eating behaviors at pre- or post-intervention.

In contrast to these null findings, an earlier study found that fasting total ghrelin was lower in women with BED relative to non-BED controls, and this difference was normalized after CBT[71]. However, results should be interpreted with caution because the ghrelin changes from pre- to post-intervention were independent of the CBT treatment and were not related to the self-reported binge-eating days[71].

Unlike the above studies that examined total ghrelin, two recent studies[72,92] specifically examined its active form—acyl ghrelin—and reported significant findings. One study compared the fasting acyl ghrelin between adults with and without subclinical binge-eating, which revealed that participants with subclinical binge-eating had significantly lower fasting acyl ghrelin concentrations than unaffected controls[72]. Similarly, a significant negative association was observed between fasting acyl ghrelin and binge-eating behaviors in a cross-sectional study conducted among 88 adults with overweight or obesity[92].

Overall, studies appeared to be consistent in indicating that fasting total ghrelin did not have a role in subclinical binge-eating, BED, disinhibition, uncontrolled eating, and food addiction. However, some evidence supports a reduced level of acyl ghrelin in patients with subclinical binge-eating that warrants future investigation.

**3.2.2 Postprandial ghrelin—**Postprandial ghrelin (total or acylated) has been assessed in 6 studies with conflicting results. In one study[71] conducted among women with BED (n=10) and controls (n=9), the authors found that postprandial total ghrelin was lower and showed a blunted decline following meal consumption in the BED group after adjusting for weight change. One recent study[72] had similar findings in that they documented that acyl ghrelin (but not des-acyl ghrelin) was significantly lower and declined slower after a meal in adults with subclinical binge-eating (n=20) than in unaffected controls (n=22). However, 3 other studies[70,81,84] were unable to replicate this finding, which reported levels and responses of total ghrelin following test meals were comparable between adults or adolescents with and without BED. Additionally, a study that was conducted among bariatric patients did not detect any significant associations between postprandial total ghrelin and uncontrolled eating before or at 12 months following bariatric surgery[87].

Two studies of the above 6 studies also tested whether postprandial ghrelin changed following CBT. One study[71] reported that the lower level and blunted response of postprandial total ghrelin in the BED group were “normalized” after CBT, although the “normalization” could not be conclusively attributed to the intervention. Conversely, the other study[70] did not find any intervention effect on postprandial total ghrelin level or response, despite 50% of the patients achieved BED abstinence at the end of the intervention.

The inconsistent results among these studies could be partially attributed to a lack of differentiation the two forms (acylated and des-acylated) of ghrelin, which may bias the

study results. Furthermore, the small sample sizes (ranged from 6 to 20 in the binge-eating group), different participant characteristics (e.g., 5 different countries: US, Italy, UK, Canada, Switzerland; a wide age range: mean age ranged from 13 to 50), and methodological differences across the studies could also contribute to the mixed findings. For example, the 6 studies used 6 different test meals with different total energy (ranged from 300 kcal to 797 kcal) and energy compositions. In addition, they adjusted for different covariates (e.g., age[72,81], sex[70,72,81,84], BMI[70,72,81,87], weight change[71], fat mass[84]), were comprised of treatment-seeking[81,84,87] or non-treatment seeking samples[70], and adopted different outcome measures (e.g., Eating Disorder Examination[70,72,84], Questionnaire on Eating and Weight Patterns[71,72], Three Factor Eating Questionnaire[87]).

In summary, study results are mixed in terms of the association between postprandial ghrelin and LOC eating. However, there is some evidence that the level and response of postprandial ghrelin, especially acyl ghrelin, to meal consumption may be lower and blunted in patients with subclinical binge-eating or BED[71,72].

**3.2.3 Fasting and postprandial CCK—**CCK is a satiety hormone that reduces food intake[96]. In the general population, the circulating level of CCK increases rapidly in response to a meal to promote meal termination[96]. Three studies have examined fasting CCK related to subclinical binge-eating or BED. All 3 of them reported that fasting CCK did not differ between adults with and without binge-eating[70,72,73]. One of these studies was longitudinal in design, in which 18 patients with BED received an 8-week CBT. Neither the fasting CCK was affected by the intervention, nor it was related to the binge-eating behaviors at post-intervention[70].

Postprandial CCK was assessed in 4 studies and findings were mixed. Two studies[72,73] did not find significant differences in postprandial CCK between adults with subclinical binge-eating or BED and unaffected controls. However, in one study[70], patients with BED relative to controls exhibited an augmented CCK secretion within 60 minutes following meal ingestion, which was not corrected by an 8-week CBT. The authors interpreted the heightened CCK stimulation as an initial effort of the central nervous system to prevent individuals with BED from bingeing. In contrast, in another study conducted among a cohort of women with overweight, the authors observed a positive association between blunted CCK secretion and high disinhibition, but the association was significant only among women who had a high level of dietary restraint[97]. This result suggested potential interactions among dietary restraint, CCK responses, and disinhibition.

The samples across the 4 studies that examined postprandial CCK tended to share similar characteristics. For example, they were mostly female, middle-aged, from US, and non-treatment seeking. However, all of the studies had small sample sizes (ranged from 11 to 20 in the binge-eating group). Additionally, there were other variations among studies, including various test meals (4 different meals), different covariates controlled in the analysis (e.g., age[72], sex[70,72], BMI[70,72], and weight change[97]), and varied outcome measurements (e.g., Questionnaire on Eating and Weight Patterns, Eating Disorder Examination).

To sum up, despite the limited number of studies that have been done, fasting CCK has been consistently found to be unrelated to subclinical binge-eating or BED. The association of postprandial CCK with BED[70] or disinhibition[97] was found in two studies. However, the responses of postprandial CCK were controversial between these studies[70,97]. Additionally, there is preliminary evidence suggesting the interactions among dietary restraint, disinhibition, and CCK secretion[97].

**3.2.4 Fasting and postprandial PYY—**PYY is a hormone that increases satiety and suppresses food intake. In the general population, PYY levels increase within 15 minutes in response to food intake and contribute to termination of food intake[98]. Eight studies have examined fasting PYY with subclinical binge-eating, BED, uncontrolled eating, disinhibition, or food addiction, and all of them reported null findings. In detail, 5 studies documented that fasting PYY did not differ between adults or adolescents with subclinical binge-eating[72,84], BED[70,71], or food addiction[69] and unaffected controls. Additionally, 2 of these studies did not find any intervention effect of CBT on fasting PYY among patients with BED[70,71]. Finally, 3 studies did not find significant cross-sectional or longitudinal associations between fasting PYY and uncontrolled eating[88] or disinhibition[94,95] among adolescents or adults with obesity.

Postprandial PYY has been assessed in 4 studies, and 3 of them reported that the PYY secretion in response to test meals was comparable between adolescents or adults with subclinical binge-eating[72,84] or BED[71] and controls. Additionally, postprandial PYY did not respond to a 6-week CBT among patients with BED[71]. In contrast, 1 study observed a higher increase in PYY within the first 80 minutes following meal ingestion in patients with BED vs non-BED controls[70]. It was interpreted that the more intense stimulation of the PYY secretion after food intake was an adaptive response from the central nervous system and the gut to counteract the initiation of binge-eating.

In summary, current studies did not support fasting PYY as a significant correlate of subclinical binge-eating, BED, uncontrolled eating, disinhibition, or food addiction. While most studies did not detect postprandial PYY alterations in subclinical binge-eating or BED, one study found an augmented response that deserves further investigation[70].

**3.2.5 Fasting and postprandial GLP-1—**GLP-1 suppresses appetite, promotes satiety, and reduces energy intake[99]. In the general population, GLP-1 increases rapidly after meal ingestion to prevent overeating[99]. Four observational studies have examined fasting GLP-1 with subclinical binge-eating, BED, uncontrolled eating, and food addiction, and they consistently reported null findings. Among these 4 studies, 3 studies did not find significant differences in fasting GLP-1 between adults with subclinical binge-eating[72], BED[71], or food addiction[69] and controls, and the fasting GLP-1 did not change after BED treatment[71]. In the remaining study, fasting GLP-1 was not related to uncontrolled eating among 12 patients at pre-, 2 and 12 months post-bariatric surgery[87]. Three of the above 4 studies also assessed postprandial GLP-1. They found that postprandial GLP-1 was comparable between adults with and without subclinical binge-eating[72] or BED[71], was nonresponsive to CBT among patients with BED[71], and was not significantly related to uncontrolled eating among bariatric patients[87].

In contrast to the above observational studies that reported null findings, 3 intervention studies that tested the effect of GLP-1 analog—liraglutide—on subclinical binge-eating, BED, and uncontrolled eating reported significant findings. One randomized controlled trial[90] assigned non-diabetic patients with subclinical binge-eating to either a 12-week lifestyle intervention (n=21) or lifestyle intervention plus liraglutide (n=21), and results revealed that at the end of the intervention, participants who received liraglutide showed significant improvement in binge-eating. The other 2 studies reported similar results by demonstrating significant reductions of BED among adults with diabetes[91] and reductions of uncontrolled eating among women with polycystic ovary syndrome[100] after 12-week treatment of liraglutide.

Taken together, while observational studies consistently reported null findings, intervention studies suggested the possible relevance of GLP-1 to subclinical binge-eating, BED, and uncontrolled eating.

**3.2.6 Fasting PP—**PP is a gut hormone that reduces food intake[99]. In the general population, PP is released in response to food ingestion to prevent overconsumption of food[99]. Only 2 studies have examined PP, with one study that reported fasting PP did not differ between adults with and without food addiction[69] and the other study reported no significant association between fasting PP and disinhibition among a cohort of women with obesity[94].

**3.2.7 Leptin—**Thirteen studies have examined leptin in relation to LOC eating, subclinical binge-eating, BED, disinhibition, uncontrolled eating, and food addiction, and 5 studies identified significantly higher levels of leptin in these eating behaviors. In detail, 4 studies found significantly higher levels of leptin in adolescents with LOC eating[78], bariatric candidates or women with BED[75,101], and adolescents with food addiction[89] relative to controls. Among these 4 studies, 1 study also reported that higher levels of leptin predicted higher odds of binge-eating behaviors among women with BED[101], and another study demonstrated a positive association between leptin and disinhibition among bariatric candidates (regardless of BED diagnosis)[75]. In line with these findings, 1 study reported that leptin levels went up in parallel with the increase of uncontrolled eating among bariatric candidates[87].

There was one study that reported LOC eating as an independent outcome. In that study the authors explored the mediating or moderating effects of dietary restraint and/or sex in the relationship between leptin and LOC eating. Results revealed that the positive relationship between leptin and LOC eating was significant for females only. Moreover, the relationship was partially mediated by higher dietary restraint after controlling for age, race, sex, socioeconomic, fat mass, height, treatment-seeking status, and pubertal status[78].

Unlike the above studies that supported significantly higher levels of leptin in LOC eating, BED, uncontrolled eating, and food addiction, 6 studies reported null findings. However, 4 of them found that although lacking statistical significance, the leptin levels were higher in adults or adolescents with subclinical binge-eating[74], BED[76,79], or food addiction[69] compared to unaffected controls. Importantly, it was found that leptin levels increased

linearly along with the increase of binge-eating severity among women with obesity[74]. It should be noted that all these 4 studies had a relatively small sample size (ranged from 18 to 35 in the binge-eating or food addiction group), which may be underpowered to detect any statistical significance. There were other 2 studies that did not detect differences of leptin between women with BED[73] or disinhibition[94] and controls; yet, statistics were not provided in these 2 studies.

Two studies found lower leptin levels in BED vs non-BED groups. Specifically, in 1 case-control study, leptin levels were found to be significantly lower in women with BED than non-BED controls[67]. However, it should be noted that BMI was significantly higher in the non-BED group than the BED group and it was not controlled as a covariate in the analysis, which may explain the contrasting finding in this study. The lower leptin levels in women with vs. without BED were observed in another study, but the difference was minor (46.4 vs. 50.7 μg), and the authors did not provide a level of statistical significance[77].

Overall, with some exceptions, studies generally supported higher leptins levels in LOC eating, subclinical binge-eating, BED, disinhibition, uncontrolled eating, and food addiction (with or without statistical significance). Additionally, there is preliminary evidence that the relationship is mediated by dietary restraint and moderated by sex.

**3.2.8 Adiponectin—**Three studies have examined adiponectin in relation to BED, disinhibition, and food addiction, and they consistently demonstrated lower adiponectin levels in individuals with these eating behaviors. Specifically, 1 study[67] observed significantly lower adiponectin levels in women with BED compared to non-BED women; a second study[69] reported lower adiponectin levels (statistically nonsignificant) in adults with food addition compared with age-, sex-, BMI-, and physical activity-matched controls; and a third study[94] detected a negative association between adiponectin and disinhibition among 67 women who participated in a 4-week lifestyle intervention.

Taken together, despite the limited number of studies, it appeared that the adiponectin levels were lower in individuals with BED, disinhibition, or food addiction.

**3.2.9 Pro- and anti-inflammatory cytokines/markers—**Five studies have examined pro- (i.e., IL-1α, IL-1β, IL-6, TNF-α, CRP, ESR) and anti-inflammatory (i.e., IL-10) cytokines/markers with LOC eating, BED, disinhibition, and food addiction. CRP has been assessed in 3 studies: 2 of them reported that high-sensitivity CRP (hsCRP) was significantly higher in adolescents with LOC eating[83] or adults with BED[82] than unaffected controls; the remaining study did not find a significant association between CRP and disinhibition among a cohort of women with obesity[94]. Notably, the latter study examined CRP instead of hsCRP and did not adjust for covariates in analysis, which may introduce bias and lack sensitivity in capturing the differences in inflammatory status. ESR has been assessed in 1 study[82], in which significantly higher ESR levels were observed in the BED vs non-BED group.

TNF-α has been examined in 2 studies: 1 study showed a significantly lower level of TNF-α in individuals with food addiction compared to those without food addiction[69]; and the other study showed no difference in levels between adults with BED and

non-BED controls (statistics not provided)[80]. The different findings may be due to the sample characteristics (e.g., Canadian[69] vs Italian[80], non-treatment seeking[69] vs treatment seeking[80]), outcome measures (food addiction[69] vs BED[80]), and covariates controlled in analysis (non-specified[69] vs depressive symptoms, sex, and age[80]). The latter study also examined other pro- and anti-inflammatory cytokines such as IL-1α, IL-1β, IL-6, and IL-10. While no significant differences were detected in IL-1α, IL-1β, or IL-6 between the BED and control groups, IL-10 was found to be significantly lower in the BED group[80].

In summary, limited studies have assessed the relationship between inflammatory cytokines/markers and LOC eating. There may be potential associations of LOC eating with elevated inflammatory status, including higher hsCRP, higher ESR, and lower IL-10.

## 4. Discussion

This scoping review synthesized current evidence regarding gut hormones, adipokines, and pro- and anti-inflammatory cytokines/markers related to LOC eating, subclinical binge-eating, BED, disinhibition, uncontrolled eating, and food addiction, among children or adults with overweight or obesity. Results can be summarized as follows: 1) only 2 studies directly examined LOC eating and 6 examined subclinical binge-eating, and only 4 studies were conducted among bariatric patients; 2) fasting total ghrelin, fasting CCK, fasting PYY, and fasting PP did not appear to be related to the eating behaviors as mentioned above; 3) although studies were scarce and findings were inconsistent, there was evidence supporting lower levels of fasting acyl ghrelin and adiponectin, higher levels of leptin and pro-inflammatory markers (e.g., hsCRP, ESR), and altered responses of postprandial ghrelin (blunted), CCK (blunted or amplified), and PYY (amplified) in the aforementioned eating behaviors; and 3) using GLP-1 analog decreased binge-eating.

The lower fasting acyl ghrelin and blunted responses of postprandial ghrelin (total or acylated) observed in individuals with subclinical binge-eating or BED suggested that ghrelin, especially acyl ghrelin, is a potential correlate of LOC eating. Considering that the acyl ghrelin acts to stimulate appetite and promote eating, the lower fasting acyl ghrelin is unlikely to cause binge-eating or LOC eating; instead, it may represent a secondary change or an adaption aiming to counteract repeated binge-eating or LOC eating. The blunted responses of postprandial ghrelin imply that the normal suppression of hunger and food craving after meal consumption is impaired, which may contribute to the initiation or maintenance of binge-eating or LOC eating. Studies in patients with bulimia nervosa have similarly observed an attenuated decrease of postprandial ghrelin[102–104] following a meal, although it is not clear whether the attenuation is due to the binge behavior or purging behavior. Furthermore, animal studies have provided additional evidence supporting the involvement of ghrelin in binge-eating or LOC eating. For example, there have been observations that ghrelin receptor-deficient mice failed to induce binge-eating[105,106] and central ghrelin infusion enhanced binge-like behaviors in palatable schedule fed rats[107].

It is worth emphasizing that the lower levels of fasting ghrelin and blunted responses of postprandial ghrelin observed in subclinical binge-eating or BED are not universal findings. In addition to reasons like small sample sizes and methodological differences across studies,

the failure to distinguish acylated and des-acylated ghrelin may bias and undermine the validity of findings based on total ghrelin concentration. Given recent evidence that des-acylated ghrelin can impair the orexigenic actions of acyl ghrelin[108,109], future studies should examine the separate forms rather than the total concentration of ghrelin.

Included studies consistently showed that fasting CCK, PYY, and PP did not differ between individuals with and without subclinical binge-eating, BED, uncontrolled eating, disinhibition, or food addiction, indicating that these fasting hormones may not be significant corelates of LOC eating. However, 2 studies reported altered postprandial CCK (amplified[70] or blunted[97]) and PYY responses (amplified[70]) in those with BED or disinhibition compared to unaffected controls, suggesting that the alterations may be relevant to LOC eating. The blunted CCK increase post-meal has also been observed in the BN population[110–112], and it is speculated that the blunted response may play a role in the diminished satiety observed in BN and contribute to the initiation, perpetuation, or relapse of this eating disorder. The finding that individuals with BED had amplified increases of postprandial CCK and PYY as reported in 1 study[70] was not replicated anywhere else, although the interpretation that the augmented responses reflect an effort to prevent binge initiation is plausible. Given that current studies produced inconsistent findings of whether and in which direction the postprandial CCK and PYY responses were altered, further investigations are needed on this topic.

All of the observational studies did not support fasting or postprandial GLP-1 as a significant indicator of subclinical binge-eating, BED, uncontrolled eating, and food addiction. However, the interventional drug trials utilizing GLP-1 analog have demonstrated effectiveness in reducing binge-eating and uncontrolled eating, suggesting there is potential GLP-1 involvement in LOC eating. Several studies conducted in the BN population have established a rationale to consider GLP-1 as an indicator of LOC eating. With that said, these studies have noted that among patients with BN, GLP-1 was positively associated with bingeing behaviors[113] but not purging behaviors[114], implying that GLP-1 may be a unique indicator of binge-eating or LOC eating.

The leptin level was found to be higher in patients with LOC eating, subclinical binge-eating, BED, disinhibition, or uncontrolled eating compared with unaffected controls, albeit a few exceptions. Since participants included in this review were all overweight or obese, the higher levels of leptin suggest a specific link between this adipokine and LOC eating that is not simply explained by the enhanced fat stores or leptin resistance associated with extra weight. Furthermore, the study that reported a strong association between leptin and LOC eating after adjusting for adiposity provides direct evidence to consider leptin as a significant indicator of LOC eating. Besides, studies conducted in the BN population have also detected higher leptin levels[115] and a positive association between leptin and bingeing behaviors[75,116] among patients with BN, which adds support to the possibility that higher leptin levels may play a role in the development or maintenance of LOC eating.

Adiponectin is less investigated than leptin, and the few studies consistently reported lower levels of adiponectin in individuals with BED, disinhibition, or food addiction compared to unaffected controls. As mentioned, the effect of adiponectin on eating regulation is glucose-

dependent. However, one limitation of these few studies is that they did not consider glucose levels, which preclude clear conclusions about the role that adiponectin plays in these eating behaviors. Despite this limitation, the lower levels of adiponectin are synchronized with the behavioral manifestations of LOC eating. For example, individuals with LOC eating show a trend of eating faster and consuming more high-energy foods, both of which are negatively associated with adiponectin levels[117–119].

The inflammation markers (hsCRP, ESR) have been found to be elevated in adolescents with LOC eating and adults with BED relative to unaffected controls, indicating that LOC eating may be associated with an elevated inflammatory status. Additional support for this association comes from the Avon Longitudinal Study of Parents and Children (ALSPAC), which followed 3480 nationally representative children from birth to 18 years of age. Using the ALSPAC data, one study found that children with higher levels of IL-6 and CRP had greater odds of binge-eating in adolescence, although these associations were weak[120]. It is worth mentioning that one study included in this review reported opposite findings, in which pro-inflammatory cytokine (TNF-α) decreased in individuals with food addiction. Beyond differences in sample characteristics and methodologies, the discrepancy may be due to the complex interaction between inflammation and gut hormones and adipokines. For example, research has shown that the gut hormones (e.g., ghrelin, CCK) and adiponectin suppress the production of pro-inflammatory cytokines such as TNF-α, IL-6 and IL-1β[121,122]. In contrast, leptin acts in opposition facilitating the secretion of these cytokines[123]. Therefore, without evaluating these interactions, it is difficult to conclude on the relationships between the inflammatory cytokines/markers and LOC eating.

Regardless of biomarker types, 4 common limitations were identified across all of the reviewed studies: studies that directly examine LOC eating are limited in the general population and are absent in bariatric population; there is an insufficient number of longitudinal studies; there is a lack of examination of potential mediators and moderators; and lastly, an underrepresentation of males.

This review only identified 2 studies that directly examined LOC eating[78,83] and 6 studies that examined subclinical binge-eating[72–74,84,90,92], all of which were conducted among non-bariatric children and adolescents. Although all other eating behaviors (e.g., BED, disinhibition) chosen for review share the core feature of “loss of control”, they are broader constructs that embrace other disordered eating behaviors. For example, BED additionally includes overeating, and disinhibition overlaps with emotional eating and external eating. Even for the studies that examined LOC eating or subclinical binge-eating, measurement limitations exist—they involved only a dichotomous assessment, which failed to reflect current evidence that LOC eating should be studied on a continuum of severity[124,125]. As LOC eating has been increasingly acknowledged as an independent construct[3] and two specific, continuous scales (Eating Loss of Control Scale, Loss of Control over Eating Scale) have been developed and validated in individuals with obesity[125–128], future research is needed that makes LOC eating a more explicit focus. Additionally, studies on bariatric patients are warranted because LOC eating is of particular importance for this population.

A few of the studies included in this review longitudinally examined the associations of gut hormones and leptin with BED, disinhibition, or uncontrolled eating following CBT[70,71], behavioral weight loss intervention[88,94,95], or surgical weight loss intervention[86,87]. However, these studies did not include patients at various eating behavior stages throughout the follow-up, including new-onset, maintenance, and remission. Consequently, it is impossible to conclude whether the biomarker alterations occur first or after these disordered eating behaviors, and whether the alterations represent state or trait markers. Bariatric surgery, in which LOC eating has particular clinical relevance, offers a unique opportunity to clarify if the biomarker alterations cause or are secondary to LOC eating. From before surgery, four longitudinal patterns of LOC eating have been observed at 6–12 months after surgery (proportion of patients in each pattern): new-onset (17–40%), maintenance (25–38%), remission (27–60%), and LOC eating-free (40–70%)[10,129,130]. Meanwhile, gut hormones, adipokines, and inflammatory cytokines/markers also change as a result of surgery, although the direction and degree of change depends on the surgical techniques. Taking sleeve gastrectomy as an example, extensive studies among adults and adolescents have shown that fasting and postprandial ghrelin (total and acylated)[131–133], leptin[133,134], and pro-inflammatory cytokines/markers (e.g., IL-1α, IL-1β, IL-6, TNF-α, CRP, ESR) decrease, while adiponectin and anti-inflammatory cytokines increase after surgery[134]. The different patterns of LOC eating and the parallel changes of biomarkers offers great value to delineation of the role of these biomarkers in LOC eating.

It has been widely acknowledged that beyond regulating homeostatic and hedonic food consumption, gut hormones, adipokines, and pro- and anti-inflammatory cytokines are closely tied to an individual's psychosocial functioning. For example, human and animal studies indicate that ghrelin, GLP-1, and leptin have anti-depressant effects[32,34,35,135], while levels of CCK and pro-inflammatory cytokines increase with elevated anxiety and depressive symptoms[136,137]. Furthermore, postprandial CCK and PYY are blunted[138,139] but leptin levels are increased[140,141] in individuals with dietary restraint. The intrinsic link between biomarkers and psychosocial functioning highlights the importance to examine the indirect associations (through the moderating or mediating effect of psychosocial functioning) between biomarkers and LOC eating. However, among the included studies, only two studies examined dietary restraint as a moderator of relationship between postprandial CCK and disinhibition[97], or as a mediation of the relationship between leptin and LOC eating[78], signaling an area that needs further research.

As commonly seen in eating disorder research, most studies included in this review consisted of female-only or female-dominant samples. Unlike BED that has a higher prevalence in women than men, the distribution of LOC eating is far less skewed, with reports of comparable prevalence between males and females both in the non-bariatric[142] and bariatric population[143]. Furthermore, given the knowledge that reproductive hormones (e.g., estradiol, progesterone) and females' menstrual cycle influence the symptoms of binge-eating[144], the relationship between biomarkers and LOC eating may differ for males and females. Therefore, future studies should increase the presentation of males and examine the gender differences when investigating biomarkers with LOC eating.

This scoping review has several limitations. First, because studies that directly report LOC eating are too scarce in number, several overlapping but broader eating behaviors were also included. The inclusion of these eating behaviors is necessary to provide richer and more comprehensive information, but it introduces heterogeneity and creates difficulty to isolate the construct of LOC eating. Second, only published full articles were searched; therefore, relevant information presented in the gray literature (e.g., unpublished manuscripts) may have been missed. Third, the literature search was limited to 3 databases. Additional literature may exist that was not included within the scope of this search. Fourth, this review only focused on the significance testing results when reporting the relationships between biomarkers and LOC eating. The lack of an examination of the effect sizes precludes the understanding of the strength of these relationships. Given that the sample size in most of the included studies was small and this scoping review provides initial evidence that several gut hormones (e.g., postprandial ghrelin), adipokines (e.g., leptin), and pro-inflammatory markers (e.g., hsCRP) may be related to LOC eating, future studies would benefit from conducting a meta-analysis and pooling the effect sizes across studies.

## 5. Conclusion

Despite the limited number of studies and conflicting results, there is evidence that supports the associations of lower levels of fasting acyl ghrelin and adiponectin, higher levels of leptin, hsCRP, and ESR, and altered responses of postprandial ghrelin (blunted), CCK (blunted or amplified), and PYY (amplified) to meal ingestion with the eating behaviors including LOC eating, subclinical binge-eating, BED, disinhibition, uncontrolled eating, and food addiction. Additionally, using GLP-1 analog may reduce binge-eating. Future studies would benefit from a direct examination of LOC eating especially in the bariatric patients, a greater focus on longitudinal studies, an in-depth exploration of the interactions between biomarkers and psychosocial functioning, and an investigation of gender differences that may shape the relationship between biomarkers and LOC eating. Other considerations include examining acyl ghrelin instead of total ghrelin, reporting glucose levels with adiponectin, and investigating the interactions among inflammation, gut hormones, and adipokines.

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## Abbreviations that are not Standard in the Field

| | |
|---|---|
| **LOC eating**[1] | Loss of control eating |

## Abbreviations:

| | |
|---|---|
| **BED** | binge-eating disorder |

| | |
|---|---|
| **BN** | bulimia nervosa |
| **AN** | anorexia nervosa |
| **BMI** | body mass index |
| **DSM** | Diagnostic and Statistical Manual of Mental Disorders |
| **CBT** | cognitive behavioral therapy |
| **CCK** | cholecystokinin |
| **PYY** | peptide YY |
| **GLP-1** | glucagon-like peptide 1 |
| **PP** | pancreatic polypeptide |
| **IL-1α** | interleukin-1α |
| **IL-1β** | interleukin-1β |
| **IL-6** | interleukin-6 |
| **TNF-α** | tumor necrosis factor-α |
| **CRP** | C-reactive protein |
| **ESR** | erythrocyte sedimentation rate |
| **IL-10** | interleukin-10 |
| **IL-13** | interleukin-13 |

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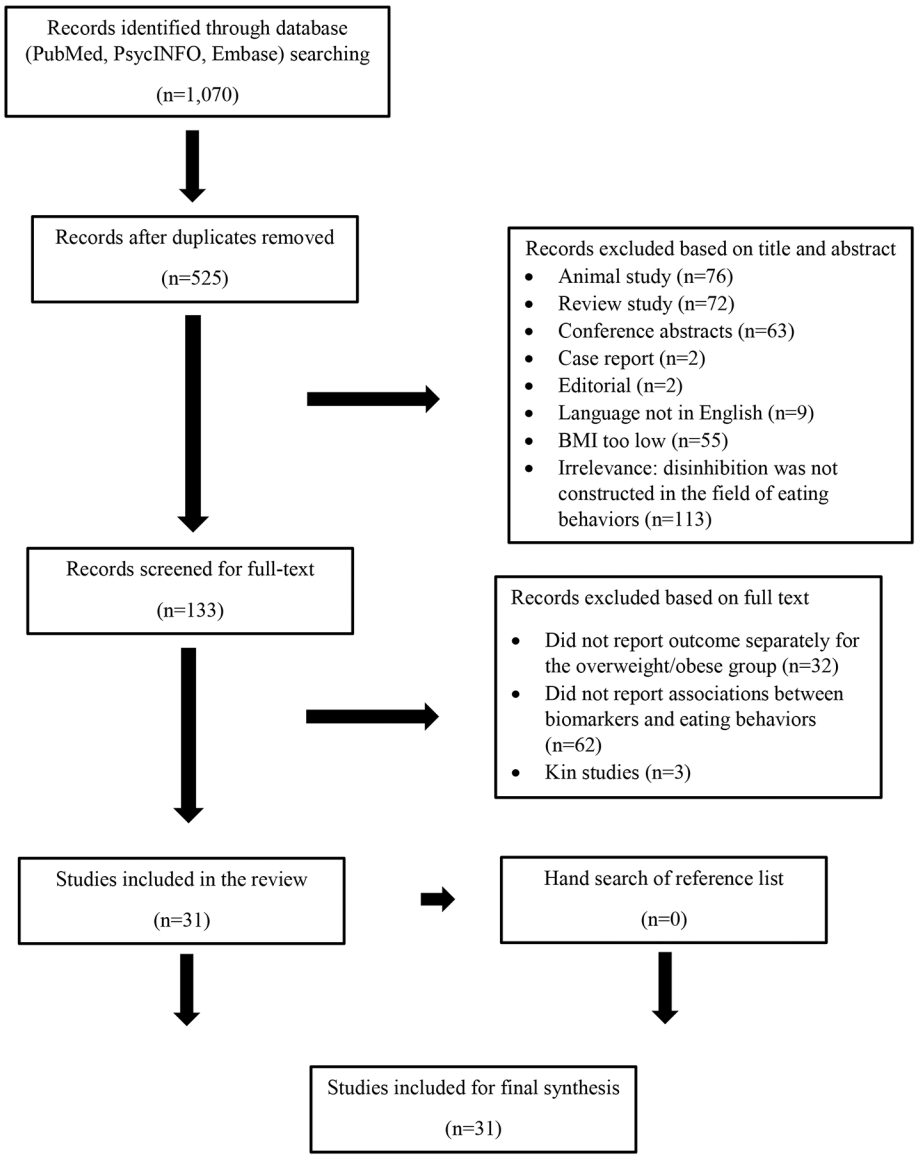


**Figure 1.**
Study Selection Flow

*Appetite*. Author manuscript; available in PMC 2023 November 28.

**Table 1**

Description of included studies (N=31)

| Study characteristics | Sample description | Biomarker | Eating behavior | Conclusion |
|---|---|---|---|---|
| **Ghrelin** | | | | |
| Circulating ghrelin is decreased in non-obese and obese women with binge eating disorder as well as in obese non-binge eating women, but not in patients with bulimia nervosa[68]<br>• Monteleone et al.<br>• 2004<br>• Italy<br>• Case-control | • 56 women with BN: age: 23.4±4.3; BMI: 21.9±3.8<br>• 34 women with BED and obesity: age: 33.6±9.1; BMI: 39.8±4.9; binge frequency: 10.9±8.1 episodes/week<br>• 13 women with BED but without obesity: age: 26.9±8.0; BMI: 25.8±2.5; binge frequency: 9.5±6.5 episodes/week<br>• 28 women with obesity but without BED: age: 38.3±14.1; BMI: 38.1±6.3<br>• 51 healthy control women: age: 22.6±3.1; BMI: 21.7±2.3<br>• Recruited from the Eating Disorder Center<br>• None of women with BED had a history of AN or BN, and they are free from drugs for at least 8 weeks | • Fasting ghrelin<br>• Covariates included BMI and body mass fat | • BED assessed by Structured Clinical Interview for DSM-IV | • Ghrelin in patients with BED and obesity did not significantly different from ghrelin in non-BED patients with obesity<br>• Ghrelin was not significantly correlated to the binge episodes among women with BED |
| Impact of laparoscopic adjustable gastric banding on plasma ghrelin, eating behaviour and body weight[86]<br>• Schindler et al<br>• 2004<br>• Australia<br>• Longitudinal | • 23 candidates for bariatric surgery (gastric banding): age: 35.6±2.12; BMI: 44.8±1.0; female: 86.9%<br>• Recruited from Department of Surgery<br>• Exclusion: type 2 diabetes, myocardial infarction, any malignancy, chronic kidney or liver disease, seizure, obesity caused by an endocrine disorder, psychiatric disorders, current pregnancy or breastfeeding. | • Fasting ghrelin<br>• Assessment timepoints: before and 6 months after surgery | • Disinhibition subscale of Three Factor Eating Questionnaire | • Before surgery, ghrelin was not correlated with disinhibition<br>• After surgery, the change of ghrelin was not correlated with the change of disinhibition |
| The acute ghrelin response to a psychological stress challenge does not predict the post-stress urge to eat[81]<br>• Rouach et al | • 8 adults with BED: age: 49.7±4.8; BMI: 36.7±1.5; female: 75%<br>• 8 non-BED adults: age: 50.2±5.7; BMI: 35.2±1.4; female: 62.5% | • Postprandial ghrelin<br>• Subjects were instructed to eat a light breakfast around 7am, and tests began at 9 am | • BED measure not specified | • Ghrelin levels in patients with BED were higher than healthy obese subjects, but this difference did not |

| Study characteristics | Sample description | Biomarker | Eating behavior | Conclusion |
|---|---|---|---|---|
| • 2007<br>• Italy<br>• Case-control | • 8 adults with normal weight: age: 32.6±3.5; BMI: 21.2±0.7; female: 62.5%<br>• Recruited from an obesity clinic<br>• Exclusion: anorexia or bulimia nervosa, any psychiatric co-morbidities, taking medication affecting the central nervous system, receiving medication known to interfere with cortisol measurements | • Covariates included age, gender and BMI | | attain statistical significance. |
| Appetite-related gut peptides, ghrelin, PYY, and GLP-1 in obese women with and without binge eating disorder (BED)[71]<br>• Geliebter et al.<br>• 2008<br>• US<br>• Longitudinal | • 10 women with BED: age: 29.9±8.2; BMI: 36.5±6.6; frequency of binge eating days: 3.2±0.8d<br>• 9 women without BED: age: 30.3±8.4; BMI: 35.8±5.5<br>• All women were premenopausal and in otherwise good health<br>• Eight BED and 8 non-BED participants were randomly assigned for 6 weeks to either (a) individual weekly treatment with nutritional counseling and cognitive behavior therapy or (b) a non-treatment control | • Fasting and postprandial ghrelin<br>• Test meal: 1254 kJ liquid meal<br>• Blood draw: −15, and 0, 5, 15, 30, 60, 90, and 120 min after test meal<br>• Covariates included weight change | • BED assessed by Questionnaire on Eating and Weight Patterns followed by a clinical interview | • Fasting ghrelin was lower and declined less postprandially in the BED group.<br>• After intervention, ghrelin normalized and there were no differences in fasting and postprandial ghrelin between groups. However, the changes in ghrelin pre to post intervention were not related to treatment condition or change in binge eating days. |
| Lifestyle intervention discloses an association of the Eating Inventory-51 factors with cardiometabolic health risks[94]<br>• Hainerová et al<br>• 2013<br>• Czech Republic<br>• Longitudinal | • 67 women with obesity: age: 48.7±12.2; BMI: 32.4±4.4<br>• Women participated in a 4-week lifestyle obesity management (e.g., low-calorie diet, physical activity, and cognitive behavioral therapy) | • Fasting ghrelin<br>• Assessment timepoints: before and after a 3-week weight management<br>• Covariates not specified | • Disinhibition subscale of Eating Inventory | • No significant associations between fasting ghrelin and disinhibition at baseline |
| Relationships among tonic and episodic aspects of motivation to eat, gut peptides, and weight before and after bariatric surgery[87]<br>• Bryant et al<br>• 2013 | • 12 candidates for bariatric surgery (gastric bypass): age: 36±2; BMI: 45.3±1.9; female: 75%<br>• Exclusion criteria not specified | • Fasting and postprandial ghrelin<br>• Test meal: liquid meal (200 ml, 300 kcal)<br>• Blood draw: −10, and 0, 10, 20, 30, 60, 90, 120, and | • Uncontrolled eating subscale of the Three Factor Eating Questionnaire | • Fasting and postprandial ghrelin was not associated with uncontrolled eating at before and 12 months following surgery |

| Study characteristics | Sample description | Biomarker | Eating behavior | Conclusion |
|---|---|---|---|---|
| • UK<br>• Longitudinal | | 180 minutes after consumption<br>• Assessment timepoints: pre-surgery, and 2 months, and 1 year post-surgery<br>• Covariates included BMI | | |
| Ghrelin and peptide YY increase with weight loss during a 12-month intervention to reduce dietary energy density in obese women[95]<br>• Hill et al.<br>• 2013<br>• US<br>• Longitudinal | • 71 women with obesity: age: 46.7±1.0; BMI: 33.3±0.3<br>• Participants were attending a 12-month intervention focused on reducing energy density<br>• Inclusion: women ages 20 – 60 years, BMI between 30–40 kg/m2.<br>• Exclusion: high blood pressure, serum triacylglycerols, and total cholesterol, major medical conditions, pregnancy/lactation, taking selective serotonin reuptake inhibitors, symptoms of depression or disordered eating, currently participating in a weight loss program. | • Fasting ghrelin<br>• Assessment timepoints: 0, 3, 6 and 12 months after intervention<br>• Covariates included energy density, body weight, hunger, dietary restraint | • Disinhibition subscale of Eating Inventory | • There was no significant longitudinal association between ghrelin and disinhibition |
| Hormonal and dietary characteristics in obese human subjects with and without food addiction[69]<br>• Pedram et al<br>• 2014<br>• Canada<br>• Case-control | • 29 adults with food addiction: age: 42.5±9.6; BMI: 32.5±6; female: 82.7%<br>• 29 non-food-addicted subjects matched for age, sex, BMI and physical activity: age: 42±8.9; BMI: 32±4.4; female: 82.7%<br>• Recruited from non-clinical setting<br>• Inclusion: age >19 years, without serious metabolic, cardiovascular or endocrine diseases, and not pregnant at the time of the study. | • Fasting ghrelin<br>• Covariates not specified | • Food addiction assessed by Yale Food Addiction Scale | • Ghrelin did not differ between the two groups |
| Appetite sensations, appetite signaling proteins, and glucose in obese adolescents with subclinical binge eating disorder[84]<br>• Adamo et al | • 6 adolescents with binge eating: age: 13.7±0.7; BMI: 35.9±2.2; female: 33.3%<br>• 9 adolescents without binge eating: age: 14.5±0.8; BMI: 38.5±3.0; female: 83.3% | • Fasting and postprandial ghrelin<br>• Test meal: 571 kcal standardized breakfast (50% carbohydrate, 35% | • Binge eating assessed by Eating Disorder Diagnostic Scale | • Overall concentrations of ghrelin across the monitoring period did not significantly differ between the two groups |

| Study characteristics | Sample description | Biomarker | Eating behavior | Conclusion |
|---|---|---|---|---|
| • 2014<br>• Canada<br>• Case-control | • Recruited from pediatric endocrinology clinic<br>• Exclusion: had type 2 diabetes or were taking medications that could influence body composition or appetite. | fat, and 15% protein)<br>• Fasting, and postprandially at 15, 30, 60, 90, 120, and 240 minutes<br>• Covariates included sex and fat mass | | • Hunger and satiety were not significantly correlated with ghrelin |
| Plasma ghrelin levels and weight regain after Roux-en-Y Gastric Bypass Surgery[85]<br>• Abu Dayyeh et al<br>• 2017<br>• US<br>• Cross-sectional | • 36 patients who have undergone bariatric surgery (gastric bypass): age: 47±10; BMI: 38±7.7; female: 94%; length post-surgery: 5±4 years; race: (white: 68%, black: 18%, Hispanic: 14%)<br>• Inclusion: at least 1 year post-surgery<br>• Exclusion: gastrogastric fistula(e) | • Fasting ghrelin | • Uncontrolled subscale of Three Factor Eating Questionnaire | • There was no association between ghrelin and uncontrolled eating |
| CCK, ghrelin, and PYY responses in individuals with binge eating disorder before and after a cognitive behavioral treatment (CBT)[70]<br>• Munsch et al.<br>• 2019<br>• Switzerland<br>• Longitudinal | • 18 adults with BED: age: 50.2±9.5; BMI: 32.4±5.4; female: 77%<br>• 20 age- and BMI-matched healthy controls: age: 48.6±9.7; BMI: 34.3±7.6; female: 95%<br>• Recruited from non-clinical setting.<br>• Inclusion: between 18 and 70 years old, BMI between 27 and 40, and meet full criteria for BED.<br>• Exclusion: unstable medical conditions, mental disorders warranting immediate treatment, pregnancy, participation weight loss treatment<br>• Patients with BED received a 8-week CBT | • Fasting and postprandial ghrelin<br>• Test meal: 797 kcal standard breakfast (62% carbohydrate, 10% protein, and 28% fat)<br>• −20 min, −5 min, and 15, 30, 45, 60, 90,120, and 180 min after the meal<br>• Covariates included baseline BMI and sex | • BED assessed by Eating Disorder Examination | • Before and short-term after intervention, fasting ghrelin did not differ between groups<br>• Before intervention, postprandial ghrelin levels did not differ between BED participants and controls<br>• In the BED group, the fasting and postprandial ghrelin did not change before and after intervention<br>• Ghrelin were not related to objective binge eating post-intervention |
| Meal-related acyl and des-acyl ghrelin and other appetite-related hormones in people with obesity and binge eating[72]<br>• Hernandez et al<br>• 2019 | • 20 adults with binge eating (10 BED and 10 subthreshold binge eating): age: 37.8±8.4; BMI: 36.2±5.5; female: 60%<br>• 22 adults without binge eating: age: 34.0±8.2; BMI: 36.4±4.9; female: 31.8% | • Fasting and postprandial ghrelin (des-acyl ghrelin, acyl ghrelin<br>• Test meal: 1254 KJ liquid meal (55% | • Binge eating assessed by Eating Disorder Examination and the Questionnaire | • Significantly lower acyl ghrelin concentrations for the binge eating group compared with the non-binge eating group |

| Study characteristics | Sample description | Biomarker | Eating behavior | Conclusion |
|---|---|---|---|---|
| • US<br>• Case-control | • Race in the total group: Black/ African American (61%), Hispanic (19.5%), non-Hispanic White (14.6%), and other (4.8%).<br>• Recruited from non-clinical settings<br>• Exclusion: individuals with other eating disorders | carbohydrate, 24% protein, 21% fat)<br>• Blood draw: −15, and 0, 10, 30, and 60 minutes after meal<br>• The two groups did not differ in age, BMI, and sex | on Eating and Weight Patterns | • Decrease of postprandial AG was significantly smaller for the binge eating group at 30 and 60 minutes than the decreases in the non-binge eating group<br>• Decrease of postprandial des-acyl ghrelin did not significantly differ between groups |
| Association between des-acyl ghrelin at fasting and predictive index of muscle derangement, metabolic markers and eating disorders: a cross-sectional study in overweight and obese adults[92]<br>• Perna et al.<br>• 2020<br>• Italy<br>• Cross-sectional | • 88 adults: age: 43.3±9.3; BMI: 30.2±3.3; female: 72.7%;<br>• Exclusion: hepatic or renal disease, diabetes, cardiovascular disease, hypertension, diagnosed bulimia, cancer, surgery for weight loss, weight loss medication, depressive disorder, female patients were excluded if they were pregnant or lactating or had entered menopause | • Fasting ghrelin (des-acyl ghrelin, acyl ghrelin)<br>• Covariates not specified | • Binge eating behavior measured by Binge Eating Scale | • Acyl ghrelin was negatively associated with binge eating, while des-acyl ghrelin was not significantly associated with binge eating |
| **CCK** | | | | |
| Gastric capacity, test meal intake, and appetitive hormones inbinge eating disorder[73]<br>• Geliebter et al.<br>• 2004<br>• US<br>• Case-control | • 11 women with BED: age: 29±8; BMI: 36.6±6.2<br>• 13 women with subclinical binge eating: age: 29±7; BMI: 35.8±5.5<br>• 13 non-binge eating women: age: 32±9; BMI: 35.1±5.3<br>• Inclusion: premenopausal, nonsmokers, not taking illegal drugs or medications affecting weight, and weight stable within past 3 months. | • Fasting and postprandial CCK<br>• Test meal: 600 ml liquid meal (with an energy density of 4.2 J/g)<br>• Blood draw: −15, and 0, 5, 15, 30, 60, 90, and 120 min after meal<br>• Covariates not specified | • Binge eating assessed by Questionnaire on Eating and Weight Patterns and clinical interview | • Fasting and postprandial CCK did not differ between groups |
| Glycemic index, cholecystokinin, satiety and disinhibition: is there an unappreciated paradox for overweight women?[97]<br>• Burton-Freeman et al. | • 21 women with overweight: age: 31±8; BMI: 27±1<br>• Recruited from non-clinical setting<br>• Exclusion: cardiovascular or metabolic disorders, pregnant or had | • Postprandial CCK<br>• Test meal: breakfast with high glycemic index (54.2% carbohydrate; 15% protein; 30.8% | • Disinhibition assessed by Three Factor Eating Questionnaire | • Among participants with dietary restraint, those with higher disinhibition scores had a blunted CCK response to both high glycemic index and |

| Study characteristics | Sample description | Biomarker | Eating behavior | Conclusion |
|---|---|---|---|---|
| • 2008<br>• US<br>• Randomized cross-over | been pregnant within 18 months before the study, were taking medications to manage body weight or control appetite. | fat); breakfast with low glycemic index (54.6% carbohydrate; 14.7% protein; 30.7% fat)<br>• Fasting, and 30, 60, 90, 120, 150, 210, 270, 360 and 480 min following the breakfast<br>• Women were instructed to maintain a stable weight | | low glycemic index meals |
| CCK, ghrelin, and PYY responses in individuals with binge eating disorder before and after a cognitive behavioral treatment (CBT)[70]<br>• Munsch et al.<br>• 2019<br>• Switzerland<br>• Longitudinal | • 18 adults with BED: age: 50.2±9.5; BMI: 32.4±5.4; female: 77%<br>• 20 age- and BMI-matched healthy controls: age: 48.6±9.7; BMI: 34.3±7.6; female: 95%<br>• Recruited from non-clinical setting.<br>• Inclusion: between 18 and 70 years old, BMI between 27 and 40, and meet full criteria for BED.<br>• Exclusion: unstable medical conditions, mental disorders warranting immediate treatment, pregnancy, participation weight loss treatment<br>• Patients with BED received a 8-week CBT | • Fasting and postprandial CCK<br>• Test meal: 797 kcal standard breakfast (62% carbohydrate, 10% protein, and 28% fat)<br>• −20 min, −5 min, and 15, 30, 45, 60, 90,120, and 180 min after the meal<br>• Covariates included baseline BMI and sex | • BED assessed by Eating Disorder Examination | • Before and short-term after intervention, fasting CCK did not differ between groups<br>• Before intervention, BED participants revealed a higher meal-induced increase and stronger decline thereafter in CCK compared to controls<br>• In the BED group, the fasting and postprandial CCK did not change before and after intervention<br>• CCK was not related to objective binge eating post-intervention |
| Meal-related acyl and des-acyl ghrelin and other appetite-related hormones in people with obesity and binge eating[72]<br>• Hernandez et al<br>• 2019<br>• US<br>• Case-control | • 20 adults with binge eating (10 BED and 10 subthreshold binge eating): age: 37.8±8.4; BMI: 36.2±5.5; female: 60%<br>• 22 adults without binge eating: age: 34.0±8.2; BMI: 36.4±4.9; female: 31.8%<br>• Race in the total group: Black/ African American (61%), Hispanic | • Fasting and postprandial CCK<br>• Test meal: 1254 KJ liquid meal (55% carbohydrate, 24% protein, 21% fat)<br>• Blood draw: −15, and 0, 10, 30, and 60 minutes after meal | • Binge eating assessed by Eating Disorder Examination and the Questionnaire on Eating and Weight Patterns | • CCK did not differ between groups |

| Study characteristics | Sample description | Biomarker | Eating behavior | Conclusion |
|---|---|---|---|---|
| | (19.5%), non-Hispanic White (14.6%), and other (4.8%).<br>• Recruited from non-clinical settings<br>• Exclusion: individuals with other eating disorders | • The two groups did not differ in age, BMI, and sex | | |
| **PYY** | | | | |
| Appetite-related gut peptides, ghrelin, PYY, and GLP-1 in obese women with and without binge eating disorder (BED)[71]<br>• Geliebter et al.<br>• 2008<br>• US<br>• Longitudinal | • 10 women with BED: age: 29.9±8.2; BMI: 36.5±6.6; frequency of binge eating days: 3.2±0.8d<br>• 9 women without BED: age: 30.3±8.4; BMI: 35.8±5.5<br>• All women were premenopausal and in otherwise good health<br>• Eight BED and 8 non-BED participants were randomly assigned for 6 weeks to either (a) individual weekly treatment with nutritional counseling and cognitive behavior therapy or (b) a non-treatment control | • Fasting and postprandial PYY<br>• Test meal: 1254 kJ liquid meal<br>• Blood draw: −15, and 0, 5, 15, 30, 60, 90, and 120 min after test meal<br>• Covariates included weight change | • BED assessed by Questionnaire on Eating and Weight Patterns followed by a clinical interview | • Fasting and postprandial PYY did not differ between groups.<br>• Fasting and postprandial PYY did not change after intervention |
| Ghrelin and peptide YY increase with weight loss during a 12-month intervention to reduce dietary energy density in obese women[95]<br>• Hill et al.<br>• 2013<br>• US<br>• Longitudinal | • 71 women with obesity: age: 46.7±1.0; BMI: 33.3±0.3<br>• Participants were attending a 12-month intervention focused on reducing energy density<br>• Inclusion: women ages 20 – 60 years, BMI between 30–40 kg/m2.<br>• Exclusion: high blood pressure, serum triacylglycerols, and total cholesterol, major medical conditions, pregnancy/lactation, taking selective serotonin reuptake inhibitors, symptoms of depression or disordered eating, currently participating in a weight loss program. | • Fasting PYY<br>• Assessment timepoints: 0, 3, 6 and 12 months after intervention<br>• Covariates included energy density, body weight, hunger, dietary restraint | • Disinhibition subscale of Eating Inventory | • There was no significant longitudinal association between PYY and disinhibition |
| Lifestyle intervention discloses an association of the Eating Inventory-51 factors with cardiometabolic health risks[94]<br>• Hainerová et al | • 67 women with obesity: age: 48.7±12.2; BMI: 32.4±4.4<br>• Women participated in a 4-week lifestyle obesity management (e.g., | • Fasting PYY<br>• Assessment timepoints: before and after a 3-week weight management | • Disinhibition subscale of Eating Inventory | • No significant associations between PYY and disinhibition at baseline |

| Study characteristics | Sample description | Biomarker | Eating behavior | Conclusion |
|---|---|---|---|---|
| • 2013<br>• Czech Republic<br>• Longitudinal | low-calorie diet, physical activity, and cognitive behavioral therapy) | • Covariates not specified | | |
| Hormonal and dietary characteristics in obese human subjects with and without food addiction[69]<br>• Pedram et al<br>• 2014<br>• Canada<br>• Case-control | • 29 adults with food addiction: age: 42.5±9.6; BMI: 32.5±6; female: 82.7%<br>• 29 non-food-addicted subjects matched for age, sex, BMI and physical activity: age: 42±8.9; BMI: 32±4.4; female: 82.7%<br>• Recruited from non-clinical setting<br>• Inclusion: age >19 years, without serious metabolic, cardiovascular or endocrine diseases, and not pregnant at the time of the study. | • Fasting PYY<br>• Covariates not specified | • Food addiction assessed by Yale Food Addiction Scale | • The 2 groups did not differ in terms of PYY |
| Appetite sensations, appetite signaling proteins, and glucose in obese adolescents with subclinical binge eating disorder[84]<br>• Adamo et al<br>• 2014<br>• Canada<br>• Case-control | • 6 adolescents with binge eating: age: 13.7±0.7; BMI: 35.9±2.2; female: 33.3%<br>• 9 adolescents without binge eating: age: 14.5±0.8; BMI: 38.5±3.0; female: 83.3%<br>• Recruited from pediatric endocrinology clinic<br>• Exclusion: had type 2 diabetes or were taking medications that could influence body composition or appetite. | • Fasting and postprandial PYY<br>• Test meal: 571 kcal standardized breakfast (50% carbohydrate, 35% fat, and 15% protein)<br>• Fasting, and postprandially at 15, 30, 60, 90, 120, and 240 minutes<br>• Covariates included sex and fat mass | • Binge eating assessed by Eating Disorder Diagnostic Scale | • Overall concentrations of PYY across the monitoring period did not significantly differ between the two groups<br>• Hunger and satiety were not significantly correlated with PYY |
| CCK, ghrelin, and PYY responses in individuals with binge eating disorder before and after a cognitive behavioral treatment (CBT)[70]<br>• Munsch et al.<br>• 2019<br>• Switzerland<br>• Longitudinal | • 18 adults with BED: age: 50.2±9.5; BMI: 32.4±5.4; female: 77%<br>• 20 age- and BMI-matched healthy controls: age: 48.6±9.7; BMI: 34.3±7.6; female: 95%<br>• Recruited from non-clinical setting.<br>• Inclusion: between 18 and 70 years old, BMI between 27 and 40, and meet full criteria for BED.<br>• Exclusion: unstable medical conditions, mental disorders warranting immediate treatment, | • Fasting and postprandial CCK<br>• Test meal: 797 kcal standard breakfast (62% carbohydrate, 10% protein, and 28% fat)<br>• −20 min, −5 min, and 15, 30, 45, 60, 90,120, and 180 min after the meal | • BED assessed by Eating Disorder Examination | • Before and short-term after intervention, fasting PYY did not differ between groups<br>• Before intervention, BED participants revealed a higher meal-induced increase and stronger decline thereafter in PYY compared to controls |

| Study characteristics | Sample description | Biomarker | Eating behavior | Conclusion |
|---|---|---|---|---|
| | • pregnancy, participation weight loss treatment<br>• Patients with BED received a 8-week CBT | • Covariates included baseline BMI and sex | | • In the BED group, the fasting and postprandial PYY did not change before and after intervention<br>• PYY was not related to objective binge eating post-intervention |
| Meal-related acyl and des-acyl ghrelin and other appetite-related hormones in people with obesity and binge eating[72]<br>• Hernandez et al<br>• 2019<br>• US<br>• Case-control | • 20 adults with binge eating (10 BED and 10 subthreshold binge eating): age: 37.8±8.4; BMI: 36.2±5.5; female: 60%<br>• 22 adults without binge eating: age: 34.0±8.2; BMI: 36.4±4.9; female: 31.8%<br>• Race in the total group: Black/ African American (61%), Hispanic (19.5%), non-Hispanic White (14.6%), and other (4.8%).<br>• Recruited from non-clinical settings<br>• Exclusion: individuals with other eating disorders | • Fasting and postprandial PYY<br>• Test meal: 1254 KJ liquid meal (55% carbohydrate, 24% protein, 21% fat)<br>• Blood draw: −15, and 0, 10, 30, and 60 minutes after meal<br>• The two groups did not differ in age, BMI, and sex | • Binge eating assessed by Eating Disorder Examination and the Questionnaire on Eating and Weight Patterns | • PYY did not differ between groups |
| Association between eating behavior, anthropometric and biochemical measurements, and peptide YY (PYY) hormone levels in obese adolescents in outpatient care[88]<br>• Fernandes et al.<br>• 2020<br>• Brazil<br>• Longitudinal | • 51 adolescents with obesity receiving outpatient treatment (nutrition and physical activity intervention): age: 12.0±0.9; BMI: 29.6±4.4; female: 56.9%<br>• Recruited from obesity outpatient<br>• Inclusion: at least 10 years old and had a pubertal stage greater than I<br>• Exclusion criteria not specified | • Fasting PYY<br>• Assessment time points: before treatment, and 24 and 48 weeks after treatment<br>• Covariates not specified | • Uncontrolled eating assessed by Three Factor Eating Questionnaire | • PYY was not significantly related to uncontrolled eating at any assessment point |
| **GLP-1** | | | | |
| Appetite-related gut peptides, ghrelin, PYY, and GLP-1 in obese women with and without binge eating disorder (BED)[71]<br>• Geliebter et al.<br>• 2008 | • 10 women with BED: age: 29.9±8.2; BMI: 36.5±6.6; frequency of binge eating days: 3.2±0.8d<br>• 9 women without BED: age: 30.3±8.4; BMI: 35.8±5.5 | • Fasting and postprandial GLP-1<br>• Test meal: 1254 kJ liquid meal<br>• Blood draw: −15, and 0, 5, 15, 30, | • BED assessed by Questionnaire on Eating and Weight Patterns followed by a | • Fasting and postprandial GLP-1 did not differ between groups. |

| Study characteristics | Sample description | Biomarker | Eating behavior | Conclusion |
|---|---|---|---|---|
| • US<br>• Longitudinal | • All women were premenopausal and in otherwise good health<br>• Eight BED and 8 non-BED participants were randomly assigned for 6 weeks to either (a) individual weekly treatment with nutritional counseling and cognitive behavior therapy or (b) a non-treatment control | 60, 90, and 120 min after test meal<br>• Covariates included weight change | clinical interview | |
| Relationships among tonic and episodic aspects of motivation to eat, gut peptides, and weight before and after bariatric surgery[87]<br>• Bryant et al<br>• 2013<br>• UK<br>• Longitudinal | • 12 candidates for bariatric surgery (gastric bypass): age: 36±2; BMI: 45.3±1.9; female: 75%<br>• Exclusion criteria not specified | • Fasting and postprandial GLP-1<br>• Test meal: liquid meal (200 ml, 300 kcal)<br>• Blood draw: −10, and 0, 10, 20, 30, 60, 90, 120, and 180 minutes after consumption<br>• Assessment timepoints: pre-surgery, and 2 months, and 1 year post-surgery<br>• Covariates included BMI | • Uncontrolled eating subscale of the Three Factor Eating Questionnaire | • Fasting and postprandial GLP-1 were not related to uncontrolled eating at before or after surgery |
| Hormonal and dietary characteristics in obese human subjects with and without food addiction[69]<br>• Pedram et al<br>• 2014<br>• Canada<br>• Case-control | • 29 adults with food addiction: age: 42.5±9.6; BMI: 32.5±6; female: 82.7%<br>• 29 non-food-addicted subjects matched for age, sex, BMI and physical activity: age: 42±8.9; BMI: 32±4.4; female: 82.7%<br>• Recruited from non-clinical setting<br>• Inclusion: age >19 years, without serious metabolic, cardiovascular or endocrine diseases, and not pregnant at the time of the study. | • Fasting GLP-1<br>• Covariates not specified | • Food addiction assessed by Yale Food Addiction Scale | • The 2 groups did not differ in terms of GLP-1 |
| Short-term intervention with liraglutide improved eating behavior in obese women with polycystic ovary syndrome[100]<br>• Jensterle et al | • 36 women with polycystic ovary syndrome: age: 31.2±7.8; BMI: 38.7±0.1<br>• Recruited from outpatients Department of Endocrinology | • GLP-1 analog<br>• 12-week liraglutide at a dose of 0.6 mg/day, which increased to 1.2 | • Uncontrolled eating subscale of Three Factor Eating Questionnaire | • After treatment with liraglutide, uncontrolled eating significantly decreased |

| Study characteristics | Sample description | Biomarker | Eating behavior | Conclusion |
|---|---|---|---|---|
| • 2014<br>• Slovenia<br>• Pre-post | • Inclusion: weight stable in the last 6 months, more than 18 years old, premenopausal, BMI >30 kg/m2, had been taking metformin 2000 mg for at least 6 months<br>• Exclusion: type 1 or type 2 diabetes, history of carcinoma, cardiovascular, kidney or liver disease and the use of medications other than metformin known to affect metabolic functions within past 90 days | mg/day after 1 week | | |
| Improvement in binge eating in non-diabetic obese individuals after 3 months of treatment with liraglutide — A pilot study[90]<br>• Robert et al<br>• 2015<br>• Malaysia<br>• RCT | • 42 adults with binge eating were randomly assigned to the liraglutide or control group<br>• 21 adults in the liraglutide group: BMI: 36.1±3.8<br>• 21 in the control group: BMI: 35.7±4.5<br>• Total group: age: 34±9<br>• Exclusion: a history of taking medications that may affect weight and appetite, contraindications to liraglutide, and any chronic illnesses such as diabetes mellitus and cardiovascular diseases | • GLP-1 analog<br>• 12-week liraglutide treatment | • Binge eating assessed by Binge Eating Scale | • Participants who received liraglutide had significant reductions in binge eating at 12 weeks<br>• 81% of those receiving liraglutide had binge eating remission |
| Dulaglutide reduces binge episodes in type 2 diabetic patients withbinge eating disorder: A pilot study[91]<br>• Porto et al<br>• 2020<br>• Italy<br>• RCT | • 60 adults with BED and diabetes were randomly assigned to the liraglutide or gliclazide group<br>• 30 adults in the dulaglutide group: age: 54.2±8.9; BMI: 34.7±5.6; female: 46.7%<br>• 30 adults in the gliclazide group: age: 55.1±6.4; BMI: 34.1±6.7; female: 60%<br>• Recruited from diabetes outpatient clinic<br>• Inclusion: diagnosis of type 2 diabetes being treated only with metformin, with suboptimal metabolic control, age below 65 years, with diagnosis of BED | • GLP-1 analog<br>• 12-week liraglutide treatment | • Binge eating assessed by Binge Eating Scale | • Participants who received liraglutide had significant reductions in binge eating at 12 weeks |

| Study characteristics | Sample description | Biomarker | Eating behavior | Conclusion |
|---|---|---|---|---|
| Meal-related acyl and des-acyl ghrelin and other appetite-related hormones in people with obesity and binge eating[72]<br>• Hernandez et al<br>• 2019<br>• US<br>• Case-control | • 20 adults with binge eating (10 BED and 10 subthreshold binge eating): age: 37.8±8.4; BMI: 36.2±5.5; female: 60%<br>• 22 adults without binge eating: age: 34.0±8.2; BMI: 36.4±4.9; female: 31.8%<br>• Race in the total group: Black/ African American (61%), Hispanic (19.5%), non-Hispanic White (14.6%), and other (4.8%).<br>• Recruited from non-clinical settings<br>• Exclusion: individuals with other eating disorders | • Fasting and postprandial GLP-1<br>• Test meal: 1254 KJ liquid meal (55% carbohydrate, 24% protein, 21% fat)<br>• Blood draw: −15, and 0, 10, 30, and 60 minutes after meal<br>• The two groups did not differ in age, BMI, and sex | • Binge eating assessed by Eating Disorder Examination and the Questionnaire on Eating and Weight Patterns | • GLP-1 did not differ between groups |
| **PP** | | | | |
| Lifestyle intervention discloses an association of the Eating Inventory-51 factors with cardiometabolic health risks[94]<br>• Hainerová et al<br>• 2013<br>• Czech Republic<br>• Longitudinal | • 67 women with obesity: age: 48.7±12.2; BMI: 32.4±4.4<br>• Women participated in a 4-week lifestyle obesity management (e.g., low-calorie diet, physical activity, and cognitive behavioral therapy) | • Fasting PP<br>• Assessment timepoints: before and after a 3-week weight management<br>• Covariates not specified | • Disinhibition subscale of Eating Inventory | • No significant associations between PP and disinhibition at baseline |
| Hormonal and dietary characteristics in obese human subjects with and without food addiction[69]<br>• Pedram et al<br>• 2014<br>• Canada<br>• Case-control | • 29 adults with food addiction: age: 42.5±9.6; BMI: 32.5±6; female: 82.7%<br>• 29 non-food-addicted subjects matched for age, sex, BMI and physical activity: age: 42±8.9; BMI: 32±4.4; female: 82.7%<br>• Recruited from non-clinical setting<br>• Inclusion: age >19 years, without serious metabolic, cardiovascular or endocrine diseases, and not pregnant at the time of the study. | • Fasting ghrelin<br>• Covariates not specified | • Food addiction assessed by Yale Food Addiction Scale | • The 2 groups did not differ in terms of PP |
| **Leptin & Adiponectin** | | | | |

| Study characteristics | Sample description | Biomarker | Eating behavior | Conclusion |
|---|---|---|---|---|
| Relationship between dietary restraint, binge eating, and leptin in obese women[74]<br>• d'Amore et al<br>• 2001<br>• Italy<br>• Case-control | • 8 women with severe binge eating: age: 46.4±5.9; BMI: 35.4±4.5<br>• 11 women with moderate binge eating: age: 46.0±14.5; BMI: 35.0±2.2<br>• 23 women without binge eating: age: 48.4±10.1; BMI: 33.9±2.9<br>• Women were recruited before the beginning of a residential weight-reduction program<br>• None of the subjects was currently dieting or had markedly lost weight during the three months preceding the start of the study.<br>• Exclusion: type 1 diabetes; cancer; anaemia; any cardiac abnormalities; any past and present cerebrovascular, kidney, liver or thyroid disease; any significant psychiatric illness; smoking and use of medications known to affect weight or energy expenditure. | • Leptin<br>• Covariates not specified | • Binge eating measured by Binge Eating Scale | • Leptin was not significantly associated with binge eating<br>• However, severe binge-eaters showed higher leptin levels compared to non-binge-eaters, although the difference did not reach statistical significance. |
| Serum leptin concentration in obese patients with binge eating disorder[75]<br>• Adami et al<br>• 2002<br>• Italy<br>• Case-control | • 30 candidates for bariatric surgery<br>• 14 women with BED: BMI: 46.4±9.9<br>• 16 non-BED women: BMI: 46.5±7.8<br>• All patients had stable weight in the past 6 months, were in completely good health, and did not take any medication known to influence metabolic parameters | • Leptin<br>• Covariates not specified | • BED assessed by Eating Disorder Inventory<br>• Disinhibition assessed by Eating Inventory | • Higher serum leptin concentrations were found in the BED patients<br>• In all patients, there eas a significant positive associations between serum leptin and disinhibition |
| Opposite modifications in circulating leptin and soluble leptin receptor across the eating disorder spectrum[76]<br>• Monteleone et al.<br>• 2002<br>• Italy<br>• Case-control | • 22 women with AN: age: 22.5±6.4; BMI: 15.9±1.5<br>• 45 women with BN-purging: age: 23.9±3.8; BMI: 20.9±1.9<br>• 18 women with BED: age: 29.0±9.8; BMI: 35.9±8.9; binge frequency 2.7±1.1 episodes per day<br>• 12 non-BED women with obesity: age: 37.4±15.4; BMI: 37.0±2.8<br>• 33 healthy women: age: 24.8±4.1; BMI: 21.6±1.8 | • Leptin<br>• Covariates included age | • BED assessed by Structured Clinical Interview for DSM-IV | • Women with BED had enhanced blood concentrations of leptin than non-BED women with obesity, but this difference did not reach statistical significance |

| Study characteristics | Sample description | Biomarker | Eating behavior | Conclusion |
|---|---|---|---|---|
| | • Recruited from outpatient unit at eating disorder center<br>• Exclusion: taking oral contraceptives, had a history of alcohol or drug abuse, present and past psychiatric disorders, endocrine diseases known to cause obesity, psychotropic drugs for more than 6 weeks | | | |
| Gastric capacity, test meal intake, and appetitive hormones inbinge eating disorder[73]<br>• Geliebter et al.<br>• 2004<br>• US<br>• Case-control | • 11 women with BED: age: 29±8; BMI: 36.6±6.2<br>• 13 women with subclinical binge eating: age: 29±7; BMI: 35.8±5.5<br>• 13 non-binge eating women: age: 32±9; BMI: 35.1±5.3<br>• Inclusion: premenopausal, nonsmokers, not taking illegal drugs or medications affecting weight, and weight stable within past 3 months. | • Leptin<br>• Covariates not specified | • Binge eating assessed by Questionnaire on Eating and Weight Patterns and clinical interview | • Leptin did not differ between groups (statistical data not provided) |
| Leptin/adiponectin ratio in obese women with and without binge eating disorder[67]<br>• Brandão et al<br>• 2010<br>• Brazil<br>• Case-control | • 8 women with BED: age: 42.1±6.3; BMI: 32.3±2.1<br>• 7 non-BED women with obesity: age: 38.3±5.5; BMI: 34.9±3.9<br>• 8 normal weight women without BED: age: 44.9±6.6; BMI: 23.6±1.0<br>• Recruited from Piquet Carneiro Policlinic<br>• Women were not taking any medications and had no evidence of disease other than obesity and BED<br>• Exclusion: a diagnosis of hypothyroidism, hyperthyroidism, diabetes, hypertension, and polycystic ovary syndrome, pregnant, breastfeeding or menopausal | • Leptin and adiponectin<br>• Covariates not specified | • Binge eating assessed by Binge Eating Scale | • Women with BED had a lower leptin concentration than non-BED women with obeisty<br>• Adiponectin was lower in women with BED compared to the obese non-BED group |
| Cardiovascular stress reactivity and recovery in bulimia nervosa and binge eating disorder[77]<br>• Messerli-Bürgy et al | • 12 women with BN: age: 24.4±5.7; BMI: 23.1±5.6<br>• 13 women with BED: age: 33.9±7.0; BMI: 37.9±6.4 | • Leptin<br>• Covariates not specified | • Binge eating assessed by Eating Disorder Inventory | • Leptin levels were lower in the BED group than non-BED group, but its statistical significance is unclear |

| Study characteristics | Sample description | Biomarker | Eating behavior | Conclusion |
|---|---|---|---|---|
| • 2010<br>• UK<br>• Case-control | • 13 non-BED women: age: 41.1±8.9; BMI: 35.9±5.0<br>• Recruited from the psychiatric outpatient clinic<br>• Participants should have stabilized electrolyte conditions, unchanged weight levels during the past 10 to 12 weeks<br>• Exclusion: medical hist<br>• ry of cardiovascular disease, metabolic disease, other disease or medication that could influence autonomic functioning | | | |
| Lifestyle intervention discloses an association of the Eating Inventory-51 factors with cardiometabolic health risks[94]<br>• Hainerová et al<br>• 2013<br>• Czech Republic<br>• Longitudinal | • 67 women with obesity: age: 48.7±12.2; BMI: 32.4±4.4<br>• Women participated in a 4-week lifestyle obesity management (e.g., low-calorie diet, physical activity, and cognitive behavioral therapy) | • Leptin and adiponectin<br>• Assessment timepoints: before and after a 3-week weight management<br>• Covariates not specified | • Disinhibition subscale of Eating Inventory | • Leptin was not associated with disinhibition at before and after intervention<br>• Adiponectin was negative related to disinhibition after weight loss |
| Relationships among tonic and episodic aspects of motivation to eat, gut peptides, and weight before and after bariatric surgery[87]<br>• Bryant et al<br>• 2013<br>• UK<br>• Longitudinal | • 12 candidates for bariatric surgery (RYGB): age: 36±2; BMI: 45.3±1.9; female: 75%<br>• Exclusion criteria not specified | • Leptin<br>• Assessment timepoints: pre-surgery, and 2 months, and 1 year post-surgery<br>• Covariates included BMI | • Uncontrolled eating subscale of the Three Factor Eating Questionnaire | • Before surgery, there was a marginal, positive, association between leptin and uncontrolled eating |
| Hormonal and dietary characteristics in obese human subjects with and without food addiction[69]<br>• Pedram et al<br>• 2014<br>• Canada | • 29 adults with food addiction: age: 42.5±9.6; BMI: 32.5±6; female: 82.7%<br>• 29 non-food-addicted subjects matched for age, sex, BMI and physical activity: age: 42±8.9; BMI: 32±4.4; female: 82.7%<br>• Recruited from non-clinical setting | • Leptin and adiponectin<br>• Covariates not specified | • Food addiction assessed by Yale Food Addiction Scale | • The 2 groups did not differ in terms adiponectin<br>• Leptin was higher in the food addiction group, but not statistically significant |

| Study characteristics | Sample description | Biomarker | Eating behavior | Conclusion |
|---|---|---|---|---|
| • Case-control | • Inclusion: age >19 years, without serious metabolic, cardiovascular or endocrine diseases, and not pregnant at the time of the study. | | | |
| Serum leptin and loss of control eating in children andadolescents[78]<br>• Miller et al<br>• 2014<br>• US<br>• Case-control | • 196 children and adolescents with LOC eating: age: 14.1±2.5; BMI: 29.1±8.9; female: 82.0%<br>• 311 children and adolescents without LOC eating: age: 13.6±2.5; BMI: 29.8±11.9; female: 58.0%<br>• Participants were either treatment-seeking or non-treatment seeking<br>• Exclusion: major medical issues, major psychiatric conditions, pregnancy, medications known to affect weight, had lost more than 5% of their body weight in the 3 months prior to assessment, were currently involved in weight loss treatment programs | • Leptin<br>• Covariates included age, race, sex, socioeconomic, fat mass (kg), height (cm), dietary restraint, treatment-seeking status, and pubertal status | • LOC eating assessed by Eating Disorder Examination: LOC eating was defined by the presence of one or more objective binge episodes and/or subjective binge episodes in the previous month. | • Those reporting at least one episode of LOC in the past month had significantly higher leptin compared to those reporting no LOC episodes<br>• This relationship was partially mediated by increased dietary restraint |
| The association of serum leptin levels with food addiction is moderated by weight status in adolescent psychiatric inpatients[89]<br>• Peters et al<br>• 2018<br>• Germany<br>• Case-control | • 45 adolescents of underweight<br>• 39 adolescents with overweight<br>• 121 adolescents of normal weight<br>• Total group: age: 16.1±1.1; BMI: 22.9±6.2; female: 60.5%<br>• All of the participants had psychiatric disorders, including mood disorder, substance abuse.<br>• Recruited from inpatient units for adolescents<br>• Exclusion: intake of any psychopharmacological drug, any known endocrinological disorder, and intellectual disability | • Leptin<br>• Covariates included sex, body fat percentage | • Food addiction assessed by Yale Food Addiction Scale | • In adolescents with overweight, there was a positive association between leptin and food addiction |
| Comparison of endocannabinoids levels, FAAH gene polymorphisms, and appetite regulatory substances in women with and without binge eating disorder: a cross-sectional study[101]<br>• Yagin et al | • 180 premenopausal women: age: 34.2±8.3; BMI: 32.5±3.7; 41.6% of the subjects were diagnosed with BED<br>• Exclusion: chronic or metabolic disorders history, pregnancy or lactating, any appetite-affecting | • Leptin<br>• Covariates included BMI | • Binge eating assessed by Binge Eating Scale | • Women with BED exhibited significantly higher levels of leptin compared to non-BED women<br>• Higher leptin was associated with |

| Study characteristics | Sample description | Biomarker | Eating behavior | Conclusion |
|---|---|---|---|---|
| • 2020<br>• Iran<br>• Cross-sectional | medicine usage, and significant weight loss over the last 3 months<br>• Participants were recruited from non-clinical settings | | | higher odds of BED, adjusting for BMI |
| Altered regional grey matter volume and appetite-related hormone levels in adolescent obesity with or without binge-eating disorder[79]<br>• Turan et al<br>• Turkey<br>• 2021<br>• Case-control | • 25 adolescents with BED: age: 15.0±1.8; BMI-Z score: 2.9±0.4; female: 68%<br>• 25 non-BED adolescents: age: 14.6±1.7; BMI-Z score: 2.9±0.4; female: 68%<br>• 27 population-based healthy controls (matched with age, gender, and education): age: 14.6±1.4; BMI-Z score: −0.3±0.9; female: 70.4%<br>• Recruited from outpatient unit at the Department of Pediatrics and Department of Pediatric Endocrinology and Metabolism<br>• Exclusion criteria: history of psychiatric illness, intellectual disability, psychotic symptoms, drug/alcohol abuse, bipolar disorder, neurological disorders, claustrophobia, ADHD, left-handedness, a history of AN or BN, and antipsychotic medication | • Fasting leptin | • BED assessed by Eating Disorder Examination Questionnaire | • Leptin was higher in the BED group than the non-BED group, but the difference was not statistically significant. |
| **Inflammatory markers** | | | | |
| Lifestyle intervention discloses an association of the Eating Inventory-51 factors with cardiometabolic health risks[94]<br>• Hainerová et al<br>• 2013<br>• Czech Republic<br>• Longitudinal | • 67 women with obesity: age: 48.7±12.2; BMI: 32.4±4.4<br>• Women participated in a 4-week lifestyle obesity management (e.g., low-calorie diet, physical activity, and cognitive behavioral therapy) | • CRP<br>• Assessment timepoints: before and after a 3-week weight management<br>• Covariates not specified | • Disinhibition subscale of Eating Inventory | • No significant associations between CRP and disinhibition at baseline |
| Hormonal and dietary characteristics in obese human subjects with and without food addiction[69]<br>• Pedram et al | • 29 adults with food addiction: age: 42.5±9.6; BMI: 32.5±6; female: 82.7%<br>• 29 non-food-addicted subjects matched for age, sex, BMI and | • TNF-α<br>• Covariates not specified | • Food addiction assessed by Yale Food Addiction Scale | • The food addiction group had a significantly lower level of TNF-α as compared to the non-food addiction group |

| Study characteristics | Sample description | Biomarker | Eating behavior | Conclusion |
|---|---|---|---|---|
| • 2014<br>• Canada<br>• Case-control | physical activity: age: 42±8.9; BMI: 32±4.4; female: 82.7%<br>• Recruited from non-clinical settings<br>• Inclusion: age >19 years, without serious metabolic, cardiovascular or endocrine diseases, and not pregnant at the time of the study. | | | |
| Obese patients with a binge eating disorder have an unfavorable metabolic and inflammatory profile[82]<br>• Succurro et al<br>• 2015<br>• Italy<br>• Case-control | • 30 adults with BED: age: 36.8±12.7; BMI: 43.7±6.8; female: 73.3%<br>• 85 non-BED adults: age: 41.8±12.8; BMI: 37.2±6.2; female: 62.3%<br>• Patients were seeking weight reduction therapy<br>• Inclusion: aged between 20 and 65 years, BMI >30 kg/m2<br>• Exclusion: pregnancy or having recently given birth, previous diagnosis of diabetes mellitus, known inflammatory disease, a history of malignant disease or pathologies, or drugs able to modify glucose metabolism | • hsCRP, erythrocyte sedimentation rate,<br>• Covariates included age, sex, and BMI | • BED assessed by Binge Eating Scale and Clinical Interview | • BED-obese group had significantly higher ESR and hsCRP |
| Pediatric loss of control eating and high-sensitivity C-Reactive Protein concentrations[83]<br>• Shank et al<br>• 2017<br>• US<br>• Case-control | • 75 children and adolescents with LOC eating: age: 13.5±2.3; BMI-z score: 1.9±0.8; female: 73.3%; race (non-Hispanic white: 37.3%, non-Hispanic black: 42.7%, Hispanic: 8%)<br>• 119 without LOC eating: age: 14.7±1.8; BMI-z score: 1.5±1.2; female: 58%; race (non-Hispanic white: 39.5%, non-Hispanic black: 48.7%, Hispanic: 2.5%)<br>• Inclusion: children or adolescents with overweight or obesity<br>• Exclusion: pregnancy, major medical or psychiatric illnesses, and use of medication known to affect weight or eating behavior | • hsCRP<br>• Covariates: sex, fat mass (kg), height (cm) | • LOC eating assessed by the child version of Eating Disorder Examination: LOC eating was deemed present if participants endorsed at least one episode of LOC eating in the past 28 days | • Presence of LOC eating was significantly associated with hsCRP concentration<br>• The number of LOC eating episodes was significantly associated with hsCRP concentration<br>• These associations were not mediated by depressive symptoms or eating-related psychopathology |
| Brain-behavior-immune interaction: serum cytokines and growth factors in patients with eating disorders at extremes of | • 14 adults with AN: age: 25.1±11.6; BMI: 16.6±1.1 | • Pro- and anti-inflammatory cytokines (IL-1α, | • BED assessed by Eating | • IL-1α was not significant different between BED and obesity group |

| Study characteristics | Sample description | Biomarker | Eating behavior | Conclusion |
|---|---|---|---|---|
| the body mass index (BMI) Spectrum[80]<br>• Caroleo et al<br>• 2019<br>• Italy<br>• Case-control | • 27 adults with BED: age: 41.0±11.8; BMI: 38.4±7.9<br>• 28 adults with obesity: age: 41.9±11.4; BMI: 42.2±10.5<br>• 21 healthy controls: age: 31.8±12.3; BMI: 21.3±2.7<br>• Total sample: female (69%)<br>• Outpatients seeking treatment for eating disorder<br>• Exclusion: aged under 18 or over 65 years, patients with BN; normal-weight persons with any psychiatric comorbidity; diabetes mellitus, neurological or other medical conditions; hormonal and pharmacological treatment; smokers; pregnancy or childbirth over the previous 12 months | IL-1β, IL-6, IL-10, TNF-α)<br>• Controlling for depressive symptoms, sex, and age | Disorder Examination | • IL-10 in the BED group was higher than obesity group (statistical difference unknown)<br>• There were no significant differences in IL-1β, IL-6, IL-8, TNF-α between BED and obesity group. |