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A biopsychosocial perspective on obesity and eating disorders: A narrative overview and exploratory study of ghrelin, LEAP2, trait impulsivity, and eating psychopathology

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Abstract
Dysregulated eating in obesity and eating disorders (ED) is associated with complex relationships between peripheral hormonal signals and neurobehavioral characteristics. Ghrelin and its endogenous antagonist liver-expressed antimicrobial peptide–2 (LEAP2) have been implicated in the regulation of energy homeostasis and food intake, while trait impulsivity has been proposed as a transdiagnostic characteristic associated with dysregulated eating. This study aimed to integrate narrative evidence with exploratory empirical data to examine associations between ghrelin, LEAP2, and trait impulsivity in women with obesity, with and without ED, and to explore their associations with food addiction (FA) and eating psychopathology. A total of 164 adult women (67 with obesity, 35 with obesity + ED, 62 healthy controls) completed anthropometric assessments, fasting ghrelin and LEAP2 determinations, and psychometric measures of trait impulsivity, FA, and eating psychopathology. Group comparisons and exploratory structural equation modeling (SEM) were used to explore associations between endocrine and behavioral variables. Women with obesity (with or without ED) showed significantly lower ghrelin levels than controls, while LEAP2 concentrations did not differ between groups. Trait impulsivity and FA scores were higher in the obesity + ED group. Within this subgroup, SEM analyses identified positive associations of trait impulsivity and FA with eating psychopathology, while LEAP2 was positively associated with trait impulsivity and FA scores. Previous research has pointed to potential associations of ghrelin and LEAP2 with obesity and ED, as well as with behavioral characteristics related to dysregulated eating, although the available evidence remains limited and heterogeneous. In our study, ghrelin was lower in women with obesity, whereas LEAP2 did not differ between groups. The observed associations involving LEAP2 emerged only in the exploratory SEM analysis and should therefore be interpreted cautiously. These findings are hypothesis-generating and do not provide evidence of mechanistic or causal relationships. Further research in larger and longitudinal samples is needed to replicate these findings and clarify the relationships among endocrine and behavioral factors.

Keywords Obesity · Eating disorder · Ghrelin · LEAP2 · Impulsivity · Food addiction

1 Introduction

Energy homeostasis is a fundamental physiological process for survival that depends on the coordinated regulation of caloric intake and energy expenditure. Traditionally, food intake has been conceptualized as the result of complex feedback mechanisms integrating short–term hunger–satiety signals with longer–term regulation of energy stores through communication between peripheral organs and the central nervous system [1]. However, eating behavior is increasingly recognized as a multidimensional process in which metabolic regulation interacts with reward processing, stress responsivity, emotional regulation, and executive control. Neural systems involved in feeding substantially overlap with circuits supporting cognitive, affective, and motivational processes, highlighting the integration of biological and psychological factors in the regulation of eating behavior [2].

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Within the central nervous system, hypothalamic and hindbrain networks integrate peripheral metabolic signals to support homeostatic feeding according to physiological needs [3], while mesocorticolimbic circuits contribute to the motivational and hedonic aspects of eating [4]. In addition, environmental, social, emotional, and cognitive factors can influence food intake and promote non-homeostatic eating behaviors that may override physiological needs [2]. Accordingly, dysregulated eating and metabolic disorders are best understood within a broader biopsychosocial framework, in which biological signals interact with psychological traits, behavioral processes, and contextual factors [5–7].

Within this multidimensional framework, peripheral hormones involved in the regulation of energy balance and feeding have received increasing attention. Among these, ghrelin and liver–expressed antimicrobial peptide–2 (LEAP2) are physiological regulators of the ghrelin signaling system and may be relevant to the regulation of food intake and energy homeostasis [8–12]. Their potential relevance to dysregulated eating has been investigated in obesity and ED, although the available evidence remains heterogeneous.

Therefore, the present work first provides a narrative overview of the current evidence on these hormonal signals, particularly ghrelin and LEAP2, in obesity and ED, with a particular focus on their associations with trait impulsivity, a transdiagnostic factor implicated in dysregulated eating across both conditions. In addition, this study also incorporates a preliminary empirical analysis within a clinical sample of women with obesity, with and without ED.

1.1 Ghrelin and LEAP2

Ghrelin, primarily produced in the stomach, but also to a much lesser extent in a range of peripheral tissues including the intestine, pancreas, liver, heart and lungs [13], is synthesized as a pre-prohormone [14] and circulates in two mature forms: the acylated form (AG) (~ 20% of circulating ghrelin, the active form), which is commonly referred to as "ghrelin" [15]; and the deacylated form (DAG), which is the predominant form of ghrelin in the bloodstream (around 80%) [16] and was initially considered inactive. Ghrelin O–acyltransferase (GOAT) converts DAG to AG, whereas proteases degrade it. AG exerts its effects through the growth hormone secretagogue receptor (GHSR), a G-protein-coupled receptor widely expressed at both central and peripheral levels [17, 18]. In vitro, GHSR is capable of forming heterodimers with other receptors involved in energy homeostasis, such as dopaminergic, melanocortin, and serotonergic receptors expressed by hypothalamic or striatal neurons [19–22]. Interestingly, while pharmacological activation of dopaminergic receptor DRD2 induces a decrease in food intake, this effect is not recapitulated in animals after pharmacological or genetic inactivation of GHSR suggesting that the heterodimerization of GHSR/DRD2 is implicated in the modulation of food intake [22].

Another key component of the system is LEAP2, which has emerged as a major endogenous regulator of the GHSR [23]. Although early studies characterized LEAP2 as a non–competitive antagonist of GHSR, more recent mechanistic work has clarified that this is not the case and LEAP2 is now recognized to function as both a competitive antagonist and a natural inverse agonist of the receptor, inhibiting its constitutive activity and ability to form heterodimers with dopaminergic receptors [23–27].

1.2 Ghrelin and LEAP2 in food intake and energy homeostasis

Ghrelin is a well-characterized peripheral orexigenic signal that promotes food intake, and has been described as an "initiator of feeding" [28].

It accesses the brain mainly across the blood–brain barrier [29]. In the hypothalamic homeostatic circuit, ghrelin agonists activate an orexigenic circuit that includes neuropeptide Y (NPY) neurons [30] that co–express agouti–related peptide (AgRP), while inhibiting anorexigenic proopiomelanocortin (POMC) neurons [31]. Ghrelin has also been implicated in the regulation of the mesolimbic reward system [32, 33], including processes related to motivation for seeking food [34–37] and food reward [38, 39]. Consistent with a role in energy homeostasis, the brain ghrelin signaling system has also been implicated in additional roles that include inhibiting thermogenesis, reducing global energy expenditure, promoting body weight gain and fat deposition [13, 40]. Its involvement in the release of neuroendocrine substrates—particularly growth hormone (GH)—as well as in the functioning of hypothalamic–pituitary–peripheral axes and glucose metabolism, further contributes to the regulation of feeding and body weight [13].

Interestingly, the central distribution of GHSR in the midbrain has led to investigations of the potential involvement of the ghrelin system in a variety of central processes closely related to feeding, including learning and memory, impulsivity, and emotional and stress regulation [41–44]. In line with this, ghrelin has been shown to increase impulsive choice [45] and to condition avoidance [46]. Ghrelin has been described as potentially exerting an anxiolytic role under acute stress, but an anxiogenic effect in non-stressful situations or during chronic stress exposure [47]. This function may be associated with enhanced aversive memory, again linked to a survival mechanism [5, 48], and could be related to stress-mediated reward processing [37] and emotional eating [49].

Studies involving LEAP2 injection suggest that it may modulate ghrelin's effects on food intake, GH secretion [23] and postprandial glucose dynamics [50]. Although the functional roles of LEAP2 are less well characterized than those of ghrelin, available evidence support the notion that it may contribute to energy homeostasis through feeding and weight regulation [51]. Moreover, central injection of LEAP2 has been reported to reduce hedonic feeding and blunt dopaminergic release in reward-associated regions in experimental models, raising the possibility that LEAP2 may also be involved in reward-related processes [27, 52].

Given its role in energy balance, feeding behavior, and glucose regulation, the ghrelin system has been suggested to be potentially involved in the pathophysiology of eating disorders (ED) and metabolic diseases [51].

1.3 Ghrelin and LEAP2 in eating disorders and obesity

Under physiological conditions, ghrelin and LEAP2 exhibit complementary but opposing fluctuations in response to feeding status. Plasma ghrelin levels rise during fasting, peak before meals, and are closely associated with subjective hunger. Following food intake, ghrelin levels decline sharply, reflecting its well–established role in meal initiation and energy mobilization [28, 53, 54]. Although earlier literature suggested that LEAP2 remained relatively stable across feeding states, more recent human and preclinical studies demonstrate that LEAP2 is nutritionally sensitive, rising after meals and during states of positive energy balance such as obesity [11, 50, 55–58]. These complementary patterns have led to the hypothesis that ghrelin is involved in meal initiation and signaling energy deficit, whereas LEAP2 may contribute to postprandial regulation of ghrelin signaling and energy balance [12, 58].

Alterations in ghrelin and LEAP2 levels across ED and obesity [10, 11, 59, 60] have raised the possibility of a potential link between peripheral hormonal signaling and behavioral and psychological factors associated with dysfunctional eating patterns and weight disturbances [61]. Alterations in ghrelin dynamics—such as impaired postprandial suppression, reduced fasting concentrations, or altered receptor sensitivity—have been reported across ED and obesity, while alterations in LEAP2 levels have also been investigated in relation to appetite regulation and reward-based eating. Accordingly, this section first outlines biological vulnerabilities associated with ED and obesity and then synthesizes the heterogeneous evidence regarding ghrelin and LEAP2 alterations across ED and obesogenic states. A conceptual overview of the metabolic and nutritional modulators of both hormones—including fasting, feeding, macronutrient composition, body weight status, and energy availability—is presented in Fig. 1.

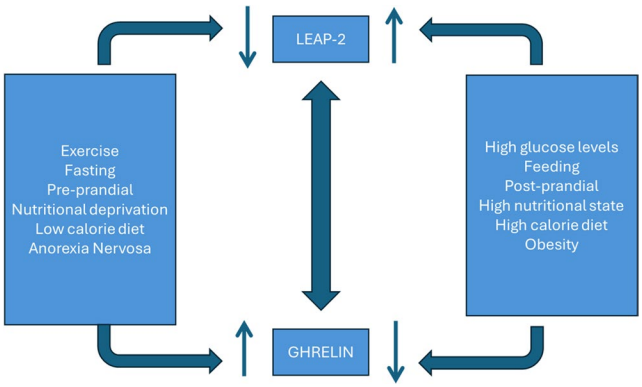


Fig. 1 Conceptual synthesis of metabolic, nutritional, and clinical modulators of the ghrelin–LEAP2 axis. Conceptual diagram illustrating how metabolic, nutritional, and behavioral conditions modulate ghrelin and LEAP2 in restrictive eating (left) versus obesogenic states (right). Situations involving energy deficit (fasting, exercise, pre–prandial state, low–calorie intake, and anorexia nervosa) are associated with increased ghrelin and decreased LEAP2. Conversely, high glucose availability, feeding, post–prandial state, high–calorie intake, and obesity are associated with elevated LEAP2 and reduced ghrelin. Central opposing arrows represent the antagonistic dynamics within the ghrelin–LEAP2 axis

1.3.1 Biological vulnerabilities in eating disorders and obesity

From a dimensional perspective, bulimia nervosa (BN) and binge eating disorder (BED) are increasingly conceptualized as part of a broader spectrum of binge–spectrum disorders (BSD), characterized by recurrent binge episodes and shared clinical features, personality traits, neuropsychological profiles, and comorbidities, most notably obesity [62–65]. Although obesity is not classified as a mental disorder or an ED [66], both conditions represent clinically significant states marked by maladaptive eating behaviors, altered adiposity, metabolic dysregulation, and disrupted nutritional patterns, which compromise health and are further amplified when they co–occur [67, 68]. Unlike anorexia nervosa (AN), an ED characterized by underweight, a substantial proportion of individuals with BN and BED exhibit overweight or obesity across the illness course [68–70], with binge episodes themselves constituting a potential vulnerability factor for excessive weight gain [68, 69, 71]. Prevalence estimates of obesity within BSD vary widely—from 30% to 90%—and are especially elevated among individuals with BED [71]. Obesity has also been identified as a risk factor for the subsequent development of an ED, with BED being the most frequent diagnosis among individuals with obesity, followed by BN [72, 73]. Collectively, these bidirectional

associations may reflect shared vulnerability mechanisms, including biological and neurobehavioral factors related to appetite dysregulation, potentially involving alterations in the reward system [74], cognitive control [75–77], and emotion regulation [67, 78–80], as well as psychological factors such as body image concern [67–70].

From a neurobiological perspective, animal models have been instrumental in identifying neurotransmitter and neuroendocrine systems underlying phenotypic traits characteristic of these conditions, providing a foundation for clinical research on biological targets in disorders associated with dysregulated eating and weight states [81–88]. Among these mechanisms, alterations of neurochemical and hormonal systems involved in reward processing—particularly within mesocorticolimbic dopaminergic pathways—have been increasingly examined in relation to food consumption, revealing notable parallels with addictive disorders [89–91]. These neurobiological convergences have informed the development of the food addiction framework, which proposes that, in a subset of individuals, maladaptive eating behaviors may share behavioral and neural features with addictive disorders, including heightened reward responsivity and persistent consumption despite negative consequences [92]. In clinical contexts, this framework has been primarily explored within ED and obesity [93, 94], where addictive–like eating patterns have been associated with greater symptom severity and poorer outcomes [95–98]. However, the food addiction framework remains debated, and its boundaries with BED and BN are not always clearly defined.

Beyond central neurobiological mechanisms, peripheral signals involved in brain–periphery communication, particularly through the gut–brain axis, may also play a role in disordered eating and weight regulation, providing a rationale for examining hormonal signals such as ghrelin and LEAP2 in ED and obesity [61, 91].

1.3.2 Ghrelin and LEAP2 levels in eating disorders and obesity

Studies examining ghrelin concentrations in individuals with obesity and patients diagnosed with ED have yielded mixed results.

Both low [99, 100] and high [101] ghrelin levels have been observed in clinical and preclinical studies of obesity. Despite these differences, ghrelin responsiveness appears to be largely preserved [101], although some metabolic effects may be attenuated, potentially reflecting a state of ghrelin resistance [58, 102]. In contrast, circulating ghrelin levels generally increase following weight loss [103–106].

Building on a comprehensive review conducted by our group a few years ago [7], ghrelin has been increasingly investigated as a potential peripheral signal involved in the pathophysiology of binge eating [107]. Based on the findings of that review, it was hypothesized that, in BSD, orexigenic factors might fail to decline postprandially, potentially sustaining binge episodes. However, the high prevalence of comorbid obesity makes it difficult to determine whether these alterations are specifically related to binge eating [7, 108–110]. Lower fasting ghrelin concentrations have also been reported in individuals with obesity, irrespective of BED comorbidity and compared with healthy controls [111], and have been hypothesized to represent an adaptive response to sustained positive energy balance [112]. Conversely, some studies have found no significant differences between groups in either fasting or postprandial ghrelin concentrations [113, 114].

In BED, some studies have specifically examined the ghrelin isoforms. Research in individuals with overweight and obesity has suggested that those with BED exhibited lower total ghrelin, and particularly lower AG during fasting, together with a smaller postprandial AG decrease, compared with non–BED groups [108, 115–117]. Notably, Hernández et al. [108] proposed a dual role for AG in BED, with lower fasting concentrations potentially reflecting a compensatory response to positive energy balance, whereas a blunted postprandial decline may contribute to the persistence of food intake. Conversely, DAG concentrations appear largely unchanged between BED and non–BED groups with obesity, suggesting that this isoform may be more closely associated with obesity itself than with binge eating [108, 118]. Nevertheless, findings remain inconsistent, particularly regarding total ghrelin concentrations, changes following interventions, and results from animal models of binge eating [115, 117, 119, 120].

In BN, evidence regarding ghrelin is more limited, particularly regarding concentrations beyond the fasting state. A previous review identified studies reporting higher ghrelin levels in patients with purging BN, similar to those observed in AN with or without purging behavior, irrespective of nutritional and weight status. This observation was in contrast to findings in individuals with non–purging BN, who had lower ghrelin concentrations [12]. In other studies, ghrelin levels were lower in patients with BN than AN [112, 113] or did not differ from healthy controls [121].

Beyond ghrelin, LEAP2 has also been investigated in relation to obesity and energy balance, although the available evidence remains scarce. Higher fasting LEAP2 levels have been observed in mice and adult humans with obesity [58]. In mice, LEAP2 levels were also increased following a high–fat diet, while experimental LEAP2 administration was associated with reduced body weight and adiposity and increased energy expenditure [122]. In adult humans, plasma LEAP2 levels have been reported to correlate

positively with body mass index (BMI), whereas decreased LEAP2 levels have been described in the context of weight loss [58]. In contrast, lower LEAP2 levels have been reported in children and adolescents with obesity compared with healthy controls [123]. These age–related differences raise the possibility that the relationship between LEAP2 and body weight may depend on developmental and metabolic context [25].

Evidence linking LEAP2 to BED or BN is very limited. For example, Cornejo et al. [120] reported no differences in plasma LEAP2 levels in mice exposed to a binge protocol. Thus, although LEAP2 is physiologically relevant to ghrelin signaling and energy balance, its clinical relevance to binge–spectrum eating pathology remains insufficiently characterized.

Overall, ghrelin and LEAP2 signaling appears to be context–dependent, influenced by nutritional status, circadian rhythm, interactions with other endocrine signals, BMI, age, and dietary patterns [24, 124]. Sex– and life–stage–related differences in ghrelin and LEAP2 concentrations have also been described and may represent additional sources of variability [12, 125, 126]. These factors should therefore be considered when interpreting circulating hormone concentrations, particularly in clinical populations characterized by substantial heterogeneity in body weight and nutritional status. Such variability may contribute to inconsistent findings across studies and underscores the importance of considering hormonal concentrations in relation to clinically relevant behavioral characteristics.

1.4 Impulsivity as a transdiagnostic trait in dysregulated eating

Impulsivity has emerged as a relevant transdiagnostic trait associated with dysregulated eating behaviors across obesity and ED [80, 127–130]. Broadly defined as a tendency to engage in rapid or poorly planned actions without adequate consideration of potential negative consequences, impulsivity encompasses both stable personality dispositions and cognitive control processes [131]. Within the context of eating behavior, impulsivity may be expressed through responses to internal states such as hunger or emotional distress, as well as to external cues associated with highly palatable foods [132, 133].

Current models conceptualize impulsivity as a multidimensional construct comprising different domains [131]. One dimension, *choice impulsivity*, reflects a preference for immediate over delayed rewards [134]. In eating–related contexts, this tendency may manifest as the selection of highly palatable foods despite anticipated long–term consequences such as weight gain or psychological distress [135–137]. A second domain, *response impulsivity*, is characterized by difficulty inhibiting prepotent actions or automatic responses [134]. In eating-related contexts, alterations in this domain may be reflected in difficulty inhibiting food intake despite satiety or internal cues signaling excess [136, 138]. Neurocognitive tasks assessing these aspects of impulsivity have identified alterations in individuals with ED and obesity, including difficulties in delaying gratification and inhibiting automatic responses [67, 78, 80, 130].

In addition to these cognitive components, impulsive personality traits capture stable dispositional tendencies toward behavioral disinhibition, novelty seeking. and emotionally driven action [131]. Trait impulsivity is frequently assessed using multidimensional self–report instruments, such as the *Impulsive Behavior Scale* (UPPS–P), which distinguishes facets including negative and positive urgency, lack of perseverance, lack of premeditation, and sensation seeking [139].

Empirical evidence indicates elevated trait impulsivity in individuals with BED, BN, and obesity [80, 132, 140, 141]. In particular, higher levels of negative and positive urgency—the tendency to act impulsively during intense emotional states—have been associated with binge eating episodes, while reduced premeditation and perseverance may be associated with greater difficulty maintaining dietary goals. Similarly, sensation seeking has been linked to a greater preference for highly palatable or energy–dense foods [136, 142]. Across ED, these patterns appear particularly pronounced in BSD, where impulsive traits are more pronounced than in restrictive conditions such as AN [130, 132].

The role of impulsivity has also been examined within the food addiction framework, in which addictive–like eating patterns have been associated with higher impulsivity, greater BMI, and increased clinical severity [143, 144], with a higher prevalence of addictive–like eating patterns across BSD than in other ED [145]. Importantly, impulsivity is not specific to eating pathology but represents a broader transdiagnostic factor observed across several psychiatric conditions [146–148], including gambling disorder, attention–deficit/hyperactivity disorder, conduct disorder, and substance use disorders [147–150]. This transdiagnostic perspective supports examining impulsivity alongside metabolic signals that have been implicated in appetite and eating behavior [154–156].

Overall, impulsivity represents a clinically relevant multidimensional construct that is associated with dysregulated eating across ED and obesity. Given the involvement of peripheral metabolic signals in appetite regulation, examining the association between impulsivity and circulating hormones such as ghrelin and LEAP2 may help clarify whether these biological measures are related to clinically relevant behavioral characteristics in individuals with BSD and obesity.

1.5 Ghrelin and LEAP2 in relation to impulsivity

Previous research has linked ghrelin signaling to impulsivity and behavioral processes related to reward and decision–making [12, 45, 151, 152]. Circulating ghrelin levels have been associated with measures of impulsivity [56] in both animal models [45] and humans [153]. In humans, higher fasting ghrelin levels have been associated with behavioral processes related to impulsive behavior (e.g., greater responsiveness to reward, reduced sensitivity to punishment, and lower self-control) [153].

However, experimental evidence in healthy humans indicates that acute ghrelin administration does not uniformly enhance reward–related processing [154]. Instead, it modulates decision-making by reducing loss aversion and temporal discounting (i.e., less impulsive choice), potentially shifting motivational priorities toward specific types of rewards [154]. These findings suggest that the effects of ghrelin may vary according to the specific behavioral domain and experimental context [12].

Moreover, behavioral effects of ghrelin on impulsivity may depend on metabolic state and clinical context. In line with this, a delay discounting paradigm in patients with AN in the underweight state (but not in recovered individuals) showed an association between elevated DAG levels and lower discounting, indicating reduced impulsivity [155]. These findings suggest that the association between ghrelin and impulsivity may vary according to nutritional and weight status, although they do not establish a causal relationship.

While ghrelin has been linked to motivation for food rewards, LEAP2 has been proposed as a physiological regulator of ghrelin signaling, but its relationship with impulsivity remains largely underexplored. Initial evidence suggests a potential involvement of LEAP2 in cognitive and behavioral control. Voigt et al. [156] reported an association between plasma LEAP2 levels and attentional control, where higher fasting LEAP2 levels were linked to faster reaction times, suggesting a possible relationship with attentional control rather than directly indicating impulsive responding. However, the associations between LEAP2 levels, attention, and responses to food cues may depend on nutritional status, particularly body weight [157]. A recent study in patients with AN found that the ghrelin/LEAP2 ratio was negatively correlated with impulse control, while in mice, cognitive impulsivity was also positively correlated with plasma LEAP2 levels [158]. Taken together, these findings suggest that not only ghrelin but also LEAP2 may be relevant to impulsivity-related processes. However, the direction and clinical relevance of these associations remain unclear.

Overall, the available evidence suggests that ghrelin and LEAP2 may be associated with behavioral dimensions relevant to dysregulated eating such as impulsivity, although findings remain limited and heterogeneous. Differences in nutritional status, body weight, diagnostic characteristics, and the specific dimension of impulsivity assessed may contribute to the variability across studies. Moreover, evidence linking these hormonal signals to trait impulsivity, particularly in clinical populations, remains insufficiently characterized. Therefore, examining circulating ghrelin and LEAP2 concentrations in relation to trait measures of impulsivity may help clarify whether these hormonal measures are associated with clinically relevant behavioral characteristics across diagnostic categories.

1.6 Bridging hormones and behavior: empirical analysis

Given the limited evidence on the specific associations between ghrelin, LEAP2, trait impulsivity, and eating psychopathology in ED and obesity, the present study aims to cross–sectionally explore these relationships in a clinical sample. We hypothesize that women with obesity, with or without comorbid ED, will have lower ghrelin levels than healthy controls, and that women with obesity and ED will show higher trait impulsivity and greater eating psychopathology. We further aim to explore whether variations in ghrelin and LEAP2 levels were associated with trait impulsivity, food addiction, and eating psychopathology. These exploratory analyses are intended to provide preliminary, hypothesis–generating evidence on the associations between hormonal and behavioral measures in the context of dysregulated eating.

The study sample comprised $n = 164$ adult female participants, $n = 102$ individuals were diagnosed with obesity, of whom $n = 35$ also met DSM 5 criteria for BSD, and $n = 62$ healthy controls without any history of neither ED nor obesity were also included in the analysis. Participants in the clinical group were recruited from specialized Units at Bellvitge University Hospital, while the control group was recruited from the same geographical area.

The study's participants were required to complete a two-session assessment. The initial session comprised a semi–structured clinical interview, the collection of sociodemographic data, and the administration of self–reported questionnaires. These questionnaires evaluated the presence of eating psychopathology (EDI–2) [159], the presence of food addiction (YFAS–2) [160], trait impulsivity (UPPS–P) [161], and general psychopathology (SCL–90R) [162]. The second session included measurements of anthropometric parameters (i.e., height, weight, BMI, and body

composition) and the collection of fasting blood samples for the determination of circulating ghrelin and LEAP2 using validated ELISA kits [58, 126, 163].

A comprehensive description of the methods, including procedures, ethical approvals, assessments and statistical analyses is provided in the supplementary materials.

2 Results

Table 1 shows the distribution of sociodemographic measurements, along with a comparison between groups in different anthropometric and psychometric measurements of the 164 women included in the study.

The lowest mean age was observed in the control group, while the highest was noted in the group of women with obesity. Conversely, the lowest BMI and fat mass averages were observed in the control group, while the highest were recorded in the group with obesity.

Regarding psychological variables, those individuals with obesity and a comorbid ED showed the greatest severity of eating and general psychopathology, as well as higher scores in impulsivity, followed by the group with obesity without a comorbid ED. The largest group differences in impulsivity were for negative urgency, lack of perseverance, and total UPPS–P score. With regard to the utilization of food addiction measures, the comorbid group has been observed to demonstrate the highest prevalence of food addiction and the highest total scores in YFAS–2.

The results of the analysis of variance (ANCOVA) for the comparison of the concentrations of ghrelin and LEAP2 between groups, adjusted by age and fat mass, are shown in Table 2. Significantly lower mean concentration values of ghrelin were found in patients with obesity, both with and without ED, when compared to healthy controls. However, no significant differences were observed between the two clinical groups. No significant differences were identified in LEAP2 concentrations.

Figure 2 shows the path diagram including the standardized coefficients. The SEM model achieved a suitable adjustment goodness of fit ($\chi^2 = 9.44$, $p = 0.491$; RMSEA = 0.001; CFI = 0.999; TLI = 0.999; RMSEA = 0.045; CD = 0.563). The final model was specified as an exploratory model, and only statistically significant associations were retained to facilitate interpretation and maintain parsimony. Given the exploratory nature of the analysis and the sample size, these associations should be considered preliminary and hypothesis–generating rather than confirmatory. Findings suggest an association between the obesity with ED group and a more severe manifestation of eating psychopathology. The OBES + ED group was also associated with higher level of impulsivity and food addiction which, in turn, were associated with higher severity of eating psychopathology.

Higher LEAP2 concentrations were associated with greater food addiction scores in the obesity groups, although no significant between-group differences in LEAP2 concentrations were observed.

A positive correlation was observed between impulsivity and food addiction. Conversely, ghrelin levels were found to be negatively correlated with LEAP2 concentrations.

3 Discussion

The present study comprised two complementary components: a narrative review of the evidence on ghrelin and LEAP2 in obesity and ED, with particular attention to their associations with impulsivity in the context of dysregulated eating, and an exploratory cross-sectional analysis in a clinical sample of women with obesity, with and without ED.

Overall, the literature suggests that ghrelin and LEAP2 are involved in the regulation of energy homeostasis, but their associations with obesity, binge–spectrum pathology, and impulsivity remain heterogeneous and context-dependent. Findings for ghrelin vary according to nutritional and metabolic status, body weight, diagnostic characteristics, and the specific measure considered. The evidence concerning LEAP2 is more limited, particularly in relation to ED and eating-related behaviors. Similarly, although previous studies have reported associations between ghrelin, LEAP2, and behavioral characteristics such as impulsivity, these findings remain limited and inconsistent across behavioral domains and populations. Taken together, the reviewed literature supports the relevance of considering endocrine and behavioral characteristics within a broader biopsychosocial perspective on obesity and ED. However, the current evidence does not establish a specific endocrine-behavioral mechanism, and the available findings are better regarded as a basis for generating hypotheses than for defining explanatory models. In particular, the heterogeneous evidence concerning LEAP2 highlights the need for further investigation of its clinical relevance in eating pathology.

The narrative nature of the review should be considered when interpreting its conclusions. Unlike a systematic review or meta-analysis, the present approach was intended to provide an integrative overview of relevant evidence rather than a quantitative synthesis of the literature. The studies considered differed in samples, clinical characteristics, nutritional and metabolic contexts, hormonal measures, and behavioral constructs, which limits direct comparison across findings. These differences may contribute to the heterogeneity of the available evidence and preclude firm

Table 1 Descriptive for the sociodemographic, body composition, and psychological measures

	HC (n=62)		OBES (n=67)		OBES+ED (n=35)		HC versus OBES		HC versus OBES+ED		OBES versus OBES+ED	
	n	%	*n*	%	*n*	%	*p*	C-V	*p*	C-V	*p*	C-V
Marital												
Single	44	71.0%	34	50.7%	21	60.0%	**0.042***	**0.222†**	0.264	0.166	0.597	0.100
Married	14	22.6%	29	43.3%	13	37.1%						
Divorced	4	6.5%	4	6.0%	1	2.9%						
Education												
Primary	11	18.0%	30	44.8%	21	60.0%	**0.001***	**0.363†**	**0.001***	**0.454†**	0.341	0.145
Secondary	16	26.2%	22	32.8%	8	22.9%						
University	34	55.7%	15	22.4%	6	17.1%						
Employment												
Unemployed	12	19.4%	18	26.9%	9	25.7%	0.313	0.089	0.465	0.074	0.900	0.012
Student or employed	50	80.6%	49	73.1%	26	74.3%						
Social position												
High	7	11.3%	3	4.5%	1	2.9%	0.563	0.152	0.496	0.187	0.918	0.096
Mean-high	14	22.6%	14	20.9%	7	20.0%						
Mean	8	12.9%	11	16.4%	8	22.9%						
Mean-low	13	21.0%	12	17.9%	7	20.0%						
Low	20	32.3%	27	40.3%	12	34.3%						
	Mean	*SD*	*Mean*	*SD*	*Mean*	*SD*	*p*	|*d*|	*p*	|*d*|	*p*	|*d*|
Age (years-old)	33.56	10.82	41.48	9.38	38.23	9.74	**0.001***	**0.78†**	0.092	0.45	0.302	0.34
Body mass index (kg/m^2)	21.94	2.18	43.76	7.65	40.06	6.59	**0.001***	**3.88†**	**0.001***	**3.69†**	**0.012***	**0.52†**
Fat mass	25.55	5.41	48.33	4.94	46.70	5.17	**0.001***	**4.39†**	**0.001***	**4.00†**	0.321	0.32
	Mean	*SD*	*Mean*	*SD*	*Mean*	*SD*	*p*	*C-V*	*p*	*C-V*	*p*	*C-V*
EDI-2 Total score	25.58	21.04	60.70	27.32	115.43	35.38	**0.001***	**1.44†**	**0.001***	**3.09†**	**0.001***	**1.73†**
SCL-90R GSI	0.52	0.46	0.95	0.55	1.92	0.67	**0.001***	**0.85†**	**0.001***	**2.43†**	**0.001***	**1.59†**
UPPS-P Lack premeditation	22.26	5.28	22.99	4.71	25.11	4.59	0.402	0.15	**0.007***	**0.58†**	**0.039***	0.46
UPPS-P Lack perseverance	19.48	5.03	21.72	4.02	25.77	5.31	**0.008***	**0.52†**	**0.001***	**1.22†**	**0.001***	**0.86†**
UPPS-P Sensation seeking	27.26	7.39	23.84	5.98	24.03	7.53	**0.005***	**0.51†**	**0.028***	0.43	0.893	0.03
UPPS-P Positive urgency	22.19	7.45	22.39	5.00	28.97	10.58	0.882	0.03	**0.001***	**0.74†**	**0.001***	**0.80†**
UPPS-P Negative urgency	24.44	6.26	28.76	5.70	35.40	6.63	**0.001***	**0.72†**	**0.001***	**1.70†**	**0.001***	**1.07†**
UPPS-P Total score	115.63	21.39	119.69	15.50	139.29	21.82	0.235	0.22	**0.001***	**1.09†**	**0.001***	**1.04†**
	Mean	*SD*	*Mean*	*SD*	*Mean*	*SD*	*p*	|*d*|	*p*	|*d*|	*p*	|*d*|
FA (YFAS-2 total)	0.58	1.72	3.90	3.31	9.09	1.95	**0.001***	**1.26†**	**0.001***	**4.63†**	**0.001***	**1.91†**
FA	*n*	*%*	*n*	*%*	*n*	*%*	*p*	*C-V*	*p*	*C-V*	*p*	*C-V*
Positive screening	6	9.7%	27	40.3%	31	88.6%	**0.001***	**0.351†**	**0.001***	**0.780†**	**0.001***	**0.463†**
Negative screening	56	90.3%	40	59.7%	4	11.4%						

EDI-2Eating Disorders Inventory-2, *FA* food addiction, *OBES* obesity, *OBES+ED* obesity with eating disorder, *SCL-90RSymptom Checklist-90 Items-Revised*, *SD* standard deviation, *UPPS-P* Impulse Behavior Scale, *YFAS-2* Yale Food Addiction Scale *2.0*. *Bold: significant comparison. †Bold: Effect size within the moderate to large range

Table 2 Comparison for the endocrine measures: ANCOVA adjusted by age and fat mass

	HC ($n=62$)		OBES ($n=67$)		OBES+ED ($n=35$)		HC versus OBES		HC versus OBES+ED		OBES versus OBES+ED	
	Mean	SD	Mean	SD	Mean	SD	*p*	|d|	*p*	|d|	*p*	|d|
Total Ghrelin (pg/mL)	1832.83	535.96	1024.67	481.36	1146.01	520.29	**0.001***	**1.59†**	**0.001***	**1.30†**	0.263	0.24
LEAP2 (ng/mL)	14.84	8.96	12.83	14.60	13.54	15.99	0.696	0.17	0.801	0.10	0.796	0.05

OBES obesity, *OBES+ED* obesity with eating disorder, *SD* standard deviation

*Bold: significant comparison. †Bold: Effect size within the moderate to large range

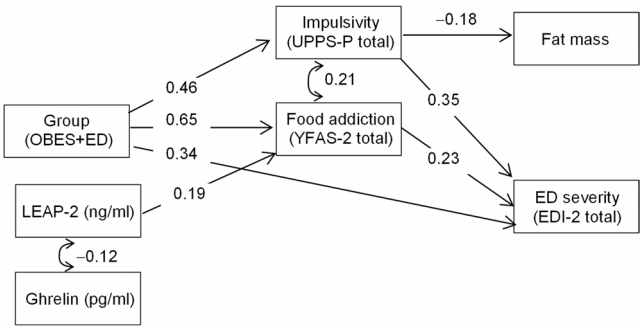


Fig. 2 Path diagram linking "obesity with eating disorder", different clinical dimensions, LEAP2 and ghrelin. *Note. EDI-2: Eating Disorders Inventory-2.FA: food addiction*. Group: 0=OBES: obesity; 1=OBES+ED: obesity with eating disorder. *SCL-90R: Symptom Checklist-90 Items-Revised.UPPS-P: Impulse Behavior Scale.YFAS-2: Yale Food Addiction Scale 2.0.* Only the significant parameters retained in the model are being shown. Fit statistics: $\chi^2=9.44$ ($p=0.491$); RMSEA=0.001; CFI=0.999; TLI=0.999; RMSEA=0.045; CD=0.563

conclusions regarding the direction or clinical significance of associations between endocrine signals and behavioral characteristics.

The empirical component provided a preliminary examination of these questions in the present clinical sample. Ghrelin concentrations were lower in both clinical groups than in healthy controls, consistent with some previous findings in obesity [99, 100, 111], although they were not specific to the presence of ED. In contrast, LEAP2 concentrations did not differ significantly between groups. The exploratory SEM analysis, however, identified an association between LEAP2 and food addiction, indicating a relationship that remains insufficiently characterized and requires further investigation.

The behavioral findings provide a complementary perspective. Women with obesity and ED showed greater trait impulsivity, particularly in negative urgency, lack of perseverance, and total UPPS–P scores, together with higher prevalence and severity of food addiction. These findings are broadly consistent with previous research linking impulsivity and food addiction to binge–spectrum pathology and obesity [143–145, 164].

Several limitations should be considered when interpreting these findings. First, the cross–sectional design precludes causal or temporal inference, and the relatively small clinical subgroups and inclusion of adult women limit generalizability and may affect the robustness and reproducibility of the findings. Larger and independently replicated samples, including more diverse populations, are needed. Second, only fasting total ghrelin and LEAP2 were measured at a single time point. Thus, the study does not capture postprandial or circadian hormonal fluctuations or distinguish between AG and DAG, which may have distinct biological functions and signaling pathways. Future studies

should incorporate repeated or dynamic measurements and assessment of ghrelin isoforms and relevant downstream pathways. Moreover, several biological, clinical, and psychosocial factors relevant to endocrine and behavioral measures were not assessed or controlled for, including insulin resistance, menstrual or menopausal status, psychotropic medication, GLP–1 receptor agonist use, stress, sleep, dietary intake, circadian factors, traumatic experiences, and emotion regulation. These factors may contribute to variability in hormone dynamics, impulsivity, and eating psychopathology and should be considered in future studies. Multimodal assessment of impulsivity, including behavioral tasks and ecological momentary assessment, may also provide complementary information to self–report measures. Finally, the SEM was exploratory and should be interpreted as a statistical representation of the observed associations rather than as evidence of mechanistic or causal pathways. The sample size and subgroup structure may limit model stability and reproducibility and the retention of statistically significant associations in the final model may have increased the risk of model–selection bias and overfitting; therefore, the observed associations, particularly those involving LEAP2, require replication in larger longitudinal samples. Future research integrating comprehensive biological, clinical, behavioral, and psychosocial assessments may help clarify the relationships among endocrine signals, impulsivity, food addiction, and eating psychopathology.

4 Conclusions

This narrative review combined with exploratory empirical findings provides preliminary evidence of associations between peripheral appetite-related hormones and behavioral characteristics within a broader biopsychosocial context of obesity and ED. Regarding the empirical component, lower ghrelin levels were observed in women with obesity compared with healthy controls, while exploratory associations involving LEAP2, impulsivity, and food addiction were identified. These findings should be interpreted cautiously, particularly given the absence of significant group differences in LEAP2 and the cross–sectional design, which limits the ability to establish mechanistic or causal relationships. Trait impulsivity was associated with eating psychopathology, particularly in women with obesity and comorbid ED, and this association warrants further investigation. Larger, longitudinal, and independently replicated studies are needed to determine whether these associations are reproducible, examine their temporal and clinical relevance, and further investigate the potential contribution of endocrine, psychological, and other biopsychosocial factors to eating psychopathology.

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Data availability The datasets generated for this study will not be made publicly available because the data used are part of the hospital database, and it is restricted to protect patients' confidentiality.

Declarations

Competing interests FFA received consultancy and speaking honoraria from Novo Nordisk. PG received during the last 5 years fees for presentations at congresses or participation in scientific boards from Biogen, Janssen, Lundbeck, MindMed, MS Pharma, Newron, Otsuka, Richter and Viatris.The other authors have no conflicts of interest to report.

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