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RESEARCH ARTICLE

Ghrelin as a possible biomarker and maintaining factor in patients with eating disorders reporting childhood traumatic experiences

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Abstract

Objective: The recent conceptualization of ghrelin as a stress hormone suggested that its chronic alterations may have a role in maintaining overeating behaviors in subjects with eating disorders (EDs) reporting childhood traumatic experiences. The aim of this study was to investigate the alterations of ghrelin levels in patients with EDs, their associations with early trauma, binge and emotional eating, and possible moderation/mediation models.

Method: Sixty-four patients with EDs and 42 healthy controls (HCs) had their plasma ghrelin levels measured and completed questionnaires evaluating general and ED-specific psychopathology, emotional eating, and childhood traumatic experiences.

Results: Participants with anorexia nervosa had higher ghrelin levels than HCs in body mass index (BMI)-adjusted comparisons. Moreover, patients reporting a history of childhood trauma had higher ghrelin levels. Childhood sexual abuse (CSA), BMI, and self-induced vomiting were independent predictors of ghrelin levels. Moderation analyses showed that ghrelin levels were associated with binge and emotional eating only for higher levels of childhood

Abbreviations: AN, anorexia nervosa; ANCOVA, analysis of covariance; ANOVA, analysis of variance; BED, binge eating disorder; BMI, body mass index; BN, bulimia nervosa; CI, confidence interval; CSA, childhood sexual abuse; CTQ-SF, Childhood Trauma Questionnaire-Short Form; DSM-5, Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition; EA, emotional abuse; EC, eating concern; ED, eating disorder; EDE-Q, Eating Disorder Examination Questionnaire; EN, emotional neglect; EES, Emotional Eating Scale; ELISA, enzyme-linked immunosorbent assay; GSI, global severity index; HC, healthy control;; PA, physical abuse; PN, physical neglect; PTSD, post-traumatic stress disorder; R, dietary restraint;; SA, sexual abuse; SC, shape concern; SCID-5, Structured Clinical Interview for DSM-5; SCL-90-R, Symptom Checklist-90-Revised; SE, standard error; TS, total score; WC, weight concern.

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trauma. Elevated ghrelin was a significant mediator for the association of CSA with binge eating.

Conclusions: These results support the hypothesis that chronic alterations in ghrelin levels following childhood traumatic experiences could represent a neurobiological maintaining factor of pathological overeating behaviors in EDs.

KEYWORDS
binge eating, childhood trauma, eating disorders, emotional eating, ghrelin

HIGHLIGHTS

- Patients with eating disorders reporting childhood trauma had higher ghrelin levels than other patients with eating disorders.
- Childhood sexual abuse, body mass index, vomiting, and binge eating were independent predictors of ghrelin.
- Ghrelin was positively associated with binge and emotional eating, but only in the presence of childhood trauma; moreover, elevated ghrelin was a significant mediator for the association of childhood sexual abuse with binge eating.

1 | INTRODUCTION AND AIMS

The role of childhood traumatic experiences in the development of eating disorders (EDs) is very well established by the existing literature (Caslini et al., 2016; Guillaume et al., 2016; Sanci et al., 2008; Wonderlich et al., 1997), with a lifetime prevalence of 20%–46% among patients with EDs (Castellini et al, 2013, 2018; Lelli et al., 2019). Several observations seem to demonstrate that besides diagnostic categories, patients with EDs reporting childhood traumatic experiences represent a distinct subpopulation with an earlier age of onset of the ED (Caslini et al., 2016; Molendijk et al., 2017), a greater clinical severity (Caslini et al., 2016; Molendijk et al., 2017), and a more unsatisfactory long-term outcome (Castellini et al., 2018). Furthermore, patients with a history of childhood trauma often report distinct clinical characteristics such as higher rates of binge-purging (Castellini et al., 2018) and dysregulated sexual behaviors (Castellini et al., 2019; Castellini, D'Anna, et al., 2020; Castellini, Rossi, & Ricca, et al., 2020), as well as a diverse longitudinal trend of menstrual alterations (Castellini, Rossi, Cassioli, et al., 2020). Recently, Rodgers et al. published a network analysis supporting the existence of a *traumatic echo-phenotype* of EDs characterized by a specific interconnection pattern between ED-symptoms and negative affects (Rodgers et al., 2019).

In recent years, a growing interest has been devoted to the biological markers of EDs, focusing not only on the correlates of malnutrition but also on possible maintaining factors for psychopathology and aberrant eating behaviors (Cassioli et al., 2020; Monteleone & Maj, 2013). Increasing evidence showed neuroendocrine alterations in patients with EDs and a history of childhood trauma, particularly regarding the hypothalamic–pituitary–adrenal axis (Lelli et al., 2019; Marciello et al., 2020). However, these alterations are not specific, and a precise neurobiological characterization of the *traumatic eco-phenotype* of EDs is still lacking. A better neurobiological characterization would allow identifying possible factors involved in the maintenance of EDs in the presence of a history of early traumatic experiences, with significant clinical implications considering these patients' inadequate response to standard treatments (Steinhausen, 2002, 2009).

In this context, the orexigenic molecule ghrelin seems to be of particular interest. This hormone is mainly produced by the endocrine cells of the gastric fundus, and its hematic levels are inversely related to body mass index (BMI) (Müller et al., 2015). Ghrelin is involved in the stimulation of appetite and the regulation of the energetic homeostasis of the organism, promoting the production and accumulation of fatty acids and fat reserves (Müller et al., 2015). In particular, ghrelin stimulates both homeostatic feeding via its effect on hypothalamic and brainstem areas, and non-homeostatic reward-related feeding given its interaction with reward systems (Dickson et al., 2011). Moreover, it has been recently hypothesized that ghrelin should be considered as a stress hormone (Stone et al., 2020). Indeed, the

conceptualization of stress as a state of low-energy availability (Picard et al., 2018), together with the numerous findings of variations in plasma ghrelin levels not just as consequences of effective reductions of energy levels, but also in the presence of acute or chronic stress states (Rouach et al., 2007; Yousufzai et al., 2018), led to the hypothesis that the role of ghrelin in the regulation of appetite might be the consequence of its involvement in the regulation of stress response, rather than of hunger per se (Stone et al., 2020). This hypothesis is supported by recent findings that highlighted the anxiolytic and antidepressant effects of ghrelin, which could, therefore, represent an adaptive response mechanism during acute stress (Stone et al., 2020). Finally, a growing amount of literature underlined the presence of chronically elevated ghrelin levels in psychiatric diseases with traumatic pathogenesis, such as post-traumatic stress disorder (PTSD) (Stone et al., 2020).

In light of the above considerations, it could be hypothesized that patients with EDs reporting a history of early trauma might show increased ghrelin levels. Accordingly, for this subpopulation of patients, ghrelin could be implicated in maintaining pathological eating behaviors related to overeating, such as binge eating and emotional eating. The preliminary studies on this topic reported BMI-dependent variations of ghrelin levels in EDs, showing a substantial increase in anorexia nervosa (AN) (Schalla & Stengel, 2018), a decrease in binge-eating disorder (BED) (Geliebter et al., 2008; Hernandez et al., 2019; Monteleone et al., 2005), and conflicting results in bulimia nervosa (BN) (Monteleone & Maj, 2013). However, to the best of our knowledge, no studies investigated the possible relationship of this hormone with experiences of childhood abuse in patients with EDs, and the possible link with overeating behaviors.

Therefore, the aims of the present study were as follows: (1) to examine the putative alterations of plasma ghrelin levels in patients with AN, BN, or BED, comparing them with healthy control subjects (HCs); (2) to investigate the possible association of ghrelin levels with pathological eating behaviors (binge eating and emotional eating); (3) to investigate whether this association was specific for those subjects reporting a history of childhood traumatic experiences (moderating role); and (4) to test the role of elevated ghrelin in mediating the association between early trauma and pathological overeating.

2 | METHODS

The study was carried out at the Psychiatry Unit of the University of Florence (Italy), as a cross-sectional observation in a consecutive series of subjects affected by EDs. The study procedures were adequately explained to all participants, and signed informed consent was required for participation. The study protocol was approved by the local Ethics Committee (Comitato Etico Regionale per la sperimentazione clinica, sezione Area Vasta Centro).

2.1 | Participants

All subjects referring for the first time to the clinic between September 2018 and January 2020 were included in the study, before the start of a specific treatment, provided they met the following inclusion criteria: female sex; age between 18 and 60 years; presence of a diagnosis of AN, BN, or BED according to the diagnostic criteria of DSM-5 (American Psychiatric Association, 2013). The exclusion criteria were as follows: presence of illiteracy, intellectual disability, or other conditions that could significantly compromise the understanding of the study protocol or the completion of the required questionnaires; presence of severe medical comorbidity requiring hospitalization in a non-psychiatric facility (e.g., heart or liver failure); previous bariatric surgery or other surgery on ghrelin-secreting tissues that could induce a variation in ghrelin's blood levels (e.g., gastric surgery). Of the 76 subjects initially included, 1 was excluded for the presence of a severe medical condition requiring external hospitalization, and 2 for previous bariatric surgery. Of the 73 remaining subjects, 9 refused to participate in the study.

A group of HCs was also enrolled as a comparison group, by spreading the study protocol in the university premises and social networks (Facebook, Twitter). The selection criteria for HCs were as follows: female sex; age between 18 and 60 years; absence of any psychiatric disorder, based on the diagnostic criteria of the DSM-5 (American Psychiatric Association, 2013); absence of any previous diagnosis of EDs according to the diagnostic criteria of DSM-5 (American Psychiatric Association, 2013); BMI between 18.5 and 25 kg/m^2; absence of illiteracy, intellectual disability, or other conditions that could significantly compromise the comprehension of the study protocol and the completion of the required questionnaires; previous bariatric surgery or other surgery on ghrelin-secreting tissues could induce a change in ghrelin's blood levels (e.g., gastric surgery). Of the 50 control subjects who initially agreed to participate in this study, 2 were excluded following the initial clinical interview due to the presence of a psychiatric disorder, 3 due to the presence of a previous EDs, 3 for the presence of underweight/overweight.

All diagnostic assessments were carried out with the administration of the Structured Clinical Interview for DSM-5 (SCID-5) (First et al., 2016).

2.2 | Study procedures

All experimental procedures were performed on the first day of admission to the clinic. In particular, blood samples were taken in the morning (8:00–8:30 AM) to evaluate ghrelin after a 10–12 h fasting. Serum ghrelin was measured with the following kit: *Human Ghrelin Platinum ELISA (Cat. N. BMS2192)—Thermo Fisher Scientific*. Socio-demographic and clinical data (weight, height, BMI, age of onset of the disorder) were collected. Medical history, psychiatric diagnosis, and childhood traumatic experiences, defined according to the DSM-5 (American Psychiatric Association, 2013), were derived through a clinical interview by two expert psychiatrists. Furthermore, data were collected about the frequency of pathological eating behaviors during the 4 weeks preceding the assessment, including binge-eating episodes, excessive exercise (as a compensatory behavior), and self-induced vomiting (as a purging behavior).

Finally, all participants were asked to complete the following self-administered tests:

- *Symptom Checklist-90-R* (SCL-90-R) (Derogatis, 1994): 90-item questionnaire for the evaluation of general psychopathology, assessed by calculating the Global Severity Index (GSI).
- *Eating Disorder Examination Questionnaire 6.0* (EDE-Q) (Calugi et al., 2016): 28-item test for the assessment of ED-specific psychopathology. In addition to the Total Score, it provides four subscales for evaluating the specific components of dietary restraint (EDE-Q R), eating concern (EDE-Q EC), shape concern (EDE-Q SC), and weight concern (EDE-Q WC).
- *Emotional Eating Scale* (EES) (Arnow et al., 1995): 25-item scale for evaluating the propensity to emotional eating, that is to eat food in response to negative emotional states (such as anger, sadness, and anxiety) even in the absence of hunger, possibly with the purpose of emotional regulation. It provides a total score.
- *Childhood Trauma Questionnaire-Short Form* (CTQ-SF) (Bernstein et al., 2003): 28-item questionnaire investigating the presence of traumatic experiences during childhood and early adolescence. It provides a Total Score (CTQ TS) and five subscales, for assessing the subject's exposure to specific categories of maltreatment: emotional neglect (CTQ EN), physical neglect (CTQ PN), emotional abuse (CTQ EA), physical abuse (CTQ PA), and sexual abuse (CTQ SA).

2.3 | Statistical analysis

Continuous variables were reported as mean and standard deviation. Socio-demographic characteristics, BMI, and plasma levels of ghrelin were compared between the different diagnostic groups (AN, BN, BED, and HCs) using Analysis of variance (ANOVA); in addition, ghrelin levels were also compared between diagnoses while adjusting the model for BMI (entered as a covariate), and between subjects with and without a history of childhood abuse while adjusting for BMI, objective binge eating, and self-induced vomiting, via covariance analysis (ANCOVA). For significant models, comparisons between groups were carried out through post hoc analyses using Tukey's method. Psychometric variables were compared between patients and HCs using ANCOVA, entering age as a covariate. Multivariate linear regression models (adjusted for age and BMI) were performed to test the psychopathological correlates of ghrelin, entering psychopathological measures as independent variables. In addition, the role of childhood abuse experiences as measured by CTQ scores in predicting plasma ghrelin levels, while adjusting for BMI and self-induced vomiting (included as covariates in the linear regression model), was investigated; for these analyses, all CTQ subscales and the total score were tested independently.

To investigate the role of childhood abuse in moderating the relationship of ghrelin with pathological behaviors (binge eating and emotional eating), multivariate BMI-adjusted linear regression models were performed on the whole sample, entering the Ghrelin*CTQ TS interaction as an independent variable, in addition to the main effects (ghrelin and CTQ TS). Statistically significant interactions were probed using simple slopes analysis, calculating the $b_{Ghrelin}$ coefficient for three different moderator levels: the 10th percentile, the median, and the 90th percentile. In addition, the Johnson–Neyman technique (Johnson & Neyman, 1936) was used to calculate the moderator value beyond which the relationship between ghrelin and overeating behaviors was statistically significant (transition point). Finally, simple mediation analyses were performed to test the role of ghrelin in mediating the association between childhood trauma and pathological overeating behaviors; bias-corrected bootstrapped confidence intervals were computed for all indirect effects, with 10,000 samples. Following recommendations for mediation analyses (Baron & Kenny, 1986), only overeating behaviors that showed a correlation with ghrelin levels were considered for these analyses. Opposite models were also tested, with overeating entered as a mediator between early trauma and ghrelin levels. All models were BMI-adjusted.

All statistical analyses were performed using a significance level of $\alpha = 0.05$. All analyses were performed using R statistical software version 4.0.2 (R Core Team, 2020).

3 | RESULTS

3.1 | Comparisons of ghrelin levels between EDs diagnoses and healthy controls

The final sample consisted of 64 patients with EDs (35 with AN, 15 with BN, and 14 with BED), and 42 control subjects. Table 1 shows the participants' sociodemographic and clinical characteristics, including plasma values of ghrelin, together with the results of unadjusted comparisons between the various diagnoses (Table 1). Overall, ANOVA was statistically significant regarding ghrelin levels, with post-hoc analysis showing that patients with AN reported higher blood levels than BED and controls (Table 1); the difference between AN and HCs was confirmed even in BMI-adjusted models (Figure 1).

BMI was negatively associated with plasma ghrelin levels ($\beta = -0.39$, $p = 0.002$). Furthermore, the comparison between patients with and without a history of childhood trauma (adjusted for the confounding variables BMI, objective binge eating, and self-induced vomiting) showed significantly higher ghrelin levels in subjects reporting early trauma ($\beta_{\text{Trauma}} = 0.21$, $p = 0.020$; $\beta_{\text{BMI}} = -0.39$, $p < 0.001$; $\beta_{\text{Binge Eating}} = 0.17$, $p = 0.121$; $\beta_{\text{Vomiting}} = 0.35$, $p = 0.002$), with a mean difference based on estimated marginal means equal to 3.00 ng/ml.

3.2 | Association between ghrelin levels and psychopathology

Table 2 reports the comparisons between patients and HCs in terms of psychopathological variables, and the associations of these variables with plasma ghrelin levels (BMI-adjusted beta coefficients). Ghrelin was significantly associated with the frequency of episodes of binge eating and self-induced vomiting, and with

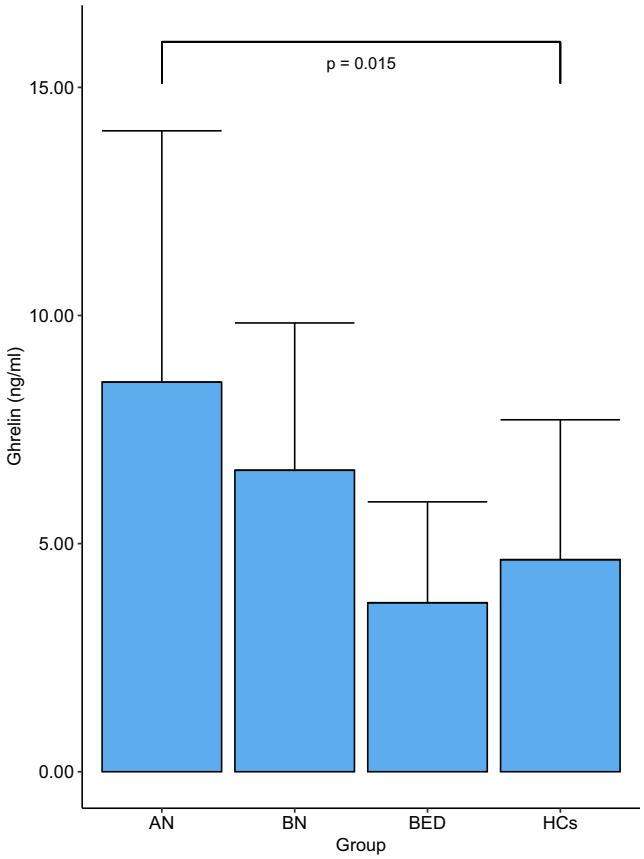

FIGURE 1 Bar graph showing the mean plasma values of ghrelin, divided by diagnostic groups. The error bars show the standard deviation. Statistically significant post hoc BMI-adjusted comparisons are reported in the upper part of the graph, with the relative *p*-value. AN, anorexia nervosa; BED, binge-eating disorder; BMI, body mass index; BN, bulimia nervosa; HCs, healthy controls [Colour figure can be viewed at wileyonlinelibrary.com]

TABLE 1 Sociodemographic and clinical characteristics of the sample, reported by mean and standard deviation, together with comparisons between groups performed using Analysis of Variance (ANOVA)

	AN ($n = 35$)	BN ($n = 15$)	BED ($n = 14$)	HCs ($n = 42$)	F
Age (years)	25.50 ± 11.09[b]	23.23 ± 4.49[b]	36.40 ± 14.06[b,c]	25.94 ± 3.03	5.56**
BMI (kg/m^2)	16.45 ± 1.90[a,b,c]	21.56 ± 1.66[a,b,c]	34.57 ± 6.87[b,c]	21.29 ± 2.50	90.24***
Age of onset (years)	17.64 ± 5.66	15.70 ± 2.63	21.88 ± 13.11	-	1.78
Ghrelin (ng/ml)	8.54 ± 5.51[b,c]	6.61 ± 3.23	3.70 ± 2.21	4.65 ± 3.07	7.24***

Note: Post-hoc analyses are reported as shown in the legend.

Abbreviations: AN, anorexia nervosa; BED, binge-eating disorder; BMI, body mass index; BN, bulimia nervosa; HCs, healthy controls.

[a]Different from BN.

[b]Different from BED.

[c]Different from HCs.

*$p < 0.05$; **$p < 0.01$; ***$p < 0.001$.

TABLE 2 Psychopathological characteristics of the sample, reported by mean and standard deviation, together with age-adjusted comparisons between groups performed using Analysis of Covariance (ANCOVA), and age and BMI-adjusted associations with ghrelin levels performed using linear regression analysis (reported by the standardized coefficient β)

	HCs ($n = 42$)	Patients ($n = 64$)	F	Association with Ghrelin (β)
SCL-90-R GSI	0.42 ± 0.46	1.32 ± 0.71	46.78***	0.10
EDE-Q dietary restraint	0.74 ± 0.91	2.69 ± 2.11	26.32***	−0.10
EDE-Q eating concern	0.36 ± 0.60	2.68 ± 1.66	61.64***	0.03
EDE-Q weight concern	1.02 ± 1.01	3.12 ± 1.83	35.81***	0.06
EDE-Q shape concern	1.30 ± 1.21	3.46 ± 2.03	29.82***	0.01
EDE-Q total score	0.86 ± 0.85	2.99 ± 1.72	44.03***	0.03
Binge eating	0.17 ± 0.61	4.98 ± 8.73	10.00**	0.30*
Self-induced vomiting	0.00 ± 0.00	2.17 ± 5.50	5.11*	0.47***
Compensatory exercise	0.00 ± 0.00	4.41 ± 8.54	9.06**	−0.08
EES total score	18.67 ± 16.39	31.69 ± 28.39	4.70*	0.15
CTQ emotional neglect	8.31 ± 3.27	10.90 ± 5.01	6.53*	0.07
CTQ emotional abuse	5.92 ± 1.70	7.45 ± 2.93	6.65*	0.42**
CTQ sexual abuse	5.00 ± 0.00	6.37 ± 3.54	4.74*	0.41**
CTQ physical neglect	5.92 ± 1.87	6.49 ± 2.24	0.95	0.26*
CTQ physical abuse	5.08 ± 0.37	5.65 ± 1.93	2.72	0.11
CTQ total score	30.22 ± 5.92	36.86 ± 12.02	7.93**	0.34**

Abbreviations: BMI, body mass index; CTQ, Childhood Trauma Questionnaire; EDE-Q, Eating Disorder Examination Questionnaire; EES, Emotional Eating Scale; HCs, healthy controls; SCL-90-R GSI, Symptom Checklist-90-R Global Severity Index.

*$p < 0.05$; **$p < 0.01$; ***$p < 0.001$.

exposure to childhood traumatic experiences, in particular physical neglect, emotional, and sexual abuse (Table 2).

In addition, the role of childhood abuse experiences in predicting plasma ghrelin levels in ED patients was further investigated using multivariate linear regression models, adjusted for BMI and frequency of self-induced vomiting: sexual abuse experiences (CTQ SA) were found to be an independent predictor of ghrelin levels ($\beta_{\text{CTQ SA}} = 0.27$, $p = 0.032$; $\beta_{\text{BMI}} = -0.38$, $p = 0.001$; $\beta_{\text{Vomiting}} = 0.35$, $p = 0.008$), while the remaining CTQ subscales and the total score did not show significant correlation.

3.3 | Moderation and mediation analyses

The Ghrelin*CTQ TS interaction significantly predicted both the frequency of binge eating episodes ($b_{\text{Ghrelin}} = -0.31$, $p = 0.299$; $b_{\text{CTQ TS}} = 0.14$, $p = 0.076$; $b_{\text{Ghrelin*CTQ TS}} = 0.02$, $p = 0.016$) and EES Total Score ($b_{\text{Ghrelin}} = -1.67$, $p = 0.191$; $b_{\text{CTQ TS}} = 0.26$, $p = 0.403$; $b_{\text{Ghrelin*CTQ TS}} = 0.06$, $p = 0.049$). The probing of the interaction through simple slope analysis showed statistically significant effects of ghrelin only for high levels of CTQ TS, on both binge eating (low CTQ TS: $b_{\text{Ghrelin}} = 0.10$, $p = 0.574$; medium CTQ TS: $b_{\text{Ghrelin}} = 0.23$, $p = 0.126$; high CTQ TS: $b_{\text{Ghrelin}} = 0.63$, $p = 0.001$) and emotional eating (low CTQ TS: $b_{\text{Ghrelin}} = -0.27$, $p = 0.709$; medium CTQ TS: $b_{\text{Ghrelin}} = 0.18$, $p = 0.779$; high CTQ TS: $b_{\text{Ghrelin}} = 1.52$, $p = 0.050$). Figure 2 shows the simple slope analysis probing (panels A and C), alongside the Johnson–Neyman plots illustrating the regions of statistical significance for the moderator (panels B and D).

Finally, the role of ghrelin as a mediator of the association between childhood trauma and binge eating was tested using mediation analysis; given its stronger association with ghrelin levels, CTQ SA was entered as the independent variable in this model, which is illustrated in Figure 3. Ghrelin significantly mediated the association of CTQ SA with objective binge eating, as indicated by the bootstrapped confidence interval of the indirect effect, which did not include zero (Figure 3). The opposite mediation model, where objective binge eating was

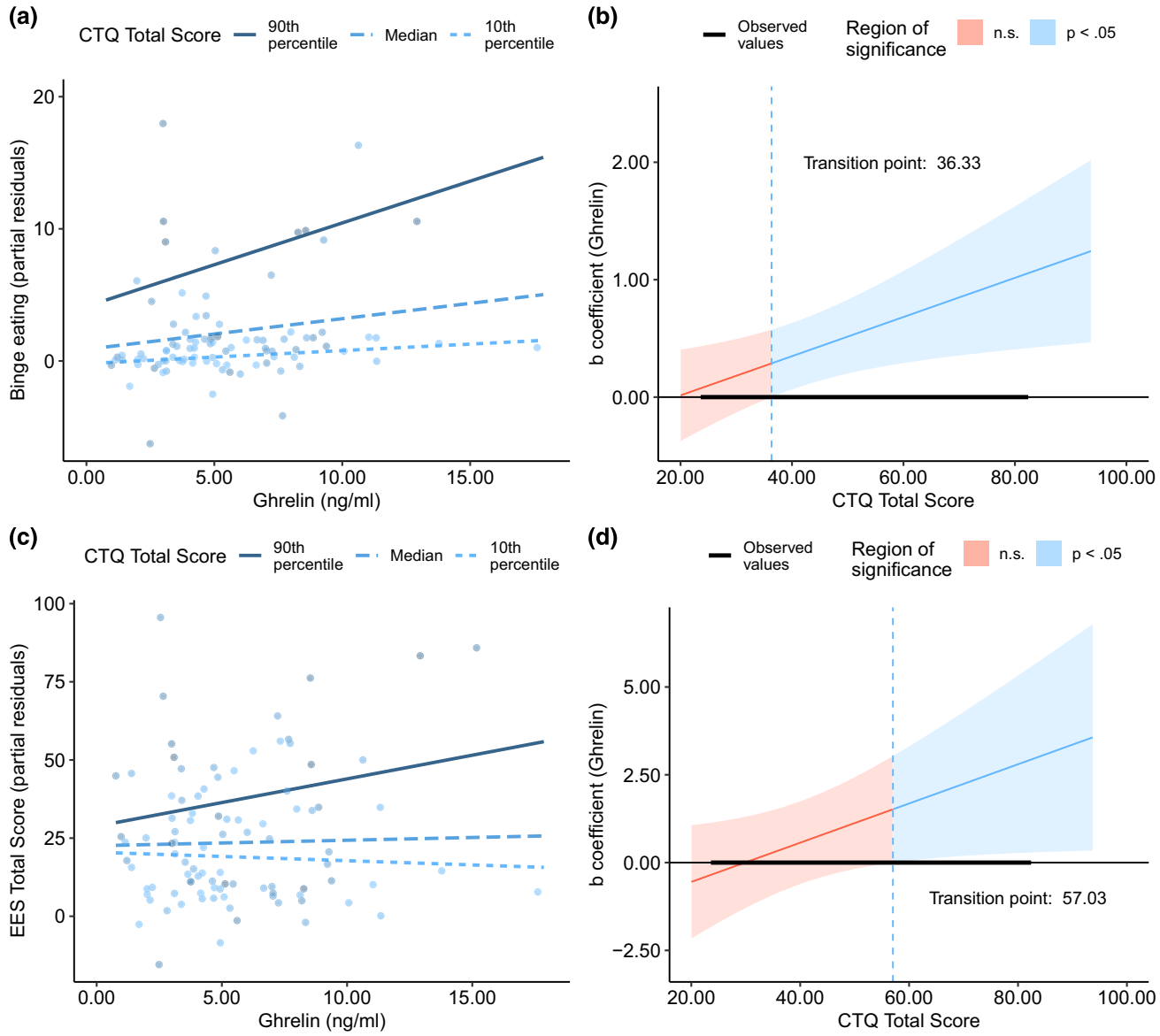

FIGURE 2 Scatter plots illustrating the association of plasma ghrelin levels with binge eating (panel A) and emotional eating (panel C) adjusted for BMI (partial residues are shown on the *y* axis). The points are colored with a gradient indicating the moderator value (CTQ Total Score). Three regression lines are reported for three different levels of the moderator. Panels B and D report the interaction probing using Johnson–Neyman graphs, which show the regions of statistical significance and the transition point of the moderator. CTQ, Childhood Trauma Questionnaire; EES, Emotional Eating Scale [Colour figure can be viewed at wileyonlinelibrary.com]

entered as a mediator for the association between CTQ SA and ghrelin, was not statistically significant (indirect effect: 0.13, 95% CI [−0.04 to −0.33]).

4 | DISCUSSION

This is the first study to highlight the role of ghrelin as a potential biomarker of psychopathology and maintaining factor in patients with EDs reporting early traumatic experiences. According to the main results of the study, patients with a history of childhood trauma had higher ghrelin levels compared with those not reporting it, even when adjusting for BMI and binge/purging behaviors, and higher ghrelin levels were associated with sexual abuse. The presence of early traumatic experiences moderated the association between ghrelin and overeating-related pathological behaviors, and elevated ghrelin was a statistically significant mediator for the association of childhood sexual abuse with objective binge eating. Between-groups comparisons showed that AN was the diagnostic category with the highest ghrelin levels, even when adjusting for BMI, confirming previous studies in this field (Schalla & Stengel, 2018).

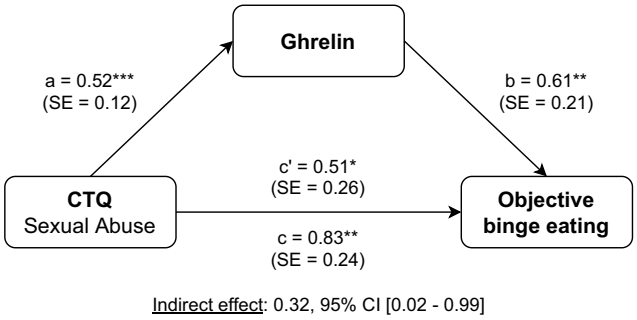

FIGURE 3 Mediation model for the relationship between childhood sexual abuse and frequency of objective binge eating, as mediated by ghrelin levels. Unstandardized regression coefficients and standard errors are reported; the total effect and the direct effect are reported as c and c', respectively. The indirect effect is also reported, together with the bootstrapped 95% confidence interval. CI, confidence interval; CTQ, Childhood Trauma Questionnaire; SE, standard error

The positive relationship between ghrelin levels and self-induced vomiting is in line with many previous studies (Castellini, D'Anna, et al., 2020; Jimerson et al., 2010; Tanaka, Naruo, Nagai, et al., 2003; Tanaka, Naruo, Yasuhara, et al., 2003), but in contrast with other results (Germain et al., 2010; Monteleone et al., 2005; Otto et al., 2004; Troisi et al., 2005). As a putative explanation, it is important to note that the latter studies did not consider the confounding effect of BMI (or fat mass) on ghrelin levels (Germain et al., 2010; Monteleone et al., 2005; Otto et al., 2004; Troisi et al., 2005), and they did not directly measure the frequency of purging behaviors (Germain et al., 2010; Otto et al., 2004; Troisi et al., 2005). Therefore, the adjustment of all statistical analysis considering the possibly confounding effect of BMI, the transdiagnostic assessment of self-induced vomiting, and the distinction of this behavior from other purging strategies are major strengths of the present study. The elevation of ghrelin levels in response to self-induced vomiting could represent an attempt to compensate for gastric dilation or delayed gastric emptying, which are often observed in subjects with binge-purging behaviors (Norris et al., 2016; Sato & Fukudo, 2015). It could also be consequent to the condition of non-atrophic gastritis (Isomoto et al., 2005; Zub-Pokrowiecka et al., 2010), which can be found in the presence of self-induced vomiting (De Caprio et al., 2000). Moreover, considering that vagal stimulation favors ghrelin secretion (Ibrahim Abdalla, 2015) and that vagal hypertonus was observed in patients with BN due to binge eating and self-induced vomiting (Faris et al., 2006), it could be hypothesized that vagal hypertonus could be involved in the relationship between self-induced vomiting and hyperghrelinemia.

Despite the association between self-induced vomiting and hyperghrelinemia and the well-known relationship between this behavior and a history of childhood trauma (Castellini et al., 2018), it is important to emphasize that the difference in terms of ghrelin levels between patients with and without a history of childhood abuse was not totally explained by purging behaviors. Indeed, BMI, self-induced vomiting, and the presence of a history of early trauma were found to be independent predictors of ghrelinemia, and subjects reporting early trauma had an average of 3.00 ng/ml higher plasma ghrelin than those not reporting it, net of BMI, and binge-purging frequency. This finding is in line with recent studies demonstrating a long-lasting association between elevated ghrelin levels and traumatic experiences, both in animals and humans (Malik et al., 2020; Singhal et al., 2014; Stone et al., 2020; Yousufzai et al., 2018). For example, higher ghrelin levels were found in adolescents who experienced a terrorist attack during their childhood (with loss of a loved one or bodily injury) as compared to peers from the same geographic area who had not experienced terrorist attacks, and these alterations persisted for more than four years after the traumatic event (Yousufzai et al., 2018). Furthermore, in a subsequent study performed by the same research group, ghrelin elevation was found only in the subgroup of trauma-exposed adolescents with PTSD, and plasma levels of the hormone were significantly associated with the severity of PTSD (Malik et al., 2020). It is well-known that the adaptive responses following acute stressors risk degenerating into maladaptive mechanisms as the stressors persist (chronic stressors) (Dhabhar, 2018; McEwen, 2003; Sapolsky, 2000), and in recent years, the ghrelinergic response to stressors has been framed in this framework (Stone et al., 2020). Indeed, while the anxiolytic, antidepressant, and metabolic effects of ghrelin could support the recovery of the organism following the exposure to an acutely stressful experience, on the other hand, the alteration of the ghrelinergic circuits due to the persistence of a chronic stressor could lead to physiological alterations and pathological behaviors, eventually leading to psychiatric disorders known to be related to stress (Stone et al., 2020). The results of the present study support this hypothesis, suggesting that an alteration of plasma ghrelin levels could represent a maintaining factor for aberrant eating behaviors such as binge eating in subjects with EDs and a history of early traumatic experiences. More specifically, multivariate regression and mediation models suggest that early experiences of sexual abuse could lead to a chronic elevation of ghrelin levels, which in turn maintains objective binge eating (mediating effect). The role of ghrelin in the vicious cycle of pathological eating behaviors could be due to the

involvement of ghrelin in the stimulation of mesolimbic dopaminergic circuits and thus of reward-related behaviors, including food intake (Dickson et al., 2011). Moreover, chronic stress was associated with ghrelin sensitization in mesolimbic areas (Stone et al., 2020), thus explaining why traumatized patients might be particularly vulnerable to ghrelinergic stimulation. The same mechanisms were hypothesized to be involved in the maintenance of alcohol dependence (Stone et al., 2020), given the stimulating effect of ghrelin on craving (Koopmann et al, 2012, 2019; Leggio et al., 2014) and the particular trend of plasma ghrelin levels in the different phases of this dependence (Badaoui et al., 2008; de Timary et al., 2012; Kim et al., 2005; Koopmann et al., 2012).

The main limitations of the present study were represented by its observational and cross-sectional nature and by the small sample size. Furthermore, the total ghrelin plasma quantity was measured, and not the active (acylated) form: in some cases, the two measurements gave discordant results (Monteleone & Maj, 2013); therefore, the results of this study should be verified using acylated ghrelin measures.

This is the first study that supports the hypothesis of the existence of neurobiological maintaining factors of pathological eating behaviors in patients with EDs and a history of childhood traumatic experiences, favored by alterations in ghrelin levels. Additional data from longitudinal studies with larger samples could highlight specific patterns and associations of this hormone with psychopathology and behaviors during the course of treatment and recovery, eventually supporting the use of ghrelin assessment in clinical practice for a better characterization of EDs. Finally, targeted pharmacological interventions could be used in patients with a history of childhood trauma, such as ghrelin O-acyltransferase inhibitors (Moose et al., 2020), to modulate reward circuits and reduce pathological behaviors.

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CONFLICT OF INTEREST

The authors have no conflict of interest to declare.

DATA AVAILABILITY STATEMENT

Research data are not shared.

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