Published in final edited form as:
J Clin Psychiatry. ; 84(3): . doi:10.4088/JCP.22m14482.

Lower Ghrelin Levels Are Associated With Higher Anxiety Symptoms in Adolescents and Young Adults With Avoidant/Restrictive Food Intake Disorder

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Abstract

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***Relevant financial relationships*:** **Drs Thomas** and **Eddy** receive royalties from Cambridge University Press for the sale of their book *Cognitive-Behavioral Therapy for Avoidant/Restrictive Food Intake Disorder: Children, Adolescents, and Adults*. **Drs Thomas, Becker**, and **Eddy** will receive royalties from Cambridge University Press for their book *The Picky Eater's Recovery Book: Overcoming Avoidant/Restrictive Food Intake Disorder*. **Dr Lawson** has served on the scientific advisory board and has a financial interest in OXT Therapeutics, a company developing oxytocin-based therapeutics to treat obesity and metabolic disease. In addition, Dr Lawson received funding for an investigator-initiated study from Tonix pharmaceuticals. **Dr Misra** has served as a consultant for Abbvie and Sanofi and on the scientific advisory board of Abbvie and Ipsen. Their interests were reviewed and are managed by Massachusetts General Brigham Hospital in accordance with their conflict of interest policies. All other authors have no conflicts of interest.

Objective: Avoidant/restrictive food intake disorder (ARFID) is associated with increased risk for anxiety, which may adversely affect prognosis. The appetite-stimulating hormone, ghrelin, increases in response to stress, and exogenous ghrelin decreases anxiety-like behaviors in animal models. The aim of this study was to evaluate the relationship between ghrelin levels and measures of anxiety in youth with ARFID. We hypothesized that lower ghrelin levels would be associated with increased anxiety symptoms.

Methods: We studied a cross-sectional sample of 80 subjects with full and subthreshold ARFID diagnosed by *DSM-5* criteria, aged 10–23 years (female, n = 39; male, n = 41). Subjects were enrolled in a study of the neurobiology of avoidant/restrictive eating conducted from August 2016 to January 2021. We assessed fasting ghrelin levels and anxiety symptoms (State-Trait Anxiety Inventory [STAI] and STAI for Children [STAI-C] measuring general trait anxiety; Beck Anxiety Inventory [BAI] and BAI for youth [BAI-Y] assessing cognitive, emotional, and somatic symptoms of anxiety; and Liebowitz Social Anxiety Scale [LSAS] assessing symptoms of social anxiety).

Results: Consistent with our hypothesis, ghrelin levels were inversely associated with anxiety symptoms as assessed by STAI/STAI-C T scores ($r = -0.28$, $P = .012$), BAI/BAI-Y T scores ($r = -0.28$, $P = .010$), and LSAS scores ($r = -0.3$, $P = .027$), all with medium effect sizes. Findings held in the full threshold ARFID group when adjusting for body mass index z scores (STAI/STAI-C T scores, $\beta = -0.27$, $P = .024$; BAI/BAI-Y T scores, $\beta = -0.26$, $P = .034$; LSAS, $\beta = -0.34$, $P = .024$).

Conclusions: These findings demonstrate that lower levels of ghrelin are associated with more severe anxiety symptoms in youth with ARFID and raise the question of whether ghrelin pathways could be targeted in the treatment of ARFID.

Avoidant/restrictive disorder (ARFID) is a *DSM-5*[1] disorder characterized by food intake that is restricted by volume and/or variety. As opposed to the body image disturbance and fear of weight gain that characterize anorexia nervosa (AN), ARFID is associated with avoidant and/or restrictive eating behaviors due to lack of interest in food or eating, sensory sensitivity to food, or concerns about aversive consequences of eating. ARFID, like AN, is associated with medical complications related to malnutrition,[2–6] and ARFID and subthreshold ARFID were also found to have an increased risk for psychiatric comorbidities,[2,3,7–9] most commonly anxiety.[2,3,7–9] Anxiety symptoms in individuals with eating disorders are associated with greater severity of eating disorder psychopathology and negatively impact prognosis.[10–12] The development of anxiety is rooted in aberrant neurobiological mechanisms, involving neurohormones, central brain structures, and functional connectivity networks.[13,14] Thus, to advance treatment of ARFID, it is important to improve our understanding of the neurobiology underlying anxiety in these individuals.[15–18]

Ghrelin, an appetite-stimulating hormone, is released into the circulation by specialized cells of the stomach (with the highest secretion in the fasted state immediately before food intake) and is negatively associated with weight and body fat.[19] The receptor for ghrelin (growth hormone secretagogue receptor; GHSR) is found predominantly in the hypothalamus, and also in brain regions involved in the stress response and anxiety, such as the amygdala and raphe nuclei.[20–22] Studies in rodents and humans show that ghrelin levels increase in response to stress and modulate anxiety-like behaviors.[21,23–36] Preclinical investigations suggest divergent effects of ghrelin, with some showing anxiolytic[21,29–31,37–39] and others reporting anxiogenic actions,[21,25,37,40–43] potentially due to differences in rodents' species, type and/or duration of stressor, and/or level of exposure to ghrelin.

In females with AN, elevated concentrations of ghrelin are well described and considered to be an adaptive response to undernutrition to stimulate appetite and therefore caloric intake.[44,45] The fact that there is low caloric intake despite high circulating levels of ghrelin is suggestive of resistance to ghrelin effects in AN.[45–47] In contrast, little is known regarding ghrelin levels in ARFID. We have shown that low-weight adolescent females with ARFID have significantly lower fasting ghrelin levels than similarly underweight adolescent females with AN.[48] Thus, the expected adaptation to undernutrition seen in AN may be absent in ARFID.[48] Whether dysregulation of ghrelin contributes to the high prevalence of anxiety in ARFID is unknown.

Few studies have examined the relationship between ghrelin levels and symptoms of anxiety in humans, and none have done so in ARFID. Ishitobi et al[49] reported higher ghrelin levels among subjects with unremitted panic disorder vs healthy controls; however, no relationship was found between serum ghrelin levels and psychological test scores. Hansson et al[50] reported a possible link between polymorphisms of the preproghrelin gene and risk for panic disorder; however, Nakashima et al[51] found no such association.

Another study examined the relationship between ghrelin levels and anxiety symptoms among women across the weight spectrum (including those with AN and normal-weight hypothalamic amenorrhea and eumenorrheic individuals with normal-weight, overweight, and obesity) and found no significant correlation.[52] Finally, in a recent study that examined associations between total serum ghrelin levels and symptoms of generalized anxiety in a large cohort of mentally healthy adults, ghrelin levels were positively associated with mild anxiety and negatively associated with more severe symptoms of anxiety (determined by categorical cut points on the 7-item Generalized Anxiety Disorder Scale).[53] Given the increased anxiety-like behaviors in ghrelin knockout rodents, our prior finding of low ghrelin levels in subjects with ARFID compared to AN, as well as studies in mentally healthy individuals demonstrating an association between ghrelin levels and generalized anxiety, we hypothesized that in ARFID, lower circulating ghrelin levels would be associated with greater anxiety symptoms, consistent with possible anxiolytic effects of ghrelin. In addition, our clinical impression that patients with ARFID who present with greater anxiety symptoms often also have lower appetite, both of which make treatment more challenging, further supports this hypothesis.

METHODS

Design

Participants were drawn from a National Institutes of Health funded study (R01MH108595) investigating the neurobiological and behavioral risk mechanisms of avoidant/restrictive eating, conducted from August 2016 to January 2021. Written consent was obtained from participants aged ≥ 18 years. For those < 18 years, written consent was signed by a parent/guardian and assent by the participant. All participants were seen at the Massachusetts General Hospital (MGH) Translational and Clinical Research Center and at the Athinoula A. Martinos Center for Biomedical Imaging. All study procedures were approved by the Mass General Brigham Institutional Review Board.

Subjects

We studied 80 subjects with full and subthreshold ARFID aged 10–23 years (female = 39, male = 41). Participants completed an initial screening visit in which they were evaluated for ARFID symptoms. After the screening visit, participants were invited for a baseline study visit if they either (*a*) met the diagnostic criteria for ARFID on the Eating Disorder Assessment for *DSM-5* (EDA-5), a semistructured interview specifically developed to derive *DSM-5* feeding and eating disorder diagnoses,[54] and/or (*b*) endorsed avoidant/restrictive eating behavior on an adapted version of the Kiddie Schedule for Affective Disorders and Schizophrenia—Present and Lifetime (K-SADS-PL),[55] a semistructured interview that generates *DSM-5* Axis I diagnoses for children and adolescents. Presence of comorbid anxiety disorders was also assessed via K-SADS. In a previous study that included a subset of the current sample, the percent agreement for K-SADS diagnoses in a randomly selected subset of participants was 96% for the anxiety and obsessive-compulsive disorders category, 94% for the depressive and bipolar disorders category, and 100% for all other categories.[8] At the baseline visit, participants completed the Pica, ARFID, and Rumination Disorder Interview (PARDI),[56] a semistructured ARFID diagnostic interview. Participants who met all diagnostic criteria for ARFID on the PARDI were categorized as having full syndrome ARFID (n = 69), whereas those who reported clear avoidant/restrictive eating but did not exhibit significant weight loss/faltering growth, nutritional deficiency, supplement dependence, and/or psychosocial impairment at the level required on the PARDI diagnostic algorithm were categorized as having subthreshold ARFID[57] (n = 11). In a previous study that included a subset of the current sample, the interrater reliability of PARDI diagnoses of ARFID was 0.75.[56]

Exclusion criteria included history of psychosis, active suicidal ideation, current feeding or eating disorder other than ARFID as evidenced by EDA-5, and any clinically significant disordered eating as evidenced by Eating Disorder Examination Questionnaire (EDE-Q). EDE-Q is a self-report questionnaire that evaluates eating disorder symptoms in the preceding 28 days. EDE-Q yields frequencies of binge eating, purging, and driven exercising in a continuous global score.[58] In addition, we excluded individuals with self-induced vomiting, use of laxatives or diuretics, purposeful fasting, or compensatory exercise in the preceding 28 days, individuals taking systemic hormones, pregnancy or breastfeeding within 8 weeks, substance or alcohol use disorder active within the past month as assessed by K-SADS-PL, and history of intellectual disability (IQ < 70).

Measures of Self-Reported Anxiety

The Trait subscale of the State-Trait Anxiety Inventory (STAI)[59] and STAI for Children (STAI-C)[60] were used to assess general anxiety symptoms in adults and children, respectively. The STAI/STAI-C is a 20-item subscale of a widely used measure for anxiety proneness that is hypothesized to be stable across threatening situations. This assesses general anxiety and includes cognitively oriented items (eg, "I worry too much over something that really doesn't matter"). We converted total scores of the STAI/STAI-C to standardized T scores for all subjects, resulting in 1 variable. Averaged combined Cronbach α for the STAI/STAI-C was 0.90. Higher STAI/STAI-C scores indicate higher general anxiety.

The Beck Anxiety Inventory (BAI) is a 20-item self-report questionnaire for adults, and the youth version (BAI-Y)[61] is validated for children and adolescents between 7 and 18 years. The BAI and BAI-Y assess cognitive and emotional aspects of anxiety, somatic symptoms of anxiety (eg, dizziness, inability to relax[62]), social components of anxiety, and specific fears. As opposed to the trait subscale of the STAI/STAI-C (which inquires about how respondents "generally feel"), the BAI/BAI-Y reflects a more acute timeframe, asking about each symptom over the past week. Averaged Cronbach alphas for the BAI and BAI-Y were 0.93 and 0.89, respectively. We converted total scores of the BAI/BAI-Y to T scores, standardized scores for all subjects, resulting in 1 variable for all. Higher BAI/BAI-Y scores indicate higher state related anxiety.

The Liebowitz Social Anxiety Scale (LSAS) is a self-report 24-item questionnaire assessing symptoms of social anxiety disorder/social phobia, focusing on feeling anxious in social situations or when interacting with other people (such as participating in a small group activity or calling someone you don't know very well).[63] Averaged Cronbach α for LSAS was 0.96. A subset of 51 participants completed the LSAS questionnaire, which was an optional measure in the current study. Higher LSAS scores indicate greater social anxiety.

Study Procedures

Following informed consent, participants completed a screening visit to determine eligibility. This included a detailed medical history, physical examination including height and weight measurements and Tanner staging, a blood sample to rule out anemia, urine β-human chorionic gonadotropin testing to rule out pregnancy, and administration of the EDA-5 and K-SADS-PL.

Eligible participants returned for a main study visit within 3 months of the screening visit. This visit included an updated medical history, physical examination, fasting blood draw for ghrelin, and the PARDI, STAI/STAI-C, BAI/ BAI-Y, and LSAS.

Biochemical Analysis

Blood samples were immediately placed on ice following venipuncture and spun in a refrigerated centrifuge, and plasma samples were stored at −80°C until measurement. Plasma total ghrelin levels were determined by an enzyme-linked immunosorbent assay (EMD Millipore; Billerica, MA), with an intraassay coefficient of variation (CV) of 1.32% and interassay CV of 6.62%. Lower limit of detection was 50.0 pg/mL.

Statistical Analysis

We conducted statistical analysis using JMP Pro 16.0.0 software. All continuous variables are presented as mean ± SD, and categorical data are presented as count (%). All variables were normally distributed. To test our hypothesis that lower fasting ghrelin levels would be associated with higher anxiety, we calculated the Pearson correlation coefficient. As a sensitivity analysis, we repeated this analysis with the full threshold ARFID group only, followed by multivariate analysis to control for body mass index (BMI) *z* scores and age. We used the Benjamini-Hochberg correction (false discovery rate) to adjust for multiple testing.

Statistical significance was defined as a 2-tailed P value < .05. We interpreted Pearson correlation coefficients by Cohen's convention as small ($r = 0.10$), medium ($r = 0.30$), and large ($r = 0.50$) effect. Data are reported as mean ±SD.

RESULTS

Clinical Characteristics

Demographic and clinical characteristics, including ghrelin levels and results of self-report anxiety measures, are presented in Table 1. Mean STAI/STAI-C T scores and BAI/BAI-Y T scores of subjects with full and subthreshold ARFID (mean ± SD, 46.6 ± 15.1 and 50.8 ± 14.5, respectively) were close to the mean T score of 50 for normative samples.[64] Standard deviations, however, were larger than 10, suggestive of a wide range of anxiety in this population. In addition, their LSAS mean score of 34.9 ± 24.6 was in the range of nongeneralized social anxiety disorder.[65]

Relationship Between Ghrelin Levels and Psychopathology

Scatterplots depicting the associations between ghrelin levels and measures of self-reported anxiety of full and subthreshold ARFID are presented in Figure 1. As hypothesized, ghrelin levels were significantly negatively associated with anxiety symptoms as assessed by STAI/STAI-C T scores ($r = -0.28$, $P = .012$), BAI/BAI-Y T scores ($r = -0.28$, $P = .010$), and LSAS scores ($r = -0.30$, $P = .027$), all with medium effect sizes. Additionally, following the Benjamini-Hochberg correction for multiple testing, findings held for all measures (STAI/STAI-C, P=.018; BAI/BAI-Y, $P = .018$; LSAS, $P = .027$) (Figure 1). As a sensitivity analysis, we repeated the analysis in the full threshold ARFID subgroup ($n = 69$, Figure 2) while adjusting for BMI *z* scores, and findings persisted, showing again that ghrelin levels were significantly associated with anxiety symptoms as assessed by all 3 measures of anxiety (STAI/STAI-C T scores, $\beta = -0.27$, $P = .024$; BAI/BAI-Y T scores, $\beta = -0.26$, P=.034; LSAS, $\beta = -0.34$, $P = .024$). These findings remained significant after correcting for multiple testing (STAI/STAI-C, $P = .035$; BAI/BAI-Y, $P = .035$; LSAS, $P = .044$).

In other words, on average, participants with lower ghrelin levels tended to have higher levels of self-reported anxiety across constructs, and the observed relationships were moderately strong.

In addition, we found a positive relationship between age and anxiety (STAI/STAI-C, $r = 0.54$, $P < .001$; BAI/BAI-Y, $r = 0.60$, $P < .001$; LSAS, $r = 0.24$, $P = .085$ respectively). When adjusting for age, the relationship between ghrelin and social anxiety as measured by the LSAS held ($\beta = -0.34$, P=.029), the relationship between ghrelin and STAI/STAI-C ($\beta = -0.20$, $P = .068$) became a trend, and the relationship between ghrelin and BAI/BAI-Y ($\beta = -0.15$, $P = .143$) was no longer significant.

DISCUSSION

In the current study, we evaluated the relationship between circulating levels of ghrelin and 3 facets of self-reported anxiety among children and adolescents with full and subthreshold ARFID. Our results suggested that, across anxiety constructs (including general anxiety, somatic symptoms, and social anxiety), lower levels of ghrelin, an appetite-stimulating hormone released in response to stress, were associated with greater severity of anxiety in youth with ARFID, an eating disorder characterized by increased risk for anxiety disorders.[3,18,66] These findings were primarily attributable to the full threshold ARFID group, where relationships between ghrelin levels and anxiety measures held also when adjusting for BMI z scores. Our data indicate a relationship between endogenous ghrelin levels and anxiety in full threshold ARFID that is not solely BMI dependent.

Of note, mean anxiety scores in our ARFID group were similar to normative levels, but scores varied widely, and our findings suggest that those who report elevated levels at the higher end of the normative distribution have lower levels of fasting ghrelin. The confluence of lower ghrelin among individuals with ARFID whose anxiety is high raises the intriguing possibility that interventions targeting ghrelin pathways could be especially beneficial to this group.

Studies in rodents show that exposure to various types of acute (eg, water deprivation, tail pinch, caloric restriction, and maternal separation[21,23–26]) and chronic (eg, social defeat stress, immobilization, mild unpredictable stress[21,27–32]) physiological or psychological stressors lead to an increase in circulating ghrelin levels. Similarly, human studies reveal elevated endogenous ghrelin levels following psychological stress exposure.[28,33–35] However, the role of ghrelin in the stress response is controversial.[25,30,38,42] Numerous studies in rodents have shown protective effects of ghrelin in reducing anxiety behaviors at baseline[29–31,37] and in response to stress,[21,29,30,37–39] potentially via the central serotonergic system.[67,68] For example, subcutaneous injection of ghrelin decreased anxiety in a rodent model of chronic social defeat.[30] In acute stress situations, knockout mice deficient in ghrelin were more anxious and had increased activation of the paraventricular nucleus (PVN) of the hypothalamus, a key brain region for the initiation of the stress response, compared to wild-type mice.[21,69] Administration of exogeneous ghrelin to knockout mice resulted in improvement in anxiety-like behaviors and increased PVN activation.[21] Others report that ghrelin promotes anxiety and despair-like behaviors in unstressed conditions[21,25,40–43] and following stress.[37,40] The effects of ghrelin may thus depend on the type (physical, emotional, social) and/or duration (acute vs chronic) of stress. Thus, while it is established that ghrelin increases in response to stress, the role of this signaling peptide in the pathophysiology of anxiety is unclear.[70]

There are several possible explanations for the inverse relationship between endogenous ghrelin levels and anxiety in youth with ARFID. The data presented here may reflect insufficient release of ghrelin (and therefore low anxiolytic signaling) in the context of anxiety. Alternatively, if the preclinical studies supporting anxiogenic actions of ghrelin translate to humans, then it is possible that anxiety symptoms in ARFID may result in suppression of ghrelin (as a mechanism to lower anxiety levels), with the negative consequence of reduced signaling of hunger by ghrelin.

Our study is cross-sectional; thus, we cannot show causality. Also, ghrelin is an appetite stimulating hormone[71] with multiple peripheral and central functions,[72] and thus we cannot speculate as to the precise biologic mechanism behind the observed inverse relationship between ghrelin and anxiety. In addition, we measured total ghrelin, which includes acyl ("active," orexigenic) and desacyl ("inactive") forms. Both forms of ghrelin are released from the stomach into the bloodstream, where acyl ghrelin is converted rapidly to desacyl ghrelin.[73] Although acyl ghrelin is considered the "active" form of ghrelin, desacyl ghrelin may also have physiological functions including effects on anxiety-like behaviors, but these actions are not well understood.[37] Future studies measuring acyl and desacyl ghrelin will be important to improve our understanding of the relationship between the different forms of ghrelin and anxiety. In addition, in our subanalysis of full threshold ARFID only, when controlling for age, the inverse association between ghrelin and anxiety remained significant for LSAS and trended for STAI/STAI-C, but was not significant for BAI/BAI-Y. The positive relationship between age and anxiety is well described, especially in the adolescent years.[74,75] Thus, it is not surprising that in our cohort, age was a correlate of anxiety. The loss of significance with some but not all anxiety measures after adjusting for age likely reflects differences in the number of participants completing these measures. This further emphasizes the need for studies with larger sample sizes and in different age groups to confirm the association between ghrelin and anxiety. Finally, although we assessed severity of anxiety by validated self-report measures, future assessments via structured clinical interview could add information to this line of investigation.

To our knowledge, this is the first study to report a relationship between lower circulating ghrelin levels and anxiety symptoms in individuals with ARFID. Further investigation is warranted to determine whether targeting ghrelin pathways is an effective treatment strategy in ARFID.

Funding/support:

This research was funded by National Institutes of Health grants R01 MH108595 (Drs Thomas, Lawson, and Micali), K24 MH120568 (Dr Lawson), T32 DK007028 (Dr Chovel Sella), K23MH125143 (Dr Becker), and 1 UL1 TR002541-01.

Role of the sponsor: These funding sources had no role in the design of this study and did not have any role during its execution, analyses, interpretation of the data, or decision to submit results.

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Clinical Points

- Avoidant/restrictive food intake disorder (ARFID) is associated with increased risk for anxiety, which may further challenge treatment and impact prognosis.
- Ghrelin is an appetite-stimulating hormone that increases in response to stress; however, its role in the anxiety and pathophysiology of psychiatric disorders—and in eating disorders specifically—is yet to be established.
- Lower ghrelin levels are associated with higher anxiety symptoms among children and adolescents with ARFID. Future studies will be important to investigate whether lower than expected ghrelin levels are a trait of ARFID that contributes to low appetite and high anxiety.

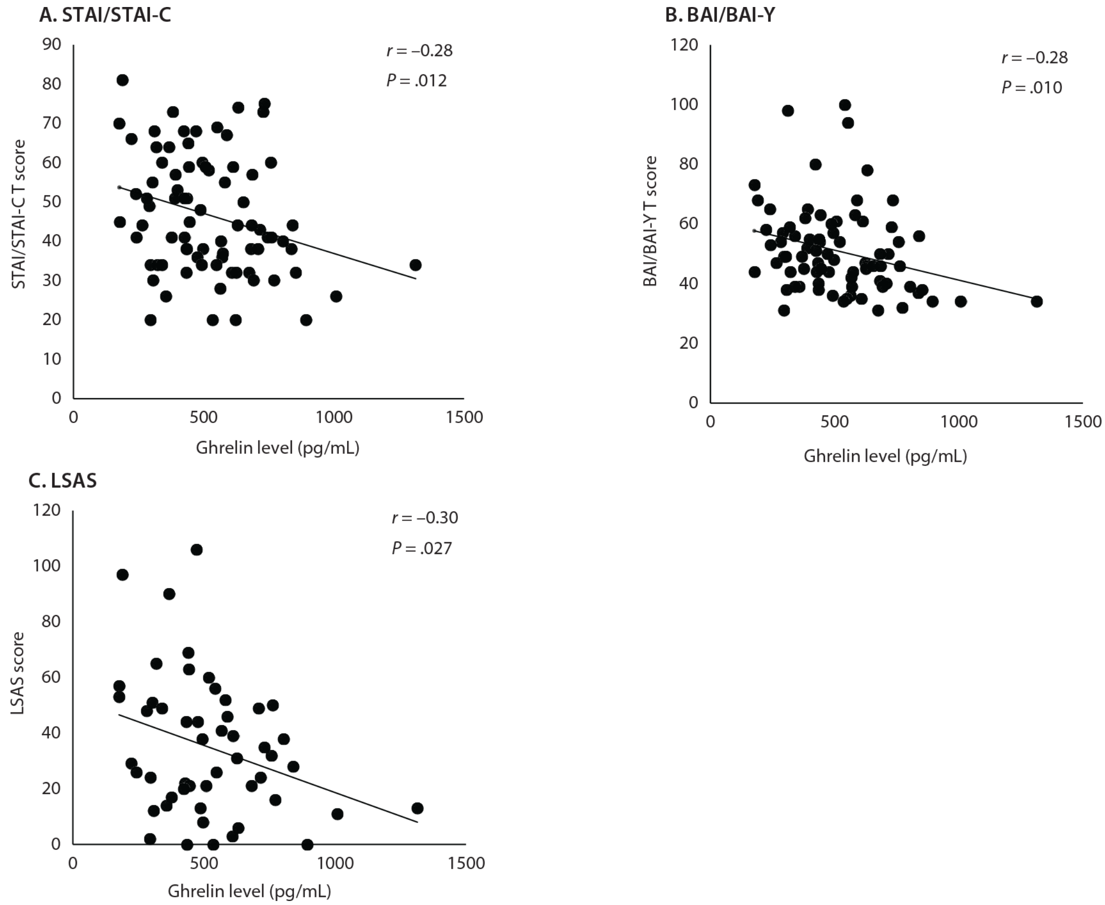

Figure 1. Relationship Between Ghrelin Levels and Symptoms of Anxiety in Youth With ARFID[a]

[a]Lower ghrelin levels were associated with more severe anxiety symptoms as assessed by (A) STAI/STAI-C, (B) BAI/BAI-Y, and (C) LSAS. Findings held after removing outliers (STAI/STAI-C, $r = -0.27$, $P = .018$; BAI/BAI-Y, $r = -0.26$, $P = .023$; LSAS, $r = -0.29$, $P = .044$), after correcting for multiple testing (STAI/STAI-C, $P = .018$; BAI/BAI-Y, $P = .018$ LSAS, $P = .027$), and after correcting for multiple testing and removing outliers (STAI/STAI-C, $P = .035$; BAI/BAI-Y, $P = .035$; LSAS, $P = .044$).

Abbreviations: ARFID = avoidant/restrictive food intake disorder, BAI = Beck Anxiety Inventory, BAI-Y = Beck Anxiety Inventory for Youth, LSAS = Liebowitz Social Anxiety Scale, STAI = State-Trait Anxiety Inventory, STAI-C = State-Trait Anxiety Inventory for Children.

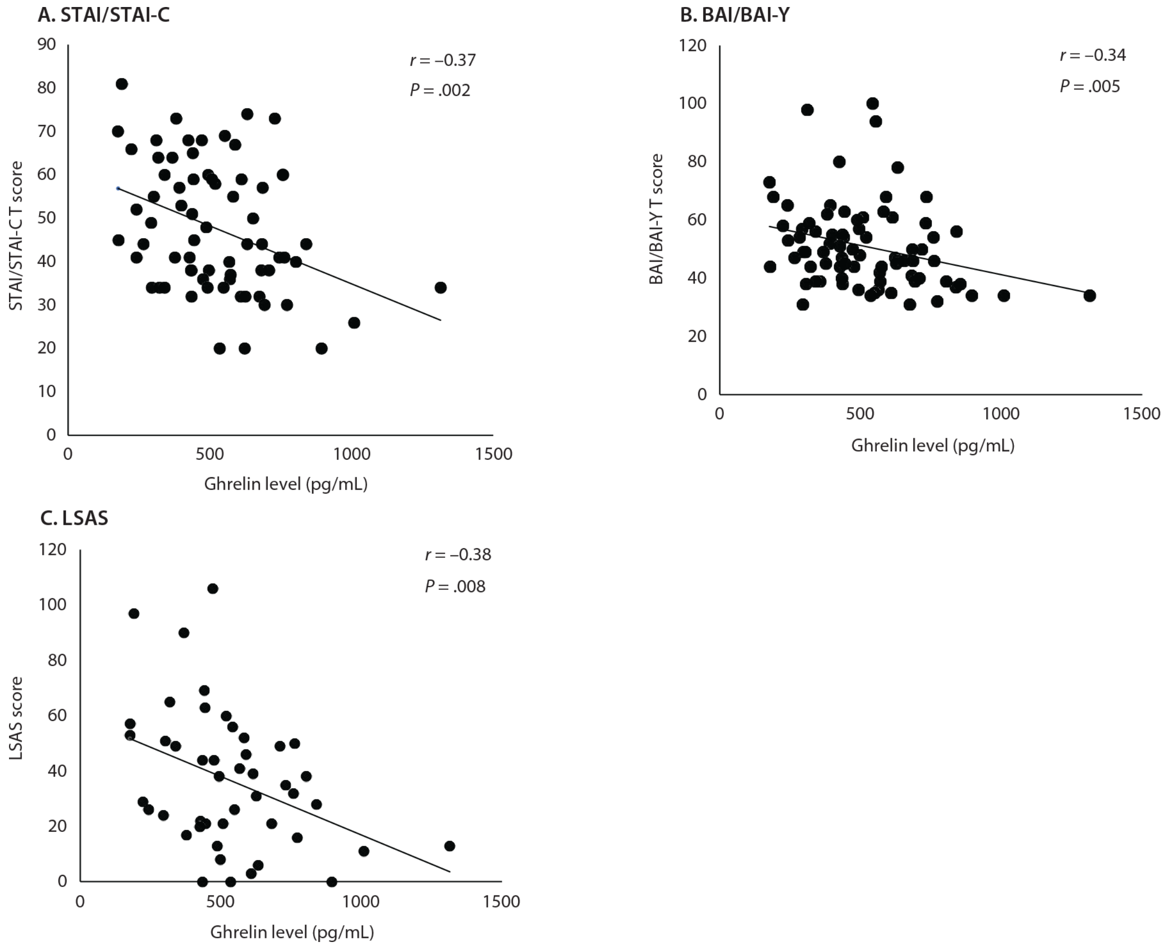

Figure 2. Relationship Between Ghrelin Levels and Symptoms of Anxiety in Youth With Full Threshold ARFID[a]

[a]Lower ghrelin levels were associated with more severe anxiety symptoms as assessed by (A) STAI/STAI-C, (B) BAI/BAI-Y, and (C) LSAS. Findings remained significant after correcting for BMI *z* scores (STAI/STAI-C, $\beta = -0.27$, $P = .024$; BAI/BAI-Y, $\beta = -0.26$, $P = .034$; LSAS, $\beta = -0.34$, $P = .024$). Findings remained significant after correcting for multiple testing (STAI/STAI-C, $P = .034$; BAI/BAI-Y, $P = .034$; LSAS, $P = .043$).

Abbreviations: ARFID = avoidant/restrictive food intake disorder, BAI = Beck Anxiety Inventory, BAI-Y = Beck Anxiety Inventory for Youth, BMI = body mass index, LSAS = Liebowitz Social Anxiety Scale, STAI = State-Trait Anxiety Inventory, STAI-C = State-Trait Anxiety Inventory for Children.

Table 1.

Demographic and Clinical Characteristics (n = 80)

Characteristic	
Age, y, mean ± SD	15.3 ± 3.6
Gender, n (%)	
Male	41 (51.3)
Female	39 (48.8)
Race, n (%)	
Asian	1 (1.3)
Black or African-American	2 (2.4)
White	73 (91.3)
More than 1 race	4(5.0)
Ethnicity, n (%)	
Hispanic	8 (10)
Non-Hispanic	72 (90)
BMI *z* score (n = 68, age < 20 y), mean ± SD	−0.8 ± 1.4
BMI, kg/m^2 (n = 12, age > 20 y), mean ± SD	25.2 ± 7.3
% Expected body weight for height, mean ± SD	96.0 ± 25.1
STAI/STAI-C combined T score (n = 79), mean ± SD	46.6 ± 15.1
BAI/BAI-Y combined T score, mean ± SD	50.8 ± 14.5
LSAS score (n = 51), mean ± SD	34.9 ± 24.6
Ghrelin, pg/mL, mean ± SD	522.8 ± 207.3
Current psychiatric comorbidities by K-SADS-PL, n (%)	
Anxiety	29 (36.3)
Obsessive-compulsive disorders	4 (5.0)
Depressive and bipolar related disorders	4 (5.0)
Neurodevelopmental, disruptive, and conduct disorders	17 (21.3)

Abbreviations: BAI = Beck Anxiety Inventory, BAI-Y = Beck Anxiety Inventory for Youth, BMI = body mass index, K-SADS-PL = Kiddie Schedule for Affective Disorders and Schizophrenia—Present and Lifetime, LSAS = Liebowitz Social Anxiety Scale, N = number of subjects, STAI = State-Trait Anxiety Inventory, STAI-C = State-Trait Anxiety Inventory for Children.