

The Association of Malnutrition, Illness Duration, and Pre-morbid Weight Status with Anxiety and Depression Symptoms in Adolescents and Young Adults with Restrictive Eating Disorders: A Cross-Sectional Study.

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Abstract

Background

Restrictive eating disorders (EDs) are often comorbid with anxiety and depression, placing patients at risk for more severe disease, worse treatment outcomes, and higher rates of mortality. To identify risks for developing such co-morbidities, we assessed the association of malnutrition, ED illness duration, and pre-morbid weight status with symptoms of anxiety and depression in adolescents/young adults (AYAs) with EDs.

Methods

145 participants with restrictive EDs (anorexia nervosa [AN], otherwise specified eating or feeding disorder [OSFED], avoidant restrictive food intake disorder [ARFID]) were included from the RECOVERY study, a longitudinal web-based registry of AYAs with EDs. We measured malnutrition as percent of expected body mass index (%eBMI), based on participants' pre-morbid growth trajectory. Outcomes were anxiety and depression scores from the Generalized Anxiety Disorder 7-item (GAD-7) and Center for Epidemiologic Studies Depression (CES-D) scales. We used multiple linear regression to examine the association of malnutrition, ED duration, and pre-morbid weight status with symptoms of anxiety and depression.

Results

Mean(SD) age was 16.4(3.0) years; 87% were female; 89% white; 85% had AN, 6% OSFED, 10% ARFID. Of these, 2/3 had ED symptoms ≥ 1 year, 1/3 had previous higher level of ED care (HLOC), and half were taking psychiatric medications. Mean %eBMI was 90% (range 57-112%). Mean GAD-7 was 9.4(5.9) and CES-D was 24(13.8), indicating most participants had clinically significant anxiety and/or depression. Degree of malnutrition was not significantly associated with anxiety or depression adjusting for age, sex, sexual orientation, ED diagnosis, and use of psychiatric medication. Those with longer duration of ED symptoms had higher depression ($p=0.038$) scores after adjusting for malnutrition, HLOC, length of ED symptoms, and time in our care. Patients with pre-morbid BMIs $\geq 75^{\text{th}}$ percentile had lower depression scores than those with pre-morbid BMIs $< 75^{\text{th}}$ percentile ($p=0.014$).

Conclusions

We find high degree of clinically relevant anxiety and depression in a population of AYAs with EDs. Our findings suggest that factors beyond malnutrition play a role in the co-morbid mood and anxiety disorders in this population. Overall, rapid ED diagnosis and comprehensive treatment for patients with EDs across the weight spectrum—and especially those with psychiatric co-morbidities—will likely aid in recovery.

Plain English Summary

People with eating disorders (EDs) often also struggle with anxiety and depression. Unfortunately, this can mean their disease is more severe, harder to treat, and more dangerous and potentially fatal. ED treatment often primarily focuses on nutrition and weight gain, and sometimes loses focus on the person's mood and anxiety. Additionally, patients can present at any weight, but not enough is known about how baseline weight before weight loss might affect mood. In this study, we focus on adolescents/young adults with restrictive EDs to understand what places them at risk for depression and anxiety. We find that the majority of our participants have clinically significant anxiety and depression. However, degree of malnutrition was not related to level of anxiety and depression. Struggling with an ED for longer time was associated with increased depression and possibly anxiety as well. We also find that those who had relatively high baseline weights prior to weight loss had *lower* depression and anxiety scores than those who had lower baseline weights. Early identification and treatment of individuals with EDs is important, and there are likely other factors beyond malnutrition that we need to understand to identify those at risk for depression and anxiety.

Introduction

Eating disorders (EDs) are psychiatric conditions associated with significant risk of medical complications and high mortality rates.¹ The medical complications of EDs can affect all organ systems and are largely driven by malnutrition.^{2,3} These complications—such as arrhythmias,^{4,5} heart failure,^{4,5} and liver failure^{6,7}—can be fatal,^{4,6} but can also be reversed with weight restoration.⁸ Thus, nutritional rehabilitation often becomes the primary focus of ED treatment.^{7,9,10} Individuals with EDs are also at high risk of co-morbid psychiatric disorders, such as affective disorders, anxiety, and substance use.^{11–13} In fact, the increased mortality rates in individuals with EDs is largely due to the co-morbid mental health conditions leading to high rates of suicide attempts and death by suicide.¹⁴ The risk of death by suicide is more than five times higher in individuals with EDs compared to the general population, and is highest in those with comorbid psychiatric illnesses, such as anxiety and depression.¹⁴ The presence of mental health comorbidities in individuals with EDs has been found to be associated with more severe ED symptoms,¹⁵ worse treatment outcomes,¹⁶ and increased mortality,¹⁷ suggesting that these psychiatric illnesses pose an immense risk if left untreated. Yet for many, the emphasis of ED-related treatment remains on weight restoration first, leaving co-morbid mental health conditions undertreated.¹⁸

The emphasis on weight restoration is largely based on the belief that malnutrition drives much of the commonly seen mood disturbances and anxiety in individuals with EDs¹⁹ and that weight restoration will improve mood and anxiety.^{19–23} Good evidence does exist for the importance of increasing nutritional intake and weight restoration for physical recovery and improvement in ED thoughts and behaviors,^{7–10} but evidence is inconsistent on the effect of malnutrition and weight restoration on co-morbid mental health conditions.^{19–25} This limited understanding of the true impact of malnutrition on anxiety and depressive symptoms among individuals with restrictive EDs makes it difficult to determine whether a primary focus on weight restoration indeed provides the best treatment. Additionally, there is limited

understanding of what other factors increase the risk of developing co-morbid depression and anxiety that in turn may worsen the course of EDs. The evidence for the benefits of improved nutrition is bolstered by the evidence supporting Family Based Treatment (FBT), a treatment modality which focuses primarily on weight restoration as the route for recovery, especially for adolescents with restrictive EDs.³ However, despite FBT having some of the best-documented efficacy of any treatment modality and viewed as the gold standard for youth with restrictive EDs, the full remission rate in studies of FBT is still less than 50%.²⁶ Thus, there are likely other factors that contribute to the lack of recovery in more than half of those seeking treatment. One potential barrier is the under-treatment of co-morbid mood disturbance or anxiety. Therefore, it is crucial that we identify factors that place individuals at risk for developing psychiatric co-morbidities as well as ED treatment strategies that effectively address mental health co-morbidities in order to improve treatment outcomes.

Currently, the few studies addressing the relationship between malnutrition and anxiety and depression focus only on individuals with AN; however, malnutrition and *relative* malnutrition (i.e., being well below one's natural growth pattern) are common in other EDs.^{1,27,28} Individuals with AN suffer from restrictive eating, fear of weight gain, and distorted body image leading to severe malnutrition, and often have low body mass indices (BMIs).¹ Those with other restrictive EDs, such as Otherwise Specified Feeding and Eating Disorders (OSFED) or atypical anorexia nervosa (AAN), also experience psychological symptoms, disordered eating behaviors, and/or medical complications related to malnutrition. Their relative malnutrition is easily missed as patients with AAN by definition have a BMI in a Centers for Disease Control and Prevention (CDC)-defined 'healthy' weight range after unsafe weight loss.^{1,29} Patients with AAN have the same rates of medical complications, anxiety and depression as those with AN, but are more likely to experience severe psychosocial distress related to eating and body image.^{28,30} Because these patients are often missed early in their disease course, they tend to present to care later and with more significant weight loss.^{31,32} Patients with avoidant/restrictive food intake disorder (ARFID), a restrictive ED recently recognized in the DSM-5¹, can also have profound malnutrition. These individuals struggle with inadequate intake due to disinterest, fear of an adverse event when eating, or aversion to certain sensory characteristics of food.¹ As with other restrictive EDs, ARFID is associated with severe malnutrition and significant psychological distress.^{27,33} Therefore, it is crucial that we clarify how malnutrition is associated with anxiety and depression across the spectrum of restrictive EDs (i.e., AN, OSFED, and ARFID) and across the weight spectrum.

In addition to the importance of nutritional rehabilitation, early treatment leading to early weight restoration is associated with improved morbidity and mortality.^{9,34} However, little data is available regarding the impact of rapid nutritional rehabilitation on changes in anxiety and depression, which may be a potential mechanism through which to improve ED outcomes.

In order to address the identified gaps in the literature, we aim to examine the association of the following ED-related characteristics with anxiety and depressive symptoms in adolescents and young adults with restrictive EDs: 1. degree of malnutrition; 2. duration of ED symptoms; and 3. pre-morbid BMI status (i.e.,

elevated pre-morbid BMI v. not). We hypothesize that more severe malnutrition and longer duration of ED symptoms will be associated with higher anxiety and depression scores. We further hypothesize that individuals with higher pre-morbid weight status will have more severe anxiety and depression symptoms compared to those with pre-morbid weight in a 'healthy' range.

Methods

Recruitment

Participants were recruited to enroll in the Registry of Eating Disorders and their Co-morbidities OVER time in Youth (RECOVERY) during a visit to the Boston Children's Hospital's (BCH) Outpatient Eating Disorder Program between 2017–2020. RECOVERY is a web-based, prospective, longitudinal study of youth and young adults with EDs. Participants between the ages of 10 and 27, with a diagnosed ED, seeking care in the BCH ED Program were eligible. For the present study, we included only those participants diagnosed with restrictive ED diagnoses (AN, OSFED/AAN, and ARFID). One patient completed their baseline survey during the COVID-19 pandemic, and was excluded due to the potential confounding effect of the COVID-19 pandemic on mental health outcomes. Informed consent/assent was obtained by a research assistant in person or by phone. Patients ≥ 18 years old provided consent. Patients < 18 years old provided assent and a parent/guardian provided consent. This study was approved by the BCH Institutional Review Board.

Data Collection

RECOVERY participants were e-mailed secure links to online surveys via RedCap. Surveys were sent at baseline and every 3 months in the first year after recruitment, and every 6 months thereafter for up to 3 years of participation. Participants were given remuneration in the form of \$20 gift cards after each survey completed and could receive up to \$180 throughout the course of the study depending on the number of surveys completed. Only the baseline survey data were used for this study. Chart review of the electronic medical records were used to determine the ED diagnosis given by a medical provider, to obtain the most recent BMI corresponding to each survey, and to determine patients' pre-morbid BMI and growth trajectory. Chart review data were confirmed by two reviewers.

Measures

Degree of malnutrition – measured by the percentage of expected BMI (eBMI), calculated by taking the ratio of most recent BMI to the BMI for age at the growth curve expected (e.g., if patient grew at 75th percentile in the past, their eBMI would be the 75th percentile). If patients fluctuated between two curves (e.g., 50-75th percentile) prior to the ED onset, an average would be used as their eBMI (e.g., 62.5 percentile). %eBMI was used to capture the spectrum of malnutrition occurring at all presenting BMIs, and also to capture malnutrition in those who had stalled weight gain rather than weight loss. Severity of malnutrition was then categorized into three groups based on the sample's 25th and 75th percentile of

%eBMIs (84.5% and 96%eBMI). This was then rounded to clinically reasonable cutoffs: moderate/severe malnutrition = < 85%eBMI, mild/moderate = 85-94.9%, and weight restored = \geq 95%.

Length of ED symptoms – obtained by self-report in the baseline survey. Participants were given five options that assessed for length of their ED symptoms, ranging from < 1 month to \geq 3 years. For analysis, answers were collapsed into three clinically meaningful categories: \leq 6 months, 7–12 months, and > 1 year.

Pre-morbid BMI status – determined by the patients' BMI percentile along which they had grown prior to the restrictive ED behaviors and weight loss. Participants were divided into those who had a pre-morbid BMI percentile \geq 75th percentile or < 75th percentile.

Anxiety – measured by the Generalized Anxiety Disorder 7-item (GAD-7) scale, a well-validated tool used to screen for anxiety in adolescents and young adults.^{35,36} The total score for GAD-7 (range 0–21) was examined as a continuous variable (with higher scores indicating more severe anxiety). The standard cut off of 10 indicates clinically meaningful anxiety.^{35,36}

Depression symptoms – measured by the Center for Epidemiologic Studies Depression (CES-D) scale, a 20-item, well-validated tool used to screen for and monitor symptoms of depression in adolescents and young adults.^{37,38} The total score for the CES-D (range 0–60) was examined as a continuous variable (with higher scores indicating more severe depressive symptoms). A cut off of 16 indicates clinically meaningful depression.^{37,38}

Demographics – age, race/ethnicity, sex assigned at birth, and sexual orientation were self-reported in the baseline survey. We included two other self-reported measures from the baseline survey: use of a psychiatric medication and previous higher-level ED treatment (e.g. partial hospitalization or residential level of care). Lastly, the length of time under the care of our ED program was determined by the days between their first ED clinic appointment and when they submitted the baseline survey.

Analysis

We described our sample using frequencies for categorical variables and means (standard deviation) for continuous variables. We addressed our aims first with bivariate analyses using ANOVA, and then with the following linear regression models to adjust for potential confounders. Our two dependent variables (anxiety [GAD-7] and depression symptoms [CES-D]) were examined separately as continuous variables with normal distributions. All analyses were performed using IBM SPSS v24.

1. The association of malnutrition with anxiety and depression symptoms.

This model adjusted for age, sex assigned at birth, sexual orientation, ED diagnosis, and use of psychiatric medication.

2. The association of duration of ED illness and anxiety and depression symptoms.

This model adjusted for prior ED treatment and severity of illness by including degree of malnutrition, past higher level of ED care (HLOC), and time in our care.

3. The association of pre-morbid BMI status and anxiety and depression symptoms.

Using a stepwise method, this model controlled for age, malnutrition, time in our care, and ED diagnosis.

Results

Sample Characteristics (see Table 1)

Table 1 Sample demographics and eating disorder characteristics (N = 145 unless otherwise stated)

	Mean (SD) or n (%)
Age	16.4 (3.0)
Sex assigned at birth	126 (87%)
Female	
Race	129 (89%)
White	
Ethnicity	11 (8%)
Hispanic/Latinx	
Sexual Orientation (n = 143)	91 (63%)
Heterosexual	
ED Diagnosis	123 (85%)
Anorexia Nervosa	8 (6%)
OSFED	14 (10%)
ARFID	
% of Expected BMI	89.7 (9.7)
Duration of ED Symptoms (n = 141)	27 (19%)
≤ 6 months	21 (15%)
7–12 months	93 (64%)
> 1 year	
Previous HLOC	49 (34%)
Yes	
Taking psychiatric medication (n = 135)	67 (46%)
Yes	
<p><i>Note. SD, Standard Deviation; ED, Eating Disorder; OSFED, Otherwise Specified Feeding and Eating Disorder; ARFID, Avoidant/Restrictive Food Intake Disorder; BMI, Body Mass Index; HLOC, Higher Level of ED Care.</i></p>	

Our sample was made up of the 145 participants in the RECOVERY registry who had a diagnosis of a restrictive ED. Mean (SD) age was 16.4 (3.0) years. The majority of our sample were female (n = 126, 87%) and white (n = 129, 89%). Eighty-five percent of our participants had a diagnosis of AN (n = 123), 6% (n = 8) OSFED, and 10% (n = 14) ARFID. Nearly two-thirds (n = 93, 64%) of patients had ED symptoms for over one year, one-third (n = 49, 34%) had previous experience with HLOC, and nearly half (n = 67, 46%)

were taking a psychiatric medication. Mean percentage of eBMI was 89.7% with a range of 57–112% eBMI. Twenty-six percent of participants had moderate/severe malnutrition, 43% had mild/moderate malnutrition, and 30% were weight restored at the time of baseline survey. Of all 145 eligible participants, 142 participants completed the GAD-7 and 140 completed the CES-D, and were ultimately included in the multivariate analyses. Mean GAD-7 score was 9.4 (5.9) and CES-D score was 24 (13.8), with nearly half of those who completed these measures ($n = 69$, 49%) having clinically significant anxiety defined by a GAD-7 score of 10 or greater and 70% ($n = 99$) having a clinically significant CES-D score ≥ 16 .

Multivariate Results (see Table 2)

Table 2 Associations of malnutrition, eating disorder duration, and pre-morbid weight status with anxiety and depression symptoms.

Model	Anxiety			Depression		
	β	95% CI	p-value	β	95% CI	p-value
Malnutrition ^a	Ref	Ref	Ref	Ref	Ref	Ref
Weight restored (<i>ref</i>)	0.07	-2.39, 2.53	0.96	0.48	-5.22, 6.17	0.87
Mild/moderate malnutrition	0.02	-2.74, 2.78	0.99	-0.10	-6.48, 6.28	0.98
Moderate/severe malnutrition						
ED duration on ^b	Ref	Ref	Ref	Ref	Ref	Ref
≤ 6 months (<i>ref</i>)	1.62	-1.98, 5.21	0.38	8.84	0.52, 17.15	0.038*
7–12 months	2.59	-0.23, 5.41	0.071	6.33	-0.23, 12.89	0.059
> 1 year						
Pre-morbid weight status ^c	Ref	Ref	Ref	Ref	Ref	Ref
<75th %ile BMI (<i>ref</i>)	-2.27	-4.70, 0.16	0.067	-7.18	-12.87, -1.48	0.014*
≥ 75 th %ile BMI						
^a Adjusted for age, sex assigned at birth, sexual orientation, ED diagnosis, and use of psychiatric medication.						
^b Adjusted for malnutrition, HLOC, and time under our care.						
^c Adjusted for age, malnutrition, time under our care, and ED diagnosis						
*Statistically significant at $p < 0.05$						

1. Association of Malnutrition with Anxiety and Depression Symptoms

Degree of malnutrition was not associated with either anxiety [mild/moderate vs. weight restored ($\beta = 0.07$; 95% CI [-2.39, 2.53]; $p = 0.96$); moderate/severe vs. weight restored ($\beta = 0.02$; 95% CI [-2.74, 2.78]; $p = 0.99$)] or depression symptoms [mild/moderate vs. weight restored ($\beta = 0.48$; 95% CI [-5.22, 6.17]; $p = 0.87$); moderate/severe vs. weight restored ($\beta = -0.10$; 95% CI [-6.48, 6.28]; $p = 0.98$)] after adjusting for age, sex assigned at birth, sexual orientation, ED diagnosis (AN, OSFED or ARFID), and use of psychiatric medication.

2. Association of Duration of Symptoms with Anxiety and Depression Symptoms

In bivariate analyses, duration of symptoms was not associated with anxiety ($p = 0.16$) or depression ($p = 0.08$), though a trend is notable of increased anxiety scores as the duration of ED symptoms increases (Fig. 1). In our multivariate regressions analyses, compared to those with the shortest duration of ED symptoms (≤ 6 months), those with longer duration of symptoms had higher GAD-7 scores [7–12 months ($\beta = 1.62$; 95% CI [-1.98, 5.21]; $p = 0.375$) and > 1 year ($\beta = 2.59$; 95% CI [-0.23, 5.41]; $p = 0.071$)] after adjusting for malnutrition, HLOC, and time under our care, though the results were not statistically different. Compared to those with the shortest length of ED symptoms (≤ 6 months), patients with symptoms for 7–12 months had significantly higher CES-D scores ($\beta = 8.84$; 95% CI [0.52, 17.15], $p = 0.038$) after adjusting for malnutrition, HLOC, and time under our care. Patients with symptoms > 1 year also had higher CES-D scores than those with symptoms ≤ 6 months, though the difference was not significant ($\beta = 6.33$; 95% CI [-0.23, 12.89]; $p = 0.059$).

3. Associations of Pre-morbid BMI status with Anxiety and Depression Symptoms

In our bivariate analyses, pre-morbid BMI percentile was significantly associated with depression symptoms ($p = 0.02$) but not anxiety ($p = 0.09$), though a similar trend is noted for both measures (Fig. 2). After adjusting for age, malnutrition, time under our care, and ED diagnosis, those with premorbid BMIs ≥ 75 th %ile had significantly lower CES-D scores ($\beta = -7.18$; 95% CI [-12.87, -1.48]; $p = 0.014$) than those who had premorbid BMIs < 75 th %ile. They also had lower GAD-7 scores, though the difference was not statistically significant ($\beta = -2.27$; 95% CI [-4.70, 0.16]; $p = 0.067$).

Discussion

Our study is one of the first to explore the association of multiple restrictive ED characteristics (malnutrition, duration of ED symptoms, and pre-morbid BMI status) with co-morbid anxiety and depression symptoms. The majority of the study participants met or exceeded the cutoffs for clinical anxiety and depression, demonstrating a high rate of clinically significant anxiety and depression in adolescents and young adults with restrictive EDs. We did not find that degree of malnutrition was associated with symptoms of anxiety and depression, after controlling for age, sex assigned at birth, sexual orientation, ED diagnosis, and use of psychiatric medication. Though this was not as we hypothesized, this highlights the importance of other factors that contribute to depression and anxiety in this vulnerable population. Longer duration of ED illness was associated with clinically meaningful and significantly worse depression and clinically meaningful worse anxiety symptoms, supporting the need

for rapid identification and treatment of EDs and its co-morbid mental health disorders. However, contrary to our hypothesis, those who had a pre-morbid BMI \geq 75th percentile had lower anxiety and depression scores than those who had BMIs $<$ 75th percentile prior to weight loss. Though the association with anxiety was not statistically significant, the trend noted is clinically relevant, and an important factor to study further.

It is critical for us to determine whether weight restoration should remain the top priority in ED treatment, or whether optimal treatment includes balanced focus on physical and psychological components of EDs. Some studies of patients with AN have found an association between severity of malnutrition and anxiety/depressive symptoms,¹⁹ and that weight restoration led to improved mental health.^{19–23} However, like us, others have found no statistically significant relationship between degree of malnutrition and depressive symptoms^{24,25} or anxiety,²⁵ and found that depression and anxiety may persist despite weight restoration.^{19,39,40} Given the dangers associated with struggling with both an ED and comorbid psychiatric illness,^{14,16,17} these inconsistent findings highlight the need for more comprehensive ED treatment that focuses on *both* nutritional rehabilitation and mental health treatment.

Our study found that longer chronicity of ED symptoms was related to more severe depression symptoms and identified a potentially similar trend with anxiety. This finding is important to consider in treatment for EDs as negative affect and internalizing symptoms can contribute to more severe ED symptoms,¹⁵ and depression is also associated with lower rates of ED recovery over time.^{42,43} Longer duration of ED illness is overall associated with worse prognosis and treatment outcomes (e.g., weight gain and ED recovery) among individuals diagnosed with AN.^{13,15,41,44,45} However, research on the effect of duration of illness on co-morbid anxiety and depression for individuals with restrictive EDs is generally limited. Our finding is in line with a previous study which showed that depression and anxiety scores were significantly higher for females with AN who had a longer duration of illness.⁴¹ And findings on duration of ED illness consistently suggest that longer duration raises the risk for worse psychological symptoms, worse prognosis, treatment outcomes, and even mortality.⁴⁶ Our study highlights the need for early identification and intervention for individuals with restrictive EDs due to the possibility of worsening depression and anxiety with a longer duration of illness. Our findings also suggest that adapting therapeutic approaches based on the illness duration may be necessary given the association between the duration of illness and psychological correlates of restrictive EDs.

Lastly, our cohort of adolescents and young adults with higher pre-morbid BMIs actually had *lower* anxiety and depression scores at the time of their baseline surveys. Of note, we used a cut off of 75th percentile due to sample size and clinical suspicion that those with a BMI 75th to 85th percentile had similar weight-stigma experiences compared to those who met CDC criteria for overweight/obese (\geq 85th percentile). A sensitivity analysis using the cutoff of 85th percentile had similar findings as the cutoff of 75th percentile (though it was not statistically significant, possibly due to sample size). Potentially, this finding is actually a reflection of improved anxiety and depression after weight loss, as those with higher weights tend to experience more weight stigma and elevated mental health concerns prior to weight

loss.^{47,48} Youth with overweight or obesity often experience weight stigma as weight-based victimization, teasing, and bullying,⁴⁹ and those with restrictive EDs with a higher pre-morbid weight status may experience social reinforcement of their disordered eating behaviors; often patients receive praise as they begin their weight loss.⁵⁰ Other studies have shown that patients with severe obesity experience improved anxiety and depression with a psychosocial weight loss intervention⁵¹ or bariatric surgery.^{52,53} However, we were not able to find studies that have observed the effects of malnutrition, ED treatment, or weight gain on the levels of anxiety and depression in this unique population of patients with higher pre-morbid weights and a restrictive ED. The temporal relationship of the mental health comorbidities in these patients could be enlightening and provide insight on effective ED treatment approaches and priorities for this population.

Our cohort included participants with not just AN, but also other EDs affected by malnutrition, such as OSFED and ARFID. Additionally, our use of eBMI, based on each patient's previous growth trajectory, allowed us to capture the effects of *relative* malnutrition. This is vital for capturing the spectrum of patients who are at different weights. However, our study was not without limitations. The sample size was not large enough to include all variables that could be of clinical significance, so for our third model, a stepwise approach was used to include the most statistically influential variables. There was also large variability in degree of malnutrition, length of time under our care when recruited, and previous experiences with intensive ED treatment. This may have a role in why a cross-sectional association between malnutrition and anxiety and depression was not found. Additionally, as a cross-sectional study, we were unable to capture individuals' changes in anxiety and depression in regards to changes in weight during treatment, a critical question in need of clarification. Therefore, a longitudinal study could be vital for answering many questions. It could demonstrate how weight restoration and rapidity of treatment aid in the treatment of anxiety and depression symptoms in patients with EDs. Additionally, a longitudinal study would allow us to explore how anxiety and depressive symptoms change throughout treatment for all patients, and especially those with high pre-morbid weight statuses.

Conclusions

Our study showed that adolescents and young adults with restrictive EDs are at high risk for anxiety and depression and that severity of malnutrition may not be an independent predictor of the level of anxiety and depression. Many factors are critical for improving treatment outcomes and the chance of ED recovery. We identified that duration of ED symptoms and pre-morbid weight status are two such important factors. Other factors that may contribute to severity of psychological symptoms include pre-existing or co-occurring depression or anxiety,^{54,55} or simply the severity of the ED itself—as more severe ED pathology may be associated with more significant depression and anxiety.^{55,56} Additionally, the literature provides evidence that genetic factors may increase patients' risk of disordered eating, depression, and even suicide,⁵⁷ and hormonal factors such as cortisol and leptin may also have a role in restrictive eating and mental health.^{58,59} Restoring weight and addressing malnutrition may not be the sole factors for full ED recovery. Above all, it is critical that we identify restrictive EDs and mental health

co-morbidities in patients of any weight and that we quickly and efficiently get our patients into comprehensive, multidisciplinary ED treatment.

Abbreviations

AAN – Atypical Anorexia Nervosa

AN – Anorexia Nervosa

ARFID – Avoidant/restrictive Food Intake Disorder

BCH – Boston Children's Hospital

BMI – Body Mass Index

CDC – Centers for Disease Control and Prevention

CES-D – Center for Epidemiologic Studies Depression Scale

CI – Confidence Interval

ED – Eating Disorder

FBT – Family Based Treatment

GAD-7 – Generalized Anxiety Disorder 7-item Scale

HLOC – Higher Level of Eating Disorder Care

OSFED – Otherwise Specified Feeding and Eating Disorder

RECOVERY - Registry of Eating Disorders and their Co-morbidities OVER time in Youth

SD – Standard Deviation

Declarations

Ethics approval and consent to participate

This study was approved by the Boston Children's Hospital Institutional Review Board.

Consent for publication

Consent was obtained for study participation and potential publication, but separate consent was not required for publication as individual data was not published.

Availability of data and materials

The datasets generated and/or analyzed during the current study are not publicly available due to protection of participants' privacy, but may be available from the corresponding author on reasonable request with IRB approval.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

JL designed the study, analyzed and interpreted the data, and was a major contributor in writing the manuscript. GJ assisted with study design, data interpretation, and was a major contributor in writing the manuscript. JV played a major role in recruitment and data collection and was a major contributor in writing the manuscript. CM assisted with study design, data analysis and interpretation and was a major contributor in writing the manuscript. RS played a major role in recruitment and data collection and was a major contributor in writing the manuscript. EW and SF played a major role in study design, data review, and were major contributors in writing the manuscript. TR was a major contributor in recruitment, study design, data interpretation, and writing the manuscript.

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References

1. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders DSM-5®*. 5th ed. Washington D.C.; 2013.
2. Westmoreland P, Krantz MJ, Mehler PS. Medical Complications of Anorexia Nervosa and Bulimia. *Am J Med*. 2016;129:30-37. doi:10.1016/j.amjmed.2015.06.031
3. Campbell K, Peebles R. Eating disorders in children and adolescents: State of the art review. *Pediatrics*. 2014;134(3):582-592. doi:10.1542/peds.2014-0194

4. Neumarker K-J. Mortality and sudden death in anorexia nervosa. *Int J Eat Disord*. 1997;21(3):205-212. doi:10.1002/(SICI)1098-108X(199704)21:3<205::AID-EAT1>3.0.CO;2-O
5. Abed J, Judeh H, Abed E, Kim M, Arabelo H, Gurunathan R. "Fixing a heart": the game of electrolytes in anorexia nervosa. *Nutr J*. 2014;13. doi:10.1186/1475-2891-13-90
6. Rich LM, Caine MR, Findling JW, Shaker JL. Hypoglycemic Coma in Anorexia Nervosa. *Arch Intern Med*. 1990;150(4):894. doi:10.1001/archinte.1990.00390160134027
7. Rautou P, Cazals-Hatem D, Moreau R, et al. Acute Liver Cell Damage in Patients With Anorexia Nervosa: A Possible Role of Starvation-Induced Hepatocyte Autophagy. *Gastroenterology*. 2008;135(3):840-848.e3. doi:10.1053/J.GASTRO.2008.05.055
8. Marzola E, Nasser JA, Hashim SA, Shih PB, Kaye WH. Nutritional rehabilitation in anorexia nervosa: review of the literature and implications for treatment. *BMC Psychiatry*. 2013;13(1):290. doi:10.1186/1471-244X-13-290
9. National Institute for Health and Care Excellence. Eating Disorders: Recognition and Treatment. NICE guideline. nice.org.uk/guidance/ng69. Published 2017. Accessed July 11, 2019.
10. Peebles R, Lesser A, Park CC, et al. Outcomes of an inpatient medical nutritional rehabilitation protocol in children and adolescents with eating disorders. *J Eat Disord*. 2017;5(1):7. doi:10.1186/s40337-017-0134-6
11. O'Brien KM, Vincent NK. Psychiatric comorbidity in anorexia and bulimia nervosa: nature, prevalence, and causal relationships. *Clin Psychol Rev*. 2003;23(1):57-74. doi:10.1016/S0272-7358(02)00201-5
12. Andrés-Pepiñá S, Plana MT, Flamarique I, et al. Long-term outcome and psychiatric comorbidity of adolescent-onset anorexia nervosa. *Clin Child Psychol Psychiatry*. 2020;25(1):33-44. doi:10.1177/1359104519827629
13. Steinhausen H-C. The Outcome of Anorexia Nervosa in the 20th Century. *Am J Psychiatry*. 2002;159(8):1284-1293. doi:10.1176/appi.ajp.159.8.1284
14. Yao S, Kuja-Halkola R, Thornton LM, et al. Familial Liability for Eating Disorders and Suicide Attempts. *JAMA Psychiatry*. 2016;73(3):284. doi:10.1001/jamapsychiatry.2015.2737
15. Monteleone AM, Mereu A, Cascino G, et al. Re-conceptualization of anorexia nervosa psychopathology: A network analysis study in adolescents with short duration of the illness. *Int J Eat Disord*. 2019;52(11):1263-1273. doi:10.1002/eat.23137
16. Eskild-Jensen M, Støving RK, Flindt CF, Sjogren M. Comorbid depression as a negative predictor of weight gain during treatment of anorexia nervosa: A systematic scoping review. *Eur Eat Disord Rev*. 2020;28(6):605-619. doi:10.1002/erv.2787
17. Himmerich H, Hotopf M, Shetty H, et al. Psychiatric comorbidity as a risk factor for mortality in people with anorexia nervosa. *Eur Arch Psychiatry Clin Neurosci*. 2019;269(3):351-359. doi:10.1007/s00406-018-0937-8
18. Bardone-Cone AM, Harney MB, Maldonado CR, et al. Defining recovery from an eating disorder: Conceptualization, validation, and examination of psychosocial functioning and psychiatric comorbidity. *Behav Res Ther*. 2010;48(3):194-202. doi:10.1016/j.brat.2009.11.001

19. Pollice C, Kaye WH, Greeno CG, Weltzin TE. Relationship of depression, anxiety, and obsessiveness to state of illness in anorexia nervosa. *Int J Eat Disord.* 1997;21(4):367-376. doi:10.1002/(SICI)1098-108X(1997)21:4<367::AID-EAT10>3.0.CO;2-W
20. Laessle RG, Schweiger U, Pirke KM. Depression as a correlate of starvation in patients with eating disorders. *Biol Psychiatry.* 1988;23(7):719-725. doi:10.1016/0006-3223(88)90056-X
21. Buehren K, Konrad K, Schaefer K, et al. Association between neuroendocrinological parameters and learning and memory functions in adolescent anorexia nervosa before and after weight recovery. *J Neural Transm.* 2011;118(6):963-968. doi:10.1007/s00702-010-0567-4
22. Accurso EC, Ciao AC, Fitzsimmons-Craft EE, Lock JD, Le Grange D. Is weight gain really a catalyst for broader recovery?: The impact of weight gain on psychological symptoms in the treatment of adolescent anorexia nervosa. *Behav Res Ther.* 2014;56(1):1-6. doi:10.1016/j.brat.2014.02.006
23. Meehan KG, Loeb KL, Roberto CA, Evelyn Attia M. Mood Change During Weight Restoration in Patients with Anorexia Nervosa. *Int J Eat Disord.* 2006;39(7):587-589. doi:10.1002/eat
24. Mattar L, Huas C, Duclos J, Apfel A, Godart N. Relationship between malnutrition and depression or anxiety in Anorexia Nervosa: A critical review of the literature. *J Affect Disord.* 2011;132(3):311-318. doi:10.1016/j.jad.2010.09.014
25. Kawai K, Yamanaka T, Yamashita S, et al. Somatic and psychological factors related to the body mass index of patients with anorexia nervosa. *Eat Weight Disord.* 2008;13(4):198-204. doi:10.1007/BF03327507
26. Lock J, Le Grange D. Family-based treatment: Where are we and where should we be going to improve recovery in child and adolescent eating disorders. *Int J Eat Disord.* 2019;52(4):481-487. doi:10.1002/eat.22980
27. Bourne L, Bryant-Waugh R, Cook J, Mandy W. Avoidant/restrictive food intake disorder: A systematic scoping review of the current literature. *Psychiatry Res.* 2020;288(April):112961. doi:10.1016/j.psychres.2020.112961
28. Sawyer SM, Whitelaw M, Le Grange D, Yeo M, Hughes EK. Physical and psychological morbidity in adolescents with atypical anorexia nervosa. *Pediatrics.* 2016;137(4). doi:10.1542/peds.2015-4080
29. Centers for Disease Control and Prevention. Growth Charts - 2000 CDC Growth Charts - United States. https://www.cdc.gov/growthcharts/cdc_charts.htm. Published 2000. Accessed January 9, 2021.
30. Pauls A, Dimitropoulos G, Marcoux-Louie G, Singh M, Patten SB. Psychological characteristics and childhood adversity of adolescents with atypical anorexia nervosa versus anorexia nervosa. *Eat Disord.* 2020;00(00):1-13. doi:10.1080/10640266.2020.1836907
31. Lebow J, Sim LA, Kransdorf LN. Prevalence of a history of overweight and obesity in adolescents with restrictive eating disorders. *J Adolesc Heal.* 2015;56(1):19-24. doi:10.1016/j.jadohealth.2014.06.005
32. Kennedy GA, Forman SF, Woods ER, et al. History of Overweight/Obesity as Predictor of Care Received at 1-year Follow-Up in Adolescents With Anorexia Nervosa or Atypical Anorexia Nervosa. *J Adolesc Heal.* 2017;60(6):674-679. doi:10.1016/j.jadohealth.2017.01.001

33. Makhzoumi SH, Schreyer CC, Hansen JL, Laddaran LA, Redgrave GW, Guarda AS. Hospital course of underweight youth with ARFID treated with a meal-based behavioral protocol in an inpatient-partial hospitalization program for eating disorders. *Int J Eat Disord*. 2019;52(4):428-434. doi:10.1002/eat.23049
34. Herpertz-Dahlmann B. Adolescent Eating Disorders: Update on Definitions, Symptomatology, Epidemiology, and Comorbidity. *Child Adolesc Psychiatr Clin N Am*. 2015;24(1):177-196. doi:10.1016/j.chc.2014.08.003
35. Spitzer RL, Kroenke K, Williams JBW, Löwe B. A Brief Measure for Assessing Generalized Anxiety Disorder. *Arch Intern Med*. 2006;166(10):1092. doi:10.1001/archinte.166.10.1092
36. Mossman SA, Luft MJ, Schroeder HK, et al. The Generalized Anxiety Disorder 7-item scale in adolescents with generalized anxiety disorder: Signal detection and validation. *Ann Clin Psychiatry*. 2017;29(4). <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5765270/>. Accessed October 12, 2019.
37. Santor DA, Zuroff D, Ramsay JO, Cervantes P, Palacios J. Examining Scale Discriminability in the BDI and CES-D as a Function of Depressive Severity. *Psychol Assess*. 1995;7(2):131-139.
38. Radloff LS. The use of the Center for Epidemiologic Studies Depression Scale in adolescents and young adults. *J Youth Adolesc*. 1991;20(2):149-166. doi:10.1007/BF01537606
39. Holtkamp K, Müller B, Heussen N, Remschmidt H, Herpertz-Dahlmann B. Depression, anxiety, and obsessionality in long-term recovered patients with adolescent-onset anorexia nervosa. *Eur Child Adolesc Psychiatry*. 2005;14(2):106-110. doi:10.1007/s00787-005-0431-5
40. Mattar L, Thiébaud MR, Huas C, Cebula C, Godart N. Depression, anxiety and obsessive-compulsive symptoms in relation to nutritional status and outcome in severe anorexia nervosa. *Psychiatry Res*. 2012;200(2-3):513-517. doi:10.1016/j.psychres.2012.04.032
41. Takakura S, Aso CS, Toda K, Hata T, Yamashita M, Sudo N. Physical and psychological aspects of anorexia nervosa based on duration of illness: A cross-sectional study. *Biopsychosoc Med*. 2019;13(1):1-7. doi:10.1186/s13030-019-0173-0
42. Keshishian AC, Tabri N, Becker KR, et al. Eating disorder recovery is associated with absence of major depressive disorder and substance use disorders at 22-year longitudinal follow-up. *Compr Psychiatry*. 2019;90:49-51. doi:10.1016/j.comppsy.2019.01.002
43. Franko DL, Tabri N, Keshaviah A, et al. Predictors of long-term recovery in anorexia nervosa and bulimia nervosa: Data from a 22-year longitudinal study. *J Psychiatr Res*. 2018;96(July 2017):183-188. doi:10.1016/j.jpsychires.2017.10.008
44. Guarda AS. Treatment of anorexia nervosa: Insights and obstacles. *Physiol Behav*. 2008;94(1):113-120. doi:10.1016/j.physbeh.2007.11.020
45. Wild B, Friederich H-C, Zipfel S, et al. Predictors of outcomes in outpatients with anorexia nervosa – Results from the ANTOP study. *Psychiatry Res*. 2016;244:45-50. doi:10.1016/j.psychres.2016.07.002
46. Franko DL, Keshaviah A, Eddy KT, et al. Do mortality rates in eating disorders change over time? A longitudinal look at Anorexia Nervosa and Bulimia Nervosa. *Am J Psychiatry*. 2013;170(8):917-925. doi:10.1176/appi.ajp.2013.12070868.Do

47. Alimoradi Z, Golboni F, Griffiths MD, Broström A, Lin C-Y, Pakpour AH. Weight-related stigma and psychological distress: A systematic review and meta-analysis. *Clin Nutr.* 2020;39(7):2001-2013. doi:10.1016/j.clnu.2019.10.016
48. Chan KL, Lee CSC, Cheng CM, et al. Investigating the Relationship Between Weight-Related Self-Stigma and Mental Health for Overweight/Obese Children in Hong Kong. *J Nerv Ment Dis.* 2019;207(8):637-641. doi:10.1097/NMD.0000000000001021
49. Pont SJ, Puhl R, Cook SR, Slusser W. Stigma Experienced by Children and Adolescents With Obesity. *Pediatrics.* 2017;140(6):e20173034. doi:10.1542/peds.2017-3034
50. Matthews A, Peterson CM, Mitan L. Adolescent males with atypical anorexia nervosa and premorbid obesity: three case reports. *Eat Weight Disord - Stud Anorexia, Bulim Obes.* 2019;24(5):963-967. doi:10.1007/s40519-019-00702-y
51. Nobles J, Radley D, Dimitri P, Sharman K. Psychosocial Interventions in the Treatment of Severe Adolescent Obesity: The SHINE Program. *J Adolesc Heal.* 2016;59(5):523-529. doi:10.1016/j.jadohealth.2016.06.014
52. Andersen J, Aasprang A, Bergsholm P, Sletteskog N, Våge V, Natvig G. Anxiety and depression in association with morbid obesity: changes with improved physical health after duodenal switch. *Health Qual Life Outcomes.* 2010;8(1):52. doi:10.1186/1477-7525-8-52
53. Thonney B, Pataky Z, Badel S, Bobbioni-Harsch E, Golay A. The relationship between weight loss and psychosocial functioning among bariatric surgery patients. *Am J Surg.* 2010;199(2):183-188. doi:10.1016/j.amjsurg.2008.12.028
54. Touchette E, Henegar A, Godart NT, et al. Subclinical eating disorders and their comorbidity with mood and anxiety disorders in adolescent girls. *Psychiatry Res.* 2011;185(1-2):185-192. doi:10.1016/j.psychres.2010.04.005
55. Puccio F, Fuller-Tyszkiewicz M, Youssef G, et al. Longitudinal Bi-directional Effects of Disordered Eating, Depression and Anxiety. *Eur Eat Disord Rev.* 2017;25(5):351-358. doi:10.1002/erv.2525
56. Measelle JR, Stice E, Hogansen JM. Developmental trajectories of co-occurring depressive, eating, antisocial, and substance abuse problems in female adolescents. *J Abnorm Psychol.* 2006;115(3):524-538. doi:10.1037/0021-843X.115.3.524
57. Thornton LM, Welch E, Munn-Chernoff MA, Lichtenstein P, Bulik CM. Anorexia Nervosa, Major Depression, and Suicide Attempts: Shared Genetic Factors. *Suicide Life-Threatening Behav.* 2016;46(5):525-534. doi:10.1111/sltb.12235
58. Liyanarachchi K, Ross R, Debono M. Human studies on hypothalamo-pituitary-adrenal (HPA) axis. *Best Pract Res Clin Endocrinol Metab.* 2017;31(5):459-473. doi:10.1016/j.beem.2017.10.011
59. Karageorgiou V, Furukawa TA, Tsigkaropoulou E, et al. Adipokines in anorexia nervosa: A systematic review and meta-analysis. *Psychoneuroendocrinology.* 2020;112(October 2019):104485. doi:10.1016/j.psyneuen.2019.104485

Figures

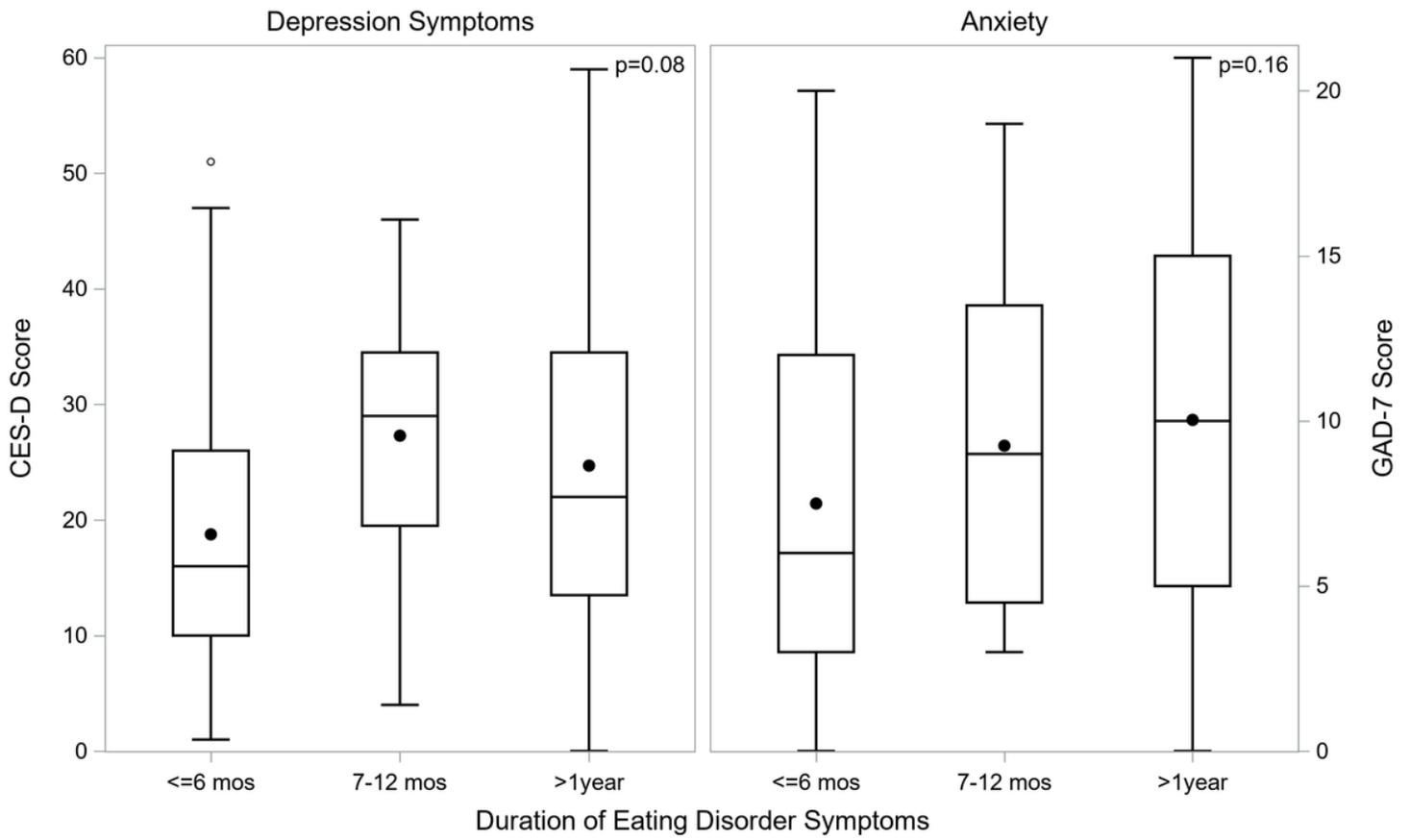


Figure 1

The Unadjusted Differences in Anxiety and Depression Symptoms by Duration of Eating Disorder Symptoms. See separate file for image.

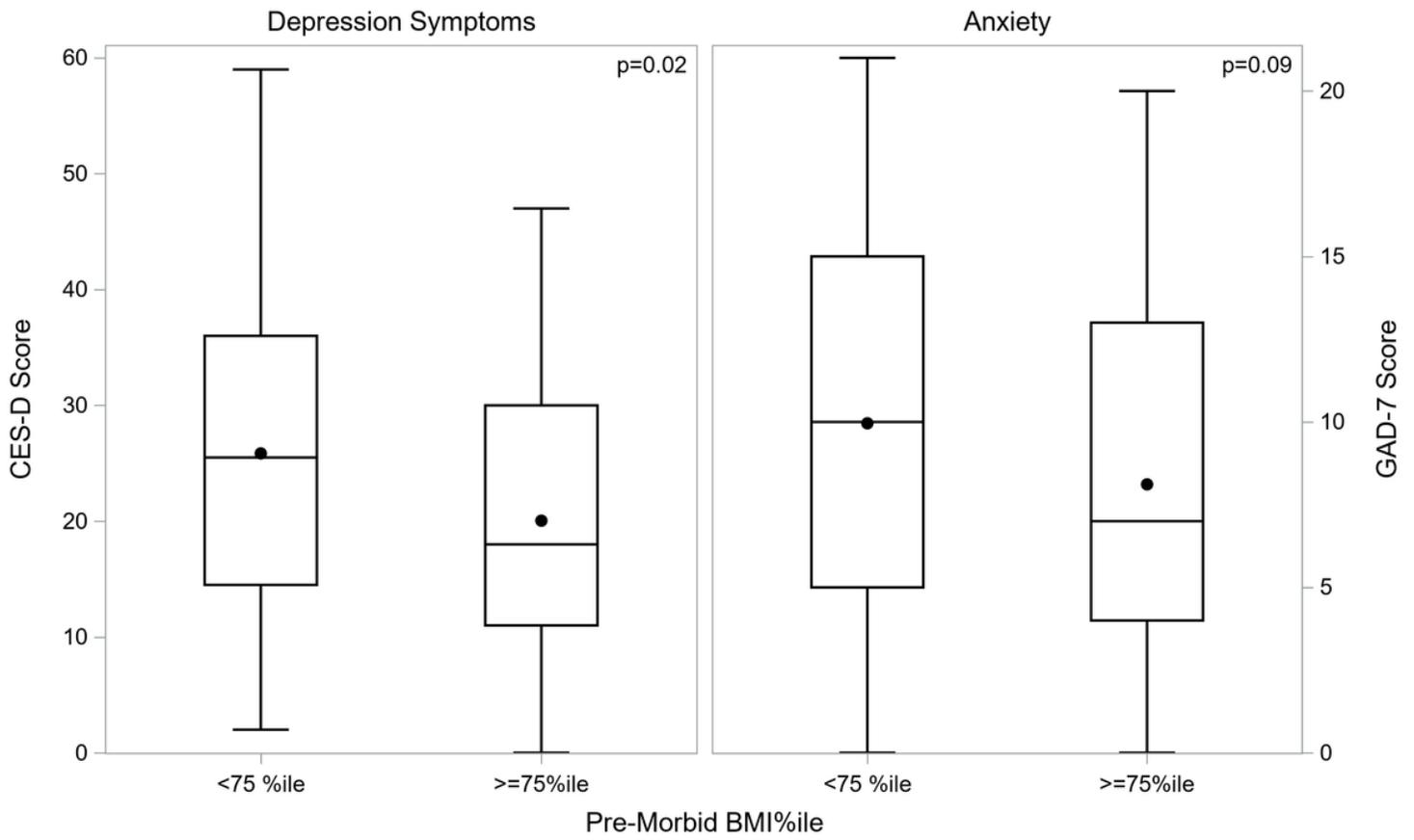


Figure 2

The Unadjusted Differences in Anxiety and Depression Symptoms by Pre-Morbid BMI percentile. See separate file for image.