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#### ORIGINAL RESEARCH

# Childhood Maltreatment and Adolescent Eating Disorders' Symptoms: A Moderated Mediation Model of Social Anxiety and Physical Activity

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**Background:** Childhood maltreatment contributes to an increased risk of eating disorders in adolescents. However, less is known regarding the underlying mechanism between childhood maltreatment and eating disorders' symptoms. This study tested the mediation effect of social anxiety in the association between childhood maltreatment and eating disorders' symptoms and whether this mediation was moderated by physical activity.

**Methods:** A longitudinal study was conducted among 848 students in grades 7–8 from a middle school in Changsha, China. The students completed measurements on childhood maltreatment (Childhood Trauma Questionnaire) at the baseline and measurements on social anxiety (The Social Anxiety Scale-Adolescents), physical activity, and eating disorders' symptoms (The Eating Attitudes Test) after six months. Mediation and moderation analyses were carried out in SPSS macro-PROCESS.

**Results:** Emotional abuse was significantly related to eating disorders'symptoms, and the association was mediated by social anxiety (indirect effect:  $\beta = 0.03$ , 95% CI: 0.01 to 0.05, p<0.05). Furthermore, physical activities moderated the path of emotional abuse to social anxiety ( $\beta = 0.32$ , 95% CI: 0.25 to 0.39, p<0.01) and social anxiety to eating disorders'symptoms ( $\beta = 0.18$ , 95% CI: 0.10 to 0.26, p<0.01).

**Conclusion:** This research emphasizes the importance of social anxiety in the relationship between childhood maltreatment and eating disorders' symptoms. Additionally, these associations are weaker for adolescents with more physical activities, addressing the importance of physical activity in the prevention and management of eating disorders' symptoms.

Keywords: childhood maltreatment, social anxiety, eating disorders, adolescent, physical activity, moderated mediation model

#### Introduction

Eating disorders (ED) are severe psychiatric disorders characterized by maladaptive eating behaviors or excessive attention to food and body weight and size.<sup>1</sup> ED includes anorexia nervosa (AN), bulimia nervosa (BN), binge eating disorder (BED) and so on.<sup>1</sup> The incidence of ED peaks during the early stages of life, especially in youth and adolescence, a critical phase for the development of eating patterns.<sup>2,3</sup> Additionally, recent research has shown a strong correlation between ED and a variety of behavioral and psychosocial problems, including substance abuse, depression, anxiety, and even suicidality.<sup>4–10</sup> Moreover, there has been a 25% rise in the occurrence of eating disorders globally, while only roughly 20% of those impacted seek out medical help.<sup>11,12</sup> In China, ED symptoms are common problems among middle school students, with a prevalence of 8.9%.<sup>13</sup> Given the early onset, high prevalence, and heavy disease burden of ED, investigating the influencing factors and underlying mechanisms of ED symptoms is critical in informing future prevention and intervention efforts.

Research has established a correlation between childhood maltreatment (CM) and the development of ED.<sup>14</sup> CM encompasses various subtypes, such as physical and emotional neglect, as well as physical and emotional abuse (EA).

Two systematic reviews and meta-analyses pointed out that individuals suffering from ED had more exposure to CM compared to other mental disorders, regardless of the specific CM type.<sup>15,16</sup> Additionally, a prospective study revealed that exposure to CM increased the likelihood of developing ED, such as AN and BN, in adulthood.<sup>17</sup> Notably, among all forms of CM, EA has been linked explicitly to symptoms of ED, such as the desire for thinness, body dissatisfaction, and bingeing and purging behaviors.<sup>18,19</sup> A network analysis study also showed that various types of CM were associated with ED core symptoms solely via EA.<sup>20</sup> These results suggest that CM, especially EA, may lead to the emergence of ED.

Previous studies have established a robust connection between CM and ED. However, the specific mechanisms through which CM affects ED symptoms are still unclear. Moderated mediation analysis is a valuable method for evaluating the associations between various factors. Two variables establish the relationship through mediators, whereas moderators affect the triangular relationship.<sup>21</sup> Therefore, identifying mediating and moderating factors from CM to ED symptoms is essential for the interventions of ED symptoms and the minimization of the adverse effects of CM.

# The Mediating Role of Social Anxiety (SA)

Social anxiety (SA) denotes elevated levels of fear in social situations, resulting in notable distress and functional impairment at a clinical level.<sup>17</sup> The association between CM and SA has been extensively documented in scholarly literature. According to Arrindell (1983 and 1989), experiencing inadequate care and rejection of family in childhood have distinct associations with difficulties in interpersonal social interactions.<sup>22,23</sup> Subsequent research has further underscored the predictive role of CM in SA. For instance, several surveys conducted both in clinical and non-clinical populations discovered that CM was linked to more severe SA symptoms and impaired functioning, particularly in cases of emotional abuse and neglect.<sup>24–26</sup>

Furthermore, abundant evidence reveals that SA is a potential risk factor for ED.<sup>27–32</sup> A meta-analysis cited SA as one of the most common comorbid conditions in ED, indicating that higher levels of SA were correlated with more severe ED psychopathology.<sup>33</sup> Moreover, it is reported that SA onset preceded ED in the majority of those with both disorders.<sup>34,35</sup> In addition, according to attachment theory, the way in which primary caregivers respond to children during early childhood (eg, CM) influences an individual's interpersonal relationships or attachment styles in later life.<sup>36,37</sup> The attachment style characterized by avoidance and anxiety may negatively affect interpersonal closeness and intimacy (eg, SA),<sup>38</sup> which have been consistently associated with symptoms of ED.<sup>33,39,40</sup> Therefore, drawing from the findings of the literature review and attachment theory, it is reasonable to hypothesize that SA mediates the relation between CM and ED symptoms.

# The Moderating Role of Physical Activity

The response of adolescents to CM varies, with some able to achieve healthy development despite experiencing maltreatment. However, there has been limited research addressing this topic. Therefore, it's important to explore the potential moderating variables in the pathway from CM to ED symptoms to minimize the adverse outcomes of CM.

Physical activity (PA) refers to any physical movement that raises caloric expenditure beyond the baseline resting level.<sup>41</sup> The World Health Organization (WHO) guidelines recommend that kids and teenagers aged 5 to 17 should participate in at least 60 minutes of daily PA with moderate to vigorous intensity.<sup>42</sup> However, a school-based survey including 11,110 European adolescents found that only 17.9% of boys and 10.7% of girls met the standard for WHO-recommended sufficient PA (60 min/day).<sup>43</sup> PA is known to have a stress-buffering effect, which can mitigate the negative psychological impacts of stressors such as CM.<sup>44</sup> According to the self-decision theory, engaging in behaviors such as PA can satisfy psychological needs, potentially reducing SA to a certain extent.<sup>45,46</sup> Furthermore, PA contributes to greater well-being and lower levels of anxiety in both sexes. A randomized controlled trial (RCT) showed that exercise intervention combined with general cognitive behavior treatment (CBT) was more effective in reducing SA than CBT combined with education.<sup>47</sup> In addition, previous studies also showed that elevated levels of PA were associated with the initiation and continuation of ED.<sup>48,49</sup> One RCT even proposed that physical exercise and dietary therapy could serve as alternative treatments of CBT for ED.<sup>50</sup> However, it remains unknown whether WHO-recommended sufficient PA could moderate the indirect link between CM and ED symptoms through SA in adolescents.

#### The Present Study

To sum up, we tested our proposed model among Chinese adolescents using a longitudinal study design. We aimed to explore whether social anxiety mediated the relationship between CM and ED symptoms and whether this triangular association was moderated by WHO-recommended sufficient PA. Collectively, these two inquiries form a model of moderated mediation. The proposed model is depicted in Figure 1.

# Methods

#### Participants and Procedure

From November to December 2020, 1162 students in grades 7–8 were recruited from a middle school in Changsha City, Hunan, China, using the clustered sampling method. Inclusion criteria included: (a) aged between 11 to 16 years old; (b) enrolled in middle school full-time; (c) willing to participate with informed consent; (d) able to understand and complete the questionnaire survey. We excluded students who were absent due to sickness or other reasons during the research period, as well as those who were not able to complete the questionnaire due to severe physical and mental illness.

Ethical approval was granted by the Ethics Committee of the Second Xiangya Hospital at Central South University. Prior to the survey, we trained school teachers on the procedures for distributing the questionnaire, offering guidance, and assisting students experiencing difficulties in completing the questionnaire. The questionnaires were distributed via WeChat, one of the largest online social media platforms in China. Permission was acquired from both parents and students. Prior to data collection, teachers notified parents and obtained their consent for their children's participation. Then, students accessed the survey using their parents' mobile phones and provided electronic informed consent on the first page of the survey.

A total of 1084 students completed the baseline assessment for CM; among them, 848 completed assessments on ED symptoms and SA six months later, from May to June 2021. Therefore, 848 students were included in the final analysis.

#### Measures

#### Sociodemographic Characteristics

Sociodemographic variables included gender, age, nationality, and only child.

#### CM

CM was evaluated using the Childhood Trauma Questionnaire (CTQ) to explore adverse childhood experiences before the age of 16 by prompting participants to recall and report on their past or present experiences. The CTQ consists of 23 items, categorized into four subscales: emotional abuse, emotional neglect, physical abuse, and physical neglect. Each item utilizes a 5-point frequency scale, ranging from "never happened" (scored as 1) to "always happened" (scored as 5).<sup>51</sup> Higher scores indicated a greater degree of trauma experienced in childhood. The CTQ has demonstrated good internal consistency in the



#### Figure I The proposed model.

current study.<sup>52,53</sup> The previous studies demonstrated that the Chinese adaptation of the CTQ exhibits strong reliability and validity for evaluating childhood trauma.<sup>54</sup>

#### **ED** Symptoms

ED symptoms were assessed using the 26-item Eating Attitudes Test (EAT-26). The scale has demonstrated good reliability, validity, sensitivity, and specificity for measuring ED symptoms, with higher scores indicating the more number of ED symptoms including disturbed eating attitudes and behaviors.<sup>55–57</sup> It is commonly employed in various populations, including students from middle high school and college and individuals with specific risk factors, such as athletes.<sup>58</sup> The Chinese version of the EAT-26 serves as a reliable and valid self-assessment tool for detecting individuals with ED' symptoms in mainland China.<sup>59</sup>

#### PA

The guidelines established by the World Health Organization recommend that children and adolescents engage in a cumulative time of 60 minutes for moderate to vigorous physical activity each day to promote their overall health.<sup>60</sup> Thus, PA was assessed by one self-reported question:

Over the past week, on how many days did you engage in a minimum of 60 minutes of moderate to vigorous physical activity, resulting in an elevated heart rate and occasional heavy breathing?

They could choose from response options ranging from 0 to 7 days per week. This question was selected from the Youth Risk Behavior Survey (YRBS).<sup>61</sup>

#### SA

SA was evaluated using the simplified version of the Social Anxiety Scale for Adolescents (SAS-A).<sup>62</sup> The SAS-A includes 13 items, which are divided into three subscales: Fear of Negative Evaluation, Social Avoidance and Distress in new social situations or with unfamiliar peers, and Social Avoidance and Distress that is more general or pervasive (SAD-G).<sup>62,63</sup> Each item is rated from "not applicable" (scored as 1) to "applicable to me very much" (scored as 5). The SAS-A has demonstrated good internal consistency in the current study.<sup>64</sup>

#### Statistical Analysis

SPSS software (Version 26.0; IB.M, Inc., Chicago, IL) was used for data analyses, with p<0.05 indicating statistical significance. A one-sample Kolmogorov–Smirnov test was performed to assess the normality of continuous. Due to the non-normality of CM, SA, and ED scores, Spearman correlation analyses were conducted to assess their correlations. To examine the hypothesized moderated mediation model, we utilized Model 59 of SPSS PROCESS 4.0 macro. Firstly, Harman's single-factor analysis was conducted to evaluate any potential common method deviation. Afterwards, the influence of PA on the model was analyzed with Model 59, as depicted in Figure 1. We standardized all the continuous variables and calculated interaction terms. Furthermore, the moderation and mediation effect was tested using a bootstrapping method with 5000 samples, with a 95% confidence interval (CI) not including zero indicating a significant effect. All models were adjusted for confounding variables, including age, gender, nationality, and single child.

# Results

After testing Model 59 on each subscale of CTQ and SAS-A, we discovered a significant moderated mediation model, which is depicted in Figure 2.

# Common Method Deviation Test

Harman's single-factor analysis was utilized to examine the presence of common method bias. An exploratory factor analysis was conducted on all the items in the EA, SAD-G, and ED symptoms' scales. The findings indicated that the first factor had an interpretation rate of 30.02%, which was less than 40% of the reference value. As a result, we could infer that the common method deviation was not statistically significant.



 Figure 2 The final moderated mediation model.

 Note: \*\*\*\*p < 0.001.</td>

 Abbreviation: SAD-G, Social Avoidance and Distress that is more general or pervasive.

#### Preliminary Analysis

Table 1 presents the descriptive statistics of all primary study variables, and zero-order correlations for EA, ED symptoms, PA and SAD-G. Results showed that EA was positively correlated with ED symptoms and SAD-G and negatively correlated with PA. Besides, PA was negatively correlated with SAD-G.

#### **Mediation Analyses**

Table 2 displays the outcomes of the mediation analyses. The total effect of EA on ED symptoms (c) was 0.17 (95% CI: 0.11 to 0.24), while the direct effect (c') was 0.14 (95% CI: 0.07 to 0.21). SAD-G was associated with both EA ( $\beta$ =0.27, 95% CI: 0.20 to 0.33) and ED symptoms ( $\beta$ =0.12, 95% CI: 0.05 to 0.19). The bootstrapping index for an indirect impact ( $\beta$ =0.03) as statistically significant with the inclusion of SAD-G as a mediating factor, as the 95% CI did not encompass zero (0.01 to 0.05). SA accounted for 18% of the total effect of EA on ED symptoms.

Variables	M, SD	EA	ED	SAD-G	PA
Age	12.59,0.64				
Gender, n(%)					
male	449(52.9)				
female	399(47.1)				
Nationality, (%)					
Han	803(94.7)				
Others	45(5.3)				
Only Child, (%)					
Yes	505(59.6)				
No	343(40.4)				
EA	7.70, 3.57	1.00	0.15**	0.27**	-0.01
ED	8.26, 10.17	0.15**	1.00	0.19**	0.03
SAD-G	4.05, 2.43	0.27**	0.19**	1.00	-0.11**
PA	4.89, 2.35	-0.01	0.36	-0.11**	1.00

Table I Descriptive Statistics	and	Correlations	of the	Main	Study
Variables					

**Note**: \*\*p < 0.01.

Outcome	SAD-G			ED		
	β	LCI	UCI	β	LCI	UCI
EA	0.27***	0.20	0.33	0.14***	0.07	0.21
SAD-G				0.12***	0.05	0.19
	R-sq	0.11***		R-sq	0.22***	
F		21.31			7.43	

**Note**: \*\*\*p < 0.001.

Abbreviations: N =848; EA, emotional abuse; ED, eating disorders' symptoms; SAD-G, Social Avoidance and Distress that is more general or pervasive; PA, physical activity; LCI, lower 95% confidence interval; UCI, 95% upper confidence interval.

#### Moderated Mediation Analyses

The moderated mediation analysis (Table 3) indicated that PA concurrently moderated the effect of EA on SAD-G ( $\beta$  = 0.32, 95% CI: 0.25 to 0.39) and the effect of SAD-G on ED symptoms ( $\beta$  = 0.18, 95% CI: 0.10 to 0.26). Nevertheless, PA did not show any significant moderating effect in the direct route from EA to ED symptoms ( $\beta$  = 0.12, 95% CI 0.04 to 0.20). The results of moderated mediation for SAD-G are displayed in Figures 3 and 4.

To further investigate the impact of EA on ED symptoms across various PA levels, we categorized PA into two levels based on the WHO guidelines: low PA (<60 min/day) and sufficient PA ( $\geq$ 60 min/day). Table 4 displays the findings. The direct effect of EA on ED symptoms was notably significant in both the low PA group (effect = 0.12, 95% CI: 0.04 to 0.20) and the sufficient PA group (effect = 0.16, 95% CI: 0.01 to 0.30). Furthermore, in the low PA group, the indirect impact of EA on ED symptoms was significant (effect = 0.06, 95% CI: 0.03 to 0.09). However, in the sufficient PA group, the indirect impact of EA on ED symptoms was nonsignificant (effect = -0.01, 95% CI: 0.03 to 0.01), suggesting that the association between EA and ED symptoms was attenuated for adolescents with sufficient PA. The index of moderated mediation is -0.05 with the 95% CI of -0.09 to -0.02.

#### Discussion

Our study showed that SA mediated the relationship between EA and adolescent ED symptoms. Moreover, PA moderated the indirect effect of EA on ED symptoms. Specifically, the effects of EA on SAD-G and of SAD-G on ED symptoms were weaker in the WHO-recommended sufficient PA group, emphasizing the possible protective effect of PA against ED symptoms.

Outcome	SAD-G			ED			
	β	LCI	UCI	β	LCI	UCI	
EA	0.32***	0.25	0.39	0.12**	0.04	0.20	
SAD-G				0.18***	0.10	0.26	
ED							
EA*PA	-0.24**	-0.40	-0.08	0.04	-0.13	0.20	
SA*PA				-0.26**	-0.43	-0.09	
	R-sq	0.36***		R-sq	0.26***		
F		17.37		6.95			

**Table 3** Moderated Mediation Analysis Results for the Relationship Between EA and ED

**Notes**: \*p < 0.05. \*\*p < 0.01. \*\*\*p < 0.001.

Abbreviations: N =848; EA, emotional abuse; ED, eating disorders' symptoms; SA/SAD-G, Social Avoidance and Distress that is more general or pervasive; PA, physical activity; LCI, lower 95% confidence interval; UCI, 95% upper confidence interval.



Figure 3 PA as a moderator between EA and SAD-G.

Abbreviations: SAD-G, Social Avoidance and Distress that is more general or pervasive.



Figure 4 PA as a moderator between SAD-G and ED symptoms. Note: SAD-G: Social Avoidance and Distress that is more general or pervasive.

# The Mediating Role of SAD-G

Our findings indicated that SAD-G mediated the relationship between EA and ED symptoms. This suggests that adolescents who have experienced EA have a higher risk of SAD-G, which further leads to an increased risk of ED symptoms. Previous studies in both clinical and non-clinical samples showed that EA was positively related to ED.<sup>65,66</sup>

	Paths	EA→ED			EA	→SA→El	D
		Effect	LCI	UCI	Effect	LCI	UCI
Low Sufficient		0.12** 0.16*	0.04 0.01	0.20 0.30	0.06* 0.01	0.03 0.03	0.09 0.01

 Table 4 Conditional Direct and Indirect Effects of EA on ED by PA

 Groups

**Notes**: \*p < 0.05. \*\*p < 0.01.

Abbreviations: N =848; EA, emotional abuse; ED, eating disorders' symptoms; SA/ SAD-G, Social Avoidance and Distress that is more general or pervasive; PA, physical activity; LCI, lower 95% confidence interval; UCI, 95% upper confidence interval; EA $\rightarrow$ ED, the direct path from EA to ED symptoms; EA $\rightarrow$ SA $\rightarrow$ ED, the indirect path from EA to ED symptoms through SA.

Our study advanced previous understanding by further exploring the underlying mechanism in the association between EA and ED symptoms among adolescents. Previous studies have identified various mediators between CM and ED symptoms, such as emotion regulation,<sup>18</sup> alexithymia,<sup>67</sup> attachment insecurity,<sup>68</sup> internal shame, and psychological distress.<sup>69</sup> Our study identified a new mediator— SAD-G, which is in line with the attachment theory. This theory pointed out that insufficient care and family rejection during childhood are distinctly linked to challenges in social interactions with others, which further leads to ED.<sup>40,70</sup> EA, as opposed to other forms of abuse, has a stronger tendency to predict the diagnosis of SA.<sup>71</sup> Moreover, EA is closely related to the severity and worse function of SA.<sup>25,72</sup> A systematic review and meta-analysis also revealed the connection between SA and ED.<sup>33</sup> SA is one of the most common comorbid anxiety disorders among ED and a risk factor for ED. Our study extends this conclusion by showing that SAD-G seems to be more closely related to ED symptoms. This may be explained by the attachment theory, in which challenges in social interactions with others caused by EA are more applicable to closer relationships.<sup>70,73</sup> Another explanation may be that SAD-G and ED share some common vulnerability factors, like alexithymia.<sup>74,75</sup> Thus, our integrated model suggests that risk factors in the environmental context (eg childhood EA) may enhance some risk traits (eg, SAD-G), which may in turn increase their ED symptoms tendency.

These findings emphasized the importance of early identification and intervention for adolescents who have experienced EA, as they are at greater risk of developing both SAD-G and ED. Clinicians should consider screening for social anxiety symptoms in patients with a history of emotional abuse and eating disorders, and interventions should target both emotional regulation and social interaction difficulties. Moreover, addressing SAD-G in adolescents could potentially reduce the risk of developing ED symptoms.

#### The Moderating Role of PA

This study revealed that PA moderated the path between EA and SAD-G (first-stage moderation) and the path between SAD-G and ED symptoms (second-stage moderation).

For the first stage of moderation, PA weakens the association between EA and SAD-G. Previous studies have demonstrated that PA has the potential to effectively treat SA or alleviate SA symptoms in both clinical and nonclinical populations.<sup>76</sup> RCT studies also showed that compared to usual treatment, the PA intervention was more effective in reducing SA symptoms.<sup>77,78</sup> Longitudinal studies also proved that SA symptoms were markedly reduced after PA treatment.<sup>79–84</sup>

For the second stage of moderation, PA attenuates the association between SA and ED symptoms. Although excessive and compulsive PA was considered a symptom of ED,<sup>85</sup> some studies also pointed out that moderate PA could decrease the frequency of BED episodes.<sup>86</sup> In the case of AN and BN, incorporating PA into treatment may enhance the quality of life, social interactions, body composition, and overall physical health.<sup>85,87,88</sup> Our findings indicate that PA could be considered as a key component of interventions aimed at adolescents with a history of EA, SA and ED symptoms. Clinicians could encourage physical activity as a comprehensive treatment plan for adolescents with SA and ED symptoms. Additionally, the significance of conducting additional research on different types, intensities, frequencies,

durations, and timing of PA is highlighted by these studies. It is important to identify the specific parameters that have the greatest influence on patients with ED.

# Limitations

Our study has several limitations. First, all data were collected based on self-reported scales, which may result in recall bias. Future studies should consider using multiple informants when collecting data to replicate our findings further. Second, the model was tested on a sample of middle school students, who may not represent other populations. Future studies are needed to test the model in different populations, such as a clinical sample. Third, PA and ED symptoms were assessed based on one self-reported item from the YRBS and EAT-26. Future studies should use more detailed questions and more objective measurement tools to get a more accurate assessment and diagnosis. Additionally, the subgroup analysis with different type of eating disorder (ie, anorexia nervosa or bulimia nervosa) should be considered in further studies. Fourth, CM was assessed using the CTQ, which may capture maltreatment experiences from several years ago and potentially impact the interpretation of the study results. Thus, we will consider longer observation periods in future research designs to better understand the persistence of these effects. Lastly, this study was carried out during the COVID-19 pandemic, which may potentially impact PA, ED symptoms, and SA, Thus, future research should more comprehensively consider the influence of pandemic factors on study outcomes and further explore this association.

# Conclusion

Our findings showed that the CM was associated with ED symptoms both directly and indirectly through SA, this highlights the importance of addressing social anxiety as a key factor in understanding the pathways from EA to ED symptoms. Additionally, PA further moderated the mediation effect, with higher levels of PA buffering the negative effects of EA on SA and, subsequently, on ED symptoms.

These findings carry significant implications and open up possibilities for potential interventions. First, interventions targeting decreasing adolescent SA, particularly in those with a history of CM, may help prevent or mitigate the development of ED. Second, PA could be an accessible, low-cost intervention that can be integrated into both clinical and community settings. Incorporating PA into intervention programs may not only improve psychological outcomes such as SA but also reduce the overall risk of developing ED symptoms. Furthermore, our findings highlight the need for prioritizing prevention and intervention efforts among adolescents with high levels of SA and low PA level. By focusing on this at-risk population, interventions can be more tailored and effective in reducing the incidence of ED symptoms.

# **Abbreviations**

CM, Childhood maltreatment; ED, Eating disorders; SA, Social anxiety; EA, Emotional abuse; SAD-G, Social Avoidance and Distress that is more general or pervasive; PA, Physical activities; CTQ, Childhood Trauma Questionnaire; YRBS, Youth Risk Behavior Survey; EAT-26, The Eating Attitudes Test; SD, Standard deviations; CBT, Cognitive behavior treatment; BED, Binge eating disorder; BN, Bulimia nervosa; AN, Anorexia nervosa; WHO, World Health Organization.

# **Data Sharing Statement**

The datasets used or analyzed during the current study are available from the corresponding author upon reasonable request.

# **Ethics Approval and Consent to Participate**

This study protocol was approved by the Ethics Committee of the Second Xiangya Hospital of Central South University. All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2000. Informed consent was obtained from all patients and their parents or legal guardians to be included in the study.

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#### **Author Contributions**

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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# Disclosure

The authors report no conflicts of interest in this work.

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