Neurobehavioral Functioning in Adolescents With and Without Obesity and Obstructive Sleep Apnea

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Study Objectives: Children and adults with obstructive sleep apnea syndrome (OSAS) exhibit neurobehavioral abnormalities, but few studies have evaluated the transitional stage of adolescence. Obesity is also associated with neurobehavioral abnormalities, and many patients with OSAS are obese. However, the confounding effect of obesity on neurobehavioral abnormalities in adolescents with OSAS has not been evaluated. We hypothesized that obese adolescents with OSAS would exhibit more neurobehavioral abnormalities than obese and lean adolescents without OSAS.

Design: Cross-sectional, case control.

Setting: Sleep Center and community.

Participants: Obese adolescents with OSAS compared to (1) nonsnoring, obese controls without OSAS, and (2) nonobese, nonsnoring controls.

Interventions: Neurobehavioral evaluation.

Measurements and Results: Obese adolescents with OSAS had significantly worse executive function and attention compared to both obese ($P < 0.001$) and lean ($P < 0.001$) controls, and more depression ($P = 0.004$) and externalizing symptoms than lean controls ($P = 0.008$). A higher percentage of participants in the OSAS group scored in the clinically abnormal range on executive functioning, attention, sleepiness, and behavioral functioning than lean controls. Mediation analyses indicated that level of sleep apnea significantly mediated the effect of body mass on executive functioning, attention, and behavior.

Conclusions: Obese adolescents with OSAS show impaired executive and behavioral function compared to obese and lean controls, and are more likely to score in the clinically abnormal range on measures of neurobehavioral functioning. These results are especially concerning given that the frontal lobe is still developing during this critical age period. We speculate that untreated OSAS during adolescence may lead to significant neurobehavioral deficits in adulthood.

Keywords: children, cognition, sleep disordered breathing

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INTRODUCTION

The estimated prevalence of obesity in adolescents in the United States is 18%.[1] Adolescent obesity is associated with significant comorbidities, including obstructive sleep apnea syndrome (OSAS).[2–4] In adolescents, obesity is one of the major etiologic factors for OSAS. As a result, OSAS has become a common disorder, affecting an estimated 2% of adolescents.[5] The medical complications of adolescent obesity and OSAS may be compounded by the adverse short- and long-term neurobehavioral effects of these conditions. Physical health and emotional, social, and school functioning have been reported to be significantly impaired in obese adolescents compared with peers of average weight, even similar to adolescents in whom cancer has been diagnosed.[6,7] OSAS also has been linked to deficits in behavior and emotion regulation, scholastic performance, sustained attention, selective attention, and alertness in children and early adolescents.[8–10] It is possible that OSAS may interrupt the acquisition of cognitive and/or behavioral and emotional regulatory skills in adolescents.[11–13] Obese adolescents with OSAS may, therefore, be at a particularly high risk for neurobehavioral deficits that affect their current level of daytime functioning, including behavior, emotion regulation and mood, social functioning, and cognition (e.g., attention and executive functioning), as well as their future skills and abilities.

OSAS is associated with sleep fragmentation, intermittent hypoxemia, and hypercapnia.[14] These factors may result in neurobehavioral deficits and possibly permanent damage, especially if the insults occur during adolescence, a time of significant neural reorganization and development. The potential neurobehavioral effects of OSAS are well documented in adults and children,[8–10,15,16] yet scientific understanding is significantly less developed for the transitional stage of adolescence.[9,17]

As the pediatric obesity epidemic continues, adolescents are one of the fastest growing groups at risk for developing OSAS.[18] To date, few studies have evaluated the confounding effect of obesity on neurobehavioral functioning in adolescents with OSAS compared to similarly obese and lean adolescents without OSAS. Given the associations of both obesity and OSAS with neurobehavioral dysfunction, the purpose of this study was to evaluate adolescent-reported and parent-reported neurobehavioral functioning in obese adolescents with OSAS compared to obese adolescents without OSAS and lean adolescents without OSAS. We hypothesized that obese adolescents with OSAS would exhibit more neurobehavioral abnormalities on adolescent- and parent-reported measures than would obese and lean controls.

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METHODS

This study was approved by the Institutional Review Board of the Children's Hospital of Philadelphia. Written informed consent was obtained from parents, and assent from adolescents. Subjects underwent a baseline polysomnogram and completed neurobehavioral measures. This study was part of a larger study examining the contribution of structural factors and upper airway reflexes on OSAS in adolescents.[19,20]

Study Group

Adolescents aged 12–16 y who had never undergone adenotonsillectomy or used continuous positive airway pressure (CPAP), were not on psychotropic medications, and did not have any major medical illnesses were eligible. Patients with craniofacial anomalies, neuromuscular disease, or obesity secondary to a genetic syndrome (such as Prader-Willi syndrome) were excluded. Participants with OSAS were recruited from the hospital Sleep Center (OSAS participants only), primary care clinics and obesity clinic (all participants), and from the general community by means of advertisements (all participants). Advertisements specified that the participant need not have sleep problems. Fewer than one third of participants with OSAS were recruited from the Sleep Center; the remainder were recruited from primary care/obesity clinics or the general community but screened positive on the Brouillette OSAS screening questionnaire.[21] Those in the obese and lean control groups were asymptomatic, nonsnoring adolescents, with a normal screening polysomnogram. Tanner pubertal staging was self-reported by the adolescents using a validated questionnaire.[22]

Adolescents were considered obese if their body mass index (BMI) was > 95th percentile for age and sex, and lean if their BMI was < 85th percentile.[23] Adolescents were considered to have OSAS if their obstructive apnea-hypopnea index (AHI) was ≥ 5/h. Because healthy adolescents have few obstructive events during sleep,[24–26] controls were required to have an AHI < 1.5/h. Subjects with an intermediate BMI or AHI were excluded.

Anthropometrics

Weight (to 0.1 kg) was measured on a calibrated digital electronic scale. Standing height (to 0.1 cm) was measured with a stadiometer (Holtain, Crymych, UK). BMI was calculated and converted to BMI z-score.[27]

Polysomnography

A Rembrandt polysomnography system (Embla, Broomfield, CO) recorded the following parameters: electroencephalogram (C3/A2, C4/A1, F_3A_2, F_4A_1, O1/A2, O2/A1), left and right electrooculograms, submental electromyogram (EMG), chest and abdominal wall motion using respiratory inductance plethysmography, heart rate by electrocardiogram, arterial oxygen saturation (SpO_2) by pulse oximetry; end-tidal partial pressure of carbon dioxide (PCO_2) measured by infrared capnometry (Novametrix Medical System, Inc., Wallingford, CT), airflow using a three-pronged thermistor (Pro-Tech Services, Inc., Mukilteo, WA), nasal pressure by a pressure transducer (Pro-Tech Services, Inc., Walnut Cove, NC) and bilateral tibialis anterior EMG. Subjects were continuously observed by a polysomnography technician, and were recorded on video with the use of an infrared video camera. Studies were scored using standard pediatric sleep scoring criteria.[28]

Neurobehavioral Assessments

Study measures include adolescent and parent reports of behaviors that have been associated with sleep disorders.

Executive Function

Executive function was assessed with the Behavior Rating Inventory of Executive Function (BRIEF). Executive function refers to a person's ability to conduct, manage, and regulate cognitive processes responsible for goal-directed behaviors, emotional control, and social interaction.[29] These processes include the ability to plan, initiate, organize, attend, monitor, problem solve, reason, and switch thinking between concepts.[29] The BRIEF is a caregiver-completed questionnaire that yields three summary scores: Behavioral Regulation Index (BRI), Metacognition Index (MI), and the Global Executive Composite scale (GEC).[30] The BRI measures the caregiver's perception of the adolescent's ability to regulate emotions and behavior with appropriate inhibitory control. The MI measures the adolescent's ability to initiate, plan, and organize self-managed tasks, and the GEC yields a summary score of the adolescent's overall performance. A T score ≥ 65 on each scale is considered abnormal.

Attention Problems

Attention problems were evaluated using both the Conners Abbreviated Symptom Questionnaire and the Attention Problems subscale of the CBCL. The Conners scale is completed by the caregiver and measures inattention, distractibility and overactivity. Scores range from 0 to 30, with a score of ≥ 15 considered clinically relevant.[31]

Sleepiness

This measure was assessed using the adolescent-completed Epworth Sleepiness Scale (ESS) modified for children.[32,33] The ESS measures a person's general level of daytime sleepiness detailing an individual's likelihood to fall asleep during common situations.[34] The minor modifications made to the adult version included eliminating the mention of alcohol from question number 7, and question 8 was taken to indicate that the participant was a passenger in the car, in order to be more applicable to a pediatric population.[32] The adult cutoff of > 10 was considered abnormal as normative data are not available for adolescents.

Depression

This measure was assessed using the Center for Epidemiologic Studies Depression Scale (CES-D).[35,36] Adolescents completed this 20-item questionnaire. Higher scores indicate more depressive symptoms. A score ≥ 16 indicates high depressive symptoms.[36]

Behavioral Problems

Behavioral problems and overall psychological functioning were assessed using the Child Behavior Checklist (CBCL).[37] This is a caregiver-completed survey of behavior competencies

that yields standardized, age-adjusted scores on internalizing, externalizing, and total behavior difficulties. Internalizing behavior problems include problems associated with overcontrol of emotions, such as social withdrawal and feelings of worthlessness or inferiority.[37] Externalizing problems include difficulties with interpersonal relationships and rule breaking, as well as emotional undercontrol resulting in irritability and belligerence.[37] In addition to the caregiver CBCL, The Youth Self-Report (YSR) version of the CBCL was completed by the adolescent. For both measures, T scores > 63 are considered abnormal.

Statistical Analyses

Histograms and one-sample Kolmogorov-Smirnov tests of normal distribution were used to examine the distribution of variables, and parametric or nonparametric methods were used as appropriate. Comparisons of continuous variables among the three groups (OSAS, obese control, lean control) were performed using analysis of variance (ANOVA) or the nonparametric equivalent, Kruskal-Wallis test. In order to examine possible effects of race, two-way ANOVA models were examined, with group and race as the two factors. Because of the preponderance of African American subjects, race was dichotomized as African American versus any other race. Pairwise *post hoc* comparisons were performed using the Bonferroni correction method. In addition, Fisher exact tests were used to examine the association between group and status of neurobehavioral scores (i.e., within the clinically abnormal range: Yes/No). Further, we performed Spearman correlations between parent-report and youth self-report CBCL domains (internalizing, externalizing, and total behavior problems).

Regression analyses were performed with BMI z-score and AHI as independent variables, neurobehavioral scores as dependent variables, and BMI-z score × AHI as an interaction term in the model. Further, we explored the possible mediating effects of AHI by constructing mediation models using the bootstrapping (resampling) methods as outlined by Preacher and Hayes.[38] In these mediation models, BMI z-score served as the independent variable, AHI was the mediator variable, and neurobehavioral outcome was the dependent variable.

Because of the testing of multiple outcome measures, we considered adjustment of the significance level for multiplicity. The primary hypothesis was that obese adolescents with OSAS would exhibit greater neurobehavioral abnormalities than obese and lean adolescents without OSAS. Our multiple outcome variables were planned to measure a broad range of neurobehavioral abnormality. The multiple outcome variables were categorized as: (1) sleepiness, (2) behavior and mood, and (3) executive function. Because there were three dimensions of neurobehavioral abnormality, the P value was adjusted for multiple comparisons, which required a $(0.05/3) \leq 0.017$ P value for statistical significance. The SPSS statistical package (IBM, Armonk, NY, USA) was used for statistical analyses.[39]

RESULTS

Study Group

Study group characteristics are shown in Table 1. As expected, BMI z-score differed significantly for lean controls compared to both obese groups ($P < 0.001$), but did not differ between the obese groups.

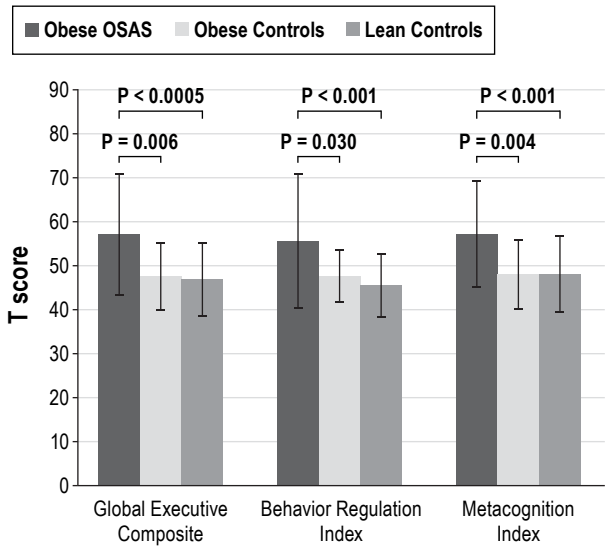

Figure 1—Differences between groups in executive functioning on subscales of the Behavior Rating Inventory of Executive Function are shown. The obese obstructive sleep apnea syndrome (OSAS) group had significantly worse executive functioning on the Global Executive Composite, Behavior Regulation Index, and Metacognition Index compared to both obese and lean control groups. No significant differences were found between the two control groups.

No significant effects of group-by-race interaction were observed for any of the polysomnographic variables or neurobehavioral outcomes with the exception of the modified ESS for sleepiness. Therefore, with the exception of sleepiness, the group-by-race interaction term was omitted from the ANOVA models.

Neurobehavioral Measures

Executive Function

The obese OSAS group had significantly worse executive function on all measures compared to both obese and lean controls (all $P \leq 0.017$) (Figure 1), except for behavior regulation between obese OSAS and obese controls ($P = 0.030$). No differences were found between the obese and lean control groups.

Attention

The obese OSAS group had significantly poorer attention compared to both obese ($P < 0.0005$) and lean controls ($P < 0.0005$) (Figure 2). Similarly, the obese OSAS group had significantly poorer attention on the Attention subscale of the parent-rated behavior scale (CBCL) compared to the obese ($P = 0.001$) and lean controls ($P < 0.0005$).

Depression and Sleepiness

Obese adolescents with OSAS reported significantly increased symptoms of depression ($P = 0.004$) compared to lean controls (Figure 2). Because a two-way ANOVA modeling of ESS indicated a significant group-by-race interaction

Table 1—Participant demographic and polysomnographic characteristics.

Parameter	Obese OSAS	Obese Controls	Lean Controls	P
N	38	21	36	
Age, y	14.3 ± 1.4	14.0 ± 1.5	14.6 ± 1.5	0.32
BMI z-score	2.4 ± 0.4	2.2 ± 0.3	0.1 ± 0.9	**< 0.0005 for obese OSAS versus lean controls and obese controls versus lean controls**
Tanner stage				0.90
Stage 1	0 (0.0)	0 (0.0)	1 (2.8)	
Stage 2	4 (10.8)	3 (14.3)	2 (5.6)	
Stage 3	6 (16.2)	5 (23.8)	8 (22.2)	
Stage 4	19 (51.4)	9 (42.9)	17 (47.2)	
Stage 5	8 (21.6)	4 (19.0)	8 (22.2)	
Male	29 (76.3)	20 (95.2)	32 (88.9)	0.15
Race				0.14
White	5 (13.2)	2 (9.5)	11 (30.6)	
African American	30 (78.9)	19 (90.5)	24 (66.7)	
Other	3 (7.9)	0 (0.0)	1 (2.8)	
Polysomnographic parameters				
AHI (N/h)	10.3 (4.9, 143.4)	0.5 (0.0, 1.3)	0.3 (0.0, 1.6)	**< 0.0005 for obese OSAS group versus obese control group and obese OSAS versus lean control**
Sleep efficiency (%)	85.7 (24.1, 95.5)	79.7 (54.4, 94.9)	83.4 (49.4, 95.9)	0.29
Arousal index (N/h)	24.6 ± 26.1	12.8 ± 4.3	12.1 ± 4.3	**< 0.0005 for obese OSAS versus obese controls and obese OSAS versus lean controls**
Stage N1 (% TST)	7.5 ± 4.6	6.9 ± 2.9	6.0 ± 3.9	0.27
Stage N2 (% TST)	52.4 ± 9.0	49.0 ± 8.1	50.1 ± 8.4	0.31
Stage N3 (% TST)	21.3 ± 8.9	24.1 ± 7.4	23.5 ± 7.4	0.37
REM (% TST)	18.8 ± 7.2	20.0 ± 5.9	20.4 ± 5.7	0.52
SpO_2 nadir (%)	82.5 ± 8.4	93.3 ± 1.6	92.4 ± 5.4	**< 0.0005 for obese OSAS versus obese controls and obese OSAS versus lean controls**
Time with SpO_2 < 90% (%TST)	0.7 (0.0, 40.2)	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)	**< 0.0005 for obese OSAS versus obese controls and obese OSAS versus lean controls**
Peak end-tidal CO_2 (mm Hg)	55.5 ± 5.3	53.9 ± 3.4	52.5 ± 4.5	0.018 for obese OSAS versus lean controls
Time with end-tidal CO_2 > 50 mm Hg (%TST)	4.7 (0.0, 91.9)	1.1 (0.0, 81.4)	0.3 (0.0, 96.4)	**0.003 for obese OSAS versus lean controls**

Data shown as N (%), mean ± standard deviation, or median (minimum, maximum values) for skewed data. Significant differences are indicated by bold print. AHI, apnea hypopnea index; OSAS, obstructive sleep apnea syndrome; REM, rapid eye movement sleep; SpO_2, arterial oxygen saturation; TST, total sleep time.

(P = 0.023), we analyzed ESS results separately for each race (African American and non-African American). We found no group effect for non-African-Americans (P = 0.19), but did find a statistically significant group effect among African Americans (P = 0.005). Pairwise tests indicated within the African American group, obese adolescents with OSAS endorsed more sleepiness than lean controls (P = 0.013). There were no other significant differences between groups on measures of sleepiness and depression.

Behavior

On the caregiver-reported CBCL, the obese OSAS group had significantly increased internalizing (P < 0.0005) and externalizing symptoms (P = 0.008) compared to lean controls,

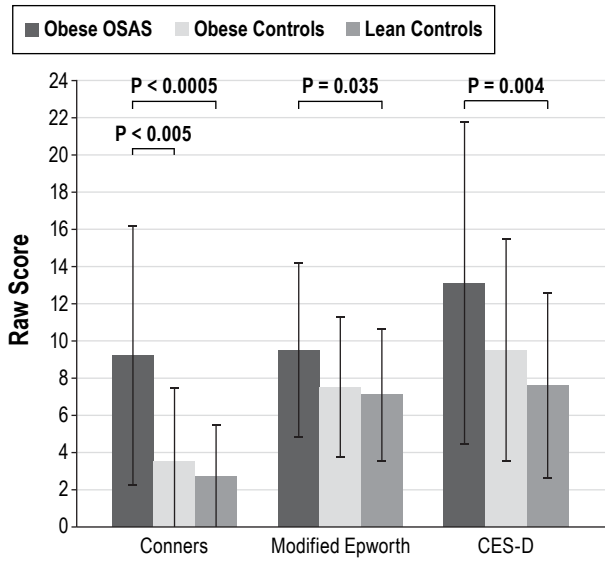

Figure 2—Differences between groups on measures of attention [Conners Abbreviated Symptom Questionnaire (Conners)], sleepiness [Modified Epworth Sleepiness Scale (Modified Epworth)], and depression [Center for Epidemiologic Studies Depression Scale (CES-D)] are shown. The obese obstructive sleep apnea syndrome (OSAS) group reported significantly worse attention, sleepiness, and depression compared to lean controls. They also reported significantly worse attention compared to obese controls. There were no differences between obese and lean controls.

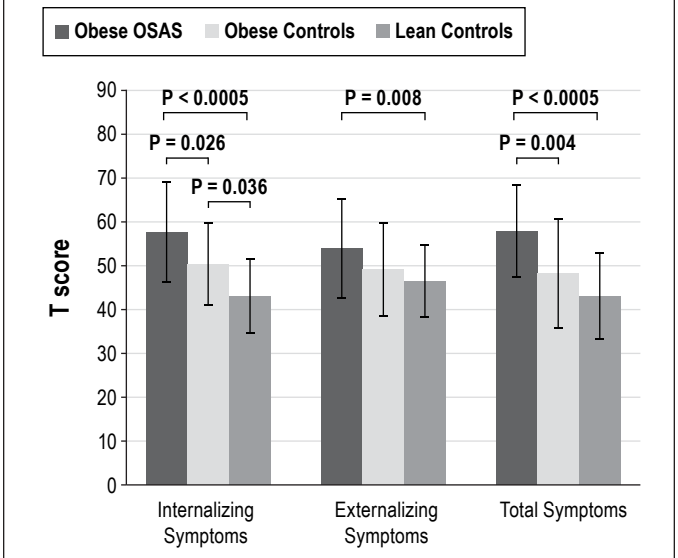

Figure 3—Differences between groups on internalizing, externalizing, and total symptoms on the Child Behavior Checklist are shown. The obese obstructive sleep apnea syndrome (OSAS) group has worse internalizing, externalizing, and total symptoms compared to lean controls, as well as worse internalizing symptoms compared to obese controls. Obese controls have worse internalizing and total symptoms compared to lean controls.

as well as increased total problem behaviors compared to obese ($P = 0.004$) and lean controls ($P < 0.0005$) (Figure 3). On the adolescent-reported behavior scale, compared to lean controls, the obese OSAS group reported significantly increased internalizing behaviors ($P = 0.001$), as well as significantly increased total behavior problems ($P = 0.002$). There were significant correlations between parent and youth self-reported CBCL scores (internalizing symptoms, $r = 0.46$; externalizing symptoms, $r = 0.41$; total problems, $r = 0.44$; attention problems, $r = 0.43$, all $Ps < 0.0001$).

Clinical Group Comparisons

A higher percentage of participants in the obese OSAS group scored in the clinically abnormal range on neurobehavioral measures of executive functioning, attention, sleepiness, and behavioral functioning compared to the lean control group (Table 2). No differences were observed in the percentage of adolescents scoring in the clinically abnormal range between the two control groups, except for youth-reported internalizing and total behavior symptoms (Table 2).

Regression Analyses

As shown in Table 3, BMI z-score was found to moderate ratings of depression ($P = 0.01$), parent-reported internalizing ($P < 0.005$), and total behavior scores ($P = 0.004$) as well as youth-reported internalizing ($P = 0.004$) and total behavior scores ($P = 0.011$). AHI was found to moderate sleepiness ($P = 0.017$), youth-reported internalizing ($P = 0.002$) and total behavior scores ($P = 0.010$). However, in combination, BMI z-score and AHI were found to moderate youth-reported ($P = 0.002$) internalizing behaviors, as well as youth-reported total behavior scores ($P = 0.014$).

Mediation Analyses

As shown in Table 4 and Figure 4, mediation analysis based on 5,000 resamples indicated that the effect of BMI z-score on AHI was statistically significant ($P \leq 0.017$) across all neurobehavioral variables. Mediation analysis further indicated a significant direct effect of AHI, controlling for BMI z-score, on attention and on metacognition, and significant indirect effects of BMI z-score through AHI on attention, parent-reported externalizing, and total behavior scores, and on executive functioning and metacognition.

DISCUSSION

Adolescence is a time of rapid development of problem solving, information processing, judgment, emotion regulation, and abstract reasoning skills, as well as a time when significant behavioral health concerns such as depression or anxiety may begin.[40,41] Hence, factors affecting neurobehavioral functioning during this developmental stage may have a significant effect on neurologic outcomes. The psychosocial and neurobehavioral concerns of obese youth are well documented,[42] yet few studies have controlled for OSAS. The neurodevelopment of obese adolescents with OSAS may be particularly vulnerable, which is highlighted by the findings of the current study.

Based on prior research on OSAS and adolescents,[8,9] as well as the physical development and reorganization of the adolescent brain, particularly the areas responsible for higher-level cognitive function (i.e., attention and executive function) and behavior, mood, and emotional regulation, we chose to focus our study on these aspects of daytime functioning. The current

Table 2—Percentage of participants with neurobehavioral scores in the clinically abnormal range.

	Obese OSAS (%)	Obese Control (%)	Lean Control (%)	Pairwise Fisher exact P value
BRIEF Global Executive Composite T score (≥ 65)	8 (22.3%)	0 (0.0%)	1 (2.9%)	0.021 for obese OSAS vs. obese controls, 0.028 for obese OSAS versus lean controls
BRIEF Behavior Regulation Index T score (≥ 65)	8 (22.3%)	0 (0.0%)	1 (2.9%)	0.021 for obese OSAS versus obese controls, 0.028 for obese OSAS versus lean controls
BRIEF Metacognition Index T score (≥ 65)	8 (22.3%)	0 (0.0%)	0 (0.0%)	0.021 for obese OSAS versus obese controls, **0.005 for obese OSAS versus lean controls**
Modified Epworth Sleepiness Scale (> 10)	5 (13.2%)	2 (9.5%)	1 (2.8%)	0.041 for obese OSAS vs. obese controls, **0.010 for obese OSAS versus lean controls**
Conners Attention Test (≥ 15)	9 (24.3%)	0 (0.0%)	0 (0.0%)	0.020 for obese OSAS versus obese controls, **0.002 for obese OSAS versus lean controls**
CES-D (≥ 16)	11 (28.9%)	5 (23.8%)	2 (5.6%)	**0.013 for obese OSAS versus lean controls**
CBCL Parent Report				
Internalizing symptoms T score (> 63)	12 (31.6%)	2 (9.5%)	0 (0.0%)	**< 0.0005 for obese OSAS versus lean controls**
Externalizing symptoms T score (> 63)	7 (18.4%)	1 (4.8%)	0 (0.0%)	**0.012 for obese OSAS versus lean controls**
Total symptoms T score (> 63)	13 (34.2%)	1 (4.8%)	0 (0.0%)	**0.011 for obese OSAS versus obese controls, < 0.0005 for obese OSAS versus lean controls**
Attention subscale T score (> 63)	11 (28.9%)	1 (4.8%)	0 (0.0%)	0.041 for obese OSAS versus obese controls, **< 0.0005 for obese OSAS versus lean controls**
CBCL Youth Self Report				
Internalizing symptoms T score (> 63)	8 (22.2%)	4 (20.0%)	0 (0.0%)	**0.005 for obese OSAS versus lean controls, 0.013 for obese control versus lean controls**
Externalizing symptoms T score (> 63)	8 (22.2%)	2 (10.0%)	1 (2.8%)	**0.028 for obese OSAS versus lean controls**
Total symptoms T score (> 63)	11 (30.6%)	4 (20.0%)	0 (0.0%)	**< 0.0005 for obese OSAS versus lean controls, 0.013 for obese control versus lean controls**
Attention Subscale T score (> 63)	6 (16.7%)	3 (15.0%)	1 (2.8%)	None

Number in parentheses is the clinical cutoff for that measure. Data shown as n (%). Pairwise trend and significant P values from Fisher exact tests for N of participants with scores in the clinically abnormal range. Significant P values (P ≤ 0.017) are in bold. BRIEF, Behavior Rating Inventory of Executive Function; CBCL, Child Behavior Checklist; CES-D, Children's Depression Inventory; OSAS, obstructive sleep apnea syndrome; YSR, Youth Self Report.

study found that, compared to obese and lean adolescents without OSAS, adolescents with obesity and OSAS experienced impaired executive functioning and increased attention problems, internalizing, and total behavioral symptoms. Obese adolescents with OSAS also experienced increased depressive symptoms and externalizing symptoms compared to lean controls, although not compared to obese controls. In addition, the percentage of obese adolescents with OSAS who scored in the clinically abnormal range on measures of executive functioning, attention, sleepiness, depression, and behavioral problems was higher than lean adolescents without OSAS, whereas there were no differences in the percentage of adolescents scoring in this range between the obese and lean control groups. These results indicate that having obesity and OSAS puts adolescents at higher risk for neurobehavioral dysfunction compared to obese and lean peers without OSAS.

Regression analyses indicated that AHI moderated the effect of BMI z-score on youth-reported internalizing and total symptoms, i.e., the effect of BMI z-score on YSR internalizing and total symptoms was greater with a higher AHI. Mediational analyses revealed a significant direct effect of AHI on attention and executive function, controlling for BMI z-score. Further, it was also shown that AHI had a significant mediating effect on the relationship between BMI z-score and attention, parent-reported externalizing and total behaviors, and executive functioning. To our knowledge, this is one of the first studies to report the interaction and mediation effects between BMI z-score and OSAS on neurobehavioral outcomes in adolescents. However, it is important to note that the degree of obstruction (i.e., the AHI) is only one aspect of OSAS; other sleep or respiratory parameters (such as sleep fragmentation and gas exchange abnormalities) are likely to affect the relationship between BMI z-score and neurobehavioral symptoms. This study was not able to explore all parameters given the limited sample size, but these results provide preliminary insight into the complex relationship of these conditions and neurobehavioral functioning. Future, larger studies should evaluate other parameters of OSAS that may affect neurobehavioral functioning, taking into consideration the level of obesity.

In this study, there was no difference in sleepiness between obese adolescents with and without OSAS. This is consistent

Table 3—Regression results.

Neurobehavioral Outcomes	BMI z-score *B* Coefficient ± SE	AHI *B* Coefficient ± SE	BMI z-score × AHI *B* Coefficient ± SE
Behavior Rating Inventory of Executive Functioning			
GEC (T score)	1.14 ± 1.06	0.67 ± 0.58	−0.17 ± 0.22
P value	0.28	0.25	0.43
BRI (T score)	2.00 ± 1.08	0.41 ± 0.59	−0.10 ± 0.22
P value	0.068	0.50	0.65
MI (T score)	0.74 ± 0.99	0.69 ± 0.54	−0.18 ± 0.20
P value	0.46	0.21	0.38
Modified Epworth Sleepiness Scale	0.44 ± 0.37	0.51 ± 0.21	−0.17 ± 0.08
P value	0.24	0.017	0.029
Conners Attention Test	1.00 ± 0.51	0.43 ± 0.28	−0.11 ± 0.10
P value	0.051	0.13	0.28
CES - D	1.67 ± 0.63	0.57 ± 0.36	−0.21 ± 0.13
P value	0.010	0.12	0.12
Child Behavior Checklist Parent Report			
Internalizing symptoms (T score)	3.56 ± 0.96	1.29 ± 0.55	−0.45 ± 0.20
P value	< 0.0005	0.021	0.029
Externalizing symptoms (T score)	1.26 ± 0.91	0.67 ± 0.52	−0.21 ± 0.19
P value	0.17	0.20	0.28
Total symptoms (T score)	3.02 ± 1.01	1.17 ± 0.58	−0.38 ± 0.21
P value	0.004	0.044	0.075
Child Behavior Checklist YSR			
Internalizing symptoms (T score)	2.72 ± 0.91	1.65 ± 0.51	−0.61 ± 0.19
P value	0.004	0.002	0.002
Externalizing symptoms (T score)	1.06 ± 0.96	0.82 ± 0.54	−0.27 ± 0.20
P value	0.27	0.13	0.18
Total problems (T score)	2.50 ± 0.96	1.42 ± 0.54	−0.50 ± 0.20
P value	0.011	0.010	0.014

Neurobehavioral Variable = BMI z-score + AHI + BMI z-score × AHI. AHI, apnea-hypopnea index; BMI, body mass index; BRI, Behavioral Regulation Index; CES-D, Center for Epidemiologic Studies Depression Scale; GEC, Global Executive Composite; MI, Metacognition Index; SE, standard error.

with other studies showing a link between obesity and sleepiness, independent of the presence of OSAS.[4]

Other studies have shown associations between OSAS and academic and behavioral functioning in children and adults, but results have been mixed in the adolescent population.[8–10,17] In the current study, parental report of executive functioning was significantly affected in obese adolescents with OSAS, as was parental report of internalizing symptoms. These findings are contrary to those of a smaller study of sleep disordered breathing and neurocognitive functioning that used a single office-based administered task with severely obese adolescents,[17] and in another study of OSAS in overweight youth.[9] The potential difference in findings between studies may be related to the type of assessments and sensitivity of measures of executive functioning. For example, the Stroop test, which was used in a prior study,[17] is a single task administered in the clinical setting, whereas the BRIEF assesses a broad range of executive functioning components observed by caregivers in the real-world setting. It is possible that a single administered task performed in a clinic does not fully capture the experience of the adolescent as he or she functions in the world, or that tasks administered in clinical settings are not sensitive to daily alterations in neurobehavioral functioning. It has also been hypothesized that some aspects of executive function may be less affected by OSAS (e.g., emotion-neutral cognitive aspects), whereas other aspects of executive function may be more likely to be affected (e.g., problems that involve affect regulation and motivation such as social and emotional decision-making).[43] Further research examining different components of executive function using a wider range of approaches in obese adolescents with OSAS is warranted. Although other studies did not find associations between OSAS and office-based neuropsychological testing, they did report associations between OSAS and school functioning, as well as reports of behavioral difficulties in real-world situations.[9] Further, in a study of youth with OSAS compared to controls, those with persistent OSAS had increased odds of having behavioral and adaptive functional deficits and were significantly more likely to meet clinical cutoff scores on indices of behavioral and adaptive functioning measures, although the role of obesity was not examined.[8] The results of the current study add to this body of literature by revealing that more adolescents with obesity and OSAS are likely to score in the clinically abnormal range on neurobehavioral measures.

The results of the current study are especially concerning because the prefrontal cortex is still developing during the critical period of adolescence. Although adolescence is associated with increased abstract thinking and a drive for independence, it is also characterized by risk taking and emotional reactivity. These psychological processes are accompanied by cerebral

Table 4—Mediation coefficients and significance.

	Direct effect of AHI on neurobehavioral variable, controlling for BMI z-score		Total effect of BMI z-score on neurobehavioral variable		Direct effect of BMI z-score on neurobehavioral variable, controlling for AHI		Indirect effect of BMI z-score on neurobehavioral variable through AHI
	Coefficient ± SE	P value	Coefficient ± SE	P value	Coefficient ± SE	P value	95% CI: Lower, Upper**
BRIEF (T scores)							
GEC	0.22 ± 0.09	0.020	2.12 ± 0.97	0.032	1.06 ± 1.05	0.32	0.08, 2.13**
BRI	0.14 ± 0.09	0.13	2.65 ± 0.97	0.008	1.95 ± 1.07	0.072	−0.40, 2.06
MI	0.21 ± 0.85	0.015	1.68 ± 0.91	0.068	0.65 ± 0.98	0.51	0.22, 1.97**
Modified Epworth Sleepiness Scale	0.05 ± 0.02	0.049	0.65 ± 0.35	0.066	0.37 ± 0.37	0.32	−0.31, 0.72
Conners Attention Test	0.13 ± 0.04	0.005	1.56 ± 0.47	0.001	0.94 ± 0.50	0.064	0.19, 1.05**
CES-D	0.01 ± 0.04	0.79	1.65 ± 0.58	0.006	1.59 ± 0.63	0.014	−0.33, 0.72
CBCL Parent Report							
Internalizing symptoms	0.08 ± 0.06	0.23	3.84 ± 0.91	0.0001	3.39 ± 0.98	0.0008	−0.17, 1.63
Externalizing symptoms	0.11 ± 0.06	0.053	1.85 ± 0.86	0.033	1.18 ± 0.90	0.20	0.01, 1.48**
Total symptoms	0.14 ± 0.06	0.029	3.72 ± 0.96	0.0002	2.87 ± 1.02	0.006	0.24, 1.76**
CBCL YSR							
Internalizing symptoms	0.02 ± 0.09	0.80	2.53 ± 0.95	0.004	2.43 ± 0.95	0.013	−1.32, 1.18
Externalizing symptoms	0.10 ± 0.09	0.26	1.40 ± 0.87	0.11	0.93 ± 0.96	0.34	−0.52, 1.30
Total symptoms	0.08 ± 0.09	0.39	2.63 ± 0.89	0.004	2.26 ± 0.99	0.024	−0.76, 1.32

The effect of BMI z-score on AHI was statistically significant ($P \leq 0.017$) across all neurobehavioral variables. **If zero is not in the 95% confidence interval, we can conclude that the indirect effect of BMI z-score on the neurobehavioral outcome through AHI is significantly different from zero at $P < 0.05$ (two-tailed). Full mediation is indicated if inclusion of the mediation variable weakens the relationship between BMI z-score (the independent variable) and neurobehavioral outcomes (dependent variable) to zero. Partial mediation maintains that AHI (the mediating variable) accounts for some, but not all of the relationship between BMI z-score (independent variable) and neurobehavioral outcomes (dependent variable). Partial mediation further implies that there is not only a significant relationship between AHI and neurobehavioral outcomes, but also some direct relationship between the BMI z-score and neurobehavioral outcomes. AHI, apnea-hypopnea index; BMI, body mass index; BRI, Behavioral Regulation Index; BRIEF, Behavior Rating Inventory of Executive Function; CBCL, Child Behavior Checklist; CBCL YSR, Child Behavior Checklist Youth Self Report; CI, confidence interval; GEC, Global Executive Composite; MI, Metacognition Index; SE, standard error.

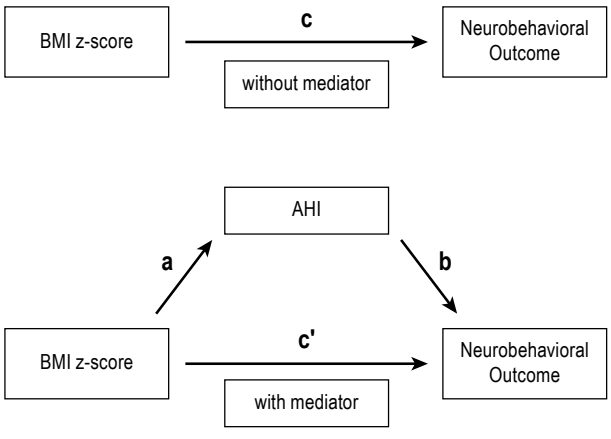

Figure 4—Representative (schematic) of figure demonstrating the impact of mediation. Top panel illustrates a direct effect, BMI (body mass index) z-score affects neurobehavioral outcome directly. Bottom panel illustrates mediation; BMI z-score affects neurobehavioral outcome indirectly through apnea-hypopnea index (AHI). a path: Effect of BMI-z score on AHI. b path: Effect of AHI on neurobehavioral outcome, controlling for BMI z-score. c path: Total effect of BMI z-score on neurobehavioral outcome. c' path: Direct effect of BMI z-score on neurobehavioral outcome, controlling for AHI. c-c': Indirect effect of BMI z-score on neurobehavioral outcome through AHI. Partial mediation is indicated when $0 < c' < c$. Complete mediation is indicated with $c' = 0$.

remodeling and growth, including synaptic pruning and metabolic and neurotransmitter changes in the limbic, subcortical, and prefrontal regions of the brain.[44–46] Imaging studies have shown that axonal alterations within the limbic system, pons, and frontal, temporal, and parietal cortices, and to and from the cerebellum have been reported to be affected by OSAS in adults.[47] These white matter alterations may be a result of repeated intermittent hypoxemia associated with OSAS, repeated deoxygenation/reoxygenation leading to oxidative and inflammatory processes that also affect neurodegeneration, and/or damage caused by stress-related compounds associated with high baseline sympathetic tone or disrupted sleep.[47]

If an adolescent with obesity presents to a primary care office with problems with attention, behavior, mood, and/or school performance, they are often evaluated for attention deficit hyperactivity disorder, depression, or other behavioral health concerns. Given the results of the current study, it is recommended that pediatricians and general practitioners also consider OSAS as an etiologic factor for behavioral problems. However, it is important to note that adolescents who participated in this study may differ from the general clinical population, as individuals were excluded if they had additional comorbidities that could affect OSAS or neurobehavioral functioning such as diabetes, genetic syndromes, developmental disorders, central nervous system disorders, chronic

lung disease, or psychopathology. The findings are, therefore, limited to a generally healthy (other than obesity and OSAS) population.

Most obese adolescents with OSAS are treated with CPAP, as adenotonsillar tissue is usually not prominent at this age. Unfortunately, adherence to CPAP tends to be poor in this age group.[48,49] It is likely that the neurobehavioral deficits uncovered in this study, such as impaired executive function, attention issues, and behavioral problems, contribute to the poor adherence. Efforts to improve CPAP adherence in obese adolescents should take possible deficits in attention and executive functioning into account in the planning of interventions. This is important, as neurobehavioral functioning can improve in children with OSAS following surgical treatment[50] and in children and adolescents using CPAP[48,49]; thus, enhancing CPAP adherence is desirable.

A limitation of the study is the small number of females, although the proportion of females did not differ significantly between groups. Evidence suggests that OSAS is more common in boys during childhood and adolescence, and the sample breakdown of this study is representative of the population.[51,52] Another limitation is the racial breakdown of participants with a high proportion of African Americans, although also not significantly different between groups. However, African Americans are at higher risk for developing both obesity and OSAS[53,54] and are, therefore, a population that may be particularly susceptible to neurobehavioral deficits and health care inequities. It should be noted that measures of socioeconomic status were not collected, which could have confounded neurobehavioral results. Future research is needed to examine the effects of these sociodemographic factors on neurobehavioral functioning in obese adolescents with consideration of OSAS. Further research in a larger sample is also needed to elucidate which demographic or sleep factors determine why some adolescents with OSAS are more susceptible than others to neurobehavioral deficits.

The results of this study are based on parent- and self-report measures, which may be subject to reporting bias and could, therefore, affect the range of T scores seen on the neurobehavioral variables examined in this study. Although reporting bias is always a concern when utilizing questionnaire-based measures, it would be expected that bias existed similarly across the three groups examined in the current study, thereby not unduly influencing findings between groups. Further, we also conducted correlation analyses between scores on the parent- and youth-reported CBCL scales, and found that they were all strongly correlated. We conclude from these results that parent and youth presented with similar perceptions of neurobehavioral functioning. However, the current study is underpowered to assess why there was significant variability among the study sample. Future studies may benefit from including multimodal assessments (e.g., self-report, parent-report, teacher-report, office-based testing) to further elucidate daytime functioning across contexts and observers. With increased power and use of multimodal assessments, more sophisticated analytic techniques could be used, such as structural equation modeling, in which a set of relationships can be examined between one or more independent variables and one or more dependent variables. With a larger sample, structural equation modeling would also better illustrate the concurrent effects of obesity, OSAS, and neurobehavioral functioning because all factors could be examined in a single model.

CONCLUSION

In summary, obese adolescents with OSAS showed impaired neurobehavioral functioning, particularly in executive functioning, even when compared to obese controls. Further, a greater percentage of obese adolescents with OSAS scored in a clinically abnormal range on these measures as compared to obese and lean controls. The results of the current study suggest that pediatricians, general practitioners, and mental health practitioners should consider OSAS as a contributing etiologic factor for attention, behavior, mood, and/or school performance problems in adolescents with obesity. Given the deficits identified in the current study during this sensitive period of brain reorganization, we speculate that untreated OSAS during adolescence may lead to neurobehavioral deficits in adulthood. Future research should evaluate changes following successful treatment of OSAS in obese adolescents and longitudinal outcomes in adulthood.

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