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Behavioral, neurocognitive, polysomnographic and cardiometabolic profiles associated with obstructive sleep apnea in adolescents with ADHD

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Abstract

Background: A high comorbidity between attention-deficit/hyperactivity disorder (ADHD) and obstructive sleep apnea (OSA) as well as similar impairments across neurobehavioral outcomes has been described in children. However, there is a paucity of research examining the comorbidity of these two disorders in adolescents. This study examined the association of OSA with sleep, neurobehavioral, and cardiometabolic outcomes in adolescents with ADHD from the general population.

Methods: 421 adolescents (16.9 ± 2.3 years, 53.9% male) underwent 9-hr polysomnography, neurobehavioral, and physical evaluation. ADHD was ascertained by a parent-or-self-report of a lifetime diagnosis/treatment of ADHD. OSA was defined as an apnea hypopnea index of ≥2 events/hour. Groups of controls (n = 208), OSA-alone (n = 115), ADHD-alone (n = 54), and ADHD+OSA (n = 44) were studied. Multivariable-adjusted general linear models tested group differences in PSG parameters, neurobehavioral, and cardiometabolic outcomes after controlling for sex, race/ethnicity, age, and/or body mass index percentile.

Results: The ADHD+OSA group had significantly longer sleep onset latency, shorter total sleep time, lower sleep efficiency, and higher percent of stage 1 sleep, as compared with all other groups, however, these differences were diminished by excluding adolescents on psychoactive medication. The ADHD-alone group showed significantly higher periodic limb movements than controls. The ADHD+OSA and ADHD-alone groups did not significantly differ on any measure of neurocognitive or behavioral functioning. The ADHD+OSA and OSA-alone groups showed significantly worse cardiometabolic and inflammatory biomarkers when compared to controls or the ADHD-alone, but did not significantly differ between each other.

Conclusions: Adolescents with a diagnosis ADHD+OSA showed phenotypic risk factors for OSA (i.e., overweight/obesity, visceral adiposity, metabolic syndrome, and inflammation) but not worse neurobehavioral outcomes when compared with ADHD-alone. While comorbidity is

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possible, these data support that adolescents with a suspicion of ADHD should be screened for OSA, before a diagnosis is reached and psychoactive medication initiated.

Keywords

OSA; ADHD; adolescence

Introduction

Youth with ADHD are at increased risk for exhibiting parent-reported, self-reported, and objectively-measured sleep problems, with comorbid sleep difficulties occurring in 25%–50% of this population (Owens, 2009). Psychotropic medications frequently used to treat ADHD, and psychiatric comorbidities, can have direct effects on sleep and neurocognitive functioning, reflecting the underlying complexity and multidirectional nature of the link between ADHD and sleep disturbances. The prevalence of obstructive sleep apnea (OSA) ranges from 20–30% among youth with ADHD (Youssef, Ege, Angly, Strauss, & Marx, 2011) and those with OSA exhibit more externalizing behaviors than controls (Perfect, Archbold, Goodwin, Levine-Donnerstein, & Quan, 2013). This suggests that pediatric ADHD and OSA may share similar sequelae including sleep, neurocognitive, and behavioral difficulties.

Youth with ADHD are also at increased risk for other sleep difficulties, including longer sleep-onset latency (SOL), more shifts in sleep stages per hour, shorter total sleep time, lower sleep efficiency, elevated periodic limb movements (PLMS), and greater daytime sleepiness (Cortese, Faraone, Konofal, & Lecendreux, 2009). However, these difficulties are not consistently confirmed using objective sleep measures (Sadeh, Pergamin, & Bar-Haim, 2006). Therefore, there is a need to understand whether the comorbidity of ADHD with OSA is associated with specific sleep disruption, as measured by polysomnography (PSG).

Ample studies have supported the presence of neurocognitive deficits as well as diverse behavioral problems in youth with ADHD (Halperin et al., 2013). Neurocognitive deficits have also been found to be impaired in youth with OSA (Chan et al., 2014), however, contradictory results and lack of association with severity of OSA across studies have been reported (Beebe, Groesz, Wells, Nichols, & McGee, 2003; Calhoun et al., 2009; Owens, Spirito, Marcotte, McGuinn, & Berkelhammer, 2000). These studies suggest that the association between OSA and neurocognitive functioning may be apparent only in specific domains or best explained by shared underlying mechanisms. Behavioral problems such as elevated inattention and hyperactivity have also been noted in this population, mirroring symptoms of ADHD (Owens, 2009); suggesting that some children with OSA may be misdiagnosed as having ADHD. Youth with OSA have also been shown to exhibit greater levels of internalizing symptoms (Gozal & Kheirandish, 2007; Yilmaz, Sedky, & Bennett, 2013). Given the similarities in neurocognitive deficits and behavioral problems in youth with OSA and ADHD independent of each diagnosis, the comorbidity of these disorders may result in even greater neurocognitive and behavioral problems.

Another important domain to take into consideration when examining the association of OSA with ADHD is the specific phenotypic risk factors. Multiple studies have demonstrated

that OSA is associated with worse anthropometric, cardiovascular, and metabolic outcomes and may play a causal role in the development of cardiometabolic disease (Gaines, Vgontzas, Fernandez-Mendoza, & Bixler, 2018). Although the association of anthropometric (i.e., obesity) and cardiometabolic (i.e., blood pressure) outcomes with OSA is present in young children (Bixler et al., 2008, 2009; Gozal, 2009; Gozal, Capdevila, & Kheirandish-Gozal, 2008), it becomes even stronger in adolescents (Fernandez-Mendoza et al., 2021; Gaines et al., 2016, 2018). It is plausible that adolescence may be a critical developmental stage in which OSA becomes a manifestation of the metabolic syndrome (MetS; Gaines et al., 2018), with visceral adiposity, insulin resistance, and inflammation being key etiopathogenic mechanisms (Frye, Fernandez-Mendoza, Calhoun, Gaines, et al., 2018). However, it is unclear whether adolescents diagnosed with ADHD who also have OSA have the same anthropometric and cardiometabolic characteristics as those with OSA-alone, or whether such comorbidity is independent of those factors.

Although a high comorbidity between ADHD and OSA as well as similar impairments across sleep and neurobehavioral outcomes in youth have been reported, there is a paucity of research examining the differential association of the comorbidity of these two disorders in adolescents. The similarity in the presentation of symptoms between ADHD and OSA, as well as medication use, makes the relationship complex and potentially confounds both the diagnosis and clinical management of each disorder. Compounding this complexity are the normative biological, psychological, and social changes that characterize adolescence and influence sleep, cognition, and cardiometabolic biomarkers. As such, we examined the association of ADHD and OSA with physiologic sleep parameters, objective neurocognitive measures, parent/self-reported behavioral outcomes, and anthropometric and cardiometabolic biomarkers. Given the known impact of medication use on sleep and neurocognitive functioning, we also examined the association of ADHD and OSA with sleep, neurocognitive, behavioral, and cardiometabolic outcomes while excluding adolescents on stimulant or other psychoactive medications. We hypothesized that adolescents with ADHD+OSA would display greater objective sleep disruption, poorer neurocognitive, and behavioral functioning and worse cardiometabolic health outcomes as compared to adolescents with OSA-alone, ADHD-alone, or controls.

Methods

Population

The Penn State Child Cohort (PSCC) is a sample of 700 children between ages 5–12 years, which was established to examine the prevalence of OSA in a population-based child sample recruited from 18 elementary schools within 3 school districts of Dauphin County, Pennsylvania (Bixler et al., 2009, 2016). Of these subjects, 421 participated in the adolescent follow-up (60.1% response rate) and comprise the present study sample (aged 12–23; 53.9% male, 21.9% racial/ethnic minority). Participants were studied in the Clinical Research Center at Penn State Hershey. After undergoing a whole-body scan, physical exam, neurocognitive, and behavioral testing and saliva sampling, participants underwent an overnight polysomnography (PSG) recording. Morning blood and saliva samples were

collected after the overnight fasting. Participants provided written informed consent. Penn State Hershey Institutional Review Board approved the study protocol.

Measures

PSG.—All participants' sleep was monitored for 9 hr with a seven-channel electroencephalography (EEG), electrooculography, and electromyography (EMG). Sleep records were scored according to standardized criteria (Rechtschaffen, & Kales, 1968). Respiration was monitored with nasal pressure, thermocouple, and thoracic and abdominal strain gauges, while hemoglobin oxygen saturation (SpO_2) was obtained from the finger. As previously reported (Bixler et al., 2016), apneas and hypopneas were scored using pediatric criteria in subjects aged <16, while adult criteria was used in subjects aged ≥16, including associated decreases in SpO2 of ≥3% or an EEG arousal for hypopneas (Iber, Ancoli-Israel, Chesson, & Quan, 2007). The apnea/hypopnea index (AHI) was calculated as the number of apneas and hypopneas summed per hour of sleep. The average apnea/hypopnea index (AHI) was 2.7 ± 5.6 events/hour. OSA was defined based on pediatric criteria as AHI≥2 (Bixler et al., 2016).

PLMS were recorded via tibial EMG and scored based on standardized criteria (i.e. four leg movements within 90 s of at least 0.5 s in duration and five seconds apart). Abnormal PLMS were defined based on pediatric criteria as PLMI ≥ 5 (Frye, Fernandez-Mendoza, Calhoun, Vgontzas, et al., 2018).

Physical exam, clinical history, and ADHD.: Tanner staging was measured using a standardized self-reported scale (Carskadon, & Acebo, 1993). The age-and-sex adjusted body mass index (BMI) percentile was calculated based on growth charts for measured height and weight (Kuczmarski, 2002). Waist circumference was measured at the top of the iliac crest.

The participant/parents reported on the presence of a lifetime history of a psychiatric/behavioral disorder diagnosis with the question "Has your child ever been treated for a psychiatric/behavioral disorder?" and specification of the disorder was ADHD and current or past treatment (Frye, Fernandez-Mendoza, Calhoun, Vgontzas, et al., 2018). Most adolescents with ADHD reported a current history of treatment ($n = 71$), whereas only about a third reported a past history of treatment ($n = 27$). Key clinical characteristics of adolescents with a past or current history of treatment for ADHD did not differ between each other; for example, there were no significant differences between them on AHI (3.4 ± 5.4 vs. 3.0 ± 5.0, $p = .755$), PLMI (6.4 ± 8.4 vs. 5.0 ± 6.7, $p = .295$), PLMS (33.3% vs. 36.6%, $p = .762$), processing speed (8.8 ± 1.9 vs. 8.8 ± 2.2, $p = .984$), working memory (5.6 ± 2.3 vs. 6.3 ± 2.3, $p = .227$), control interference (42.7 ± 6.7 vs. 41.2 ± 10.1, $p = .448$), or CBCL's global behavioral problems (54.2 ± 7.8 vs. 56.1 ± 10.3, $p = .394$). Additionally, elevated CBCL-ADHD scores (≥60 and ≥70) were present in 12.1% and 2.4% of controls, 16.2% and 1.8% of OSA-alone, 56.6% and 17.0% of ADHD-alone, and 54.5% and 15.9% of ADHD + OSA, respectively. Current use of stimulants and other psychoactive medications ($n = 67$) was recorded and classified by a pediatric nurse.

Excessive daytime sleepiness (EDS).: Adolescents were classified as having self-reported EDS when they reported “yes” for “Do you have a problem with sleepiness during the day?” and classified as having observed EDS when, in addition, they reported “yes” for “Has a teacher or other supervisor commented that you appear sleepy during the day?”

Neurocognitive functioning.: All participants underwent a 2.5-hr neurocognitive evaluation in the afternoon prior to the PSG administered by a trained psychometrist. The *Gordon Diagnostic System*, a continuous performance test, was administered, which measured vigilance and distractibility (Gordon, & McClure, 1983). The *Wechsler Intelligence Scale for Children*, *Fourth Edition* (Wechsler, 2003) or *Wechsler Adult Intelligence Scale, Third Edition* (Wechsler, 1997) assessed processing speed (Coding and Symbol Search) and working memory (Digit Span backward). The *Stroop Color and Word Test*, Child (Golden, Freshwater, & Zarabeth, 2003) and Adult Versions (Golden, 2002), measured executive functioning that involves control interference. *The Wechsler Abbreviated Scales of Intelligence* measured verbal, performance, and full-scale intelligence (Wechsler, 1999). Math and reading achievement was assessed using the *Wide Range Achievement Test, Third Edition* (Wilkinson, 1993).

Behavioral functioning.: The *Child Behavior Checklist*, was completed by the parents of participants aged 12–17 years and self-reported on the *Adult Behavior Checklist* if participants ≥18 years. For each scale and subscale, T-scores with a mean of 50 and a standard deviation of 10 were obtained (Achenbach, & Rescorla, 2001, 2003) and elevated scores were defined as a T-score ≥ 60 or ≥70, as noted above.

Dual-energy X-ray absorptiometry (DXA) scan.: Whole-body scans were performed using a Hologic-Discovery-W scanner (Hologic Inc., Waltham, MA). Android region, gynoid region, visceral, and subcutaneous adipose tissue were selected as regions of interest (ROI). All ROI were identified by Hologic APEX 4.0 software and verified by an experienced certified technician. Android/gynoid fat mass ratio, android/whole body fat mass proportion, gynoid/whole body fat mass proportion, visceral and subcutaneous areas were used in this study (Frye, Fernandez-Mendoza, Calhoun, Gaines, et al., 2018).

Continuous MetS score.: cMetS, derived from a *Z*-score approach, was used to represent the MetS risk (Eisenmann, Laurson, DuBose, Smith, & Donnelly, 2010). To be consistent with the adult MetS criteria, five established MetS components were included to quantify metabolic burden: waist circumference, mean arterial pressure (calculated as diastolic pressure+1/3 systolic pressure), homeostasis model assessment of insulin resistance (calculated as fasting insulin level*glucose level/22.5), fasting triglycerides (TG), and inverse fasting high-density lipoprotein (HDL). The five individual components were age and gender-adjusted and converted to Z-scores then summed to create the cMetS. A higher score indicates a higher MetS burden.

Hypothalamic-pituitary-adrenal (HPA) axis.: An evening saliva sample (18:00–19:00) before dinner and a morning saliva sample (06:00–07:00) before breakfast were obtained for cortisol and stored in salivary tubes in a 20°C freezer until assayed. Cortisol

concentrations were assessed using commercially available enzyme immunoassays (EIA; ALPCO Diagnostics, Salem, NH, USA).

Inflammatory biomarkers.: A blood sample was provided by 392 (93.1%) of the 421 participants at 07:00 following the evening PSG recording. Samples were collected in an ethylenediamine tetraacetic acid-containing tube, centrifuged, and aliquoted into cryotubes and stored at 80°C until assayed. Plasma biomarkers were measured via enzyme-linked immunosorbent assay (R&D Systems; Minneapolis, MN). The intra- and interassay coefficients of variation have been reported elsewhere (Gaines et al., 2016).

Statistical analysis

Categorical and continuous variables were analyzed with Chi-square test and analysis of variance, respectively. We defined a priori four mutually exclusive groups consisting of ADHD+OSA, ADHD-alone, OSA-alone, and controls (i.e., reference group without ADHD or OSA). Multivariable-adjusted general linear models examined differences between the four study groups on PSG parameters and neurobehavioral outcomes after controlling for sex, race, age, BMI percentile, and on anthropometric, cardiometabolic, stress, and inflammatory biomarkers controlling for sex, race, and age. Sensitivity analyses were conducted by excluding subjects on stimulant and/or other psychoactive medications. The critical statistical confidence level for all analyses was $p < .05$, two-tailed. Cohen's d effect sizes were also calculated and are provided in Tables S1–S3. All analyses were performed using SPSS Statistics version 25.

Results

Demographic and clinical characteristics

The demographic and clinical characteristics of the sample are presented in Table 1. Overall, adolescents with ADHD + OSA were significantly more likely to be older ($p = .008$) and obese ($p < .001$), than those with ADHD-alone, and more likely to report observed EDS ($p = .016$) than those with OSA-alone. Those with ADHD-alone were more likely to be male ($p < .001$) and normal weight ($p = .037$), when compared to controls. Adolescents with ADHD-alone and ADHD + OSA were equally likely to be taking stimulant ($p = .675$) or other psychoactive medications ($p = .952$). Among those with ADHD-alone, 38.5% had a comorbid learning disorder and 28.8% a comorbid internalizing disorder, while, 20.5% of those with ADHD+OSA had a comorbid learning disorder, 20.0% a comorbid externalizing disorder, and 15.3% a comorbid internalizing disorder.

Polysomnographic parameters

Compared to controls, the OSA-alone group had significantly higher number of awakenings ($d = 0.25$) indicating a small effect size, while the ADHD-alone group had a significantly higher PLMI ($d = 0.47$) and percent of PLMS (Table 2). The ADHD + OSA group had significantly longer SOL, shorter TST, lower SE, and higher percent of stage N1, as compared to all other study groups ($d = 0.33–0.60$) indicating small-to-medium effect sizes, as well as higher number of awakenings when compared to the ADHD-alone group ($d = 0.40$) indicating a small-to-medium effect size. After excluding adolescents on stimulant

medication (Table S4) and other psychoactive medications (Table S5), adolescents with ADHD + OSA had significantly higher number of awakenings and those with ADHD-alone higher PLMI and percent of abnormal PLMS, when compared to controls. However, no significant differences were found between the two groups for other sleep continuity parameters.

Neurobehavioral functioning

As expected, the ADHD-alone group significantly differed from controls on all measures of neurocognitive and behavioral functioning (d = 0.33–1.60) indicating small-to-large effect sizes, except for anxious-depressed, somatic complaints, and somatic problems (Table 3). Similarly, the ADHD+OSA group significantly differed from controls on all measures of neurocognitive and behavioral functioning (d = 0.31–1.41) indicating small-to-large effect sizes, except for distractibility and internalizing problems. The ADHD-alone group significantly differed from the ADHD+OSA group only on processing speed (d = 0.42) indicating a small effect size. When excluding adolescents on stimulant or other psychoactive medications (Table S6), similar differences, or lack thereof, between groups were found. However, adolescents in the ADHD-alone group no longer significantly differed from controls in internalizing problems.

Cardiometabolic, stress, and inflammatory biomarkers

Compared with controls or the ADHD-alone group, adolescents with OSA-alone and ADHD+OSA had significantly more subcutaneous and visceral fat and higher android/whole body ratio, MetS score, and CRP levels (d = 0.16–0.74) indicating small-to-medium effect sizes (Table 4). There were no statistically significant differences in any biomarker data between the ADHD + OSA group and the OSA-alone group, except leptin levels that were marginally higher in the ADHD + OSA group than in the OSA-alone group. However, after excluding adolescents on stimulant or other psychoactive medications, the ADHD + OSA group's leptin levels (14.2 ± 2.2) were not significantly higher when compared with the control (11.8 ± 0.8, p = .317), OSA-alone (13.1 ± 1.1, p = .647) or ADHD-alone (9.4 ± 2.0, p = .108) groups.

Discussion

This is the first population-based study to examine the association of OSA with polysomnographic parameters, neurocognitive and behavioral outcomes, and cardiometabolic, stress, and inflammatory biomarkers in adolescents diagnosed with ADHD. Our data showed that adolescents with ADHD + OSA present differential cardiometabolic profiles as compared to adolescents with ADHD-alone. However, contrary to our hypothesis, ADHD + OSA did not lend to worse executive functioning or behavioral problems, indicating that the presence of OSA is not associated with greater severity of ADHD from a neurocognitive and behavioral standpoint. Adolescents with ADHD + OSA showed a cardiometabolic profile characterized by increased visceral adiposity, MetS, and low-grade inflammation, which provided phenotypic characteristics strikingly different from those with ADHD-alone and identical to those with OSA-alone. These data reject the hypothesis that OSA in adolescents with ADHD is related to etiopathogenic mechanisms distinct from those

found in adolescents with OSA-alone or that it represents a (sub)phenotype of ADHD. Collectively, these findings further support that screening and assessment protocols for ADHD in adolescents need to include anthropometric risk factors for OSA, and evaluation for signs and symptoms of OSA to determine whether the ADHD diagnosis accurately reflects the clinical presentation of the adolescent.

The comorbidity of ADHD and OSA in young, school-aged children is well established, however, a dearth of studies have examined this relationship in adolescents. Previous research assessing sleep parameters has been inconsistent given the myriad of assessment tools employed for both sleep and ADHD. Despite these inconsistencies, previous PSG studies in youth with ADHD have demonstrated greater rates of OSA, PLMS, and sleep disruption (Cortese et al., 2009; Sadeh et al., 2006). In this study, adolescents with ADHD + OSA showed specific physiological sleep differences, primarily characterized by sleep fragmentation (i.e. increased number of awakening and stage N1), and subsequent suboptimal sleep latency, duration, and efficiency, with small-to-medium effect sizes. However, these differences did not remain significant after excluding those who were on stimulant or other psychoactive medications, which suggests that these medications account for a significant proportion of the sleep continuity disruption. Future studies examining the influence of stimulant and other psychoactive medications on sleep EEG biomarkers in adolescents with ADHD and/or OSA are necessary. Interestingly, it was the adolescents with ADHD-alone who showed a greater rate of PLMS (medium effect size) in our study, suggesting that, despite the known relationship between OSA and PLMS, abnormal PLMS in adolescents with a diagnosis of ADHD may be more prevalent when OSA is not present. From a clinical standpoint, these data support the importance of screening and evaluating, based on phenotypic risk factors, OSA and PLMS in adolescents with a suspicion of ADHD as they suggest different pathophysiological mechanisms for their sleep disruption. Longitudinal studies examining premorbid OSA before the diagnosis of ADHD will be able to elucidate the etiological relationship between the two disorders. Future studies should examine potential underlying mechanisms of ADHD+OSA compared to ADHD-alone using neuroimaging methods.

Contrary to our hypothesis, the presence of OSA was not associated worse neurocognitive functioning or behavioral problems. The lack of differences between adolescents with ADHD-alone and those with ADHD + OSA remained similar and in the same direction even after excluding those on psychoactive medications. Furthermore, adolescents with OSA-alone showed similar neurocognitive and behavioral profiles when compared to controls and better profiles when compared to adolescents with ADHD+OSA, with small-to-large effect sizes. Previous research has found that OSA is associated with deficits in attention and executive functioning, and ADHD-like symptoms in young children; however, there have been numerous failures to replicate these findings across study populations (Beebe, 2006; Calhoun et al., 2009; Mayes, Calhoun, Bixler, & Vgontzas, 2008) and limited studies in adolescents (Beebe et al., 2003). Beebe, Ris, Kramer, Long, and Amin (2010) found that OSA in overweight adolescents was associated with greater parent-reported ADHD and internalizing symptoms and teacher-reported inattention and learning problems. Our data appears to indicate that OSA does not significantly contribute to worse neurocognitive or behavioral symptomatology in adolescents. Longitudinal studies examining premorbid OSA

before the diagnosis of ADHD will be able to truly decipher the etiological relationship between OSA and ADHD and ADHD-like symptoms. However, screening and evaluation of the well-known anthropometric and cardiometabolic factors associated with OSA can also help disentangle this issue.

In this study, adolescents with OSA-alone or with ADHD + OSA demonstrated significantly worse anthropometric, cardiometabolic, and inflammatory profiles when compared to controls or to those with ADHD-alone, with small-to-large effect sizes. In contrast, there were no significant differences between adolescents with OSA-alone and those with ADHD + OSA on any of those biomarkers. It is important to note that leptin levels were marginally higher in those with ADHD + OSA than in those with OSA-alone, however, these differences did not remain after excluding adolescents on stimulant or other psychoactive medications, which suggests that leptin levels, as a biomarker of appetite regulation, were confounded by appetite-suppressing medication in those adolescents. Importantly, adolescents with ADHD-alone did not differ on any of these biomarkers from controls, being primarily normal weight (82%) and metabolically healthy. These data support the contention that, by neglecting these key phenotypic characteristics of OSA, adolescents may be diagnosed with ADHD when in fact OSA has not yet been ruled out and go untreated for the underlying sleep disorder and metabolic underpinnings. From a clinical standpoint, adolescents with observable or readily available anthropometric features consistent with OSA risk (i.e. male sex, overweight/obese, weight gain, enlarged tonsils/adenoids, snoring, EDS, elevated blood pressure) should be screened for OSA, with an overnight PSG, and a diagnosis of ADHD tentatively deferred to avoid potential misdiagnosis. However, the complexity of this task in clinical settings may warrant a stepped-care approach and the clinical suspicion of comorbidity should prevail until both disorders of ADHD and OSA have been adequately tested. Nevertheless, our findings support that screening for OSA should be part of the routine assessment of adolescents with a suspicion of ADHD based on the phenotypic characteristics of OSA detailed above and a subsequent PSG study. This is important because adolescents who are obese are significantly more likely to receive a diagnosis of ADHD and be treated with stimulants without addressing the underlying body weight and metabolic dysregulation and potential presence of OSA.

In summary, there are at least two potential explanations for the results from this study. First, adolescents with ADHD + OSA do have symptomatic OSA, as indicated by their neurocognitive or behavioral symptomatology being as severe as that of those with ADHD-alone. This suggests that youth may have received a misdiagnosis of ADHD. This explanation is supported by the fact that it was the distinct presence of phenotypic risk factors of OSA (i.e. overweight or obesity, excessive daytime sleepiness) and its cardiometabolic underpinnings (i.e. MetS, visceral fat, inflammation) that are not typical of adolescents with ADHD that separated the two groups. Alternatively, ADHD and OSA in these adolescents are truly comorbid conditions, but OSA does not add any greater neurocognitive deficits or behavioral problems to the coexisting ADHD. However, our data clearly indicate that the presence of risk factors phenotypic of OSA should be thoroughly evaluated in at least a subset of these adolescents. Overweight or obesity should not be regarded as a coexisting phenomenon in ADHD but rather as an indicator of risk of OSA and necessary screening for the sleep disorder; unfortunately, this is not currently considered

in the routine assessment of ADHD. Furthermore, such youth who undergo a PSG to rule out OSA may defer an ADHD diagnosis and stimulant medication, given that the latter appears to contribute to greater sleep continuity disruption beyond the sleep fragmentation associated with the presence of OSA.

Some limitations of our study should be noted. This was a cross-sectional study and, therefore, we could not assess causality. The diagnosis of ADHD was based on past/current treatment/diagnosis for ADHD that explains why 23% of participants reported a lifetime diagnosis of ADHD, which exceeds national estimates of 12% for adolescents, and should be interpreted with caution. Given the population-based sample, we did not utilize CBCL-ADHD scores for the ADHD case definition, since there could be many reasons (i.e. stimulant medication and/or from participation in behavioral/schoolbased interventions) why adolescents with ADHD may report within-normal scores at this developmental stage, despite differing on objective neurocognitive performance. Furthermore, data on time since ADHD diagnosis/clinical remission was not available and should be examined in future prospective studies. While we controlled for age in the analyses, we could not examine possible age- and pubertal-related subgroup differences in study outcomes, and future studies with larger sample sizes should explore developmental associations. One night of PSG may not represent the participants' habitual sleep in the home environment. Although research has suggested that the "first night effect" is of lower magnitude for respiratory parameters than that observed for other sleep parameters (Picchietti et al., 2009), our findings on sleep continuity and architecture should be interpreted with caution given the absence of an adaptation night. Lastly, a standardized measure of EDS was not used in this study; therefore, percentages for EDS should be interpreted with caution.

In conclusion, adolescents with ADHD + OSA showed anthropometric, cardiometabolic, and inflammatory characteristics that deviate from the typical presentation of ADHD. Adolescents with ADHD+OSA did not differ in the severity of their neurocognitive or behavioral problems when compared to those with ADHD-alone, which raises the question whether OSA worsens ADHD or whether OSA "mimics" ADHD during this important developmental period and should be ruled out in a specific subset of adolescents. In order to limit misdiagnosis of ADHD, systematic screening for OSA is important, especially in males who are overweight and present with other phenotypic characteristics of OSA that are not currently routine in the differential diagnosis of ADHD.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Key points

- Prior research describes an increased prevalence of OSA in children with ADHD, while data in adolescents has been lacking.
- ADHD with or without OSA do not differ in their neurobehavioral outcomes in adolescents from the general population.
- ADHD with OSA is associated with sleep fragmentation, while ADHD without OSA with periodic limb movements.
- ADHD with OSA presents with distinct anthropometric, cardiometabolic and inflammatory profiles that are not typically considered part of the clinical work-up of the assessment of youth with ADHD.
- Adolescents with a suspicion of ADHD and phenotypic risk factors for OSA should be routinely screened for the sleep disorder, which will help clinicians with differential diagnosis and tailoring treatments.

Table 1

Demographic and clinical characteristics of the sample

	Overall (*N* = 421)	None (*n* = 208)	OSA (*n* = 115)	ADHD (*n* = 54)	ADHD+OSA (*n* = 44)	*p*-Value
Male (%)	53.9	39.9	66.1	66.7	72.7	<.01*
Ethnic/Racial Minority (%)	21.9	16.8	31.3	18.5	25.0	.021*
Age (years)	16.4 ± 2.3	16.1 ± 2.2	17.2 ± 2.3	15.8 ± 2.0	17.0 ± 2.1	<.01*
Tanner stage (score)	4.2 ± 0.8	4.2 ± 0.8	4.3 ± 0.7	4.1 ± 0.7	4.2 ± 0.8	0.446
BMI (percentile)	65.3 ± 28.4	61.4 ± 29.5	73.2 ± 25.3	58.9 ± 25.1	71.1 ± 30.0	<.01*
Normal weight (%)	66.0	70.7	53.9	81.5	56.8	<.01*
Overweight (%)	18.8	14.9	27.8	16.7	15.9	
Obesity (%)	15.2	14.4	18.3	1.9	27.3	
Adenotonsillectomy (%)	11.4	8.2	15.7	13.0	13.6	.208
Excessive daytime sleepiness						
None (%)	34.2	34.1	35.7	37.0	27.3	<.01*
Self-reported (%)	38.2	42.8	41.7	24.1	25.0	
Observed (%)	27.6	23.1	22.6	38.9	47.7	
Medication use						
Allergy/asthma (%)	21.6	24.5	20.9	20.4	11.4	.278
Steroid (%)	6.9	7.7	7.8	1.9	6.8	.475
Other physical health (%)[a]	25.7	25.0	22.6	31.5	29.5	.590
Stimulant (%)	9.7	0.0	1.7	40.7	38.6	<.01*
Sleep (%)	1.9	1.0	1.7	5.6	2.3	.179
Other psychoactive (%)[b]	8.6	6.3	4.3	18.5	18.2	<.01*

Data are mean ± *SD*. BMI, body mass index.

*$p < .05$

[a]Other physical health medications included insulin, anti-hypertensive, and cardiac medications.

[b]Other psychoactive medications included antidepressants and anxiolytic and other sedatives.

Table 2

Polysomnographic parameters across study subgroups

	1. None (*n* = 208)	2. OSA (*n* = 115)	3. ADHD (*n* = 54)	4. ADHD+OSA (*n* = 44)	1 vs. 2	1 vs. 3	1 vs. 4	2 vs. 4	3 vs. 4
Sleep continuity									
Sleep onset latency (min)	26.3 ± 1.7	22.8 ± 2.3	23.2 ± 3.3	37.6 ± 3.6	.248	.406	.007*	.001*	.004*
Awakenings (#)	35.4 ± 0.8	38.3 ± 1.1	33.9 ± 1.6	38.6 ± 1.8	.058*	.409	.124	.887	.057*
Wake after sleep onset (min)	69.6 ± 3.0	67.6 ± 4.1	66.1 ± 5.9	77.2 ± 6.5	.708	.601	.308	.209	.213
Total sleep time (min)	446.8 ± 3.9	450.9 ± 5.3	452.6 ± 7.5	428.1 ± 8.4	.556	.496	.049*	.020*	.031*
Sleep efficiency (%)	82.5 ± 0.7	83.5 ± 0.9	83.7 ± 1.3	79.1 ± 1.5	.438	.435	.050*	.014*	.026*
Sleep architecture									
Stage 1 (%)	0.9±.1	0.8±.1	1.0 ± 0.2	1.5 ± 0.2	.430	.770	.018*	.004*	.078
Stage 2 (%)	53.4 ± 0.6	54.4 ± 0.8	51.5 ± 1.2	53.4 ± 1.3	.366	.178	.970	.544	.296
Stage 3 (%)	27.2 ± 0.5	25.8 ± 0.8	28.2 ± 1.1	27.2 ± 1.2	.166	.461	.984	.334	.568
Stage R (%)	18.3 ± 0.3	18.8 ± 0.4	19.1 ± 0.6	17.6 ± 0.7	.384	.279	.434	.168	.142
Sleep disordered breathing									
AHI (events/hr)	1.0 ± 0.3	5.2 ± 0.5	1.1 ± 0.7	5.5 ± 0.7	<.001*	.935	<.001*	.708	<.001*
SpO_2	91.7 ± 0.3	91.1 ± 0.5	91.3 ± 0.7	91.2 ± 0.7	.372	.661	.606	.894	.918
Periodic limb movements									
PLMI (events/hr)	3.3 ± 0.4	3.8 ± 0.5	6.0 ± 0.8	4.0 ± 0.9	.486	.003*	.465	.830	.109
PLMS (percent)	20.8%	22.3%	40.7%	27.2%	.772	.003*	.380	.517	.124

Data are mean ± *SEM* adjusted for covariates. *p*-Values are post-hoc comparisons from multivariable-adjusted linear models. AHI, apnea/hypopnea index; PLMI, periodic limb movement index; PLMS, abnormal periodic limb movement index.

*$p < .05$.

Table 3

Neurocognitive and behavioral functioning across study subgroups

	1. None (*n* = 208)	2. OSA (*n* = 115)	3. ADHD (*n* = 54)	4. ADHD+OSA (*n* = 44)	1 vs. 2	1 vs. 3	1 vs. 4	2 vs. 4	3 vs. 4
Neurocognitive									
Vigilance	103.6 ± 0.9	103.5 ± 1.3	99.2 ± 1.9	99.5 ± 2.1	.942	.035*	.085	.102	.915
Processing speed	10.1±.1	10.0±.2	8.6 ± 0.3	9.5 ± 0.3	.525	<.001*	.050*	.142	.041*
Distractibility	108.1 ± 0.7	108.2 ± 0.9	104.6 ± 1.4	106.1 ± 1.6	.929	.020*	.247	.260	.442
Working memory	7.2 ± 0.2	7.0±.2	6.3 ± 0.3	5.8 ± 0.4	.615	.023*	.001*	.411	.244
Control interference	38.6 ± 0.6	38.8 ± 0.8	42.2 ± 1.1	41.3 ± 1.3	.823	.005*	.060	.093	.594
Achievement	105.1 ± 0.7	105.5 ± 0.9	96.0 ± 1.3	97.7 ± 1.5	.769	<.001*	<.001*	<.001*	.389
Intelligence quotient	105.9 ± 0.7	104.9 ± 1.0	100.6 ± 1.4	99.9 ± 1.6	.419	.001*	.001*	.007*	.746
Internalizing problems	50.1 ± 0.7	49.8 ± 1.0	53.9 ± 1.4	53.0 ± 1.6	.811	.021*	.108	.084	.689
Anxious depressed	53.6 ± 0.4	53.4 ± 0.7	55.0 ± 0.8	55.3 ± 0.9	.752	.131	.095	.066	.800
Withdrawn depressed	54.6 ± 0.5	54.4 ± 0.7	58.0 ± 1.0	56.6 ± 1.7	.840	.002*	.095	.079	.327
Somatic complaints	55.3 ± 0.5	55.0 ± 0.7	57.0 ± 0.9	57.4 ± 1.0	.761	.106	.071	.050*	.777
Attention problems	53.6 ± 0.5	54.6 ± 0.6	61.2 ± 0.9	60.5 ± 1.0	.203	<.001*	<.001*	<.001*	.609
Thought problems	53.9 ± 0.4	53.9 ± 0.6	59.0 ± 0.8	58.5 ± 0.9	.967	<.001*	<.001*	<.001*	.701
Externalizing problems	47.7 ± 0.7	46.6 ± 0.9	55.7 ± 1.3	53.5 ± 1.5	.350	<.001*	<.001*	<.001*	.244
Rule-breaking behaviors	52.9 ± 0.4	53.3 ± 0.5	57.3 ± 0.8	56.4 ± 0.8	.599	<.001*	<.001*	<.001*	.428
Aggressive behaviors	52.8 ± 0.4	52.7 ± 0.5	57.1 ± 0.7	56.2 ± 0.8	.841	<.001*	<.001*	<.001*	.413
DSM-oriented scales									
Anxious problems	53.4 ± 0.4	53.5 ± 0.5	55.1 ± 0.7	55.2 ± 0.8	.846	.034*	.038*	.062	.898
Somatic problems	54.8 ± 0.5	54.9 ± 0.7	56.0 ± 1.0	57.3 ± 1.1	.889	.273	.048*	.069	.404
ADHD problems	53.3 ± 0.4	54.1 ± 0.6	62.4 ± 0.8	61.4 ± 0.9	.264	<.001*	<.001*	<.001*	.430

Data are mean ± SEM adjusted for covariates. *p*-Values are post-hoc comparisons from multivariable-adjusted linear models.

*$p < .05$.

Table 4

Cardiometabolic, stress and inflammatory biomarkers across study subgroups

	1. None	2. OSA	3. ADHD	4. ADHD+OSA	1 vs. 2	1 vs. 3	1 vs. 4	2 vs. 4	3 vs. 4
DXA scan	(*n* = 197)	(*n* = 102)	(*n* = 49)	(*n* = 43)					
Gynoid/whole body ratio (%)	18.0 ± 0.02	18.0 ± .02	18.0 ± 0.03	17.0 ± 0.03	.639	.358	.170	.325	.669
Android/whole body ratio (%)	6.0 ± 0.01	7.0 ± 0.01	6.0 ± 0.02	7.0 ± 0.02	.001*	.484	.001*	.426	.001*
Subcutaneous adipose tissue (cm^2)	210.9 ± 10.1	241.1 ± 14.1	174.1 ± 19.7	269.7 ± 21.2	.030*	.212	.005*	.253	.001*
Visceral adipose tissue (cm^2)	55.2 ± 2.8	69.9 ± 3.9	48.7 ± 5.4	69.5 ± 5.8	.003*	.283	.029*	.958	.009*
Metabolic Syndrome	(*n* = 182)	(*n* = 107)	(*n* = 50)	(*n* = 42)					
cMetS (z-score)	−0.4 ± 0.2	0.7 ± 0.3	−0.6 ± 0.4	0.8 ± 0.5	.006*	.620	.021*	.792	.021*
HPA axis	(*n* = 203)	(*n* = 115)	(*n* = 54)	(*n* = 44)					
Evening cortisol (μg/dl)	7.9 ± 0.5	9.1 ± 0.7	8.0 ± 1.3	7.2 ± 1.1	.198	.942	.589	.154	.612
Morning cortisol (μg/dl)	20.8 ± 0.6	19.7 ± 0.9	18.9 ± 1.2	18.1 ± 1.4	.326	.186	.078	.310	.638
Inflammation	(*n* = 182)	(*n* = 106)	(*n* = 51)	(*n* = 42)					
CRP (mg/L)	0.7 ± 0.1	1.2 ± 0.1	0.6 ± 0.2	1.4 ± 0.2	.001*	.574	.001*	.476	.001*
IL-6 (pg/ml)	1.1 ± 0.1	1.3 ± 0.1	1.1 ± 0.1	1.2 ± 0.2	.049*	.914	.678	.306	.788
TNF-α (pg/ml)	1.9 ± 0.1	2.1 ± 0.1	1.6 ± 0.2	2.0 ± 0.2	.327	.130	.845	.609	.189
Adiponectin (μg/ml)	7.9 ± 0.4	7.6 ± 0.5	8.8 ± 0.7	6.9 ± 0.8	.592	.257	.242	.449	.064
Leptin (ng/ml)	11.7 ± 0.8	13.7 ± 1.1	9.0 ± 1.6	17.4 ± 1.7	.165	.127	.003*	.062	<.001*

Data are mean ± SEM adjusted for covariates. *p*-values are post-hoc comparisons from multivariable-adjusted linear models. cMetS, continuous metabolic syndrome standardized score; CRP, C-reactive protein; DXA scan, dual-energy X-ray absorptiometry scan; HPA, hypothalamic-pituitary-adrenal; IL-6, interleukin 6; TNF-α, tumor necrosis factor alpha.

* $p < .05$.