Obstructive Sleep Apnea Syndrome in a Sickle Cell Anemia Cohort: Prevalence and Risk Factors

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Short title: Obstructive Sleep Apnea Prevalence in Sickle Cell Anemia

Abbreviations: BMI – body mass index; CPAP – continuous positive airway pressure; ESS – Epworth sleepiness scale; FEV_1 - forced expiratory volume in 1-second; FEV_1/FVC - ratio of forced expiratory volume in 1-second/forced vital capacity; FVC - forced vital capacity; $HbS\beta^0$ - sickle beta thalassemia; HbSS – homozygous sickle cell anemia; IQR – interquartile range; NREM – non-rapid eye movement; OAHI - obstructive apnea hypopnea index; OAI – obstructive apnea index; OSAS – obstructive sleep apnea syndrome; PSG – polysomnography; REM – rapid eye movement; SAC – sleep and asthma cohort; SCA – sickle cell anemia; SD – standard deviation; SpO_2 – oxygen saturation by pulse oximetry

Key Words: sickle cell anemia, obstructive sleep apnea, polysomnography, sleep disorders, epidemiology, cohort study, blood disorders, sleep medicine

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What's Known on This Subject: Obstructive sleep apnea syndrome (OSAS) prevalence in children with sickle cell anemia (SCA) is not well described. Although these children often experience nocturnal oxygen desaturation, it is unclear whether they are more likely to have OSAS.

What This Study Adds: Children with SCA have a high prevalence of OSAS with typical symptoms that represents more than simple nocturnal desaturation. This study supports the need for increased efforts to screen for, diagnose and treat OSAS in this vulnerable population.

Contributor's Statement Page

Carol L. Rosen: Dr. Rosen helped develop the data collection instruments for sleep, supervised sleep data collection at one site, designed the concepts for this manuscript, interpreted the data, created the initial draft and revised the manuscript for final submission.

Michael R. Debaun: Dr. Debaun, the principal investigator for the NIH sponsored SAC project, was the principal investigator for one site, reviewed and help revised the manuscript, and approved the final manuscript as submitted.

Robert C. Strunk: Dr. Strunk contributed to the development of the SAC project, study concepts and procedures; supervised the quality assurance for pulmonary function testing, reviewed and helped revise this manuscript, and approved the final manuscript as submitted.

Susan Redline: Dr. Redline developed the procedures for sleep data collection and analysis, was the principal investigator for one site, oversaw the quality of the acquired sleep study data, reviewed and helped revise the manuscript, and approved the final manuscript as submitted.

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Mark Rodeghier: Dr. Rodeghier developed the statistical approach, performed those analyses and reviewed the integrity of those analyses.

Fenella J. Kirkham: Dr. Kirkham was the principal investigator for one site, helped develop the concepts for this SAC project and this manuscript, analyzed and interpreted the data, contributed to the development of the initial draft, reviewed/revised the manuscript, and approved the final manuscript as submitted.

ABSTRACT

OBJECTIVES: To ascertain the prevalence of and risk factors for obstructive sleep apnea syndrome (OSAS) in children with sickle cell anemia (SCA).

METHODS: Cross-sectional baseline data were analyzed from the Sleep and Asthma Cohort study, a multi-center prospective study designed to evaluate the contribution of sleep and breathing abnormalities to SCA-related morbidity in children ages 4 to 18 years, unselected for OSAS symptoms or asthma. Multivariable logistic regression assessed the relationships between OSAS status based on overnight in-laboratory polysomnography and putative risk factors obtained from questionnaires and direct measurements.

RESULTS: Participants included 243 children: median age 10 years, 50% male, 99% African heritage, 95% homozygous for β^S hemoglobin. OSAS, defined by obstructive apnea hypopnea indices (oAHI) was present in 100 (41%) or 25 (10%) of children at s of ≥ 1 or ≥ 5, respectively. In univariate analyses, OSAS was associated with higher levels of habitual snoring, lower waking oxyhemoglobin saturation (SpO_2), reduced lung function, less caretaker education, and non-preterm birth. Lower sleep-related SpO_2 metrics were also associated with higher oAHI. In multivariable analyses, habitual snoring and lower waking SpO_2 remained risk factors for OSAS in children with SCA.

CONCLUSIONS: The prevalence of OSAS in children with SCA is higher than in the general pediatric population. Habitual snoring and lower waking SpO_2 values, data easily obtained in routine care, were the strongest OSAS risk factors. Since OSAS is a treatable condition with adverse health outcomes, greater efforts are needed to screen, diagnose, and treat OSAS in this high-risk, vulnerable population.

INTRODUCTION

Obstructive sleep apnea syndrome (OSAS) is a disorder of breathing during sleep in which episodic upper airway collapse disrupts ventilation and leads to oxyhemoglobin desaturation and poor sleep quality. This common pediatric disorder, prevalence 1-5%, is associated with adverse health outcomes: behavioral problems, daytime sleepiness, cognitive deficits, cardiovascular changes and reduced quality of life.[1,2] In adults, untreated OSAS is associated with increased risk of incident cardiovascular disease and stroke.[3] Adenotonsillar hypertrophy is the most commonly identified risk factor for childhood OSAS and adenotonsillectomy is effective treatment. Otherwise normal children with OSAS are more likely to be African-American,[4-7] exposed to environmental tobacco smoke,[7] born preterm,[5], have undergone adenotonsillectomy, [8] and live in disadvantaged neighborhoods. [9,10] It is unknown whether these risk factors generalize to children with sickle cell anemia.

Sickle cell anemia (SCA), affecting 1 in 600 African–Americans, is characterized by chronic hemolytic anemia and complications are related to recurrent vaso-occlusion. One of the strongest triggers for vaso-occlusion is oxyhemoglobin desaturation which has been linked to several complications of SCA: increased pain,[11] greater risk of central nervous system events,[12] cognitive dysfunction,[13] and history of acute chest syndrome.[14] Oxyhemoglobin desaturation is a well-known phenomenon in SCA attributable to hypoxemia and low partial pressure of oxygen, a rightward shift of the oxyhemoglobin dissociation curve, and dyshemoglobins which are elevated in the presence of intravascular hemolysis, but incapable of transporting oxygen. Since desaturation is common to both SCA and OSAS, the relationship between SCA and OSAS is of great interest.

The prevalence of OSAS in children with SCA is not well defined and there is uncertainty whether OSAS is more common in this disorder.[15,16] Previously reported prevalence rates range from 5% to 79%. Except for one study,[17,18] prevalence estimates have been based on samples clinically referred for OSAS symptoms[19-23] or with desaturation.[24,25] Furthermore, clinicians are uncertain whether the same symptoms, signs, and risk factors associated with OSAS in otherwise healthy children have clinical utility in screening for OSAS in children with SCA.[1]

We used data from participants in the prospective Sleep and Asthma Cohort (SAC) study who were unselected for OSAS symptoms to investigate the prevalence and risk factors for OSAS in children with SCA. We hypothesize that 1) children with SCA will have a higher than expected prevalence of OSAS for children of African heritage and 2) higher obstructive apnea hypopnea indices (oAHI) will be associated with more OSAS symptoms and greater nocturnal oxyhemoglobin desaturation.

PATIENTS AND METHODS

A detailed description of the testing procedures and statistical approach is provided in the supplemental on-line appendix. In brief, we conducted a cross-sectional analysis of baseline data collected as part of the Sleep and Asthma Cohort (SAC) study, a prospective observational cohort of children ages 4 to 18 years with SCA [homozygous for sickle hemoglobin (HbSS) or compound heterozygotes for sickle beta thalassemia zero ($HbS\beta^0$)], designed to evaluate the contribution of asthma and sleep abnormalities to SCA-related morbidity. Participants were recruited (66% participation rate) from three pediatric centers: St. Louis, Missouri, Cleveland,

Ohio, and London, England. Children were enrolled without regard to past morbidity from or symptoms of sleep-disordered breathing or asthma. Children were ineligible for participation if they were receiving chronic transfusions, hydroxyurea, oxygen, or continuous positive airway pressure (CPAP) at the time of enrollment; had chronic lung disease other than asthma or structural heart disease; or were human immunodeficiency virus positive. Participants placed on hydroxyurea or transfusion therapy during the study were retained in the cohort. Institutional Review Boards for each site approved the study protocol. Written, informed parental consent and patient assent were obtained for all participants.

Questionnaires and Definitions

Parents/primary caretakers of participants completed standardized questionnaires about demographics and medical history including asthma, allergies, and sleep.[26-29]. Asthma was defined as a "yes" response to any of the following three questions: "Has a doctor ever said that the participant has asthma? Does the participant take any asthma medications? Does the participant still have asthma?" Hayfever was defined as a "yes" response to "Has a doctor ever said that the participant has hayfever?" Household tobacco smoke exposure was defined as a "yes" response to current exposure.

Habitual snoring was assessed using the sleep questionnaire by response to, "How many times did your child snore in the previous month?" and defined as snoring 3 or more nights per week. Trouble breathing or witnessed apnea were defined when these symptoms occurred at least "sometimes" (1 to 2 times per week). Enuresis was defined as bedwetting at least 1 to 2 times per week. Prior tonsillectomy or adenoidectomy was indicated by a "yes" response to removal

of tonsils or adenoids. Family history of OSAS was defined as positive if there were any "yes" responses to a family member either diagnosed with OSAS or using CPAP. Sleepiness was assessed using the Epworth Sleepiness Scale modified for children, in which scores range from 0 to 24, with higher scores indicating greater daytime sleepiness.[29]

Physiological assessments included standardized measurements of height, weight, body mass index (BMI) converted to age and sex adjusted z-scores,[30] and blood pressure converted age-, gender-, and height-adjusted systolic and diastolic percentiles based on auscultatory normative data for children with SCA.[31] Allergy skin tests using the prick puncture technique with the multitest (Lincoln Diagnostics, Decatur, Illinois) to 9 aeroallergens were performed as previously reported.[32] Atopy was defined as having at least 2 positive skin tests.

Spirometry measures [forced expiratory volume in 1-sec (FEV_1), forced vital capacity (FVC) and the ratio of FEV_1/FVC] were performed by study-certified technicians using standardized protocols[33] and compared with normative data for healthy black children.[34,35] Waking SpO_2 values were collected using a standardized 5-minute period. Other laboratory data were collected as part of clinical care.

Children underwent full channel, in-laboratory PSG by study-certified technicians with standardized protocols and equipment following American Academy of Sleep Medicine guidelines for data acquisition and scoring, except carbon dioxide was not collected.[36] Because there is no consensus about what oAHI threshold should be used to define OSAS status, oAHI data were summarized using several commonly used pediatric cutpoints: oAHI $\geq$1,[37] oAHI $\geq$1

plus habitual snoring,[37,38] oAHI≥1.5,[39] oAHI≥ 2,[40] and oAHI≥5.[4-6,38] Primary snoring was defined as an oAHI value of < 1 with habitual snoring 3-5 nights per week.

Statistical Analyses

Means, standard deviations, medians and interquartile ranges were computed for continuous variables. Frequencies and percentages were computed for categorical variables. Continuous data were analyzed using analysis of variance or the non-parametric equivalent for non-normal distributions. Categorical data were analyzed with a chi-square test and the Fisher's Exact test was used where expected cell counts did not meet minimum requirements. Logistic regression was used for the multivariable analyses to assess the association between potential risk factors and OSAS status. For analytic purposes, the dependent variable, oAHI, was categorized into 3 OSAS status groups: no OSAS (oAHI<1), mild OSAS (1≤oAHI<5) and moderate to severe OSAS (oAHI≥5). Associations between the risk factors and OSAS status were expressed as odds ratios with 95% confidence intervals. All tests for significance were 2-tailed. P values of <0.05 were considered significant. All analyses were performed using SPSS version 21.

RESULTS

The final analytic sample included 243 children: 59 (24%) from Cleveland, 94 (39%) from London, and 90 (37%) from St. Louis. Median age was 10 years, 50% were male, 99% had African heritage, and 95% were homozygous for HbSS. The oAHI data were not normally

distributed: mean (SD, range) = 2.1 (4.6, 0 to 37.2) while the median (IQR) was 0.6 (0.2, 1.9). Figure 1 shows the prevalence of OSAS based on commonly used oAHI cutpoints and definitions: 41% for ≥ 1, 34% an oAHI≥1 plus habitual snoring, 28% for ≥1.5, 24% for ≥2, and 10% for ≥5. Among the 143 (59%) participants with oAHI values <1, 21% were habitual snorers (at least 3-5 night per week) and 48% snored at least 1 to 2 nights per week.

Participant characteristics and OSAS symptoms by oAHI categories

Table 1 shows associations of participant characteristics and OSAS symptoms by oAHI categories. The frequency of OSAS symptoms (habitual snoring, trouble breathing, witnessed apnea, nocturnal enuresis) increased with higher oAHI values, but not for nocturnal restlessness or daytime sleepiness. Only less caretaker education varied significantly with increasing oAHI values, while age, male gender, and household income did not. Lower waking SpO_2 values were significantly associated with greater oAHI values, while lower hemoglobin values, higher BMI-z scores, and elevated blood pressures were not. SCA participants were rarely obese. Greater oAHI values were significantly associated with reduced lung function (lower FEV_1 and FEV_1/FVC ratio), but not with lower FVC. Preterm birth was associated with the lower, not higher AHI values. Other potential OSAS risk factors: family history of OSAS, prior adenotonsillectomy, and other allergic or inflammatory conditions (asthma, hayfever, atopy, and environmental tobacco smoke exposure) were not associated with increasing oAHI. Hydroxyurea prescription was caretaker reported for 10% of the sample, but was not associated with lower oAHI (p=0.46).

PSG findings and oximetry metrics by increasing oAHI cutpoints

PSG results stratified by oAHI cutpoints are shown in table 2a for cardiorespiratory data and table 2b for sleep data. Higher oAHI cutpoints were significantly associated with higher respiratory and desaturation indices and lower SpO_2 metrics. Obstructive hypopneas were seen in oAHI cutpoints below 2, but obstructive apneas were not. Central apneas tended to be more frequent with higher oAHI indices, but remained within the normal range. Higher arousal index was the only sleep variable associated with higher oAHI cutpoints ($p<0.001$).

Risk factors for OSAS: multivariable models using two OSAS severity groups

Table 3 summarizes the final multivariable models in which the dependent variable, OSAS status, is categorized into 3 groups: no OSAS (oAHI<1), mild OSAS (1≤oAHI<5) and moderate to severe OSAS (oAHI≥5). When the β-value is negative, significant associations will have odds ratios less than one. This means that a lower variable value is associated with a greater odds of being a member of the OSAS group. To improve clinical interpretability of the significant, but negative odds ratios, we have "reformatted" them to present the effect with an odds ratio greater than one.

There were 218 participants in the two groups: no OSAS and mild OSAS group. In the screening model with 13 variables of interest, 186/218 participants had full data (loss of 14.7%) and the following 6 variables passed screening with $p<0.20$: habitual snoring, waking SpO_2

<96%, FEV_1 percent predicted, environmental tobacco smoke exposure, caretaker education less than high school, and full term birth. Using the 6 variables from the first step with the 186 participants to estimate a reduced model, multivariable analyses revealed that 4 variables were significantly and independently associated with a greater odds of mild OSAS: waking SpO2 values <96% (OR 7.69; 95%CI 3.70, 16.6; p<0.001); habitual snoring (OR 2.76; 95%CI 1.24, 6.17; p=0.013); lower FEV_1, percent predicted (OR 1.4; 95%CI 1.01, 1.07; p=0.010); and non preterm birth (OR 5.00; 95%CI 1.19, 2.08; p=0.028). The final model was 57.6% accurate at predicting mild OSAS in this sample (sensitivity 0.78, specificity 0.67; given a prevalence rate of 31% for mild OSAS in this sample, positive predictive value was 0.52 and negative predictive value was 0.87).

For no OSAS *vs.* moderate to severe OSAS (oAHI≥5), there were 168 participants. Using the 4 variables from the final model for mild OSAS (plus age and gender) in the model for moderate to severe OSAS (oAHI≥5), there were 148 participants with full data (loss of 11.9%). Multivariable analyses revealed that only two factors significantly and independently associated with moderate to severe OSAS status: habitual snoring (OR 16.9, 95% CI 4.98, 57.5, p<0.001) and lower waking SpO2 <96%, (OR 5.55, 95% CI 1.61, 18.6, p=0.006). This final model was 56% accurate at predicting moderate to severe OSAS status in this sample (sensitivity = 0.92, specificity 0.78; given a prevalence rate of 10% for moderate to severe OSAS status, positive predictive value was 0.32 and negative predictive value was 0.99).

DISCUSSION

This report summarizes clinical characteristics and PSG data from the largest sample of children with SCA, unreferred for signs or symptoms of OSAS. The OSAS prevalence rates, ranging from 41% at a cutpoint of oAHI≥1 to 10% at a cutpoint of oAHI≥5, are higher than those reported in: otherwise normal children (1 to 5% at a cutpoint ≥5)[1,5,6]; in African-American children (8.7% at a cutpoint ≥5)[5] and in a Brazilian cohort of children with SCA (10.6% at a cutpoint ≥ 1.[18]

Habitual snoring was a strong risk factor for OSAS in children with SCA while many of the previously reported risk factors for OSAS for otherwise healthy children were not observed: age, gender, obesity, hypertension, daytime sleepiness, asthma, hayfever, atopy, environmental tobacco smoke exposure, family history of OSAS, prior adenotonsillectomy, and preterm birth. The association of enuresis with OSAS was previously reported for this cohort.[41] Lower caretaker education was a risk factor in univariate analyses, but not multivariable analysis. Other unique risk factors to SCA were suggested by univariate analyses (lower waking SpO_2 values and reduced lung function). However, in multivariable analyses, only lower waking SpO_2 was retained at both OSAS categories. Lower FEV_1 was associated with the mild oAHI category, but not at the higher oAHI category.

Higher oAHI values were not associated with asthma or hayfever. It is possible that our definitions of asthma and allergy, based on parent report of symptoms from questionnaire data, were not reliable enough to pick up this association. A parent report of doctor-diagnosed asthma has been associated with an increased rate of pain and acute chest syndrome,[42-46], so this definition has clinical relevance in this sickle cell anemia sample. Using more quantitative measures of allergy and respiratory disease, we found that atopy was not associated with OSAS,

while findings of reduced FEV_1 and FEV_1/FVC ratio, which support a diagnosis of asthma, were associated with OSAS. There was no evidence that hydroxyurea prescription was associated with a lower OSAS prevalence, but this study was not designed to evaluate whether hydroxyurea treatment decreases the risk of sleep-disordered breathing.

In otherwise healthy children, habitual snoring is very sensitive, not very specific for predicting OSAS. Lower waking SpO_2 had the strongest association with mild OSAS followed by habitual snoring, but this order was reversed for oAHI values ≥5 suggesting that oAHI values in the milder range may be less specific for OSAS. The models were only slightly more than 50% predictive of PSG-defined OSAS at either range, similar to the positive and predictive values of clinical assessment for the diagnosis of OSAS in otherwise children of 65% and 46%, respectively which has led to the recommendation that objective testing such as PSG be used in the diagnosis of OSAS.[2] This recommendation becomes even more important in children with SCA in whom other disturbances to oxygen delivery like anemia, oxyhemoglobin desaturation and other pulmonary dysfunction are often present.

While we evaluated OSAS prevalence and risk factors based on commonly used oAHI cutpoints for children, the "gold standard" for OSAS diagnosis is not PSG alone, but rather the skillful integration of clinical and PSG findings by experienced clinicians.[15] AHI is a popular metric to determine the presence of OSAS, but there is no consensus on how AHI should be used to indicate disease severity. Previous studies have shown that AHI has not been useful in predicting either baseline neurobehavioral morbidity or response to OSAS treatment in children[40,47-53]. Even "primary snoring", that is snoring with an AHI < 1, has been associated with neurobehavioral morbidity. [54-56] For these reasons, we cannot identify an AHI threshold at

which OSAS needs to be addressed. Since the study was based on cross-sectional data, the impact of OSAS or greater hypoxemia on health outcomes in children with SCA cannot be assessed. Further outcome evaluation is required to determine what threshold is associated with SCA-related morbidity.

While OSAS appears to be one contributor to sleep-disordered breathing in SCA, the oximetry metrics show that some children also experience more sustained nocturnal desaturation. Greater desaturation time was associated with higher oAHI cutpoints, but desaturation can also be related to comorbid lower respiratory tract pathology. In our SCA sample, the oximetry metrics for sleep time below 95% and 92% were similar to the upper limits of normal reported for otherwise healthy children.[57-59] Nevertheless, the oximetry and lung function findings suggest that a portion of the sleep-disordered breathing in children with SCA may be an indicator of lower respiratory tract problems rather than a specific marker of upper airway obstruction and OSAS.

The strengths of this study include participants who were unselected for symptoms of OSAS, the large, multi-center sample, and objective assessment of sleep-disordered breathing by standardized full PSG scored centrally without clinical correlates. Nevertheless, several limitations are noted. With a participation rate of 66%, it is possible that sample included families with greater concerns about sleep disordered breathing leading to higher OSAS prevalence rates. We recognize that questionnaire data and parent report of symptoms are imperfect measures of the presence and severity of OSAS[2] and potential OSAS risk factors. On the other hand, in this cohort, parent report of wheezing symptoms was a better predictor of a physician diagnosis of asthma than lung function testing.[60] In terms of data collection, tonsil size was not assessed, end-tidal carbon dioxide was not measured, daytime behavioral problems were

not evaluated, so the assessment of OSAS signs, symptoms and consequences could have been more comprehensive. Finally, although validated in comparison with arterial saturation, the accuracy of simple pulse oximetry as a measurement blood oxygenation in SCA patients may be~~is~~ variable and may underestimate decreases in status because the dyshemoglobins are not measured[61].

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CONCLUSIONS

This study confirms that children with sickle cell anemia have a higher prevalence of sleep-disordered breathing consistent with OSAS, beyond greater nocturnal desaturation and that these children experience typical nocturnal symptoms of snoring and breathing/sleep disturbances. Since OSAS is a treatable condition with adverse health outcomes, greater efforts are needed to implement and evaluate procedures for screening, diagnosing, and treating OSAS in this high-risk, vulnerable population.

TABLE 1 Distribution of Participant Characteristics and OSAS symptoms by OSAS Categories

	All N = 243	oAHI < 1 n = 143 (59%)	oAHI ≥ 1 < 2 n = 42 (17%)	oAHI ≥ 2< 5 n = 33 (14%)	oAHI ≥ 5 n = 25 (10%)	p value
Demographics						
Mean age, yr (SD)	10.6 (4.2)	10.6	11.1	11.4	8.8	0.11
Male sex, %	50.2	47.6	50.0	48.5	68.0	0.31
Caretaker education < high school, % (no.reported = 239)	39.3	33.1	50.0	57.6	32.0	0.03
Household income < $30,000, % (no. reported = 207)	59.9	56.3	73.0	61.3	55.0	0.32
Sleep and breathing symptoms						
Habitual snoring ≥ 3 nights/week, % (no. reported = 232)	34.0	21.1	36.8	50.0	80.0	<0.001
Trouble breathing ≥ 1 night/week, % (no. reported = 219)	19.2	14.0	13.2	25.9	48.0	0.001
Witnessed apnea ≥ 1 night/week , % (no. reported = 218)	9.2	5.6	2.6	14.3	32.0	<0.001

Nocturnal enuresis, ≥ 1 night/week , % (no. reported = 227)	30.0	27.6	20.0	32.9	56.0	0.016
Restless, ≥ 1 night/week , %	31.7	32.9	33.3	30.3	24.0	0.84
*Mean Epworth sleepiness scale (SD) (no. reported = 237)	7.1 (4.2)	7.0	6.9	8.1	7.0	0.59
Physiological measurements						
Mean hemoglobin, g/dl (SD)	8.2 (1.2)	8.4	8.1	8.0	7.9	0.10
Waking SpO_2, % median (IQR) (no. reported = 236)	97.1 (94.0, 98.6)	98.3	96.5	94.0	95.8	<0.001
Z score for body mass index, median (IQR) (no. reported = 241)	0.02 (-0.71, 0.82)	0.06	0.04	-0.10	-0.02	0.90
Systolic blood pressure > 90th percentile, % (no. reported = 241)	23.7	27.7	11.9	21.2	24.0	0.21
Diastolic blood pressure > 90th percentile, % (no. reported n = 240)	2.5	2.1	2.4	3.0	4.0	0.95
Atopy (≥ 2 positive skin tests), % (no. reported = 217)	26.3	25.0	26.3	37.9	18.2	0.41
FVC, % predicted (no. reported = 241)	92.2 (14.3)	93.8	89.6	92.0	87.8	0.13
FEV1, % predicted	88.0 (13.8)	90.7	84.3	83.6	84.4	0.003

(no. reported = 241						
FEV1/FVC, %	0.86 (0.07)	0.87	0.85	0.81	0.87	<0.001
(no. reported = 241)						
Other medical and/or family history						
Prior tonsillectomy or adenoidectomy, %	19.6	17.6	28.6	16.1	20.0	0.43
(no. reported = 240)						
Household smoking exposure , %	28.6	27.0	23.8	39.4	32.0	0.44
(no. reported = 241)						
Asthma, %	27.6	23.1	35.7	33.3	32.0	0.30
Hayfever, %	18.9	20.0	15.8	18.5	18.8	0.95
(no. reported = 196)						
Preterm birth, %	12.0	17.0	7.5	0.0	8.0	0.03
(no. reported = 233)						
Prescribed hydroxyurea at time of PSG, %	10.3	12.6	9.5	6.1	4.0	0.46
(no. reported = 218)						
Family history of OSAS or CPAP use, %	10.0	9.2	17.1	12.5	0.0	0.15
(no. reported = 239)						

TABLE 2A Cardiorespiratory PSG Variables by oAHI Diagnostic Cutpoints

Characteristic	All n = 243	oAHI <1 n = 143	oAHI ≥1 n = 100	oAHI ≥2 n = 58	oAHI ≥5 n = 25	p value
oAHI in NREM, median (IQR)	0.23 (0.0, 1.18)	0.0	0.85	1.68	4.62	<0.001
oAHI in REM, median (IQR)	2.0 (0.0, 8.0)	1.00	4.5	11.0	47.0	<0.001
Obstructive apnea index, median (IQR)	0.0	0.0	0.0	0.13	0.71	<0.001
Central apnea index, median (IQR)	0.29 (0.12, 0.68)	0.24	0.50	0.35	0.38	0.005
Sleep-wake SpO_2 difference, % , mean (SD) (no. reported = 236)	-0.85 (1.74)	-0.63	-0.90	-1.24	-1.46	0.073
SpO_2 during sleep, % , median (IQR)	96.4 (93.8, 98.1)	97.7	96.0	92.5	93.9	<0.001
SpO_2 during NREM sleep, %, median (IQR)	96.4 (94.0, 98.8)	97.5	95.9	92.4	94.4	<0.001
SpO_2 in REM sleep, % median (IQR) (no. reported = 242)	96.7 (93.8, 98.4)	98.0	96.0	92.5	93.0	<0.001
Minimum NREM SpO_2, % median (IQR)	92.0 (86.6, 95.2)	93.8	90.8	85.9	85.1	<0.001
Minimum REM SpO_2, % median (IQR)	91.7 (84.8, 95.0)	93.3	90.0	84.0	76.0	<0.001

3% desaturation index, median (IQR)	2.2 (0.6, 6.3)	0.9	3.2	7.0	15.9	<0.001
3% desaturation index in NREM, median (IQR)	1.40 (0.39, 4.44)	.70	2.35	4.90	8.33	<0.001
3% desaturation index in REM, median (IQR)	3.79 (1.06, 10.52)	1.44	5.74	11.87	39.04	<0.001
Sleep time with SpO_2 <95%, %, median (IQR)	6.2 (0.2, 81.2)	0.4	20.2	88.9	68.2	<0.001
Sleep time with SpO_2 <92%, %, median (IQR)	0.07 (0, 8.91)	0.02	0.115	46.7	7.66	<0.001
Sleep time with SpO_2 <90%, % median (IQR)	0.02 (0.0, 0.6)	0.0	0.03	1.74	1.91	<0.001
Sleep time with SpO_2 <85%, % , median (IQR)	0.0 (0.0, 0.4)	0.0	0.0	0.06	0.69	<0.001
Heart rate, asleep, beats per min, mean (SD) (no. reported = 242)	84.5 (10.7)	82.9	83.7	86.6	92.3	<0.001

TABLE 2B Sleep PSG Variables by oAHI Diagnostic Cutpoints

Characteristic	All n = 243	oAHI <1 n = 143	oAHI ≥1 n = 100	oAHI ≥2 n = 58	oAHI ≥5 n = 25	p value
Total sleep time, min, mean (SD)	438.7 (68.2)	438.4	450.2	431.5	430.9	0.60
Sleep latency, min, median (IQR)	20.5	20.0	24.8	20.5	15.0	0.88
REM latency, min, median (IQR)	83.5	80.8	89.0	92.0	90.0	0.28
Sleep efficiency, %, median (IQR)	85.5 (78.6, 89.5)	85.9	84.5	84.4	82.2	0.21
NREM stage 1 sleep, %, mean (SD)	5.2 (2.7)	5.0	5.0	5.9	5.8	0.22
NREM stage 2 sleep, % , mean (SD)	45.6 (8.2)	45.5	46.7	45.5	44.7	0.78
NREM stage 3 sleep, % , mean (SD)	22.5 (8.1)	22.4	20.9	22.7	25.7	0.13
REM sleep, % mean (SD)	26.6 (6.3)	27.0	27.3	25.9	23.9	0.10
Supine sleep time, % , mean (SD)	0.46 (0.26)	0.47	0.42	0.41	0.57	0.09
Arousal index, mean (SD)	8.6 (3.0)	8.2	8.3	9.1	10.9	<0.001

Table 3 Final Models of Logistic Regression Predicting OSAS at Two Severity Levels

	β	OR	95% CI	P value
No OSAS vs. 1 ≤ oAHI <5				
Male gender	0.331	1.39	0.66, 2.92	0.381
Age	0.031	1.013	0.93, 1.11	0.773
Waking SpO_2 values <96%*	-2.065	0.13	0.06, 0.27	<0.001
		7.6989*	3.7066, 1617.602*	
Habitual snoring	1.016	2.76	1.24, 6.17	0.013
FEV_1, percent predicted*	-0.041	0.96	0.93, 0.99	0.010
		1.04*	1.01, 1.07*	
Caretaker education < high school	0.546	1.73	0.71, 4.22	0.231
Non-Preterm birth*	-1.606	0.2	0.48, 0.84	0.028
		5.004.98*	1.198, 20.0897	
Environmental tobacco smoke exposure	0.550	1.73	0.77, 3.92	0.187
No OSAS vs. oAHI ≥ 5				
Male gender	0.836	2.31	0.64, 8.25	0.199
Age	-0.122	0.89	0.77, 1.02	0.096
Waking SpO_2 values <96%*	-1.706	0.18	0.05, 0.61	0.006
		5.551*	1.613, 18.561*	
Habitual snoring	2.829	16.93	4.98, 57.50	<0.001

Commented [MR2]: I recommend not doing this here.

FEV_1, percent predicted	-0.320	0.97	0.93, 1.01	0.127
Caretaker education < high school	0.500	1.65	0.35, 7.69	0.525
Non-Preterm birth	-1.026	0.36	0.05, 2.41	0.292
		2.79	0.41, 18.81	
Environmental tobacco smoke exposure	-0.247	0.78	0.21, 2.94	0.715

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TABLE LEGENDS

Table 1: Continuous data with normal distributions are reported as mean (SD) while data with non-normal distributions are reported as median (IQR). Categorical data are reported as a percentage of the entire sample (n = 243) or number (no.) reported. *The range for the Epworth Sleepiness Scale Score is 0-24 with higher scores indicating greater daytime sleepiness and normal values less than 11 in children

Table 2A: Continuous data with normal distributions are reported as mean (SD) while data with non-normal distributions are reported as median (IQR). Categorical data are reported as a percentage of the entire sample (n = 243) or the number (no.) of participants reported.

Table 2B: Continuous data with normal distributions are reported as mean (SD) while data with non-normal distributions are reported as median (IQR).

Table 3: * When the β-value is negative, significant associations will have odds ratios less than one. This means that a lower variable value is associated with a greater odds of being a member of an OSAS group. To improve clinical interpretability of the significant, but negative odds ratios, we have "reformatted" them to present the effect with an odds ratio greater than one.

REFERENCES

1. Marcus CL, Brooks LJ, Draper KA, et al. Diagnosis and management of childhood obstructive sleep apnea syndrome. *Pediatrics.*2012;130(3):576-584.

2. Marcus CL, Brooks LJ, Draper KA, et al. Diagnosis and management of childhood obstructive sleep apnea syndrome. *Pediatrics.*2012;130(3):e714-755.

3. Loke YK, Brown JW, Kwok CS, Niruban A, Myint PK. Association of obstructive sleep apnea with risk of serious cardiovascular events: a systematic review and meta-analysis. *Circulation. Cardiovascular quality and outcomes.*2012;5(5):720-728.

4. Redline S, Tishler PV, Schluchter M, Aylor J, Clark K, Graham G. Risk factors for sleep-disordered breathing in children. Associations with obesity, race, and respiratory problems. *Am J Respir Crit Care Med.*1999;159(5 Pt 1):1527-1532.

5. Rosen CL, Larkin EK, Kirchner HL, et al. Prevalence and risk factors for sleep-disordered breathing in 8- to 11-year-old children: association with race and prematurity. *J Pediatr.*2003;142(4):383-389.

6. Bixler EO, Vgontzas AN, Lin HM, et al. Sleep disordered breathing in children in a general population sample: prevalence and risk factors. *Sleep.*2009;32(6):731-736.

7. Weinstock TG, Rosen CL, Marcus CL, et al. Predictors of obstructive sleep apnea severity in adenotonsillectomy candidates. *Sleep.*2014;37(2):261-269.

8. Morton S, Rosen C, Larkin E, Tishler P, Aylor J, Redline S. Predictors of sleep-disordered breathing in children with a history of tonsillectomy and/or adenoidectomy. *Sleep.*2001;24(7):823-829.

9. Brouillette RT, Horwood L, Constantin E, Brown K, Ross NA. Childhood sleep apnea and neighborhood disadvantage. *J Pediatr.*2011;158(5):789-795 e781.

10. Spilsbury JC, Storfer-Isser A, Kirchner HL, et al. Neighborhood disadvantage as a risk factor for pediatric obstructive sleep apnea. *J Pediatr.*2006;149(3):342-347.

11. Hargrave DR, Wade A, Evans JP, Hewes DK, Kirkham FJ. Nocturnal oxygen saturation and painful sickle cell crises in children. *Blood.*2003;101(3):846-848.

12. Kirkham FJ, Hewes DK, Prengler M, Wade A, Lane R, Evans JP. Nocturnal hypoxaemia and central-nervous-system events in sickle-cell disease. *Lancet.*2001;357(9269):1656-1659.

13. Hollocks MJ, Kok TB, Kirkham FJ, et al. Nocturnal oxygen desaturation and disordered sleep as a potential factor in executive dysfunction in sickle cell anemia. *J Int Neuropsychol Soc.*2012;18(1):168-173.

14. Rackoff WR, Kunkel N, Silber JH, Asakura T, Ohene-Frempong K. Pulse oximetry and factors associated with hemoglobin oxygen desaturation in children with sickle cell disease. *Blood.*1993;81(12):3422-3427.

15. Wise MS, Nichols CD, Grigg-Damberger MM, et al. Executive summary of respiratory indications for polysomnography in children: an evidence-based review. *Sleep.*2011;34(3):389-398.

16. Wise MS, Nichols CD, Grigg-Damberger MM, et al. Respiratory indications for polysomnography in children: an evidence-based review. *Sleep.*2011;34(3):389-398AW.

17. Salles C, Ramos RT, Daltro C, Nascimento VM, Matos MA. Association between adenotonsillar hypertrophy, tonsillitis and painful crises in sickle cell disease. *Jornal de pediatria.*2009;85(3):249-253.

18. Salles C, Ramos RT, Daltro C, Barral A, Marinho JM, Matos MA. Prevalence of obstructive sleep apnea in children and adolescents with sickle cell anemia. *J Bras Pneumol.*2009;35(11):1075-1083.

19. Brooks LJ, Koziol SM, Chiarucci KM, Berman BW. Does sleep-disordered breathing contribute to the clinical severity of sickle cell anemia? *J Pediatr Hematol Oncol.*1996;18(2):135-139.

20. Maddern BR, Reed HT, Ohene-Frempong K, Beckerman RC. Obstructive sleep apnea syndrome in sickle cell disease. *Ann Otol Rhinol Laryngol.*1989;98(3):174-178.

21. Samuels MP, Stebbens VA, Davies SC, Picton-Jones E, Southall DP. Sleep related upper airway obstruction and hypoxaemia in sickle cell disease. *Arch Dis Child.*1992;67(7):925-929.

22. Kaleyias J, Mostofi N, Grant M, et al. Severity of obstructive sleep apnea in children with sickle cell disease. *J Pediatr Hematol Oncol.*2008;30(9):659-665.

23. Rogers VE, Lewin DS, Winnie GB, Geiger-Brown J. Polysomnographic characteristics of a referred sample of children with sickle cell disease. *J Clin Sleep Med.*2010;6(4):374-381.

24. Spivey JF, Uong EC, Strunk R, Boslaugh SE, DeBaun MR. Low daytime pulse oximetry reading is associated with nocturnal desaturation and obstructive sleep apnea in children with sickle cell anemia. *Pediatr Blood Cancer.*2008;50(2):359-362.

25. Needleman JP, Franco ME, Varlotta L, et al. Mechanisms of nocturnal oxyhemoglobin desaturation in children and adolescents with sickle cell disease. *Pediatr Pulmonol.*1999;28(6):418-422.

26. Ferris BG. Epidemiology Standardization Project (American Thoracic Society). *Am Rev Respir Dis.*1978;118(6 Pt 2):1-120.

27. The Childhood Asthma Management Program (CAMP): design, rationale, and methods. Childhood Asthma Management Program Research Group. *Controlled clinical trials.*1999;20(1):91-120.

28. Owens JA, Spirito A, McGuinn M. The Children's Sleep Habits Questionnaire (CSHQ): psychometric properties of a survey instrument for school-aged children. *Sleep.*2000;23(8):1043-1051.

29. Johns MW. A new method for measuring daytime sleepiness: the Epworth sleepiness scale. *Sleep.*1991;14(6):540-545.

30. Kuczmarski RJ, Ogden CL, Grummer-Strawn LM, et al. CDC growth charts: United States. *Adv Data.*2000(314):1-27.

31. Pegelow CH, Colangelo L, Steinberg M, et al. Natural history of blood pressure in sickle cell disease: risks for stroke and death associated with relative hypertension in sickle cell anemia. *Am J Med.*1997;102(2):171-177.

32. Field JJ, Stocks J, Kirkham FJ, et al. Airway hyperresponsiveness in children with sickle cell anemia. *Chest.*2010;139(3):563-568.

33. Strunk RC, Szefler SJ, Phillips BR, et al. Relationship of exhaled nitric oxide to clinical and inflammatory markers of persistent asthma in children. *J Allergy Clin Immunol.*2003;112(5):883-892.

34. Wang X, Dockery DW, Wypij D, Fay ME, Ferris BG, Jr. Pulmonary function between 6 and 18 years of age. *Pediatr Pulmonol.*1993;15(2):75-88.

35. Pellegrino R, Viegi G, Brusasco V, et al. Interpretative strategies for lung function tests. *Eur Respir J.*2005;26(5):948-968.

36. Iber C, Ancoli-Israel S, Chesson A, Quan S, for the American Academy of Sleep Medicine. *The AASM Manual for Scoring of Sleep and Associated Events: Rules, Terminology and Technical Specification.* 1st ed. Westchester, Illinois: American Academy of Sleep Medicine; 2007.

37. *American Academy of Sleep Medicine. International Classification of Sleep Disorders: Diagnostic & Coding Manual.* 2nd (Jan 2005) ed. Westchester, Illinois: American Academy of Sleep Medicine; 2005.

38. Li AM, Au CT, Ng SK, et al. Natural history and predictors for progression of mild childhood obstructive sleep apnoea. *Thorax.*2010;65(1):27-31.

39. Beck SE, Marcus CL. Pediatric Polysomnography. *Sleep Med Clin.*2009;4(3):393-406.

40. Marcus CL, Moore RH, Rosen CL, et al. A randomized trial of adenotonsillectomy for childhood sleep apnea. *N Engl J Med.*2013;368(25):2366-2376.

41. Lehmann GC, Bell TR, Kirkham FJ, et al. Enuresis associated with sleep disordered breathing in children with sickle cell anemia. *J Urol.*2012;188(4 Suppl):1572-1576.

42. Glassberg JA, Chow A, Wisnivesky J, Hoffman R, Debaun MR, Richardson LD. Wheezing and asthma are independent risk factors for increased sickle cell disease morbidity. *Br J Haematol.*2012;159(4):472-479.

43. Boyd JH, Macklin EA, Strunk RC, DeBaun MR. Asthma is associated with increased mortality in individuals with sickle cell anemia. *Haematologica.*2007;92(8):1115-1118.

44. Boyd JH, Macklin EA, Strunk RC, DeBaun MR. Asthma is associated with acute chest syndrome and pain in children with sickle cell anemia. *Blood.*2006;108(9):2923-2927.

45. Glassberg J, Spivey JF, Strunk R, Boslaugh S, DeBaun MR. Painful episodes in children with sickle cell disease and asthma are temporally associated with respiratory symptoms. *J Pediatr Hematol Oncol.*2006;28(8):481-485.

46. Leong MA, Dampier C, Varlotta L, Allen JL. Airway hyperreactivity in children with sickle cell disease. *J Pediatr.*1997;131(2):278-283.

47. Chervin RD, Archbold KH. Hyperactivity and polysomnographic findings in children evaluated for sleep-disordered breathing. *Sleep.*2001;24(3):313-320.

48. O'Brien LM, Holbrook CR, Mervis CB, et al. Sleep and neurobehavioral characteristics of 5- to 7-year-old children with parentally reported symptoms of attention-deficit/hyperactivity disorder. *Pediatrics.*2003;111(3):554-563.

49. Beebe DW, Wells CT, Jeffries J, Chini B, Kalra M, Amin R. Neuropsychological effects of pediatric obstructive sleep apnea. *J Int Neuropsychol Soc.*2004;10(7):962-975.

50. Gottlieb DJ, Chase C, Vezina RM, et al. Sleep-disordered breathing symptoms are associated with poorer cognitive function in 5-year-old children. *J Pediatr.*2004;145(4):458-464.

51. Huang YS, Chen NH, Li HY, Wu YY, Chao CC, Guilleminault C. Sleep disorders in Taiwanese children with attention deficit/hyperactivity disorder. *J Sleep Res.*2004;13(3):269-277.

52. Mulvaney SA, Goodwin JL, Morgan WJ, Rosen GR, Quan SF, Kaemingk KL. Behavior problems associated with sleep disordered breathing in school-aged children--the Tucson children's assessment of sleep apnea study. *J Pediatr Psychol.*2006;31(3):322-330.

53. Chervin RD, Weatherly RA, Garetz SL, et al. Pediatric Sleep Questionnaire: Prediction of Sleep Apnea and Outcomes. *Arch Otolaryngol Head Neck Surg.*2007;133(3):216-222.

54. Blunden S, Lushington K, Kennedy D, Martin J, Dawson D. Behavior and neurocognitive performance in children aged 5-10 years who snore compared to controls. *J Clin Exp Neuropsychol.*2000;22(5):554-568.

55. O'Brien LM, Mervis CB, Holbrook CR, et al. Neurobehavioral implications of habitual snoring in children. *Pediatrics.*2004;114(1):44-49.

56. Emancipator JL, Storfer-Isser A, Taylor HG, et al. Variation of cognition and achievement with sleep-disordered breathing in full-term and preterm children. *Arch Pediatr Adolesc Med.*2006;160(2):203-210.

57. Montgomery-Downs HE, O'Brien LM, Gulliver TE, Gozal D. Polysomnographic characteristics in normal preschool and early school-aged children. *Pediatrics.*2006;117(3):741-753.

58. Verhulst SL, Schrauwen N, Haentjens D, Van Gaal L, De Backer WA, Desager KN. Reference values for sleep-related respiratory variables in asymptomatic European children and adolescents. *Pediatr Pulmonol.*2007;42(2):159-167.

59. Tapia IE, Karamessinis L, Bandla P, et al. Polysomnographic values in children undergoing puberty: pediatric vs. adult respiratory rules in adolescents. *Sleep.*2008;31(12):1737-1744.

60. Strunk RC, Cohen RT, Cooper BP, et al. Wheezing Symptoms and Parental Asthma Are Associated with a Physician Diagnosis of Asthma in Children with Sickle Cell Anemia. *J Pediatr.*2013.

61. Caboot JB, Jawad AF, McDonough JM, et al. Non-invasive measurements of carboxyhemoglobin and methemoglobin in children with sickle cell disease. *Pediatr Pulmonol.*2012.