

# Obstructive Sleep Apnea and Sick Cell Anemia

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## KEY WORDS

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

## ABBREVIATIONS

AHI—apnea hypopnea index  
FEV<sub>1</sub>—forced expiratory volume in 1 second  
FVC—forced vital capacity  
HbS—sickle cell hemoglobin  
OAH—obstructive apnea hypopnea index  
OSAS—obstructive sleep apnea syndrome  
SCA—sickle cell anemia  
SpO<sub>2</sub>—pulse oxygen saturation

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**WHAT'S KNOWN ON THIS SUBJECT:** Obstructive sleep apnea syndrome (OSAS) prevalence in children with sickle cell anemia 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 sickle cell anemia have a high prevalence of OSAS with typical symptoms, beyond just nocturnal oxyhemoglobin desaturation. This study supports the need for increased efforts to screen for, diagnose, and treat OSAS in this vulnerable population.

## abstract



**OBJECTIVE:** 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 multicenter 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 on the basis of overnight in-laboratory polysomnography and putative risk factors obtained from questionnaires and direct measurements.

**RESULTS:** Participants included 243 children with a median age of 10 years; 50% were boys, 99% were of African heritage, and 95% were homozygous for  $\beta^S$  hemoglobin. OSAS, defined by obstructive apnea hypopnea indices, was present in 100 (41%) or 25 (10%) children at cutpoints of  $\geq 1$  or  $\geq 5$ , respectively. In univariate analyses, OSAS was associated with higher levels of habitual snoring, lower waking pulse oxygen saturation (SpO<sub>2</sub>), reduced lung function, less caretaker education, and non-preterm birth. Lower sleep-related SpO<sub>2</sub> metrics were also associated with higher obstructive apnea hypopnea indices. In multivariable analyses, habitual snoring and lower waking SpO<sub>2</sub> 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<sub>2</sub> values, data easily obtained in routine care, were the strongest OSAS risk factors. Because 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. *Pediatrics* 2014;134:273–281

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, with a prevalence of 1% to 5%, is associated with adverse health outcomes, such as behavioral problems, daytime sleepiness, cognitive deficits, cardiovascular changes, and reduced quality of life.<sup>1,2</sup> In adults, untreated OSAS is associated with increased risk of incident cardiovascular disease and stroke.<sup>3</sup> 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,<sup>4-7</sup> exposed to environmental tobacco smoke,<sup>7</sup> born preterm,<sup>5</sup> have undergone adenotonsillectomy,<sup>8</sup> and live in disadvantaged neighborhoods.<sup>9,10</sup> It is unknown whether these risk factors generalize to children with sickle cell anemia (SCA).

SCA affects 1 in 600 African-Americans and is characterized by chronic hemolytic anemia and complications 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, such as increased pain,<sup>11</sup> greater risk of central nervous system events,<sup>12</sup> cognitive dysfunction,<sup>13</sup> and history of acute chest syndrome.<sup>14</sup> Oxyhemoglobin desaturation is a well-known phenomenon in SCA resulting from a combination of calibration of the pulse oximeter for hemoglobin A, and not hemoglobin S, a rightward shift of the oxyhemoglobin dissociation curve, and dyshemoglobins, which are elevated in the presence of intravascular hemolysis but incapable of transporting oxygen. Because 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.<sup>15,16</sup> Previously reported prevalence rates range from 5% to 79%. Except for 1 study,<sup>17,18</sup> prevalence estimates have been based on samples clinically referred for OSAS symptoms<sup>19-23</sup> or with desaturation.<sup>24,25</sup> 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.<sup>1</sup>

We used data from participants in the prospective Sleep and Asthma Cohort Study who were unselected for OSAS symptoms to investigate the prevalence and risk factors for OSAS in children with SCA. We hypothesized 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 (OAHIs) will be associated with more OSAS symptoms and greater nocturnal oxyhemoglobin desaturation.

## METHODS

A detailed description of the testing procedures and statistical approach is provided in the Supplemental Information. In brief, we conducted a cross-sectional analysis of baseline data collected as part of the Sleep and Asthma Cohort Study, a prospective observational cohort of children ages 4 to 18 years with SCA (homozygous for sickle cell 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 3 pediatric centers: St Louis, Missouri; Cleveland, Ohio; and London, United Kingdom. Children were enrolled without regard to past morbidity from or

symptoms of sleep-disordered breathing or asthma. Children were ineligible for participation if they themselves were smokers, receiving long-term blood transfusions, or receiving long-term continuous positive airway pressure therapy at the time of enrollment; were participating in a clinical trial evaluating blood transfusion, oxygen, or hydroxyurea therapy; had chronic lung disease (other than asthma); or were HIV positive. Participants placed on 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 demographic characteristics and medical history, including asthma, allergies, and sleep.<sup>26-29</sup> Asthma was defined as a “yes” response to any of the following 3 questions: (1) “Has a doctor ever said that the participant has asthma?”, (2) “Does the participant take any asthma medications?”, and (3) “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 by using the sleep questionnaire by response to “How many times did your child snore in the previous month?” and was defined as snoring  $\geq 3$  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. Previous 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 continuous positive airway pressure. Sleepiness was assessed by using the Epworth Sleepiness Scale modified for children, in which scores range from 0 to 24, with higher scores indicating greater daytime sleepiness.<sup>29</sup>

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

Spirometry measures (forced expiratory volume in 1 second [FEV<sub>1</sub>], forced vital capacity [FVC], and the ratio of FEV<sub>1</sub> to FVC [FEV<sub>1</sub>:FVC]) were performed by study-certified technicians with the use of standardized protocols<sup>33</sup> and compared with normative data for healthy black children.<sup>34,35</sup> Waking pulse oxygen saturation (SpO<sub>2</sub>) values were collected by using a standardized 5-minute period. Other laboratory data were collected as part of clinical care.

Children underwent full channel, in-laboratory polysomnography by study-certified technicians with standardized protocols and equipment following American Academy of Sleep Medicine guidelines for data acquisition and scoring, except for carbon dioxide, which was not collected.<sup>36</sup> Because there is no consensus about what OAHl threshold should be used to define OSAS status, OAHl data were summarized by using several commonly used pediatric cutpoints: OAHl  $\geq 1$ ,<sup>37</sup> OAHl  $\geq 1$  plus habitual snoring,<sup>37,38</sup> OAHl

$\geq 1.5$ ,<sup>39</sup> OAHl  $\geq 2$ ,<sup>40</sup> and OAHl  $\geq 5$ .<sup>4–6,38</sup> Primary snoring was defined as an OAHl value of  $<1$  with habitual snoring 3 to 5 nights per week.

### Statistical Analyses

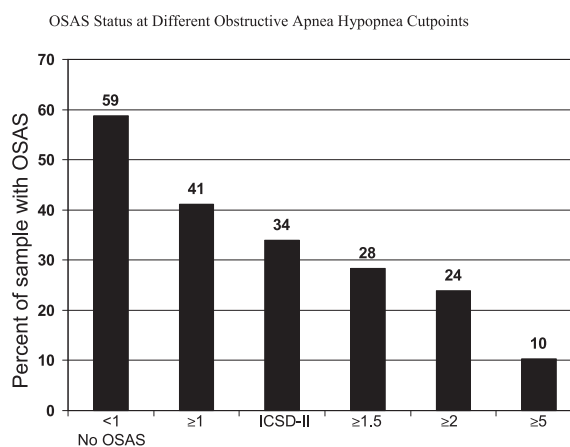
Means, SDs, medians, and interquartile ranges were computed for continuous variables. Frequencies and percentages were computed for categorical variables. Continuous data were analyzed by using analysis of variance or the non-parametric equivalent for nonnormal distributions. Categorical data were analyzed with a  $\chi^2$  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, OAHl, was categorized into 3 OSAS status groups: no OSAS (OAHl  $<1$ ), mild OSAS ( $1 \leq$  OAHl  $<5$ ), and moderate to severe OSAS (OAHl  $\geq 5$ ). Associations between the risk factors and OSAS status were expressed as odds ratios (ORs) with 95% confidence intervals (CIs). All tests for significance were 2-tailed. *P* values of  $<.05$  were considered significant. All analyses were performed by using SPSS version 21 (IBM SPSS Statistics, IBM Corporation, Armonk, NY).

## RESULTS

The final analytic sample included 243 children: 59 (24%) from Cleveland, 94 (39%) from London, and 90 (37%) from St Louis. The median age was 10 years, 50% were boys, 99% had African heritage, and 95% were homozygous for HbSS. The OAHl data were not normally distributed: mean (SD, range) = 2.1 (4.6, 0–37.2), whereas the median (interquartile range) was 0.6 (0.2–1.9). Figure 1 shows the prevalence of OSAS based on commonly used OAHl cutpoints and definitions: 41% for an OAHl  $\geq 1$ , 34% for an OAHl  $\geq 1$  plus habitual snoring, 28% for an OAHl  $\geq 1.5$ , 24% for an OAHl  $\geq 2$ , and 10% for an OAHl  $\geq 5$ . Among the 143 (59%) participants with OAHl values  $<1$ , 21% were habitual snorers (at least 3–5 nights per week) and 48% snored at least 1 to 2 nights per week.

### Participant Characteristics and OSAS Symptoms by OAHl Categories

Table 1 shows associations of participant characteristics and OSAS symptoms by OAHl categories. The frequency of OSAS symptoms (habitual snoring, trouble breathing, witnessed apnea, nocturnal enuresis) increased with higher OAHl values but not for nocturnal restlessness or daytime sleepiness. Only less caretaker education varied significantly with increasing OAHl values, whereas age, male gender, and



**FIGURE 1** OSAS status at different OAHl cutpoints. ICSD-II, International Classification of Sleep Disorders II.

**TABLE 1** Distribution of Participant Characteristics and OSAS Symptoms by OAHl Categories

	All (N = 243)	OAHl <1 (n = 143; 59%)	OAHl ≥1 and <2 (n = 42; 17%)	OAHl ≥2 and <5 (n = 33; 14%)	OAHl ≥5 (n = 25; 10%)	P
<b>Demographic characteristics</b>						
Age, mean (SD), y	10.6 (4.2)	10.6	11.1	11.4	8.8	.11
Male gender, %	50.2	47.6	50.0	48.5	68.0	.31
Caretaker education less than high school (n reported = 239), %	39.3	33.1	50.0	57.6	32.0	.03
Household income <\$30 000 (n reported = 207), %	59.9	56.3	73.0	61.3	55.0	.32
<b>Sleep and breathing symptoms</b>						
Habitual snoring ≥3 nights/week (n reported = 232), %	34.0	21.1	36.8	50.0	80.0	<.001
Trouble breathing ≥1 night/week (n reported = 219), %	19.2	14.0	13.2	25.9	48.0	.001
Witnessed apnea ≥1 night/week (n reported = 218), %	9.2	5.6	2.6	14.3	32.0	<.001
Nocturnal enuresis, ≥1 night/week (n reported = 227), %	30.0	27.6	20.0	32.9	56.0	.016
Restless, ≥1 night/week, %	31.7	32.9	33.3	30.3	24.0	.84
Epworth Sleepiness Scale <sup>a</sup> (n reported = 237), mean (SD)	7.1 (4.2)	7.0	6.9	8.1	7.0	.59
<b>Physiologic measurements</b>						
Hemoglobin, mean (SD), g/dL	8.2 (1.2)	8.4	8.1	8.0	7.9	.10
Waking Sp <sub>o2</sub> (n reported = 236), median (IQR), %	97.1 (94.0 to 98.6)	98.3	96.5	94.0	95.8	<.001
BMI z score (n reported = 241), median (IQR)	0.02 (−0.71 to 0.82)	0.06	0.04	−0.10	−0.02	.90
Systolic blood pressure >90th percentile (n reported = 241), %	23.7	27.7	11.9	21.2	24.0	.21
Diastolic blood pressure >90th percentile (n reported = 240), %	2.5	2.1	2.4	3.0	4.0	.95
Atopy (≥2 positive skin tests; n reported = 217), %	26.3	25.0	26.3	37.9	18.2	.41
FVC (n reported = 241), % predicted	92.2 (14.3)	93.8	89.6	92.0	87.8	.13
FEV <sub>1</sub> (n reported = 241), % predicted	88.0 (13.8)	90.7	84.3	83.6	84.4	.003
FEV <sub>1</sub> :FVC (n reported = 241)	0.86 (0.07)	0.87	0.85	0.81	0.87	<.001
<b>Other medical and/or family history, %</b>						
Previous tonsillectomy or adenoidectomy (n reported = 240)	19.6	17.6	28.6	16.1	20.0	.43
Household smoking exposure (n reported = 241)	28.6	27.0	23.8	39.4	32.0	.44
Asthma	27.6	23.1	35.7	33.3	32.0	.30
Hayfever (n reported = 196)	18.9	20.0	15.8	18.5	18.8	.95
Preterm birth (n reported = 233)	12.0	17.0	7.5	0.0	8.0	.03
Prescribed hydroxyurea at time of polysomnography (n reported = 218)	10.3	12.6	9.5	6.1	4.0	.46
Family history of OSAS or CPAP use (n reported = 239)	10.0	9.2	17.1	12.5	0.0	.15

Continuous data with normal distributions are reported as means (SD), whereas data with nonnormal distributions are reported as medians (IQR). Categorical data are reported as a percentage of the entire sample (N = 243) or numbers (n) reported. IQR, interquartile range; CPAP, continuous positive airway pressure.

<sup>a</sup> The range for the Epworth Sleepiness Scale score is 0 to 24, with higher scores indicating greater daytime sleepiness and normal values <11 in children.

household income did not. Lower waking Sp<sub>o2</sub> values were significantly associated with greater OAHl values, whereas lower hemoglobin values, higher BMI z scores, and elevated blood pressure were not. Participants with SCA were rarely obese. Greater OAHl values were significantly associated with reduced lung function (lower FEV<sub>1</sub> and FEV<sub>1</sub>:FVC), but not with lower FVC. Preterm birth was associated with lower, not higher, apnea hypopnea index (OAHl) values. Other potential OSAS risk factors, such as family history of OSAS, previous adenotonsillectomy, and other allergic or inflammatory conditions (asthma, hayfever, atopy, and environmental tobacco smoke exposure), were not associated with in-

creasing OAHl. Hydroxyurea prescription was caretaker reported for 10% of the sample but was not associated with lower OAHl (P = .46).

### Polysomnography Findings and Oximetry Metrics by Increasing OAHl Cutpoints

Polysomnography results stratified by OAHl cutpoints are shown in Table 2 for cardiorespiratory data and are shown in Table 3 for sleep data. Higher OAHl cutpoints were significantly associated with higher respiratory and desaturation indices and lower Sp<sub>o2</sub> metrics. Obstructive apneas had a negligible contribution to the overall OAHl at cutpoints <2. Central apneas tended to be more frequent with

higher OAHls, but remained within the normal range. Higher arousal index was the only sleep variable associated with higher OAHl cutpoints (P < .001).

### Risk Factors for OSAS: Multivariable Models Using 2 OSAS Severity Groups

Table 4 summarizes the final multivariable models in which the dependent variable, OSAS status, is categorized into 3 groups: no OSAS (OAHl <1), mild OSAS (1 ≤ OAHl <5), and moderate to severe OSAS (OAHl ≥5). When the β-value is negative, significant associations will have ORs <1, which means that a lower variable value is associated with a greater odds of being a member of the

**TABLE 2** Cardiorespiratory Polysomnography Variables by OAH1 Diagnostic Cutpoints

Characteristic	All (N = 243)	OAH1 <1 (n = 143)	OAH1 ≥1 (n = 100)	OAH1 ≥2 (n = 58)	OAH1 ≥5 (n = 25)	P
<b>OAH1</b>						
In NREM, median (IQR)	0.23 (0.0–1.18)	0.0	0.85	1.68	4.62	<.001
In REM, median (IQR)	2.0 (0.0–8.0)	1.00	4.5	11.0	47.0	<.001
Median (IQR)	0.0	0.0	0.0	0.13	0.71	<.001
Central apnea index, median (IQR)	0.29 (0.12–0.68)	0.24	0.50	0.35	0.38	.005
Sleep-wake SpO <sub>2</sub> difference (n reported = 236), mean (SD), %	−0.85 (1.74)	−0.63	−0.90	−1.24	−1.46	.073
<b>SpO<sub>2</sub>, %</b>						
During sleep, median (IQR)	96.4 (93.8–98.1)	97.7	96.0	92.5	93.9	<.001
During NREM sleep, median (IQR)	96.4 (94.0–98.8)	97.5	95.9	92.4	94.4	<.001
In REM sleep (n reported = 242), median (IQR)	96.7 (93.8–98.4)	98.0	96.0	92.5	93.0	<.001
Minimum NREM SpO <sub>2</sub> , median (IQR), %	92.0 (86.6–95.2)	93.8	90.8	85.9	85.1	<.001
Minimum REM SpO <sub>2</sub> , median (IQR), %	91.7 (84.8–95.0)	93.3	90.0	84.0	76.0	<.001
<b>3% Desaturation index</b>						
Median (IQR)	2.2 (0.6–6.3)	0.9	3.2	7.0	15.9	<.001
In NREM, median (IQR)	1.40 (0.39–4.44)	0.70	2.35	4.90	8.33	<.001
In REM, median (IQR)	3.79 (1.06–10.52)	1.44	5.74	11.87	39.04	<.001
Sleep time with SpO <sub>2</sub> <95%, median (IQR), %	6.2 (0.2–81.2)	0.4	20.2	88.9	68.2	<.001
Sleep time with SpO <sub>2</sub> <92%, median (IQR), %	0.07 (0–8.91)	0.02	0.115	46.7	7.66	<.001
Sleep time with SpO <sub>2</sub> <90%, median (IQR), %	0.02 (0.0–0.6)	0.0	0.03	1.74	1.91	<.001
Sleep time with SpO <sub>2</sub> <85%, median (IQR), %	0.0 (0.0–0.4)	0.0	0.0	0.06	0.69	<.001
Heart rate asleep (n reported = 242), mean (SD), beats/min	84.5 (10.7)	82.9	83.7	86.6	92.3	<.001

Continuous data with normal distributions are reported as means (SD), whereas data with nonnormal distributions are reported as medians (IQR). Categorical data are reported as a percentage of the entire sample (N = 243) or the numbers (n) of participants reported. IQR, interquartile range; NREM, nonrapid eye movement; REM, rapid eye movement.

OSAS group. To improve clinical interpretability of the significant, but large, negative ORs, we “reformatted” waking SpO<sub>2</sub> values <96% to present the effect with an OR >1 and recoded preterm birth as non-preterm birth.

There were 218 participants in the 2 groups: a no-OSAS group and a mild-OSAS group. In the screening model with 13 variables of interest, 186 of 218 participants had full data (loss of 14.7%) and the following 6 variables passed screening with *P* < .20: habitual snoring, waking SpO<sub>2</sub> <96%, FEV<sub>1</sub> percent predicted, environmental tobacco smoke exposure, caretaker education less than

high school, and non-preterm birth. By 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 SpO<sub>2</sub> values <96% (OR: 7.89; 95% CI: 3.66–17.02; *P* < .001), habitual snoring (OR: 2.76; 95% CI: 1.24–6.17; *P* = .013), lower FEV<sub>1</sub> percent predicted (OR: 0.96; 95% CI: 0.93–0.99; *P* = .010), and non-preterm birth (OR: 4.98; 95% CI: 1.1–20.97; *P* = .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, the positive predictive value was 0.52 and the negative predictive value was 0.87).

For no OSAS versus moderate to severe OSAS (OAH1 ≥5), there were 168 participants. With the use of the 4 variables from the final model for mild OSAS (plus age and gender) in the model for moderate to severe OSAS (OAH1 ≥5), there were 148 participants with full data (loss of 11.9%). Multivariable analyses revealed that only 2 factors significantly and independently associated with moderate to severe OSAS status: habitual

**TABLE 3** Sleep Polysomnography Variables by OAH1 Diagnostic Cutpoints

Characteristic	All (N = 243)	OAH1 <1 (n = 143)	OAH1 ≥1 (n = 100)	OAH1 ≥2 (n = 58)	OAH1 ≥5 (n = 25)	P
Total sleep time, mean (SD), min	438.7 (68.2)	438.4	450.2	431.5	430.9	.60
Sleep latency, median (IQR), min	20.5	20.0	24.8	20.5	15.0	.88
REM latency, median (IQR), min	83.5	80.8	89.0	92.0	90.0	.28
Sleep efficiency, median (IQR), %	85.5 (78.6–89.5)	85.9	84.5	84.4	82.2	.21
NREM stage 1 sleep, mean (SD), %	5.2 (2.7)	5.0	5.0	5.9	5.8	.22
NREM stage 2 sleep, mean (SD), %	45.6 (8.2)	45.5	46.7	45.5	44.7	.78
NREM stage 3 sleep, mean (SD), %	22.5 (8.1)	22.4	20.9	22.7	25.7	.13
REM sleep, mean (SD), %	26.6 (6.3)	27.0	27.3	25.9	23.9	.10
Supine sleep time, mean (SD), %	46 (0.26)	.47	.42	41	57	.09
Arousal index, mean (SD) events/hr	8.6 (3.0)	8.2	8.3	9.1	10.9	<.001

Continuous data with normal distributions are reported as means (SD), whereas data with nonnormal distributions are reported as medians (IQR). IQR, interquartile range; NREM, nonrapid eye movement; REM, rapid eye movement.

**TABLE 4** Final Models of Logistic Regression Predicting OSAS at 2 Severity Levels

	$\beta$	OR	95% CI
No OSAS versus $1 \leq \text{OAHl} < 5$			
Male gender	0.331	1.39	0.66–2.92
Age	0.031	1.01	0.93–1.11
Waking $\text{SpO}_2$ values $< 96\%^a$	–2.065 <sup>a</sup>	0.13	0.06–0.27
		7.89 <sup>a</sup>	3.66–17.02 <sup>a</sup>
Habitual snoring	1.016	2.76	1.24–6.17
FEV <sub>1</sub> , percent predicted <sup>a</sup>	–0.041	0.96	0.93–0.99
Caretaker education $<$ high school	0.546	1.73	0.71–4.22
Non–preterm birth	1.606	4.98	1.18–20.97
Environmental tobacco smoke exposure	0.550	1.73	0.77–3.92
No OSAS versus $\text{OAHl} \geq 5$			
Male gender	0.836	2.31	0.64–8.25
Age	–0.122	0.89	0.77–1.02
Waking $\text{SpO}_2$ values $< 96\%^a$	–1.706 <sup>a</sup>	0.18	0.05–0.61
		5.51 <sup>a</sup>	1.631–18.61 <sup>a</sup>
Habitual snoring	2.829	16.93	4.98–57.50
FEV <sub>1</sub> , % predicted	–0.320	0.97	0.93–1.01
Caretaker education less than high school	0.500	1.65	0.35–7.69
Non–preterm birth	1.026	2.79	0.41–18.18
Environmental tobacco smoke exposure	–0.247	0.78	0.21–2.94

<sup>a</sup> When the  $\beta$ -value is negative, significant associations will have ORs  $< 1$ , which 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 ORs, we “reformatted” some of them to present the effect with an OR  $> 1$ .

snoring (OR: 16.93; 95% CI: 4.98–57.5;  $P < .001$ ) and lower waking  $\text{SpO}_2 < 96\%$  (OR: 5.51; 95% CI: 1.63–18.61;  $P = .006$ ). 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, the positive predictive value was 0.32 and the negative predictive value was 0.99).

## DISCUSSION

This article summarizes clinical characteristics and polysomnography data from the largest sample of children with SCA, un-referred for signs or symptoms of OSAS. The OSAS prevalence rates, ranging from 41% at a cutpoint of an  $\text{OAHl} \geq 1$  to 10% at a cutpoint of an  $\text{OAHl} \geq 5$ , are higher than those reported in otherwise normal children (1%–5% at a cutpoint  $\geq 5$ ),<sup>1,5,6</sup> in African-American children (8.7% at a cutpoint  $\geq 5$ ),<sup>5</sup> and in a Brazilian cohort of children with SCA (10.6% at a cutpoint  $\geq 1$ ).<sup>18</sup>

Habitual snoring was a strong risk factor for OSAS in children with SCA, although many of the previously reported risk factors for OSAS for oth-

erwise healthy children were not observed, such as age, gender, obesity, hypertension, daytime sleepiness, asthma, hayfever, atopy, environmental tobacco smoke exposure, family history of OSAS, previous adenotonsillectomy, and preterm birth. The association of enuresis with OSAS was previously reported for this cohort.<sup>41</sup> Lower caretaker education was a risk factor in univariate analyses, but not in multivariable analysis. Other unique risk factors to SCA were suggested by univariate analyses (lower waking  $\text{SpO}_2$  values and reduced lung function). However, in multivariable analyses, only lower waking  $\text{SpO}_2$  was retained at both OSAS categories. Lower FEV<sub>1</sub> was associated with the mild  $\text{OAHl}$  category, but not at the higher  $\text{OAHl}$  category.

Higher  $\text{OAHl}$  values were not associated with asthma or hayfever. It is possible that our definitions of asthma and allergy, based on parent report of symptoms, 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,<sup>42–46</sup> so this definition

has clinical relevance in this SCA sample. By using more quantitative measures of allergy and respiratory disease, we found that atopy was not associated with OSAS, but reduced FEV<sub>1</sub> and FEV<sub>1</sub>:FVC were, suggesting an association of lower airway disease 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 sensitive but not very specific for predicting OSAS. Lower waking  $\text{SpO}_2$  had the strongest association with mild OSAS followed by habitual snoring, but this order was reversed for  $\text{OAHl}$  values  $\geq 5$ , suggesting that  $\text{OAHl}$  values in the milder range may be less specific for OSAS. The models were only slightly more than 50% predictive of polysomnography-defined OSAS at either range, similar to the positive and predictive values of history and physical examination (65% and 46%, respectively) for the diagnosis of OSAS in otherwise healthy children, which led to the recommendation that objective testing such as polysomnography be used in the diagnosis of OSAS.<sup>2</sup> This recommendation becomes even more important in children with SCA in whom other disturbances to oxygen delivery such as anemia, oxyhemoglobin desaturation, and other pulmonary dysfunction are often present.

Although we evaluated OSAS prevalence and risk factors on the basis of commonly used  $\text{OAHl}$  cutpoints for children, the gold standard for OSAS diagnosis is not polysomnography alone, but rather the skillful integration of clinical and polysomnography findings by experienced clinicians.<sup>16</sup> The AHI is a popular metric to determine the presence of OSAS, but there is no consensus on how the AHI should be used to indicate disease severity. Previous

studies have shown that the AHI was not useful in predicting either baseline neurobehavioral morbidity or response to OSAS treatment in children in the general population.<sup>40,47–53</sup> Even “primary snoring,” that is snoring with an AHI <1, has been associated with neurobehavioral morbidity.<sup>54–56</sup> For these reasons, we cannot identify an AHI threshold at which OSAS needs to be addressed. Because 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 outcomes studies are required to determine what threshold is associated with SCA-related morbidity.

Although OSAS appears to be 1 contributor to sleep-disordered breathing in SCA, the oximetry metrics reveal that some children also experience more sustained nocturnal desaturation. Greater desaturation time was associated with higher OAHl cutpoints, but desaturation can also be related to comorbid lower respiratory tract pathology. In our sample with SCA, the oximetry metrics for sleep time of <95% and <92% were similar to the upper limits of normal reported for otherwise healthy children.<sup>57–59</sup> 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 multicenter sample, and objective assessment of sleep-disordered breathing by standardized full polysomnography scored centrally without clinical correlates. Nevertheless, several limitations are noted. With a participation rate of 66%, it is possible that the 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<sup>2</sup> 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.<sup>60</sup> In terms of data collection, tonsil size was not assessed, end-tidal carbon dioxide was not measured, and 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 in patients with SCA,<sup>61</sup> simple pulse oximetry may underestimate oxygenation status because the dyshemoglobins are not measured.<sup>62</sup>

## CONCLUSIONS

This study confirms that children with SCA 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. Because 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.

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