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Predictors of Obstructive Sleep Apnea Severity in Adenotonsillectomy Candidates

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Study Objectives: There is uncertainty over which characteristics increase obstructive sleep apnea syndrome (OSAS) severity in children. In candidates for adenotonsillectomy (AT), we evaluated the relationship of OSAS severity and age, sex, race, body mass index (BMI), environmental tobacco smoke (ETS), prematurity, socioeconomic variables, and comorbidities.

Design: Cross-sectional screening and baseline data were analyzed from the Childhood Adenotonsillectomy Trial, a randomized, controlled, multicenter study evaluating AT versus medical management. Regression analysis assessed the relationship between the apnea hypopnea index (AHI) and risk factors obtained by direct measurement or questionnaire.

Setting: Clinical referral setting.

Participants: Children, ages 5 to 9.9 y with OSAS.

Measurements and Results: Of the 1,244 children undergoing screening polysomnography, 464 (37%) were eligible (2 ≤ AHI < 30 or 1 ≤ obstructive apnea index [OAI] < 20 and without severe oxygen desaturation) and randomized; 129 (10%) were eligible but were not randomized; 608 (49%) had AHI/OAI levels below entry criteria; and 43 (3%) had levels of OSAS that exceeded entry criteria. Among the randomized children, univariate analyses showed significant associations of AHI with race, BMI z score, environmental tobacco smoke (ETS), family income, and referral source, but not with other variables. After adjusting for potential confounders, African American race (P = 0.003) and ETS (P = 0.026) were each associated with an approximately 20% increase in AHI. After adjusting for these factors, obesity and other factors were not significant.

Conclusions: Apnea hypopnea index level was significantly associated with race and environmental tobacco smoke, highlighting the potential effect of environmental factors, and possibly genetic factors, on pediatric obstructive sleep apnea syndrome severity. Efforts to reduce environmental tobacco smoke exposure may help reduce obstructive sleep apnea syndrome severity.

Clinical Trial Registration: Clinicaltrials.gov (#NCT00560859).

Keywords: Adenotonsillectomy, apnea hypopnea index, disparities, obstructive sleep apnea syndrome, polysomnography, tobacco

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INTRODUCTION

Obstructive sleep apnea syndrome (OSAS) is a disorder in which the soft tissues of the upper airway collapse during sleep, resulting in recurrent episodes of hypopneas and apneas, arousal, and intermittent hypoxemia, and is associated with adverse behavioral, cognitive, quality of life, and health outcomes. More than 10% of children are reported to have habitual snoring, a symptom of OSAS,[1] whereas estimates of objectively measured OSAS criteria range from 0.1% to 4.7%.[1,2] In two community-based nonclinical samples, OSAS prevalence was increased among racial/ethnic minorities, children with socioeconomic disadvantage, and those born prematurely.[1,3] It is unknown whether these risk factors generalize to otherwise healthy children seen for snoring and adenotonsillar hypertrophy from clinical settings from across the US.

To develop better strategies for screening and managing OSAS, it is important to identify risk factors for the presence and severity in OSAS in a clinical practice setting. We analyzed screening and baseline data from the Childhood Adenotonsillectomy Trial, a randomized, controlled multicenter study of health outcomes in children with mild to moderate OSAS, randomized to early adenotonsillectomy (AT) or to watchful waiting with supportive care, to identify demographic and health characteristics associated with the presence and severity of OSAS in snoring children considered to be candidates for AT. We hypothesized that OSAS severity would be associated with African American (AfA) race, low socioeconomic status, prematurity, obesity, and asthma. We also hypothesized that a history of atopy and environmental tobacco smoke (ETS), which may increase nasopharyngeal swelling or inflammation, also would be associated with OSAS severity. Because AfA race may be a surrogate for environmental or health factors, we hypothesized that any relationship between AfA race and OSAS would be attenuated after considering potential mediators such as obesity and ETS.

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METHODS

Study Design and Sample

The design of the Childhood Adenotonsillectomy Trial has been described before.[4] In brief, the targeted sample was children ages 5.0-9.9 y with mild to moderate OSAS, defined by parental report of the child's snoring and a standardized, centrally scored polysomnogram showing an obstructive apnea index (OAI, number of obstructive apneas per hour of sleep) ≥ 1 or apnea hypopnea index (AHI) ≥ 2.[5] (Children with an AHI between 1 and 2, who may be classified with OSAS, were excluded to increase specificity for OSAS; in this analysis, they are considered to have "minimal OSAS.") Children with severe OSAS defined as having an OAI > 20, AHI > 30, or percentage sleep time at an oxyhemoglobin saturation of < 90% for > 2% of total sleep time were ineligible for randomization. Other inclusion criteria included tonsillar size ≥ 1 based on a standardized scale of 0-4 and deemed to be a candidate for AT by otolaryngology (ear, nose, and throat [ENT]) evaluation. Exclusion criteria included comorbidities, medication use for attention deficit hyperactivity disorder, and a BMI z-score ≥ 3.[4] Subjects were recruited from pediatric sleep centers/sleep laboratories, pediatric ENT clinics, general pediatric clinics, and the general community from seven clinical centers.[4] Ethics approval was obtained by each institution, children provided assent, and parents provided written informed consent.

Study Procedures

Study personnel screened the clinical records of children referred to clinics and sleep laboratories to identify potentially eligible children with snoring and/or adenotonsillar hypertrophy. After informed consent was obtained, the child underwent further evaluation that included assessment of polysomnography (PSG) eligibility through the central scoring of a standardized polysomnogram and an ENT examination to confirm appropriateness for AT. Caregivers completed questionnaires addressing the child's medical, social, and family histories and the child underwent standardized assessments of anthropometric characteristics, neurocognitive and behavioral functions, and other measures.

Definitions

Categorical variables were defined using standardized questions. ETS was considered positive if the primary caregiver reported current smoking one or more cigarette per day[6]; maternal prenatal smoking was considered positive if the biological mother reported smoking one or more cigarettes per day while pregnant with the child; prematurity was based on a report of birth at least 4 weeks early; history of asthma, hay fever, or atopy (identified as reported eczema) were considered positive if the caregiver reported that the child had this condition diagnosed or treated by a physician. A history of allergies was considered positive based on parent report of "any allergies." Socioeconomic status was defined on the basis of a reported family income < or ≥ $30,000 per year. Family history of OSAS was identified if the caregiver reported that OSAS had been diagnosed in the child's parent or sibling. Weight was assessed from measured weight and height values, expressed as body mass index (BMI), age, and sex adjusted percentiles and z-scores (http://www.cdc.gov/growthcharts/) as well as categorical variables (obesity: BMI > 95th percentile for age and sex; overweight BMI > 85% percentile. Birth weight was assessed as a continuous variable from recalled weight at birth, with low birth weight defined as < 2,500 g. Race was categorized as Caucasian, black/African American (AfA), and other. Season of recruitment was defined as December-July (lower allergen exposure) versus August-November.

Statistical Analysis

We analyzed data from two samples: (1) all subjects undergoing screening PSG; and (2) subjects who met study eligibility criteria and were randomized. Screened subjects were categorized into four groups according to OSAS severity and enrollment status: (1) excluded because of a low OAI and AHI (OAI < 1 or AHI < 2 ; primary snorers/minimal OSAS); (2) eligible by PSG but who were not randomized due to caregiver decisions not to proceed in the study; (3) eligible and enrolled; (4) excluded due to severe OSAS (AHI ≥ 30, OAI ≥ 20 or > 2% total sleep time with a saturation of peripheral oxygen [SpO_2] < 90%). We compared those with the most severe OSAS (group 4) to all others (groups 1, 2, and 3); primary snorers/minimal OSAS (group 1) to those with mild to severe OSAS (groups 2, 3, and 4); and those who were eligible and randomized (group 3) to those eligible and not randomized (group 2). These comparisons allowed us to assess two sets of objectives: variation of risk factors across a wide range of OSAS severity, and variation of risk factors in children whose parents elected to continue in the study contrasted to those who did not continue. Group differences were compared using t-tests or linear regression for continuous variables and chi-square tests, the Cochran-Armitage trend test, or logistic or multinomial logistic regression for categorical variables. For descriptive analyses among randomized subjects, OSAS severity groups were defined to identify approximately equal quartiles in the AHI distribution (AHI < 3; AHI 3 to 4.9; AHI ≥ 5 to 9.9; AHI ≥ 10). Among the randomized children (who had more extensive data), we also evaluated the association between OSAS severity and subject characteristics. In multivariate regression models, the outcome was log-transformed AHI level. We used a fivefold cross-validation method to select variables to be included in the final multivariate model[7] in addition to age, sex, race, obesity, and recruitment site, which were always included in the base model. We explored additional multivariate models by changing the variables included in the base model or by including variables of interest as covariates to assess their effects on model fit. We assessed whether the effect of race on AHI severity was mediated by obesity, ETS, family income, history of asthma, or birth weight, individually and in combination, using published methods.[8] Tests were two-sided and significance tests were not adjusted for multiple comparisons. Analyses were performed using SAS 9.2 (SAS Institute, Inc., Cary, NC) and R version 2.13.0 or higher.

RESULTS

A total of 1,244 children underwent screening PSG. Of these, 464 (37%) had an AHI/OAI level in the eligibility range and were enrolled. An additional 129 children (10%) were eligible by PSG but not enrolled due to changes in caregiver interest.

Almost one-half (n = 608; 49%) of the snoring children considered to be AT candidates and screened with PSG were not eligible due to AHI/OAI levels below the study's threshold, whereas 43 children (3%) were ineligible due to PSG characteristics indicating severe OSAS (Figure 1).

Summary statistics, by study eligibility and enrollment status, for children who underwent screening PSG are shown in Table 1. The distributions of age and sex were comparable across groups. Among children who met PSG eligibility, those who were randomized compared to those not randomized had comparable levels of BMI but were more likely to be AfA. A greater proportion of children identified from ENT clinics compared to sleep centers were randomized, whereas fewer children from pediatric/community sources compared to ENT or sleep centers were randomized.

Table 2 illustrates the distributions of subject characteristics across the spectrum of OSAS severity among all

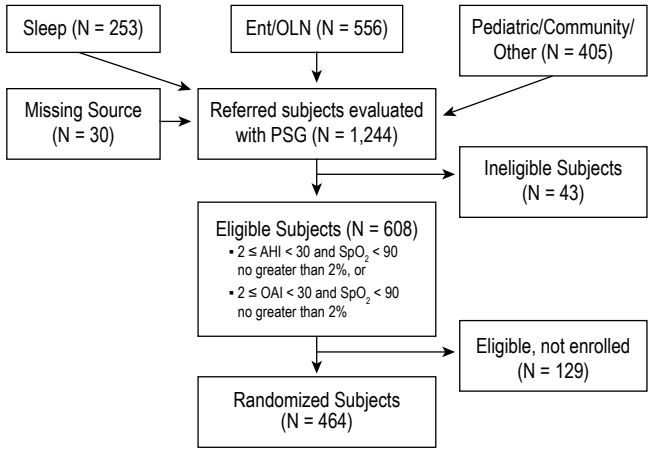

Figure 1—Consort diagram indicating flow of participants in the Childhood Adenotonsillectomy Trial. CHAT study.

Table 1—Subject characteristics by polysomnography eligibility and randomization status

	Ineligible due to minimal OSAS (AHI < 2 and OAI < 1)	Eligible, not randomized (AHI 2-30 or OAI 1-20)	Eligible and randomized (AHI 2-30 or OAI 1-20)	Ineligible due to severe OSAS (AHI ≥ 30, OAI > 20, or % desaturation high)	Eligible subjects randomized vs. eligible subjects not randomized
	N = 608	N = 129	N = 464	N = 43	P value[a]
Age (y; mean, SD)	7.3 (1.5)	7.0 (1.4)	7.0 (1.4)	7.5 (1.6)	0.61
Sex					0.54
Male	279 (47.5%)	57 (9.7%)	226 (38.5%)	25 (4.3%)	
Race[b]					< 0.001
African American	241 (41.6%)	46 (7.9%)	254 (43.8%)	39 (6.7%)	
White	276 (56.8%)	50 (10.3%)	159 (32.7%)	1 (0.2%)	
Other	70 (46.7%)	26 (17.3%)	51 (34.0%)	3 (2.0%)	
Ethnicity[b]					0.24
Hispanic	42 (43.3%)	14 (14.4%)	39 (40.2%)	2 (2.1%)	
BMI percentile[b]					0.61
Underweight (< 5th %ile)	15 (45.5%)	2 (6.1%)	15 (45.5%)	1 (3.0%)	
Normal (5th to 85th %ile)	306 (51.1%)	59 (9.8%)	225 (37.6%)	9 (1.5%)	
Overweight (> 85th %ile)	96 (50.5%)	22 (11.6%)	67 (35.3%)	5 (12.6%)	
Obese (≥ 95th %ile)	150 (40.3%)	37 (9.9%)	157 (42.2%)	28 (7.5%)	
BMI z-score	0.8 (1.3)	0.8 (1.3)	0.9 (1.3)	1.6 (1.4)	0.59
Referral site					< 0.0001
Site 10 CHOP	210 (51.6%)	31 (7.6%)	147 (36.1%)	19 (4.7%)	
Site 20 CINN	151 (57.4%)	27 (10.3%)	79 (30.0%)	6 (2.3%)	
Site 30 CLD	104 (41.1%)	14 (5.5%)	124 (49.0%)	11 (4.3%)	
Site 40 LVL	16 (53.3%)	3 (10.0%)	11 (36.7%)	0	
Site 50 SLU	49 (41.5%)	3 (2.5%)	60 (50.8%)	6 (2.3%)	
Site 60 MNYC	11 (29.7%)	9 (24.3%)	16 (43.2%)	1 (2.7%)	
Site 70 Boston	67 (49.3%)	42 (30.9%)	27 (19.9%)	0	
Referral source					< 0.0001
ENT/OLN	263 (47.3%)	44 (7.9%)	231 (41.5%)	18 (3.2%)	
Sleep clinic	24 (54.5%)	8 (18.2%)	9 (20.5%)	3 (6.8%)	
Sleep lab	34 (36.6%)	6 (6.5%)	50 (53.8%)	3 (3.2%)	
Pediatrics/community/other	271 (52.0%)	68 (13.1%)	163 (31.3%)	19 (3.6%)	

[a]P values are reported testing the associations of demographic variables and OSAS severity. For continuous variables (age and BMI z score), P values are based on t-tests. For categorical variables, P values are based on chi-square tests or with Fisher exact tests. [b]Data on race is missing for 28 subjects; ethnicity for 43 subjects and BMI for 50 subjects. % are row percentages. AHI, apnea hypopnea index; BMI, body mass index; ENT, ear, nose, and throat; OAI, obstructive apnea index; SD, standard deviation.

Table 2—Characteristics according to obstructive sleep apnea syndrome severity, all screened children

	Severe OSAS (AHI > 30, OAI > 20, or % desaturation high) vs. all others			Primary snorer/minimal OSAS (AHI < 2 and OAI < 1) vs. all others (AHI ≥ 2 or OAI ≥ 1)		
	Severe OSAS (n = 43)	Nonsevere OSAS (n = 1,201)	P value[a]	Snorer/minimal OSAS (n = 608)	Mild to severe OSAS (n = 636)	P value[a]
Age (y; mean, SD)	7.5 (1.6)	7.1 (1.4)	0.14	7.3 (1.5)	7.0 (1.4)	< 0.01
Sex						0.59
Male	25 (58.1%)	562 (46.8%)	0.18	279 (45.9 %)	308 (48.4%)	
Race[b]						< 0.0001
African American	39 (90.7%)	541 (45.0%)	< 0.0001	241 (39.6%)	339 (53.3%)	
Ethnicity[b]						0.34
Hispanic	2 (4.7%)	95 (7.9%)	0.57	42 (6.9%)	55 (8.6%)	
BMI z score	1.6 (1.6)	0.8 (1.3)	< 0.001	0.8 (1.3)	0.9 (1.3)	0.06
Obese	28 (65.1%)	344 (28.6%)	< 0.0001	150 (24.7%)	222 (34.9%)	< 0.001
Tonsillar size			0.73			0.09
0-25%	0	13 (2.4%)		4 (6.3%)	9 (1.9%)	
26-50%	2 (25.0%)	128 (23.9%)		17 (27.0%)	113 (23.5%)	
51-75%	6 (75.0%)	332 (61.9%)		36 (57.1%)	302 (62.9%)	
76-100%	0	63 (11.8%)		6 (9.5%)	57 (11.9%)	
Season recruited			0.09			0.01
Aug-Nov	7 (16.3%)	338 (28.1%)		188 (30.9%)	157 (24.7%)	
Dec-Jul	36 (83.7%)	863 (71.9%)		420 (69.1%)	479 (75.3%)	
Referral source			0.57			0.03
ENT/OLN	18 (41.9%)	538 (45.9%)		263 (44.4%)	293 (47.1%)	
Sleep clinic	3 (7.0%)	41 (3.5%)		24 (4.1%)	20 (3.2%)	
Sleep lab	3 (7.0%)	90 (7.7%)		34 (5.7%)	59 (9.5%)	
Pediatric/community/other	19 (44.2%)	502 (42.9%)		271 (45.8%)	250 (40.2%)	
Recruitment site			0.06			< 0.001
Site 10 CHOP	19 (44.2%)	388 (32.3%)		210 (34.5%)	197 (31.0%)	
Site 20 CINN	6 (14.0%)	257 (21.4%)		151 (24.8%)	112 (17.6%)	
Site 30 CLD	11 (25.6%)	242 (20.1%)		104 (17.1%)	149 (23.4%)	
Site 40 LVL	0	30 (2.5%)		16 (2.6%)	14 (2.2%)	
Site 50 SLU	6 (14.0%)	112 (9.3%)		49 (8.1%)	69 (10.8%)	
Site 60 MNYC	1 (2.3%)	36 (3.0%)		11 (1.8%)	26 (4.1%)	
Site 70 Boston	0	136 (11.3%)		67 (11.0%)	69 (10.8%)	

[a]P values were reported for association of demographic variables with OSAS severity. For continuous variables (age and BMI z score), P values are based on linear regression (two-way analysis of variance). For ordinal variables (tonsillar size), P values are based on Cochran-Armitage trend test. For other categorical variables, P values are based on chi-square tests or with Fisher exact tests (referral source and recruitment site). % indicates column percentages. [b]Missing data: 28 for race; 43 for ethnicity; 50 for BMI. AHI, apnea hypopnea index; BMI, body mass index; ENT, ear, nose, and throat; OSAS, obstructive sleep apnea syndrome; SD, standard deviation.

screened children by comparing the most severe OSAS group (AHI > 30 or OAI > 30) to all others, and the primary snoring/minimal OSAS group (AHI < 2 and OAI < 1) to children with mild to severe OSAS (AHI ≥ 2 or OAI ≥ 1). Children with the most severe OSAS were more likely to be AfA and obese than children with less severe OSAS; i.e., of the 43 children who were ineligible due to severe OSAS, 39 were AfA and two were Hispanic. The group with severe OSAS did not differ by age, sex, referral site, or recruitment source compared to those with primary snoring or less severe OSAS. Similarly, when comparing the primary snorers/minimal OSAS to those with mild or more severe OSAS, those with OSAS were more likely to be AfA and obese. A higher percentage of children from the pediatric/community sites were determined to be primary snorers or have minimal OSAS compared to children referred from sleep laboratories.

Table 3 shows the summary statistics for the more detailed clinical characteristics available for eligible children who were randomized. In univariate analyses, increasing levels of OSAS severity were associated with AfA race, family income, obesity, and ETS. OSAS severity was not associated with age, sex, tonsillar size, asthma, eczema, hay fever, prematurity, family history of OSAS, *in utero* tobacco exposure, or recruitment site.

Multivariate analyses showed that AfA race was significantly associated with the AHI level after considering potential confounders such as maternal education and family income (neither of which was significant in race-adjusted models) as well as age, sex, obesity, referral source, ETS, prenatal smoking, prematurity, birth weight, allergies, hay fever, and asthma. The results of the final multivariable model relating the log-transformed AHI level and risk factors in the group of randomized children are depicted in Table 4. This model estimated that AfA

Table 3—Randomized participants' characteristics by AHI level

	AHI < 3 N = 137	AHI = 3 to 5 N = 104	AHI ≥ 5 to 10 N = 130	AHI ≥ 10 N = 93	P value[a]
Age (y), mean (SD)	6.95 (1.36)	7.02 (1.46)	7.18 (1.45)	6.93 (1.36)	0.73
Sex					0.31
Male	74 (54.0%)	48 (46.2%)	59 (45.4%)	45 (48.4%)	
Race					0.0002
African American	58 (42.3%)	57 (54.8%)	79 (60.8%)	60 (64.5%)	
Ethnicity					0.55
Hispanic	10 (7.3%)	7 (6.7%)	15 (11.5%)	7 (7.5%)	
Maternal education					0.38
High school and less	42 (30.9%)	30 (29.7%)	41 (31.8%)	33 (36.7%)	
Family income					0.05
< $30,000	50 (36.5%)	35 (33.7%)	61 (46.9%)	41 (44.1%)	
≥ $30,000	71 (51.8%)	52 (50.0%)	50 (38.5%)	36 (38.7%)	
No response	16 (11.7%)	17 (16.4%)	19 (14.6%)	16 (17.2%)	
BMI- z-score (kg/m^2), mean (SD)	0.7 (1.2)	0.8 (1.4)	1 (1.4)	1 (1.3)	0.07
Obesity (BMI > 95% percentile)	34 (24.8%)	38 (36.5%)	51 (39.2%)	34 (36.6%)	0.03
Tonsillar size					0.20
0-25%	4 (50.0%)	0	2 (25.0%)	2 (25.0%)	
26-50%	29 (26.9%)	29 (26.9%)	31 (28.7%)	19 (17.6%)	
51-75%	92 (31.7%)	62 (21.4%)	78 (26.9%)	58 (20.0%)	
76-100%	9 (16.7%)	13 (24.1%)	18 (33.3%)	14 (25.9%)	
Environmental tobacco smoke exposure					0.02
Current smoking in home	35 (25.5%)	32 (30.8%)	40 (30.8%)	38 (40.9%)	
Asthma	38 (27.7%)	34 (32.7%)	40 (30.8%)	33 (35.5%)	0.28
Allergies	59 (43.1%)	48 (46.2%)	37 (28.5%)	46 (49.5%)	0.78
Eczema	39 (28.5%)	27 (26%)	29 (22.3%)	30 (32.3%)	0.87
Hay fever (allergic rhinitis)	37 (27%)	25 (24%)	21 (16.2%)	27 (29%)	0.66
Tobacco use during pregnancy					
At least 1 cigarette per day during pregnancy	17 (12.4%)	14 (13.5%)	15 (11.5%)	18 (19.4%)	0.23
Prematurity (> 4 weeks early)	26 (19%)	10 (9.6%)	20 (15.4%)	13 (14%)	0.43
Birth weight (lb), mean (SD)	6.9 (1.6)	6.8 (1.3)	6.7 (1.6)	6.6 (1.4)	0.20
Site					0.08
CHOP	40 (29.2%)	31 (29.8%)	44 (33.8%)	32 (34.4%)	
CINN	29 (21.2%)	16 (15.4%)	24 (18.5%)	10 (10.8%)	
CLD	33 (24.1%)	31 (29.8%)	36 (27.7%)	24 (25.8%)	
LVL	1 (0.7%)	2 (1.9%)	3 (2.3%)	5 (5.4%)	
SLU	20 (14.6%)	17 (16.3%)	10 (7.7%)	13 (14%)	
MNYC	4 (2.9%)	1 (1%)	5 (3.8%)	6 (6.5%)	
Boston	10 (7.3%)	6 (5.8%)	8 (6.2%)	3 (3.2%)	
Referral source					0.78
ENT/OLN	65 (47.8%)	57 (55.9%)	62 (48.8%)	47 (53.4%)	
Sleep clinic	3 (2.3%)	2 (2.0%)	4 (3.7%)	0	
Sleep lab	17 (12.5%)	12 (11.8%)	12 (9.5%)	9 (10.3%)	
Pediatrics/community/other	51 (37.5%)	31 (30.4%)	49 (38.9%)	32 (36.4%)	

[a]P values were based on association between AHI severity (assumed to have a linear trend and as predictor variable) and outcomes of interest. For continuous outcomes (age, BMI, birthweight), linear regression models were fit. For ordinal outcome (tonsillar size), ordered logistic regression model was fit. For multileveled categorical outcomes (referral source and recruitment site), multinomial logistic regression models were fit. For other dichotomized categorical outcomes, logistic regression models were fit. % indicate column percentages. AHI, apnea hypopnea index; BMI, body mass index; ENT, ear, nose, and throat; SD, standard deviation.

children had an average increase in log AHI (events/h) that was 0.2 higher (P = 0.004) compared with other children, which corresponds to a 20% increase in AHI. The magnitude of the race effect was similar in alternative models that adjusted for prematurity, ETS exposure, maternal education, and family income. After adjusting for race, ETS (P = 0.026) and referral source (P = 0.049) were also significantly associated with log AHI. Exposure to ETS was associated with a 0.17 increase in

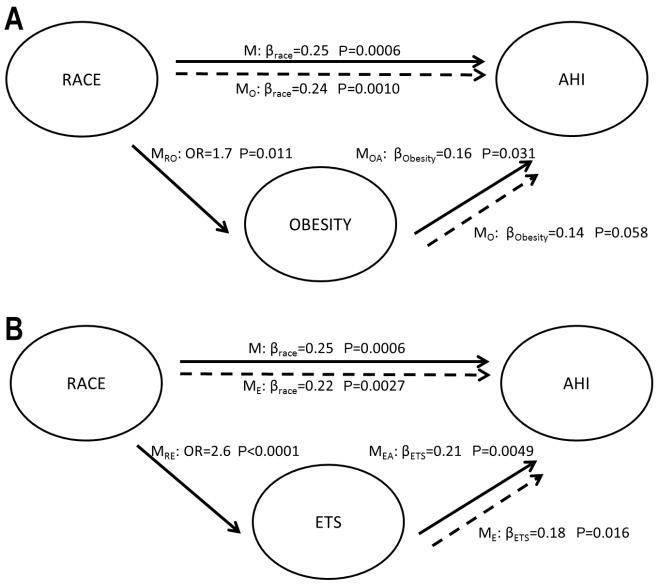

Figure 2—Schematic depicting the result of mediation analyses, evaluating the potential mediating role of obesity in the relationship between race and log apnea hypopnea index (AHI) **(A)**, and the potential mediating role of environmental tobacco smoke (ETS) and log AHI **(B)**. The regression coefficients (β) and significance level for the identified coefficients for each respective model (M) are shown. The respective regression models are:

Model	Outcome	Covariates		
M	AHI	Design variables*	Race	
M_O	AHI	Design variables*	Race	Obesity
M_E	AHI	Design variables*	Race	ETS
M_{RO}	Obesity		Race	
M_{RE}	ETS		Race	
M_{OA}	AHI			Obesity
M_{EA}	AHI			ETS

*Design variables are age, sex, recruitment site, and referral source.

log AHI compared to no exposure, which corresponds to an almost 20% increase in AHI.

We further investigated whether obesity was a potential mediator for the association between race and AHI. Figure 2 presents the regression coefficients and their significance levels from various statistical models to illustrate the changes in relevant effects before and after adjusting for other variables. The odds of obesity increased 1.7-fold (95% confidence interval [CI]: 1.1-2.5) for AfA race using univariate logistic regression (Figure 2A). Obesity was also associated with a 1.2-fold increase in AHI level in univariate analysis (β = 0.16, P = 0.03). After controlling for race, the magnitude of this effect declined to 1.1-fold (β = 0.14, P = 0.058). In contrast, adjustment for obesity did not affect the association of AfA race and AHI (β 0.25 and 0.24, respectively). Therefore, obesity did not appear to mediate the relationship between AfA race and AHI levels.

Similar analyses were performed to assess whether ETS was a potential mediator. The odds of ETS increased 2.6-fold (95% CI: 1.7-4.0) for AfA race in univariate analysis (P < 0.0001). ETS also was significantly associated with AHI, both in univariate (β = 0.21, P = 0.005) and in multivariate analysis controlling for AfA race (β = 0.18, P = 0.016). However, the associations of AfA race and AHI levels were similar whether or not adjusting for ETS (Figure 2B), suggesting that ETS was not a mediator for the relationship of AfA race and AHI levels.

We also evaluated the association between race and other potential mediators that could partially explain OSAS severity. Although family income, maternal education, asthma, and birth weight were related to race, mediation analysis demonstrated that these factors did not mediate the relationships between race and AHI.

Table 4—Results of multivariable regression model; randomized participants (N = 408) Outcome: Log (AHI)

	Best prediction model	
	Beta ± SE	P value
Age (y)	-0.0089 ± 0.0257	0.7295
Female sex	0.0865 ± 0.0678	0.2027
African American race	0.2152 ± 0.0733	0.0035
Obesity (BMI > 95%ile)	0.1109 ± 0.0756	0.1432
Environmental tobacco smoke	0.1679 ± 0.0754	0.0264
Referral source		0.0489
Sleep clinic/lab	-0.1752 ± 0.0967	
Pediatric/community/other ENT/OLN (reference)	0.1059 ± 0.1070	

AIC-based stepwise model selection was performed to yield the final model. To obtain robust modeling results, K-fold cross-validation was applied. Age and sex were retained in the model regardless of significance. AHI, apnea hypopnea index; BMI, body mass index; ENT, ear, nose, and throat; SE, standard error.

DISCUSSION

In a large sample of children considered to be AT candidates, we considered the potential influences of a large number of patient characteristics in predicting OSAS severity. As reported before in two community samples,[1,3] we found that the strongest predictor for OSAS severity was AfA race. The association between OSAS severity and AfA race could not be explained by differences in the available measures of socioeconomic status, obesity, or reports of inflammatory respiratory tract comorbidities such as asthma or hay fever. In addition, we observed a novel association between ETS and OSAS severity. No significant association between OSAS severity and sex or age was observed within the study's age range. In this sample selected to have tonsillar hypertrophy, no significant association was observed between category of tonsillar size (from examination) and OSAS severity.

Race and Socioeconomic Factors

Almost all children with polysomnographic values indicating a level of OSAS that exceeded study severity thresholds were AfA. Even within the randomized group and after accounting for potential confounders, AfAs had an average AHI value 20% higher than that of other children. A statistical mediation analysis did not identify any socioeconomic variable, co-morbid condition, or design variable that explained this association.

Several prior studies have examined the relationship of OSAS and race in adults and children in community settings.[1,3,9-11] Two

nonclinic studies[3,1] each demonstrated higher AHI levels in AfA compared with white children. One study suggested that the association between race and OSAS is stronger in younger than in older individuals.[9] Thus, there may be genetic factors that influence susceptibility to OSAS, perhaps through influences on body fat distribution, inflammation, ventilatory control, or craniofacial structure. The latter is supported by a candidate gene association study providing preliminary evidence of variants in inflammatory and ventilatory control genes in OSAS.[12]

Race is confounded with socioeconomic status, and it is likely that an association with race also may reflect environmental exposures that preferentially affect poor families. In a study that addressed the combined influence of race and neighborhood disadvantage on OSAS, it was estimated that approximately 50% of the race effect could be explained by neighborhood-level variables.[10] A recent Canadian study also showed an association between neighborhood disadvantage and OSAS.[13] Although the putative triggers for OSAS have not been identified, exposures to indoor and outdoor irritants and allergens may exacerbate nasopharyngeal inflammation and predispose to airway collapse during sleep. In the current analysis, family-level measures of socioeconomic status were not associated with OSAS. In contrast, ETS was significantly associated with OSAS severity. However, adjusting for ETS did not appreciably attenuate the association between race and OSAS severity, suggesting that other unmeasured factors are likely important.

Obesity

Obesity is a well-established risk factor for adult OSA,[14-16] and has been implicated in pediatric OSAS.[17-19] Obesity may reduce airway patency through pharyngeal fat deposition, increased levels of circulating inflammatory mediators, or altered ventilation and oxygen reserves. Although we observed a significant association between levels of obesity with OSAS severity in unadjusted analyses, multivariable analysis demonstrated little effect of obesity after adjusting for race in the overall sample. Because most of our patient sample was AfA, it is possible that obesity may play a larger role in white patient samples, as has been reported before.[20] To explore this, we examined the association between obesity and log AHI in race-stratified analyses and observed a significant positive association between obesity and log AHI in the non-AfA group (beta coefficient = 0.26, P = 0.030); in contrast, in the AfA group, no association was observed (beta coefficient = 0.04; P = 0.699). These exploratory analyses suggest that risk factors for OSAS may differ across population groups. Future research is needed to address which risk factors other than obesity (such as nasal allergy, tonsillar mass or ventilatory control) influence OSAS susceptibility.[21-24]

Environmental Tobacco Smoke

We observed a significant relationship between OSA severity and ETS that was independent of race. ETS has been shown to be associated with sleep disturbances in adults,[25] pregnant women,[26] and in young children.[27] ETS also has been associated with snoring and OSAS in adults[28-30] and with snoring in children.[24] One study using serum cotinine to quantify ETS showed a dose-dependent association with snoring and reported apneas in asthmatic children.[31] Our findings support the importance of ETS as a risk factor for objectively measured OSAS in children. Mechanisms may include chronic irritant exposure causing upper airway inflammation. It is possible that prenatal tobacco exposure (which is highly correlated with post-natal exposure) may influence neurotransmitter levels involved in ventilatory control.[32] Although we tested for an association between *in utero* smoking and OSAS, misclassification of this exposure due to inaccurate maternal reporting may have diminished any real association.

Wheeze, Asthma, Atopy

Asthma, wheeze, atopy, and OSAS may coaggregate.[24] Atopy may cause upper airway nasopharyngeal inflammation as well as bronchial hyperresponsiveness,[33-36] and possibly exacerbate OSAS by triggering gastroesophageal reflux.[37] Prior research has shown an association between childhood OSAS with asthma control[11] and improvement of asthma symptoms in patients with OSAS who are treated with CPAP.[38,39] Although we did not demonstrate an association between asthma, hay fever, or eczema and OSAS using questionnaire-based assessments, it is possible that quantitative measures of allergic and respiratory disease are needed to identify the relevant exposures. Additionally, we may have been limited in our ability to detect associations given the exclusion of individuals with severe asthma from the study participation.

Inferences Related to Recruitment and Study Enrollment

In this study, nearly half of snoring children considered to be AT candidates had very low AHI levels. The lack of PSG evidence for OSAS among children referred for suspected OSAS is consistent with prior literature indicating weak associations between symptoms and signs of OSAS and polysomnographic abnormality.[40]

Commonly, there are concerns about recruitment of minority populations into clinical research. Among our eligible pool of subjects, AfA families were more likely to enroll in this clinical trial than were individuals of other races. This may be because AfAs have less strong treatment preferences or perhaps perceive greater research participation benefits than other races. It is plausible that white children with severe OSAS were underrepresented due to strong parental treatment preferences. However, almost all children with severe OSAS excluded during PSG screening were AfA. The current findings also concur with data showing more severe OSAS in AfA children recruited for observational research from the community.[1]

The observed differences in enrollment by geography and referral site underscore the importance of the local factors and culture influencing recruitment to clinical trials.

Strengths and Limitations

Strengths of this study include its large sample size; inclusion of children from geographically diverse sites; and use of standardized, centrally scored sleep studies. Statistical mediation analyses systematically evaluated the interrelationships among a number of possible risk factors. Data were available for children screened as well as those who continued on to randomization, allowing for greater generalizability and a wider assessment of OSAS severity. The study also has several

limitations. Although a comprehensive set of risk factors was assessed, many risk factors were identified by questionnaire only, and may have resulted in nondifferential misclassification resulting in underestimation of the strength of association. Quantitative evaluation of ETS with biological measures, such as cotinine level, is needed to better understanding the dose-response association between this exposure and OSAS severity.

Little information was available on children who declined screening PSG, preventing further evaluation of the entire targeted sample.

Summary

This study identifies AfA race and ETS as risk factors for OSAS severity in children. These findings suggest the presence of environmental and possibly genetic factors that potentially interact in the pathogenesis of pediatric sleep apnea. These findings suggest the potential utility of developing OSAS screening approaches that target high risk groups, such as AfA children and children exposed to ETS. Additional research is needed to define these specific factors, including other environmental risk factors that may predispose AfA children to OSAS. Further efforts to reduce ETS, and possibly other sources of inhaled irritants, may be important to diminish OSAS severity.

ABBREVIATIONS

AfA, African American
AHI, apnea hypopnea index
AI, arousal index
AT, adenotonsillectomy
BMI, body mass index
CHAT, Childhood Adenotonsillectomy Trial
ETS, environmental tobacco smoke
OAI, obstructive apnea index
OSAS, obstructive sleep apnea syndrome
PSG, polysomnography

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