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SCIENTIFIC INVESTIGATIONS

Associations between sleep, obesity, and asthma in urban minority children

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Study Objectives: Although obesity, asthma, and sleep-disordered breathing are interrelated, there is limited understanding of the independent contributions of body-mass index and pulmonary function on polysomnography in children with asthma.

Methods: We conducted a retrospective chart review on 448 7- to 18-year-old children with asthma who had undergone polysomnography testing between 1/2007–12/2011 to elucidate the association between spirometry variables, body-mass index, and polysomnography parameters, adjusting for asthma and antiallergic medications.

Results: Obese children had poorer sleep architecture and more severe gas exchange abnormalities compared to healthy weight children. Multivariate analysis revealed an independent association of body-mass index with sleep efficiency, with more light and less deep sleep in both obese and healthy-weight children, and with baseline oxygen saturation and oxygen nadir in obese children. In obese children, forced vital capacity was independently associated with less deep sleep (time in N3 sleep) as well as with oxygen nadir, while among healthy-weight children, forced expiratory volume directly correlated but forced vital capacity inversely correlated with deep sleep. In obese children, inhaled corticosteroid was associated with baseline oxygen saturation, and montelukast was associated with lower end-tidal carbon dioxide. In healthy-weight children, inhaled corticosteroid was associated with arousal awakening index, and montelukast was associated with light sleep. Antiallergic medications were not independently associated with polysomnography parameters.

Conclusions: Pulmonary function, body-mass index, and asthma medications have independent and differing influences on sleep architecture and gas exchange polysomnography parameters in obese and healthy-weight children with asthma. Asthma medications are associated with improved gas exchange in obese children and improved sleep architecture in healthy-weight children with asthma.

Keywords: asthma, obesity, lung function, sleep-disordered breathing, polysomnography

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BRIEF SUMMARY

Current Knowledge/Study Rationale: Asthma, sleep-disordered breathing, and obesity are highly prevalent among urban, minority children, and adversely influence each other. However, the mechanisms underlying their association are not well understood. The purpose of this study was to quantify the association of sleep parameters, objectively measured using polysomnography, with pulmonary function and body-mass index, among children with asthma.

Study Impact: Pulmonary function, obesity, and asthma medications have independent and differing influences on sleep architecture and gas exchange polysomnography measures among children with asthma. Asthma medications are associated with improved gas exchange in obese children and improved sleep architecture in healthy-weight children with asthma.

INTRODUCTION

The prevalence of childhood obesity has almost tripled over the last 3 decades.[1] A fifth of all children and adolescents 2–19 years of age in the United States are obese. The burden is borne more by those of non-Hispanic black and Hispanic ancestry compared to other races.[2] Several epidemiological studies have established a causal association between obesity and respiratory morbidity involving both the upper and the lower airway.[3,4] Obese children are predisposed to higher incidence of obstructive sleep apnea (OSA)[5] as well as incident asthma.[6] While the general prevalence of OSA in children ranges between 2% and 4%, presence of obesity increases the risk of OSA by more than 4- to 5-fold.[7] Similarly, obesity increases the risk of incident asthma in children by 1.3- to 1.5-fold.[6] Furthermore, asthma has been independently linked with sleep-disordered breathing (SDB) in children.[7–10] This relationship between asthma and OSA is thought to be bidirectional since both disease processes have common risk factors that cause airway inflammation.[11] For instance, uncontrolled asthma increases the risk of OSA, and improvement in asthma symptoms has been reported with effective treatment of OSA.[10,12,13] Although obesity, asthma, and OSA are highly prevalent among urban minority children, the mechanisms explaining the association between these morbidities are not well defined.

Polysomnography (PSG) is considered the gold standard technique for the diagnosis and classification of severity of OSA,[14] and spirometry is an objective and reliable measure for

evaluating asthma severity and control in children.[15] Yet, few studies that have reported an association between OSA and asthma among children have investigated the relationship between objective measures of OSA and asthma,[16] and no studies have been conducted in urban minority children.

To address this gap in knowledge, we conducted a retrospective analysis of PSG and its association with spirometry on children with asthma seen at the pulmonary clinics affiliated with Children's Hospital at Montefiore. We hypothesized that spirometry variables influenced by asthma, including measures of lower airway obstruction, forced expiratory volume (FEV_1), and FEV_1/forced vital capacity (FVC) ratio, correlate with sleep architecture and respiratory perturbations resulting from OSA. We also hypothesized that body mass index (BMI) and asthma medications may mediate the association of spirometry variables with OSA.

METHODS

A retrospective chart review was conducted on 448 children, ages 7–18 years, with physician diagnosis of asthma in the electronic medical records, who had undergone PSG testing at the Children's Hospital at Montefiore, Bronx, NY, over a span of 5 years, between January 2007 and December 2011. Children with coexistent obstructive or restrictive lung disease contributing to abnormalities on spirometry, including bronchiectasis, cystic fibrosis, scoliosis, sickle cell disease, or rheumatologic or neuromuscular conditions, were excluded. Similarly, children with diseases contributing to SDB, including craniofacial, chromosomal, or neuromuscular anomalies, were also excluded. The Institutional Review Board at the Montefiore Medical Center approved this study (IRB# 12-06-223).

Demographic and clinical data

Demographic data including age, sex, race, ethnicity, body weight, height, and BMI were extracted from electronic medical records. Asthma classification was based on physician diagnosis of asthma. Prescriptions for asthma medications, including inhaled corticosteroids (ICS) and montelukast, a leukotriene receptor antagonist, and for allergy medications, including oral antiallergic medications and steroid nasal spray, were extracted from the electronic medical records. BMI *z*-scores, calculated using the Epi Info software,[17] were used to classify weight status, as healthy-weight or obese. Obesity was defined as BMI *z*-score ≥ 1.64 corresponding to 95th percentile for body weight corrected for age and sex, and healthy-weight was defined as a cutoff of BMI *z*-score < 1.04, corresponding to 5th percentile for body weight. Data on children who were overweight (BMI *z*-score between 1.04 and 1.639, BMI between 85th to 94th percentile) (n = 33) were excluded from the analysis.

Spirometry testing

Spirometry testing was conducted per the American Thoracic Society guidelines[18] as part of a routine pulmonary outpatient visit and was performed by the same respiratory therapist on all children. Included in the analysis were: percent-predicted values of FVC, FEV_1, and forced mid-expiratory flow ($FEF_{25\%–75\%}$), and percent FEV_1/FVC ratio, calculated using the National Health and Nutrition Examination Survey reference sets and here referred to as FVC, FEV_1, FEV_1/FVC ratio, and $FEF_{25\%–75\%}$.[19] For children with more than 1 spirometry in the 12 months prior to PSG, the spirometry values closest to the date of PSG testing were included in the analysis.

Polysomnography testing

Data was collected from the PSG database (Xltek, Oakville, ON, Canada) in the sleep laboratory. Sleep staging and scoring of arousals, awakenings, and apneic and hypopneic events were performed per standard criteria.[20] Variables included in the analysis were subcategorized into sleep architecture and respiratory variables.

Sleep architecture variables

Sleep architecture variables included sleep efficiency (SE, percent time spent sleeping/total time in bed), arousal and awakening index (AAI, reported as number of arousals and awakenings per hour), percent time spent in each sleep stage, rapid eye movement (REM) and nonrapid eye movement (non-REM stages N1, N2, N3; N1 and N2 are considered lighter stages of sleep and N3 as deeper stage of sleep), and periodic limb movement index (PLMI, total number of periodic limb movements/h).

Respiratory variables

Respiratory variables included apnea-hypopnea index (AHI, total number of apneas and hypopneas per hour), and gas exchange measures (baseline oxygen saturation, oxygen saturation nadir, and baseline and peak end-tidal carbon dioxide ($ETCO_2$) levels). We additionally dichotomized apnea-hypopnea index using a cutoff of greater than 1.5 events per hour to classify presence of OSA.[21]

Statistical analysis

All variables were checked for normality. Descriptive analysis was performed on demographic variables including age, sex, ethnicity, and BMI. Based on the variable distribution, Student *t* test or nonparametric Mann Whitney *U* test were used to compare spirometry and PSG results between the obese and healthy-weight children and between those with and without asthma medications. Pearson or Spearman correlation coefficients were calculated to elucidate the associations between spirometry measures and BMI as well as with PSG parameters, as detailed preceding, for the 2 study groups. Since we found differences in the association of PSG parameters with pulmonary function test indices, with BMI, and with asthma medications in the 2 study groups, we conducted a multivariable linear regression analysis, retaining the PSG indices as outcomes of interest and including pulmonary function test indices, asthma medications, and obese study group as predictors, with the healthy-weight group serving as the reference group. Since OSA can affect sleep architecture as well as gas exchange parameters, presence of OSA (defined as AHI > 1.5 events/h) was included

as 1 of the covariates in the multivariable analysis. The multivariable analysis was also stratified by weight status, based on the 2 study groups. Given the differences in predictor variables by body weight status, we additionally included interaction terms between body weight status and predictor variables in multivariable models investigating their association with PSG parameters. All PSG variables except percent time in N2, N3, and REM sleep were $\log_{10}$ transformed to achieve normal distribution. In light of the known association between OSA and sleep abnormalities,[22] we also included OSA, as defined above, as another predictor of sleep architecture and gas exchange in the regression analysis. Statistical analysis was performed on STATA version 14.[23]

RESULTS

Characteristics of the study cohort

The demographic and clinical characteristics of the study cohort are summarized in **Table 1**. In comparison to healthy-weight children with asthma, obese children with asthma were older. With regard to sleep architecture, obese children with asthma

Table 1—Demographic and clinical characteristics of the study population.

Variable	Total Cohort (n = 443)	Obese Asthma (n = 289)	Healthy-Weight Asthma (n = 154)	*P*
Demographics				
Age	10.2 ± 4.1	10.8 ± 4.1	9.1 ± 4	< 0.0001
Ethnicity (% Hispanic)	266 (64.4)	175 (60.6)	99 (64.3)	0.7
Sex (% male)	256 (57.1)	163 (56.4)	93 (60.4)	0.4
BMI (kg/m^2)	27.3 ± 10.4	31.7 ± 9.8	19 ± 5.2	< 0.0001
BMI *z*-score	1.7 ± 1.1	2.4 ± 0.4	0.4 ± 0.8	< 0.0001
Sleep architecture				
SE (%)	82.6 ± 13.5	81.4 ± 14.5	84.8 ± 11.1	0.02
AAI[a]	12.8 ± 8.2	13.3 ± 9	11.8 ± 6.5	0.08
Percent time in N1	7.1 ± 5.9	7.7 ± 6.8	5.8 ± 3.4	0.005
Percent time in N2	46.5 ± 11.1	47.6 ± 11.6	44.6 ± 9.6	0.006
Percent time in N3	29.1 ± 11.4	28.1 ± 12.2	31 ± 9.6	0.009
Percent time in REM sleep	17.7 ± 6.4	17.1 ± 6.4	18.7 ± 6.1	0.01
PLMI[a]	22.3 ± 39.7	18.7 ± 35.2	28.9 ± 46.4	0.009
Sleep respiratory parameters				
AHI[a]	4.9 ± 10.3	5.9 ± 12.1	3.1 ± 5.7	0.009
OSA (obstructive AHI > 1.5 events/h)	190 (42.9)	129 (44.6)	61 (39.6)	0.22
Baseline O_2 saturation (%)	98.2 ± 2.6	97.9 ± 3	98.6 ± 1.4	0.007
O_2 saturation nadir (%)	89.8 ± 8.6	89.3 ± 9	90.6 ± 7.8	0.11
Baseline $ETCO_2$ (mm Hg)[b]	40.8 ± 5.5	41.3 ± 5.3	40.1 ± 5.8	0.05
Peak $ETCO_2$[b]	48.9 ± 6	48.9 ± 6	48.8 ± 6.1	0.9
Pulmonary function indices				
FVC[c]	93.8 ± 16.6	93.9 ± 16.5	93.6 ± 16.8	0.9
FEV_1[c]	84.2 ± 17.4	83.1 ± 16.5	86.4 ± 18.7	0.05
FEV_1/FVC ratio[c]	82.3 ± 8.5	81.6 ± 8	83.5 ± 9.4	0.03
$FEF_{25\%–75\%}$[c]	75.5 ± 27.1	74.8 ± 26.5	76.8 ± 28.2	0.4
Medication use				
Inhaled steroids	339 (76.5)	214 (74.1)	125 (81.2)	0.09
Montelukast	266 (60.1)	174 (60.2)	92 (59.7)	0.92
Antihistamines	119 (26.9)	69 (23.9)	50 (32.5)	0.05
Nasal steroids	133 (30)	89 (30.8)	44 (28.6)	0.63

Continuous variables are reported as mean ± SD and categorial variables are reported as proportions, n (%). [a]Reported in events/h. [b]$ETCO_2$ measured in 378 sleep studies. [c]FVC, FEV_1, and $FEF_{25\%–75\%}$ are reported as percent predicted values while FEV_1/FVC ratio is reported as a percentage. AAI = arousal awakening index, AHI = apnea-hypopnea index, BMI = body-mass index, $ETCO_2$ = end-tidal carbon dioxide, $FEF_{25\%–75\%}$ = forced mid-expiratory flow, FEV_1 = forced expiratory volume, FVC = forced vital capacity, OSA = obstructive sleep apnea, PLMI = periodic limb movement index, REM = rapid eye movement, SE = sleep efficiency.

had reduced SE, higher percent time in N1 and N2 sleep, lower percent time in N3 and REM sleep, but fewer periodic limb movements compared to healthy-weight children. Comparing sleep respiratory parameters, obese children had higher AHI, lower baseline oxygen saturation, and a borderline significant trend toward higher baseline $ETCO_2$ compared to healthy-weight children. OSA, defined as more than 1.5 AHI events/h, was prevalent in 43% of the total study cohort but did not differ between obese and healthy-weight children. Although spirometry indices for the study cohort were in the normal range, obese children had lower FEV_1/FVC ratio and a borderline significant trend toward lower FEV_1 compared to healthy-weight children (Table 1). Medication prescription patterns were similar between study groups. Since both spirometry indices and sleep parameters differed between obese and healthy-weight children, we investigated the association between these stratified by obesity status.

Association of spirometry variables and BMI with sleep parameters

Few spirometry variables correlated with sleep parameters in either obese or healthy-weight children (Table 2). While percent time in N1 sleep correlated with FVC and FEV_1 in obese children, percent time in N3 sleep correlated with FVC in obese children and with FEV_1/FVC ratio in healthy-weight children. Among the sleep respiratory parameters, AHI and peak $ETCO_2$ correlated with FEV_1 only among obese children, with no associations observed in healthy-weight children.

Association of BMI with sleep parameters

As summarized in Table 3, BMI correlated with several measures of sleep architecture, including SE and percent time in N1 and N3 sleep in both obese and healthy-weight children. It additionally correlated with time in N2 and REM sleep in obese children. BMI correlated with sleep respiratory parameters, including AHI, baseline $ETCO_2$, baseline oxygen saturation, and oxygen saturation nadir only in obese children, with no associations observed in healthy-weight children.

Association of asthma medications with sleep parameters

Among obese children with asthma, SE was higher and percent time in N1 sleep were lower in those prescribed ICS (**Table S1** in the supplemental material) and montelukast (**Table S2**). Montelukast was also associated with lower AAI, and more percent time in N3 sleep (**Table S2**). Among healthy-weight children, AAI and percent time in N1 sleep were lower in those prescribed ICS (**Table S1**). Percent time in N1 sleep was also lower among those on montelukast (**Table S2**).

With regard to respiratory parameters, in obese children with asthma, both ICS and montelukast were associated with lower AHI and higher oxygen saturation nadir. In addition, montelukast was associated with higher baseline oxygen saturation, and lower baseline and peak $ETCO_2$ (**Table S2**). Neither ICS nor montelukast were associated with sleep respiratory parameters in healthy-weight children with asthma.

Compared to asthma medications, there were few associations between antiallergic medications and sleep parameters in obese and healthy-weight children. In obese children, nasal corticosteroids were associated with lower percent time in N2 sleep (**Table S3**) while oral antihistamines were associated with higher oxygen saturation nadir and lower peak $ETCO_2$ (**Table S4**). In healthy-weight children, nasal corticosteroids were associated with higher oxygen saturation nadir (**Table S3**) while oral antihistamines were not associated with any sleep parameters (**Table S4**).

Multivariable analysis

As summarized in Table 4, FVC was an independent predictor of sleep architecture (time spent in N1, N2, and N3) as well as

Table 2—Association of spirometry variables with sleep parameters in obese and healthy-weight children with asthma.

	Obese Asthma (*r*, *P*)			Healthy-Weight Asthma (*r*, *P*)		
Variable	FVC	FEV_1	FEV_1/FVC Ratio	FVC	FEV_1	FEV_1/FVC Ratio
SE (%)	−0.18, 0.002	−0.12, 0.048	0.07, 0.23	−0.03, 0.70	−0.04, 0.61	−0.01, 0.94
AAI[a]	0.02, 0.74	0.02, 0.73	0.03, 0.62	−0.01, 0.91	−0.06, 0.51	−0.09, 0.26
% Time in N1	0.19, 0.001	0.15, 0.01	−0.01, 0.76	0.15, 0.06	0.13, 0.10	0.001, 0.98
% Time in N2	0.07, 0.24	−0.01, 0.94	−0.09, 0.15	0.02, 0.81	−0.15, 0.06	−0.20, 0.01
% Time in N3	−0.20, < 0.001	−0.11, 0.07	0.09, 0.14	−0.12, 0.12	0.03, 0.71	0.17, 0.03
% Time in REM sleep	0.04, 0.47	0.05, 0.42	−0.01, 0.88	0.06, 0.48	0.12, 0.12	0.13, 0.12
PLMI[a]	−0.001, 0.99	−0.04, 0.52	−0.08, 0.25	0.02, 0.79	0.01, 0.90	0.004, 0.96
AHI[a]	−0.12, 0.06	−0.14, 0.03	−0.04, 0.51	0.13, 0.13	0.09, 0.29	−0.04, 0.66
Baseline O_2 saturation (%)	−0.002, 0.96	0.01, 0.87	0.04, 0.50	0.04, 0.59	0.12, 0.13	0.09, 0.30
O_2 saturation nadir	0.1, 0.09	0.09, 0.13	0.02, 0.75	−0.04, 0.66	−0.04, 0.62	−0.01, 0.91
Baseline $ETCO_2$	−0.01, 0.94	−0.02, 0.72	0.004, 0.95	0.10, 0.25	0.13, 0.13	0.10, 0.28
Peak $ETCO_2$	−0.1, 0.1	−0.13, 0.04	−0.1, 0.11	−0.09, 0.31	−0.02, 0.85	0.12, 0.16

[a]Reported in events/h. AAI = arousal awakening index, AHI = apnea-hypopnea index, $ETCO_2$ = end-tidal carbon dioxide, FEV_1 = forced expiratory volume, FVC = forced vital capacity, PLMI = periodic limb movement index, REM = rapid eye movement, SE = sleep efficiency.

Table 3—Association of BMI with sleep parameters in obese and healthy-weight children with asthma.

Variable	Obese Asthma (*r*, *P*)	Healthy-Weight Asthma (*r*, *P*)
SE (%)	−0.19, 0.001	−0.27, < 0.001
AAI[a]	0.1, 0.09	−0.001, 0.99
% Time in N1	0.19, 0.002	0.27, < 0.001
% Time N2	0.18, 0.003	0.08, 0.32
% Time in N3	−0.3, < 0.001	−0.18, 0.03
% Time in REM sleep	−0.18, 0.002	−0.04, 0.59
PLMI[a]	−0.05, 0.39	−0.01, 0.87
AHI[a]	0.28, < 0.001	0.19, 0.03
Baseline O_2 saturation (%)	−0.24, 0.0001	0.02, 0.77
O_2 saturation nadir	−0.18, 0.003	−0.07, 0.38
Baseline $ETCO_2$ (mm Hg)	0.14, 0.03	−0.02, 0.84
Peak $ETCO_2$	0.12, 0.07	−0.005, 0.96

[a]Reported in events/h. AAI = arousal awakening index, AHI = apnea-hypopnea index, BMI = body-mass index, $ETCO_2$ = end-tidal carbon dioxide, PLMI = periodic limb movement index, REM = rapid eye movement, SE = sleep efficiency.

of O_2 saturation nadir, while FEV_1 predicted time spent in N2 and N3. Montelukast also predicted time in N2 and N3 as well as baseline $ETCO_2$. Obese status predicted the most PSG parameters, including SE; time in N1, N2, and REM sleep; PLMI; as well as baseline O_2 and $ETCO_2$. We found significant interactions only for O_2 saturation nadir between body weight and FVC, and for sleep efficiency between body weight and montelukast, suggesting that the association of spirometry variables and medications with PSG variables were largely independent of their association with body weight. In light of the independent contribution of obese status to sleep parameters, we stratified the multivariable model by obese and healthy-weight status to quantify the independent associations of spirometry indices and asthma medications with PSG parameters in each weight group.

In obese children with asthma (**Table 5**), FVC predicted percent time in N3 sleep, BMI predicted SE, and percent time in all sleep stages, and OSA predicted AAI, percent time in N1 sleep, and PLMI. Among sleep respiratory parameters, FVC and FEV_1, as well as BMI and OSA were predictors of O_2 saturation nadir. BMI also predicted baseline O_2 saturation while OSA predicted peak $ETCO_2$. In addition, ICS predicted baseline O_2 saturation and montelukast predicted baseline $ETCO_2$.

In healthy-weight children with asthma (**Table 6**), FVC and FEV_1 predicted percent time in N2 and N3 sleep, while BMI and montelukast predicted percent time in N1 sleep, and OSA and ICS predicted AAI. While OSA predicted O_2 saturation nadir and baseline and peak $ETCO_2$, there was no independent association of FVC, FEV_1, BMI, or asthma medications with sleep respiratory parameters in healthy-weight children with asthma.

DISCUSSION

We found high prevalence of OSA, with sleep architecture and gas exchange disturbances, in our large cohort of urban minority children with asthma referred for a sleep evaluation. Relative to healthy-weight children with asthma, obese children had poorer sleep architecture and more severe gas exchange abnormalities, although BMI was an independent predictor of worse sleep architecture in both obese and healthy-weight children. Exploring the contribution of pulmonary function and asthma medications to sleep, we found that higher FEV_1 protected against oxygen desaturations in obese and improved sleep architecture with more time in deep sleep in healthy-weight children, while FVC had an opposite association with sleep architecture, being inversely correlated with deep sleep in both study groups. ICS and montelukast use were protective with improved gas exchange in obese and improved sleep architecture in healthy-weight children. These associations were independent of the effects of OSA on sleep architecture and gas exchange.

Several studies have explored the associations between OSA and asthma in children, but few included spirometry and medication use as objective measures of asthma severity, and PSG parameters as objective quantification of sleep disturbance, as we did in our study.[16,24] OSA prevalence of 43% in our cohort is in keeping with 20%–60% prevalence reported in prior studies, the variability being driven by differences in the AHI criteria used to define OSA, and the level of asthma control in these studies.[11,25] Our findings of reduced sleep efficiency, and increased time spent in light sleep in our cohort validate prior reports of sleep architecture disturbances in children with asthma relative to the general population.[11,26,27] In keeping with the association of restless legs during sleep with poor asthma control,[27] PLMI in our cohort was much higher than the reported normal of 5 events/h.[28,29] We build on these findings by identifying an independent contribution of OSA, rather than pulmonary function, to periodic limb movements in both groups, suggesting that asthma influences limb movements in children due to OSA, rather than due to pulmonary function deficits. We additionally validated the well-established association of obesity with SDB,[5] and highlighted its greater contribution to both sleep architecture and gas exchange abnormalities in obese children compared to healthy-weight children with asthma.

Ours is the first study to quantify the independent and differing contribution of spirometric variables to SDB among obese and healthy-weight children with asthma. Higher FEV_1 was associated with better sleep architecture in both study groups; it was additionally associated with higher oxygen saturations in obese children with asthma. Since higher FEV_1 suggests decreased airway resistance and less upper airway tugging during sleep, our findings highlight the important contribution of improved airway mechanics to deeper and more consolidated sleep.[30] Paradoxically, FVC was inversely associated with deep sleep in both obese and healthy-weight children. This counter-intuitive finding emphasizes the importance of optimum lung volume to balance cranial displacement and caudal tug on the

Table 4—Multivariable analysis of the association of PSG parameters with pulmonary function test indices, asthma medications and obese status among children with asthma.

	SE (%)[a]	AAI[a]	% Time in N1[a]	% Time in N2	% Time in N3	% Time in REM Sleep	PLMI[a]	Baseline O_2 Saturation[a]	O_2 Saturation Nadir[a]	Baseline $ETCO_2$[a]	Peak $ETCO_2$[a]
FEV_1	1.00, 0.18	0.99, 0.48	0.99, 0.29	−0.21, < 0.001	0.22, < 0.001	0.05, 0.13	0.99, 0.47	1.00, 0.63	1.00, 0.30	1.00, 0.53	1.00, 0.67
FVC	0.99, 0.06	1.00, 0.52	1.01, 0.01	0.22, < 0.001	−0.32, < 0.001	−0.02, 0.52	1.00, 0.70	0.99, 0.99	1.00, 0.04	1.00, 0.88	1.00, 0.10
ICS	1.05, 0.05	0.94, 0.40	0.87, 0.14	1.98, 0.18	0.48, 0.75	−0.67, 0.43	0.85, 0.38	0.99, 0.05	1.01, 0.43	1.03, 0.18	0.99, 0.47
Montelukast	1.04, 0.06	0.94, 0.28	0.89, 0.13	−2.57, 0.04	3.31, 0.01	0.78, 0.27	1.11, 0.50	1.00, 0.01	0.99, 0.72	0.96, 0.02	0.97, 0.08
Obese group	0.95, 0.02	1.06, 0.34	1.22, 0.006	2.34, 0.047	−1.80, 0.13	−1.67, 0.01	0.68, 0.01	0.99, 0.04	0.98, 0.31	1.04, 0.02	1.01, 0.70
OSA	0.98, 0.39	1.29, < 0.001	1.35, < 0.001	−1.44, 0.20	−0.91, 0.42	−0.07, 0.92	1.65, < 0.001	1.00, 0.18	0.93, < 0.001	1.05, 0.005	1.06, < 0.001

For all variables, the β coefficient, or [a]its geometric mean for log-transformed variables and corresponding *P* value are reported. AAI = arousal and awakening index, $ETCO_2$ = end-tidal carbon dioxide, FEV_1 = forced expiratory volume, FVC = forced vital capacity, ICS = inhaled corticosteroids, OSA = obstructive sleep apnea, PLMI = periodic limb movement index, REM = rapid eye movement, SE = sleep efficiency.

Table 5—Multivariable analysis of the association of sleep architecture and gas exchange with spirometry variables, asthma medications, and BMI in obese children with asthma.

	SE (%)[a]	AAI[a]	% Time in N1[a]	% Time in N2	% Time in N3	% Time in REM Sleep	PLMI[a]	Baseline O_2 Saturation[a]	O_2 Saturation Nadir[a]	Baseline $ETCO_2$[a]	Peak $ETCO_2$[a]
FEV_1	1.00, 0.78	1.01, 0.34	1.00, 0.71	−0.08, 0.39	0.05, 0.55	−0.03, 0.50	1.00, 0.89	1.00, 0.24	0.99, 0.04	0.99, 0.69	0.99, 0.36
FVC	0.99, 0.41	1.00, 0.47	1.00, 0.38	0.11, 0.26	−0.18, 0.05	0.06, 0.23	0.99, 0.66	1.00, 0.11	1.00, < 0.001	1.00, 0.96	1.00, 0.67
ICS	0.04, 0.34	1.01, 0.87	0.90, 0.35	3.14, 0.10	−0.14, 0.94	−1.09, 0.30	0.84, 0.47	0.99, 0.03	1.02, 0.37	1.02, 0.37	0.98, 0.51
Montelukast	1.06, 0.06	0.92, 0.31	1.03, 0.77	−2.94, 0.08	2.63, 0.11	0.37, 0.69	1.22, 0.36	1.01, 0.11	0.98, 0.49	0.94, 0.01	0.97, 0.10
BMI	1.00, 0.02	1.01, 0.16	1.02, 0.001	0.24, 0.006	−0.41, < 0.001	−0.13, 0.007	1.02, 0.13	0.99, < 0.001	1.00, < 0.001	1.00, 0.47	1.00, 0.36
OSA	0.99, 0.78	1.31, < 0.001	1.34, 0.001	−2.62, 0.08	0.72, 0.62	−0.29, 0.73	0.70, 0.006	1.00, 0.39	0.93, < 0.001	1.04, 0.09	1.05, 0.002

For all variables, the β coefficient, or [a]its geometric mean for log-transformed variables and corresponding *P* value are reported. AAI = arousal and awakening index, BMI = body-mass index, $ETCO_2$ = end-tidal carbon dioxide, FEV_1 = forced expiratory volume, FVC = forced vital capacity, ICS = inhaled corticosteroids, OSA = obstructive sleep apnea, PLMI = periodic limb movement index, REM = rapid eye movement, SE = sleep efficiency.

Table 6—Multivariable analysis of the association of sleep architecture and gas exchange with spirometry variables, asthma medications, and BMI in healthy-weight children with asthma.

	SE (%)[a]	AAI[a]	% Time in N1[a]	% Time in N2	% Time in N3	% Time in REM Sleep	PLMI[a]	Baseline O_2 Saturation[a]	O_2 Saturation Nadir[a]	Baseline $ETCO_2$[a]	Peak $ETCO_2$[a]
FEV_1	−1.00, 0.84	0.99, 0.08	1.00, 0.98	−0.24, 0.002	0.19, 0.02	0.09, 0.08	0.98, 0.30	1.00, 0.22	1.00, 0.82	1.00, 0.24	1.00, 0.09
FVC	1.00, 0.80	1.01, 0.13	1.01, 0.35	0.22, 0.01	−0.23, 0.01	−0.06, 0.27	1.01, 0.38	1.00, 0.37	1.00, 0.92	0.99, 0.67	1.00, 0.06
ICS	1.05, 0.11	0.79, 0.04	0.90, 0.48	1.00, 0.67	−0.65, 0.78	−0.31, 0.83	0.85, 0.61	0.99, 0.49	1.01, 0.79	1.04, 0.37	0.99, 0.73
Montelukast	0.97, 0.22	1.03, 0.69	0.79, 0.04	−0.44, 0.81	1.64, 0.36	0.30, 0.79	1.13, 0.63	1.00, 0.68	0.98, 0.26	0.98, 0.61	0.99, 0.67
BMI	0.99, < 0.001	0.99, 0.21	1.03, 0.009	0.09, 0.57	−0.21, 0.20	−0.07, 0.52	0.97, 0.22	1.00, 0.37	1.00, 0.30	0.99, 0.76	1.00, 0.89
OSA	1.01, 0.62	1.21, 0.02	1.19, 0.10	−0.71, 0.68	−1.41, 0.41	1.15, 0.29	1.55, 0.07	0.99, 0.92	0.95, 0.01	1.07, 0.04	1.05, 0.03

For all variables, the β coefficient or [a]its geometric mean for log-transformed variables and corresponding *P* value are reported. AAI = arousal and awakening index, BMI = body-mass index, $ETCO_2$ = end-tidal carbon dioxide, FEV_1 = forced expiratory volume, FVC = forced vital capacity, ICS = inhaled corticosteroids, OSA = obstructive sleep apnea, PLMI = periodic limb movement index, REM = rapid eye movement, SE = sleep efficiency.

trachea during supine sleep, both of which are associated with altered upper airway resistance in animal models.[31] In support of these observations, although not studies in children, adult studies found a decline in functional residual capacity in non-REM sleep that is worse in obese individuals[32] and in nocturnal asthma with hyperinflated lungs, which is associated with worsening airway resistance at lower lung volumes. This higher airway resistance causes greater tracheal tugging and upper airway resistance and thereby more sleep fragmentation and less deep sleep.[33] Based on our observations, we hypothesize that airway dysynapsis,[34] uniquely reported in obese children, may also contribute to the association of FVC with sleep architecture abnormalities. Given the importance of the dynamic interaction between upper and lower airways,[5] pulmonary physiology studies, in conjunction with clinical measures of asthma control, are needed to quantify the impact of change in lung volumes on airway caliber and tugging and their cumulative effect on sleep architecture in both obese and healthy-weight children with asthma.

ICS use had an independent protective effect on gas exchange in obese and sleep architecture in healthy-weight children with asthma. These novel findings extend into pediatrics the beneficial effects of ICS on SDB reported in adults with well-controlled asthma in whom decrease in upper airway resistance due to antiinflammatory effect of ICS led to reduction in critical airway pressure[35] and improved pulmonary mechanics.[15] Simultaneous use of nasal ICS for allergic rhinitis, a common comorbidity with asthma, may also contribute to decrease in upper airway inflammation.[14,36] Intriguingly, ICS has also been linked with development of OSA due to pharyngeal muscle remodeling and weight gain,[37] a relationship likely influenced by the duration of ICS treatment. Although about 80% of our study population was prescribed ICS, we do not have details on treatment duration or adherence. Moreover, although not statistically significantly different, fewer obese children in our study were on ICS, suggesting that these factors were unlikely to have influenced our findings. We also noted improved sleep architecture and respiratory parameters among those on montelukast, particularly in obese children with asthma.[26] Since obesity, asthma, and SDB are proinflammatory conditions, associated with activation of innate immune pathways,[38] with elevated leukotrienes and cytokines,[39–42] and both nonobese children with OSA and obese children with asthma benefited with montelukast treatment,[42,43] we speculate that antiinflammatory effects of montelukast underlie these improvements. However, the extent to which montelukast is effective in treating coexistent obesity, asthma, and SDB in children, relative to singular presence of any of these problems, needs further investigation.

In keeping with prior studies,[44] BMI was strongly predictive of worse sleep architecture in both obese and healthy-weight children, but of gas exchange abnormalities uniquely in obese children with asthma. These associations were independent of OSA. BMI also attenuated the beneficial associations of ICS and of montelukast with several sleep parameters, suggesting a stronger influence of BMI on upper airway and pulmonary mechanics relative to the antiinflammatory effects of montelukast or ICS. Although many aspects of obesity may explain its higher contribution to SDB, it is important to highlight the

complex negative cycle of links between obesity, short sleep duration, and reduced sleep efficiency,[45,46] since both sleep abnormalities are known risk factors for weight gain. Since myriad complications of obesity,[47] such as systemic inflammation[48] and metabolic disturbances, including dyslipidemia and insulin resistance,[49,50] are associated with SDB, prospective studies are needed to explore these relationships further, accounting for the mechanical effects of obesity on airway caliber.[5]

Although our study has several strengths, including the large cohort and inclusion of objective measures of asthma severity and SDB severity, we recognize that there are several limitations to our study, most of which are inherent to a retrospective chart review. We analyzed pulmonary function among children who carried a physician diagnosis of asthma but without details on asthma control. Since asthma is associated with nocturnal symptoms that disrupt sleep, and SDB is associated with worse asthma control, which improves with treatment, we are not able to separate the individual role or the impact of therapy on each morbidity in our cross-sectional study. Exclusion of the overweight category precluded our ability to examine the linear relationship between BMI and measures of SDB for the entire cohort. Also, given our minority cohort, we recognize that ethnicity-specific differences in craniofacial anatomy, known to influence SDB,[51,52] may have played a role in our findings and may limit the generalizability or our findings. We also acknowledge that our classification of OSA is based on total AHI and a low cutoff of 1.5 events/h. Furthermore, our cohort was limited to children with asthma who were referred for a sleep study. Although this selection would suggest that our findings are not reflective of associations in a general pediatric population, we did find substantial overlap between our findings and those reported on the effect of obesity and asthma on SDB in the general pediatric population.[5,11,26,27] In addition, our findings are pertinent, since obesity and SDB affect children with asthma to a disproportionately higher extent, and our study highlights the complex interaction between these entities.[7]

In conclusion, we found a high prevalence of OSA and sleep architecture and gas exchange disturbances among obese and healthy-weight urban minority children with asthma. Pulmonary function, asthma medications, and BMI were all associated with SDB in children with asthma, and influenced both sleep architecture and gas exchange disturbances in the obese, and primarily sleep architecture in healthy-weight children. Our findings identify the need for mechanistic studies with simultaneous investigation of the role of inflammation and airway mechanics in children with asthma, with or without obesity, to better understand the links between asthma, obesity, and SDB, particularly among the minority populations that bear a disproportionately high burden of these 3 chronic morbidities.

ABBREVIATIONS

AAI, arousal and awakening index
AHI, apnea-hypopnea index
BMI, body-mass index
$ETCO_2$, end-tidal carbon dioxide
FEV_1, forced expiratory volume
FVC, forced vital capacity
ICS, inhaled corticosteroids
N1, stage N1 sleep
N2, stage N2 sleep
N3, stage N3 sleep
OSA, obstructive sleep apnea
PLMI, periodic limb movement index
PSG, polysomnography
REM, rapid eye movement
SDB, sleep-disordered breathing
SE, sleep efficiency

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