Obstructive sleep apnea screening in children with asthma

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Abstract

RATIONALE: Obstructive sleep apnea is highly prevalent in children with asthma, particularly in obese children. The sleep related breathing disorder screening questionnaire has low screening accuracy for obstructive sleep apnea in children with asthma. Our goal was to identify the questions on the sleep related breathing disorder survey associated with obstructive sleep apnea in children with asthma. **METHODS:** Participants completed the survey, underwent polysomnography and their body mass index z-score was measured. Participants with survey scores above 0.33 were considered high risk for obstructive sleep apnea and those with an apnea hypopnea index [?] 2 events/hour classified as having obstructive sleep apnea. Logistic regression was used to examine the association of each survey question and obstructive sleep apnea. Positive and negative predictive values were calculated to estimate screening accuracy. **RESULTS:** The prevalence of obstructive sleep apnea was 40% in our sample (n=136). Loud snoring, morning dry mouth and being overweight were the questions associated with obstructive sleep apnea. A combined model of loud snoring, morning dry mouth and being overweight had positive and negative predictive values of 57.4% and 81.0% respectively, while the composite survey score had positive and negative predictive values of 51.0% and 65.5%. Body mass index z-score had positive and negative predictive values of 76.3% and 72.2%. **CONCLUSIONS:** The body mass index z-score is useful for obstructive sleep apnea screening in children with asthma and should be applied routinely given its simplicity and concerns that obstructive sleep apnea may contribute to asthma morbidity.

INTRODUCTION

Obstructive sleep apnea (OSA) is highly prevalent in children with asthma, and is thought to contribute to poorer asthma control[1–3]. Similarly, asthma has been shown to increase the likelihood of OSA[4,5], thus leading to a potential spiraling cascade of cumulative morbidity. The global increasing trend in childhood obesity[6,7] also portends a future with a higher burden of OSA, which can further elevate the risk for worse asthma control. OSA risk stratification in children with asthma is therefore imperative and offers an opportunity to mitigate OSA related health consequences, yet there are currently no reliable methods for identifying children with asthma at risk for OSA.

Both asthma and OSA can lead to nocturnal breathing difficulties, sleep disturbance and daytime sleepiness, which are symptoms elicited in OSA screening questionnaires. The sleep related breathing disorders (SRBD) survey, derived from the Pediatric Sleep Questionnaire, is the most common screening tool for OSA in children. It has an OSA screening sensitivity of 78% and specificity of 72% in the general population[8]. A recent study that validated the SRBD survey in children with asthma found an OSA screening sensitivity of 81% and specificity of 14%, with a maximum negative predictive value of 64% and positive predictive value of 29% at an OSA cutoff of two events per hour[2]. The low OSA screening accuracy of the SRBD in children

with asthma might be due to an overlap in the symptoms caused by asthma and OSA. In fact, previous studies have shown that children with asthma have high SRBD scores, particularly those with poor asthma control[9,10]. As such, a closer look at the twenty-two questions of the SRBD survey may reveal the OSA risk factors or symptoms beneficial for accurate initial OSA screening in children with asthma.

Our goal was to identify the questions on the SRBD survey useful for predicting OSA in a cohort of children with asthma in order to develop a simple but accurate tool for wide scale OSA risk stratification. Children with asthma enrolled in the AIRWEIGHS study, underwent an in-laboratory overnight sleep study and completed the SRBD survey, providing a unique opportunity to address this research goal.

METHODS

Participant recruitment and characterization

AIRWEIGHS is a single-center, randomized, parallel-assignment, quadruple-masked clinical trial of an air purifier intervention for obesity-associated asthma (NCT02763917). The study was approved by the IRB-1 Committee of the institutional review board of Johns Hopkins University School of Medicine (IRB00074171). All participants gave assent, and all primary caretakers gave written informed consent.

Participants were recruited from patients seen at the Johns Hopkins outpatient clinics and the pediatric emergency department, community engagement activities, recruitment flyers posted in public locations and a registry of previous study participants. Eligible participants were aged 8–17 years, nonsmokers, and had physician-diagnosed asthma by National Asthma Education and Prevention Program (NAEPP) criteria with at least one exacerbation in the prior year[11]. Those who had other significant cardiopulmonary disease were excluded. A diagram of the participant flow is shown in **Figure 1** .

Sociodemographic information was obtained by participant or caregiver report. Body weight and height were measured in triplicate and each averaged, from which body mass index (BMI) was calculated and converted to a normalized z-score based on the 2000 Centers for Disease Control and Prevention (CDC) growth charts[12,13].

SRBD survey

We administered the SRBD questionnaire, a 22-item survey divided into 3 domains, nighttime, daytime and cognitive symptoms. Symptoms evaluated include snoring, observed apneas, difficulty breathing during sleep, daytime sleepiness, inattention/hyperactivity, enuresis, morning headache, delayed growth and obesity [14,15]. The number of symptom-items endorsed positively ("yes") is divided by the number of items answered positively or negatively; resulting in a proportion that ranges from 0.0 to 1.0. The details on the development of the SRBD and score calculation have also been previously published[15]. We used an SRBD score of 0.33 as the screening threshold for OSA[14], since this threshold has been previously shown to offer the best OSA screening accuracy.

Polysomnography

Participants underwent overnight in-laboratory polysomnography at the Johns Hopkins Pediatric Sleep Center. Polysomnography was performed according to standard American Academy of Sleep Medicine (AASM) guidelines[16,17]. Parameters monitored included electroencephalogram, electrooculogram, submental and pretibial electromyogram, electrocardiogram, nasal airflow monitored with a pressure transducer and thermistor, thoracic and abdominal plethysmography, end-tidal CO_2 and pulse oximetry.

Scoring of the polysomnography was performed by a trained sleep technician and reviewed by a pediatric sleep physician (LS). An obstructive apnea was defined by the absence of airflow in the nasal and oronasal airflow with ongoing respiratory effort for at least two breath cycles. An obstructive hypopnea was defined as a drop-in airflow ($>$ 30% of baseline) with ongoing respiratory effort for at least two breath cycles terminated by an arousal from sleep or a [?] 3% fall in oxyhemoglobin saturation. OSA was defined as an obstructive apnea-hypopnea-index (AHI) of [?]2 events per hr.

Statistical Analyses

Logistic regression was used to examine the association of the SRBD score as well as sub-questions with the presence of OSA. Screening accuracies of the SRBD score and sub-questions associated with OSA were examined by calculating the positive predictive values (PPV), negative predictive values (NPV), sensitivities, specificities, and the area under the curve (AUC) for the receiver-operating characteristic (ROC). AUCs were compared using the Delong's test for two ROC curves.

Since asthma may increase the susceptibility for upper airway obstruction[4,5], in post-hoc analyses, we examined whether the odds of having OSA increased with asthma severity using logistic regression in an unadjusted model and a model adjusted for age, sex and BMI z-score.

All analyses were performed using R (www.r-project.org, with the "stats", "remotes", "ggplot2", and "lme4" packages)[18] and a two-sided $P < 0.05$ was considered statistically significant. All values were reported as means ± SD interquartile ranges and N (%) as appropriate.

RESULTS

Participant Characteristics

Participants' demographic and anthropometric characteristics, SRBD scores, apnea-hypopnea-index, and asthma severity, are presented in**Table 1** . The study population had an average age of 11 +- 2.6 years, comprised 54 females and 84% were Black or of African American ethnicity. The mean BMI z-score range was -0.89 (5th percentile) to 2.85 (99th percentile), and 45% of the participants were obese by CDC criteria. 60% of the participants had moderate to severe persistent asthma. The average SRBD score was 0.4 +- 0.2 with 56% of the participants at or above the high OSA risk threshold of 0.33, and the average obstructive AHI was 4.6 +- 12.6 with 40% of the participants having OSA.

Multivariable OSA prediction (MOP) model

As shown in **Table 2** , reported loud snoring, dry mouth in the morning and being overweight were the questions on the SRBD we found to associate with OSA in univariable logistic regression. In multivariable logistic regression, all three predictors remained significantly associated with OSA (**Table 3**). OSA probability was calculated for each participant with the beta coefficients of the logistic regression equation (**Figure 2**).

OSA screening accuracy

Figure 3 shows the ROC curve for the predicted probabilities derived from the MOP model alongside ROC curves for the SRBD survey and BMI z-score as an objective measure of body size. The NPVs, PPVs, sensitivities and specificities are also presented in **Figure 3** . The AUC was statistically significantly greater for the MOP model compared to the SRBD (P =0.007). Of note, the AUC for the BMI z-score was statistically significantly greater than that of the SRBD (P =0.038), but not statistically different compared with the AUC of the MOP model (P =0.500).

The optimal OSA screening cut-off for the MOP model was 0.428 or an OSA probability of 42.8%, while that of BMI z-score was 2.07, which corresponds to the 98$^{\text{th}}$ BMI percentile (**Figure 4**). Logistic regression analyses revealed 6-fold higher odds of having OSA for children with OSA probabilities [?] 42.8% compared to those with OSA probabilities < 42.8% (OR = 5.73, 95% CI = 2.56 – 13.53, P<0.001), and 8-fold higher odds of having OSA for children with BMI z-scores [?] 2.07 (OR = 8.35, 95% CI = 3.62 – 20.91, P<0.001) compared to those with BMI z-scores < 2.07.

Association of asthma severity and OSA

Post-hoc analyses revealed that participants with moderate to severe persistent asthma had twofold higher odds of having OSA compared to those with mild persistent and intermittent asthma, which was nominally significant in the unadjusted model (OR=1.97, 95% CI=0.97 – 4.116,P =0.064) and statistically significant in the model adjusted for age, sex and BMI z-score (OR=2.45, 95% CI=1.10 – 5.69,P =0.031), **Table 4** .

DISCUSSION

Our goal was to identify the components of the SRBD survey useful for OSA screening in children with asthma, a patient population with heightened susceptibility to OSA. Our cohort of consecutively recruited children with asthma demonstrated a high prevalence of OSA, confirming results from previous studies. We report four novel findings. First, of the 22 SRBD survey questions, only loud snoring, morning dry mouth and being overweight were associated with OSA. Second, a combined model of reported loud snoring, morning dry mouth and being overweight generated a probability index (MOP) with greater OSA screening accuracy compared to the composite SRBD score. Third, the BMI z-score also had greater OSA screening accuracy compared to the composite SRBD score, but had similar OSA screening accuracy compared with the combined model of reported loud snoring, morning dry mouth and being overweight. Fourth, children with moderate to severe persistent asthma had twofold higher odds of having OSA compared to those with mild persistent and intermittent asthma. These findings confirm the high burden of OSA amongst children with asthma, particularly those with concomitant obesity, and suggest that a simple yet objective anthropometric measure such as the BMI z-score can be used to effectively screen for OSA in children with asthma, thereby identifying those at risk for adverse health consequences.

The objective of initial OSA screening is to identify the persons with a high likelihood of having OSA in a subsequent sleep study. Another rationale is to recognize persons who might have OSA in the context of their underlying disease. For children with asthma, undetected OSA presents an extra-ordinary high risk for morbidity. Since in-laboratory polysomnography, the only objective and clinically valid method of OSA assessment in children is expensive and often difficult to obtain, a simple yet accurate low-cost approach is critical to identify children with asthma who need sleep studies in a timely manner.

Several studies investigating sleep disordered breathing in children have reported a higher prevalence of OSA in children with asthma compared to the general population[1,19–21]. Ramagopal et al reported an OSA prevalence of 81% in children with asthma referred for adenotonsillectomy[21]. Similarly, Kheirandish-Gozal et al studied children with poorly controlled asthma and showed an OSA prevalence of 63%[1]. Furthermore, a recent study by Ehsan et al reported an OSA prevalence of 47% in a retrospective patient chart review of children with asthma referred for sleep studies[2]. As seen in our study, the prevalence of OSA was 40%, confirming the relatively higher OSA prevalence in children with asthma. Our result along with those of previous reports suggest that asthma contributes to OSA pathophysiology, which might explain the increased prevalence. Moreover, in our cohort, children with moderate to severe persistent asthma had twofold higher odds of having OSA compared to those with mild persistent and intermittent asthma (**Table 4**). Interestingly, we also found that boys had three-fold higher odds of OSA compared to girls (**Table 4**) possibly due to inclusion of children in the post-pubertal age group[22,23] in whom differences in anatomy have begun to emerge resulting in different susceptibilities for OSA. It is likely, however, that the gender difference in predilection for asthma[24,25] contributed to the higher odds for OSA in boys compared to girls, but such an inference will need to be examined and verified in studies that have controls without asthma.

Currently, OSA screening in children is often done with the SRBD questionnaire, a 22-item survey derived from the Pediatric Sleep Questionnaire[14], for which a score greater than 0.33 indicates a high OSA risk. In the general population, the SRBD questionnaire has a sensitivity of 78% and a specificity of 72% as reported by Chervin et al[8]. In that study, OSA was defined as an AHI [?] 1 events/hr. and was enriched with children scheduled to have adenotonsillectomy. Ehsan et al conducted a validation study of the SRBD in children with asthma, which revealed a screening sensitivity of 81.6% and specificity of 14.4% at an OSA definition of AHI[?]2 events/hr[2]. In our study, we found a screening sensitivity of 47.3% and specificity of 68.8% at the same OSA and SRBD thresholds. The differences in our results may be because their study population comprised patients specifically referred for clinical sleep studies unlike our study that investigated consecutive research participants, thus lowering but not eliminating the potential bias related to sleep study referrals. Interestingly, we found that our MOP model that comprised loud snoring, morning dry mouth and BMI z-score was comparatively better than the SRBD. In fact, the BMI z-score alone had an NPV and PPV of 72.2% and 76.3% compared to 65.5% and 51.0% for the SRBD (**Figure 3**). From a clinical utility and

practical standpoint, the BMI z-score may provide the best combination of OSA screening accuracy and ease of application. At the optimal cut-off of 2.07, the predictive values suggest that 76% of patients above this threshold will have an AHI[?] 2 events/hr, hence a 24% false positive rate. Conversely, 72% of the patients with BMI z-scores below 2.07 will have an AHI$<$ 2 events/hr, leaving a 28% chance for false negatives. Based on this paradigm, therefore, children with asthma that have BMI z-scores $<$ 2.07, should still be further evaluated for indicators or risk factors for upper airway obstruction including enlarged tonsils, rhinitis, and asthma severity, particularly if they also report loud snoring or have dry mouth in the morning. Bearing in mind that in our cohort, the odds of having OSA was higher in boys compared to girls (**Table 4**), future work will need to explore whether the OSA screening accuracy of the BMI z-score, MOP model and SRBD survey, differs between boys and girls.

Previous studies have shown that children with asthma who have OSA had higher BMI z-scores compared to those without OSA[26,27]. Our results confirm these reports, as we showed that children with asthma with BMI z-scores [?] 2.07 had 8-fold higher odds of having OSA compared to those with BMI z-scores $<$ 2.07. Obesity may also contribute to asthma morbidity[28–30], although the causal mechanisms remain unclear. Since OSA has been associated with asthma morbidity, obesity related increase in OSA risk may be one of the links between obesity and worse asthma control. On the other hand, increased upper airway inflammation in asthma may lead to higher susceptibility for OSA thus setting up a vicious cycle of cumulative morbidity[5,31]. While the potential bi-directional OSA-asthma relationship is complex, the shared risk factor in obesity presents a target for mitigating both the OSA and asthma burden[32], which as suggested by our study, could be achieved by monitoring BMI z-scores and identifying those at risk for OSA early.

Strengths and Limitations

Our cohort is the largest sample of children with asthma with gold-standard in-laboratory polysomnography in a prospective study design. Objective characterization of sleep and breathing allowed for accurate assessment of obstructive disordered breathing events leading to precise classification of participants with OSA, thus strengthening our findings. A few limitations should be considered. First, our sample was 84% African American; therefore, our findings may not be generalizable to all children with asthma. Nonetheless, it is worth noting that the study by Ehsan et al[2] also demonstrated a high prevalence of obesity and OSA in an asthma cohort that comprised 36% African American, therefore, the results described in this study may be applicable to asthma populations of other ethnicities. Second, our sample was not large enough to be split into adequate training and validation sets, which would have allowed for internal performance testing of our OSA screening model. Nevertheless, given the simplicity of obtaining anthropometry and calculating BMI z-scores, our findings may be easily replicated in other asthma cohorts, which would enhance external validity and generalizability.

Implications

Obesity is a potent predictor of OSA in children with asthma as indicated by our findings. The BMI z-score with or without reported loud snoring and morning dry mouth may be used for OSA screening with several implications for health systems, global public health and our understanding of the impact of OSA on asthma disease management. First, the questionnaire-based approach has been the mainstay for initial OSA screening. In the past two decades, however, electronic medical records and health informatics systems have reshaped healthcare delivery. Given that anthropometric measures such as BMI and BMI z-scores are available on such platforms, OSA risk stratification may be implemented in an automated fashion on a wide scale. Second, in low to middle income countries were such databases may not exist, OSA screening may be deployed via mobile applications that have a BMI z-score calculator or the MOP algorithm incorporated. Thus, the BMI z-score or MOP algorithm may serve as low-cost OSA screening methods for children with asthma in these locations where sleep study facilities may also be non-existent. Finally, the impact of OSA on asthma and vice-versa may be tracked by examining retrospective and prospective trends in BMI z-scores, as a biomarker of OSA, along with metrics of asthma control, which may reveal disease management practices most likely to decrease the future burden of OSA and asthma.

In conclusion, we recommend that children with asthma who have BMI z-scores of 2.07 or greater be referred for in-laboratory polysomnography and OSA evaluation. Future efforts should refine OSA screening tools that are specific to children with asthma.

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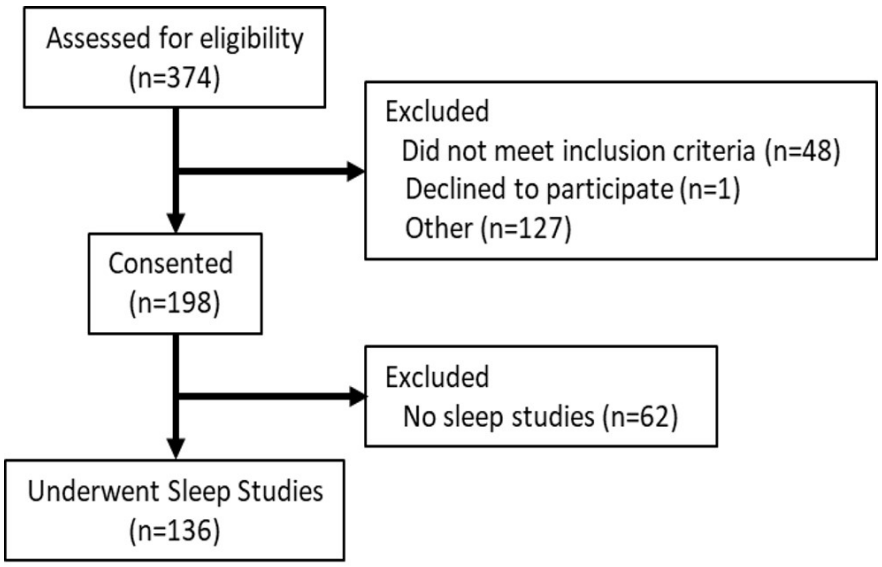
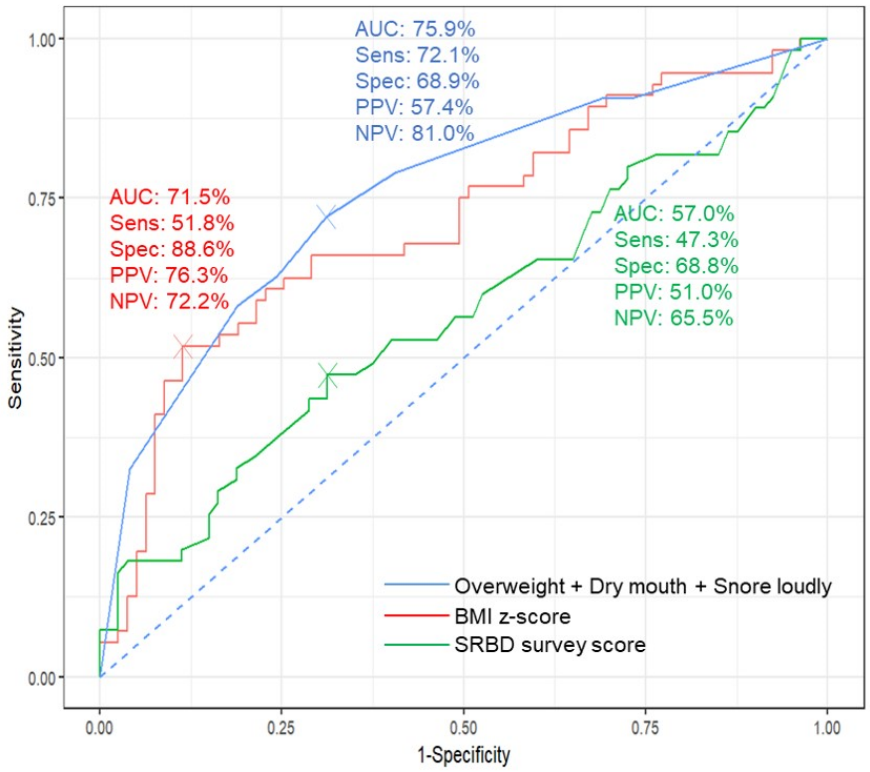
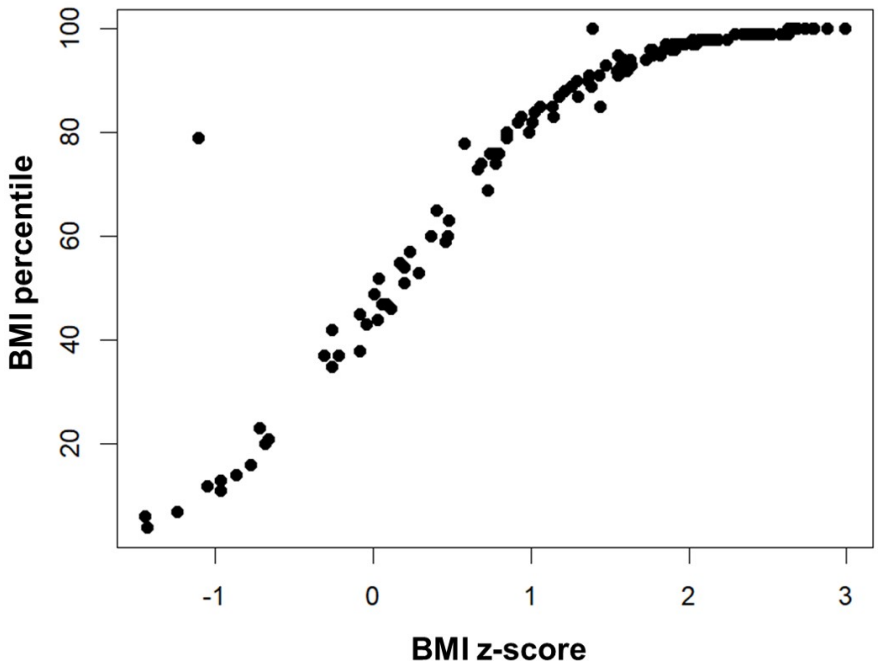


$$\textbf{OSA Probability} = \frac{e^{x}}{1+e^{x}}$$

where $\mathbf{X} = -2.188 + (Overweight * 0.903) + (Loud\ snoring * 1.298) + (Dry\ mouth * 0.999)$,

overweight = 1 if yes, and 0 if no, loud snoring = 1 if yes, and 0 if no, and dry mouth = 1 if yes, and 0 if no





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