

Association between Obstructive Sleep Apnea and Obesity in a Pediatric Population

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Abstract

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Introduction: In adult populations, the pathology of obstructive sleep apnea syndrome (OSAS) is mainly related to obesity. In contrast, early studies in pediatric populations suggested adenoid and tonsillar hypertrophy (ATH) to be the main causes of OSAS in children, making adenotonsillectomy the first line of treatment. Early consensus was that, in contrast to adults, pediatric OSAS patients often present with inadequate weight gain and even failure to thrive. In fact, the past three decades have witnessed a 2-3-fold increase in the prevalence of childhood obesity. This fact sparked a shift in the pediatric OSAS paradigm towards combining obesity and ATH as the main causes of the disease. This represents a major change from the traditional view that ATH alone was the primary cause. Thus, further research on the pathology and outcomes of pediatric OSAS is needed. Especially given the increased prevalence of childhood obesity.

Methods: Correlations between patients' sleep apnea severity, indicated by apnea hypopnea index (AHI) score, and patients' body weight, indicated by the body mass index Z-score (BMI Z-score) were studied in a pediatric population from Seattle Children's Hospital Sleep Center (n=500). Analysis was carried out in the overall group and then stratified by body weight.

Results: Nearly half of the study subjects were overweight or obese. There was a significant

association between AHI scores and the BMI Z-scores in the non-underweight group (n=480). This association remained significant after adjusting for sociodemographic and comorbidity factors. No significant association was found between AHI scores and the BMI Z-scores in the all-subject group (n=500) or in the underweight group (n=20). **Conclusion:** Obesity has become another major risk factor and potential cause for OSAS in the pediatric population. Weight management should become an important first line of treatments for OSAS patients in addition to the traditional surgical approach.

Introduction

Obstructive sleep apnea syndrome (OSAS) is a severe type of sleep-disordered breathing (SDB) characterized by prolonged episodes of blockage or intermittent blockage of the upper airway that affects normal sleep cycles¹. Habitual snoring is often present in OSAS patients²⁻⁴. OSAS might occur in 1-10% of the pediatric population^{4,5}. The current gold standard for diagnosis of sleep apnea is in-laboratory Polysomnography (“The Sleep Study”).³

In the adult population, OSAS is strongly associated with the onset of obesity⁶. The mechanism behind this association is that, first, obese patients have altered soft tissue conformation such as larger soft palate, tongue, fat pads and thicker lateral pharyngeal walls, all of which contribute to the narrowing of the upper airway⁷⁻⁹. In addition, one previous study has shown that excess visceral fat deposition causes reduction in lung volume, making it more prone to collapse¹⁰. It has been shown that small changes in body mass index (BMI, kg/m²) can cause considerable changes in the severity of OSAS in adults¹¹⁻¹⁴. Pediatric sleep medicine emerged in the early 1970s but was advancing very slowly until the recent decade¹⁵. Though the mechanisms behind adult OSAS can also present in some pediatric patients, the etiology of OSAS in pediatric patients is not completely defined.

Early studies suggested adenoid and tonsillar hypertrophy (ATH) to be the main causes of OSAS in children, making adenotonsillectomy (surgical removal of the adenoids and tonsils) the first line of treatment^{16,17}. In terms of weight profile of children with OSAS, early consensus was that, in contrast to adult patients, pediatric OSAS patients often present with inadequate weight gain and even failure to thrive^{18,19}. The past three decades has witnessed a 2-3 fold increase in the

prevalence of childhood obesity²⁰. The increase in obesity prevalence has shifted the pediatric OSAS paradigm to combinations of obesity and variable ATH as the main influences from the traditional view of ATH alone as the primary cause (which led to low body weight and failure to thrive). Thus, further research on the pathology and outcomes of pediatric OSAS is needed, especially given the rapid increase of obesity prevalence in younger children²⁰⁻²².

In 2005, the sleep center at Seattle Children's Hospital completed a preliminary study profiling the pediatric population referred to the sleep center for initial OSAS screening with polysomnography. The results of this preliminary work confirmed previous findings from other centers of high obesity prevalence in pediatric OSAS populations²³. Data from this preliminary study also showed a positive association between age- and sex-adjusted BMI percentile and severity of obstructive sleep apnea as indicated by apnea-hypopnea index (AHI). However, factors such as comorbidities and household income status were not adjusted for in these analyses. Prior studies have associated SES and asthma with increased prevalence of OSAS^{2,5}. Thus we do not know whether the expected association is still significant after controlling for these important confounding variables. In addition, the relative contributions of ATH and obesity to the etiology of pediatric OSAS are debatable (age and sex-adjusted BMI percentile and AHI might be associated differentially depending on weight status). Thus, to simply examine the overall association between BMI and AHI across the pediatric population is not sufficient. Instead, it is necessary to identify the association between BMI and AHI by weight status in pediatric patients.

This present study re-characterized the sleep study patient population at Seattle Children's Hospital sleep center using more recent data. It profiled the patient population's sociodemographic status, weight status and severity of breathing problems. Similar to the previous study, the present study examined the overall association between the severity of sleep apnea and patient's weight status. More importantly, by stratifying the subjects into different body weight groups (underweight group and normal weight, over weight and obese group), this study explored the differences between groups in terms of the association between body weight and OSAS severity. In addition, the available data made it possible to statistically control for factors such as household income and comorbidities (asthma, history of adenotonsillectomy etc.) in order to minimize study bias.

The primary hypothesis of this study is that the severity of OSAS as measured by apnea-hypopnea index (AHI) is significantly correlated with BMI percentile, after controlling for age, sex, SES, medical comorbidities, and race. Secondly, the association between the severity of OSAS and BMI-percentile differs among different body weight groups. In the underweight group, a higher AHI score is associated with lower BMI percentiles whereas in the overweight/obese group, this relationship is reversed such that higher AHI scores are associated with higher BMI percentiles.

Methods

Subjects

This study was a cross sectional study. Secondary data analysis was conducted using a data set from Seattle Children's Hospital Sleep Disorders Center at Overlake. The original data set included first time diagnostic Polysomnography (PSG) (sleep study) in patients aged 2-21 years old who were seen in the Sleep Center between May 2011 and October 2013. The majority of the sleep study patients were referred by their primary care providers or other subspecialists (otolaryngology, neurology) to Seattle Children's Hospital Sleep Clinic first, and then directed to the Sleep Center for sleep studies. A small percentage of the patients were referred directly for sleep studies from their subspecialists, who had established specific referral relationships with the Sleep Center. The data set provided information on each patient's age, gender, and weight status, zip code, race as well as sleep study data. Each subject's electronic medical record was revisited through Seattle Children's Hospital's Clinical Information System (CIS) and additional information were collected on the following comorbidities: whether the patient had adenotonsillectomy prior to the sleep study and whether the patient was diagnosed with asthma. Seattle Children's Hospital Institutional Review Board approved this study.

Measurements

In this study, the severity of sleep apnea was indicated by apnea-hypopnea index (AHI). AHI represents the total number of respiratory disturbances averaged per hour of total sleep time. A higher AHI score is correlated with more severe sleep apnea symptoms. Each subject's household income was estimated based on the zip code database from University of Michigan Population Study Center²⁴. This database provided national mean and median household incomes in corresponding to each zip code area. BMI score was transformed to BMI Z-score based on a CDC national database²⁵. The batch calculation of BMI Z-score for the full dataset was

completed using Growth-Z, a Microsoft® Excel workbook-based program provided by researchers at British Columbia Children's Hospital²⁶.

Statistical Analysis

Subjects younger than 2 years old, older than 21 years old and subjects who came for non-diagnostic sleep studies (follow up sleep studies) were excluded from the original dataset. There were 1985 subjects in the original dataset and the most recent 500 subjects were included in the analysis.

Descriptive statistics were carried out to characterize sex, age, race, household income status and body weight distribution of the subjects. The associations between the severity of sleep apnea (using AHI scores), and subjects' BMI percentiles (using Z-scores) were examined using multi-factorial regression models. In the first model, only the association between subjects' AHI scores and their age and sex adjusted BMI-Z scores were examined. In the subsequent model, adjustments were added for age, sex, race, estimated household income and two comorbidity variables (history of pre-study adenotonsillectomy and diagnosis of asthma). After examining the association for all subjects, the subjects were stratified into two groups by body-weight. One group included only subjects who were underweight (BMI% < 5th percentile). The other group included normal weight, over weight and obese patients (BMI% ≥ 5th percentile). The same multi-factorial regression model was used in both groups separately. Statistical analysis was performed by software STATA version 13.1. The level of significance was set at $\alpha=0.05$.

Results

Select sociodemographic data of the study sample is shown in Table 1. All numbers are presented in the forms of means \pm standard deviations or numbers and percentages where appropriate.

Table 2 presents body weight distributions of the study subjects. The number and percentages of subjects in three body-weight categories: underweight (BMI% $<$ 5), normal-weight (BMI% \geq 5, $<$ 85), Overweight and obese (BMI% \geq 85) are shown.

Figure 1 to 3 shows the general trend of the association between AHI scores and BMI Z-scores. There appears to be a slight positive association based on the graph in the all-subject group and in the non-underweight group (Figure 1, 2a). On the other hand, in the underweight group, this association appears to be negative. Results of the multifactorial regression analysis are shown in Table 3-4. The association between AHI scores and the BMI Z-scores in the non-underweight group is significant ($P<0.05$) (table 4). This association remains significant after adjusting for age, gender, median household income, race and comorbidities (table 4). However, there is no significant association between AHI scores and the BMI Z-scores in the all-subject group and in the underweight group (Table 3, 4).

Discussion

The results of the present study indicate that overweight and obesity are very prevalent in the patient population at Seattle Children's Hospital Sleep Center. Nearly half of the study subjects (46.8%) had a BMI percentile of 85th or above. This finding is consistent with the preliminary

study results from the same patient group in 2005²³. In the literature, there is a considerable variation in reported incidence of underweight or growth failure in patients with sleep disordered breathing, ranging from 1% to 52%. In our study population, only 4% of all study subjects are underweight. Though studies have shown that OSAS can be associated with both underweight and overweight problems^{27,28}, overweight appears to be more prevalent in our study population.

The results of the multifactorial regression show a significant positive correlation between the subjects' AHI scores and BMI Z-scores in the normal weight, overweight and obese group ($P = 0.02$). (Table 4) This association is still significant after adjusting for age, gender, race, estimated household income and comorbidities ($P = 0.02$, coefficient = 0.8). In other words, among two groups of individuals with similar race, age, gender, household income, history of asthma, and history of adenotonsillectomy, differing in BMI z-score by 1 unit, the group with the higher BMI z-score can be expected on average to have AHI score 0.774 (units) higher than the group with lower BMI z-score, which is a significant increase in AHI ($p=0.002$). This observed estimate of increase in AHI would not be uncommon if the true increase were between 0.3 and 1.3 units. (Table 4) In a previous study, Redline and her colleagues also found positive correlations between obesity and sleep breathing problems such as obstructive sleep apnea in a pediatric population. However, socioeconomic status such as household income was not adjusted. In addition, Redline's study examined only the incidences of OSAS. The severity of OSAS was not a parameter in the study²⁷. The findings of this present study suggest that the majority of our pediatric patients at Seattle Children's Hospital Sleep Center resemble the adult population in terms of OSAS etiology. Obesity has become a main risk factor and potential cause of OSAS in this pediatric population in addition to adenoid and tonsillar hypertrophy (ATH).

Figure 3 shows a negative association between the subjects' AHI scores and their BMI Z-scores in the underweight group. (Figure 3) This trend consists with our hypothesis that the AHI scores and the BMI Z-scores associate differently in different body weight groups. However, this association is not statistically significant; one contributing factor might be the small sample size of this group (n=20). Based on Bonuck et al, growth failure is more likely to be one of the complications of sleep breathing problems rather than the cause²⁸. The primary mechanism behind this negative relationship is believed to be dysphagia caused by adenoid and tonsillar hypertrophy (ATH)²⁸ or underlying conditions. More recent studies also suggested that changes in serum insulin-like growth factor-1 play a role in affecting the normal growth patterns²⁹. Patients regardless of weight status usually show catch-up growth after removal of the enlarged adenoids and/or tonsils.

The association between AHI scores and the BMI Z-scores in the entire study subject group is insignificant. (Table 3) The differential associations between different bodyweight groups as stated above also contribute to the attenuated relationship.

In this present study, it is shown that patients with overweight and obesity problems are at higher risk of developing more severe sleep-breathing problems. In fact, as these patients experience more sleep disturbance, they are also at higher risk of gaining more weight. Weight control in overweight and obese OSAS patients is more challenging than in patients without sleep breathing problems. Studies have shown that poor sleep quality is associated with increased risk of obesity³⁰. Shortened nighttime sleep duration can lead to low energy level as well as more

sedentary activities during the day. It is also associated with behavioral changes in food choices towards calorie dense foods. In addition, decreased sleep time can cause a series of metabolic changes that can lead to weight gain. Examples of these changes include altered growth hormone, prolactin, thyrotropin, cortisol, insulin secretion and appetite regulation hormones leptin and ghrelin³⁰. Thus a well-designed bodyweight management program taking into account these interrelated factors is crucial to break the sleep-breathing problem and unhealthy weight gain cycle.

The present study was a cross sectional study. Thus results from this study could only indicate correlation, not causal relationships. This study used zip code to estimate patients' household income. This method might not be very accurate. However, given the limited resources available, this was the optimal choice. Lastly, this was a single-center study. Our subjects were all from Seattle Children's Hospital Sleep Center. The demographical and medical characteristics only represent this specific patient population group. However, the associations revealed in this study are still expected to be generalizable to the pediatric OSAS population.

Conclusion and Indications

Early studies suggested that pediatric OSAS, different from the adult onset of the disease, was caused mainly by adenoid and tonsillar hypertrophy. These patients usually presented with growth failure and were usually treated effectively with adenotonsillectomy²⁸. However, findings of the present study indicate that with the recent childhood obesity epidemic, obesity has become another major risk factor and potential cause for OSAS in the pediatric population. Nearly half of

our study subjects were overweight or obese. Their weight status correlates significantly with the severity of their OSAS symptoms after adjusting for age, sex, sociodemographic factors and comorbidities. For this group of patients, weight management should be considered the first line treatment option or in combination with adenotonsillectomy.

Right now, Seattle Children's Sleep Center does not have onsite professionals for weight management. Since body weight is a sensitive topic, many physicians avoid this conversation with their patients. Some physicians at the sleep clinic refer OSAS patients with weight problems to outside sources for weight management services. However, families rarely follow through on referrals due to varieties of reasons. Possible next steps for Seattle Children's Hospital Sleep Center and Sleep Clinic would be to incorporate a dietitian into the health care team to provide onsite nutrition counseling and weight management services. In addition, it would be very helpful to develop tools such as talking points to help physicians overcome barriers discussing weight problems with their patients.

Table 1. Select age and demographic and age (11.5 ± 3.6 years) characteristics of study subjects, data obtained from Seattle Children's Hospital Sleep Clinic. Contained subjects from February to October 2013 (N=500).

Age	11.5 ± 3.6
Male	303 (61%)
Female	197 (39%)
Median household income	$\$68639 \pm \20411
Caucasian	260 (52%)
Alaska Native	10 (2%)
Asia	30 (6%)
Black	30 (6%)
Hispanic	105 (21%)
Other	65 (13%)

Table 2. Body weight distribution of study subjects in three groups: underweight (n=20, BMI = 12.4-16.8), normal weight (n=246, BMI = 13.6- 25.9) and overweight/obese (n=234, BMI = 17.4- 48.1) (. Results are shown as numbers and percentages of subjects.)

Underweight (<5th percentile)	20 (4%)	BMI Range: 12.4 – 16.8
Normal Weight (5 th -85 th percentile)	246 (49.2%)	BMI Range: 13.6 – 25.9
Overweight + Obese (≥ 85th percentile)	234 (46.8%)	BMI Range: 17.4 – 48.1

Table 3. Result of Multifactorial regressions on the association between AHI scores and BMI Z-scores of all 500 subjects. Model 1 shows unadjusted results. Model 2 shows results after adjusted for age, sex, race, SES and comorbidities. Analysis showed no significant association between BMI Z-score and AHI scores among all 500 subjects.

	Model 1. Unadjusted		Model 2. Adjusted for age, sex, household income and Comorbidities	
	Coefficient	95% Confidence interval	Coefficient	95% Confidence interval
All subjects (N=500)	0.4	-0.01 - 0.9	0.4	-0.5 - 0.9

Table 4. Result of Multifactorial regressions on the association between AHI scores and BMI Z-scores stratified by body weight status. Subjects were examined in two body weight groups, the underweight group (BMI% < 5th percentile, N=20) and the normal weight and obese group (BMI% ≥ 5th percentile, N=480). Model 1 shows unadjusted results. Model 2 shows results after adjusted for age, sex, race, SES and comorbidities. Analysis showed significant association between AHI scores and BMI Z-scores in non-underweight group. This association was still significant after adjusting for age, sex, household income and Comorbidities. (P = 0.002)

	Model 1. Unadjusted		Model 2. Adjusted for age, sex, household income and Comorbidities	
	Coefficient	95% Confidence interval	Coefficient	95% Confidence interval
Subjects who were Underweight (N=20)	-3.5	-17.7 - 10.8	5.6	-17.4 - 28.7
Subjects who were Normal Weight and Obese (N=480)	0.8	0.3 - 1.2*	0.8	0.3 -1.3*

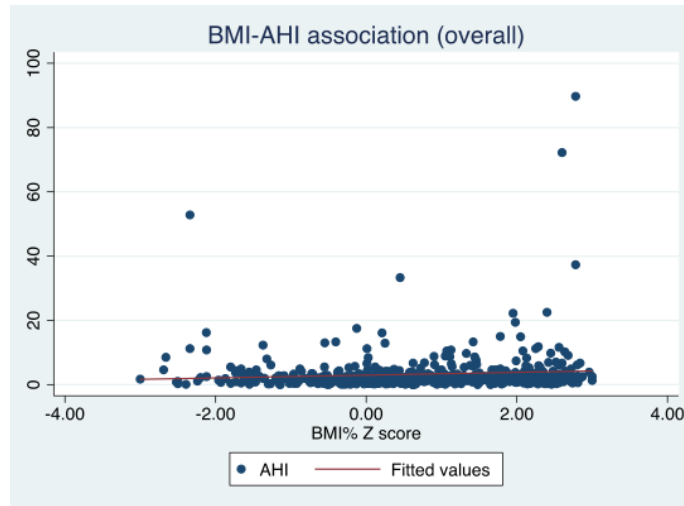


Figure 1. Association between AHI scores (Y axis) and BMI% Z-scores (X axis) in all study subjects appears to be positive (N= 500).

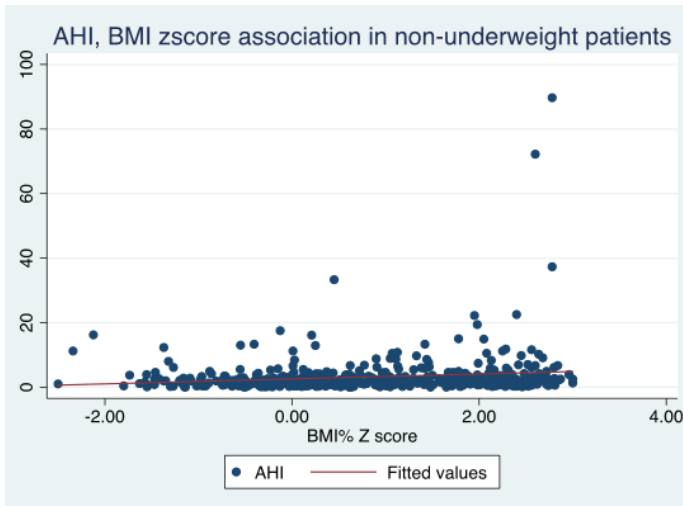


Figure 2 a. The association between AHI scores (Y axis) and BMI% Z-scores (X axis) in normal weight, overweight and obese patients appears to be slightly positive (N=480).

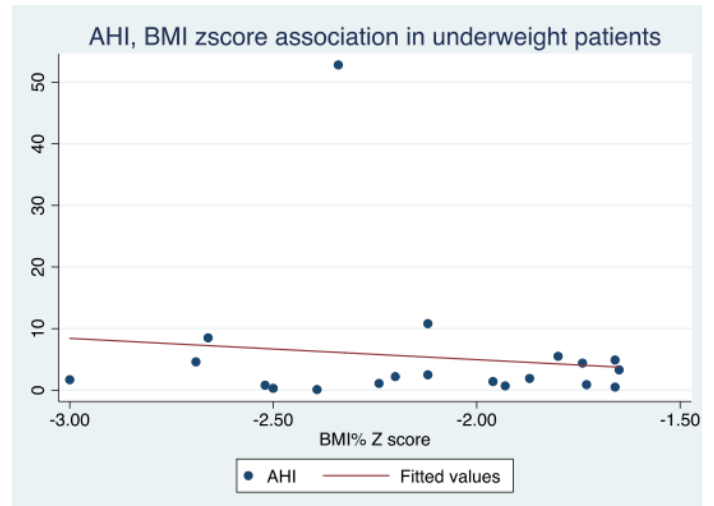


Figure 2 b The association between AHI scores (Y axis) and BMI% Z-scores (X axis) in under weight patients appears to be negative (N=20).

Appendix I. Preliminary study data on the patient population at Seattle Children's Sleep Clinic.

Table 1: Baseline Characteristics	
Subject Number	n = 1057
Gender	63% male; 37% female
Mean Age (years)	9.7 ± 4.6, range 2 - 21
Mean BMI Overall	22.2 ± 9.2, range 10.7 - 80.8
Female	22.9 ± 9.4, range 12.8 - 72.9
Male	21.8 ± 9.1, range 10.7 - 80.8
Mean BMI% Overall	67.4 ± 31.6
Female	69.5 ± 29.8
Male	66.1 ± 32.5
Mean AHI Overall	17.1 ± 17.7, range 0.0 - 155.7
Female	16.5 ± 18.2, range 0.3 - 155.7
Male	17.4 ± 17.3, range 0.0 - 128.3
% adolescents (≥12 y)	32%

Chen et al, 2008 (abstract) AJRCCM

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