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Short title/running head: Sex differences in sleep-disordered breathing in pediatric severe asthma

Sex differences in the relationship of sleep-disordered breathing and asthma control among children with severe asthma

Sigfus Gunnlaugsson, MD^{1,4}, Kimberly F. Greco, MPH², Carter R. Petty, MA², Gabriella C. Sierra, BS¹, Natalie P. Stamatiadis, BS¹, Christine Thayer, BS¹, Adam G. Hammond, BS¹, Lauren M. Giancola, RN¹, Umakanth Katwa, MD^{1,4}, Tregony Simoneau, MD^{1,4}, Sachin N. Baxi, MD^{3,4}, Jonathan M. Gaffin MD, MMSc^{1,4}

¹Division of Pulmonary Medicine, Boston Children's Hospital, Boston, MA, USA

²Institutional Centers for Clinical and Translational Research, Boston Children's Hospital, Boston, MA, USA

³Division of Allergy and Immunology, Boston Children's Hospital, Boston, MA, USA

⁴Harvard Medical School, Boston, MA, USA

Corresponding Author: Jonathan M. Gaffin, Division of Pulmonary Medicine, Boston Children's Hospital, 300 Longwood Ave., Boston, MA 02115; Phone: 617-355-1900; Fax: 617-730-0084; Email: jonathan.gaffin@childrens.harvard.edu

Abstract

Objective: Children with severe asthma are underrepresented in studies of the relationship of sleep-disordered breathing (SDB) and asthma and little is known about sex differences of these relationships. We sought to determine the relationship of SDB with asthma control and lung function among boys and girls within a pediatric severe asthma cohort.

Methods: Patients attending clinic visits at the Boston Children's Hospital Pediatric Severe Asthma Program completed the Pediatric Sleep Questionnaire (PSQ), Asthma Control Test (ACT) and Spirometry. The prevalence of SDB was defined as a PSQ score >0.33. We analyzed the association between PSQ score and both ACT score and spirometry values in mixed effect models, testing interactions for age and sex.

Results: Among 37 subjects, mean age was 11.8 years (4.4) and 23 (62.2%) were male, the prevalence of SDB was 43.2% (16/37). Including all 80 observations, there was a moderate negative correlation between PSQ and ACT scores ($r=-0.46$, $p<0.001$). Multivariable linear regression models revealed a significant sex interaction with PSQ on asthma control ($p=0.003$), such that for each 0.10 point increase in PSQ there was a 1.88 point decrease in ACT score for females but only 0.21 point decrease in ACT score for males. A positive PSQ screen was associated with a 9.44 point (CI 5.54, 13.34, $p<0.001$) lower ACT score for females and a 3.22 point (CI 0.56, 5.88, $p=0.02$) lower score for males.

Conclusions: SDB is common among children with severe asthma. Among children with severe asthma, SDB in girls portends to significantly worse asthma control than boys.

Key words: Sleep-disordered breathing, Obstructive sleep apnea, Severe asthma, Pediatric, Pediatric sleep questionnaire

Abbreviation list:

SDB - sleep-disordered breathing

OSA - obstructive sleep apnea

PSQ - pediatric sleep questionnaire

ACT - asthma control test

PSG - polysomnography

c-ACT - childhood asthma control test

FEV1 - forced expiratory volume in one second

FVC - forced vital capacity

FEF 25-75 - forced expiratory flow between the 25th-75th percentile

IgE - immunoglobulin E

ICS - inhaled corticosteroid

LABA - long-acting beta agonist

LAMA - long-acting muscarinic antagonist

LTRA - leukotriene receptor antagonist

BMI - body mass index

Introduction

Asthma and sleep-disordered breathing (SDB) are common respiratory disorders of childhood. Asthma prevalence is 8.3% in children under 18 years of age in the United States(1) and is associated with significant morbidity and healthcare utilization. Severe asthma, which accounts for only 4-5% of pediatric asthma, contributes disproportionately to morbidity, healthcare costs and resource utilization(2–5). Sleep-disordered breathing ranges in character from habitual snoring to obstructive sleep apnea (OSA) of varying severity. OSA is common in childhood, with a prevalence estimated to be 1-5%(6). Asthma and OSA frequently co-exist and share multiple risk factors, including obesity, allergic rhinitis, atopy and race(7–9). Children with asthma are more likely to have habitual snoring and OSA than those without asthma(10,11). In general pediatric asthma cohort studies, the relationship between asthma and SDB has been well established(12,13). SDB has also been shown to be associated with asthma burden(14) and asthma control(15,16) in children. However, few studies have focused specifically on children with severe asthma and its relationship with SDB. Given its high risk for asthma morbidity, further understanding the relationship of SDB within this group is a high priority. Furthermore, while asthma prevalence and severity are known to be influenced by sex(17), little is known about how specifically sex differences affect the relationship of SDB and severe asthma. Therefore, we sought to assess the relationship of SDB with asthma control and lung function in a pediatric severe asthma cohort and determine if there was an age or sex difference in the effect.

Methods

Patient population

Study participants were children referred to the Severe Asthma Program of Boston Children's Hospital for further evaluation of severe or difficult to treat asthma and who had consented to the Pediatric Severe Asthma Registry. The Severe Asthma Program is a multidisciplinary clinical program staffed by a pediatric pulmonologist, allergist, asthma nurse specialist, social worker, and consultative services of pediatric gastroenterology, endocrinology and otorhinolaryngology, as indicated. Patients are only accepted if referred by subspecialists (allergists, pulmonologists) or intensivists following life-threatening exacerbations. Subjects included in this study had to be on asthma medication step 3 or higher according to NHLBI Asthma Guidelines(18). Participants completed the Pediatric Sleep Questionnaire (PSQ)(19), the age-appropriate Asthma Control Test (ACT)(20,21), and performed spirometry at each clinic visit. Medical history, demographic, anthropometric, and allergy sensitization data were extracted from the electronic medical record for each clinical encounter. Written informed consent was obtained from the subjects' guardians and assent from subjects, when applicable, prior to enrollment. The Severe Asthma Program Registry is an approved clinical research protocol by the investigational review board at Boston Children's Hospital (IRB-P00010053).

Assessments

Pediatric Sleep Questionnaire

The presence of SDB was assessed by using the PSQ(22) which is a validated 22-item questionnaire that incorporates symptoms of SDB and subscale domains of snoring, daytime sleepiness and behavioral symptoms. Each question is answered yes=1, no=0 or don't know=missing. The questionnaire is scored by dividing the items answered 'yes' by the total of non-missing items, resulting in a scale of 0.0 to 1.0. A score of > 0.33 has sensitivity of 0.85 and specificity of 0.87 for the diagnosis of OSA by polysomnography (PSG)(19).

Asthma control

Children ages 4 to 11 completed the Childhood Asthma Control Test (c-ACT)(20) and children 12 years and older completed the standard ACT(21) to measure asthma control. The c-ACT consists of two parts, one of which is supplemented by the child and a second part which is completed by the parent or guardian resulting in a score from 0 to 27. The ACT is completed by the adolescent and consists of 5 items with a total score ranging from 5 to 25. A score ≤ 19 indicates uncontrolled asthma on both versions.

Lung function

Spirometry was performed per ATS standards(23) using a Morgan rolling seal spirometer (Morgan Scientific, Haverhill, MA, USA) at each clinic visit. We collected the following data: forced expiratory volume in one second (FEV1) percent predicted, forced vital capacity (FVC) percent predicted, forced expiratory flow between the 25th and 75th percentile of FVC (FEF25-75), and the FEV1/FVC ratio. Percent predicted values were derived from the Global Lung Initiative normative reference equations(24).

Covariates

Allergic sensitization was defined as at least one positive skin prick test or specific IgE for aeroallergens. If subjects had a history of adeno -and/or tonsillectomy (T&A), the timing of the T&A was dichotomized as occurring before or after each PSQ observation (previous T&A). Medication step was determined from the participants' current medications at the time of each encounter and coded into step category to conform with current NHLBI categorizations(18). In cases where the

medications seemed to exceed one step but not achieve the next a half step was added. For example, a medium dose inhaled corticosteroid (ICS)/long-acting beta agonist (LABA) combination plus a long-acting muscarinic antagonist (LAMA) and/or leukotriene receptor antagonist (LTRA), were considered in between step 3 and 4 and were given a numerical value of step 3.5 for use in analytic models.

Statistical analyses

Descriptive statistics characterized the cohort and prevalence of SDB. We considered the PSQ score, a continuous variable, and a positive PSQ screen, a dichotomous variable (score of > 0.33), as predictors of ACT score and FEV1/FVC. Pearson correlation was used to evaluate the unadjusted linear relationship of PSQ score with ACT score and spirometry measures. The primary analysis estimated a linear mixed effects model with a random intercept for subject to evaluate the adjusted predictor-outcome relationship between asthma control and lung function with continuous and binary predictors. We used a compound symmetry covariance structure and robust standard errors to account for dependence across repeated observations clustered at the participant level. We chose this modelling approach due to its suitability for unbalanced repeated measures data(25). The following covariates were considered for inclusion in adjusted models: body mass index (BMI), age, sex, allergic sensitization, asthma medication step, and prior T&A. Leukotriene receptor antagonist use was considered separately due to its known effect on SDB(26). All models were adjusted for BMI, and additional covariates were included if associated with PSQ or outcome at $\alpha \leq 0.1$. Interaction terms were included for age and sex if significant in the model at $\alpha \leq 0.1$. To further understand the nature of the relationship between PSQ and ACT, we performed the same multivariable regression models between the three subscales of the PSQ (snoring, sleepiness, behavior) and ACT. The linear mixed model assumes a Gaussian distribution of residual and random effects. For each model, conditional and marginal residual plots were generated to assess distributional assumptions and confirm that random and fixed effects were correctly specified. Iterative influence analysis was used to detect any highly influential clusters impacting model stability. FEV1/FVC ratios were scaled by 100% and PSQ scores are scaled by 10% (i.e. change in outcome per 0.1 unit change PSQ score) for modelling. Results were considered significant if two-tailed p-values < 0.05 (SAS 9.4, SAS Institute, Cary NC).

Results

Eighty observations for thirty-seven subjects were included for analysis. Subjects had up to six repeated observations as follows: T0 (n=37), T1 (n=19), T2 (n=13), T3 (n=8), T4 (n=2), and T5 (n=1) (**e-Figure 1**). Sixteen (43.2%) subjects had at least one positive PSQ. The subjects' clinical characteristics are shown in **Table 1**. The mean age was 11.8 (4.4) and there were 23 males (62.2%). About 40% of the subjects had adeno- and/or tonsillectomy performed prior to the observation period and none during the study period. Roughly half of the subjects were overweight or obese, 21.6% and 32.4% respectively. A majority (83.8%) of the patients had aeroallergen sensitization, and average medication step was step 5 (0.8), as expected for severe asthma(3); most (78.4%) were prescribed an LTRA. Across the study period, the mean PSQ score was 0.2 (0-0.9). The mean ACT score was 18.8 (4.6), reflecting poorly controlled asthma. The mean FEV1/FVC was borderline low at 0.82 (0.08), consistent with the diagnosis of asthma, however FEV1, FVC and FEF25-75 were within normal range.

On univariate analyses we found a moderate inverse correlation between PSQ score and ACT score ($r = -0.46$, $p < 0.001$). There was a significant inverse correlation between PSQ score and FEF25-75% ($r = -0.30$, $p = 0.006$), and FEV1/FVC ($r = -0.37$, $p < 0.001$), but no correlation with FEV1% ($r = -0.17$, $p = 0.13$) or FVC% ($r = 0.04$, $p = 0.69$).

After adjusting for sex, age, BMI class, allergic sensitization, asthma medication step and prior T&A, the association between PSQ score and ACT score was significantly different for females compared to males ($p=0.003$, **Table 2, Figure 1**). For each 0.10 point increase in PSQ score there was a 1.88 point decrease in ACT score for females ($p<0.001$, 95%CI 1.03, 2.72), compared to a 0.21 point decrease in ACT score for males ($p=0.43$, 95%CI -0.32, 0.75). Multivariable linear models did not reveal any significant association between PSQ score and lung function outcomes (**e-Table 1**) and there was no age-related interaction with either outcome. We did not detect any influential clusters or departures from the assumptions of the linear mixed model.

We further assessed the dichotomized PSQ (positive >0.33 , indicative of OSA) in multivariable linear regression models with ACT and spirometry outcomes. While adjusting for sex, age, BMI class, allergic sensitization, asthma medication step and prior T&A, we found that a positive PSQ screen predicted significantly lower ACT scores for males and females. Again, we observed a significant interaction between PSQ screen and sex ($p=0.007$, **Figure 2, e-Table 2**). Among girls, the mean ACT score for those with a positive PSQ screen was 12.59 ± 1.11 compared to those with a negative screen where average ACT score was 22.03 ± 1.44 , with a mean difference of 9.44 (95%CI 5.54, 13.34, $p<0.001$). For boys with a positive PSQ screen the mean ACT score was 16.46 ± 1.01 compared to a mean ACT score of 19.68 ± 0.89 for those with a negative screen, with a mean difference of 3.22 points (95%CI 0.56, 5.88, $p=0.02$). There was no significant association between a positive PSQ screen and any lung function outcomes.

Some of the symptoms assessed in the PSQ may overlap with the ACT. Therefore, we further evaluated whether the association between PSQ score and asthma control was driven primarily by any one of the three subscales of the PSQ. While adjusting for the same covariates as in the overall analysis, we found that each subscale was inversely associated with ACT scores, though only the behavioral subscale was statistically significant (**Table 3**).

Discussion

Little is known about how SDB specifically affects children with severe asthma, who represent a small group with the highest asthma morbidity. Here we demonstrate that there is a high rate of SDB in a dedicated severe asthma clinic and a novel sex-specific association of SDB with poor asthma control that is far greater for girls than boys. Within our pediatric severe asthma cohort, SDB identified on the validated PSQ was highly prevalent at 43%. We extend previous health outcome findings to identify a novel sex-dependent relationship between PSQ and ACT where the magnitude of the association was significantly greater for females compared with males. Girls with a positive PSQ scored 9 points lower on the ACT and boys scored 3 points lower, both clinically meaningful differences in asthma control.

This study highlights how common SDB is among children with severe asthma. Forty-three percent of the subjects had SDB, which is on the higher end of the range of previous reports. Pediatric studies have consistently shown that SDB is more common among children with asthma, though with wide variation of prevalence ranging 7.1% to 77.3%(27) due to methodologic differences between studies. Additionally, SDB has been associated with asthma severity(10,14) which may explain the high prevalence in our cohort. To our knowledge, this is the first study to focus exclusively on children with severe asthma. We specifically evaluated this relationship in children with physician-diagnosed severe asthma, followed in a severe asthma clinic and prescribed a high asthma medication step for therapy. Our findings are in line with two pediatric studies which included children with severe asthma but that differ in regard to number of subjects with, and definitions of, severe asthma. In a recent study, Goldstein and colleagues reported the prevalence of SDB based on positive PSQ screen was 25.9% among 263 asthmatic patients and 10.6% among 266 controls(10). They also noted that children with severe asthma had higher odds of SDB with a “dose

effect” but included only 7 children with severe asthma. Ross et al. found an overall prevalence of SDB among children with asthma to be 29.6% and about 50% for severe asthmatics(14). The definition of severe asthma in that study was based on low ACT scores, medication burden, or high exacerbation frequency which may have enriched for a more poorly controlled cohort; only a third of severe asthma subjects met medication step criteria. Our cohort of participants included all children referred to a subspecialty asthma clinical program with high medication step and included those with severe asthma regardless of symptom or exacerbation burden, likely including a broader spectrum of well-controlled and poorly-controlled children with severe asthma. Moreover, this sample reflects the real-world population of children presenting to severe asthma clinical programs for evaluation.

We found a significant association between SDB and asthma control within a unique cohort of children with severe asthma whose disease was relatively poorly controlled and were on average step 5 asthma medication based on NHLBI guidelines. A potential reason for this finding may be a common inflammatory pathway for SDB and asthma(11,28,29). Even after adjusting for important potential confounders in our models the relationship between PSQ and asthma control remained strong. Our findings are consistent with two studies which utilized the PSQ and ACT. In a study of 408 children with mostly mild to moderate asthma the presence of SDB was associated with a 6-fold higher odds of not-well-controlled asthma(15). Another study of 140 children with asthma, asthma and allergic rhinitis or allergic rhinitis alone, the authors found an inverse correlation between PSQ and ACT ($r=-0.356$)(30) which is slightly lower than in our study. However, only 9 patients had poorly controlled asthma and patients were not classified based on asthma severity. We extend these finding from general pediatric asthma cohorts to a well-characterized group of children with pediatric severe asthma. In addition, our repeated measures analysis allowed for variability in the relationship between SDB symptoms and asthma control over time compared to a more restrictive cross-sectional study design.

The finding of a sex-dependent relationship of SDB and asthma control in our study is novel and warrants further discussion. The presence of SDB was associated with significantly worse asthma control for girls compared to boys. We observed a mean difference in ACT score of 9.44 for girls with positive PSQ screens compared to those with negative screens and a mean difference of 3.22 for boys with positive PSQ screens compared to those with negative screens. It is worth highlighting that the differences in ACT scores for both girls and boys are above the clinically minimal important difference of 3 points on the ACT(31). It is known that the prevalence of asthma and OSA differ among males and females depending on age. Asthma is more common among younger boys than girls and then prevalence and severity shift towards females after puberty(17). Both asthma control and lung function may be influenced by sex specific hormones, where male hormones may have a protective effect and female hormones a deleterious effect(32). OSA is more common(33) and more severe(34) among males after puberty whereas in younger children, where tonsil and adenoid size are major determinants of OSA(35), the prevalence is relatively equal. Interestingly, among asthmatic adults, females are more likely than males to have OSA which is opposite of the general population(28). As this relationship of SDB and asthma control among females in our study held true despite adjusting for covariates which could all influence this relationship, it seems plausible that this dynamic relationship is too, driven by hormonal effects. It will be important to replicate this in other asthma and severe asthma cohorts.

Finally, the lack of association between SDB and lung function parameters in our analysis is consistent with most prior studies that have assessed asthmatic children(14,15,30). Only one study has reported a significant relationship between OSA and lung function in 85 asthmatic children in which subjects with asthma and OSA had significantly lower FEV1% predicted compared to those with asthma alone(36). Based on the theory that SDB and asthma share a common inflammatory pathway, we hypothesized that SDB would be associated with worse obstruction on spirometry. However, we did not find a relationship between the PSQ and any lung function outcome. We conducted a post hoc power analysis to determine if statistical power influenced our ability to

observe an effect of SDB on FEV1/FVC, the primary lung function measure, in our cohort. Based on this analysis, the power to detect an observed mean difference in FEV1/FVC of 2% with a standard deviation of 4% is limited; and specifically is 66% (T0, n=37), 31% (T1, n=19), 18% (T2, n=13), and 9% (T3, n=8) (paired sample t-test, $\alpha = 0.05/4 = 0.0125$). Due to small sample size, T4 (n=2) and T5 (n=1) were excluded from this power analysis. It is therefore plausible that the sample was underpowered to detect true statistical differences in FEV1/FVC and related measures of lung function. Alternatively, the absence of an observed association may reflect differential effects of the comorbidity on individual domains of pediatric severe asthma(37), consistent with the pediatric asthma literature that SDB has a specific effect on asthma symptom control without measurably affecting airway caliber.

Asthma and SDB appear to have a bidirectional relationship and can affect or modify disease expression. Asthma increases the likelihood of needing CPAP among children with severe OSA compared to those without asthma(38) and treatment of OSA with adenotonsillectomy can improve asthma outcomes. Children with asthma and OSA who undergo adenotonsillectomy have fewer exacerbations(39) and improved asthma control(40). OSA is a known risk factor for asthma exacerbations among adults with difficult to treat asthma(41) and children with asthma and OSA are at higher risk of longer hospital stay than those with asthma alone(42). These factors highlight the importance of assessing for SDB among children with severe asthma for whom identifying and treating comorbidities is particularly important.

One of our study's main strengths is the rigorous diagnosis of severe asthma which was accomplished in two ways. First, the severe asthma program primarily takes referrals only from pulmonologists and allergists who have sent patients for further evaluation of refractory asthma and second, we cross-validated participants by medication burden and only included those patients who were on high asthma medication step. We also used objective measures with validated questionnaires to assess presence of SDB and asthma control. Many questionnaires rely heavily, and sometimes exclusively, on snoring for diagnosis of SDB which may lead to misclassification since asthmatic patients with OSA may only have snoring as a presenting symptom half of the time(39). Given the potential overlap of symptoms on the PSQ and ACT we specifically assessed the subdomain associations with our main outcomes and found that each was consistent with the overall risk relationship found with the overall PSQ score, and not just the breathing subscale. Therefore, we are confident that the association is not merely due to survey similarities. In addition, the PSQ is highly correlated with OSA based on polysomnography(19). Due to potential confounding of risk factors common to both asthma and SDB, we specifically included obesity(43) and allergic sensitization(44), which are known to be associated with SDB in children, in all models. We also adjusted for LTRA(26) use and adenotonsillectomy(45), which are known treatments for OSA in children. Despite adjusting for these confounders, along with age and sex, the relationships of PSQ and asthma control remained strong. Our use of repeated measures allowed for assessment of the relationship between SDB and asthma control, which both may vary across encounters. There are some limitations as well. Given that our study cohort includes only patients that have been referred because of severe asthma and therefore a selected patient population, this could introduce prevalence-incidence bias which may overestimate the association between SDB and ACT. As this was a single center study with a relatively small sample size, it will be important to replicate these findings in other severe asthma cohorts in the future. While the PSQ is a validated and highly utilized tool in assessing SDB, utilizing a questionnaire may result in misclassification of SDB compared to the gold standard, PSG, which may affect relationships with asthma control. We were careful to include previously identified factors related to SDB and asthma in our analyses. However, we did not have systematic assessments of nasal obstruction or gastroesophageal reflux, which may be considered possible confounders to the association of asthma and SDB. It is also possible that other unmeasured confounders could have affected our study results.

Conclusions

We found that SDB is highly prevalent among children with severe asthma and that there is a strong and important association between SDB and asthma control. Clinicians caring for children with severe asthma should remain highly vigilant in assessing this common comorbidity, especially for those with poorly controlled disease. This appears to be particularly true for females and this relationship warrants further investigation in future studies. Prompt diagnosis and appropriate management of SDB among children with severe asthma may lead to improved asthma control, in addition to other well-known direct effects of treatment of SDB or OSA.

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Author contributions: SG and JMG had full access to all of the data in the study and take responsibility of the integrity of the data and accuracy of the data analysis. SG and JMG contributed substantially to the study design, data analysis and interpretation, and the writing of the manuscript. KFG and CRP contributed substantially to study design, analysis and interpretation of data for the work, to revising the work critically and to final approval of the version to be published. TG, UK, SB, LG contributed substantially to interpretation of data for the work, critical revision for important intellectual content and final approval of the version to be published. NPS, GCS, CT and AGH contributed substantially to data acquisition, interpretation of results, revising the work and final approval of the version to be published.

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References:

1. Zahran HS, Bailey CM, Damon SA, Garbe PL, Breyse PN. Vital Signs: Asthma in Children - United States, 2001-2016. *MMWR Morb Mortal Wkly Rep*. 2018 Feb;67(5):149–55.
2. Zeiger RS, Schatz M, Dalal AA, Qian L, Chen W, Ngor EW, et al. Utilization and Costs of Severe Uncontrolled Asthma in a Managed-Care Setting. *J allergy Clin Immunol Pract*. 2016;4(1):120-9.e3.
3. Chung KF, Wenzel SE, Brozek JL, Bush A, Castro M, Sterk PJ, et al. International ERS/ATS guidelines on definition, evaluation and treatment of severe asthma. *Eur Respir J*. 2014 Feb;43(2):343–73.

4. Engelkes M, Baan EJ, de Ridder MAJ, Svensson E, Prieto-Alhambra D, Lapi F, et al. Incidence, risk factors and re-exacerbation rate of severe asthma exacerbations in a multinational, multidatabase pediatric cohort study. *Pediatr allergy Immunol Off Publ Eur Soc Pediatr Allergy Immunol*. 2020 Jul;31(5):496–505.
5. Chipps BE, Haselkorn T, Paknis B, Ortiz B, Bleecker ER, Kianifard F, et al. More than a decade follow-up in patients with severe or difficult-to-treat asthma: The Epidemiology and Natural History of Asthma: Outcomes and Treatment Regimens (TENOR) II. *J Allergy Clin Immunol*. 2018 May;141(5):1590-1597.e9.
6. Marcus CL, Brooks LJ, Draper KA, Gozal D, Halbower AC, Jones J, et al. Diagnosis and management of childhood obstructive sleep apnea syndrome. *Pediatrics*. 2012 Sep;130(3):576–84.
7. Redline S, Tishler P V, Schluchter M, Aylor J, Clark K, Graham G. Risk factors for sleep-disordered breathing in children. Associations with obesity, race, and respiratory problems. *Am J Respir Crit Care Med*. 1999 May;159(5 Pt 1):1527–32.
8. Tamanyan K, Walter LM, Davey MJ, Nixon GM, Horne RS, Biggs SN. Risk factors for obstructive sleep apnoea in Australian children. *J Paediatr Child Health*. 2016 May;52(5):512–7.
9. Prasad B, Nyenhuis SM, Imayama I, Siddiqi A, Teodorescu M. Asthma and Obstructive Sleep Apnea Overlap: What Has the Evidence Taught Us? *Am J Respir Crit Care Med*. 2020 Jun;201(11):1345–57.
10. Goldstein NA, Aronin C, Kantrowitz B, Hershcopf R, Fishkin S, Lee H, et al. The prevalence of sleep-disordered breathing in children with asthma and its behavioral effects. *Pediatr Pulmonol*. 2015;50(11):1128–36.
11. Kaditis AG, Kalampouka E, Hatzinikolaou S, Lianou L, Papaefthimiou M, Gartagani-Panagiotopoulou P, et al. Associations of tonsillar hypertrophy and snoring with history of wheezing in childhood. *Pediatr Pulmonol*. 2010;45(3):275–80.
12. Zandieh SO, Cespedes A, Ciarleglio A, Bourgeois W, Rapoport DM, Bruzzese J-M. Asthma and

- subjective sleep disordered breathing in a large cohort of urban adolescents. *J Asthma*. 2017 Jan;54(1):62–8.
13. Li L, Xu Z, Jin X, Yan C, Jiang F, Tong S, et al. Sleep-disordered breathing and asthma: evidence from a large multicentric epidemiological study in China. *Respir Res*. 2015 May;16(1):56.
14. Ross KR, Storfer-Isser A, Hart MA, Kibler AM V, Rueschman M, Rosen CL, et al. Sleep-disordered breathing is associated with asthma severity in children. *J Pediatr*. 2012 May;160(5):736–42.
15. Ginis T, Akcan FA, Capanoglu M, Toyran M, Ersu R, Kocabas CN, et al. The frequency of sleep-disordered breathing in children with asthma and its effects on asthma control. *J Asthma*. 2017 May;54(4):403–10.
16. Dooley AA, Jackson JH, Gatti ML, Fanous H, Martinez C, Prue DC, et al. Pediatric sleep questionnaire predicts more severe sleep apnea in children with uncontrolled asthma. *J Asthma*. 2020 Sep;1–8.
17. Dharmage SC, Perret JL, Custovic A. Epidemiology of Asthma in Children and Adults. *Front Pediatr*. 2019;7:246.
18. Expert Panel Report 3 (EPR-3): Guidelines for the Diagnosis and Management of Asthma-Summary Report 2007. *J Allergy Clin Immunol*. 2007 Nov;120(5 Suppl):S94-138.
19. Chervin, Hedger, Dillon, Pituch. Pediatric sleep questionnaire (PSQ): validity and reliability of scales for sleep-disordered breathing, snoring, sleepiness, and behavioral problems. *Sleep Med*. 2000 Feb;1(1):21–32.
20. Liu AH, Zeiger R, Sorkness C, Mahr T, Ostrom N, Burgess S, et al. Development and cross-sectional validation of the Childhood Asthma Control Test. *J Allergy Clin Immunol*. 2007 Apr;119(4):817–25.
21. Nathan RA, Sorkness CA, Kosinski M, Schatz M, Li JT, Marcus P, et al. Development of the asthma control test: a survey for assessing asthma control. *J Allergy Clin Immunol*. 2004 Jan;113(1):59–65.

22. Ehsan Z, Kercksmar CM, Collins J, Simakajornboon N. Validation of the pediatric sleep questionnaire in children with asthma. *Pediatr Pulmonol*. 2017 Mar;52(3):382–9.
23. Miller MR, Hankinson J, Brusasco V, Burgos F, Casaburi R, Coates A, et al. Standardisation of spirometry. *Eur Respir J*. 2005 Aug;26(2):319–38.
24. Quanjer PH, Stanojevic S, Cole TJ, Baur X, Hall GL, Culver BH, et al. Multi-ethnic reference values for spirometry for the 3-95-yr age range: the global lung function 2012 equations. *Eur Respir J*. 2012 Dec;40(6):1324–43.
25. Cnaan A, Laird NM, Slasor P. Mixed Models: Using the General Linear Mixed Model to Analyse Unbalanced Repeated Measures and Longitudinal Data. In: D'Agostino Sr. RB, editor. *Tutorials in Biostatistics* [Internet]. New York (NY): John Wiley & Sons; 2004. p. 127–58. (Wiley Online Books). Available from: [https://doi.org/10.1002/0470023724.ch1c\(i\)](https://doi.org/10.1002/0470023724.ch1c(i))
26. Kheirandish-Gozal L, Bandla HPR, Gozal D. Montelukast for Children with Obstructive Sleep Apnea: Results of a Double-Blind, Randomized, Placebo-Controlled Trial. *Ann Am Thorac Soc*. 2016 Oct;13(10):1736–41.
27. Brockmann PE, Bertrand P, Castro-Rodriguez JA. Influence of asthma on sleep disordered breathing in children: a systematic review. *Sleep Med Rev*. 2014 Oct;18(5):393–7.
28. Teodorescu M, Consens FB, Bria WF, Coffey MJ, McMorris MS, Weatherwax KJ, et al. Predictors of habitual snoring and obstructive sleep apnea risk in patients with asthma. *Chest*. 2009 May;135(5):1125–32.
29. Teodorescu M, Broytman O, Curran-Everett D, Sorkness RL, Crisafi G, Bleecker ER, et al. Obstructive Sleep Apnea Risk, Asthma Burden, and Lower Airway Inflammation in Adults in the Severe Asthma Research Program (SARP) II. *J allergy Clin Immunol Pract*. 2015;3(4):566-75.e1.
30. Perikleous E, Steiropoulos P, Nena E, Iordanidou M, Tzouveleakis A, Chatzimichael A, et al. Association of Asthma and Allergic Rhinitis With Sleep-Disordered Breathing in Childhood. *Front Pediatr*. 2018;6:250.
31. Schatz M, Kosinski M, Yarlal AS, Hanlon J, Watson ME, Jhingran P. The minimally important

- difference of the Asthma Control Test. *J Allergy Clin Immunol*. 2009 Oct;124(4):719-23.e1.
32. DeBoer MD, Phillips BR, Mauger DT, Zein J, Erzurum SC, Fitzpatrick AM, et al. Effects of endogenous sex hormones on lung function and symptom control in adolescents with asthma. *BMC Pulm Med*. 2018 Apr;18(1):58.
33. Spilsbury JC, Storfer-Isser A, Rosen CL, Redline S. Remission and incidence of obstructive sleep apnea from middle childhood to late adolescence. *Sleep*. 2015 Jan;38(1):23–9.
34. Inoshita A, Kasai T, Matsuoka R, Sata N, Shiroshita N, Kawana F, et al. Age-stratified sex differences in polysomnographic findings and pharyngeal morphology among children with obstructive sleep apnea. *J Thorac Dis*. 2018 Dec;10(12):6702–10.
35. Kang K-T, Chou C-H, Weng W-C, Lee P-L, Hsu W-C. Associations between adenotonsillar hypertrophy, age, and obesity in children with obstructive sleep apnea. *PLoS One*. 2013;8(10):e78666.
36. Nguyen-Hoang Y, Nguyen-Thi-Dieu T, Duong-Quy S. Study of the clinical and functional characteristics of asthmatic children with obstructive sleep apnea. *J Asthma Allergy*. 2017;10:285–92.
37. Bossley CJ, Fleming L, Ullmann N, Gupta A, Adams A, Nagakumar P, et al. Assessment of corticosteroid response in pediatric patients with severe asthma by using a multidomain approach. *J Allergy Clin Immunol*. 2016 Aug;138(2):413-420.e6.
38. Kilaikode S, Weiss M, Megalaa R, Perez G, Nino G. Asthma is associated with increased probability of needing CPAP in children with severe obstructive sleep apnea. *Pediatr Pulmonol*. 2019 Mar;54(3):342–7.
39. Kheirandish-Gozal L, Dayyat EA, Eid NS, Morton RL, Gozal D. Obstructive sleep apnea in poorly controlled asthmatic children: effect of adenotonsillectomy. *Pediatr Pulmonol*. 2011 Sep;46(9):913–8.
40. Goldstein NA, Thomas MS, Yu Y, Weaver DE, Watanabe I, Dimopoulos A, et al. The impact of adenotonsillectomy on pediatric asthma. *Pediatr Pulmonol*. 2019 Jan;54(1):20–6.
41. ten Brinke A, Sterk PJ, Masclee AAM, Spinhoven P, Schmidt JT, Zwinderman AH, et al. Risk

factors of frequent exacerbations in difficult-to-treat asthma. *Eur Respir J*. 2005 Nov;26(5):812–8.

42. Shanley LA, Lin H, Flores G. Factors associated with length of stay for pediatric asthma hospitalizations. *J Asthma*. 2015 Jun;52(5):471–7.
43. Andersen IG, Holm J-C, Homoe P. Obstructive sleep apnea in children and adolescents with and without obesity. *Eur Arch Otorhinolaryngol*. 2019 Mar;276(3):871–8.
44. Guo Y, Pan Z, Gao F, Wang Q, Pan S, Xu S, et al. Characteristics and risk factors of children with sleep-disordered breathing in Wuxi, China. *BMC Pediatr*. 2020 Jun;20(1):310.
45. Rp V, Bj H, Chandrasekharan D, Blackshaw H, Lim J, Agm S. Tonsillectomy or adenotonsillectomy versus non-surgical management for obstructive sleep-disordered breathing in children (Review). 2015;

Table 1. Subject characteristics

Subject Characteristics		N = 37 subjects
Age in Years, Mean (SD)		11.8 (4.4)
Sex, N (%)	Male	23 (62.2%)
	Female	14 (37.8%)
Race, N (%)	White	16 (43.2%)
	Black	6 (16.2%)
	Other	10 (27.0%)
	Unknown	5 (13.5%)
BMI Category, N (%)	Normal	17 (45.9%)
	Overweight	8 (21.6%)
	Obese	12 (32.4%)
Previous T&A, N (%)	Yes	15 (40.5%)
	No	22 (59.5%)
Any Sensitization, N (%)		31 (83.8%)
IgE Sensitization, N (%)		13 (35.1%)
Skin Sensitization, N (%)		20 (54.1%)
Medication Step, Mean (SD)		5.2 (0.8)
LTRA (Montelukast), N (%)		29 (78.4%)
Time-Varying Covariates		N = 80 observations
ACT Score, Mean (SD)		18.8 (4.6)
ACT Score (4-11 Years), Mean (SD)		18.9 (4.2)
ACT Score (12+ Years), Mean (SD)		18.7 (5.2)
FEV1% Predicted, Mean (SD)		95.7 (15.3)
FVC% Predicted, Mean (SD)		102.2 (12.6)
FEF25-75% Predicted, Mean (SD)		88.0 (32.7)
FEV1/FVC, Mean (SD)		81.9 (8.0)
PSQ Score, Median (Range)		0.2 (0.0, 0.9)
-Snoring, Median (Range)		0.3 (0, 1.0)
-Daytime Sleepiness, Median (Range)		0.3(0, 1.0)
-Inattention, Median (Range)		0.2 (0, 1.0)
PSQ Screen, N (%)	Positive Screen	34 (42.5%)
	Negative Screen	46 (57.5%)

Abbreviations: BMI – Body mass index; T&A – Adenotonsillectomy; IgE – Immunoglobulin E; LTRA – Leukotriene receptor antagonist; ACT – Asthma control test; FEV1 – Forced expiratory volume in 1 second; FVC – Forced vital capacity; FEF 25-75 – Forced expiratory flow at 25 to 75% of forced vital capacity; PSQ – Pediatric sleep questionnaire (positive screen defined as PSQ score >0.33); Any sensitization defined as specific IgE to aeroallergen ≥ 0.35 or wheel size 3mm greater than saline control on skin prick test for aeroallergen.

Table 2. Adjusted Linear model predicting ACT score from PSQ score

		β	95% CI	P-Value
PSQ Score ^a		-0.21	-0.75, 0.32	0.43
BMI	Obese	0.10	-4.33, 4.54	0.93
	Overweight	-1.31	-5.61, 2.99	0.32
	Underweight	1.20	-1.46, 3.87	0.19
	Normal	0		
Any Sensitization	Yes	0.18	-2.32, 2.69	0.88
	No	0		
Medication Step		-0.15	-1.89, 1.59	0.86
Sex	Female	3.72	-0.85, 8.30	0.11
	Male	0		
Age		-0.22	-0.59, 0.15	0.24
Previous T&A	Yes	1.35	-1.12, 3.82	0.27
	No	0		
PSQ Score * Sex	Female	-1.66	-2.72, -0.61	0.003
	Male	0		

Abbreviations: BMI – Body mass index; T&A – Adenotonsillectomy

PSQ score - The questionnaire is scored by dividing the items answered 'yes' by the total of non-missing items, resulting in a score of 0.0 to 1.0.

Any sensitization defined as specific IgE to aeroallergen ≥ 0.35 or wheel size 3mm greater than saline control on skin prick test for aeroallergen.

^a β coefficient reflects each 0.1 point increase in PSQ score

Table 3. Adjusted linear model predicting ACT score from Snoring, Sleepiness and Behavioral subscales

		Snoring			Sleepiness			Behavior		
		β	95% CI	P-Value	β	95% CI	P-Value	β	95% CI	P-Value
Subscale Score ^a		-0.17	-0.55, 0.20	0.36	-0.02	-0.44, 0.39	0.90	-0.13	-0.46, 0.20	0.42
BMI	Obese	-0.39	-5.16, 4.37	0.76	-0.68	-5.48, 4.11	0.60	-1.03	-5.89, 3.83	0.46
	Overweight	-1.45	-6.30, 3.39	0.33	-1.40	-5.62, 2.82	0.29	-1.62	-6.45, 3.20	0.28
	Underweight	0.74	-1.49, 2.96	0.29	0.43	-1.26, 2.12	0.39	0.37	-1.92, 2.66	0.56
	Normal	0			0			0		
Any Sensitization	Yes	-0.21	-3.02, 2.60	0.88	-0.21	-3.67, 3.26	0.90	1.14	-2.13, 4.41	0.48
	No	0			0			0		
Medication Step		-0.23	-2.43, 1.96	0.83	-0.44	-2.58, 1.71	0.68	-0.72	-2.52, 1.08	0.42
Sex	Female	0.50	-3.80, 4.80	0.81	0.35	-3.05, 3.75	0.84	1.00	-3.37, 5.38	0.64
	Male	0			0			0		
Age		-0.12	-0.55, 0.31	0.59	-0.15	-0.59, 0.30	0.51	-0.29	-0.70, 0.13	0.17
Previous T&A	Yes	0.03	-3.23, 3.29	0.99	-0.48	-3.38, 2.41	0.74	-0.19	-2.86, 2.47	0.88
	No	0			0			0		
Subscale Score * Sex	Female	-0.55	-1.35, 0.25	0.17	-0.31	-0.84, 0.23	0.25	-0.50	-1.16, 0.15	0.13
	Male	0			0			0		

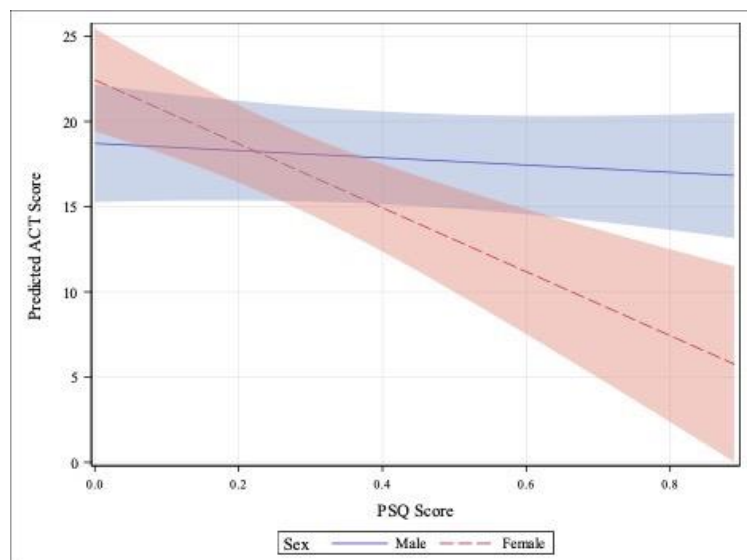
Abbreviations: BMI – Body mass index; T&A – Adenotonsillectomy

Subscale score - The subscale is scored by dividing the items answered 'yes' by the total of non-missing items within the subscale, resulting in a score of 0.0 to 1.0.

Any sensitization defined as specific IgE to aeroallergen ≥ 0.35 or wheel size 3mm greater than saline control on skin prick test for aeroallergen.

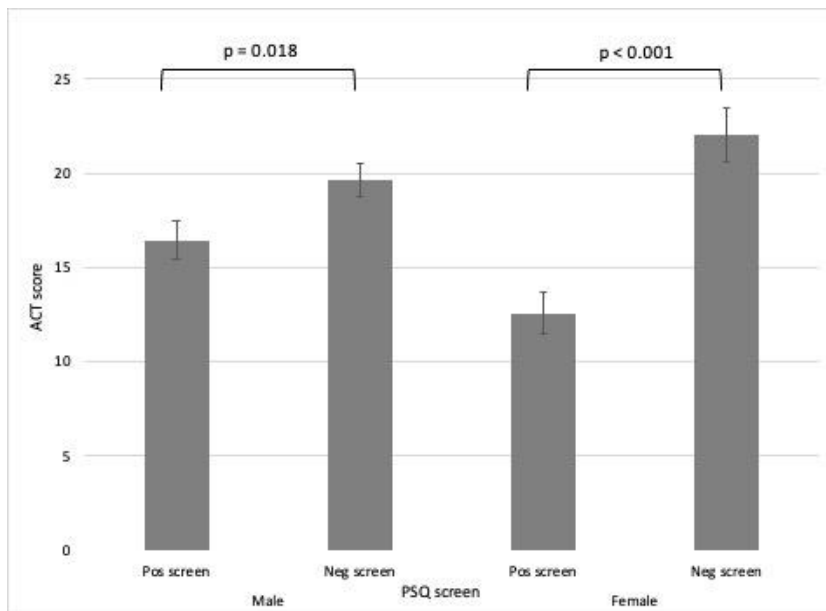
^a β coefficient reflects each 0.1 point increase in PSQ subscale score

Figure 1. Plot of PSQ with ACT with sex interaction



Multivariable linear regression with interaction for sex. PSQ - Pediatric Sleep Questionnaire(19); ACT – Asthma Control Test(21) or childhood Asthma Control Test (cACT)(20). Shading represents the 95% confidence intervals.

Figure 2. Comparison of ACT scores for girls and boys with positive vs negative PSQ screens



Comparing adjusted means of ACT scores for boys and girls with positive or negative PSQ screens. Mean ACT score is 12.59 (1.1) for girls with a positive PSQ screen and mean ACT score is 22.03 (1.44) for girls with a negative PSQ screen. Difference in mean ACT scores for girls is 9.44 (CI 5.54, 13.34, $p < 0.001$). Mean ACT score is 16.46 (1.01) for boys with a positive PSQ screen and mean ACT score is 19.68 (0.89) for boys with a negative PSQ screen. Difference in mean ACT scores for boys is 3.22 (CI 0.56, 5.88, $p = 0.02$). PSQ – Pediatric Sleep Questionnaire(19) (Positive screen defined as PSQ score > 0.33); ACT – Asthma Control Test(21) or childhood Asthma Control Test (cACT)(20).