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The frequency of sleep-disordered breathing in children with asthma and its effects on asthma control

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ABSTRACT

Background: The presence of sleep-disordered breathing (SDB) in children with asthma may cause difficult to control asthma. **Objectives:** The aim of this study was to determine the frequency of SDB in children with asthma, to evaluate its effects on asthma control and to assess the risk factors associated with the presence of SDB. **Methods:** Parents of children who Sleep Questionnaire (PSQ) and the Childhood Asthma Control Test (C-ACT). Asthma control level was assessed according to Global Initiative for Asthma (GINA). Same ear–nose–throat (ENT) specialist evaluated all patients. A 4-point tonsil grading method and adenoid–nasopharynx ratio were used to categorize tonsil and adenoid size, respectively. **Results:** A total of 408 children (275 male, 67.4%) with a mean age of 8.1 ± 3.2 years were included. Nearly 40% of asthmatic children were not-well-controlled according to GINA and 34.6% of all patients had SDB according to PSQ. Multivariate logistic regression analysis revealed that coexistence of SDB [OR: 6.62, 95% CI (4.21–10.41); $p < 0.001$] and tonsillar hypertrophy [OR: 3.47; 95% CI (1.05–11.5); $p < 0.041$] were independent risk factors for not-well-controlled asthma in asthmatic children after other established contributors to asthma control were adjusted. **Conclusions:** Our study showed that SDB is a strong risk factor for not-well-controlled asthma in asthmatic children independent of other confounders. In addition, tonsillar hypertrophy may have a role in the association between SDB and not-well-controlled asthma in childhood.

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Introduction

Asthma is one of the most common chronic disorders in children and its morbidity also remains high despite evidence-based guidelines for evaluation and treatment [1–4]. Achieving optimal control of asthma requires a comprehensive approach that addresses the underlying pathophysiologic disturbances. Thus, in addition to the pharmacologic approach to asthma, one must minimize exposure to asthma triggers and treat the presence of concomitant diseases or conditions, which influence asthma control [5].

One of the potential co-morbid conditions that affect asthma control is pediatric sleep-disordered breathing (SDB). SDB has a broad clinical presentation, ranging from primary snoring to obstructive sleep apnea (OSA) [6]. Adenotonsillar hypertrophy is the most important predisposing factor for SDB in otherwise healthy children [7]. However, the relationship between asthma, SDB and adenotonsillar size is not clear. Recent studies indicate that adenotonsillectomy (AT) leads to significant

improvement in most cases of SDB and asthma outcomes in children [8].

Sleep-disordered breathing and asthma are inflammatory diseases of the upper and lower airway tract respectively, with diurnal and nocturnal symptoms (4). In addition, SDB may be associated with local and systemic inflammation. There is accumulating evidence for etiologic interactions between the two conditions, apart from mere coexistence due to their common occurrence [9]. Studies report higher prevalence of SDB symptoms in asthmatic patients or in relationship with asthma severity [10,11]. Also, SDB may be associated with poorly controlled asthma [12,13]. Moreover, treatment for SDB improves asthma outcomes [8,14].

An association between SDB and asthma has been supported by several large epidemiologic studies worldwide [15,16]. However, there have been few studies estimating the rate of SDB, evaluating its effects on asthma control and further quantifying the relationship between SDB, the

tonsil/adenoid size and the level of asthma control in children with asthma.

The aim of this study was to determine the frequency of SDB in children with asthma, to evaluate its effects on asthma control and to assess the risk factors associated with the presence of SDB. We hypothesized that the presence of SDB in children with asthma is a risk factor for having poorly controlled asthma.

Materials and methods

Study population

Children 4 to 18 years of age who were previously diagnosed with asthma and followed up by our outpatient clinic for at least 1 year between January 2013 and June 2014 were invited to participate in the study. Patients were given the Sleep Disordered Breathing Subscale (SDBS) of Pediatric Sleep Questionnaire (PSQ) [17] and the age-appropriate Asthma Control Test (ACT) (18) before the visit. Thereafter, a brief medical history was obtained, and following the physical examination, pulmonary function tests were performed on patients who were able to carry them out. Their control level of asthma according to Global Initiative for Asthma (GINA) was determined by a pediatric allergist who was blinded to C-ACT scores. Also, ENT specialist examined all patients. Patients with a history of any adenoidectomy/tonsillectomy and additional or coexisting chronic lung diseases (eg, bronchiectasis) and/or other chronic diseases were excluded.

Demographic characteristics, passive smoking exposure, concomitant atopic diseases, aeroallergen sensitization, and peripheral blood eosinophil counts were provided from the regular medical records of the patients. The study was approved by the local ethics committee and written consent was obtained from their parents.

Diagnosis and assessment of asthma control

Asthma was diagnosed based on a history of recurrent wheezing, shortness of breath, cough, and the demonstration of objective signs of reversible airway obstruction as characterized by at least a 12% improvement in FEV₁ following bronchodilator administration or improvement in asthma symptoms after oral/inhaled steroid therapy [19]. The control status of asthma was determined by the pediatric allergist according to GINA including the frequency of the daily symptoms, nocturnal symptoms, use of rescue bronchodilators, degree of limitation in daily activities, and lung functions [19]. Initially, physicians grouped patients as having well controlled, partly controlled, or uncontrolled asthma. Patients with partly controlled and

uncontrolled asthma were then classified as having not-well-controlled asthma.

Childhood Asthma Control Test (C-ACT): The official Turkish version of the C-ACT questionnaire was used [18]. Children and parents answered their respective parts of the test separately, and the sum of their scores was used for analysis.

Study measurements

Anthropometric measures

Anthropometric measures including height, weight were obtained. Height and weight were measured by trained technicians using standardized protocols and calibrated equipment. Height was measured to the nearest 0.5 cm on a standard height board (Seca 213 portable stadiometer, Hamburg, Germany) and weight was determined using a calibrated electronic scale without shoes or coats (Barimed Electronic Body Scale Sc 105, China). Obesity was defined as a BMI >95th percentile for age and sex.

Spirometry

Spirometry was performed pre- and postbronchodilator in study participants who were older and able to comply with American Thoracic Society standards [20]. Study members were seated in the upright position; at least 3 acceptable maneuvers were obtained and the best FEV₁ was used. Testing equipment was calibrated daily to ensure accuracy and precision.

Skin-prick tests

All patients were subjected to skin-prick-tests for common inhalant allergens including animal dander, house dust mite, mixed tree and mixed grass pollen, and mold. Histamine and a negative control solution were also used. A mean wheal diameter greater than 3 mm was considered positive. The patients who had sensitization for any of the inhalant allergens in skin prick test were considered to have allergic sensitization [21].

Pediatric Sleep Questionnaire: Sleep Disordered Breathing Subscale (PSQ-SDBS)

In this study, the Turkish version of Pediatric Sleep Questionnaire (PSQ) was used to assess the presence of sleep-disordered breathing (SDB) [17]. The Pediatric Sleep Questionnaire, Sleep Disordered Breathing Subscale (PSQ-SDBS) is a 22 item parent/proxy questionnaire that assesses specific symptoms of SDB including snoring, breathing problems, mouth breathing, daytime sleepiness, and inattention/hyperactivity. Each item is answered yes = 1, no = 0, or don't know = missing. The number of items answered positively ('yes') is divided by the total items answered to give a proportion that ranges

from 0.0 to 1.0. Scores >0.33 are considered suggestive of high risk of SDB [22].

Assessment of tonsils and adenoids

The same ENT specialists evaluated all children. Tonsil size was assessed using the Brodsky grading scale [23]. The adenoids were graded from 1 to 4 with flexible endoscopy, based on the relationship of the adenoids to the adjacent structures in the rear of nasal cavity [24].

Statistical Analyses

All analyses were performed using SPSS 15 (SPSS Inc, Chicago, IL, USA). Descriptive statistics were calculated for demographic, anthropometric data and questionnaire scores. In addition, the percentage of patients meeting the threshold considered suggestive of SDB on the PSQ-SDBS was calculated. Data are expressed as mean standard deviation (SD) or median [25–75% interquartile range (IQR)]. Categorical variables were compared using chi-square test. Two-way comparisons of numerical values were made using either Student's *t*-test for independent samples or the Mann–Whitney U-test. Multiple logistic regression was performed to predict PSQ score >0.33 with the predictors of SDB, age, gender, obesity, atopy, accompanying allergic rhinitis, passive smoking, blood eosinophilia (eosinophil $>4\%$). The strength of associations between risk factors for uncontrolled asthma and SDB in children with asthma was expressed by odds ratio (ORs) and 95% confidence intervals (CI). The *p* value <0.05 was considered statistically significant.

Results

Patients

Out of 475 children, 408 were included in the study and 67 children were excluded because ENT assessments could not be performed. The mean age of the patients was 8.1 ± 3.2 years and 67.4% of patients were male. Forty-nine children (12.0%) were obese (BM > 95 percentile) and the mean BMI was 17.8 ± 3.7 kg/m². General characteristics of patients are listed in Table 1.

Findings related to SDB

One hundred and forty-one (34.6%) of all patients had SDB according to PSQ –SDB. The median score of PSQ was 0.22 (IQR: 0.13–0.40). According to endoscopic assessment, 89 patients (21.8%) had grade III–V adenoid.

Table 2 shows the differences between asthmatic children with and without SDB. Asthmatic children with SDB

Table 1. Demographic and clinical characteristics of patients with asthma ($n = 408$).

Patients	<i>n</i> (%)
Male	275 (67.4)
Age (y) mean (SD)	8.1 ± 3.2
Duration of follow-up period in years mean (SD)	3.4 ± 2.4
BMI kg/m ² mean (SD)	17.83 ± 3.75
Obese	49 (12)
Concomitant allergic rhinitis	128 (31.4)
Aeroallergen sensitization	154 (37.7)
Passive smoking exposure	161 (39.5)
Hospitalizations due to asthma last year	17 (4.2)
Emergency department visits due to asthma last year	139 (34.1)
C-ACT median (IQR)	21 (19–24)
ACT median (IQR)	23 (19.5–25)
Asthma control status	
Well-controlled	247 (60.5)
Not-well-controlled	161 (39.5)
Asthma therapy	
As needed salbutamol	111 (27.2)
ICS monotherapy	176 (43.1)
LTRA monotherapy	45 (11)
ICS and LTRA	55 (13.5)
ICS and LABA	21 (5.1)
Spirometric parameters, median (IQR)	
FEV ₁ (IQR)	92 (84–100)
FEV ₁ /FVC (IQR)	93.2 (88.7–97.9)
FEF _{25–75} (IQR)	94 (77.2–112)
Adenoid grade III–IV	89 (21.8)
Tonsil grade III–IV	20 (4.9)
The number of patients with positive PSQ (> 0.33)	141 (34.6)
PSQ score median (IQR)	0.22 (0.13–0.40)

Note. Q: Pediatric Sleep Questionnaire; IQR: interquartile range.

were younger than those without SDB (7.7 ± 3.2 vs. 8.3 ± 3.2 years, $p = 0.045$). Coexistence of SDB was significantly more frequent in children with not-well-controlled asthma when compared with those without SDB (68.3% vs. 21.3%, $p < 0.001$).

Enlarged tonsils and adenoids (grade III, IV) were more frequent in asthmatic children with SDB than those without SDB (37.6% vs. 13.5%; 11.3% vs. 1.5%; $p < 0.001$). There was no difference between children with SDB and without SDB in gender, BMI, obesity, concomitant allergic rhinitis, allergic sensitization, passive smoking exposure, blood eosinophilia counts and percent eosinophils ($p > 0.05$).

Findings related to asthma control status

When the patients were divided into two groups according to asthma control status, there was no difference between the groups in gender, BMI, obesity, concomitant allergic rhinitis, allergic sensitization, passive smoking exposure, blood eosinophilia (eosinophil $>4\%$) ($p > 0.05$) (Table 3). The mean age of children with not-well-controlled asthma was younger than those with well-controlled asthma. (7.7 ± 3.2 vs 8.3 ± 3.2 years; $p = 0.033$). Coexistence of SDB according to PSQ scoring was significantly more frequent in children with not-well-controlled asthma when compared with those with

Table 2. General characteristics of patients according to SDB.

Clinical/demographic characteristics	SDB (+) <i>n</i> = 141	SDB (−) <i>n</i> = 267	<i>P</i>
Age (y) mean (SD)	7.7 ± 3.2	8.3 ± 3.2	0.045
Male <i>n</i> (%)	100 (70.9)	175 (65.5)	0.270
BMI (kg/m ²) mean (SD)	18.08 ± 4.38	16.7 ± 3.38	0.807
Obese <i>n</i> (%)	20 (14.2)	29 (10.9)	0.326
Concomitant allergic rhinitis <i>n</i> (%)	48 (34)	80 (30)	0.398
Allergic sensitization <i>n</i> (%)	52 (36.9)	102 (38.2)	0.793
Exposure to smoke <i>n</i> (%)	54 (38.3)	107 (40.1)	0.398
Not-well-controlled asthma <i>n</i> (%)	96 (68.1)	65 (24.3)	<0.001
Positive PSQ > 0.33 <i>n</i> (%)	0.45 (0.40–0.54)	0.18 (0.09–)	<0.001
Adenoid grade III–IV <i>n</i> (%)	53 (37.6)	36 (13.5)	<0.001
Tonsil grade III–IV <i>n</i> (%)	16 (11.3)	4 (1.5)	<0.001
Pulmonary function tests			
FEV ₁ (IQR*)	91.5 (80.5–102)	92 (84–99)	0.430
FEV ₁ /FVC (IQR)	93.9 (88.9–97.9)	92.9 (88.5–97.6)	0.356
FEF _{25–75} (IQR)	90 (74–111)	95.5 (79–115)	0.087
Blood eosinophil (> 4%)	2.2 (1.2–4.6)	2.3 (1–4.1)	0.949
Blood eosinophil counts (IQR)	200 (100–400)	200 (100–300)	0.805

Note. *p*-values in bold are statistically significant. BMI: Body mass index; PSQ: Pediatric Sleep Questionnaire; IQR: Interquartile range.

well-controlled asthma. (59.6% vs 18.2%; $p < 0.001$) The median score of PSQ in children with not-well-controlled asthma was higher than in patients with well-controlled asthma (0.36 vs 0.18; $p < 0.001$). Enlarged tonsils and adenoids (grade III, IV) were more frequent in children with not-well-controlled asthma than those with well-controlled asthma. (31.1% vs. 15.8%; 10% vs. 1.6%, $p < 0.001$) (Table 3).

Multivariate logistic regression analysis revealed that coexistence of SDB [OR: 6.62, 95% CI (4.21–10.41); $p < 0.001$] and tonsillar hypertrophy [OR:3.47; 95% CI (1.05–11.5); $p < 0.041$] were independent risk factors for not-well-controlled asthma in children with asthma when adjusted for the age, sex, obesity, atopy, accompanying allergic rhinitis, passive smoking, blood eosinophilia (Table 4).

Discussion

In our study, nearly 40% of children with asthma were not-well-controlled according to GINA. We found that

34.6% of these patients scored above the threshold for risk of SDB on the Pediatric Sleep Questionnaire (PSQ). Coexistence of SDB according to PSQ scoring was significantly more frequent in children with not-well-controlled asthma when compared with those with well-controlled asthma. We also showed that coexistence of SDB and tonsillar hypertrophy (grade 3 or 4) were risk factors for not-well-controlled asthma in these patients independent of age, gender, obesity, atopy and other confounders. Furthermore, our study revealed that high SDB risk in these patients was associated with 6 times [OR: 6.62, 95% CI (4.21–10.41)] higher odds for not-well-controlled asthma.

Our asthma population is likely representative of children who have unidentified SDB managed in tertiary-care clinic settings. However our study group has a lower rate of obesity and concomitant allergic rhinitis compared to previous studies [11,25]. Rhinitis was not associated with asthma control in our population, likely due to its rigorous management by expert providers, which counteracted its detrimental influence on asthma control.

Table 3. General characteristics of patients according to asthma control status.

	Well controlled <i>n</i> = 247	Not-well-controlled <i>n</i> = 161	<i>p</i>
Age (y) mean (SD)	8.3 ± 3.2	7.7 ± 3.2	0.033
Male gender (%)	160 (65)	111 (70.7)	0.236
BMI kg/m ² mean (SD)	16.7 (15.3–19.1)	16.7 (15.3–20)	0.669
Obese (%)	28 (11.3)	21 (13)	0.604
Concomitant allergic rhinitis (%)	81 (32.8)	47 (29.2)	0.444
Allergic sensitization (%)	98 (39.7)	56 (34.8)	0.319
Exposure to smoke (%)	92 (37.4)	68 (43.3)	0.257
PSQ score median (IQR)	0.18 (0.09–0.27)	0.36 (0.22–0.54)	<0.001
Positive PSQ > 0.33 <i>n</i> (%)	45 (18.2)	96 (59.6)	<0.001
Adenoid grade III–I (%)	39 (15.8)	50 (31.1)	<0.001
Tonsil grade III–IV (%)	4 (1.6)	16 (10)	<0.001
Pulmonary function tests			
FEV ₁ (IQR)	93 (86–100)	90 (79–100.5)	0.032
FEV ₁ /FVC (IQR)	93.2 (88.7–97.2)	92.4 (88.7–97.9)	0.076
FEF _{25–75} (IQR)	98 (82–117)	90 (72–107)	0.003

Note. *p*-values in bold are statistically significant.

Table 4. Risk factor for sleep-disordered breathing in patients with uncontrolled asthma.

	Univariate			Multivariate		
	OR*	CI**	p	OR*	CI**	P
Age (y) mean (SD)	1.06	0.99–1.12	0.062			
Gender male	1.29	0.84–1.9	0.237			
Obese (%)	0.85	0.46–1.56	0.604			
Concomitant allergic rhinitis (%)	1.18	0.76–1.82	0.444			
Patients with allergic sensitization (%)	1.23	0.81–1.86	0.319			
Exposure to smoke (%)	0.79	0.52–1.18	0.257			
Positive PSQ > 0.33 n (%)	6.45	4.11–10.10	<0.001	6.62	4.21–10.41	<0.001
Adenoid grade III–IV (%)	2.40	1.49–3.87	<0.001			
Tonsil grade III–IV (%)	6.70	2.19–20.43	0.001	3.47	1.05–11.50	0.041

Note, p-values in bold are statistically significant. OR*: Odds ratio; CI**: Confidence Interval.

OR are estimated from multiple logistic regression analysis, adjusted by age, sex, obesity, concomitant allergic rhinitis, atopy, SDB, smoking, adenotonsil grade.

Several studies examined the association between SDB and asthma. Calhoun et al. (26) studied 508 children and found that 13.3% of those who had excessive daytime sleepiness also had a diagnosis of asthma. A systematic review of 17 studies involving 45,155 children found that children with asthma had a significantly higher risk of SDB (OR: 1.9, 95% CI: 1.2–2.2) (15). Moreover, in a multicentric cross-sectional epidemiological study involving 22,478 children showed that there is further evidence for the independent association between SDB and asthma (OR = 1.92, 95%CI: 1.34–2.76) [27]. In consistence with the literature, we found a rate of 34.6% that is significantly higher than the 0–5.7% prevalence of SDB in the general childhood population as reported by the American Academy of Pediatrics [28].

Previous studies have demonstrated a relationship between asthma severity and SDB in adults. However, there have been few studies evaluating its effects on asthma control in asthmatic children. A retrospective cross-sectional study showed that children with difficult-to-control asthma can have an increase in the number of episodes of OSA [29]. In another study of 108 asthmatic children aged 4–18 years children with SDB had 3.62-fold increased odds of having severe asthma after adjusting for obesity, race, and sex [11]. Kheirandish-Gozal et al. [14] evaluated 92 children with poorly controlled asthma using polysomnography (PSG), and found that 63% of them had OSA. Due to the above mentioned reasons, the US National Asthma Education and Prevention Program recommends that patients with difficult-to control asthma should be screened for OSA [1]. In our study we also found a 6-fold increased risk for poorly controlled asthma among children with both SDB and asthma.

The relationship between asthma and SDB appears to be bidirectional [30,31]. SDB, especially OSA, may exacerbate asthma by altering oropharyngeal reflexes and increasing negative intrathoracic pressure, increasing cholinergic tone, and promoting bronchoconstriction [32]. A large retrospective cohort study showed that SDB

may even prolong the recovery of children after hospitalization due to asthma [33]. In addition, a recent study demonstrated that asthmatic patients with high OSA risk have increased neutrophil numbers in the induced sputum compared with normal subjects and high OSA risk was significantly associated with worse indices of asthma [34,35]. Therefore, the presence of concomitant SDB in asthmatic patients may further increase the severity of the inflammation in their airways and make their asthma control worse.

On the other hand, many studies showed that asthma may exacerbate SDB disrupting sleep, resulting in sleep deprivation and increasing the frequency of apneas in snorers [32]. Also, poorly controlled asthma might accentuate the hypoxemia in SDB and vice versa; intermittent nocturnal hypoxemia in children with OSA could initiate and maintain upper and lower airway inflammation [10,36]. Therefore, this bidirectional association may be explained due to common risk factors that promote airway inflammation, sharing a common pathogenetic pathway. This is referred as the “one-airway” hypothesis, suggesting that upper airway inflammation and intermittent hypoxia from obstruction may influence the expression and severity of disease of the lower respiratory tract [37]. Lower and upper airway inflammation is related to atopy and incremented cysteinyl leukotriene activity, and can lead to decreased lower airway caliber and increased nasal resistance and pharyngeal collapsibility predisposing to wheeze and snore during sleep [38].

Adenotonsillar hypertrophy has been identified as the major pathophysiological cause of upper airway obstruction in pediatric OSA [28]. The peak incidence of pediatric OSA is between 2 and 8 years of age, when the tonsils and adenoids are largest in relation to the size of the underlying airway [7]. In our study, asthmatic children with SDB were younger (mean age: 7.7 vs 8.3 years) than those without SDB and nearly half of these patients had adenotonsillar hypertrophy (grade III, IV), findings consistent with literature.

While the size of the adenoids and tonsils plays a significant role in the severity of OSA, the role of adenotonsillar hypertrophy in asthmatic children with SDB is not clear. In a study reported by Kaditis et al. [39] children with history of wheezing had more frequently tonsillar hypertrophy than those without wheezing. Authors suggested that the inflammatory processes in the lower airways might promote the proliferation of lymphadenoid tissues in the upper airway. A recent study also demonstrated that increased cysteinyl leukotrienes activity is present in tonsils excised from children with OSA, seeming to promote tonsillar cell proliferation [40,41]. These results indicate that recurrent airway infections preceding asthma may be associated with the enlargement of tonsillar tissue, which is a part of the airway.

There is a debate whether adenotonsillar hypertrophy affects the severity of asthma. Busino et al. [42] reported reductions in the number of hospital visits, and use of systemic steroids and asthma medications in a cohort of 93 asthmatic children, 1 year after AT. Similar results were reported by Saito et al. [43] in a smaller cohort of asthmatic children who underwent surgical excision of tonsils and adenoids. Kheirandish-Gozal et al. [14] demonstrated that the annual frequency of acute asthmatic exacerbations in children post-AT decreased significantly compared to those without AT. In addition, Bhattacharjee et al. [44] reported that AT proved to be beneficial in patients with asthma, as their acute exacerbations were reduced by 30.2% compared to a relative 2% reduction in children with asthma who did not undergo surgery. These studies support the idea that detection and treatment of adenotonsillar tissue hypertrophy may serve as an important strategy for improving asthma control.

Obesity is a well-established risk factor for asthma in adults and has an important role in promoting the development SDB [4,45]. Moreover, available data suggest that SDB is associated with uncontrolled asthma in children with asthma [12,46]. Of note, this effect in some studies has been reported to be independent of obesity [11,47]. In our study we also found that coexistence of SDB and tonsillar hypertrophy (grade 3 or 4) were risk factors for not-well-controlled asthma in asthmatic children independent of obesity, findings consistent with the literature.

The strengths of our study are the large number of patients, its single-center design and the fact that the same ENT specialist evaluated the patients. There are also some limitations. Firstly, this study is questionnaire-based. No objective measurement, such as attended polysomnography, was performed to diagnose SDB. This approach has been common in the OSA and OSA/asthma literature, where the expense of technology and personnel time would have made carrying out such a large study cost prohibitive. Another drawback was the direction of

the cause-effect relationship between SDB and asthma or whether there is a true cause-effect relationship, due to the limitation of cross-sectional data in drawing causality conclusion. Last, the relationship between SDB and asthma severity was not evaluated in our cross-sectional study due to the limited information obtained from the questionnaires.

In conclusion, this study of a population of children with asthma found an association between SDB and risk of not-well-controlled asthma, as incorporated in the current guidelines, independent of obesity and other confounders. In addition, tonsil hypertrophy may be a contributor to not-well-controlled asthma especially in younger patients. Our findings support existing guideline recommendations based on expert consensus to screen children with difficult-to-control asthma for SDB. Further studies that incorporate objective assessments of SDB, which allow differentiating its pathogenic features, may deepen our understanding of these mechanisms and may offer new interventions for a phenotype that responds poorly to current standard therapies.

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