

# Sleep-disordered breathing in children with asthma: a systematic review on the impact of treatment

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**Background:** The objective was to perform a systematic review in order to describe the relationship between asthma and sleep-disordered breathing (SDB) in children, especially regarding the impact of treatment and management.

**Methods:** We performed an electronic search in MEDLINE, EMBASE, and LILACS database. Study inclusion criteria were the following: 1) studies that examined the relationship between asthma/wheezing and SDB/obstructive sleep apnea (OSA); and 2) studies conducted in children <18 years of age. Primary outcomes were the prevalence of asthma and SDB, the tests used for diagnosis, and the influence of their treatment and management.

**Results:** One thousand and twenty studies were identified, among which 32 were selected (n=143,343 children; 51% males; age [mean ± standard deviation] 8.4±2.5 years). Most studies (n=26) diagnosed SDB using questionnaires or clinical history. Nine studies performed a sleep study for diagnosing OSA. The diagnosis of asthma was based on clinical history (n=16), previous medical diagnosis (n=4), questionnaires (n=12), and spirometry (n=5). Children with asthma were more likely to develop habitual snoring and OSA, and children with SDB were more likely to develop asthma. Moreover, asthma was associated with more severe OSA, and the presence of SDB was associated with severe asthma. Treatment of SDB with adenotonsillectomy was associated with significant asthma improvement.

**Conclusion:** The relationship between asthma and SDB appears to be bidirectional, and adenotonsillectomy appears to improve asthma control. Future trials on how asthma treatment could impact on SDB are needed.

**Keywords:** obstructive sleep apnea, wheezing, children, Asthma, sleep-disordered breathing

## Introduction

Asthma is known to be one of the most common chronic diseases in childhood.<sup>1</sup> Asthma most frequently starts early in life and has a variable clinical evolution and different phenotypes which may progress or remit over time.<sup>2</sup> Around half of preschool wheezers become asymptomatic by school age irrespective of treatment.<sup>3</sup> However, asthma symptoms (eg, sleep disturbance and cough at night) may persist, often lifelong, especially among atopic children and in more severe cases. The impact of asthma on the quality of life and health cost of patients is very high.<sup>4,5</sup> Therefore, appropriate asthma management may have a major impact on the quality of life of patients and their families, as well as on public health outcomes.<sup>3</sup>

On the other hand, sleep-disordered breathing (SDB) is also a prevalent disease in children.<sup>6</sup> Similar to asthma, SDB has a broad clinical presentation, ranging from primary snoring to obstructive sleep apnea (OSA).<sup>7</sup> The cardinal symptom of SDB

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is habitual snoring (ie, snoring in more than three nights weekly). Similar to asthma, symptoms of SDB may remain unrecognized for a long time.<sup>8</sup> Treatment of SDB, for example, adenotonsillectomy (AT), often resolves snoring and concomitant symptoms. However, a large multicenter study in asthmatic children<sup>9</sup> showed that SDB may persist even after AT.

Furthermore, asthma and SDB may coexist, as they are both inflammatory diseases of the lower and upper airway tract, respectively.<sup>10</sup> Similar symptoms during the night may also lead to confusion in clinical history. The similarities and parallel rise of prevalence of both diseases in the last decades arise the question that if there is a relationship between asthma and SDB.<sup>11</sup>

Therefore, we launched the present systematic review, in order to describe the relationship between asthma and SDB, especially regarding the impact of treatment and management of these diseases.

## Methods

### Search and selection criteria

We identified all published studies in MEDLINE, EMBASE, and LILACS (up to November 2015) database, using following keywords: “(asthma OR wheezing) AND (sleep) AND (obstructive sleep apnea OR sleep disordered breathing) AND (children OR child OR adolescent)”. Studies published solely in abstract form were excluded because methods and results could not be fully analyzed. To be included, studies had to meet all the following criteria: case-control, cohort, or intervention studies that examined the relationship between asthma/wheezing and SDB/OSA in subjects aged <18 years of age; and all kinds of treatments were accepted (especially AT, considered the first-line treatment for SDB). No language restriction for the studies was applied. We excluded studies in which participants had any other chronic underlying disease such as craniofacial abnormalities, neurological disorders, dysmorphic genetic disorders or metabolic disorders, or other chronic respiratory illness different from asthma/wheezing. All references were managed by reference manager software (Mendeley® 1.14; Elsevier Inc, Philadelphia, PA, USA).

### Target conditions

Childhood asthma was accepted as a clinical diagnosis (ie, “chronic inflammatory disease of the lower respiratory tract with recurrent or persistent wheezing”).<sup>3</sup> Most of the studies usually diagnosed asthma by questionnaire. On the other hand, SDB was defined according to the International Classification of Sleep Disorders-third edition<sup>12</sup> (ie, habitual

snoring, upper airway resistance syndrome, and OSA). It was accepted that SDB diagnosis was made clinically or through questionnaire or polysomnography (PSG).

Our primary outcomes were 1) prevalence of asthma and SDB (using different tests for their diagnoses), 2) asthma as a risk factor for SDB and vice versa, and 3) the influence of their management.

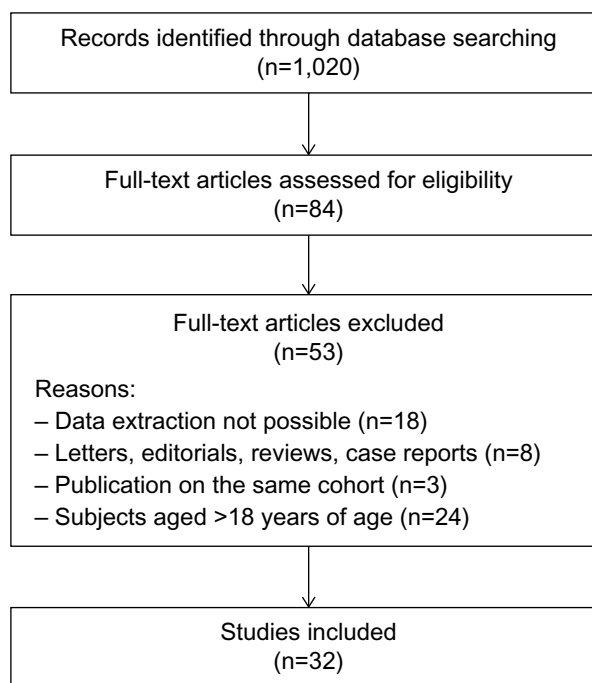
## Data extraction and assessment of risk of bias

Titles, abstracts, and citations were independently analyzed by two authors (TS and PEB). Based on the full-text form, all studies were evaluated for inclusion/exclusion criteria, type of intervention, population included, study design, and outcomes. After obtaining full reports about potentially relevant trials, eligibility was assessed. Disagreements were discussed and resolved by consensus.

## Results

### Studies description

In total, 1,020 (n) studies were identified. Among those, 32 (N) studies<sup>9,10,13-42</sup> met the inclusion criteria (Figure 1). The studies included a total of 143,343 children (51.3% were males) of age (mean  $\pm$  standard deviation)  $8.4 \pm 2.5$  years. Fourteen studies came from USA,<sup>9,22,24,25,29,31,34-36,38-42</sup> nine from Asia,<sup>13,14,18,20,28,30,32,33,37</sup> seven from Europe,<sup>10,15-17,19,23,26</sup>



**Figure 1** Study selection process of the included/excluded studies.

and two from Oceania.<sup>21,27</sup> Almost all studies diagnosed SDB using questionnaires (ie, the Pediatric Sleep Questionnaire [PSQ]),<sup>18,29,32,33</sup> clinical history,<sup>10,13–17,19–23,26–28,35</sup> or previous medical diagnosis.<sup>36,38,39,42</sup> Eight studies performed PSG,<sup>9,24,30,31,34,37,40,41</sup> and only one, a home cardiorespiratory polygraphy.<sup>25</sup> On the other hand, the diagnosis of asthma was based on clinical history exclusively in 16 studies,<sup>9,10,15,17,19,23–26,30–32,35,39,40,42</sup> previous medical asthma diagnosis in four studies,<sup>20,29,36,38</sup> general questionnaires in six studies,<sup>14,15,17,18,21,33</sup> and the International Study of Asthma and Allergies in Childhood<sup>43</sup> questionnaire in six studies.<sup>13,16,22,27,28,34</sup> Only five studies performed spirometry for assessing asthma.<sup>16,22,25,34,41</sup>

## Studies on association and/or risk of SDB in asthmatics

Table 1 shows the studies that investigated the association between asthma and SDB.<sup>9,10,16,21,24,25,27–32,34,35,37</sup> The aim of eleven studies was to describe the prevalence and risk factors of SDB, among which we were able to find data on asthma.<sup>13–15,17,18,20,22,26,33,40,41</sup> Table 2 gives the result of them.

Overall, the studies showed that children with asthma/wheeze were more likely to have a higher risk for habitual snoring and OSA than those without asthma. For example, a study in Belgian children<sup>28</sup> reported that wheezing was related to an increased risk of snoring (odds ratio [OR] =2.8, 95% CI 1.1–2.6). A study on Austrian children<sup>27</sup> showed a strong and significant association between SDB symptoms and wheeze/asthma, especially between snoring (OR =5.4, 95% CI 3.6–8.1) and snorting (OR =5.3, 95% CI 2.6–10.8) with wheezing in the last 12 months. In another study, children with wheezing had a significantly higher prevalence of snoring, and more nocturnal awakenings than non-wheezing children (46% vs 26% and 30% vs 20%, respectively); after multiple logistic regression analysis, wheeze remained as a risk factor for difficulties falling asleep (OR =2.0, 95% CI 1.0–4.0), restless sleep (OR =5.0, 95% CI 2.2–11.1), daytime sleepiness (OR =3.8, 95% CI 1.8–8.0), and tiredness (OR =5.1, 95% CI 2.2–12.1).<sup>16</sup> Asthma was also associated with tonsillar hypertrophy. In a prospective cohort of 442 Greek children who consulted the emergency department (ED) and pulmonology clinic, history of wheezing was significantly associated with the presence of tonsillar hypertrophy and snoring (OR =2.36, 95% CI 1.46–3.79 and OR =1.88, 95% CI 1.24–2.86, respectively).<sup>10</sup> When questionnaires (eg, PSQ) were used,<sup>29</sup> the prevalence of a positive test (>0.33) was significantly higher in asthmatic children than in non-asthmatic children (25.9% vs 10.6%,

$P < 0.001$ , respectively; OR =2.94, 95% CI 1.82–4.75). Interestingly, the effect of asthma was “dose dependent”, as children with more severe asthma had increased OR for snoring and a positive PSQ.

Studies using PSG to determine SDB showed similar results. A study in 50 African-American children<sup>34</sup> concluded that poorly controlled asthma was associated with more severe OSA; a history of lifetime asthma increased the apnea–hypopnea index (AHI) by 8.8 ( $P < 0.005$ ) in the PSG. A study<sup>24</sup> that investigated parameters of sleep fragmentation by PSG concluded that asthmatic snorer’s children had worse sleep quality as judged by indices of sleep fragmentation than those without asthma. Moreover, a study of OSA diagnosed by PSG in a sleep center in the USA<sup>31</sup> reported that maximal %SpO<sub>2</sub> rapid-eye-movement (REM) desaturation, REM–obstructive AHI, and prevalence of REM-related OSA were significantly increased in asthmatic children with OSA compared to subjects with only OSA, showing that asthma is associated with REM-related breathing abnormalities in children with moderate–severe OSA. A cross-sectional study<sup>37</sup> that investigated sleep quality by PSG in children aged 6–12 years found that asthmatics had significantly longer sleep latency and less slow-wave sleep compared with non-asthmatics; also, asthmatics (either with or without OSA) had significantly more leg movement than non-asthmatics. This study supports the hypothesis that nonobese asthmatic children, with or without OSA, may exhibit poor sleep quality as compared with nonobese non-asthmatic children. There is a known seasonal variability described in SDB.<sup>44</sup> In our studies, asthma and atopy did not explain this variation. Greenfeld et al<sup>30</sup> in a review on 2,178 PSG of children and adolescents referred for suspected SDB, with a prevalence of asthma of 18%, found that the mean obstructive AHI in the winter was significantly higher compared to the summer ( $9.1 \pm 9.6$  vs  $7.5 \pm 7.0$ ,  $P = 0.01$ ; Cohen  $d = 0.19$ ), particularly in children younger than the age of 5 years ( $10.2 \pm 10.5$  vs  $7.9 \pm 7.3$ ,  $P = 0.008$ ; Cohen  $d = 0.25$ ), and asthma/atopy had no significant effect on seasonal variability.

In contrast to the studies described, only one study showed that a history of asthma decreased the likelihood of OSA.<sup>24</sup> That was a retrospective review of patients referred to a sleep laboratory for an overnight PSG, and it compared the definition of OSA as an AHI >2 or >5. No significant differences in OSA prevalence or severity for asthmatics compared to non-asthmatics were found. The authors of that study explained these findings due to a possible referral bias; since parents of asthmatics would be more vigilant regarding night-time symptoms, they may have mistaken night noises

**Table 1** Association of asthma and SDB

Author (year)	Country	N	Male	Mean age (years)	Asthma diagnosis	SDB diagnosis	Prevalence of asthma (%)	Prevalence of SDB (%)
Lu et al (2003) <sup>21</sup>	Australia	974	516	Not given	Questionnaire	Snoring for +4 nights/week	28	10.5
Valery et al (2004) <sup>27</sup>	Australia	1,650	Not given	8.5	ISAAC questions	Snoring	15.6	14.2
Sulit et al (2005) <sup>25</sup>	USA	788	393	9.5	History or spirometry	Portable polygraphy AHI >5	13.3	20.1
Desager et al (2005) <sup>16</sup>	Belgium	1,234	Not given	9.6	ISAAC questions, spirometry	Snoring	8.8	28
Verhulst et al (2007) <sup>28</sup>	Sri Lanka	652	432	8.4	ISAAC questions	Snoring	14	32.6
Ramagopal et al (2008) <sup>24</sup>	USA	236	147	7.2	History	PSG AHI >2	31.4	41.1
Ramagopal et al (2009) <sup>34</sup>	USA	50	32	9.3	ISAAC questions + spirometry	PSG AHI >2	44	100
Kaditis et al (2010) <sup>10</sup>	Greece	442	241	7.6	History	Habitual snoring	47.5	28.5
Bhattacharjee et al (2010) <sup>9</sup>	USA	578	355	6.9	History	PSG	29.6	100
Ross et al (2012) <sup>35</sup>	USA	108	73	9.1	History	Snoring for + 3 nights/week + $\geq 3$ desaturations >3%/hour	100	29.6
Greenfeld et al (2013) <sup>30</sup>	Israel	2,178	1,415	4.9	History	PSG OAH1 >1	18	100
Gutierrez et al (2013) <sup>31</sup>	USA	141	85	6.1	History	PSG OAH1 >1.5	43.9	100
Goldstein et al (2015) <sup>29</sup>	USA	529	298	5.8	Previous diagnosis	PSQ >0.33	50	18.2
Teng et al (2014) <sup>37</sup>	Taiwan	102	56	9.4	History + methacholine test	PSG AHI >5	50	50
Li et al (2015) <sup>32</sup>	People's Republic of China	22,478	10,227	9	History	CSHQ	3.5	12
Mean prevalence							33.2	41.8

**Abbreviations:** SDB, sleep-disordered breathing; ISAAC, International Study on Asthma and Allergies in Childhood; AHI, apnea-hypopnea index; PSG, polysomnography; OAH1, obstructive apnea-hypopnea index; PSQ, Pediatric Sleep Questionnaire; CSHQ, Children's Sleep Habits Questionnaire.

(asthma symptoms and noisy breathing) for snoring, having an “over”-report of night symptoms.

## Studies on association and/or risk of asthma in children with SDB

Children with SDB were more likely to develop asthma/wheeze than those without asthma/wheeze. Lu et al<sup>21</sup> reported that 42.2% of children who snored had asthma (OR =2.03, 95% CI 1.34–3.10). There was also a highly significant association between snoring and nocturnal cough (OR =3.68, 95% CI 2.41–5.63). In that study, nocturnal cough was strongly associated with asthma; in the asthmatic group, the prevalence of nocturnal cough was significantly higher among children who snored vs children who did not snore (86.1% vs 52.6%, respectively,  $P=0.001$ ; OR =5.56, 95% CI 2.26–13.67). Sulit et al<sup>25</sup> in a US community-based cohort study of 788

participants (aged 8–11 years) found that children with SDB had nearly twice the odds of wheeze compared with those without SDB (OR =1.89, 95% CI 1.26–2.85). Recently, a large Chinese epidemiological study<sup>32</sup> ( $n=20,672$  children, mean age  $9.0\pm 1.61$  years) concluded that habitual snoring and OSA remained a statistically significant predictor of asthma (OR =1.28, 95% CI 1.01–1.62 and OR =1.92, 95% CI 1.34–2.76, respectively). In a prospective study on 108 asthmatic patients (mean age  $9.1\pm 3.4$  years), children with SDB had more than three times the risk for having severe asthma at follow-up (OR =3.62, 95% CI 1.26–10.4).<sup>35</sup>

Only three studies that analyzed risk factors for asthma development investigated SDB.<sup>19,23,36</sup> Those results are given in the following. In the study of Hoskyns et al,<sup>19</sup> the relationship between night cough and other indices of asthma severity was studied in 21 children with clinically stable asthma and

**Table 2** Prevalence of SDB and asthma as a risk factor

Author (year)	Country	N	Male	Mean age (years)	Asthma diagnosis	SDB diagnosis	SDB prevalence (%) – asthma vs controls	OR (95% CI)
Redline et al (1999) <sup>41</sup>	USA	399	194	10.9	History + spirometry	PSG AHI >10	11.8 vs 28	3.83 (1.39–10.55)
Corbo et al (2001) <sup>15</sup>	Italy	2,209	722	12.5	Previous diagnosis or questionnaire	Snoring “often”	12.2 vs 7.6	1.79 (0.97–3.33)
Chng et al (2004) <sup>14</sup>	Singapore	11,114	5,212	5.8	Questionnaire	Snoring for > 3 nights/ week	8.6 vs 5.1	1.83 (1.50–2.24)
Urschitz (2004) <sup>26</sup>	Germany	1,144	585	9.6	History	“Frequently” or “always” snoring	7.1 vs 9.8	0.68 (0.24–1.94)
Ersu et al (2004) <sup>17</sup>	Turkey	2,147	1,074	8.5	History, questionnaire	“Often” or “always” snoring	9.1 vs 7.6	1.25 (0.75–2.09)
Bidad et al (2006) <sup>13</sup>	Iran	2,900	1,200	14	ISAAC questions	Snoring for ≥ 3 nights/ week	10.7 vs 7.1	1.64 (1.05–2.58)
Marshall et al (2007) <sup>22</sup>	USA	219	107	5	ISAAC questions, spirometry	Snoring for ≥ 3 nights/ week	29.1 vs 16.9	2.71 (1.42–5.16)
Li et al (2010) <sup>20</sup>	People’s Republic of China	20,152	9,890	9	Previous diagnosis	“Frequently” or “almost always” snoring	17.8 vs 10.5	2.09 (1.72–2.54)
Kheirandish-Gozal et al (2011) <sup>40</sup>	USA	92	49	6.6	History	PSG AHI 5/hour TST	63.0 vs 4.0	40.9 (12.9–144.1)
Fadzil et al (2012) <sup>18</sup>	Malaysia	550	285	8.5	Questionnaire	PSQ >0.33	29.2 vs 13.5	2.62 (1.34–5.15)
Ng et al (2014) <sup>33</sup>	People’s Republic of China	2,005	1,173	15.3	Questionnaire	Snoring for ≥ 6 nights/ week	17.9 vs 9.7	2.18 (1.25–3.71)

**Abbreviations:** SDB, sleep-disordered breathing; OR, odds ratio; CI, confidence interval; PSG, polysomnography; AHI, apnea-hypopnea index; ISAAC, International Study on Asthma and Allergies in Childhood; TST, total sleep time; PSQ, Pediatric Sleep Questionnaire.

persistent night cough; there was an association of SDB with asthma. A study aimed to develop an asthma prediction tool for preschoolers with wheeze or cough; snoring resulted as a predictive factor for asthma 5 years later (77.4% vs 69.6%, asthma vs no asthma,  $P=0.006$ ).<sup>23</sup> Finally, a retrospective cohort study<sup>36</sup> of asthmatic children ( $n=25,900$ ) who required hospitalization showed a higher risk of hospital length of stay >2 days (OR =2.3, 95% CI 1.8–2.9) for those with previous diagnosis of OSA (1.4% of the group) than those without OSA. The authors of that study suggested that children with OSA and asthma experience a higher severity of nocturnal hypoxemia and hypoventilation; therefore, it may possibly take longer time to return to an acceptable respiratory status after an asthma crisis.

## Studies on therapy

Table 3 shows the results from the studies analyzing treatment’s impact. No studies of asthma treatment that influence SDB were found. On the other hand, five studies investigated the effect of AT in asthma control.<sup>9,38–40,42</sup> Bhattacharjee et al<sup>38</sup> conducted a large study of asthmatic children ( $n=13,506$ ) who underwent AT, and the surgical procedure was associated with significant reductions in acute asthmatic exacerbations

(30.2%, 95% CI 25.6%–34.3%;  $P<0.0001$ ), acute status asthmaticus (37.9%, 95% CI 29.2%–45.6%;  $P<0.0001$ ), asthma-related ED visits (25.6%, 95% CI 16.9%–33.3%;  $P<0.0001$ ), and asthma-related hospitalizations (35.8%, 95% CI 19.6%–48.7%;  $P=0.02$ ). Moreover, AT was associated with significant reductions in most asthma prescription refills, including bronchodilators, inhaled corticosteroids, leukotriene receptor antagonists (LTRAs), and systemic corticosteroids. Kheirandish-Gozal et al<sup>40</sup> conducted a prospective study on 92 poorly controlled asthma children (aged 3–10 years) with a mean frequency of acute asthmatic exacerbations of  $3.4\pm 0.4$ /year. Overnight PSG revealed the presence of OSA (AHI >5/hour of total sleep time) in 63.0% of patients (OR =40.9, 95% CI 12.9–144.1) compared to the maximal estimated prevalence of OSA in a non-asthmatic population. From this group, information at 1-year follow-up was available for 35 asthmatics with OSA after AT, and for 24 without OSA. The annual frequency of acute asthmatic exacerbations in the post-AT subgroup significantly decreased (from  $4.1\pm 1.3$  to  $1.8\pm 1.4$ /year,  $P<0.0001$ ), with no changes in the non-OSA group. Similar favorable improvement occurred after AT in the frequency of  $\beta$ -agonist rescue use or in asthma symptom scores. Busino et al<sup>39</sup> reviewed

**Table 3** Studies on impact of treatment of SDB and asthma

Author (year)	Country	N	Male	Mean age (years)	Asthma diagnosis	SDB diagnosis	Type of study	Main results
Bhattacharjee et al (2010) <sup>9</sup>	USA	578	355	6.9	History	PSG	Retrospective study: 578 children with OSA undergoing AT studied with PSG preoperatively and postoperatively	AT resulted in a significant AHI reduction from 18.2±21.4 to 4.1±6.4/hour total sleep time. 27.2% had complete resolution of OSA; asthma was a modest contributing factor for post-AT AHI
Bhattacharjee et al (2014) <sup>38</sup>	USA	40,518	22,320	7.7	ICD-9-CM	ICD-9-CM	Retrospective study: 13,506 children with asthma with AT compared to 27,012 matched children with asthma without AT	AT associated with reductions in AAE (30.2%), ASA (37.9%), ARERs (25.6%), ARHs (35.8%), bronchodilators (16.7%), inhaled corticosteroids (21.5%), leukotriene receptor antagonists (13.4%), and systemic corticosteroids (23.7%)
Busino et al (2010) <sup>39</sup>	USA	465	263	5.9	Clinical history	Previous diagnosis	Retrospective study: 465 children with AT, 16.6% asthmatics	AT associated with reductions of asthma therapies (eg, corticosteroids) and improvements in ACT scores
Kheirandish-Gozal et al (2011) <sup>40</sup>	USA	92	49	6.6	Clinical history	PSG AHI >5/hour TST	Prospective study: 92 children with poorly controlled asthma, 63% with OSA and AT	AT associated with reduction in AAE (4.1±1.3 to 1.8±1.4/year), β-agonist rescue use (4.3±1.8 to 2.1±1.5/week), and ACT scores (3.1±1.9 to 1.9±1.7)
Levin et al (2014) <sup>42</sup>	USA	130	55	6.1	Clinical history	Previous diagnosis	Longitudinal observational study: 130 children with AT (66 asthmatics and 64 controls)	AT associated in children with asthma with improvement in ACT scores (22–25) and decrease in emergency department/urgent care visits (1.88–0.4), oral corticosteroid courses (1.11–0.21), missed school days due to asthma (3.86–2.0), total missed parental work days due to illness (2.79–1.13), and circulating chitinase activity (0.4 nmol/L/mL/h)

**Abbreviations:** SDB, sleep-disordered breathing; PSG, polysomnography; OSA, obstructive sleep apnea; AT, adenotonsillectomy; AHI, apnea-hypopnea index; ICD-9-CM, International Classification of Diseases, Ninth Revision, Clinical Modification; AAE, acute asthmatic exacerbation; ASA, acute status asthmaticus; ARERs, asthma-related emergency room visits; ARHs, asthma-related hospitalizations; ACT, asthma control test; TST total sleep time.

retrospectively 560 children who underwent AT; 16.6% were asthmatics, 97.8% of this group underwent AT for OSA. AT was associated with significant reductions in asthma therapies, including corticosteroids, and with improvements in asthma control test scores.

## Discussion

In this systematic review of 32 studies, we found a mean prevalence of asthma of 33.2%, and of SDB 41.8%. Asthma is estimated to affect 7.1 million US children under the age of 18 years.<sup>1</sup> The prevalence of asthma in children varies through different countries. In the studies we reviewed, the asthma prevalence ranged from 8.8% in Belgium<sup>16</sup> to 28% in Australia.<sup>21</sup>

On the other hand, the prevalence of snoring is estimated to be 3.2%–12.1%, and the prevalence of OSA ranges from 0.7% to 10.3%.<sup>45</sup> When parents were asked about habitual snoring (usually three or four times per week), the prevalence reported in the studies of this systematic review was 6% in a group of Singapore children,<sup>14</sup> 7% in Turkey,<sup>17</sup> 10.1% in Germany,<sup>26</sup> 12% in the People's Republic of China,<sup>20,21,32,33</sup> 14.6% in Australia,<sup>22</sup> and 28% in Belgium.<sup>16</sup> When standardized questionnaires were used (eg, the PSQ), the prevalence of SDB symptoms was 14.9% in Malaysia.<sup>18</sup> However, PSG is known to be the gold standard for SDB but has important limitations due to availability and cost. This may explain the reason why only a few studies in our systematic review used it for SDB and OSA diagnosis. Redline et al<sup>41</sup> reported the

prevalence of SDB in a general population of children in the USA to be 1.6% and 10.3% by using a PSG diagnostic criteria of AHI >10 and 5, respectively.

In order to discuss the current evidence of an association between SDB/OSA and asthma, it is important to mention the definitions of sleep-related breathing disorders. Childhood SDB is a spectrum of abnormal breathing patterns during sleep that ranges from primary snoring to OSA. OSA in children is an SDB characterized by prolonged partial upper airway obstruction and/or intermittent complete obstruction that affects normal ventilation during sleep.<sup>46</sup> OSA is considered the most severe disease within the spectrum of SDB. It is associated with symptoms including habitual snoring, sleep difficulties, and daytime neurobehavioral problems and has the potential to result in serious long-term consequences, such as cognitive deficits, academic failure, cardiovascular complications, and metabolic syndrome.

There is a growing body of evidence of an association between SDB and asthma, supported by most of the studies described in our review. Our previous systematic review on prevalence of asthma and SDB including 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).<sup>47</sup> However, the relationship between asthma and SDB appears bidirectional. SDB, especially OSA, may exacerbate asthma by altering oropharyngeal reflexes and increasing negative intrathoracic pressure, increasing cholinergic tone, and promoting bronchoconstriction.<sup>14</sup> Studies like the one by Pescatore et al reinforce that SDB may even predict asthma development.<sup>23</sup> In addition, a large retrospective cohort showed that SDB may even prolong the recovery of children after hospitalization due to asthma.<sup>36</sup>

On the other hand, we found many studies showing that asthma may exacerbate SDB disrupting sleep, resulting in sleep deprivation and increasing the frequency of apneas in snorers.<sup>14</sup> 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.<sup>48,49</sup>

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.<sup>50,51</sup> 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,<sup>52–54</sup>

predisposing to wheeze and snore during sleep. Also, adenotonsillar hypertrophy increases upper airway resistance and is the first cause of SDB in children. It seems that asthma is associated with tonsillar hypertrophy,<sup>10</sup> and children with history of wheezing have larger tonsils than subjects without wheezing. Hypertrophic tonsils could mediate at least in part the known association between asthma and obstructive SDB in childhood. This is reinforced by two studies,<sup>55,56</sup> demonstrating that increased cysteinyl leukotrienes activity is present in tonsils excised from children with OSA, seeming to promote tonsillar cell proliferation.

In addition to what we already knew concerning the possible relationship of asthma and SDB,<sup>49</sup> we aimed to analyze in the present systematic review how treatment impacts on both diseases. We found several studies addressing how SDB treatment impacts on asthma. However, no studies were found so far that compared how asthma treatment impacts on SDB.

The first-line treatment for OSA in children is AT (if the patient has demonstrated adenotonsillar hypertrophy and does not have contraindications to surgery).<sup>15,46</sup> In the past years, there has been increasing interest in studying the effect of AT, as first-line SDB/OSA treatment, and improvement of childhood asthma.<sup>38–40</sup> Kheirandish-Gozal et al<sup>40</sup> demonstrated that the annual frequency of acute asthmatic exacerbations in children post-AT decreased significantly compared to those without AT. Based on this interesting study, one may hypothesize that upper airway inflammatory processes may play a role in lower airway inflammation and asthma, and conversely, lower airway inflammatory disease may promote adenotonsillar proliferation, and therefore increase the propensity for OSA.<sup>40</sup> Therefore, treatment of OSA may benefit control of asthma. In a study of Bhattacharjee et al<sup>38</sup> on 13,506 children with asthma, only 6.2% of those who underwent AT and 0.6% of those who did not undergo the surgical procedure had some form of evaluation for SDB as determined by searching for specific sleep diagnostic testing. This finding shows that most patients are operated without having a sleep diagnosis, even if they are scheduled for a surgical procedure. Considering that asthmatics might have a higher prevalence and severity of OSA, a formal sleep study should be considered case by case, especially before surgical procedures. In another multicenter study by Bhattacharjee et al<sup>9</sup> (n=578 children), the presence of asthma was a significant factor for persisting with OSA after AT, and the study underlined the importance of a post-AT PSG in children with asthma undergoing AT. A longitudinal observational study<sup>42</sup> on 130 children (aged 2–18 years), both with and without asthma, undergoing AT showed that asthma control test scores and chitinase activity

in the circulation (biomarkers of airway inflammation, such as upper airway and asthmatic disease) measured at time of surgery and at 6-month follow-up had a significant improvement. A significant improvement in asthma control test scores after 6 months and decrease in several asthma-related outcomes (eg, rate of ED visits, oral corticosteroid courses, missed school days due to asthma, and total missed parental work days) and in circulating chitinase activity (median decrease 0.4 nmol/L/mL/h,  $P < 0.01$ ) suggest that AT also may modulate airway inflammation in asthma. These studies support the idea that detection and treatment of adenotonsillar tissue hypertrophy may serve as an important strategy for improving asthma control. However, randomized controlled studies are needed to confirm this.

There are certainly other treatment for OSA (ie, nasal corticosteroids sprays<sup>57,58</sup> and LTRAs).<sup>59</sup> Dental devices or oral appliance therapy, surgical procedures, and continuous positive airway pressure may be considered as second-line treatment. Most of them have specific indications for patients with specific chronic diseases (eg, neuromuscular disorders). We did not find eligible studies of these treatments in patients with asthma and SDB.

The present study, as usual in this kind of systematic reviews, has limitations that need to be addressed. We made the highest effort in finding most available studies on the topic. However, there are some interesting studies that might have escaped our search strategy. Prevalence of asthma and SDB was originally calculated only in some studies; we recalculated it from the data of several other included studies. Hence, this may have biased this outcome, as some studies were not intended as epidemiologic studies for prevalence estimation. In most included studies, asthma and SDB were among a long list of factors analyzed, but only few studies aimed to analyze specifically the relationship between them. Hence, a data extraction bias is also possible. Future studies specifically designed for demonstrating the bidirectional relationship between both diseases may help to confirm our results. As mentioned earlier, only studies that analyzed AT as treatment for SDB were found. Therefore, we do not know if other therapeutic options for SDB, for example, nasal corticosteroids, LTRAs, or maxillary interventions, may have some influence on asthma.

## Conclusion

The present systematic review shows that asthma and SDB are both very frequent conditions in childhood, and may have a bidirectional relationship. Treatment of SDB seems to impact positively on the clinical evolution of asthma in children. It is yet to be proven whether or not optimizing asthma control could prevent consequences of SDB.

## Disclosure

The authors report no conflicts of interest in this work.

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