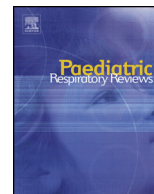




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Review

Relation between asthma and sleep disordered breathing in children: is the association causal?

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EDUCATIONAL AIMS

The reader will be able:

- To understand the concept of causality association between asthma and sleep disordered breathing (SDB) in children using the most widely accepted epidemiologic criteria for causality, the nine Bradford Hill criteria.

ARTICLE INFO

Keywords:

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SUMMARY

Over the last few decades, asthma and sleep disordered breathing (SDB) in children have experienced similar increases in prevalence, and have both been shown to have airway inflammation, leading investigators to postulate an association between asthma and SDB. However, whether this relationship is causal or not needs to be proven. In this manuscript, we use the most widely accepted epidemiologic criteria for causality, the Bradford Hill criteria, to test step-by-step whether the relation between asthma and SDB in children is causal or not. We found studies supporting 8 of the 9 criteria (strength, consistency, specificity, biological gradient, coherence and biological plausibility, experiment, and analogy) for association between asthma and SDB. However, we did not find any study showing temporality or directionality between asthma and SDB. Therefore, establishing a causal association between asthma and SDB is not yet possible.

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INTRODUCTION

Asthma is among one of the most prevalent chronic diseases in children [1]. The prevalence of asthma has rapidly increased worldwide over the past decades [2]. Similarly, snoring and sleep disordered breathing (SDB) have also increased, reaching, in some places, a similar prevalence to asthma [3]. There seems to be a

similar inflammatory component to both diseases, as similar mediators have been measured in asthma and SDB [4]. For example, the inflammatory mediators, cysteinyl leukotrienes, have been identified in asthma [5] and also in SDB [6]. Furthermore, the presence of cysteinyl leukotrienes seems to play an important role in the development of adenotonsillar hyperplasia, which is one of the leading factors for developing SDB [7]. Moreover, asthma and SDB can be treated to some degree with topical (inhaled or nasal) corticosteroids and leukotriene antagonists (LTRA). Also, the similar increase in prevalence and the shared common inflammation of the airway have led investigators to postulate an association between asthma and SDB. In previous studies on the relationship between asthma and SDB, our group showed that there was a consistent link between both diseases [8,9]. However, whether the relation between asthma and SDB is causal or not needs to be proven.

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Abbreviations: AHI, apnoea hypopnea index; BMI, body mass index; IL, interleukin; LMI, leg movement index; LOS, length of stay; LTRA, leukotriene antagonist; OSA, obstructive sleep apnoea; OAH, obstructive apnoea–hypopnea index; OR, odds ratio; NREM, non-rapid eye movement; PSG, polysomnography; REM, rapid eye movement; SDB, sleep disordered breathing; TNF, tumour necrosis factor.

METHODS AND RESULTS

In this study, we used the most common epidemiology criteria for causality, the Bradford Hill criteria [10] (Table 1), as further explicated by Lucas and McMichael [11]. Step-by-step we tested whether the relation between asthma and SDB is really causal. In the following we show a step by step analysis of these nine criteria:

1. Strength: “Strong associations were more likely to be causal than weak associations [11].” In this case, one of the studies with the highest odds was published by Redline et al. [12]. They examined risk factors for SDB, defined by apnoea hypopnea index (AHI) >10 on polysomnography (PSG) in 399 children (2–18 years of age). After adjusting for obesity and African American race, asthmatic children had a higher risk for SDB than controls (OR = 3.83 [1.39–10.55]). Kaditis et al. [13] studied 442 children (aged 7.6 ± 3.6 [SD] years) and reported a significantly higher prevalence of tonsillar hypertrophy among children with wheezing vs. without wheezing (28.1% vs. 14.2%, $p < 0.001$). After adjusting for covariants, tonsillar hypertrophy and history of wheezing were independently associated with snoring (OR = 1.58 [1.01–2.45], $p = 0.044$; and OR = 2.08 [1.27–3.43], $p = 0.004$, respectively). Therefore, the strength criterion was filled.
2. Consistency: Bradford Hill “felt more confidence in a causal explanation for an association if the same answer had been achieved in a variety of different situations,” e.g., “prospectively and retrospectively and in different populations” [11]. In this case, a systematic review with meta-analysis published by our group on 17 studies, $n = 45155$ children (mean 8.5 ± 2.5 years old) reported a higher prevalence of SDB in children with asthma vs. those without asthma (23.9% vs. 16.7%, $p < 0.0001$) [9]. Asthma seemed to be a consistent and independent risk factor for SDB (OR = 1.9 [1.69–2.18], $p < 0.0001$, with low heterogeneity (I^2 index = 39%). In a sensitivity analysis of studies using only studies with PSG or polygraphy (2 studies, $n = 957$ children), the risk of SDB in children with asthma was increased (OR = 1.49 [1.04–2.13], $p = 0.03$, with high heterogeneity ($I^2 = 77\%$). Therefore, the consistency criterion was filled.
3. Specificity: “This criterion is often stated to mean that any exposure may give rise to only a single outcome. While this may be true for some infectious diseases, . . . Bradford Hill recognized that disease may have more than one cause and that one-to-one relationships are not frequent. However, if an association is limited to specific groups with a particular environmental exposure or is greatly increased in these groups, then the case for a causal association is strengthened” [11]. In this regard, at least one study has shown that OSA characteristics are different in the presence of asthma. Gutierrez et al. [14] hypothesized that asthmatic children have a distinct obstructive sleep apnoea (OSA) phenotype relative to children with OSA alone. In a retrospective, cross-sectional analysis of 141 children aged 2–12 years with OSA diagnosed by PSG, they found that baseline respiratory parameters, obstructive apnoea–hypopnea index (OAHl) severity, and oxygenation during non-rapid eye movement (NREM) sleep were unaffected by the presence of asthma

in children with OSA. In contrast, maximal % REM SpO₂ desaturation, REM OAHl and the prevalence of REM-related OSA in children with moderate to severe OSA were significantly increased in asthmatic children with OSA compared to subjects with OSA alone. The presence of REM-related OSA in asthmatics was unaffected by rhinitis or atopy status. Multivariate analysis revealed that the association between asthma and REM-related OSA parameters was independent (OR = 10.4, $p = 0.009$) of asthma control, body mass index (BMI), age, and gender, thus showing a link between asthma and OSA that was independent of some of the known risk factors for OSA. This would suggest that the specificity criterion was fulfilled. As a caveat, however, it should be noted that asthmatics (even without OSA) may be more likely to desaturate during REM sleep than non-asthmatics [15]. As obstructive hypopneas are only scored if they are associated with arousal or a 3% desaturation, the sleep-related desaturation in asthmatics may lead to increased scoring of these subtle events and a resultant overestimation of SDB. Therefore, it may be more accurate to state that further research is needed before it can be agreed that the specificity criterion was totally fulfilled.

4. Temporality: This “is a necessary criterion for a causal association between an exposure and an outcome, that is, the exposure must precede the outcome” [11]. We did not find any published studies related to temporality. This is an important task for future studies involving cohorts, as the development of asthma and SDB seem to be parallel, based to the age span in which both diseases typically emerge (i.e., preschoolers).
5. Biological gradient: “It seems logical that the likelihood of a causal association is increased if a biological gradient or dose-response curve can be demonstrated [11].” Ross et al. [16] evaluated 108 subjects (mean age 9.1 ± 3.4 years) and reported that SDB (defined as habitual loud snoring and ≥ 3 desaturations/hour of > 3% during overnight oximetry) was less common among mild to moderate asthmatics vs. severe asthmatics (20.3% vs. 55.2%, $p < 0.001$, OR = 4.85 [1.94–12.10]). After adjusting for obesity, race and sex, children with SDB had a 3.62-fold increased odds of having severe asthma at follow-up (95% CI, 1.26–10.40). Obesity was not associated with asthma severity. Similarly, Ramagopal et al. [17] performed a prospective study of 50 African American children (aged 9.3 ± 3.4 years) with OSA diagnosed by PSG and reported that the AHI was higher in subjects with poorly controlled asthma than in good control/no asthma (AHI 13.67 ± 15.4 vs. 5.56 ± 6.26 , $p = 0.039$). Furthermore, in a parsimonious ordinary least squares model controlling for sleep efficiency and age, a history of lifetime asthma increased the AHI by 8.8 ($p < 0.05$). Recently, Li et al. [18] reported in a meta-analysis that SDB in children had an OR for asthma of 1.58 [1.35–1.80], $p < 0.001$, with high heterogeneity ($I^2 = 70.2\%$), while for severe asthma was 1.92 [1.48–2.35], $p < 0.001$, without heterogeneity ($I^2 = 0\%$). Shanley et al. [19] studied a cohort 25,900 patients (2–17 years old) with a primary asthma diagnosis who were discharged from 42 hospitals in the USA, with a mean length of stay (LOS) of 1.9 days. Using generalized estimating equation logistic regression analyses to identify factors associated with LOS for asthma hospitalizations, after adjusting for severity of illness, they found that OSA had the highest odds (OR 2.3 [1.8–2.9]) of asthma LOS >2 days; and this was higher than older age, obesity, complex chronic conditions, winter admissions, female sex and weekend admissions. Biological gradient criterion was fulfilled.
6. Plausibility: According to Bradford Hill “this is a feature I am convinced we cannot demand. What is biologically plausible depends upon the biological knowledge of the day” [11]. This point is developed together with point #7, below.
7. Coherence: “Coherence and biological plausibility share a requirement that the cause-and-effect interpretation of an

Table 1
Bradford Hill's criteria of causality.¹⁰

1.	Strength
2.	Consistency
3.	Specificity
4.	Temporality
5.	Biological gradient
6.	Plausibility
7.	Coherence
8.	Experiment
9.	Analogy

association should fit with the known facts of the natural history and biology of the disease” [11]. In this sense, the two main drugs used for the chronic control of asthma: LTRA (e.g., montelukast) and inhaled corticosteroids, have also been used to treat SDB, which supports the coherence and biological plausibility between asthma and SDB. Goldbart et al. [6] in a small study of 24 children with mild SDB, completed an open-label intervention study for 16 weeks with daily montelukast therapy. Montelukast treatment induced significant reductions in adenoid size (by lateral neck X-ray) and in the obstructive AHI (although the difference was small: decline in AHI from 3.0 ± 0.22 to 2.0 ± 0.3 , $p = 0.017$), which were absent in 16 children with SDB who did not receive treatment with montelukast. In a parallel study, adenoid and tonsillar tissues from children with OSA or recurrent throat infections were subjected to quantitative polymerase chain reaction, immunohistochemistry, and Western blotting for gene and protein expression of leukotriene receptors LT1-R and LT2-R, and for concentrations of LTB4 and LTC4/D4/E4. LT1-R and LT2-R mRNA were similarly abundant in adenoidal tissue, but increased LT1-R and LT2-R protein expression and higher levels of LTB4 and LTC4/D4/E4 emerged in children with OSA. Recently, a prospective, randomized, double blind, controlled trial of PSG-diagnosed OSA in 64 children aged 2–10 years who were treated with either montelukast (4 or 5 mg/daily) or placebo for 16 weeks showed that the AHI decreased from 9.2 ± 4.1 to 4.2 ± 2.8 ($p < 0.0001$) in montelukast-treated children while the AHI did not change in children receiving placebo [20]. Whole tissue cell cultures of adenoids and tonsils provide a useful approach for in vitro assessment of therapeutic efficacy of corticosteroids in the management of lymphoid hypertrophy that underlies OSA in children. Kheirandish-Gozal et al. [21] hypothesised that topical corticosteroids would reduce cellular proliferation and the production of pro-inflammatory cytokines in a tonsil/adenoid mixed-cell culture system. Dissociated tonsils or adenoids harvested intra-operatively from children with OSA (diagnosed by PSG) were cultured in control medium or after stimulation with lipopolysaccharide and concanavalin A, and incubated with dexamethasone, fluticasone and budesonide. Proliferation and apoptosis were assessed, and supernatants were assayed for the cytokines tumour necrosis factor (TNF)- α , interleukin (IL)-6 and IL-8. Tonsillar and adenoidal proliferation increased in the stimulated condition compared with the control condition ($1,976 \pm 133$ vs. 404 ± 69 counts min^{-1}). All three corticosteroid preparations reduced cellular proliferation rates and increased cellular apoptosis. Furthermore, TNF- α , IL-8 and IL-6 concentrations in the supernatant were increased in the stimulated condition, and markedly reduced by all corticosteroids. Kheirandish-Gozal & Gozal [22] performed a double-blind, randomized, crossover trial in 62 children with mild OSA (by PSG) of intranasal budesonide or placebo for 6 weeks, followed by an additional 6-week treatment in the alternative treatment arm after allowing for a 2-week washout period. They reported a significant improvements in AHI and adenoid size (by X-ray) among the children who completed the treatment phase compared to those who received placebo in the initial arm. Furthermore, discontinuation of treatment for 8 weeks revealed a sustained duration of the initial treatment effect.

Currently, the primary treatment for childhood OSA is adenotonsillectomy [23]. Several studies have shown an improvement in asthma after adenotonsillectomy for OSA in children with coexistent conditions. Kheirandish-Gozal et al. [24] prospectively studied 92 children (aged 3–10 years) with poorly controlled asthma (3.4 ± 0.4 acute asthma exacerbations per year) referred for an overnight sleep study. Adenotonsillectomy was performed in 58 patients (AHI $> 5/\text{hr}$), and information at 1-year follow-up was available for 35 of these children. The annual

frequency of acute asthma exacerbations, rescue inhaled corticosteroids and asthma symptoms in this subgroup decreased compared to no changes in the group without OSA. Piessens et al. [25] retrospectively evaluated the use of respiratory medications the year before and the year after adenotonsillectomy in 11,114 subjects (aged 0–15 years). Of the 4,654 children who received at least one prescription for respiratory medication the year before surgery, there was a median 32% decrease in medication use. Of note, however, these respiratory medications included antihistamines and mucolytics in addition to bronchodilators and inhaled corticosteroids. Recently, Bhattacharjee et al. [26] evaluated asthma outcomes based on a database of 13,506 children with asthma who underwent adenotonsillectomy. Asthma outcomes during the year preceding adenotonsillectomy were compared to those during the year following adenotonsillectomy. In addition, 27,012 age-, sex- and geographically-matched children with asthma without adenotonsillectomy were included to examine asthma outcomes among children without known adenotonsillar morbidity. Comparing the year following adenotonsillectomy to the year prior, adenotonsillectomy was associated with significant reductions in acute asthma exacerbations (30.2%), acute status asthmaticus episodes (37.9%), asthma-related emergency room visits (25.6%) and asthma-related hospitalizations (35.8%). Moreover, adenotonsillectomy was associated with significant reductions in most asthma prescription refills, including bronchodilators (16.7%), inhaled corticosteroids (21.5%), LTRA (13.4%) and systemic corticosteroids (23.7%). In contrast, there were no significant reductions in these outcomes in children with asthma who did not undergo adenotonsillectomy over an overlapping follow-up period. Several years prior, Bhattacharjee et al. [27] reported that, in 578 children, adenotonsillectomy resulted in a significant reduction in AHI from 18.2 ± 21.4 to 4.1 ± 6.4 ($p < 0.001$), but that only 157 children (27.2%) had complete resolution of OSA (i.e., post-adenotonsillectomy AHI < 1). Age ($p < 0.001$) and BMI z-score ($p < 0.001$) emerged as the two principal factors contributing to post-adenotonsillectomy AHI, with modest contributions by the presence of asthma ($p = 0.006$) and magnitude of pre-adenotonsillectomy AHI ($p < 0.015$) among non-obese children. Coherence and biological plausibility criteria were fulfilled.

8. Experiment: “With overtones of Koch’s postulates, this criterion offered, in Bradford Hill’s view, the strongest support of a causal interpretation. Laboratory experimentation and human randomized clinical trials allow the manipulation of exposures in a controlled environment unlike human observational or epidemiological studies. The randomized clinical trial design aims to control bias and confounding in human studies in order to allow estimation of the true association between exposure and outcome” [11]. Recently, Marcus et al. [28] in the first randomized controlled trial of adenotonsillectomy for childhood OSA (the CHAT study), assigned 464 children (aged 5–9 years) with OSA (by PSG) to early adenotonsillectomy vs. a strategy of 6 months of watchful waiting. There were 18 adverse events related to asthma in the 203 children in the watchful waiting group, compared to 3 events in the 194 children in the surgical group ($p = 0.002$). Therefore, at least this study fulfils the experiment criterion.
9. Analogy: “Bradford Hill and other epidemiologists recognized that the notion of analogy can be taken to impractical extremes, and may depend on the imagination of scientist to see analogies. Clear-cut analogies, however, may add to the weight of evidence for otherwise weak associations... Bradford Hill did not prescribe these criteria as rules that must be fulfilled before an association can be judged as causal, but as ways of examining whether cause and effect is the reasonable inference” [11]. If we were considering wheezing as analogous to asthma, the study

done by Redline et al. [12] reported that after adjusting for obesity and race, children with occasional wheezing and persistent wheezing had a higher risk (OR = 3.29 [1.2–8.9] and OR = 7.45 [2.0–27.4], respectively) for SDB than controls. Therefore, we can consider having fulfilled this criterion.

LIMITATIONS

It is important to consider that most studies conducted so far aiming to assess the association between asthma and SDB have been conducted without PSG, hence lacking the gold standard for SDB diagnosis. Only a few studies specifically compared OSA diagnosed with PSG and the presence of asthma. Nevertheless, the association was still present in those studies that used PSG [8,9]. Additionally, the diagnosis of asthma was often based on questionnaires, and included children younger than 5 years of age, where several wheezing phenotypes exist.

CONCLUSION

The association between asthma and SDB in children is well established, with several studies showing an increased risk for SDB in children with asthma. The similar inflammatory basis and, therefore, similar treatment options, present an interesting fact for the clinician. Although several Bradford-Hill criteria were fulfilled, there is still a lack of evidence concerning the temporality criterion. Therefore, final proof of a causal association between asthma and SDB is not yet possible. Also according to the well-known epidemiologist Mervyn Susser [29], the two most important criteria for an association to be considered causal are temporality: causal factor (X) must precede the effect (Y), and directionality: X leads to Y. Future cohort studies testing temporality and directionality between asthma and SDB are needed. However, even if the relationship between asthma and SDB is an association and not causal, we consider it important from a clinical point of view: when managing asthma in a child, always look for the presence of SDB, and vice versa, in order to improve both conditions.

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DIRECTIONS FOR FUTURE RESEARCH

- Future studies testing temporality and directionality between asthma and SDB need to be done.

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