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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

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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 SBD 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.

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 (SBD) 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 SBD [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 SBD 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; OAHI, obstructive apnoea–hypopnea index; OR, odds ratio; NREM, non-rapid eye movement; PSG, polysomnography; REM, rapid eye movement; SBD, sleep disordered breathing; TNF, tumour necrosis factor.

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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 SBD 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 (OAHI) 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 SpO_2 desaturation, REM OAHI 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