The Causal Association Between Obstructive Sleep Apnea and Child-Onset Asthma Come to Light: A Mendelian Randomization Study

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Purpose: Obstructive sleep apnea (OSA) had been associated with asthma in observational studies, but the effect of OSA on the onset of asthma in childhood or adulthood remains unclear, and the causal inferences have not been confirmed. This study aims to investigate the potential causal association between OSA with asthma, including different age-of-onset subtypes, providing reliable basis for the clinical treatment of OSA and asthma.

Patients and Methods: Causality between OSA and asthma was assessed using a two-sample bi-directional Mendelian randomization (MR) analysis. OSA data were obtained from the FinnGen consortium R9, while asthma and its subtypes (adult-onset asthma, child-onset asthma, and moderate-to-severe asthma) were sourced from the IEU OpenGWAS project. The inverse-variance weighted (IVW) method was chosen as the primary analysis and was complemented by various sensitivity analyses. The MR-PRESSO outlier test was employed to systematically identify and remove outlier variants, mitigating heterogeneity and potential effects of horizontal pleiotropy.

Results: The MR analyses provided evidence of genetically predicted OSA having a promoting effect on child-onset asthma (OR, 1.49; 95% CI, 1.05–2.11; P=0.025) and moderate-to-severe asthma (OR, 1.03; 95% CI, 1.00–1.06; P=0.046). However, no causal association between OSA with asthma and adult-onset asthma was observed.

Conclusion: Our study revealed a causal association between OSA and child asthma, but not in adults. Moderate-to-severe asthma may have a potential promoting effect on OSA. These findings underscore the importance of age-specific considerations in managing asthma and suggests the need for personalized approaches in clinical practice.

Keywords: asthma, obstructive sleep apnea, Mendelian randomization, genetic

Introduction

Obstructive sleep apnea (OSA) and asthma are widespread respiratory conditions that have significant health implications. OSA is a sleep-related breathing disorder characterized by recurrent episodes of complete or partial upper airway obstruction, leading to intermittent hypoxia, hypercapnia, or arousals during sleep. On the other hand, asthma is distinguished by chronic airway inflammation and bronchial hyperresponsiveness, and it affects individuals of all ages. The prevalence of asthma of around 10% in children and adolescents, and 6–7% in adults, thus impacting approximately 300 million people worldwide.
Although there has been extensive individual research into asthma and OSA, their potential relationship remains a topic of ongoing investigation. Several studies have attempted to establish a link between the two diseases. For instance, a 2008–2009 national survey analysis found the prevalence of asthma with OSA to be 2.7 times higher than that without OSA. A recent meta-analysis has shown that difficult-to-control asthma was independently associated with OSA.

While previous studies have suggested a possible association between asthma and OSA, the impact of OSA on the onset of asthma in childhood or adulthood is unclear. Moreover, current evidence is largely limited to observational studies, which complicates establishing a cause-and-effect relationship. Tao and colleagues’ study shown that compared to those without OSA, allergic rhinitis, chronic tonsillitis and adenoid hypertrophy were independent risk factors for OSA in children with asthma. Moreover, studies had shown that the asthma symptoms can be relieved after treating OSA, especially in patients with uncontrolled asthma. A recent study has demonstrated that frequent asthma in childhood is associated with OSA in middle-age. All of these indicated the potential relationship between OSA and asthma. However, Jose et al aimed to explore the causality between OSA and asthma, but the result was inconclusive. Thus, it is crucial to understand the potential causal association between these two conditions as a step towards improving therapeutic approaches and patient outcomes. In recent years, the use of Mendelian randomization (MR) analysis as a method to assess causality in observational studies by leveraging genetic variants as instrumental variables has gained prominence. This analytical approach enables the investigation of causal associations between exposures and outcomes, providing a more reliable estimate of causality compared to traditional observational studies. Therefore, we sought to examine the causal influence of asthma on the development of OSA and vice versa by employing a bi-directional MR approach, considering potential confounders and genetic predisposition as well. Furthermore, we aimed to investigate whether the causal association between asthma and OSA varies between childhood and adult asthma, which could aid in tailoring treatment strategies for specific age groups.

By unraveling the causal pathways between asthma and OSA, our findings can potentially contribute to clinical practice, early prevention strategies, and treatment interventions for both conditions. Ultimately, such knowledge has the potential to enhance health outcomes and improve quality of life for individuals affected by these respiratory conditions.

**Materials and Methods**

**Study Design**

The MR design was summarized in Figure 1. Single nucleotide polymorphisms (SNPs) were used as the instrumental variables (IVs) in the MR analysis to estimate the causal association between exposure and development of disease. The IVs must base on three critical assumptions: (1) IVs must be strongly associated with exposure; (2) IVs are not related to confounding factors; (3) IVs affect outcome risk only through the risk factor rather than any other ways.

**Data Source**

All the datasets used are publicly available. The genome-wide association study (GWAS) summary-level data for OSA comes were obtained from the FinnGen biobank (www.finngen.fi/en), which contains information from 41,704 patients and 335,573 controls. The database integrates imputed genotype data from Finnish biobanks, and Finnish health registries. For asthma and its subtypes, namely adult-onset asthma and child-onset asthma, the datasets were extracted from UK Biobank (UKBB, www.ukbiobank.ac.uk). The asthma GWAS data comprised 56,167 asthma patients and 352,255 controls. The adult-onset asthma dataset, defined as asthma onset after the age of 26, contained 22,296 cases and 347,481 controls. The child-onset asthma dataset, defined as asthma onset before the age of 12, included 9676 cases and 347,481 controls. Additionally, data for moderate-to-severe asthma, defined by patients taking medication or being diagnosed by a doctor, consisted of 5135 cases and 25,675 controls. Detailed information about the data sources is presented in Table 1.
The Selection of Genetic Instrumental Variables (IVs)

MR analysis used IVs as mediators between exposure factors and outcomes to explore causal association. Firstly, the genome-wide significance level is set at $p<5\times10^{-8}$, which is commonly accepted in the MR analysis. All selected IVs must meet the criteria of being meaningfully associated with exposure and unrelated to outcome. Secondly, to ensure the independence, IVs clumping is performed using a cutoff of $R^2<0.001$ within a genetic window of 10,000 kb. $R^2$, which represents the proportion of exposure explained by IVs, can be calculated using the formula: $R^2 = \frac{\beta^2}{(SE^2 \times N + \beta^2)}$. For a strong association between IVs and exposure, the F statistic is calculated using the formula $F = \frac{R^2}{(1-R^2) \times (N-2)}$, where $N$ represents the sample size. To avoid bias from weak instruments, IVs with an F-statistic $<10$ are removed.

Table 1 Characteristics of GWAS Consortiums Used for Each Variable

<table>
<thead>
<tr>
<th>Traits</th>
<th>Sample Size(Cases/Controls)</th>
<th>Population</th>
<th>Consortium</th>
<th>PMDI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Obstructive sleep apnea</td>
<td>41,704/335,573</td>
<td>European</td>
<td>FINNGen</td>
<td>–</td>
</tr>
<tr>
<td>Asthma</td>
<td>56,167/352,255</td>
<td>European</td>
<td>UKBB</td>
<td>34103634</td>
</tr>
<tr>
<td>Adult-onset asthma</td>
<td>22,296/347,481</td>
<td>European</td>
<td>UKBB</td>
<td>31619474</td>
</tr>
<tr>
<td>Child-onset asthma</td>
<td>9,676/347,481</td>
<td>European</td>
<td>UKBB</td>
<td>31619474</td>
</tr>
<tr>
<td>Moderate-to-severe asthma</td>
<td>5,135/25,675</td>
<td>European</td>
<td>UKBB</td>
<td>30552067</td>
</tr>
</tbody>
</table>

Abbreviations: GWAS, genome-wide association studies; UKBB, UK Biobank; FINNGen, Finnish Gene.
Finally, the use of PhenoScanner V2, an expanded tool for searching human genotype–phenotype associations, helps exclude IVs related to outcome traits.17

Mendelian Randomization Analyses
The multiplicative random-effect inverse variance-weighted (IVW) method is considered to have the highest ability to detect causal associations in MR analysis, which regarded as the primary criterion for assessing the result. The weighted median and the MR-Egger are used as supplementary methods.18 The statistical significance threshold is commonly set 0.05. To assess heterogeneity among individual SNPs, Cochran’s Q test is employed. If significant heterogeneity is observed, the random-effects model is chosen.19 Stability of the results is evaluated using MR–Egger regression and MR pleiotropy residual sum and outlier (MR-PRESSO). MR-Egger regression can detect directional pleiotropy, accounting for the possibility of non-zero intercepts.20 MR-PRESSO is used to identify and remove any horizontal pleiotropic outlier by calculating p-values for each SNP.21 These outliers are eliminated prior to each MR analysis. The leave-one-out sensitivity method is employed to assess if the results are influenced by the removal of any single SNP. Scatterplots, forest plots, and funnel plots are generated to further examine the sensitivity of the results. All analyses are conducted using the TwoSampleMR and MR-PRESSO packages in R Software 4.3.1. The forest plot is created using ggplot2 package.

Results
Causal Effect of Obstructive Sleep Apnea on Asthma
At first, we conducted the MR analyses to investigate the causal effect of OSA on asthma and its subtypes. Figure S1 show the main flowcharts of genetic instrument screening. We identified 22, 12, 12, and 19 SNPs as IVs for asthma, adult-onset asthma, child-onset asthma, and moderate-to-severe asthma, respectively. To account for the influence of BMI as a confounding factor, we excluded SNPs associated with BMI by PhenoScanner. We further used the MR-PRESSO method to detect and remove any outliers, resulting in a final set of 12, 7, 7 and 12 SNPs for the MR analyses. Detailed information on the selected SNPs is provided in Table S1. Using the IVW method, we found that genetically predicted OSA was significantly associated with an increased incidence of child-onset asthma (IVW OR,1.49; 95% CI, 1.05–2.11; P=0.025) (Figure 2). Similar results were observed when applying the weighted median method (Table S2). However, none of the three methods provided causal association evidence between OSA with asthma (IVW OR,1.08; 95% CI, 0.97–1.19; P=0.148), adult-onset asthma (IVW OR,1.03; 95% CI, 0.82–1.30; P=0.784), or moderate-to-severe asthma (IVW OR,0.93; 95% CI,0.60–1.46; P=0.761) (Figure 2 and Table S2). Heterogeneity was observed in the results of OSA on moderate-to-severe asthma, as indicated by Cochran’s Q statistical test (P=0.029), thus supporting the use of the random-effects IVW method (Table S3). The MR-Egger intercept analysis did not reveal any evidence of pleiotropy, except the moderate-to-severe asthma (Table S3). Forest plots and scatter plots depicting the results are shown in Figure S2 and Figure 3 respectively. Leave-one-out analysis confirmed the robustness of the positive results (Figure S3). Funnel plots indicated little evidence of heterogeneity (Figure S4).

<table>
<thead>
<tr>
<th>Exposure</th>
<th>Outcome</th>
<th>nSNP</th>
<th>OR (95% CI)</th>
<th>Pvalue</th>
</tr>
</thead>
<tbody>
<tr>
<td>OSA</td>
<td>Asthma</td>
<td>12</td>
<td>1.08 (0.97 to 1.19)</td>
<td>0.148</td>
</tr>
<tr>
<td>OSA</td>
<td>Adult-onset asthma</td>
<td>7</td>
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<td>0.761</td>
</tr>
</tbody>
</table>

Figure 2 The forest plot of the MR analysis results about causal associations of OSA on asthma, adult-onset asthma, child-onset asthma and moderate-to-severe asthma. Significant threshold was set at p-value < 0.05 for the inverse variance weighted method (IVW).

Abbreviations: OSA, obstructive sleep apnea; MR, Mendelian randomization; SNP, single-nucleotide polymorphisms; OR, odds ratio; CI, confidence interval.
Causal Effect of Asthma on Obstructive Sleep Apnea

We conducted a reverse MR study to explore the causal effect of asthma on OSA, using the same methodology to screen SNPs (Figure S5). Finally, we identified 66, 13, 41, and 14 SNPs linked to asthma, adult-onset asthma, child-onset asthma, and moderate-to-severe asthma respectively. Details of SNPs can be found in Table S4. Based on IVW method, only moderate-to-severe asthma was found to have a significant causal effect on OSA (IVW OR, 1.03; 95% CI, 1.00–1.06; P=0.046), as shown in Figure 4. However, we did not observe significant causal effects of asthma or the other two subtypes on OSA (Figure 4 and Table S2). Furthermore, the results of asthma and adult-onset asthma on OSA showed

Figure 3 The scatter plots of SNP effect. (A) the scatter plots of SNP effect about OSA on asthma, (B) the scatter plots of SNP effect about OSA on adult-onset asthma, (C) the scatter plots of SNP effect about OSA on child-onset asthma, (D) the scatter plots of SNP effect about OSA on moderate-to-severe asthma.

Abbreviations: OSA, obstructive sleep apnea; SNP, single-nucleotide polymorphisms; MR, Mendelian randomization.
heterogeneity tested by Cochran’s Q statistical (Table S3). We presented the forest plots, leave-one-out analysis, scatter plots and funnel plots in Figures S6–S9 respectively to provide more detailed information.

Discussion

We investigated the causal association between OSA and asthma, including some of its subtypes, using bi-directional MR analysis. To our knowledge, it is the first MR study on this topic, providing valuable insights into the causality between asthma and OSA. Our results indicate that OSA is a risk factor for the development of childhood asthma at the genetic level, and moderate-to-severe asthma may serve as potential risk factors for OSA. However, our forward and reverse MR analyses did not find a significant causal association between OSA and asthma, including adult-onset asthma.

Based on previous studies, the relationship between asthma and OSA appears to be bidirectional. The prevalence of OSA is higher in patients with asthma compared to those without OSA. A randomized population-based prospective study showed that participants with asthma had a significantly increased risk of OSA (RR=2.72, P=0.045) compared to those without asthma. Asthma and OSA share similar pathophysiological mechanisms. The intermittent hypoxia in OSA can lead to oxidative stress and systemic inflammation, ultimately leading to airway hyperreactivity. Then, chronic airway inflammation caused by asthma can lead to the infiltration of inflammatory cells and undermine protective mechanisms of pharyngeal upper-airway (pUAW) patency. Long-term use of inhaled corticosteroid (ICS) for asthma also can potentially lead to upper airway collapse during sleep. These factors may contribute to the development of OSA in asthmatic patients. However, current researches on OSA combined with asthma consists of observational or cross-sectional studies, which without discussing the causal association in depth. Additionally, the heterogeneity of the two diseases suggests that they are strongly influenced by similar acquired factors, such as occupational exposures, smoking, air pollution and hormonal changes, which may overshadow the potential impact of OSA on asthma development.

Furthermore, the persistent airway inflammation characteristic of adult-onset asthma may have a complex etiology, involving multiple genetic and environmental factors that mitigate the causal effect of OSA. However, our study, while excluding the interference of acquired environmental factors, found no causal association between OSA and asthma at the genetic level. This finding does not conflict with the results of current observational studies but further emphasizes the important role of environmental factors in the occurrence and development of the two diseases. On the other hand, the result indicating that moderate-to-severe asthma may have a potential promoting effect on OSA suggest that individuals with more severe asthma may have more “fragile” airways, with more intense inflammation responses and increased airway hyperresponsiveness, which is more likely to lead to the production of OSA.

Most importantly, the significant causal association between OSA and child-onset asthma is intriguing. Our study demonstrates that OSA contributes to the development of child-onset asthma at a genetic level. Child-onset asthma is mostly associated with genetic factors, including lung growth and development, and immune system development. Therefore, chronic airway inflammation in early life can increase the respiratory system’s plasticity, leading to impaired
lung function and eventually resulting in various respiratory diseases. Pediatric OSA is most commonly observed in children aged 2 to 8 years old, and is mostly associated with tonsillar and adenoid hypertrophy. A study demonstrated that tonsillar hypertrophy (OR=3.15; 95% CI 2.04–4.88) and adenoidal hypertrophy (OR=1.89; 95% CI 1.19–3.00) significantly increased OSA risk, and this influence decreases in adolescence. Thus, adenotonsillectomy (AT) be considered as the first-line therapy for pediatric OSA. Rakesh et al research shown that after 1 year following, the control of asthma symptoms had significantly improved in children who underwent AT, indicating that the presence of OSA in children may aggravate underlying asthma. Chronic inflammation caused by allergic rhinitis, enlarged tonsils and adenoids results in an overexpression of leukotrienes and their receptors. This overexpression can promote the proliferation of adenotonsillar cells, forming a vicious circle that affects the occurrence and development of asthma and OSA in children. Another study shown that montelukast, a cysteinyl-leukotriene receptor antagonist, could effectively reduce the severity of pediatric OSA and adenoidal size. Substantially, compared with adults, children’s respiratory system function and immune respiratory response are still developing and may be more susceptible to chronic airway inflammation, which may be the main reason for asthma in children with OSA and aggravation of asthma symptoms. Thus, our findings are consistent with previous studies highlighting the potential impact of OSA on childhood respiratory health. The results also provided reliable clinical evidences that screening for OSA in children with asthma and early treatment of OSA are meaningful for reducing the incidence of asthma and optimizing asthma symptom control, consistent with previous conclusions.

The findings of our study suggest that chronic, low-grade inflammation in the early life can lead to impaired lung function and have long-term effects on the development and progression of chronic respiratory diseases, such as asthma. Additionally, recurrent hypoxemia and hypercapnia induced by OSA can worsen airway hyperreactivity and cause airway inflammation. These effects may be more pronounced in children compared to adults. It has been observed that children have more active upper airway reflexes during sleep, which decrease during adolescence, which can result in a stronger response to hypoxemia and hypercapnia, and may leading to more frequent alternations between phases of hypoxemia and hyperventilation. Consequently, the airway inflammatory response may be more intense in children with OSA. Identifying OSA as a potential causal factor for childhood asthma highlights the importance of early intervention and management of OSA in pediatric populations to prevent the development of asthma.

It is worth noting that the MR analysis used in this study relies on certain assumptions, including the validity of instrumental variables and the absence of pleiotropy. Although we rigorously accounted for potential confounders and employed robust sensitivity analyses, we did not find age-stratified OSA databases and sex-stratified OSA and asthma databases, so the possibility of unmeasured confounding or pleiotropy cannot be completely ruled out. Additionally, we exclusively enrolled individuals of European descent in our study population, indicating that our findings might not be generalizable to individuals of other ethnic ancestries. Finally, limited by the current genome-wide association studies (GWAS) studies, we were unable to get detailed gender-specific and age-stratified information, which prevented us from conducting in-depth subtype analyses.

In conclusion, our study using a comprehensive MR approach provides evidence of a causal association between OSA and childhood asthma, implying that OSA acts as a risk factor for asthma development in early life. However, no significant causal association was observed between OSA and adult-onset asthma. These findings underscore the importance of considering developmental factors and age-specific mechanisms in the understanding the interactions between asthma and OSA. Further research is needed to unravel the underlying mechanisms governing these relationships and to guide the development of personalized interventions for individuals affected by asthma and OSA.

Conclusions
Our Mendelian randomization study revealed a causal association between OSA and childhood asthma, as well as a potential promoting effect of moderate-to-severe asthma on OSA. However, we observed no causal association between OSA and asthma in adults. These findings emphasize the significance of early intervention and targeted treatments for childhood asthma induced by OSA and pay more attention to the influence of moderate and severe asthma. Further research is needed to uncover the underlying mechanisms and explore other factors influencing this relationship. Overall,
our study highlights the importance of age-specific considerations in managing asthma and suggests the need for personalized approaches in clinical practice.

**Data Sharing Statement**

All data are publicly available GWAS summary data. The website of datasets using in this research shown in method part of this paper.

**Ethics Declaration**

The ethics committee of the First Affiliated Hospital of Guangzhou Medical University strictly follows the Declaration of Helsinki and International Ethical Guidelines for Health-related Research Involving Humans, etc, to perform independent ethical review duties. All genome-wide association studies included in this study all originate from publicly published GWAS summary databases, which complies with the conditions for exemption from review as stated in the “Ethical Review Measures for Life Sciences and Medical Research Involving Humans”.

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**Disclosure**

The authors declare no conflicting interest associated with this manuscript.

**References**


