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Causal associations of obstructive sleep apnea with Chronic Respiratory Diseases: a Mendelian Randomization study

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Abstract

Purpose This study aimed to elucidate the causal relationship between Obstructive Sleep Apnea (OSA) and Chronic Respiratory Diseases (CRDs), employing Mendelian Randomization (MR) to overcome limitations inherent in observational studies.

Methods Utilizing a two-sample MR approach, this study analyzed genetic variants as instrumental variables to investigate the causal link between OSA and various CRDs, including chronic obstructive pulmonary disease (COPD), asthma, bronchiectasis, and idiopathic pulmonary fibrosis (IPF). Data were sourced from the FinnGen Consortium (OSA, $n = 375{,}657$) and UK Biobank, focusing on genome-wide associations between single-nucleotide polymorphisms (SNPs) and the diseases. Instrumental variables were selected based on strict criteria, and analyses included a random-effects inverse-variance weighted method supplemented by several sensitivity analyses.

Results The study suggests a protective effect of OSA against COPD (OR = 0.819, 95% CI 0.722–0.929, P-value = 0.002), which becomes non-significant after adjusting for BMI, indicating a potential mediating role of BMI in the OSA-COPD nexus. No significant causal links were found between OSA and other CRDs (asthma, IPF, bronchiectasis) or between COPD, asthma, and OSA.

Conclusions Our findings reveal a BMI-mediated protective effect of OSA on COPD, with no causal connections identified between OSA and other CRDs. These results emphasize the complex relationship between OSA, BMI, and COPD, guiding future clinical strategies and research directions, particularly in light of the study's genetic analysis limitations.

Keywords Obstructive sleep apnea, Chronic respiratory diseases, Mendelian randomization analysis, Chronic obstructive pulmonary disease

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Introduction

According to conservative estimates, the prevalence of obstructive sleep apnea(OSA) is 3% for women, 10% for men in the 30- to 49-year-old age range, and 9% for women and 17% for men in the 50- to 70-year-old age range [1]. The characteristic features of OSA include the episodic collapse of the upper airway, which depends on the sleep state [2]. This leads to periodic decreases or cessations in breathing, which can cause hypoxia, hypercapnia, or arousal from sleep [3, 4]. Nocturnal hypoxemia is often present in OSA and especially in overlap cases with COPD because the result of hypoxia is the development or worsening of cerebro-cardio-vascular, metabolic and other diseases, which cause a high risk of death [5, 6]. As noted by Tondo, et al. [6], OSA is closely associated with these health risks, underlining the need for effective management and intervention strategies.

Chronic respiratory diseases (CRDs) continue to be the main cause of death and disability worldwide [7, 8]. There were 544,9 million chronic respiratory disease sufferers globally in 2017, a 39.8% increase from 1990 [7]. Some of the most common chronic respiratory diseases are chronic obstructive pulmonary disease (COPD) and asthma [9]. The concurrent prevalence of CRDs, such as COPD [10 11], asthma [12], bronchiectasis [13], and idiopathic pulmonary fibrosis (IPF) [14, 15] has been repeatedly highlighted by modern observational research, highlighting a significant clinical overlap with OSA.

The prevalence of OSA is estimated to be 10–30% in patients with COPD [16] and 20–60% in those with asthma [17, 18]. OSA exacerbates chronic respiratory diseases such as COPD, asthma, interstitial lung disease, and pulmonary hypertension [19]. OSA with CRDs not only deteriorates the progression of these diseases but also adversely affects the quality of life of the affected individuals.

These ongoing findings point to a significant convergence in the clinical characteristics of these illnesses. Nevertheless, a thorough definition of the causal link between OSA and CRDs is still pending.

Mendelian randomization (MR), an innovative statistical approach, offers a method to appraise the causal links between OSA and CRDs, utilizing genetic variants as instrumental variables [20]. MR analysis can eliminate potential unmeasured confounders and reverse causation, a significant limitation of evidence from observational studies because the genetic variants are assigned randomly at conception [21]. In this work, we used MR techniques to assess the causal relationship between OSA and CRDs.

Methods

Study design and data sources

This study encompasses a comprehensive review of supporting information within the article. Employing a two-sample MR approach, we investigated the causal relationship between OSA and CRDs (Fig. 1). In our MR framework, genetic variations serve as instrumental variables to ascertain if exposure significantly influences disease development. This method offers robust causal inferences, mitigating the impact of unmeasured confounders. Our MR design adhered to three critical criteria for credible causal estimations: (1) Instrumental variables must exhibit a substantial association with the exposure; (2) The instrumental variables should be independent of known confounders. The exposure is the sole pathway through which the instrumental variables influence the outcomes; (3) Genome-wide association studies (GWAS) have demonstrated associations between single-nucleotide polymorphisms (SNPs) and exposure. The data utilized were derived from publicly available GWAS summary statistics, thus obviating the

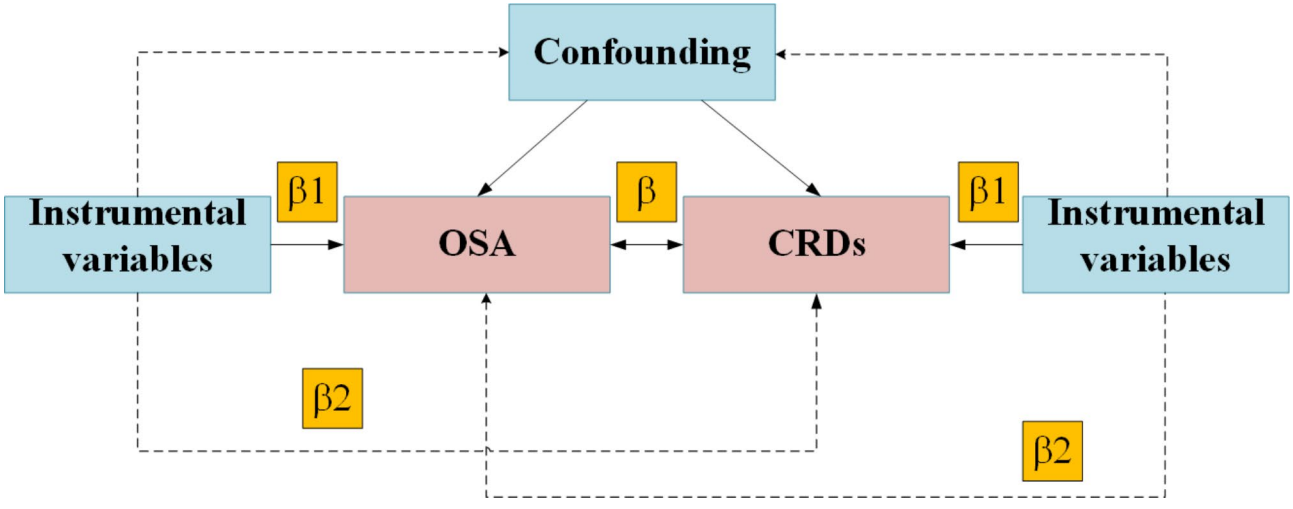

Fig. 1 Mendelian randomization model of OSA and CRDs. Abbreviation OSA, obstructive sleep apnea; CRDs: chronic respiratory diseases

need for additional ethical approval or informed consent. GWAS data for OSA were obtained from the FinnGen Consortium (G6_SLEEPAPNO _INCLAVO) (gs://finngen-public-data-r9/summary_stats/finngen_R9_G6_SLEEPAPNO_INCLAVO.gz), comprising 41,704 cases and 335,573 controls. OSA diagnosis was according to the International Classification of Diseases, Tenth Revision (ICD-10) and Ninth Revision (ICD-9) codes (ICD-10: G47.3, ICD-9: 3472 A), which was based on subjective symptoms, clinical examination, and sleep registration applying AHI ≥ 5/h or respiratory event index ≥ 5/h. The CRDs outcomes were COPD, asthma, bronchiectasis, IPF, and pulmonary hypertension. Genetic instruments for COPD (25,054 cases and 392,709 controls), asthma (2,365 cases and 453,983 controls), bronchiectasis (583 cases and 455,765 controls), IPF (1,369 cases and 435,866 controls) were obtained from the UK Biobank (https://gwas.mrcieu.ac.uk/, COPD GWAS ID: ebi-a-GCST90042687, asthma GWAS ID: ebi-a-GCST90044072, bronchiectasis GWAS ID: ebi-a-GCST90044075, IPF GWAS ID: ebi-a-GCST90399723) (Table 1). COPD was defined using post-bronchodilator spirometry according to modified GOLD criteria in both studies.

Instrumental variable selection

In this study, SNPs were meticulously selected for each exposure factor in accordance with the principal assumptions underpinning MR. Initially, SNPs achieving genome-wide significance ($p<5\times10$^−8) were considered for inclusion. Subsequently, to identify independent instrumental variables (IVs), we selected variants demonstrating the lowest p-values, ensuring minimal linkage disequilibrium (LD) as evidenced by an r^2 threshold greater than 0.1, based on the European 1000 Genome reference panel. Finally, the robustness of these instrumental variables was quantified using *F*-statistics [22], with an *F*-statistic value exceeding ten generally deemed suitable for MR analysis.

Statistical analysis

In this investigation, for binary exposures, causal estimates were articulated as odds ratios (ORs) with 95% confidence intervals (CIs) per logarithmic odds increment in the genetically predisposed risk of the exposures. Regarding continuous exposures, the causal estimate was denoted as an OR accompanied by a 95% CI for each standard deviation (SD) increase in exposure. MR analysis employed the primary analytic approach of the random-effects inverse-variance weighted (IVW) method. This was chosen to estimate the potential bidirectional causal relationships between OSA and CRDs, offering robust causal estimations in scenarios devoid of directional pleiotropy. Complementary analyses incorporated methods such as the weighted median, simple mode, weighted mode, and MR-Egger. Directional horizontal pleiotropy was assessed using the MR-Egger intercept test. Heterogeneity in MR-Egger regression and the IVW method was evaluated through Cochran's Q statistics and funnel plot analyses [23]. Additionally, sensitivity was examined via leave-one-out analysis. Post hoc power assessments for MR leveraged online resources (https://sb452.shinyapps.io/power/) [24]. All statistical procedures were executed using the TwoSampleMR packages within R (version 4.1.2, www.r-project.org/). All p-values were two-tailed. A Bonferroni-adjusted p-value threshold of <0.004 (0.05/12) was set for determining statistical significance in MR analyses. In contrast, p-values <0.10 were deemed significant for MR-Egger tests and heterogeneity assessments.

Results

Instrumental variable selection

In the initial phase of our analysis, we rigorously selected SNPs that demonstrated a robust association with the exposure, applying stringent criteria ($p<5\times10$^−8, F-value >10) and ensuring independence ($r^2 < 0.001$ within a 10,000 kb physical window). This process yielded 22 SNPs from the FinnGen Consortium (G6_SLEEPAPNO_INCLAVO) designated as IVs after excluding SNPs with LD ($r^2>0.001$). No proxy SNP was missing for other CRDs outcomes. Detailed information for each SNP for OSA used in the current study can be found in the supplementary file (Supplementary material, Table S1).

The causal effect of OSA on CRDs

The results of the MR analyses are shown in Fig. 2; Table 2, and the scatter plots and forest plots are

Table 1 Details of the GWASs included in the mendelian randomization

Consortium	Phenotype	Participants		Web source
		ncase	ncontrl	
FinnGen	OSA	38,998	336,659	https://r9.finngen.fi/
UK Biobank	COPD	25,054	392,709	https://www.nealelab.is/uk-biobank
UK Biobank	Asthma	2365	453,983	https://www.nealelab.is/uk-biobank
UK Biobank	bronchiectasis	583	455,765	https://www.nealelab.is/uk-biobank
UK Biobank	IPF	1369	435,866	https://www.nealelab.is/uk-biobank

Abbreviation OSA, obstructive sleep apnea; COPD, chronic obstructive pulmonary disease; IPF, idiopathic pulmonary fibrosis

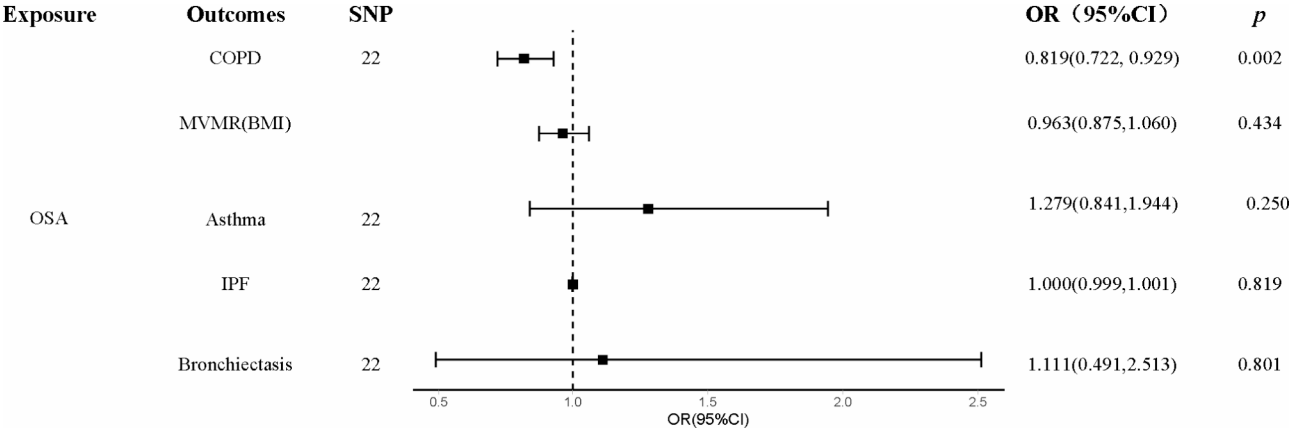

Fig. 2 The causal effect of OSA on chronic respiratory diseases. Abbreviation OSA, obstructive sleep apnea; SNP: single-nucleotide polymorphisms; COPD: chronic obstructive pulmonary disease; MVMR: multivariate Mendelian randomization analysis; BMI: body mass index; IPF: idiopathic pulmonary fibrosis

Table 2 MR results for the relationship between OSA on CRDs

Exposures	Outcomes	No. of SNPs	Method	OR(95%CI)	*p*	Heterogeneity test		Pleiotropy test
						Cochran's Q(I^2) *p*		*p* pintercept
OSA*	COPD#	21	IVW	0.82(0.72 ~ 0.93)	0.002	37.207(46.25%)	0.011	0.158
			MR Egger	1.20(0.71 ~ 2.03)	0.502	33.401(43.12%)	0.021	
			Weighted median	0.92(0.80 ~ 1.06)	0.269			
			Simple mode	0.96(0.72 ~ 1.28)	0.796			
			Weighted mode	0.97(0.80 ~ 1.17)	0.734			
OSA*	Asthma#	21	IVW	1.28(0.84 ~ 1.94)	0.250	42.332(52.75%)	0.003	0.232
			MR Egger	3.80(0.64 ~ 22.45)	0.158	39.192(51.52%)	0.004	
			Weighted median	1.05(0.65 ~ 1.68)	0.841			
			Simple mode	2.13(0.80 ~ 5.68)	0.145			
			Weighted mode	0.87(0.43 ~ 1.73)	0.691			
OSA*	IPF#	22	IVW	1.00(0.99 ~ 1.00)	0.819	8.638(0%)	0.991	0.856
			MR Egger	1.00(0.99 ~ 1.01)	0.488	8.187(0%)	0.992	
			Weighted median	1.00(0.99 ~ 1.00)	0.799			
			Simple mode	1.00(0.99 ~ 1.00)	0.743			
			Weighted mode	1.00(0.99 ~ 1.00)	0.764			
OSA*	Bronchiectasis#	21	IVW	1.11(0.49 ~ 2.51)	0.801	39.852(49.81%)	0.005	0.407
			MR Egger	0.49(0.14 ~ 1.72)	0.388	38.397(50.52%)	0.005	
			Weighted median	0.64(0.26 ~ 1.57)	0.331			
			Simple mode	3.69(0.57 ~ 24.03)	0.186			
			Weighted mode	0.53(0.14 ~ 1.95)	0.352			

*data form The FinnGen Consortium(G6_SLEEPAPNO)

#data form UK Biobank

Abbreviation OSA, obstructive sleep apnea; SNPs, single-nucleotide polymorphisms; COPD, chronic obstructive pulmonary disease; IPF, idiopathic pulmonary fibrosis; IVW, inverse-variance weighted

presented in Supplementary Figure S1 and Figure S2, respectively. In the univariable IVW analysis, genetically predicted OSA is negatively associated with COPD [IVW: odds ratio (OR)=0.819, 95% CI 0.722–0.929, P-value=0.002]. The Cochran's Q value suggested a moderate level of heterogeneity (Q=37.207, $p<0.05$) obtained from individual variants. Furthermore, the leave-one-out analysis suggested that the observed association was not significantly changed after removing any single variant (Supplementary Figure S3). In order to exclude the influence of confounding factors, we used multivariate Mendelian randomization analysis (MVMR). The MVMR estimates remained unchanged after an BMI adjustment accounting for multiple testing (P-value=0.434). No genetic association of OSA with asthma, IPF, and bronchiectasis was found with all P values>0.05.

The causal effect of CRDs on OSA

As shown in Supplementary Table S2, the scatter plots (Supplementary Figure S5), and forest plots (Supplementary Figure S6), the MR results showed COPD and asthma were not causally related to OSA, with ORs close

to 1 ($p>0.05$). Egger's test showed that no potential horizontal pleiotropy exists. Cochran's Q test indicated no heterogeneities. The leave-one-out analysis also revealed the stability of the results (Supplementary Figure S7). Insufficient SNPs were present in IPF and bronchiectasis to facilitate a conclusive Mendelian analysis.

Discussion

In this investigation, we present what we believe to be the inaugural bidirectional MR study elucidating the impact of OSA on a spectrum of CRDs. Our analysis discerned a diminished and statistically non-significant association between OSA and COPD upon adjustment for BMI. Importantly, no significant causal linkage was observed between OSA and other respiratory conditions such as asthma, IPF, and bronchiectasis.

Furthermore, our data suggest that OSA may act as a protective factor against COPD, a relationship that loses significance upon BMI adjustment. This finding highlights the complex interplay between BMI and respiratory diseases, suggesting that BMI may mediate the relationship between OSA and COPD. Similarly, Tondo, et al. [25] found BMI significantly modulates the impact of OSA on various comorbidities, providing an observational perspective that complements our Mendelian randomization approach. A body of extant observational studies buttresses this hypothesis. Shin, et al. [26] reported heightened exacerbation risks in COPD patients with a BMI below 25 kg/m², in contrast to those with higher BMI values. Complementing this, a substantial Japanese cohort study demonstrated an inverse relationship between BMI and COPD mortality risk, evidenced by a hazard ratio of 0.48 per standard deviation increase in BMI. This study also highlighted the inverse correlation between weight gain post-age 20 and COPD mortality risk, underscoring the prognostic significance of BMI and weight trajectories in COPD [27]. Moreover, the causal relationship between OSA and BMI [28] emerges as a positive prognostic factor in COPD patients within our study's context. Obesity significantly increases the risk and severity of OSA due to mechanical, physiological, and inflammatory factors that compromise airway patency and respiratory function [29]. Nevertheless, a higher BMI can indicate better nutritional status, which is crucial for patients with advanced COPD who often experience weight loss and muscle wasting [30]. These reserves provide essential energy to support breathing and other physical activities, potentially slowing the progression of disability [31]. The intricate interplay between OSA, BMI, and COPD warrants further investigative efforts to elucidate the underlying mechanisms.

This investigation discerned no causal link between OSA and several CRDs, namely asthma, IPF, and bronchiectasis. This absence of causal association diverges from the conclusions of previous observational studies, potentially attributable to confounding variables inherent in such study designs. Moreover, our findings did not identify a causal relationship in the reciprocal analysis concerning COPD, asthma, and OSA. However, it is crucial to note that the validity of these results may be constrained by the limited number of SNPs utilized in the study. The limited SNP count potentially undermines the robustness of these findings, indicating the necessity for further research with a more extensive genetic dataset to corroborate or challenge these preliminary observations.

A major strength of this MR study lies in its ability to circumvent reverse causality and minimize residual confounding. Additionally, the study boasts significant investigatory power and accuracy in estimating effect magnitudes by employing the most comprehensive dataset for exposures and the most extensive summary-level data for OSA risk and CRDs. Nonetheless, there are limitations. Firstly, the functions of the genetic instruments and their impact on risk factors are not completely understood. Secondly, potential pleiotropic effects, possibly obscured by a limited number of genetic instruments or small sample sizes, remain a concern, although the MR-Egger intercept indicates minimal horizontal pleiotropy. Thirdly, our study did not differentiate the impacts of various BMI ranges on both OSA and COPD, a limitation we aim to address in future research.

In summary, our study elucidates a potentially protective influence of OSA on COPD, an effect that appears to be mediated through BMI. These findings underscore clinicians' need to consider the interplay among OSA, BMI, and COPD in clinical practice. Such awareness could inform more nuanced diagnostic and therapeutic approaches, enhancing patient outcomes in managing these conditions.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12890-024-03228-x.

Supplementary Material 1

Supplementary Material 2

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Not applicable.

Author contributions
Conception and design: P-Y Hong, D Liu and A Liu. Collection and assembly of data: X Su and X-B Zhang. Data analysis and interpretation: P-Y Hong and Y-M Zeng. Manuscript writing: All authors. Final approval of manuscript: All authors.

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Data availability
The datasets generated and/or analysed during the current study are available in the FinnGen and UK Biobank (https://r9.finngen.fi/ and https://gwas.mrcieu.ac.uk/).

Declarations

Ethics approval and consent to participate
The experimental protocol was established, according to the ethical guidelines of the Helsinki Declaration and was approved by the Human Ethics Committee of Zhongshan Hospital of Xiamen University, Xiamen, China.

Consent for publication
No applicable.

Competing interests
The authors declare no competing interests.

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