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Depression as a Mediator in the Causal Pathway from Sleep Apnea to Cardiovascular Diseases: A Two-Step Mendelian Randomization Analysis

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ABSTRACT

Aim: To investigate the causal relationships and the potential mediating role of depression in the association between sleep apnea (SA) and cardiovascular diseases (CVDs) using a two-step Mendelian randomization (MR) approach.

Methods and Results: We applied a two-step MR framework to evaluate

(1) The causal effect of genetically predicted SA on CVDs,

(2) SA on depression, and

(3) Depression on CVDs. Summary-level data were obtained from FinnGen, the UK Biobank, and the Psychiatric Genomics Consortium. Genetically predicted SA (from FinnGen) was not directly associated with CVDs in the UK Biobank cohort (OR = 1.01, 95% CI: 0.98–1.04, *P* = 0.47). However, SA was causally associated with an increased risk of depression (OR = 1.03, 95% CI: 1.00–1.05, *P* = 0.033), and depression was significantly associated with CVDs (OR = 1.02, 95% CI: 1.01–1.03, *P* = 0.001). Sensitivity analyses, including MR-Egger regression and leave-one-out analysis, confirmed the robustness of the findings, with no evidence of horizontal pleiotropy (*P* > 0.05).

Conclusion: Depression partially mediates the causal pathway between sleep apnea and cardiovascular diseases, suggesting that integrated management of sleep apnea and depressive symptoms may help reduce cardiovascular risk.

Keywords: Sleep Apnea; Depression; Cardiovascular Diseases

Abbreviations: OSA: Severe Obstructive Sleep Apnea; IH: Intermittent Hypoxia; CPAP: Continuous Positive Airway Pressure; ACS: Acute Coronary Syndrome; SA: Sleep Apnea; MR: Mendelian Randomization; STROBE: Strengthening The Reporting Of Observational Studies In Epidemiology; SNPs: Single Nucleotide Polymorphisms; IVs: Instrumental Variables; GWAS: Genome-Wide Association Study; CVDs: Cardiovascular Diseases; MR: Mendelian Randomization; IVW: Inverse Variance Weighting; RCTs: Randomized Controlled Trials; AHI: Apnea-Hypopnea Index; GWAS: Genome-Wide Association Studies; UKB: UK Biobank

Introduction

Sleep apnea is a highly prevalent sleep-related breathing disorder, affecting approximately 1 billion adults aged 30–69 years worldwide, with mild to severe obstructive sleep apnea (OSA). Of these, an estimated 425 million individuals have moderate to severe OSA [1,2]. The condition is characterized by recurrent episodes of upper airway collapse during sleep, leading to intermittent hypoxia (IH), sleep fragmentation, and frequent arousals [3]. These pathophysiological disturbances contribute to oxidative stress, systemic inflammation, hypercoagulability, and heightened sympathetic activity, all of which are implicated in the development of cardiovascular diseases [4,5]. Epidemiological and observational studies consistently report an association between sleep apnea and increased cardiovascular risk [4-7]. Despite this evidence, the causal nature of the relationship between sleep apnea and cardiovascular diseases remains debated.

Some randomized controlled trials suggest that continuous positive airway pressure (CPAP) therapy may reduce cardiovascular risk in patients with sleep apnea [8]. However, conflicting results exist; for example, the ISAACC trial found that CPAP treatment did not significantly reduce major adverse cardiovascular events in non-hypersomnolent patients with OSA. Additionally, the presence of OSA was not associated with a higher incidence of cardiovascular events among non-symptomatic patients with acute coronary syndrome (ACS) [9].

Bradley et al. also reported that ventilatory support did not significantly alter the rates of cardiovascular events or all-cause mortality in patients with sleep apnea [10]. Observational studies have demonstrated an association between sleep apnea (SA) and depression [11,12], and depression itself has been independently linked to cardiovascular diseases [13,14]. However, the extent to which depression mediates the relationship between SA and CVDs remains unclear. Therefore, we hypothesize that depression may act as a partial mediator in the causal pathway linking sleep apnea to cardiovascular diseases.

Methods

We conducted a two-sample, two-step Mendelian randomization (MR) analysis in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines for MR studies. Single nucleotide polymorphisms (SNPs) were selected as instrumental variables (IVs), under the assumption that they are strongly associated with the exposure, independent of confounders, and influence the outcome only through the exposure. The study population was restricted to individuals of European ancestry due to the limited availability of genome-wide association data for the traits of interest in multi-ethnic cohorts; inclusion of diverse populations could introduce population stratification bias. All selected instrumental variables met the genome-wide significance threshold ($*P* < 5 \times 10^{-8}$) and were clumped to ensure independence ($R^2 < 0.01$). Instrumental variables for sleep apnea were obtained from the UK Biobank (7,902 cases, 248,112 controls) and FinnGen data (3,898 cases, 353,425 controls). Depression-related instrumental variables were sourced from FinnGen's genome-wide association study (GWAS) database (43,280 cases, 301,058 controls) and the Psychiatric Genomics Consortium (excluding 23andMe and UK Biobank) (Table 1). Cardiovascular diseases (CVDs) included self-reported conditions such as angina, heart attack, heart failure, arrhythmia, and cardiomyopathy from the UK Biobank (52,320 cases, 340,784 controls). Definitions of CVDs in the Finnish study (excluding 23andMe and UK Biobank) differed.

Table 1: Overview of Genome-Wide Association Studies Used.

Trait	Study	Cohorts	Phenotype definition	Population
Exposure Sleep apnoea	Ben Elsworth, et al. 2018	UK Biobank	Case: dignosed main ICD10 sleep apnea Control:not classified as cases	Cases:7902 Contols:248112
Sleep apnoea	Kurki, et al. 2023	FinnGen release 9	Case:FinnGen codeG6_SLEEPAPNO Control: not classified as cases	Cases:389 98 Female:156 35 Male: 233 63 Controls: 353 425
Depression	Kurki, et al. 2023	FinnGen release 9	Case:FinnGen code F5_DEPRESSIO Control: not classified as cases and code F5_MOOD	Cases:432 80 Female:291 50 Male: 141 30 Controls: 301 058
Depression		UK Biobank	Cases: depression self-reported Controls: not classified as cases	Cases: 34975 Controls:393104
Depression	Wray, et al. (2018)	the Psychiatric Genomics Consortium(-excluding 23and Me and UK Biobank)	Cases:clinically diagnosed major depressive disorder (MDD) Controls:not classified as cases	Cases:135485 Controls:344901
Outcome CVDs	Alicia Martin, et al. 2018	UK Biobank	Cases:self-reported angina/heart failure/AF et al Controls: not classified as cases	Cases:52320 Controls:340784
CVDs	Kurki, et al. 2023	FinnGen release 9	Cases: code FG_CVD Controls:not classified as cases	Cases:185353 Female: 8849 Male:96504 Controls:207070

Single nucleotide polymorphisms (SNPs) associated with CVDs were extracted from FinnGen's GWAS database for sensitivity analysis validation (185,353 cases, 207,070 controls) (Table 1). For all Mendelian randomization (MR) analyses, the inverse variance weighting (IVW) method was used as the primary analytical approach. Sensitivity analyses included MR-Egger regression, heterogeneity testing, multiple validity assessments, and leave-one-out analysis. Data formatting and statistical analyses were performed using R version 4.3.1 and the TwoSampleMR package (version 0.5.7). Two-step MR analyses were conducted to evaluate bidirectional associations between sleep apnea (SA) and depression, depression and CVDs, and the direct association between SA and CVDs. Additionally, the proportion of the effect of SA on CVDs mediated by depression was estimated.

Results

In the primary univariate inverse variance weighting (IVW) analysis, genetically predicted sleep apnea (SA) derived from FinnGen data was not significantly associated with cardiovascular diseases (CVDs) in the UK Biobank (P > 0.05) (Figure 1). Additional analyses using SA data from the UK Biobank and CVD data from FinnGen corroborated these findings. However, genetically predicted SA based on Finnish genomic data was positively associated with depression risk in the UK Biobank (IVW, odds ratio [OR] = 1.03, 95% confidence interval [CI]: 1.00–1.05, P = 0.033) (Figure 1). The MR-Egger intercept test indicated no evidence of directional horizontal pleiotropy, with all P values exceeding 0.05 (data not shown). Scatter plots demonstrated consistent positive associations between genetically predicted SA and depression risk (Figure 2), as well as between genetically predicted depression and CVD risk (Figure 3), across different analytical methods. In sensitivity analyses, depression from the Psychiatric Genomics Consortium (PGC) was used as the exposure, with CVD outcomes selected from FinnGen and the UK Biobank. Both analyses indicated that genetically predicted depression was significantly associated with increased CVD risk (FinnGen: OR = 1.16, 95% CI: 1.07–1.25, P = 0.001; UK Biobank: OR = 1.02, 95% CI: 1.00–1.03, P = 0.001) (Figure 1).

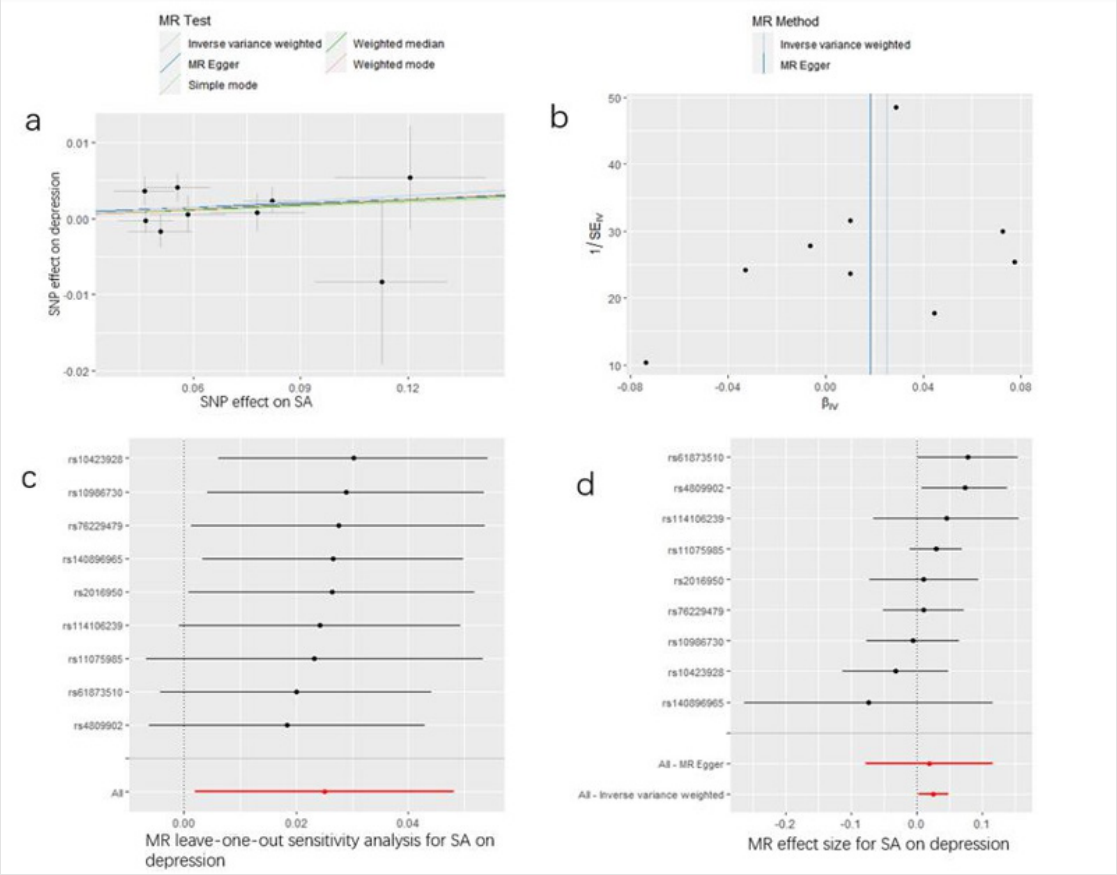

Figure 1:

a) Scatter plot of the SNP effects on SA(FinnGen) and Depression(UKB), with the slope of each line corresponding to the estimated MR effect per method.

b) Funnel plots show the Mendelian randomization(MR) causal estimates for each variant against their precision, with asymmetry in the plot indicating potential violations of the assumptions of MR.

c) Leave-one-out plot, MR sensitivity analysis for SA and Depression;

d) Forest plot of genetic associations between SA and depression; SNP: single-nucleotide polymorphism.

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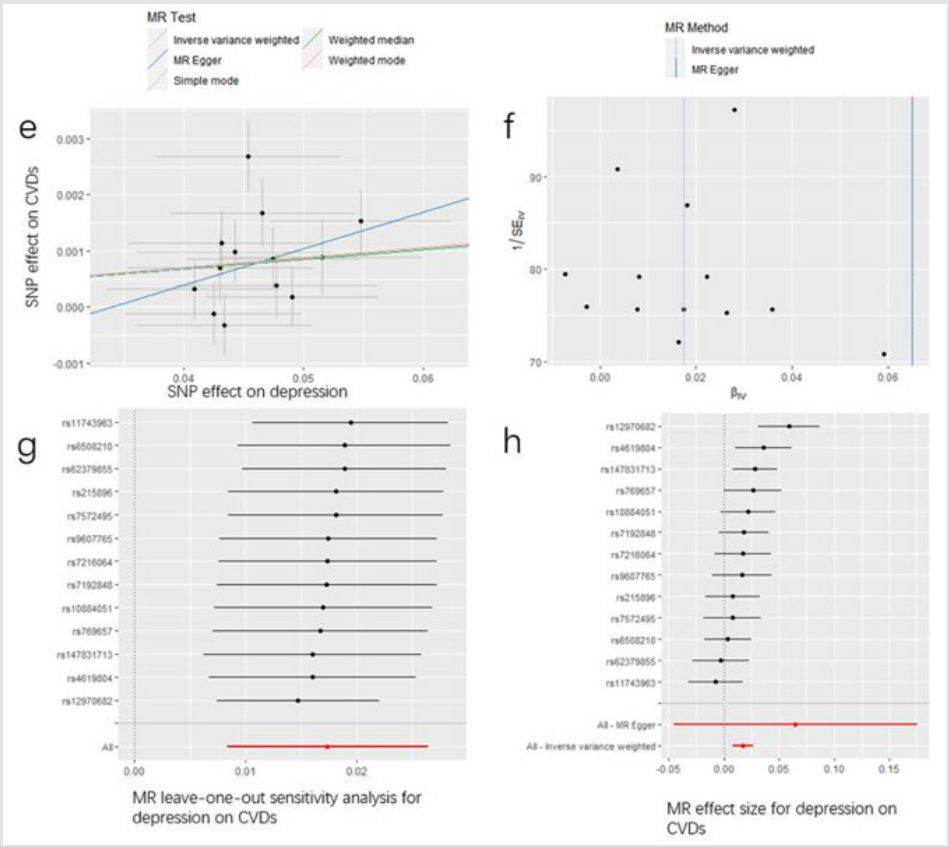

Figure 2:

e) Scatter plot of the SNP effects on Depression(FinnGen) and CVDs(UKB), with the slope of each line corresponding to the estimated MR effect per method.

f) Funnel plots show the Mendelian randomization (MR) causal estimates for each variant against their precision, with asymmetry in the plot indicatingpotential violations of the assumptions of MR.

g) Leave-one-out plot, MR sensitivity analysis for Depression and CVDs;

h) Forest plot of genetic associations between Depression and CVDs; SNP: single-nucleotide polymorphism; CVDs: cardiovascular diseases.

Exposure	Outcome	Method	SNP/F-statistics	OR(95%CI)	P.value
Sleep Apnea(UKB)	CVD(FinnGen)	IVW	3	0.09 (0.00 to 43.00)	0.832
Sleep Apnea(FinnGen)	CVD(UKB)	IVW	9	0.99 (0.99 to 1.01)	0.710
Sleep Apnea(FinnGen)	Depression(UKB)	IVW	9(41)	1.03 (1.00 to 1.05)	0.033
Depression(PGS)	CVD(FinnGen)	IVW	52(39)	1.16 (1.07 to 1.25)	0.001
Depression(PGS)	CVD(UKB)	IVW	23(39)	1.02 (1.00 to 1.03)	0.001
Depression(FinnGen)	CVD(UKB)	IVW	13(38)	1.02 (1.01 to 1.03)	0.001

Figure 3: Mendelian Randomization (MR) Analyses of the Association Between Genetically Predicted SA and Risk of CVDs, SA and risk of depression, Depression and risk of CVDs.

Discussion

This study did not find a direct causal relationship between genetically predicted sleep apnea (SA) and cardiovascular disease (CVD) risk. However, through two-step Mendelian randomization analyses, potential causal links were observed between genetically predicted SA and depression, as well as between genetically predicted depression and CVD. These findings suggest that the association between SA and CVD may be partially mediated by depression. The existence of a direct causal relationship between sleep apnea (SA) and cardiovascular diseases (CVDs) remains controversial. Previous observational cohort studies have generally suggested that SA increases the risk of CVDs. For instance, Azarbarzin et al. demonstrated that hypoxic burden in patients with SA was predictive of CVD risk and all-cause mortality [11]. Marin et al.'s observational study indicated that untreated severe SA was associated with a higher incidence of fatal and non-fatal cardiovascular events compared to mild-to-moderate SA [8]. However, findings from randomized controlled trials (RCTs), including those evaluating continuous positive airway pressure (CPAP) therapy, have been inconsistent. McEvoy et al. reported no significant reduction in cardiovascular events among CPAP-treated participants after a mean follow-up of 3.7 years [13]. Labarca et al.'s meta-analysis suggested that CPAP improved hypertension but did not confer benefits on atherosclerosis progression [14].

The limited duration of follow-up and other methodological factors in most RCTs have contributed to divergent interpretations of these results [15]. A potential causal association between SA and depression was observed in this study. Epidemiological evidence consistently supports an association between obstructive sleep apnea (OSA) and depression [11-13]. Data from the Veterans Health Administration beneficiaries revealed a significantly higher prevalence of mood disorders among individuals with OSA [14]. Peppard et al. identified SA as an independent risk factor for depression [15]. Furthermore, improvement in depressive symptoms following CPAP treatment provides additional support for the link between SA and depression [16-22]. Genetic analyses have also indicated shared genetic predispositions between OSA and depression [23]. The findings of this study indicate a causal association between genetically predicted depression and an increased risk of CVDs. In contrast, no causal effect of CVDs on depression was observed. This is consistent with a recently published study using similar methodologies [24]. Population-based studies further corroborate depression as a significant risk factor for the development of CVDs [25,26]. Traditionally, SA has been regarded as an independent risk factor for CVDs, supported by substantial epidemiological and clinical evidence. However, recent in-depth investigations and the publication of large-scale RCTs on CPAP therapy have prompted re-evaluation of this relationship. The current study provides a novel perspective, suggesting that the impact of SA on CVDs may be partially mediated through depression. Nevertheless, further mechanistic studies and larger RCTs are required to confirm these findings.

Strengths and Limitations

A key strength of this study lies in the use of three relatively independent samples for instrumental variable selection and the implementation of bidirectional Mendelian randomization analysis. These approaches provide alternative insights into the complex interplay between sleep apnea (SA) and cardiovascular diseases, as well as potential mediating factors. However, several limitations should be acknowledged. First, the data were derived exclusively from populations of European ancestry, necessitating validation in diverse ethnic groups. Second, the study lacked a more refined classification of cardiovascular disease subtypes, which may introduce potential bias. Third, SA was defined solely based on the Apnea-Hypopnea Index (AHI), without further stratification by symptom severity such as daytime sleepiness, arousal frequency, or degree of hypoxia, potentially leading to misclassification of exposure. Therefore, further basic science research and well-designed clinical randomized controlled trials are needed to validate the proposed hypothesis.

Conclusion

The findings of this Mendelian randomization study are consistent with those of certain prior observational studies, including the SAVE study, thereby reinforcing their conclusions. Furthermore, the results support the hypothesis that the impact of sleep apnea (SA) on cardiovascular disease (CVD) outcomes may be partially mediated by depression. Future research is warranted to evaluate the combined effect of SA and depression on response to continuous positive airway pressure (CPAP) therapy. Such an approach may enhance the identification of high-risk populations and assist clinicians in developing individualized treatment strategies.

Author's Contributors

Liu Hui wrote the manuscript and performed the statistical analysis; Shen Yi primarily conducted the statistical analysis; Li Chong was primarily responsible for study design and manuscript revision; all other authors contributed to the research and study design.

Ethical Statement

This Mendelian randomization study utilized publicly available summary-level data and did not require specific ethical approval.

Acknowledgment

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