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ORIGINAL RESEARCH

Causal Effect of Obstructive Sleep Apnea on Sick Sinus Syndrome: A Bidirectional Mendelian Randomization Study

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Background: Despite previous research establishing a connection between OSA and an increased risk of Bradyarrhythmias, the specific causal link between obstructive sleep apnea (OSA) and sick sinus syndrome (SSS) remains unexplored. This study aims to investigate the potential causal relationship between OSA and the development of SSS.

Methods: To evaluate the association between OSA and SSS, we utilized a bidirectional two-sample Mendelian randomization (MR) method. Genetic variant OSA association data were sourced from FinnGens genome-wide association studies, comprising 410,385 individuals, while SSS association data were obtained from deCODE genetics, involving a dataset of 1, 000,187 individuals. Effect estimates were computed through the utilization of inverse-variance weighting (IVW), MR-Egger, weighted median, maximum likelihood techniques, and sensitivity analyses were conducted using the Mendelian Randomization Pleiotropy Residual Sum and Outlier (MR-PRESSO) approaches.

Results: Our MR analyses utilizing IVW (fixed effects) revealed a heightened susceptibility to SSS among individuals with genetically predisposed OSA (OR= 1.493; 95% CI, 1.120–1.990; *P*= 0.006), utilizing a set of 7 single nucleotide polymorphisms as the instrumental variables. MR-Egger analysis indicated an absence of evidence for genetic pleiotropy, as reflected by the intercept value of −0.002 (SE 0.030, *P*= 0.930; global *P*= 0.719), but genetically predicted SSS did not causally contribute to OSA (OR= 0.997, 95% CI: 0.926–1.072, P= 0.930).

Conclusions: This MR analysis suggests a causal link between genetically predicted OSA and increased SSS risk. While finding no evidence for a causal relationship where SSS influences OSA.

Keywords: sick sinus syndrome, obstructive sleep apnea, causal association, Mendelian randomization

Introduction

Sick sinus syndrome (SSS) represents a cluster of syndromes characterized by the compromised function of the sinoatrial node (SAN) and its surrounding tissues, culminating in pathological conditions such as sinus bradycardia, sinoatrial block, or alternating episodes of atrial brady- and tachyarrhythmias.[1] Fatigue, decreased ability to exercise, and episodes of syncope are typical symptoms of SSS,[2] If untreated, SSS can result in significant morbidity and mortality, making it the leading cause for permanent pacemaker implantation worldwide.[3] Genome-wide association studies (GWAS) have identified six loci associated with SSS, and the role of Atrial Fibrillation (AF) in its development has been supported by Mendelian randomization (MR).[4] The prevalence of pronounced nocturnal sinus bradycardia in obstructive sleep apnea (OSA) ranges from 7.2% to 40%, accompanied by sinus pauses ranging from 3.3% to 33%.[3] While literature hints at a plausible association between OSA and various arrhythmias like atrial fibrillation and ventricular arrhythmias, the precise relationship between OSA and SSS remains relatively underexplored, necessitating further investigation.

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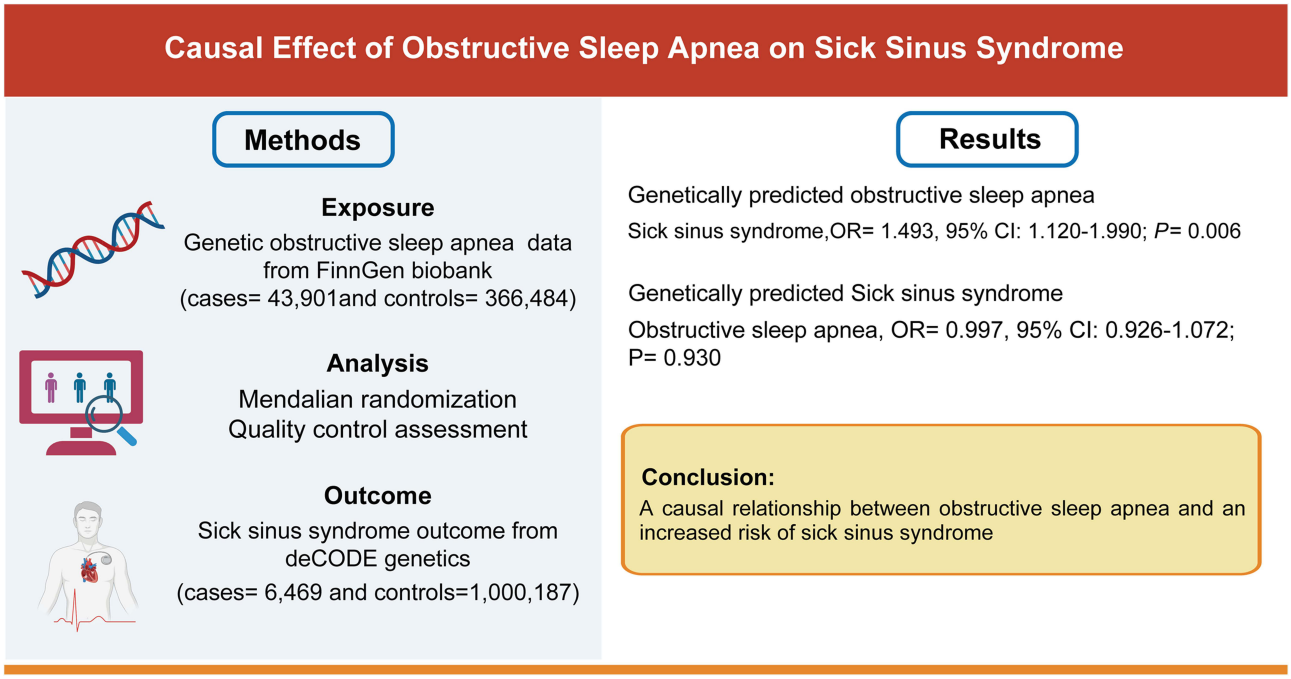
Graphical Abstract



OSA is a common sleep-related breathing disorder characterized by intermittent upper airway obstruction, resulting in low oxygen levels and disturbed sleep patterns. This results in intermittent hypoxia, disturbed sleep patterns, and increased sympathetic activity. OSA poses a significant public health concern, estimated to impact approximately 20–30% of men and 10–15% of women globally.[5] Observational studies have highlighted the prevalence of OSA among individuals with cardiovascular diseases (CVD), stroke, hypertension, myocardial infarction, cardiac arrhythmias, heart failure, and sudden cardiac death.[6,7] There is significant evidence indicating a connection between OSA and specific supraventricular arrhythmias, especially atrial fibrillation.[8] OSA can be associated with arrhythmias for a variety of reasons, including fluctuations in the autonomic nervous system, recurrent episodes of hypoxia, changes in carbon dioxide and acid-base balance, disruptions in sleep patterns, and increased negative pressure in the chest. Notably, prior investigations have indicated a ten times greater occurrence of OSA in individuals diagnosed with SSS in comparison to the overall population.[9,10] An extensive polysomnographic study conducted in multiple European centers discovered a remarkably high occurrence of undiagnosed OSA in patients with pacemakers, although the effect of OSA treatment on the requirement for pacing remains unclear.[10] While various studies have associated bradycardia and sinus pauses with OSA, statistically significant variations remain elusive.[11] A meta-analysis demonstrated a notably high prevalence of bradycardia among patients with OSA during both daytime (25%) and nocturnal (69.8%) periods, with 56.8% of individuals experiencing both conditions, suggesting a strong comorbidity between OSA and bradycardia.[2] Although existing literature hints at a plausible association between OSA and diverse arrhythmias, including atrial fibrillation, studies specifically addressing the link between OSA and SSS are scarce and often inconclusive.

Genetic factors are believed to play a key role in the susceptibility to both OSA and SSS. GWAS have identified several loci associated with OSA, in particular, SNPs in genes related to the autonomic nervous system, oxygen sensing, and ion channel regulation have been implicated in both OSA and arrhythmic disorders. The question of whether OSA contributes causally to the onset or aggravation of SSS remains a subject of substantial debate, necessitating further exploration. In observational studies, there is a risk of reverse causation and confounding bias that make it challenging to establish a causal link between OSA and SSS.

The role of Mendelian randomization studies in this context is crucial, as it employ genetic variants as instrumental variables to assess causality between risk factors and diseases.[12] The use of genetic variants in MR studies takes advantage of their random allocation during conception, which remains unaffected by disease progression or development. This characteristic minimizes the likelihood of unmeasured confounding factors and mitigates the challenges of reverse causation, commonly encountered in observational studies. In light of the gaps in current knowledge and the potential clinical significance of uncovering a causal link between OSA and SSS, this study aims to employ Mendelian randomization techniques to investigate the causal effect of OSA on the occurrence of SSS. By employing genetic instruments associated with OSA to evaluate its potential causal effect on the risk of SSS, this investigation seeks to offer valuable insights into their interrelation.

Methods

Study Design

Figure 1 illustrates the study design. This study utilized a two-sample MR approach to investigate the causal relationship between OSA and SSS. We used summary-level data obtained from recently accessible GWAS involving European-ancestry individuals. The genetic variations depend on three essential assumptions: (1) being related to the exposure in a reliable and robust manner; (2) remaining independent of confounding factors associated with both risk factors and outcomes; and (3) affecting the outcome solely through the exposure.[13] Throughout the analysis, we adhered to the STROBE-MR guidelines for conducting and reporting the MR analyses.[14] It is important to note that the original studies received ethical approval, and all GWAS summary statistics cited in this study were publicly available.

Data Sources

OSA. The genetic variants associated with OSA (n = 43,901) were sourced from a recent comprehensive GWAS released by Finland's national health registry (www.finngen.fi/en, phenocode: R10_G6_SLEEPAPNO).[15] FinnGen, a genomics

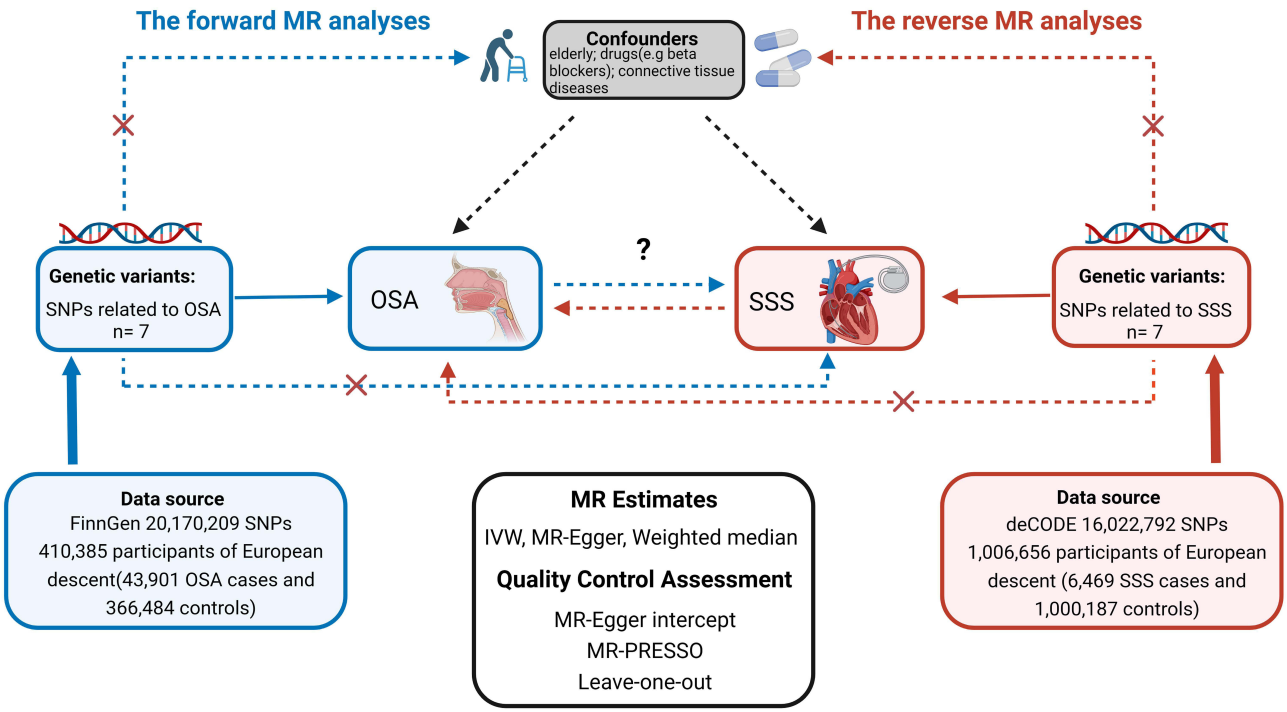


Figure 1 Study design. The purpose of this bidirectional two-sample MR analysis is to investigate the causal relationship between OSA and SSS. The GWAS meta-analysis for this study is from mixed-sex European cohorts.

Abbreviation: GWAS, Genome-wide association study; IVW, inverse variance weighted; MR, Mendelian randomization; OSA, obstructive sleep apnea; SNP, single-nucleotide polymorphisms; SSS, sick sinus syndrome.

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project of significant magnitude, has examined more than half a million samples from the Finnish biobank. By linking genetic variations with health information, the study aims to comprehend the causes and susceptibilities of diseases. The collaboration involves research institutions and biobanks in Finland, as well as international industry partners. The study cohort encompassed 410,385 individuals of predominantly European ancestry, among whom 43,901 were identified as OSA patients through Finland's national health records. OSA was diagnosed based on the International Classification of Diseases, Tenth Revision (ICD-10) and Ninth Revision (ICD-9) codes (ICD-10: G47.3, ICD-9:3472A). Subjective symptoms, clinical examination, and sleep registrations were combined in the diagnostic process, using an apnea-hypopnea index or respiratory event index of 5/hour as the determining factor. The study primarily includes middle-aged and older adults, with a higher proportion of men, reflecting the typical demographic distribution of OSA in the general population. The cohort also includes individuals with comorbid conditions, such as hypertension and cardiovascular disease, which are frequently associated with OSA.

SSS. We accessed summary-level data on SSS outcomes from a comprehensive meta-analysis of GWAS comprising 6,469 SSS cases and 1,000,187 controls from deCODE genetics, the Copenhagen Hospital Biobank (CHB-CVS/DBDS), the UK Biobank, and The Nord-Trøndelag Health Study (HUNT).[4] Diagnosis of SSS was established based on the criteria outlined in the International Classification of Diseases 9th (ICD-9: 427.8) or 10th revision (ICD-10: I49.5), derived from hospital records and/or outpatient clinic visits. The majority of patients are Icelandic descent, also includes participants from other European backgrounds due to the inclusion of data from international biobanks such as UK biobank and Copenhagen Hospital Biobank. Patients with SSS were predominantly middle-aged or older, as the condition is more commonly seen in adults, particularly with increasing age. The study cohort showed a higher prevalence of SSS in males than females, included patients with various cardiovascular comorbidities, including atrial fibrillation, coronary artery disease, and hypertension. Our access to these datasets involved retrieving the information from the deCODE genetics database (https://www.decode.com), and we refer to the cited GWAS papers for detailed information regarding quality control measures adopted in these studies.

Genetic Instrumental Variables

As instrumental variables, we selected single-nucleotide polymorphisms (SNPs) reaching genome-wide significance levels ($P< 5\times10^{-8}$). Utilizing the 1,000 Genomes European reference panel, we estimated linkage disequilibrium (LD) among these SNPs.[16] The SNPs examined in our study were located in separate gene regions and did not show any notable linkage disequilibrium (r2 < 0.001) or proximity (distance > 10,000 kb) to one another. In addition, any SNPs that overlapped or were associated with LD were not included in the analysis of Mendelian randomization (MR). Furthermore, we removed palindromic single nucleotide polymorphisms (SNPs) that had allele frequencies between 0.45 and 0.55, specifically referring to SNPs with A/T or G/C alleles and falling within the range of an "intermediate allele frequency". Afterward, we obtained genetic variations and their associated data from the GWAS dataset related to the result, excluding genetic variations with a minor allele frequency (MAF) less than 0.01. To ensure the accuracy of our analysis, we thoroughly investigated every instrumental variable for any possible confounding characteristics by utilizing the PhenoScannerV2 database, which contains information on human genotype-phenotype associations. SNPs representing these confounding traits above a threshold of $r^2 > 0.80$ were disregarded.[17] Finally, to ensure the reliability of our analysis, we excluded SNPs that were strongly linked to outcomes (P> 5×10-8) from the MR design. After these filtering steps, the remaining SNPs were used in the MR analysis.

Strength of Instrumental Variables

In our MR analysis, we calculated the proportion of phenotypic variation explained by each instrument using the formula: $R^2 = 2 \times (1 - MAF) \times MAF \times \beta/SD$, MAF represents the minor allele frequency, β is the effect size of the SNP on the exposure, and SD is the standard deviation which is not obtained directly, it needs to be converted as follows: $SD = SE \times \sqrt{N}$ Here, SE refers to the standard error, and N represents the sample size. To assess the strength of the selected genetic instruments in MR analysis, we computed the F-statistic utilizing the equation: $F = R^2/\left(1 - R^2\right) \times (N - k - 1)/k$. Here, R^2 represents the total ratio of phenotypic variability elucidated by all SNPs, N stands for the sample size of the GWAS associated

with SNP-physical activity association, and *k* represents the total count of SNPs selected for the MR analysis. F statistics greater than 10 generally indicate robust instrumental bias in explaining phenotypic variation, whereas IVs with an F statistic< 10 were deemed "weak instruments" and subsequently excluded.[18]

Statistical Analysis

MR Analysis

The primary statistical analysis employed the two-sample MR approach, known for its reduced susceptibility to bias from observational confounding effects compared to MR with overlapping samples. Specifically, as the primary analytical technique, we employed the IVW method, which utilizes inverse variance weighting.[19] The IVW method offers advantages over MR-Egger models by effectively balancing pleiotropic effects and addressing heterogeneity concerns arising from variant-specific effects. Furthermore, to visualize the causal estimates, every single SNP was methodically graphed against its impact on the susceptibility to SSS. The MR analysis results were succinctly summarized in both graphical and tabular formats, featuring odds ratios (ORs) and corresponding 95% confidence intervals (CIs) for all beta estimates. The causal estimates were visually represented by the slopes and directions of the trend lines, elucidating the relationship between the genetic instrument and SSS risk.

Heterogeneity, Pleiotropy, and Sensitivity Assessment

To enhance robustness against pleiotropic and/or invalid instruments, we performed sensitivity analyses using a range of complementary MR methods:

Weighted Median Approach:[20] A robust estimator that provides reliable causal estimates even if up to 50% of the genetic variants are invalid instruments.

MR-Egger Regression:[21] This method accounts for pleiotropy by performing weighted linear regression between SNP-exposure and SNP-outcome associations, assuming the Instrument Strength Independent of Direct Effect (InSIDE) assumption. A non-significant MR-Egger intercept was observed, indicating no evidence of directional pleiotropy.

MR-PRESSO:[22] Mendelian Randomization Pleiotropy Residual Sum and Outlier analysis was used to identify and correct horizontal pleiotropic outliers.

Contamination Mixture Model:[23] Applied to handle complex scenarios where instruments exhibit substantial heterogeneity.

Additionally, we conducted heterogeneity tests using Cochrans Q-statistics and I^2 to detect SNP-specific variability within the IVW analysis. To identify and rectify horizontal pleiotropic outliers in MR analysis involving multiple instruments, we employed the Mendelian Randomization Pleiotropy Residual Sum and Outlier approach. Additionally, our supplementary analysis entailed a leave-one-out sensitivity analysis across iterations to assess whether the removal of different SNPs affected the overall MR estimates.[24] We used these combined approaches ensured the robustness and reliability of our findings, reducing the likelihood of bias or influence from outliers.

Statistical Power

Moreover, we performed a power analysis utilizing the mRnd power calculator, an online tool application (http://cnsgenomics.com/shiny/mRnd/). Given the sample size of 1006 656 individuals and an α of 5%, we possess 80% power to detect an OR of 1.49 for SSS with OSA.

Software and Packages

Significant evidence for a causal effect was determined with a two-sided P-value < 0.05 was observed. All statistical analyses were performed using the TwoSampleMR,[25] MR-PRESSO[22], LDlinkR, and Mendelian Randomization packages[26] within the R statistical software environment (Version 4.0.5; https://www.R-project.org).

Results

Causal Relationship Estimates for OSA on SSS

Initially, we first investigated the causal impact of OSA on the risk of SSS. The OSA exposure dataset for OSA initially comprised 22 instrumental SNPs identified from the SSS outcome GWAS datasets. Following the harmonization of exposure and outcome datasets, we further excluded 5 SNPs (rs12167677, rs1800437, rs200370809, rs4794016, rs7683676) due to their palindromic nature and moderate allele frequencies. 2 SNPs with a MAF< 0.01 were excluded (rs114106239, rs143490656). Additionally, we eliminated SNPs associated with confounding factors, 3 SNPs (rs11981973, rs1228509, rs61873510) were excluded due to obesity-related parameters including weight, BMI, waist circumference, hip circumference, and total body fat mass. These exclusion criteria were applied to reduce potential biases in the results, as palindromic SNPs and those with moderate allele frequencies may lead to ambiguous allele matching across datasets, while SNPs associated with confounders could distort the estimated effect.

Subsequently, the MR-PRESSO outlier test was performed to check for outliers that could bias the results. No outlier variants were identified in this analysis. Ultimately, a total of 12 SNPs were retained for Mendelian randomization analyses assessing the causal relationship between OSA and SSS risk. According to F-statistics, 5 SNPs (rs10507084, rs113955098, rs45551238, rs59333125, rs76229479) as weak instrumental variants (F< 10), we obtained 7 SNPs as strong instrumental variants (F≥10), as detailed in Supplementary Table S1. We focused on the 7 strong genetic instrumental variants to illustrate the impact of OSA on SSS (Table 1). Collectively, these selected instruments explained approximately 0.053% of the phenotypic variation associated with OSA, yielding an F-statistic of 30.887.

Utilizing these 7 SNPs as instrumental variables, the two-sample MR analyses demonstrated a causal impact of genetically predicted OSA on the likelihood of SSS. Both the IVW-fixed and IVW-random approaches exhibited a noteworthy correlation, suggesting that genetically anticipated OSA was associated with a heightened susceptibility to SSS (OR 1.493; 95% CI, 1.120–1.990; *P*= 0.006). Weighted median analysis showed consistent directional effects (OR 1.471; 95% CI, 1.026–2.109; *P*= 0.036) (Figure 2, Supplementary Table S2). This indicates that individuals genetically predisposed to OSA may have approximately a 47–49% higher risk of developing SSS compared to those without genetic risk factors for OSA. Clinically, this highlights the importance of early identification and management of OSA in preventing SSS. Figure 3A shows that the scatter plots and trend lines suggest a positive correlation between genetically predicted OSA and the risk of SSS. For detailed individual SNP effects of OSA on SSS, please refer to the forest plot in Supplementary Figure S1.

MR Quality Control Assessment

Heterogeneity analysis utilized Cochrans Q statistic. The variant-specific effects did not exhibit significant heterogeneity (MR Egger Q= 4.350, *P*= 0.500; IVW Q= 4.359, *P*= 0.628). The MR-Egger regression intercepts and global tests did not provide any indication of a directional pleiotropic effect among the genetic variants, suggesting that the identified SNPs are

Table 1 Characteristics of Instrumental Variables Associated with OSA

SNP	Chrom	Position	Prioritized Genes	Other Allele	Effect Allele	EAF	Effect on OSA			Effect on SSS		
							Beta	SE	*P* value	Beta	SE	*P* value
rs10986727	chr9	125375336	GAPVD1	A	G	0.619	−0.045	0.007	1.22E-09	0.006	0.020	0.755
rs11075985	chr16	53771295	FTO	C	A	0.429	0.084	0.007	3.10E-30	0.034	0.020	0.087
rs13040169	chr20	52322997	ZFP64	A	G	0.167	−0.060	0.010	1.16E-09	−0.022	0.025	0.375
rs1885767	chr13	53167993	OLFM4	A	G	0.594	−0.043	0.007	5.58E-09	0.019	0.020	0.331
rs28815269	chr2	136221960	CXCR4	G	A	0.616	0.045	0.008	1.74E-09	−0.003	0.022	0.903
rs557359	chr9	76650301	PRUNE2	A	G	0.747	0.047	0.008	2.18E-08	−0.065	0.025	0.010
rs6955671	chr7	75073650	RCC1L	C	T	0.628	−0.043	0.008	9.46E-09	0.011	0.020	0.573

Abbreviations: CHR, chromosome; EAF, Effect allele frequency; OSA, obstructive sleep apnea; SE, standard error; SNP, single nucleotide polymorphism; SSS, sick sinus syndrome.

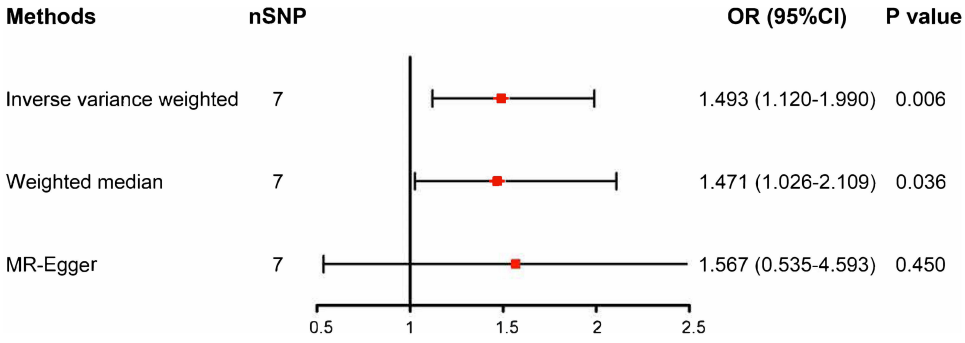

Figure 2 Associations of genetically predicted OSA with risk of SSS. P-value and 95CI% specific value are listed on the right side.
Abbreviations: CI, confidence interval; MR, Mendelian randomization; OR, odds ratio; OSA, obstructive sleep apnea; SNP, single-nucleotide polymorphism; SSS, sick sinus syndrome.

unlikely to be influenced by other confounding factors or alternate pathways. The intercept was −0.002 with a standard error of 0.030 and a *P*-value of 0.930. The global test yielded a *P*-value of 0.719 (Supplementary Table S3). Hence, a fixed-effects model was adopted to estimate the MR effect size. This strengthens the clinical confidence in using these genetic markers as reliable predictors for the causal relationship between OSA and SSS. Moreover, Leave-one-out sensitivity analysis showed that no individual SNP significantly impacted the association between OSA and SSS (Figure 3B). The detailed results of the leave-one-out analysis for the effects of the seven OSA SNPs on SSS are presented in Supplementary Table S4. With a statistical power of 0.98, the MR analysis demonstrates a robust capability to detect a significant causal effect of OSA on SSS, even in large populations. This high power ensures that the findings are not due to random chance and can be confidently applied to clinical settings, guiding future interventions for OSA management to reduce the risk of SSS.

Reverse Mendelian Randomization Analysis

We conducted reverse-directional MR analyses to investigate the causal impact of SSS on OSA. The GWAS datasets of SSS were utilized as exposure data, comprising 8 instrumental SNPs. Notably, an outlier was identified in the MR-PRESSO analyses, prompting us to performed outlier correction before assessing the relationship between these SNPs and OSA (Supplementary Table S5).

MR analysis employing the IVW method showed that genetically predicted SSS did not causally contribute to OSA (OR= 0.997, 95% CI: 0.926–1.072, P= 0.930) (Supplementary Figure S2A). Consistently, similar results were observed across other statistical methods (Supplementary Table S6). No indications of heterogeneity were detected using the Cochrans Q test (Q= 11.641, I^2= 0.485, P= 0.070), MR-Egger intercept test (intercept, 0.005; SE 0.015; P= 0.755) and Global test showed no pleiotropic effect (P= 0.082). In the leave-one-out plot, no single SNP significantly impacts the causal relationship between SSS and OSA (Supplementary Figure S2B).

Discussion

This Mendelian randomization study aimed to explore the potential causal relationship between obstructive sleep apnea and sick sinus syndrome. Results of the two-sample MR study derived from large-scale GWAS data combined revealed that genetically predicted obstructive sleep apnea increases the risk of developing SSS. These findings provide compelling evidence supporting a causal effect of OSA on the onset and progression of SSS. Moreover, diverse MR models consistently yielded robust results, affirming the stability and reliability of our findings across various sensitivity analyses. The convergence of evidence from these multiple approaches strengthens the confidence in the observed association between OSA and the development of SSS.

The clinical implications of these results are noteworthy. Recognizing the substantial prevalence of both OSA and SSS, comprehending their potential causal association underscores the criticality of early identification and proactive management of OSA in individuals vulnerable to SSS. A literature-based analysis for 16 countries from 17 studies using American Academy of Sleep Medicine (AASM) 2012 diagnostic criteria and AHI threshold values, estimated a global prevalence of 936 million adults

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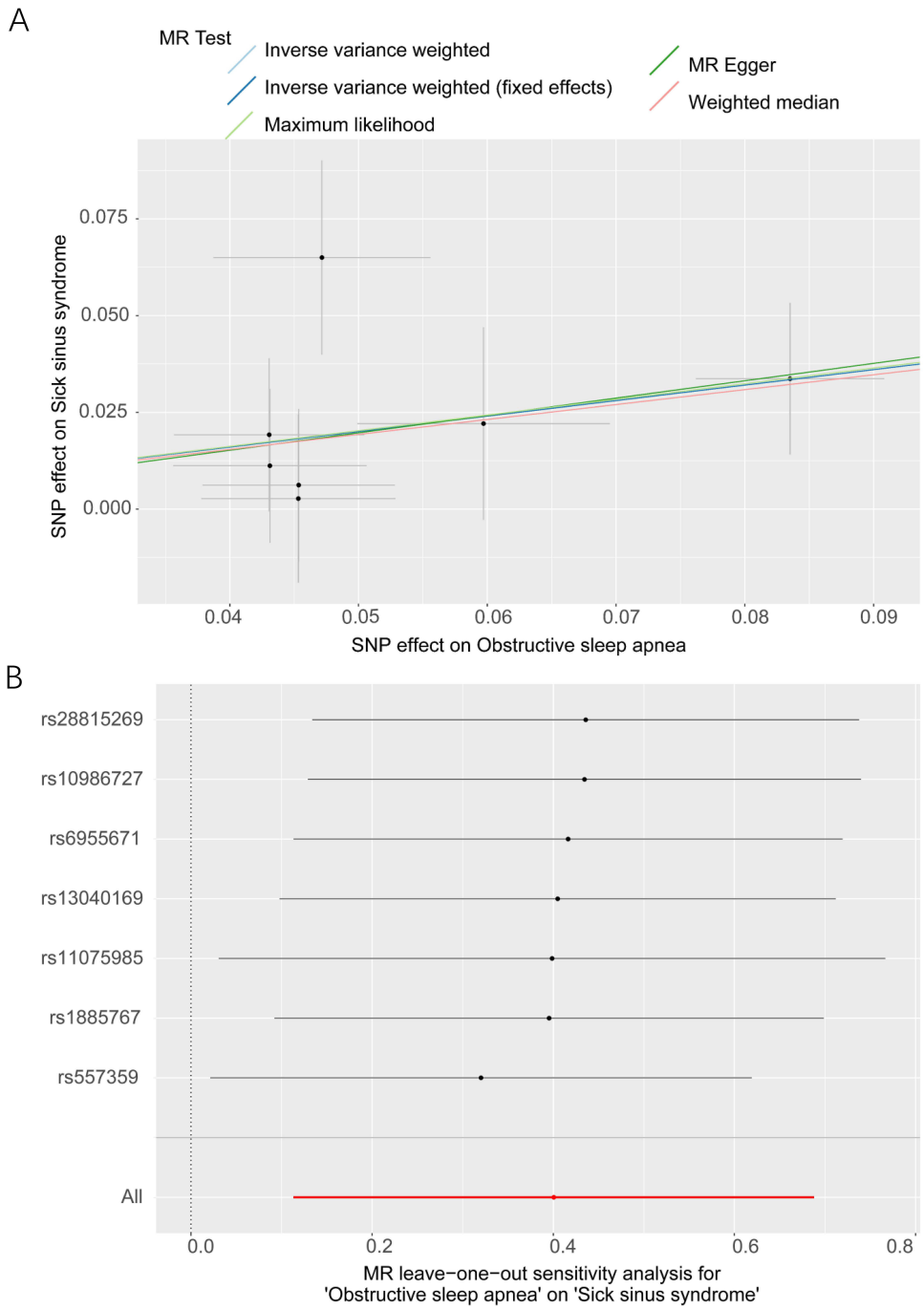

Figure 3 Scatter plots of causal associations and leave-one-out sensitivity analysis for OSA on SSS. (**A**) Individual estimates about the causal effect of OSA on SSS. (**B**) leave-one-out analysis for OSA on SSS.
Abbreviations: CI, confidence interval; MR, Mendelian randomization; OSA, obstructive sleep apnea; SNP, single-nucleotide polymorphism; SSS, sick sinus syndrome.

aged 30–69 years with mild to severe obstructive sleep apnea,[27] with the highest prevalence observed among Chinese individuals, followed by Americans, Brazilians, and Indians.[27] OSA patients frequently experience long pauses in breathing and bradycardia. A study featured in the *European Heart Journal* enrolled 23 patients with moderate to severe OSA, where all subjects received insertable loop recorders capable of monitoring their heart rhythm for 16 months. Results indicated that 11 (47%) patients exhibited severe cardiac rhythm disorders. The long-term monitoring demonstrated heightened sensitivity in detecting bradycardia and prolonged pauses.[28] Sleep-related bradyarrhythmias, such as sinus bradycardia, sinus pauses, and first-degree and Mobitz I second-degree atrioventricular block, are frequently observed in OSA patients during sleep.[3]

Moreover, indirect evidence suggests an association between OSA and SSS. For instance, atrial stimulation has shown to reduce OSA episodes, and the application of continuous positive airway pressure (CPAP) via noninvasive ventilation methods can effectively mitigate sleep-related bradyarrhythmias.[29] A systematic review and meta-analysis included 34 articles from 7204 records and 4852 patients highlighted the pooled prevalence of daytime and nocturnal bradycardia among OSA patients, further supporting the potential connection between OSA and bradycardia.[2]

Our study substantiates a causal relationship between OSA and SSS, while no evidence was found for a reverse causal relationship from SSS to OSA. These findings support existing guidelines recommending OSA screening in all SSS patients, underlining the possibility of undiagnosed OSA as a potential cause of SSS. According to the European Society of Cardiology guidelines, sleep-disordered breathing should be considered as a possible diagnosis in cases of bradyarrhythmias.[30] Simultaneously, our findings emphasize the importance of screening for SSS in individuals with OSA.

Interventions targeting OSA, such as CPAP therapy or lifestyle modifications, may hold promise in potentially mitigating the risk of developing SSS or slowing its progression. However, prospective studies are essential to validate these hypotheses and establish concrete clinical recommendations. While CPAP therapy is well-established as an effective treatment for OSA, recent studies suggest that its impact on cardiovascular outcomes, including arrhythmias may vary. A multicenter randomized controlled trial conducted at 15 hospitals in Spain, involving patients diagnosed with acute coronary syndrome (ACS) who underwent respiratory polygraphy, OSA patients were randomly assigned to either CPAP treatment or usual care, while those without OSA were placed in the reference group. After a median follow-up of 3.35 years, the results showed that OSA was not associated with a higher incidence of cardiovascular events, and CPAP treatment did not significantly reduce this risk.[31] On the other hand, insights from the Pays de la Loire cohort were linked to health administrative data and showed that patients with OSA who demonstrate elevated OSA-specific hypoxic burden are at higher risk of a cardiovascular event and all-cause mortality.[32] The benefits of CPAP treatment on arrhythmias,[33] ameliorating vascular inflammation, and reducing unstable plaque volume.[34] The association of bradycardia and sinus arrest with OSA has been noted across various studies. However, establishing a causal link in this association remains unclear. There is great variation in the proportions reported in previous studies of OSA patients with bradycardia. Most of these studies recruited less than 100 subjects, and they differed in their definition of bradycardias and inclusion of bradyarrhythmias. Addressing this gap in knowledge, our study employed Mendelian randomization methodology to provide novel insights into this relationship.

OSA and SSS share several common risk factors, such as advancing age and obesity, which may contribute to the escalating prevalence of both OSA and SSS, along with atrial fibrillation (AF). Obesity and OSA commonly coexist, often interact, and may have similar consequences. As compared to obesity and AF (HR, 1.49 [95% CI, 1.67–1.87]), OSA demonstrates a stronger association with AF (HR, 2.18 [95% CI, 1.34–3.54]), suggesting that OSA may be a stronger AF driver.[35] This implies that OSA could be considered an independent cause of AF, a conclusion supported by a previous MR study.[8] The biological mechanisms underlying the observed causal relationship between OSA and SSS likely involve multiple interconnected pathways. One prominent mechanism is the dysregulation of the autonomic nervous system, with increased sympathetic and reduced parasympathetic tone in OSA patients. This imbalance is known to promote arrhythmic events, including bradycardia and sinus arrest, which are key features of SSS. Furthermore, intermittent hypoxia during apneas has been shown to cause structural changes in the myocardium, including atrial dilation and fibrosis, which predispose individuals to arrhythmia. The genetic overlap between OSA and cardiac arrhythmia may also contribute to this relationship, with specific genetic variants influencing both airway regulation and cardiac ion channel function. Lifestyle factors such as obesity, physical activity, and smoking are well-known risk factors for both conditions and may interact with genetic susceptibility to increase the risk of SSS. Environmental exposures such as air pollution and psychosocial stress could also influence the relationship between OSA and SSS. Further research is warranted to explore whether interventions aimed at ameliorating OSA could lead to a reduction in the incidence or severity of SSS and other related arrhythmias. This potential connection could offer new avenues for preventive strategies in clinical practice.

The strength of this study lies in its utilization of a two-sample Mendelian randomization analysis design, incorporating exposure to OSA and the effects of SSS related SNPs obtained from large-scale GWAS. We investigated the impact of OSA on SSS based on the latest and extensive sample size data. MR study can strengthen causal inference compared to observational studies. However, it is important to acknowledge that, despite the application of Mendelian

randomization to minimize confounding and reverse causation, the potential for pleiotropy or incomplete control of confounders cannot be entirely eliminated. To strengthen the robustness of our findings and provide a more comprehensive understanding of the underlying mechanisms, future studies employing larger sample sizes and more extensive genetic instruments are warranted.

Several limitations must be acknowledged in this study. First, the OSA dataset primarily consists of selected populations, specifically individuals from the Finnish cohort, which may limit the generalizability of our findings to broader populations. The genetic associations identified in this study may not necessarily hold in populations with different genetic backgrounds, environmental exposures, or lifestyle factors. Therefore, the findings should be interpreted with caution, and future research should aim to replicate them in more diverse cohorts to assess their applicability across various populations. The presence of different proportions of comorbidities and medication use between SSS cases and controls could introduce confounding factors that may influence the observed associations between OSA and SSS. Although we attempted to control for these variables, residual confounding remains a possibility. A major strength of SSS dataset is the large sample size of SSS patients and the availability of comprehensive phenotypic and genotypic data. While differing rates of comorbidities and medication use between SSS cases and controls may introduce confounding, the consistent associations of SSS variants with both SSS and pacemaker implantation across cohorts support their genuine impact on cardiac conduction. The GWAS data on SSS are restricted to an older population, which might limit the generalizability of the findings to younger individuals who may have different risk factors or disease mechanisms. Similarly, The Finland G6_SLEEPAPNO dataset may not representative of other ethnic groups, which could restrict the applicability of the findings to populations outside of Finland. While the dataset may contain a significant number of participants, it might still lack sufficient power to detect rare variants or associations, especially in subgroups. Furthermore, Sleep apnea can present with varying phenotypes, and the dataset may not capture the full spectrum of these variations, potentially skewing results. The prevalence of comorbid conditions may differ from other populations, introducing confounding factors that could impact the interpretation of sleep apnea associations. Finally, the uneven age or gender distribution within the dataset could affect the validity of findings and their applicability to broader demographics.

Conclusions and Public Health Implications

We present compelling genetic evidence supporting a causal relationship between obstructive sleep apnea and an increased risk of sick sinus syndrome, however we found no evidence supporting a causal relationship in the reverse direction, where SSS influences OSA. While our findings do not imply that OSA is a modifiable risk factor for SSS in the genetic sense, they underscore the clinical relevance of addressing OSA as a potential contributor to SSS risk. Considering the significant burden of SSS, a leading indication for pacemaker implantation globally, improving the management of OSA could help reduce healthcare costs associated with device implantation, hospitalizations, and related complications. Public health campaigns emphasizing the recognition and management of OSA as a modifiable risk factor for cardiovascular disease could enhance awareness and reduce disease burden. Policies incentivizing sleep health assessments and promoting adherence to OSA therapies may have far-reaching benefits for cardiovascular outcomes, including arrhythmia prevention.

Data Sharing Statement

The data presented in this study are available on reasonable request from the corresponding author. Original data on OSA were sourced from FinnGen study (www.finngen.fi/en, phenocode: R10_G6_SLEEPAPNO), and SSS datasets involved retrieving the information from the deCODE genetics database (https://www.decode.com).

Ethics Declarations

The ethics committee of Soochow University strictly adheres to the Declaration of Helsinki and the International Ethical Guidelines for Health-related Research Involving Humans. Our study used publicly available GWAS summary statistics that has been legally obtained, and data generated by observation and without interfering with public acts, meeting the conditions for exemption from review as item 1 and 2 of Article 32 of the Measures for Ethical Review of Life Science and Medical Research Involving Human Subjects dated February 18, 2023, China.

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Author Contributions

WC, Conceptualization, Data curation, Formal analysis, Writing – original draft; JL, Conceptualization, Data curation, Writing – review and editing; TJ, Conceptualization, Data curation, Visualization, Project administration, Writing – review and editing; LL, Conceptualization, Data curation, Visualization, Writing – review and editing; WP, Formal analysis, Writing – original draft; BJ, Visualization, Writing – review and editing; YZ, Visualization, Writing – review and editing; XS, Project administration, Writing – review and editing;

All authors agreed on the journal to which the article will be submitted, agreed on all versions of the article before submission and agreed to take responsibility and be accountable for the contents of the article.

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Disclosure

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