

Genetic Evidence for the Association Between Sjögren's Syndrome and Cardiovascular Disease Risk

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Abstract

Background: Previous studies have indicated that patients with Sjögren's syndrome (SS) exhibit an increased risk of cardiovascular disease (CVD). However, the causal association between SS and CVD risk remains to be elucidated.

Objectives: This investigation explored the genetic relationship between SS and CVD risk through Mendelian randomization (MR).

Methods: We identified the genetic association between SS and CVD incidence via two-sample MR analysis based on summary statistics from publicly available genome-wide association studies (GWAS). The inverse-variance weighting (IVW) method was used for the primary analysis in our study. Additionally, we conducted several sensitivity analyses to confirm the stability and reliability of the MR results.

Results: MR analysis revealed that SS was not significantly associated with the risk of various CVDs, including atrial fibrillation (AF) (odds ratio [OR] = 0.98, 95% confidence interval [CI] = 0.95–1.01; $p = 0.22$), ischemic stroke (IS) (OR = 0.99, 95% CI = 0.93–1.05; $p = 0.68$), heart failure (HF) (OR = 1.00, 95% CI = 0.96–1.04; $p = 0.91$), coronary artery disease (CAD) (OR = 0.99, 95% CI = 0.94–1.04; $p = 0.60$), and myocardial infarction (MI) (OR = 1.01, 95% CI = 0.97–1.06; $p = 0.61$).

Conclusions: Our MR study did not provide genetic evidence supporting a causal association between SS and CVD incidence. The associations reported in prior observational studies may be due to residual confounding and reverse causality.

Keywords: Sjogren's Syndrome; Cardiovascular Diseases; Mendelian Randomization Analysis; Coronary Artery Disease.

Introduction

Cardiovascular disease (CVD) is the foremost cause of morbidity and mortality worldwide; every year, millions of people are affected by conditions such as atrial fibrillation (AF), heart failure (HF), coronary artery disease (CAD), myocardial infarction (MI), and ischemic stroke (IS). A recent epidemiological study indicated that CVD was projected to cause approximately 19 million deaths globally in 2020, representing an 18.7% increase from 2010.¹ According to the Medical Expenditure Panel Survey (MEPS), the combined annual direct and indirect costs of CVD in the United States were estimated at \$378 billion between 2017 and 2018.² Individuals with CVD typically experience a diminished quality of life, limited physical functionality, frequent

hospitalizations, and a need for ongoing medical care. These factors collectively contribute to significant productivity losses and broader economic impacts on society.^{3,4} Common autoimmune diseases, such as systemic lupus erythematosus and rheumatoid arthritis, have been identified as risk factors for CVD.⁵⁻⁷ However, the causal relationship between CVD and Sjögren's syndrome (SS) is still unclear. A meta-analysis by Beltai et al. highlighted that patients with SS exhibited an increased risk of HF, coronary morbidity, cerebrovascular morbidity, and thromboembolic morbidity.⁸ Another meta-analysis indicated a potential link between SS and subclinical atherosclerosis.⁹ However, a large-scale retrospective study revealed no association between SS and HF.¹⁰ Additionally, the consistency of the association between SS and various types of CVD has varied across different studies.^{8,10-12} The interference of confounders and the issue of reverse causality further complicate the interpretation of results from traditional observational studies.¹³ This prevailing uncertainty underscores the imperative for methodologically robust investigations, such as Mendelian randomization (MR) studies, to elucidate the potential genetic underpinnings of the causal relationship between SS and CVD outcomes. MR represents a novel epidemiological method that employs single-nucleotide polymorphisms (SNPs)

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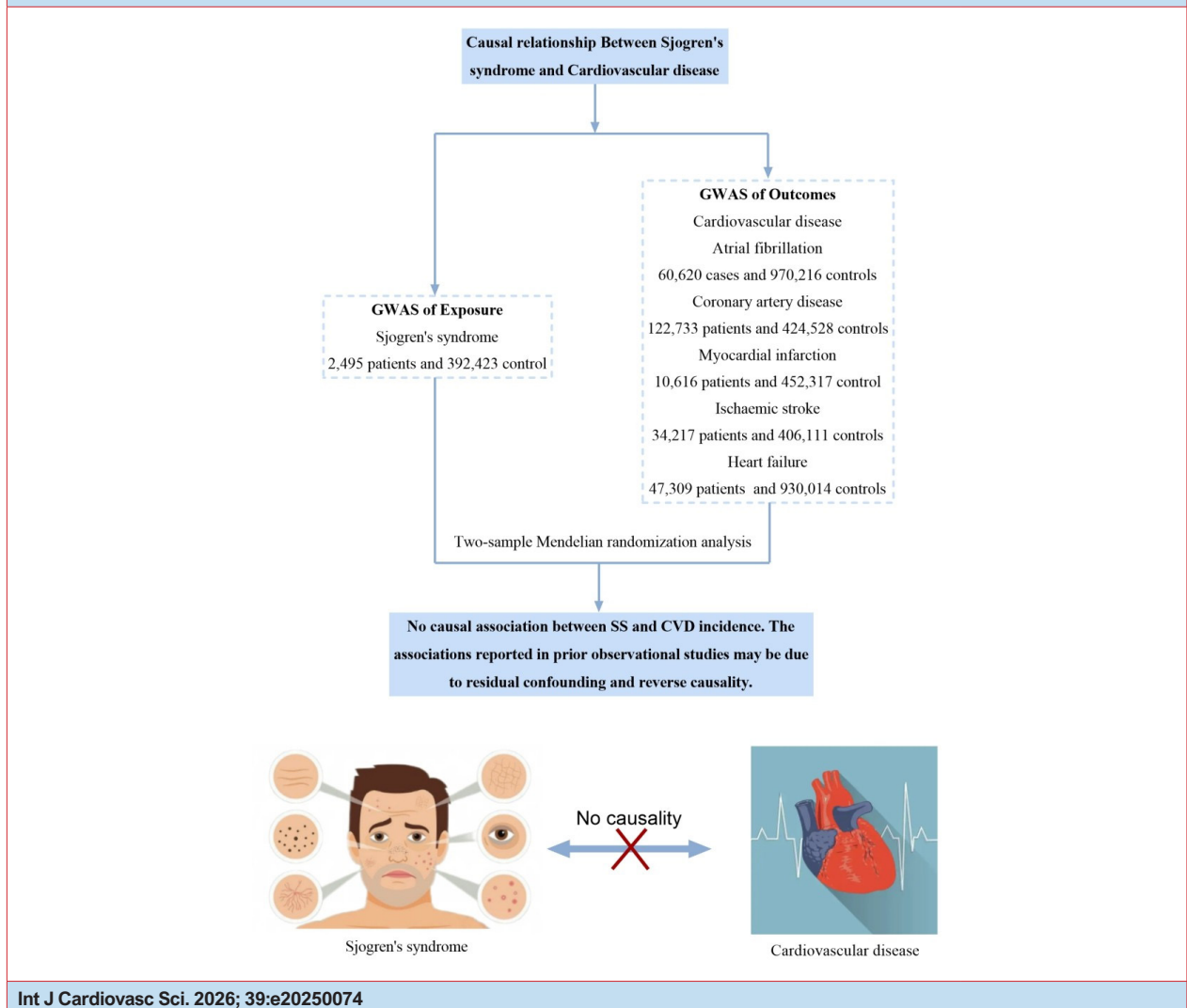
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Central Illustration: Genetic Evidence for the Association Between Sjögren's Syndrome and Cardiovascular Disease Risk

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No casual association between SS and CVD risk through MR

as instrumental variables (IVs) to infer causal relationships between exposures and outcomes.¹⁴ MR offers a significant advantage in mitigating the influence of confounding variables and preventing reverse causation. At conception, individuals inherit a random assortment of genetic variants from their parents. This random allocation mimics the random assignment in a randomized controlled trial, which is the gold standard for avoiding confounders.¹⁵ Moreover, MR helps to prevent reverse causation by utilizing genetic variants as IVs, which are fixed at birth and hence are not influenced by the outcomes under study. This ensures that the direction of causation flows from the exposure to the outcome, not the other way around.¹⁶ Therefore, MR can be thought of as “nature’s randomized controlled trial.”

In this study, genetic variants associated with SS were utilized as IVs to investigate potential causal links between SS and CVD risk.

Materials and methods

Ethics statement

The data used in this analysis were obtained from publicly available databases that had been previously scrutinized and approved by respective ethical committees in earlier studies or by governing institutions.

Study design

In the present study, we explored the potential causal relationship between SS and CVD incidence using a two-sample MR analysis of data obtained from a publicly available database of large-scale genome-wide association studies (GWAS). For MR to provide unbiased causal estimates, three core assumptions

must be satisfied.¹⁷ First, the genetic variants used as an instrument must be robustly associated with the exposure of interest (SS).

Second, the genetic variant must be independent of any confounder of the exposure–outcome relationship. Third, genetic variants must affect outcomes (CVDs) only through their effect on the exposure variable (SS) and not through any other pathways. The principle of the design is shown in Figure 1.

Selection criteria for genetic IVs

The following criteria were used to select SNPs for use in this study: (1) Each chosen SNP should exhibit a significant association with SS at the genome-wide level ($p < 5 \times 10^{-8}$).¹⁸ (2) Individual SNPs must adhere to the condition of independence, as evidenced by linkage disequilibrium with a threshold of $r^2 \leq 0.001$, indicating that they are not connected with confounders affecting the exposure–outcome relationship. (3) We ensured the robustness of our

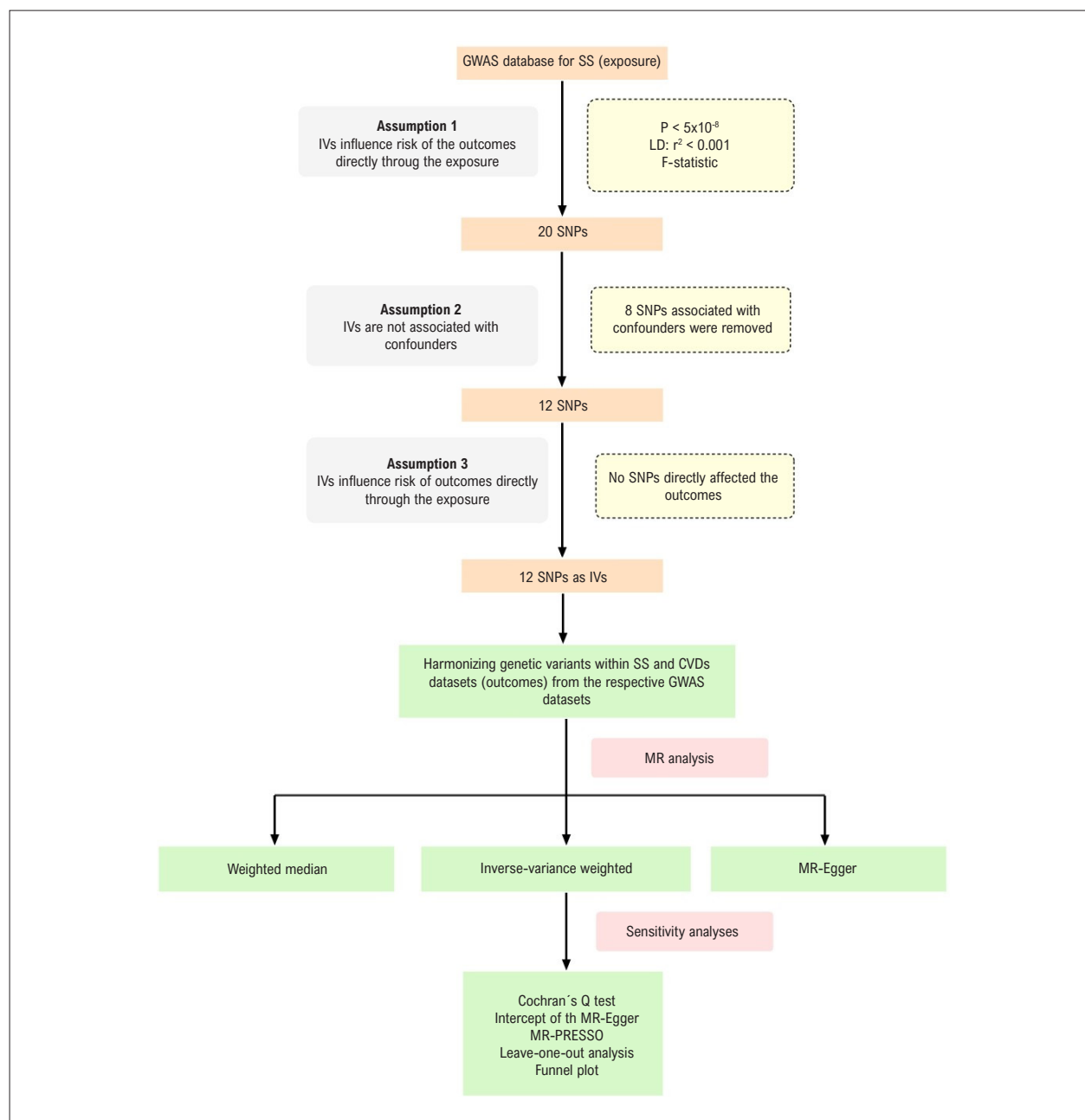


Figure 1 – Overview of the study design. CVD: cardiovascular disease; GWAS: genome-wide association studies; IV: instrumental variable; LD: linkage disequilibrium; MR: Mendelian randomization; MR-PRESSO: Mendelian randomization pleiotropy residual sum and outlier; SNP: single-nucleotide polymorphism; SS: Sjögren's syndrome.

genetic instruments through the selection of SNPs based on a minor allele frequency threshold of > 0.05 . (4) Proxy SNPs ($R^2 > 0.8$) were also used to strengthen our analysis when SNPs were not directly genotyped in the validation datasets. (5) To avoid bias caused by weak variants, the F-statistic for each SNP should be greater than 10.¹⁹ The F-statistic was calculated as $R^2 \times (n - 2) / (1 - R^2)$. R^2 represents the amount of variance in the exposure variable explained by a single IV, and n is the sample size of the exposure GWAS.²⁰ Additional details can be found in Supplementary Table 1. (6) PhenoScanner V2 (www.phenoscanter.medschl.cam.ac.uk) was used to identify and exclude SNPs associated with confounding factors of CVD, thus ensuring the absence of pleiotropy for each SNP.²¹

Data sources

The data utilized in this study were sourced from the largest publicly available GWAS database, and the populations used in this study included only participants of European ancestry. The diagnostic criteria were based on the International Classification of Diseases codes. The SNP information extracted included parameters such as effect size (β), p value, effect frequency, and effect allele.

The SS data were obtained from the FinnGen consortium, specifically from its R9 version (URL: <https://www.finnngen.fi/en>), which comprises 394,918 samples, including 2,495 patients and 392,423 control participants. For AF, we selected a GWAS comprising 1,030,836 individuals, of whom 60,620 were AF patients and 970,216 were control participants.²² The CAD data were sourced from a meta-analysis conducted using UK Biobank data and supplemented with data from the CAD Genome Wide Replication and Meta-analysis (CARDIOGRAM) plus the CAD Genetics; in total, the meta-analysis included 122,733 patients and 424,528 control participants.²³ Data concerning HF were derived from the HF Molecular Epidemiology for Therapeutic Targets (HERMES) consortium, which included 47,309 patients of European ancestry and 930,014 control participants.²⁴ The IS dataset included 34,217 patients and 406,111 control participants.²⁵ The MI dataset, which was provided by UK Biobank, included 10,616 patients and 452,317 control participants (URL: <https://www.ukbiobank.ac.uk/>). The GWAS data sources employed in our study are provided in Table 1.

Statistical analysis

In our MR study, we employed three methods: inverse-variance weighting (IVW), weighted median (WM), and MR-Egger. These analytical methods assist in determining more accurate causal effect estimates by mitigating various potential biases and errors. The IVW method combines the estimates from multiple genetic variants into a single estimate of the causal effect. It assumes that each genetic variant is a valid instrument and weights each estimate according to its precision. This method is most efficient when all genetic variants are valid instruments.^{26,27} The WM method provides a median-based estimate of causal effects, which allows for up to 50% of the weight to come from invalid instruments. This method is more robust to invalid instruments than IVW, as long as the majority of the weight comes from valid instruments. It complements IVW by offering a more robust estimate when some genetic variants are invalid instruments, providing useful sensitivity analysis.²⁸ The MR-Egger method allows for the detection and adjustment of pleiotropic effects, where genetic variants affect the outcome through pathways other than the exposure pathway. It includes an intercept term that provides a test for directional pleiotropy. MR-Egger is particularly useful when there is suspicion of pleiotropy. It complements the IVW and WM methods by providing a means to assess and correct for pleiotropy at the cost of reduced precision and power.²⁹

Sensitivity analyses are essential for assessing the robustness of MR results and identifying potential violations of IV assumptions. Cochran's Q test was used to assess the heterogeneity of the causal effect estimates for individual genetic variants. A statistically significant Q statistic ($p < 0.05$) indicates heterogeneity in causal estimates derived from individual SNPs.³⁰ The MR-Egger intercept can indicate horizontal pleiotropy. A significantly different intercept from zero suggests the presence of horizontal pleiotropy. The MR pleiotropy residual sum and outlier (MR-PRESSO) test is a method for detecting and correcting pleiotropy and heterogeneity by identifying outlier SNPs. The global p test within MR-PRESSO assesses the overall presence of pleiotropy by testing the null hypothesis that all genetic instruments are valid and free from pleiotropy. A significant global p value indicates horizontal pleiotropy, suggesting that some genetic instruments are likely invalid due to pleiotropic effects.³¹ Leave-one-out analysis is a cross-validation method in which MR analysis is repeated multiple times with one of the SNPs

Table 1 – Details of the GWAS included in the MR

Trait	Population	Cases	Controls	Sample size	Consortiums/DOI
Sjögren's syndrome		2,495	392,423	394,918	FinnGen R9
atrial fibrillation		60,620	970,216	1,030,836	DOI: 10.1038/s41588-018-0171-3
coronary artery disease		122,733	424,528	547,261	DOI: 10.1161/CIRCRESAHA.117.312086
European					
heart failure		47,309	930,014	977,323	DOI:10.1038/s41467-019-13690-5
ischemic stroke		34,217	406,111	440,328	DOI: 10.1038/s41588-018-0058-3
myocardial infarction		10,616	452,317	462,933	UK Biobank

removed each time. This approach helps to determine whether the MR results are driven by a single SNP.³² Funnel plots were used to assess the presence of pleiotropy or other biases among the IVs.

Results

Genetic instruments for SS

In this study, we extracted SNPs that were both significantly and independently associated with SS from the most extensive GWAS database available, initially identifying 20 viable SNPs. Follow-up selection using the PhenoScanner V2 tool resulted in the exclusion of 8 of those SNPs because they were found to be associated with immunological diseases, such as rheumatoid arthritis, systemic lupus erythematosus, and ankylosing spondylitis. Finally, 12 SNPs were included in our study, as detailed in Table 2. The F-statistics of all included SNPs were greater than 10, indicating that our study did not suffer from weak instrument bias. The harmonized data on SS and CVD incidence are detailed in Table S1.

MR estimates and sensitivity analyses

The results of the MR analysis are shown in Figure 2.

According to the IVW results, no significant causal relationship was found between SS and AF risk (odds ratio [OR] = 0.98, 95% CI = 0.95–1.01; $p = 0.22$). Moreover, the MR-Egger (OR = 0.99, 95% CI = 0.88–1.13; $p = 0.93$) and WM (OR = 0.98, 95% CI = 0.93–1.02; $p = 0.32$) results were also consistent (Figure S1A, Figure S2A). Cochran's Q statistic showed no significant heterogeneity in the estimates of the included SNPs ($p = 0.23$) (Table S3). In addition, leave-one-out analysis also showed that the MR estimates were stable (Figure S3A). MR-Egger intercept (intercept = -0.041 ; $p = 0.80$) and MR-PRESSO (global $p = 0.21$) did not show significant horizontal pleiotropy in our study (Figure S2A, Table S2).

For CAD, Cochran's Q test demonstrated significant heterogeneity ($p = 0.01$) (Table S3). Consequently, we employed the random-effects model of IVW, which did not reveal any evidence of a potential causal relationship between SS and CAD risk (OR = 0.99, 95% CI = 0.94–1.04; $p = 0.60$). The MR-Egger (OR = 1.11, 95% CI = 0.93–1.34; $p = 0.30$) and WM (OR = 0.98, 95% CI = 0.94–1.03; $p = 0.39$) results were consistent (Figure S1B, Figure S2B). MR-PRESSO analysis identified two outliers. We removed those SNPs and found that the results were still not statistically significant. The adjusted MR-PRESSO results suggested that our original IVW results were robust (global p value = 0.32) (Table S2). In addition, the leave-one-out test and funnel plot confirmed that our results were stable (Figure S3B, Figure S4B).

For HF, we did not find a significant causal association between SS and HF risk (OR = 1.00, 95% CI = 0.96–1.04; $p = 0.91$). Moreover, the MR-Egger (OR = 1.00, 95% CI = 0.85–1.18; $p = 0.98$) and WM (OR = 1.00, 95% CI = 0.96–1.04; $p = 0.97$) results supported that finding (Figure S1C, Figure S2C). Cochran's Q test indicated no

significant heterogeneity in the estimates of the included SNPs ($p = 0.17$) (Table S3). In addition, leave-one-out analyses showed that the MR estimates were stable (Figure S3C). The MR-Egger intercept (-0.0010 ; $p = 0.96$) and MR-PRESSO (global $p = 0.24$) results indicated that no significant horizontal pleiotropy existed in the analysis (Figure S2C, Table S2). The symmetry of the funnel plot showed that the results were reliable (Figure S4C).

For IS, no statistically significant genetic association was found (OR = 0.99, 95% CI = 0.93–1.05; $p = 0.68$). MR-Egger (OR = 0.99, 95% CI = 0.83–1.18; $p = 0.92$) and WM (OR = 0.96, 95% CI = 0.89–1.03; $p = 0.29$) showed similar results (Figure S1D, Figure S2D). The results of Cochran's Q test, MR-Egger regression, the MR-PRESSO test, the leave-one-out test, and the funnel plot indicated that the MR estimates were relatively robust (Figure S2D, Figure S4D, Table S2, Table S3).

For MI, we did not detect a genetic causal association between SS and MI risk according to the IVW (OR = 1.01, 95% CI = 0.97–1.06; $p = 0.61$), MR-Egger (OR = 1.09, 95% CI = 0.95–1.26; $p = 0.27$), or WM (OR = 1.01, 95% CI = 0.95–1.07; $p = 0.77$) analyses (Figure 2, Figure S1E, Figure S2E). Cochran's Q statistic showed no significant heterogeneity in the estimates of the SNPs we included ($p = 0.52$) (Table S3). Leave-one-out analyses also showed that the MR estimates were stable (Figure S3E). The MR-Egger intercept (-0.02 ; $p = 0.31$; Figure S2E) and MR-PRESSO (global $p = 0.24$; Table S2) results indicated that there was no significant horizontal pleiotropy. The symmetry of the funnel plot indicated the robustness of our results (Figure S4E).

Discussion

We used a two-sample MR approach with the largest publicly available GWAS database to investigate potential genetic causal associations between SS and various CVDs. Our findings did not indicate any significant associations of SS with AF, HF, CAD, MI, or IS, as shown in the Central Illustration. Thus, it can be inferred that SS does not genetically predispose individuals to an elevated risk of developing CVD.

Atherosclerosis serves as the primary etiology of CVD, and chronic immune-mediated diseases (IMDs) play a significant role in mediating the processes underlying coronary atherosclerosis.³³ Recent research conducted by Yuetian Yu et al.³⁴ in 2023, which analyzed data from 414,495 UK Biobank participants over a period of 12.1 years, indicated that individuals with IMDs were at a significantly increased risk of developing CVD. Complementary evidence from another extensive study involving 991,546 participants underscores the strong association between certain IMDs and elevated cardiovascular risk in the broader population.³⁵ Specific IMDs, such as rheumatoid arthritis and systemic lupus erythematosus, contribute to increased cardiovascular morbidity and mortality, predominantly through the acceleration of atherosclerosis.^{35–38} Nevertheless, it is crucial to note that most of the existing related research has focused primarily on IMDs such as rheumatoid arthritis and systemic lupus erythematosus. The relationship between

Table 2 – Characteristics of IVs for SS

	SNP	E A	OA	Sample size	SE	β	EAF	P value	R ^{2*}	F-statistic**	Reasons for exclusion after using PhenoScanner V2
1	rs10168266	C	T	392423	0.0341	0.1878	0.2024	3.81E-08	0.0114	4520.15	rheumatoid arthritis, systemic lupus erythematosus
2	rs4712936	G	T	392423	0.0659	-0.3769	0.9614	1.10E-08	0.0105	4177.95	
3	rs185466530	C	G	392423	0.1086	0.9126	0.0144	4.42E-17	0.0236	9484.30	
4	rs144958615	G	A	392423	0.0536	-0.3033	0.0922	1.52E-08	0.0154	6139.38	rheumatoid arthritis
5	rs1611250	C	T	392423	0.0318	0.2674	0.2392	3.7E-17	0.0260	10489.04	
6	rs887466	G	A	392423	0.0285	-0.1663	0.4717	5.43E-09	0.0138	5482.52	
7	rs2395004	G	C	392423	0.0289	0.1814	0.3739	3.37E-10	0.0154	6137.12	rheumatoid arthritis, ankylosing spondylitis
8	rs805262	C	T	392423	0.0285	0.1935	0.4096	1.12E-11	0.0181	7234.67	
9	rs382259	T	C	392423	0.0399	-0.2480	0.1672	5.19E-10	0.0171	6837.77	
10	rs2395163	T	C	392423	0.0383	-0.2162	0.1867	1.61E-08	0.0142	5650.66	rheumatoid arthritis, inflammatory bowel disease
11	rs62405651	T	C	392423	0.0543	-0.3394	0.0884	4.13E-10	0.0186	7421.53	
12	rs2267647	A	G	392423	0.0304	-0.2203	0.7123	3.94E-13	0.0199	7965.27	
13	rs9277052	T	C	392423	0.0315	0.2475	0.2445	4.18E-15	0.0226	9086.43	rheumatoid arthritis
14	rs4713614	C	A	392423	0.0283	-0.1812	0.5019	1.48E-10	0.0164	6547.79	
15	rs115703363	G	A	392423	0.0550	0.3217	0.0590	4.96E-09	0.0115	4564.61	
16	rs182700050	C	T	392423	0.0574	0.4062	0.0518	1.42E-12	0.0162	6461.01	
17	rs73410897	G	A	392423	0.0493	0.2810	0.0782	1.16E-08	0.0114	4517.19	
18	rs113858286	C	G	392423	0.0752	0.4263	0.0289	1.41E-08	0.0102	4040.14	
19	rs150724213	G	A	392423	0.0751	0.4505	0.0287	1.99E-09	0.0113	4483.80	
20	rs4731531	G	A	392423	0.0284	0.1825	0.4428	1.38E-10	0.0164	6557.28	

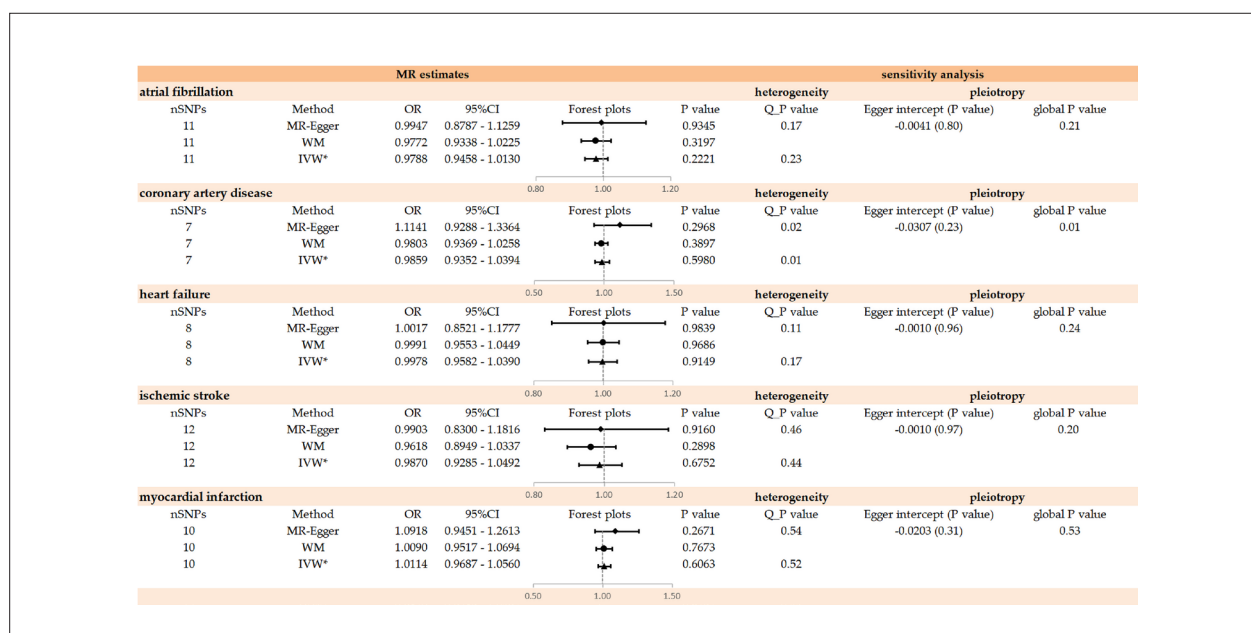


Figure 2 – MR estimates and sensitivity analysis for association of AF, CAD, HF, IS, and MI with the risk of Sjögren's syndrome. IVW: inverse-variance weighting; MR: Mendelian randomization; SNP: single-nucleotide polymorphism; WM: weighted median. *Main MR analysis method.

SS and CVD incidence remains a topic of limited research and inconsistent findings. J Mofors et al. analyzed a sample of 9,995 Swedish patients and control participants and reported significant associations of SS with an increased risk of CVD (OR = 1.6, 95% CI = 1.2–2.1) and stroke (OR = 1.2, 95% CI = 0.9–1.7).¹¹ However, Yong et al. observed in their meta-subgroup analysis that, while SS was linked to an elevated risk of CAD, no significant association with stroke risk was noted.³⁹ Furthermore, Bartoloni's research team found no statistical relationship between the risk of SS and that of HF,⁴⁰ which is consistent with our findings. In addition, other studies have revealed similar findings.^{10,41} In contrast, Fosbøl et al. utilized the Danish national registry system to compare 5,092 newly diagnosed SS patients with the general population. They found that SS patients had a significantly greater risk for CVD, including HF (hazard ratio = 1.42, 95% CI = 1.20–1.68), than did participants in the general population.⁴² Beltai et al. conducted a meta-analysis of 14 studies including 67,124 patients with SS, and they reported significantly greater incidences of CAD (relative risk = 1.34, 95% CI = 1.06–1.38; $p = 0.01$; $I^2 = 95\%$) and HF (OR = 2.54, 95% CI = 1.30–4.97; $p < 0.01$; $I^2 = 85\%$) in patients with SS than in control participants.⁸ However, the significant heterogeneity in that meta-analysis may be due to the disparate diagnostic criteria employed across numerous studies or from limited data, which precluded the evaluation of significant cardiovascular risk factors such as smoking, hypertension, hyperlipidemia, diabetes, and corticosteroid usage. This might have resulted in an exaggerated estimation of the correlation between SS and CVD incidence.¹⁰

Our study revealed no causal association between SS and CVD incidence, for several possible reasons. Initially, SS manifests with a broad spectrum of clinical presentations and varying degrees of severity, complicating the task of delineating a

direct causal association with CVDs.⁴³ Additionally, patients with SS frequently exhibit comorbidities, such as hypertension,^{44,45} diabetes,⁴⁶ and hyperlipidemia, which are also independent risk factors for CVD. Inevitably, those observational studies could not control for all residual confounders. This lack of causality could be attributed to the inability of observational studies to fully control for residual confounders.⁴⁷ Finally, the use of specific pharmaceutical agents, including glucocorticosteroid therapy, to ameliorate SS or its associated symptoms can potentially exert adverse effects on cardiovascular health, influencing factors such as blood pressure and cholesterol levels and thereby escalating the risk for CVD.⁴⁸ All of these factors may lead to an overestimation of the association between SS and the risk of CVD in the clinical setting. Our findings enable patients and clinicians to prioritize the management of modifiable CVD risk factors, including hypertension, diabetes status, smoking status, and hyperlipidemia status, rather than focusing on SS itself. These results can also inform healthcare providers about the effective monitoring and management of SS patients. In the absence of a direct causal link to CVD, emphasis should remain on addressing the primary symptoms of SS and any coexisting conditions. Furthermore, individuals with SS may experience reassurance from the knowledge that SS may not increase their risk of CVD.

To our knowledge, this is the first MR study to systematically investigate the genetic causality between SS and CVD incidence. Our study has several advantages. The use of an MR design allowed for the mitigation of reverse causation and the influence of confounding variables, which are limitations inherent in observational studies. Moreover, this methodology proved to be more cost-effective than that of an . Furthermore, we executed a rigorous selection process for IVs, enhancing

the precision of our MR estimates. However, our study has several limitations. First, the SS data were obtained from the FinnGen consortium, comprising exclusively individuals from Finland, thereby limiting the generalizability of the findings. Consequently, caution is warranted when extrapolating these results to diverse populations. Second, even though we used the most extensive GWAS database, the SS population included only 2,495 patients; this is a small sample size for the context of an MR study, as gene variants typically yield only small changes in the exposure variable. Third, our MR analysis was limited by the nature of the genetic instruments available to us. Specifically, we had access only to GWAS summary-level data, which limited our ability to conduct in-depth subgroup MR analyses that could consider factors such as age, sex, subtypes and clinical symptoms of SS. Fourth, one critical assumption underlying MR analysis is the absence of horizontal pleiotropy. We employed several methods, including MR-Egger regression and global tests, to identify and adjust for potential pleiotropic effects. However, the possibility of undetected pleiotropy remains, and the potential impact on our findings cannot be entirely ruled out. Finally, we selected SNPs associated with SS based on the latest and largest publicly available GWAS. However, we acknowledge that these SNPs might not encompass all genetic determinants of SS. The multifactorial nature of SS, involving immune system dysfunction, environmental factors, and possibly other unknown genetic factors, suggests that our findings need to be viewed within the broader context of the disease etiology.

Conclusions

In conclusion, our MR study revealed no significant causal association between SS and CVD incidence. This insight enhances our understanding of the pathophysiological underpinnings of SS and implies that cardiovascular risk management for SS patients could mirror general population strategies. Future updated MR studies are crucial for validating our findings, especially when more extensive and comprehensive GWAS data become available.

Moreover, further research should include validation in independent cohorts and investigation into potential biological mechanisms underlying SS and CVD incidence.

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Author Contributions

Conception and design of the research, acquisition of data, analysis and interpretation of the data and statistical analysis: Gao Y, Wu G; writing of the manuscript: Gao Y, Wu G, Jin T, Shen Z; critical revision of the manuscript for intellectual content: Gao Y, Huang X; study supervision and final approval of the manuscript: Zhou N, Huang X.

Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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Study Association

This study is not associated with any thesis or dissertation work.

Ethics Approval and Consent to Participate

This article does not contain any studies with human participants or animals performed by any of the authors.

Use of Artificial Intelligence

During the preparation of this work, the authors used ChatGPT to perform non-substantive visual refinement of the figures, including layout, alignment, and presentation optimization, without altering the underlying scientific content or interpretation. After using this tool, the authors reviewed and edited the content as needed and take full responsibility for the content of the published article.

Availability of Research Data

The underlying content of the research text is contained within the manuscript.

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*Supplemental Materials

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