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Post-genome-wide association study dissects genetic vulnerability and risk gene expression of Sjögren's disease for cardiovascular disease

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Abstract

Objectives This study aims to clarify the genetic associations between Sjögren's Disease (SD) and cardiovascular disease (CVD) outcomes, and to conduct an in-depth exploration of specific pleiotropic susceptibility genes.

Methods We performed two-sample and multivariable Mendelian randomization (MR) analysis to investigate the association between SD and the risk of ischemic heart disease (IHD) and stroke. Linkage disequilibrium score regression (LDSC) and Bayesian co-localization analyses were employed to assess the genetic associations between traits. Cross-phenotype analyses were employed to identify shared variants and genes, followed by a Transcriptome-Wide Association Study (TWAS) and Multi-marker Analysis of Genomic Annotation (MAGMA) based on Multi-Trait Analysis of GWAS (MTAG) results. To validate the pleiotropic genes, we further analyzed tissue-specific differentially expressed genes (DEGs) related to SD using RNA sequencing data.

Results The two-sample and multivariable MR analyses revealed that SD confers a genetic vulnerability to IHD and stroke. LDSC and co-localization analyses indicated a strong genetic linkage between SD and CVDs. Cross-phenotype analyses identified 38 and 37 pleiotropic single nucleotide polymorphisms (SNPs) for SD-Stroke and SD-IHD, respectively, primarily located within the MHC class region on 6p21.32:33 loci. Additionally, TWAS and MAGMA analyses identified pleiotropic genes located outside the MHC regions—seven associated with stroke (UHRF1BP1, SNRPC, BLK, FAM167A, ARHGAP27, C8orf12, and PLEKHM1) and two associated with IHD (UHRF1BP1 and SNRPC). Proxy variants within these genes in SD suggested an increased causal risk for stroke or IHD. Co-localization analysis further reinforced that SD and stroke share significant SNPs within the loci of FAM167A, BLK, C8orf12, SNRPC, and UHRF1BP1. DEG analysis revealed a significant up-regulation of the identified genes in SD-specific tissues.

Conclusions SD appears genetically predisposed to an increased risk of CVDs. Moreover, this research not only identified pleiotropic genes shared between SD and CVDs, but also, for the first time, detected key gene expressions that elevate CVD risk in SD patients—findings that may offer promising therapeutic targets for patient management.

Keywords Sjögren's disease, Cardiovascular disease, Genome-wide association study, Mendelian randomization

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Introduction

Sjögren's Disease (SD) is a chronic immune inflammatory disorder, with an incidence rate of 6.92 cases and a prevalence rate of 60.82 cases per 100,000 individuals. It primarily affects women, particularly those between the ages of 40 and 50 [1] The SD, which can also occur secondary to conditions such as rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), and systemic sclerosis (SSc), typically presents with lymphocytic infiltration of exocrine glands and frequently accompanied by various extraglandular manifestations [2]. An increasing number of observational studies have indicated that patients with SD, regardless of the presence of other rheumatic diseases, are at a significantly higher risk of cardiovascular events compared to healthy individuals [3]. For instance, a comprehensive review of data, encompassing a large cohort of SD subjects, has substantiated the increased risk of cardiovascular disease (CVD) in individuals diagnosed with SD [4]. Moreover, research has indicated that a greater percentage of individuals with SD are prone to developing dyslipidemia and hypertension, factors that might elevate the risk of cardiovascular events such as ischemic heart disease (IHD) in this population [5]. Extended follow-up investigations have further shown that Ro/SSA and La/SSB autoantibodies can increase the likelihood of CVD by threefold [6].

These findings underscore an association between SD and CVD, identifying SD as a potential independent risk factor for cardiovascular conditions. However, the precise pathogenesis linking SD and CVD, as well as the genetic risk factors related to anti-Ro/La antibodies and CVD, remain unclear. Various modifiable all-known factors, such as smoking, obesity, et al., may act as confounders, affecting both autoimmune diseases and CVDs. Bolstad's research, utilizing single nucleotide variant (SNV) analysis, suggested there existed shared genetic variant in both SD and myocardial infarction [7]. Most recently, a Mendelian randomization (MR) analysis aimed at investigating the genetic predisposition of SD to various CVDs suggested a potential genetic risk for CVD development in SD patients, providing a foundation for the current study [8]. However, it should be noted that this study did not explore gene-trait associations, and there remains a need for larger-scale post-Genome-Wide Association Study (GWAS) to further elucidate the underlying pathogenesis and pathways contributing to this phenomenon.

In the current study, we aimed to elucidate the genetic associations between SD and ischemic diseases, including stroke and IHD, using MR and cross-phenotype post-GWAS analyses. This approach not only helps clarify the causal relationships between these two diseases but also explores the genetic basis of their comorbidity, laying the groundwork for the development of targeted therapies and personalized treatment strategies. Ultimately, this could lead to improved clinical outcomes and more efficient allocation of healthcare resources.

Methods

Overview

Given the background of the unclear association between SD and CVD events, this study aimed to elucidate the genetic causal associations between these conditions. The primary objectives were to determine whether patients with SD are genetically predisposed to cardiovascular outcomes and to detect potential pleiotropic genes and pathways involved in these phenotypes. This study employed a multi-level genetic analysis approach, including MR to explore causal relationships, post-GWAS analysis to identify pleiotropic genes, and validation of these genes using RNA sequencing data from GSE84844 and GSE7451, as detailed below and illustrated in the flowchart (Fig. 1).

First, two-sample as well as multivariable MR analyses were carried out between the exposure GWAS of SD and CVDs, including IHD and stroke. Mendelian randomization leverages genetic variants, particularly single nucleotide polymorphisms (SNPs), to infer causal relationships between traits. This approach relies on three fundamental assumptions: (1) The genetic variants selected as instrumental variables (IVs) must be linked to the exposure; (2) These variants should be independent of confounders affecting both the exposure and outcome; (3) The genetic variants should influence the outcome exclusively through the exposure, without alternative pathways. These stringent conditions make MR comparable to a natural randomized controlled trial (RCT), thereby enhancing its credibility in identifying causal relationships [9].

Recognizing that MR analysis alone may struggle to address the complex pleiotropy inherent in trait phenotypes, particularly in immune inflammatory diseases, a series of post-GWAS strategies were employed to understand the biological implications of risk loci. First, linkage disequilibrium (LD) score regression (LDSC) between SD and CVDs was calculated, followed by Bayesian co-localization to assess the shared genetic variants at the same genomic loci. Subsequently, cross-phenotype analysis was conducted using Multi-Trait Analysis of GWAS (MTAG) [10] to amplify the effects of single SNPs within GWAS data, and the findings were further validated through the Cross-Phenotype Association (CPASSOC) approach [11]. Pleiotropic genes were identified through ANNOVAR mapping,

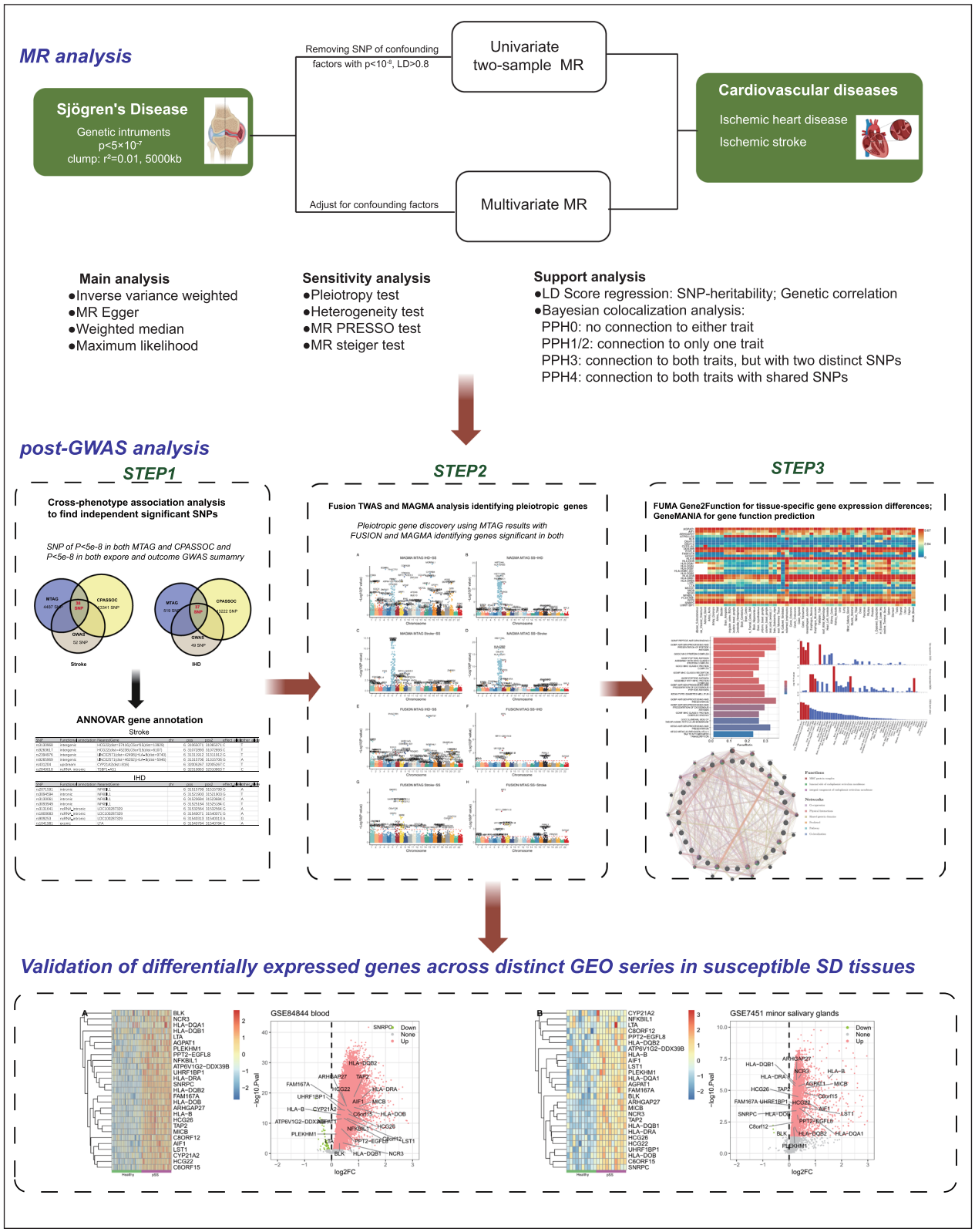

Fig. 1 Flowchart plot

Transcriptome-Wide Association Study (TWAS), and Multi-marker Analysis of Genomic Annotation (MAGMA) [12].

Given the potential confounding from overlapping cases of SLE or RA in the FinnGen database, which could skew gene expression profiles in SD, further validation of the identified genes was performed using two independent Gene Expression Omnibus (GEO) RNA sequencing datasets from vulnerable SD tissues.

Data sources of GWAS summary

We leveraged the most extensive and up-to-date GWAS datasets available, utilizing primary data from the FinnGen 11 consortium (https://risteys.finregistry.fi/) for SD as the exposure variable and CVD-related outcomes. FinnGen offers the most comprehensive genetic data for SD currently accessible [13]. Within the FinnGen consortium, the minimal genetic and epidemiological overlap between SD and other systemic connective tissue diseases implies that most SD cases arise as primary disorders. For multivariable MR analysis, additional datasets were employed, encompassing potential confounders such as body mass index (BMI), type 2 diabetes mellitus (T2D), smoking status, low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), and other autoimmune diseases including SSc, rheumatoid arthritis (RA) and SLE. These datasets were predominantly obtained from the IEU OpenGWAS Project and the FinnGen consortium. Detailed descriptions of all data sources are provided in Supplementary Table S1.

Statistical analysis

Mendelian randomization

To explore the causal link between SD and CVD risk, an initial two-sample MR analysis was conducted, with SD as the exposure and CVDs as the outcomes. SNPs significantly associated with SD were identified and selected based on a clumping threshold using PLINK, with a criterion of $P < 5 \times 10^{-7}$, $r^2 < 0.01$, and a window size of 5000 kb. Only SNPs with an F-statistic > 10, indicating a robust association with SD, were included in the MR analysis. The F-statistic calculation follows Burgess's methodology [14].

To adhere to the core assumptions of MR and mitigate potential pleiotropy, we conducted a rigorous exclusion of SNPs associated with confounders such as SLE, RA, SSc, HDL-C, LDL-C, BMI, and smoking status. This was achieved through a meticulous screening process, eliminating SNPs with a P-value $< 5 \times 10^{-8}$ or those with LD $r^2 > 0.8$ with these confounding factors, employing the LDlink tool (ldlink.nih.gov/) [15].

The random-effects inverse-variance weighted (IVW) method was selected as the primary analytical approach due to its strong statistical power. To enhance the reliability of our results, we conducted sensitivity analyses using complementary methods, including the weighted median, maximum likelihood estimation, and MR-Egger regression. A significance threshold of Bonferroni corrected $P < 0.025$ (0.05/2) was set to infer robust evidence of causality on above methods. To address the vulnerability of the IVW method to pleiotropy, the MR-Pleiotropy RESidual Sum and Outlier (MR-PRESSO) test [16] was applied to detect and exclude potential outlier SNPs for each outcome, with the number of distributions (NbDistribution) set at 3000. Furthermore, we implemented Steiger directionality tests [17] to rigorously evaluate the stability of the causal direction, which involved comparing the R-squared values of each SNP and the correlation strength between the SNPs and both exposure and outcome summary statistics. This also served to assess pleiotropy and enhanced the robustness of our findings. To account for identified confounders, a multivariable MR approach was employed, utilizing the same SNP inclusion and clumping criteria. Furthermore, to determine whether the effects of SD on IHD and stroke are mediated through risk factors such as HDL-C, LDL-C, BMI, and smoking status, we conducted two-sample Mendelian randomization analyses to assess the associations between SD and these factors. A significance threshold of Bonferroni-corrected $P < 0.01$ (0.05/5) was set to infer causal evidence. This approach also allows for the evaluation of potential bias in the MR results, particularly the risk of an increased false positive rate due to population overlap between the FinnGen exposure and outcome cohorts.

Linkage disequilibrium magnitude and co-localization analysis

To estimate trait heritability (h^2) and assess genetic correlation (rg) between exposure and outcome traits, we applied LD Score Regression (LDSC) using GWAS summary statistics. LDSC dissects the polygenic architecture of complex traits, differentiating true polygenic signals from confounding factors by evaluating the contribution of individual SNPs to trait heritability and computing genetic correlations across traits. The strength of the genetic correlation (rg) quantifies the extent of shared genetic etiology, while the sign of rg denotes the directional relationship between traits [18].

To further investigate shared causal variant between traits, Bayesian co-localization analysis was performed, aiming to confirm that the observed genetic associations are attributable to shared causal variants rather than coincidental overlap [19]. Methodological details and

assumptions underlying this approach were thoroughly described in previous literature. For this analysis, the most significant instrumental variable (IV) for SD was identified using PLINK, adhering to stringent clumping criteria: $P < 5 \times 10^{-8}$, $r^2 < 0.01$, and a window size of 5000 kb. The co-localization analysis focused on a 1 Mb genomic interval centered on this IV (250 kb upstream and downstream), specifically targeting the region on chromosome 6 (chr 6, pos: 31442644–31942644). A posterior probability threshold of 0.8 for hypothesis 4 (PPH4), which indicates a shared causal variant between the traits, was set to determine whether robust evidence exists for shared genetic variants between the exposure and outcome traits.

Post-GWAS analysis

Multi-trait analysis of GWAS MTAG is an advanced IVW meta-analysis method that leverages summary data from single-trait GWAS, improving association statistics for each trait. By allowing the combined analysis of multiple traits, MTAG substantially boosts statistical power, thereby improving the detection of shared genetic architectures among different traits. In our post-GWAS analysis, we applied MTAG to SD-IHD and SD -Stroke, both of which demonstrated significant associations in the prior co-localization analysis. This analysis yielded four trait-pairs: $MTAG_{SD\text{-}IHD}$, $MTAG_{IHD\text{-}SD}$, $MTAG_{SD\text{-}Stroke}$, and $MTAG_{Stroke\text{-}SD}$, which served as input for further downstream analyses. To mitigate the risk of false discoveries within the MTAG framework, we supplemented our analysis with a CPASSOC analysis as a supplementary analysis, with the SHet statistic playing a crucial role in discerning these shared genetic variants [20].

Independent significant SNP definition and function annotation Variants meeting the stringent threshold of $P < 5 \times 10^{-8}$ in the MTAG analysis, SHet $< 5 \times 10^{-8}$ in CPASSOC, and $< 5 \times 10^{-8}$ in both GWAS summary datasets were designated as independent significant SNPs. These shared variants underwent further functional annotation using the ANNOVAR mapping method, allowing for the determination of their potential biological roles and identification of the nearest genes within approximately 100 kb clumping regions.

Identification of pleiotropic genes Acknowledging that ANNOVAR's proximity-based gene annotation approach may be overly simplistic, we extended our analysis by employing two complementary methods: Functional Summary-based Imputation (FUSION) for TWAS and MAGMA. FUSION leverages expression quantitative trait loci (eQTL) data [21], while MAGMA performs proximity-based gene burden testing. Only genes identified as significant by both FUSION and MAGMA were classified as pleiotropic. FUSION analysis was conducted using MTAG summary data in conjunction with eQTL data from pertinent tissues, including the artery, whole blood, brain, spleen, Epstein-Barr virus (EBV)-transformed lymphocytes, and whole blood. GTEx v8, the most extensive human eQTL database [22], was utilized to train locus-based prediction models within the FUSION framework. Concurrently, MAGMA was applied to MTAG summary data for gene and gene set analysis, using the 1000 Genomes European population as the reference panel for LD calculation. To control for false discovery, the Benjamini-Hochberg (BH) correction was applied to adjust P values in both methodologies.

Pathway enrichment and functional prediction for pleiotropic genes Enrichment analysis of the identified genes was conducted using the Functional Mapping and Annotation of Genetic Associations (FUMA) web-tool [23], integrating gene data from 53 normal tissues in the GTEx project to estimate tissue-specific differentially expressed genes (DEGs). Then, pathway enrichment was conducted utilizing the Molecular Signatures Database (MSigDB), identifying important biological pathways with an adjusted P-value < 0.05. Further genetic interactions and functional exploration were carried out utilizing GeneMANIA, providing insights into the biological roles of the identified genes [24].

Identification of therapeutic targets for reducing cardiovascular disease comorbidities We identified 42 pleiotropic genes shared between SD and the comorbid conditions of stroke and IHD. These genes were then cross-referenced with the Drug Gene Interaction Database (DGIdb) and DrugBank to discover potential therapeutic targets, offering avenues for reducing cardiovascular disease risks associated with SS [25, 26].

Validation of differential expression of pleiotropic genes using GEO RNA sequencing data Given the potential confounding effects due to overlapping cases of other immune inflammatory diseases in the FinnGen database, we sought to validate the pleiotropic genes identified earlier by analyzing differentially expressed genes (DEGs) specific to SD. This analysis was conducted using RNA sequencing data from the GEO database, focusing on two GEO database series related to SD derived from minor salivary glands (GSE7451) and blood samples (GSE84844). Gene expression levels were meticulously analyzed and visualized using heatmaps and volcano plots, with P-values adjusted using the BH correction method [27–29]. DEGs were identified based on a corrected P-value < 0.05 and a fold change > 1.

Sensitivity analysis

Considering that our two-sample MR analysis in Sect."Multi-Trait analysis of GWAS"was constrained by the exclusion of confounding SNPs, which led to an insufficient number of SNPs and necessitated the use of relatively lenient thresholds for P-values and clumping criteria, we conducted a sensitivity analysis of the MR analysis. Initially, we identified the most susceptibility-associated SNPs for SD as reported in the studies by Lessard, Taylor et al., which are listed in Table S2 [30–38]. These SNPs were extracted from the exposure GWAS data under the conditions of $P < 5 \times 10^{-8}$, clumping with $r^2 < 0.001$, and a window size of 10,000 kb, to perform the two-sample MR analysis. Statistical significance was determined based on a Bonferroni-corrected P-value threshold of < 0.025 (0.05/2).

To determine whether the association between the identified susceptible pleiotropic genes located outside the MHC class complex in the *3.3.4* section for SD and CVDs was direct, we performed an MR analysis. Initially, due to the limitation in the number of SNPs, we extracted SNPs located within the corresponding genes (including 50 kb upstream and downstream regions) that met a P-value threshold of 5×10^{-6}, and applied clumping to identify independent SNPs ($r^2 < 0.001$). Since only one independent IV was available, MR effect we assessed the by the Wald ratio method, using a significance threshold of P < 0.05. Subsequently, a co-localization analysis was conducted to confirm whether SD and CVDs share causal variants within the corresponding genes (50 kb upstream and downstream). We restricted our analysis to genes with PPH3 + PPH4 ≥ 0.8 due to limited power in the co-localization analysis [39].

Results

LDSC

We performed LDSC to assess the heritability between SD and CVD outcomes. SNP-based heritability was acceptable for SD and CVDs, with relatively higher h^2 values and significant h^2 P-values, although the h^2 for SD had a lower Z-score than the recommended threshold of 4 (Z = 2.51) (Table S3). Analysis using GWAS data revealed that the genetic correlation estimates between SD and CVDs were all significant (rg P < 0.05) (Table S4, Fig. 2).

Causal relationship between SD and CVDs

We first conducted a two-sample MR analysis. After applying standard clumping thresholds, 19 SNPs were identified as significantly associated with SD. To ensure the validity of our instruments, we excluded 8 SNPs that links with potential confounding factors ($P < 5 \times 10^{-8}$ or LD $r^2 > 0.8$), including rs10174238 (SLE), rs75782365 (HDL-C), rs185466530 (BMI), rs3093958 (blood pressure), rs41423345 (RA), rs9277476 (SLE), rs150724213 (SLE), and rs2004640 (RA). Following these exclusions, 11 SNPs were retained as IVs for SD, including rs35948093, rs2517830, rs1056429, rs72891915,

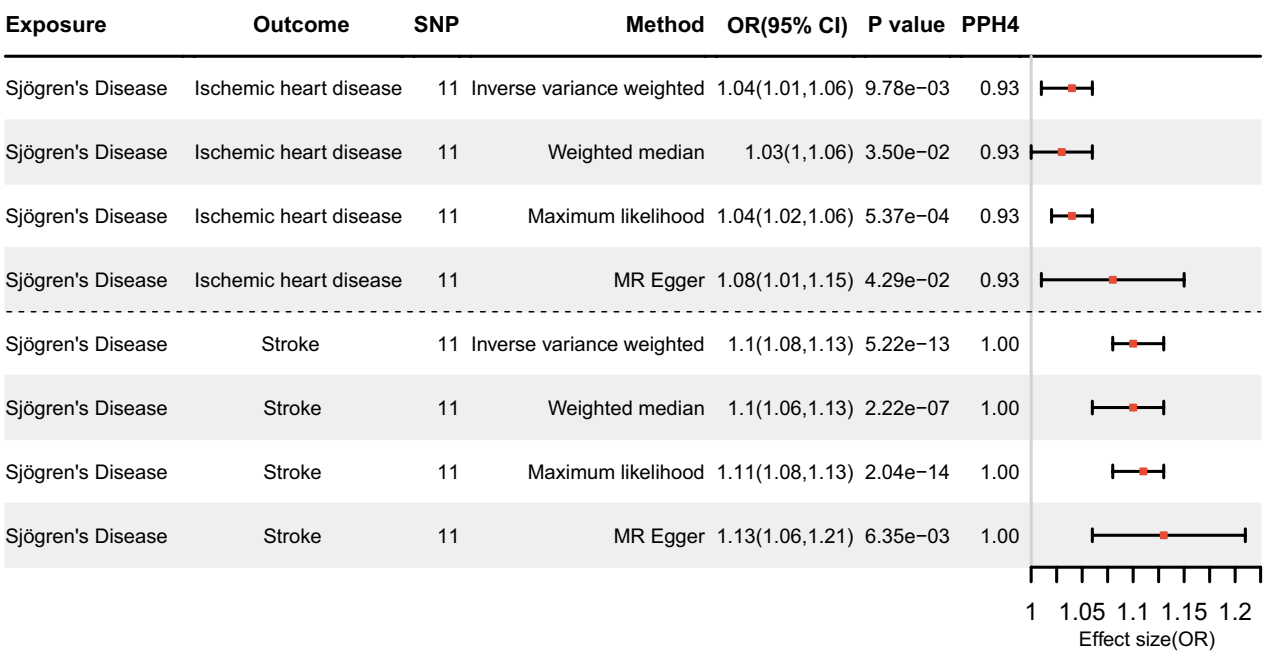

Fig. 2 Causal relationship between Sjögren's syndrome (SD) and cardiovascular events in two-sample Mendelian Randomization (MR) analysis

rs9469586, rs79756150, rs9366833, rs1064994, rs9277928, rs62404122, and rs937033 (Table S5).

As shown in Fig. 2, the IVW analysis demonstrated positive causal effects of SD on CVD events of IHD (OR: 1.04, 95% CI: 1.01–1.06, P = 9.78 $\times 10^{-3}$) and stroke (OR: 1.10, 95% CI: 1.08–1.13, P = 5.22 $\times 10^{-13}$). Even under the Bonferroni correction condition of P < 0.025, the result still reached significance. Cochran's Q test yielded P values > 0.05, indicating no significant heterogeneity exists. The results from the maximum likelihood, weighted median and MR-Egger methods were aligned with the IVW results (Fig. 2, Figure S1). The MR-PRESSO test did not identify any of horizontal pleiotropy across all CVD outcomes (Table S6). The leave-one-out analysis further confirmed that the results remained robust, with no significant changes observed upon the exclusion of any single SNP associated with SD (Figure S2). Moreover, we conducted the Steiger directionality test, which confirmed that all causal directions were correctly specified (Table S7).

In the multivariate MR analysis, consistent results were both observed IHD (OR: 1.02, 95% CI: 1.00–1.03, P = 0.03) and stroke (OR: 1.03, 95% CI: 1.02–1.05, P = 5.35 $\times 10^{-5}$) after controlling for confounding variables (Fig. 3, Table S8). In addition, we evaluated the causal effects of SD on common risk factors for CVDs; however, no significant associations were observed (Figure S3).

Co-localization

To further confirm the complex genetic association between SD and CVD events, we conducted co-localization analysis based on the selected loci region (chr 6, pos: 31442644–31942644). The analysis identified shared causal variants between SD and stroke, as well as between SD and IHD, both with the most significant SNP of rs3093958, with PPH4 values of 0.99 and 0.93, respectively (Fig. 2, Figure S4, Table S9).

Post-GWAS analysis

Cross-trait meta-analysis

In MTAG, we conducted cross-phenotype analyses between $GWAS_{SD}$ and $GWAS_{Stroke}$, as well as between $GWAS_{SD}$ and $GWAS_{IHD}$. This resulted in four MTAG trait-pairs: $MTAG_{SD\text{-}IHD}$, $MTAG_{IHD\text{-}SD}$, $MTAG_{SD\text{-}Stroke}$, and $MTAG_{Stroke\text{-}SD}$, which will serve as input for subsequent FUSION TWAS and MAGMA analyses. For SD-Stroke, $MTAG_{SD\text{-}Stroke}$ and $MTAG_{Stroke\text{-}SD}$ shared a total of 4,487 variants with P of MTAG $< 5 \times 10^{-8}$, whereas for SD-IHD, $MTAG_{SD\text{-}IHD}$ and $MTAG_{IHD\text{-}SD}$ shared a total of 519 variants. In CPASSOC, 13,341 and 13,222 variants were identified for SD-Stroke and SD-IHD, respectively, with a P of SHet $< 5 \times 10^{-}8$. The substantial overlap

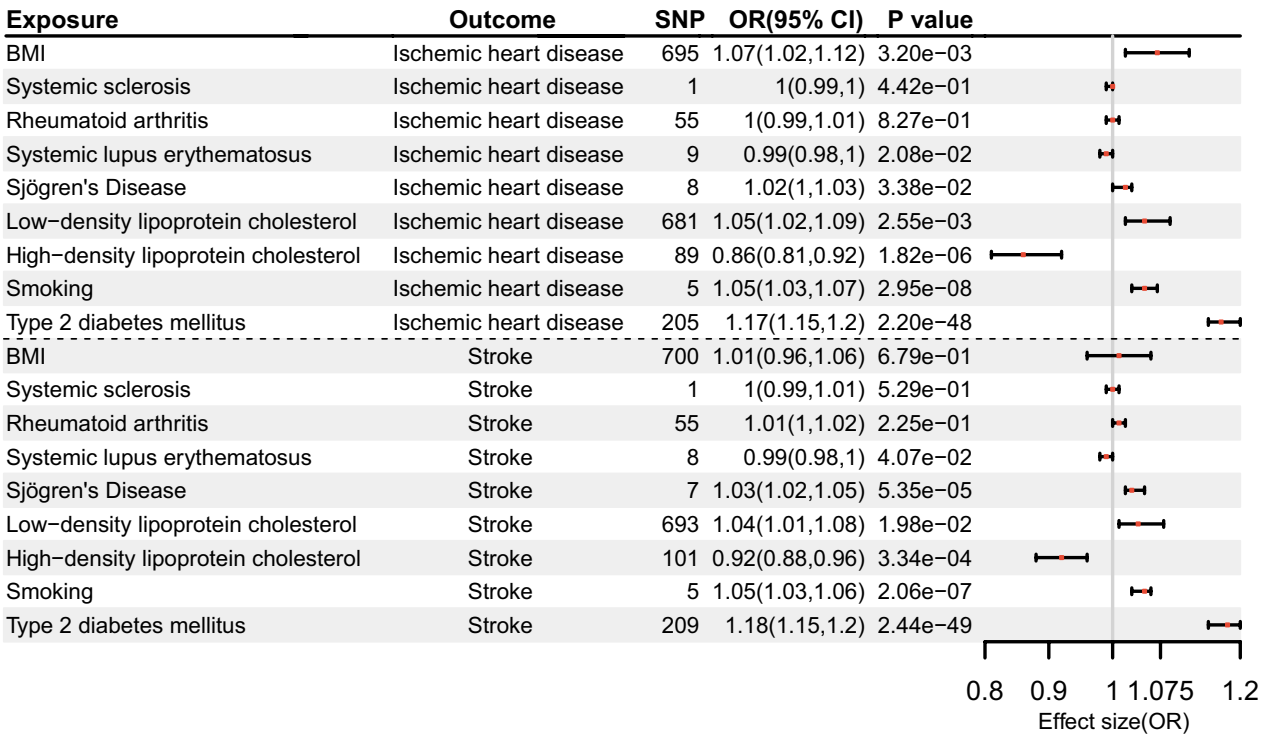

Fig. 3 Causal relationship between SD and cardiovascular events (CVDs) in multivariable MR analysis

between the MTAG and CPASSOC results highlights the robustness of the MTAG analysis (Table S10).

Identification and functional annotation of independent significant variants

After applying a stringent P-value threshold of 5×10^{-8} across MTAG, CPASSOC, and GWAS analyses, we identified 38 and 37 independent significant variants for SD-Stroke and SD-IHD, respectively. Notably, only one SNP, rs62397687, was shared between SD-Stroke and SD-IHD. Among the non-coding variants identified, intergenic variants were the most prevalent, accounting for 54.79% of the total SNPs, suggesting a potential regulatory role rather than direct involvement in protein-coding functions. Furthermore, a significant proportion of SNPs were located within ncRNA intronic (16.44%) and intronic (13.70%) regions. Four SNPs—rs1041981, rs14597, rs1766, and rs7383287—were mapped to exonic regions, directly impacting the nearest genes LTA, HCG26, HLA-DQB1-AS1, and HLA-DOB, respectively, thereby contributing substantially to disease susceptibility. As a result, 19 and 15 nearest genes within the 100 kb clumping regions were mapped from the identified SNPs for SD-Stroke and SD-IHD, respectively. All these genes are situated within the 6p21.32 and 6p21.33 loci, regions recognized for their dense concentration of immune-related genes (Table S11).

Pleiotropic genes and pathways

Given the limitations of proximity-based gene annotation, we extended our analysis by performing FUSION-TWAS and MAGMA analyses on the MTAG summary results to identify pleiotropic genes (Fig. 4). The combined FUSION and MAGMA analyses identified two genes, UHRF1BP1 and SNRPC, as being shared between both SD and IHD, with a BH-corrected P value <0.05 (Table 1, Table S12). Additionally, seven genes—UHRF1BP1, SNRPC, BLK, FAM167 A, ARHGAP27, C8orf12 (FAM167 A-AS1), and PLEKHM1—were found to be shared between SD and stroke (Table S13). Notably, UHRF1BP1 and SNRPC were shared across SD, stroke, and IHD.

In total, 21 and 22 pleiotropic genes shared between SD-IHD and SD-Stroke were identified through ANNOVAR annotation of pleiotropic SNPs, FUSION-TWAS, and MAGMA gene set analyses (Table S14). These genes were further visualized using FUMA gene2function across 54 different normal tissues. Predominant expression of these genes was observed in tissues such as the small intestine, EBV-transformed lymphocytes, spleen, blood and lung highlighting their primary involvement in immune system processes (Fig. 5A). This was particularly evident for genes such as HLA-DOB, HLA-DQA1, HLA-DQA2, HLA-DQB1, HLA-DRB5, LTA, LST1, BLK, ARHGAP27, AIF1, MICB, and UHRF1BP1, which play crucial roles in immune response pathways and exhibited significantly elevated expression levels in EBV-transformed lymphocytes and spleen (Fig. 5B).

A total of 401 pathways were identified with significant adjusted P values using the MSigDB database. The 15 most significant pathways, illustrated in Fig. 5C, were primarily related to immune cell activation, particularly those involved in T cell-mediated immunity and leukocyte adhesion. This underscores the critical roles of adaptive immune responses in these conditions. The network analysis through GeneMANIA revealed significant interconnections between antigen processing, MHC-mediated presentation, and the cellular infrastructure that supports these functions. Co-expression and physical interaction comprised approximately 77% of the total network, suggesting that these genes likely collaborate within the same biological processes, pathways, or cellular structures. This strong connectivity emphasizes the coordinated activity of these genes in immune responses, particularly in antigen presentation and immune cell regulation (Fig. 5D).

Validation of DEGs using the gene expression omnibus database

To account for potential confounding effects due to overlapping cases of other immune inflammatory diseases in the FinnGen database, we validated the pleiotropic genes identified in our analysis by examining DEGs specific to SD using RNA sequencing data. A total of 27 genes were identified, excluding 7 non-coding RNA genes that were

(See figure on next page.)

Fig. 4 Manhattan plots. **A** Manhattan plot of MAGMA analysis based on MTAG results for IHD-SD (IHD as input data); **B** Manhattan plot of MAGMA analysis based on MTAG results for SD-IHD (SD as input data); **C** Manhattan plot of MAGMA analysis based on MTAG results for Stroke-SD (Stroke as input data); **D** Manhattan plot of MAGMA analysis based on MTAG results for SD-Stroke (SD as input data); **E** Manhattan plot of FUSION-TWAS analysis based on MTAG results for IHD-SD (IHD as input data); **F** Manhattan plot of FUSION-TWAS analysis based on MTAG results for SD-IHD (SD as input data); **G** Manhattan plot of FUSION-TWAS analysis based on MTAG results for Stroke-SD (Stroke as input data); **H** Manhattan plot of FUSION-TWAS analysis based on MTAG results for SD-Stroke (SD as input data). The red dashed line indicates the significance threshold for adjusted P values. MAGMA: Multi-marker Analysis of Genomic Annotation; MTAG: Multi-Trait Analysis of GWAS; IHD: ischemic heart disease; FUSION: Functional Summary-based Imputation; TWAS: Transcriptome-Wide Association Study

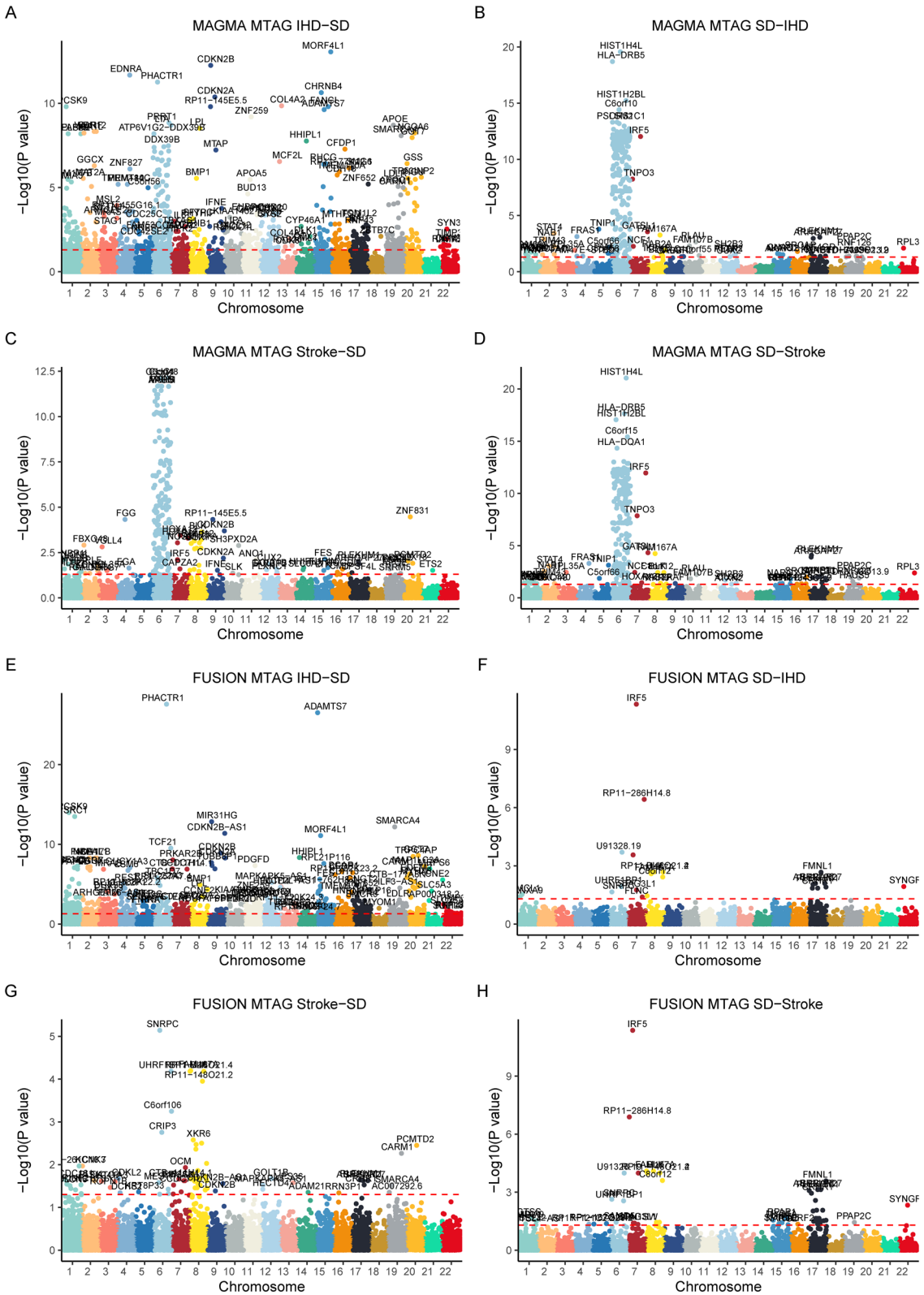

Fig. 4 (See legend on previous page.)

Table 1 MAGMA Results for SD and CVDs Analysis

Trait pair	Gene_name	START	STOP	Z statistics	P_Trait	P_SS	Gene_biotype
SD-Stroke	UHRF1BP1	34759857	34850915	5.136	3.08E-05	1.14E-03	protein_coding
SD-Stroke	SNRPC	34725183	34741571	5.3243	1.20E-05	1.36E-03	protein_coding
SD-Stroke	BLK	11351510	11422113	4.6968	2.33E-04	3.71E-03	protein_coding
SD-Stroke	FAM167 A	11278972	11332224	4.3812	9.17E-04	5.77E-05	protein_coding
SD-Stroke	ARHGAP27	43471275	43511787	3.6712	1.36E-02	1.25E-04	protein_coding
SD-Stroke	C8orf12	11225911	11296167	4.4714	6.22E-04	3.71E-03	protein_coding
SD-Stroke	PLEKHM1	43513266	43568115	3.7655	9.69E-03	8.30E-05	protein_coding
SD-IHD	UHRF1BP1	34759857	34850915	3.6765	8.21E-03	8.22E-03	protein_coding
SD-IHD	SNRPC	34725183	34741571	3.8185	5.37E-03	1.07E-02	protein_coding

SD, Sjögren's Disease; CVDs, cardiovascular diseases. P values were adjusted using the Benjamini–Hochberg correction

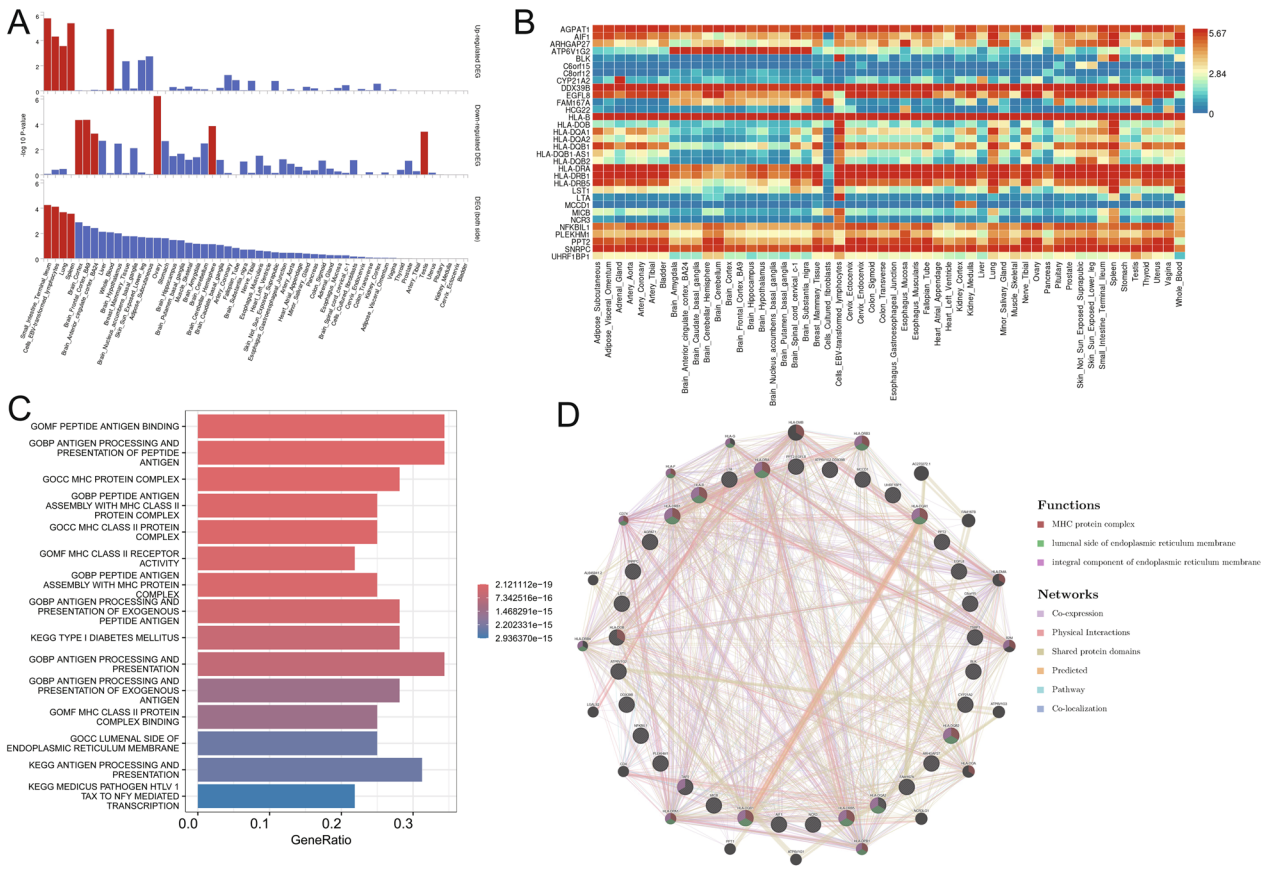

Fig. 5 Tissue-specific gene expression differences, pathway enrichment, and gene–gene interaction analysis. **A** Differentially Expressed Genes (DEGs) across 54 normal tissues using the FUMA tool and GTEx v8. **B** Tissue-specific gene expression differences in 54 normal tissues using the FUMA tool and GTEx v8. **C** The 15 most significantly enriched pathways identified through GOMF, GOBP, GOCC, and KEGG analyses in MSigDB. **D** Gene-gene interaction and functional exploration conducted using GeneMANIA. DEGs: Differentially Expressed Genes; GOMF: Gene Ontology Molecular Function; GOBP: Gene Ontology Biological Process; GOCC: Gene Ontology Cellular Component; KEGG: Kyoto Encyclopedia of Genes and Genomes; MSigDB: Molecular Signatures Database.

not detected. Among these, 26 DEGs were validated in blood tissue (GSE84844, Fig. 6A) and 23 DEGs in minor salivary gland tissue (GSE7451, Fig. 6B). These results indicate a high validation rate of pleiotropic genes across different SD tissues, which are consistent with findings from post-GWAS analyses, confirming the specific involvement of these genes in SD. This validation step effectively reduces the potential confounding influence of overlapping cases from SLE or RA in the FinnGen data.

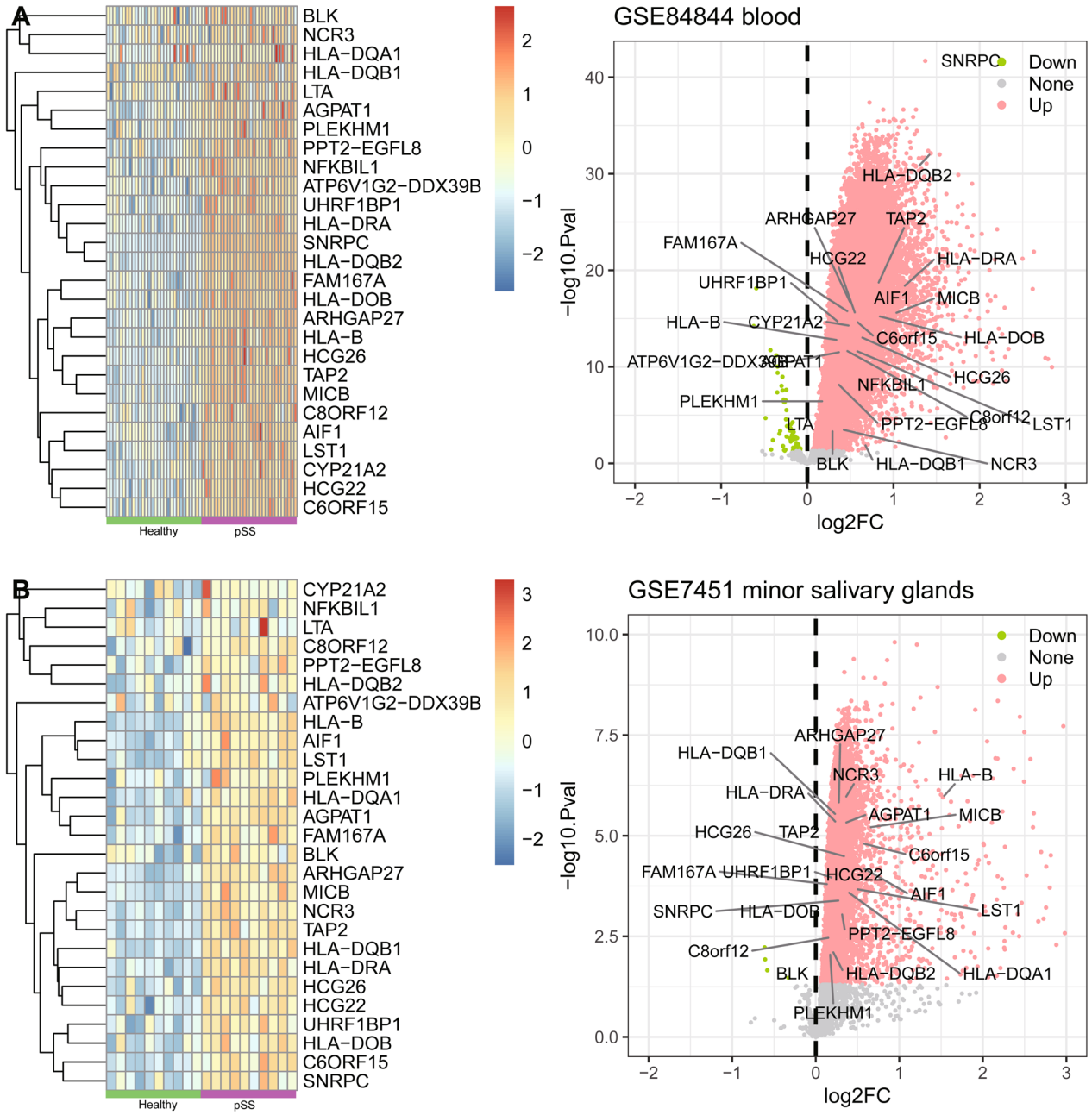

Fig. 6 Expression of identified pleiotropic genes in SD patients. **A** Heatmap and volcano plot of differentially expressed genes (DEGs) in blood tissue from SD patients. **B** Heatmap and volcano plot of DEGs in minor salivary gland tissue from SD patients

Sensitivity analysis

As shown in Table S2, a total of 42 SNPs were extracted from the SD GWAS data based on previously published research [29–36]. Among these, 15 SNPs reached the significance threshold of 5×10^{-8}. After applying stringent clumping criteria ($r^2 < 0.001$ within a 10,000 kb window), 4 independent SNPs were identified: rs11889341 (STAT4), rs3135394 (HLA-DRA), rs117026326 (NCF1), and rs3757387 (IRF5). IVW analysis demonstrated that genetic proxies for SD have causal effects on CVD events, including IHD (OR: 1.05, 95% CI: 1.02–1.081, $P = 9.41\times 10^{-4}$) and stroke (OR: 1.08, 95% CI: 1.036–1.127, $P = 3.15\times 10^{-4}$) (Fig. 7). Even under the Bonferroni correction condition of $P < 0.025$, the result still reached significance.

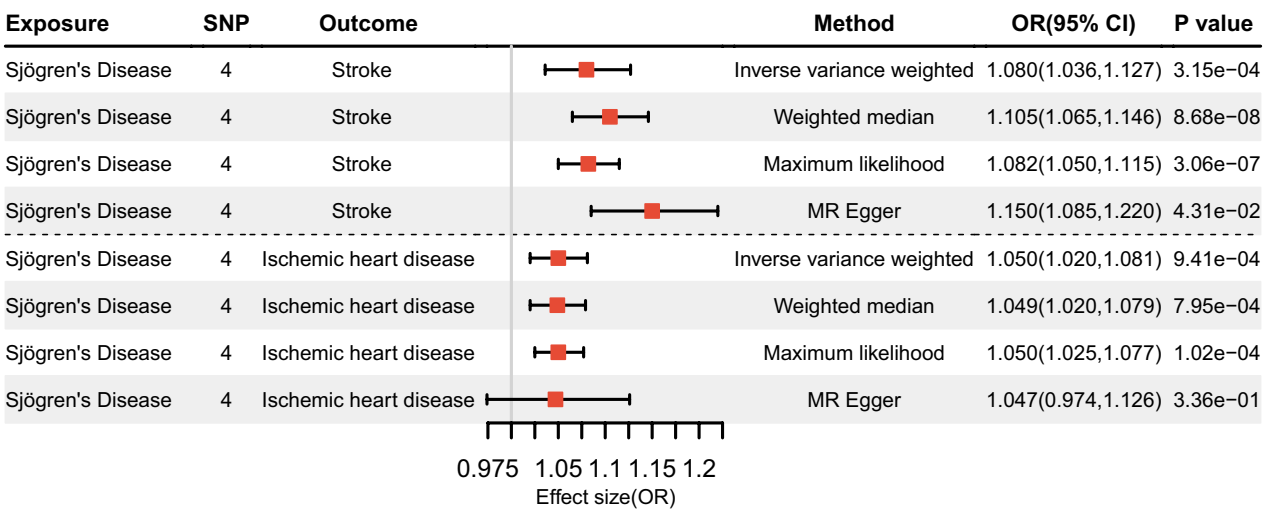

Fig. 7 Causal relationship between SD and cardiovascular events in a two-sample MR analysis using genetic proxies identified from published studies

Four independent SNPs were identified to represent susceptibility genes outside the MHC class regions. Specifically, rs62065377 represents ARHGAP27 and PLEKHM1; rs7001675 represents BLK, FAM167 A, and FAM167 A-AS1; rs184242965 represents UHRF1BP1; and rs546271365 represents SNRPC. Mendelian randomization analysis using the Wald ratio method indicated that the predicted enhanced expression of these genes in SD patients was significantly correlated with an increased risk of IHD and stroke (Fig. 8). Co-localization results for SD-stroke showed that BLK, FAM167 A, and FAM167 A-AS1 (with the most significant SNP being rs998683), SNRPC (with the most significant SNP being rs2744944), and UHRF1BP1 (with the most significant SNP being rs142415291) further strengthened the association of these genes with SD and its associated complications. However, this analysis did not demonstrate that UHRF1BP1 and SNRPC for SD-IHD, or ARHGAP27 and PLEKHM1 for SD-stroke, met the pre-defined threshold of PPH3 + PPH4 > 0.8, indicating that the causal relationship between these genes and SD-related complications requires further validation (Table S15).

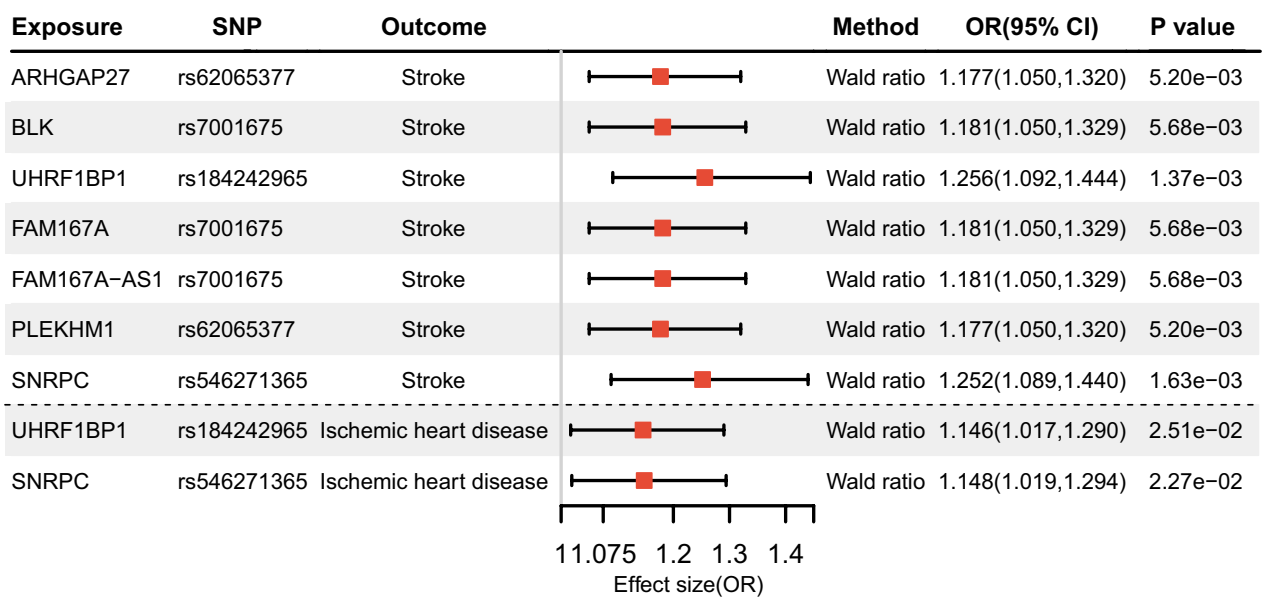

Fig. 8 Association between predicted expression of pleiotropic genes located outside MHC regions and the risk of CVDs in SD patients

Potential drugs for reducing the likelihood of CVD events

By utilizing the pleiotropic genes shared between SD and CVDs, we queried drug databases such as DGIdb and DrugBank to directly identify potential therapeutic agents. Among the 77 approved drugs identified, several corticosteroids and Disease-Modifying Anti-Rheumatic Drugs (DMARDs) were found to have potential in reducing SD and its cardiovascular complications risks, including triamcinolone (HCG22), etanercept (LTA, HLA-B, HLA-DRB1), infliximab (HLA-DRB1, HLA-B), mercaptopurine (HLA-DRB1, HLA-DQA1), azathioprine (HLA-DQA1, HLA-DRB1), tocilizumab (HLA-DRB1), rilonacept (HLA-DRB1), and canakinumab (HLA-DRB1). These hormone-based or monoclonal antibody drugs for treating inflammatory connective tissue diseases demonstrate potential in reducing CVD risks. However, further pathway analyses and clinical studies should be conducted in the future to validate their efficacy (Table S16).

Discussion

Recent years have seen increased recognition of the potential cardiovascular implications of SD, independent of associations with other systemic immune-mediated conditions such as RA and SLE. The proposed mechanisms include chronic systemic inflammation, which may drive accelerated atherosclerosis, contribute to endothelial dysfunction, and facilitate plaque formation-key processes in the pathogenesis of CVDs [40]. However, it is important to consider that various factors, including smoking, obesity, and vitamin D deficiency, may act as confounders, influencing both autoimmune diseases and CVDs. This interplay complicates the elucidation of a direct causal relationship between SD and CVDs, highlighting the need for rigorous research to disentangle these associations [41–44]. To ensure the robustness of the MR study, it is crucial to rigorously adhere to the principle of removing confounding IVs. In the current study, SNPs associated with mutual risk factor confounders such as RA, SLE, SSc, smoking, obesity, among others, were excluded based on both P values and LD values. This conclusion was also validated using genetic proxies identified from previously published studies [30–38]. The stringent approaches substantiate a direct causal relationship from SD to cardiovascular diseases, including stroke and IHD. The causal relationship was further validated using multivariate MR, which confirmed that both of stroke and IHD retained significance after accounting for potential confounding factors. Furthermore, through sufficient sensitivity tests, including maximum likelihood, MR-Egger regression, weighted median, MR-PRESSO, and Steiger methodology, the absence of pleiotropy and correct directionality was assured. Previous retrospective and cross-sectional study have confirmed that CVD outcomes may be correlated with immune dysregulation of SD patients [2–6]. Some observational studies have suggested a higher prevalence of dyslipidemia in SD patients; however, these studies observed imbalances in age and gender as confounding variables [45, 46]. In contrast, in a comparable observational study, SD showed similar distributions of total cholesterol (TC), HDL, LDL, triglycerides (TG), and TC/HDL [47]. Our genetic analysis also did not reveal a causal relationship between SD and dyslipidemia. Therefore, this result may support the notion that SD's susceptibility to CVDs may not be influenced by lipids, but rather more likely by immune responses.

SD developed owing to patient's genetic variants triggering from environmental risk factors which activating innate and adaptive immune responses. In SD, critical immunopathological factors include heightened interferon system activity and B cell hyperactivation, resulting in hypergammaglobulinemia and the generation of autoantibodies [48, 49]. The presence of common anti-Ro/La antibodies are linked to endothelial dysfunction, increased intima-media thickness and impaired nitric oxide, serving as indicators of higher immune inflammatory activity and an elevated risk of cardiovascular events [50, 51].

The genes within the MHC region have long posed a challenge for understanding and exploration due to extensive LD, yet they have been consistently shown to be strongly correlated with chronic inflammatory processes, particularly in autoimmune diseases. In 2001, Bolstad et al. reported a strong association between SD-specific autoantibodies and the HLA-DQB1 allele [52]. Further analysis revealed that the SNP rs1041981, causing an amino acid substitution in exon 3 of the LTA gene, was in complete LD with rs909253 and significantly associated with SD. These associations were particularly pronounced in seropositive individuals carrying anti-SSA and anti-SSB antibodies [52]. Additionally, rs909253 has been strongly associated with an increased likelihood of myocardial infarction and infection [53]. These findings not only reinforce the critical role of anti-Ro/La antibodies in the comorbidity between SD and IHD but also validate our observation of significant up-regulation of LTA and its LD-associated genes of LST1 and NCR3 in both conditions. Additional research has provided valuable insights, suggesting that genes within the MHC region may work synergistically, contributing to autoimmune inflammation. Notably, Yau and colleagues identified the LTA-LST1-NCR3 haplotype as a conserved unit, where genes may interact directly or indirectly. They observed notable variations in both allele-specific

gene expression and alternative RNA splicing, which were strongly associated with arthritis susceptibility [54]. Yau's findings are also mirrored in our study. Specifically, our evidence indicates that LTA, LST1, NCR3, and the LD-linked gene AIF1 within the MHC class III region may function as pleiotropic genes, contributing to the pathogenesis of both SD and IHD. AIF1 within the MHC III region is recognized as a highly pleiotropic gene, critically involved in the activation of macrophages and implicated in antibody production processes in various immune inflammatory diseases, and cardiovascular diseases like IHD, where it promotes the growth of blood vessel smooth muscle cells and T cells [55–60]. In our analysis, MAGMA identified a significant association between AIF1 and SD ($P_{FDR} = 6.23 \times 10^{-8}$). Additionally, the SNP rs3130632, located near AIF1 at chr6:31592986–31596987, showed strong associations in GWAS datasets for both SD ($P = 4.71 \times 10^{-38}$) and IHD ($P = 4.73 \times 10^{-9}$), as well as in MTAG results for SD ($P = 6.95 \times 10^{-41}$) and IHD ($P = 5.26 \times 10^{-12}$). Consistently, Nevado et al. reported AIF1 as a critical mediator of IHD in T2DM patients, demonstrating strong statistical significance ($P < 0.001$) [61]. However, despite earlier evidence implicating AIF1 in cytokine-induced ischemic stroke, our current findings do not corroborate this association.

MHC-II genes, including HLA-DQA1, HLA-DQA2, HLA-DQB1, HLA-DQB2, and HLA-DOB, HLA-DRA, HLA-DRB1, HLA-DRB5, along with MHC-I genes such as HCG26, MICB, and HLA-B, were identified as key genetic factors contributing to the comorbidity between SD and CVDs. Pathway analysis of these genes indicated that their primary role involves the presentation of antigenic peptides that are critical for adaptive immune responses and the development of immune inflammatory diseases. The involvement of these MHC class genes in the pathophysiology of SD aligns with established research findings [62–66]. Moreover, the targeted drug RO5459072, which inhibits a specific cysteine protease involved in MHC-II expression on antigen-presenting cells, has shown efficacy in treating SD and other autoimmune diseases [67].

In 2000, a strong association was first reported between unstable plaques in IHD and CD4 + T lymphocyte proliferation, attributed to chronic inflammation [68]. Tuttolomondo et al. highlighted that interactions between HLA genes and killer immunoglobulin-like receptors (KIRs) might contribute to the pathogenesis of ischemic stroke or coronary artery disease [69]. Furthermore, research has shown a strong association between HLA gene expression and dysregulated autophagy genes in ischemic stroke patients [70]. Further research has shown a strong relationship between MHC-II genes, particularly HLA-DRB1 and HLA-DQB1, and DNA methylation, which may contribute to the onset of ischemic stroke [71]. Here, we validated that MHC class genes act as a critical link, rendering SD patients genetically predisposed to ischemic outcomes-a relationship earlier also identified in diseases like SLE and RA [72, 73]. The pathway enrichment of genes within MHC region revealed that the most significant pathways were associated with immune cell activation, particularly those involved in T cell-mediated immunity and leukocyte adhesion.

Another important finding of our study was the identification of susceptibility genes located outside the MHC region that contribute to both SD and CVDs, achieved through the application of TWAS and MAGMA. Using these approaches, we identified two genes (SNRPC, UHRF1BP1) associated with SD-IHD and seven genes (SNRPC, UHRF1BP1, FAM167 A, BLK, C8orf12 [FAM167 A-AS1], ARHGAP27, and PLEKHM1) associated with SD-stroke. Subsequent MR analyses revealed that elevated expression of these genes in SD patients was genetically linked to an increased risk of CVDs. Furthermore, co-localization analyses showing that these loci share significant variants provide robust genetic evidence that FAM167 A, BLK, C8orf12, SNRPC, and UHRF1BP1 act as key pleiotropic genes contributing to both SD and stroke pathogenesis. Notably, FAM167 A, BLK, and C8orf12 demonstrated the highest PPH4 values, approaching 0.80. The involvement of the FAM167 A-BLK locus in SD is consistent with previous findings and has been substantiated in European and Han Chinese cohorts [74]. Notably, the FAM167 A-BLK locus has been associated with EBV infection and the enhancement of B-cell processes. Expression of the FAM167 A-BLK gene has also been implicated in SLE, chronic myeloid leukemia (CML), and aging [75–81]. Although its direct role in cardiovascular diseases has not been previously reported, recent research indicates a 14-fold increase in BLK expression in hypertension patients, as determined by microarray analyses [82], with a significant longitudinal association with stroke. The BLK protein plays a critical role in B-cell receptor signaling and B-cell development. This may contribute to stroke risk by enhancing B-cell activation in response to angiotensin II (AngII), leading to increased production of IgG autoantibodies, which exacerbate vascular inflammation and oxidative stress. Additionally, BLK may promote the secretion of pathogenic IgG antibodies targeting plaque antigens through the regulation of B2 cells, thereby accelerating plaque instability and elevating the risk of stroke [83]. SNRPC has been reported to have

its upregulation significantly correlated with metabolic diseases such as obesity [84]. It also regulates the expression of the ADIPOQ and SLC2 A4 genes, which encode adiponectin and GLUT4 proteins, respectively. The downregulation of these genes is closely associated with insulin resistance and the development of diabetes, thereby linking SNRPC expression to stroke and IHD [85]. However, regarding the UHRF1BP1 gene, Veroniqa et al. observed that the regulation of UHRF1BP1 expression leads to a transient and modest increase in the expression of adipogenesis genes (PPARG and CEBPA), but it has no impact on glycerol release in the medium [85].

To further substantiate our findings, we validated 34 unique contributing genes using two independent GEO RNA sequencing datasets, with careful consideration of potential confounding from overlapping cases of SLE or RA that might skew gene expression profiles in SD. Out of the 27 detected genes, 26 DEGs were validated in blood tissue and 23 in minor salivary gland tissue of SD patients, demonstrating strong concordance with post-GWAS analysis. These results not only reinforce the reliability of our findings but also suggest that gene expression in blood tissue could operate as a valuable biomarker for predicting CVDs in SD patients.

In our drug identification analysis, we preliminarily explored potential drugs that interact with pleiotropic genes, identifying candidates such as etanercept, infliximab, and azathioprine. However, it is important to highlight that some of these drugs have not been approved by clinical guidelines for the treatment of SD or CVDs. Moreover, TNF-alpha inhibitors like etanercept and infliximab have not been shown in clinical trials to significantly reduce inflammatory markers in SD patients, falling short of expected outcomes [86, 87]. Despite these challenges, new targeted therapies, such as the BTK inhibitor remibrutinib, have demonstrated promising results in phase II clinical trials, offering improved symptom relief and a favorable safety profile. This drug functions by blocking B-cell activation and autoantibody production, which subsequently disrupts pathogenic antigen presentation. Additionally, our findings indicate that remibrutinib may play a significant role in reducing the risk of CVDs, suggesting potential beneficial effects in this domain [88].

Although this research presents a comprehensive variant-based analysis, it has certain limitations. First, the study included only individuals of European ancestry due to data availability, which may limit the generalizability of the findings to other populations. Second, it should be noted that due to the high LD in the MHC region, the results should be interpreted with caution. Further laboratory validation is necessary to confirm the identified pleiotropic genes and variants. Thirdly, although this research identified a series of pleiotropic genes associated with SD, IHD, and ischemic stroke, which were validated using RNA sequencing data, the detailed regulatory mechanisms and pathways still require further validation through functional validation in vivo. Fourthly, this study did not explore the mediating roles of plasma proteins in pleiotropy, which we plan to address in future research. Lastly, this study utilized exposure and outcome GWAS data from the FinnGen11 consortium. Although we employed various methods to as comprehensively as possible capture genetic associations, the potential for type I errors remains. In future research, we plan to leverage larger-scale GWAS datasets to verify these pleiotropic susceptibility genes and to further validate the findings through biological or animal-based experiments.

Conclusion

In conclusion, this study employed MR and post-GWAS analyses to assess the genetic susceptibility of SD to the risk of IHD and stroke. Both the univariable and multivariable MR analyses showed significant associations across CVDs, with sensitivity analyses confirming these results. LDSC revealed significant genetic correlations between SD and all CVDs, while Bayesian co-localization indicated pleiotropy between SD-IHD and SD-Stroke, with PPH4 > 0.8 at specific loci. Leveraging MTAG and CPASSOC for meta-analysis, we identified 38 and 37 independent significant SNPs for SD-Stroke and SD-IHD, respectively. MHC class I, II, and III genes emerged as primary pleiotropic determinants for SD and CVDs, with pathway enrichment analyses underscoring the extensive influence of antigen presentation and immune response. Notably, excluding the MHC region, the expression of two genes (SNRPC, UHRF1BP1) was associated with an increased risk of IHD in SD patients, while the expression of seven genes (SNRPC, UHRF1BP1, FAM167 A, BLK, C8orf12 [FAM167 A-AS1], ARHGAP27, and PLEKHM1) was associated with stroke risk. Co-localization analysis further reinforced that SD and stroke share significant SNPs within the loci of FAM167 A, BLK, C8orf12, SNRPC, and UHRF1BP1. DEG analysis using RNA sequencing data from SD provided further reinforcement for these conclusions.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12967-025-06568-2.

Additional file 1.

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Author contributions
YW designed the research and directed the study. XY wrote the manuscript, did the analyses and developed the figures. EL interpreted the results, reviewed the literature and extracted data from website. All authors commented on this paper and approved the final version. Responsibility for the overall content as guarantor: YW.

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Data availability
Data are available in a public, open access repository.

Declarations

Competing interests
None declared.

Patient and public involvement
Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication
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