



Genetic Association Between Systemic Lupus Erythematosus and Cerebrovascular Disorders

Yu GUO^{1,2*}, Yonggang XU^{3*}, Chao LIU³, Meilin CHEN⁴, Hengzhu ZHANG^{1,2}, Wenmiao LUO³

¹Northern Jiangsu People's Hospital Affiliated to Yangzhou University, Department of Neurosurgery, Yangzhou, Jiangsu, China

²Northern Jiangsu People's Hospital, Department of Neurosurgery, Yangzhou, Jiangsu, China

³Xiamen Susong Hospital, Department of Neurosurgery, Xiamen, China

⁴Xiamen Susong Hospital, Department of Pathology, Xiamen, China

*Yu Guo and Yonggang Xu are joint first authors.

Corresponding author: Wenmiao LUO ✉ wenmiaoluo@outlook.com

ABSTRACT

AIM: To evaluate the potential genetic differences between systemic lupus erythematosus (SLE) and cerebrovascular disorders (CVDs) patients.

MATERIAL and METHODS: This genetic association study conducted Mendelian randomization (MR) analyses on the derived exposures and outcomes from summary statistics of genome-wide association studies (GWAS). This study employed univariate MR (UVMR) analysis, multivariable MR (MVMR) analysis, and meta-analysis, using data from large genomic databases such as the UK Biobank, FinnGen, and OpenGWAS. These methods aim to overcome confounding factors by using genetic variants as instrumental variables to infer causal relationships.

RESULTS: UVMR analysis revealed a genetic causal relationship between SLE and ischemic stroke, with a positive correlation (odds ratio [OR] 1.000367; 95% confidence interval [CI] 1.000074--1.00066; $p=0.014$). No evidence of a genetic causal relationship was found between SLE and other types of CVDs, including cerebral aneurysm, intracerebral hemorrhage, subarachnoid hemorrhage, stroke, and transient ischemic attack. MVMR analysis, after adjusting for confounders such as smoking and type 2 diabetes, confirmed the robustness of the association between SLE and ischemic stroke. Furthermore, a meta-analysis of multiple MR outcomes was conducted to verify the stability of the results (OR, 1.00037; 95% CI, 1.00008-1.00067).

CONCLUSION: Our study enhances the understanding of the genetic basis between SLE and various CVDs, particularly suggesting a positive causal association between SLE and ischemic stroke, and we emphasize the need for further research.

KEYWORDS: Systemic lupus erythematosus, Cerebrovascular disorders, Mendelian randomization, Genetic susceptibility

ABBREVIATIONS: SLE: Systemic lupus erythematosus, CVDs: Cerebrovascular disorders, MR: Mendelian randomization, UVMR: Univariate Mendelian randomization, MVMR: Multivariable Mendelian randomization, LD: Linkage disequilibrium, IS: Ischemic stroke, AN: Cerebral aneurysm, ICH: Intracerebral hemorrhage, SAH: Subarachnoid hemorrhage, TIA: Transient ischemic attack

Yu GUO : 0000-0003-0969-5913
Yonggang XU : 0000-0003-2978-2715
Chao LIU : 0000-0001-6994-8703

Meilin CHEN : 0009-0003-1787-5823
Hengzhu ZHANG : 0000-0003-3240-5689
Wenmiao LUO : 0000-0003-0340-9867



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■ INTRODUCTION

Systemic lupus erythematosus (SLE) is a multifaceted, chronic autoimmune condition, and its development is influenced by genetic, environmental, and immune factors, leading to impacts on various organ systems. Recently, a growing body of epidemiological research has indicated that SLE patients face a substantially increased risk of cerebrovascular disorders (CVDs), including both ischemic and hemorrhagic strokes (40). The likelihood of CVDs in individuals with SLE is reported to be 2 to 10 times greater than that in the general population (12). However, despite these findings highlighting a link between SLE and CVDs, the causal relationship remains unclear, largely owing to the challenges posed by potential confounding factors and reverse causality in observational studies, which complicate the ability to draw definitive conclusions (15).

CVDs rank among the primary causes of illness and death globally. In patients with SLE, the intricate progression of the disease, combined with conventional risk factors such as hypertension, diabetes, and smoking, highlights the critical need for investigating the genetic predisposition of individuals with SLE to various forms of CVDs (14).

The advent of Mendelian randomization (MR) techniques offers a robust means to address these limitations by employing genetic variants as instrumental variables (IVs) to infer causality. Owing to the random distribution of genetic variants, this method is less susceptible to biases from unmeasured confounding or reverse causation (30). However, previous MR analyses have produced inconsistent findings when examining the connection between SLE and the risk of CVDs (16, 21). Furthermore, while prior research has focused primarily on specific cardiovascular events, such as one study identifying a significant link between SLE and ischemic stroke and another failing to replicate this finding, our study broadens the scope by thoroughly examining the relationship between SLE and a wide range of cerebrovascular outcomes. In this study, the core scientific challenge lies in the selection and validation of appropriate genetic instruments for MR analysis. It is crucial to ensure that these IVs are strongly associated with SLE and that their effect on stroke risk is mediated solely through SLE, without confounding due to horizontal pleiotropy. This study enhances the robustness of the findings by applying stringent criteria for selecting IVs, using sensitivity analyses to assess pleiotropy, and incorporating data from diverse populations. Finally, a meta-analysis of MR outcomes across various datasets was conducted to validate the robustness of the conclusions.

This study conducts two-sample MR analysis, along with multivariable MR analysis (MVMR) and meta-analysis, by leveraging data from several extensive genomic databases, including the UK Biobank (UKB), FinnGen, and OpenGWAS, to investigate the genetic links between SLE and a range of CVDs. By addressing the shortcomings of prior research, this study aims to offer stronger evidence for the causal connections between SLE and specific CVDs, such as ischemic stroke (IS), cerebral aneurysm (AN), intracerebral hemorrhage (ICH), subarachnoid hemorrhage (SAH), stroke, and transient ischemic attack (TIA).

■ MATERIAL and METHODS

This study adheres to the STROBE-MR guidelines, which are essential for reporting observational epidemiological research employing MR framework (31). Statistical analyses were conducted via R version 4.2.3, which employs the TwoSampleMR and MR packages for robust computational processing (18).

No human subjects were directly involved in this study. All data used in this study were derived from existing de-identified biospecimens from previous studies. Therefore, this study did not require ethical approval or patient consent.

Study Design

In our MR analysis, we articulate three principal hypotheses: (i) There exists a robust association between IVs and exposures. (ii) These IVs are statistically independent of confounding variables. (iii) The influence of IVs on the risk of outcomes is mediated directly via exposure rather than through alternative pathways. Figure 1 presents the flowchart of the study design.

Instrumental Variables Selection

The data on SLE and CVDs were obtained from a study of the European population (Table I). The SLE data were derived from the study conducted by Bentham et al. (3). For cerebrovascular diseases, data on AN, ICH, IS, SAH, stroke, and TIA were extracted from the UKB (33). From the FinnGen database, data on AN, ICH, SAH, stroke, and TIA were obtained (23). Additionally, from the Genome-Wide Association Studies (GWAS), we extracted stroke data on AN, ICH, ischemic stroke, and SAH published by Sakaue et al. (27); stroke data published by Donertas et al. (11); TIA data published by Traylor et al. (36); data on ICH, SAH, and TIA published by Jiang et al. (22); and IS and stroke data published by Malik et al. (25). Using the TwoSampleMR package, genome-wide significant SNPs ($p < 5 \times 10^{-8}$) were identified and combined to maintain independence, with a linkage disequilibrium (LD) threshold of $r^2 < 0.001$ and a distance of 10,000 kb. LD refers to the non-random association between adjacent genes or genetic markers in the genome. By using stringent criteria to select IVs, studies can better explain causal relationships while reducing confounding effects caused by LD (32). To assess the strength of the association between the selected IVs and exposures, F statistics are computed for each instrumental variable. To evaluate the robustness of the genetic instruments, an F statistic threshold of 10 is applied to determine instrument validity, reducing the risk of bias introduced by weak instruments (17). Additionally, sensitivity analyses are performed via the MR-PRESSO approach to further assess the robustness of the results.

Study Outcomes

UKB is a biomedical database and research resource that contains genetic, lifestyle, and health information of approximately 500,000 participants aged between 40 and 69 years from the UK (8). Data from individuals of pan-European ancestry were obtained from the UKB. Stroke-related data of interest were selected, and summary statistics were downloaded from the Neale-UKB project portal website.

FinnGen is a research resource that includes analyses of genomic and health registry data of approximately 500,000 Finn-

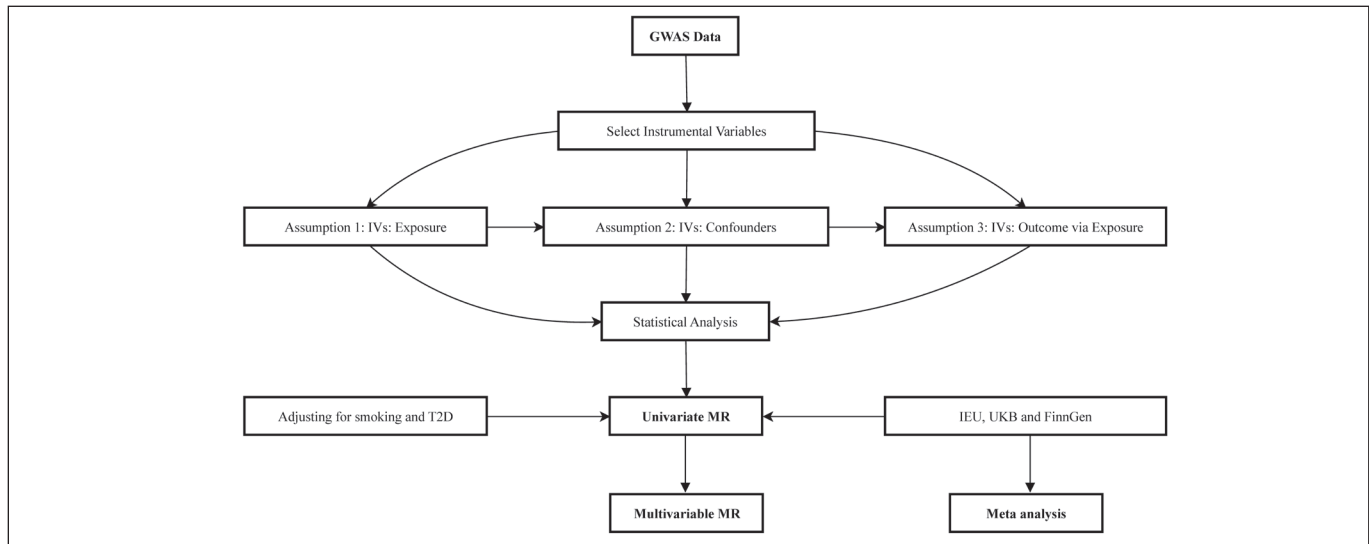


Figure 1: A diagram of the study workflow.

Table I: Characteristics of the Genome Wide Association Studies Used in This Study

Data sources	Traits	GWAS ID	Sample.size	Cases	Controls	Ancestry	R ² for SLE	F statistic for SLE
Bentham J.	SLE	ebi-a-GCST003156	14267	5201	9066	European		
UK Biobank	AN	I9_ANEURYSM	361194	225	360969	European	0.223	97.5
UK Biobank	ICH	ICD10_I61	361197	496	360701	European	0.238	90.2
UK Biobank	IS	I9_STR_EXH	361194	3314	357880	European	0.253	96.2
UK Biobank	SAH	ICD10_I60	361178	626	360552	European	0.256	94.7
UK Biobank	Stroke	ICD10_I64	361194	742	360452	European	0.258	93.1
UK Biobank	TIA	20002_1082	361141	1369	359772	European	0.271	95.2
FinnGen	AN	I9_ANEURYSM	345255	2582	342673	European	0.271	95.2
FinnGen	ICH	I9_ICH	343663	3749	339914	European	0.271	95.2
FinnGen	IS	I9_STR_EMBOLIC	344046	1373	342673	European	0.254	96.4
FinnGen	SAH	I9_SAH	343211	3289	339922	European	0.265	98.0
FinnGen	Stroke	I9_STR	311635	39818	271817	European	0.221	91.0
FinnGen	TIA	I9_TIA	360692	18398	342294	European	0.237	87.6
Sakaue	AN	ebi-a-GCST90018816	473683	945	472738	European	0.271	95.2
Sakaue	ICH	ebi-a-GCST90018870	473513	1935	471578	European	0.271	95.2
Sakaue	IS	ebi-a-GCST90018864	484121	11929	472192	European	0.237	87.6
Sakaue	SAH	ebi-a-GCST90018923	473255	1693	471562	European	0.271	95.2
Handan	Stroke	ebi-a-GCST90038613	484598	6925	477673	European	0.271	95.2
Traylor	TIA	ebi-a-GCST90014123	232596	7338	225258	European	0.234	91.1
Jiang L	ICH	GCST90043996	456348	158	456190	European	0.226	88.0
Malik R	IS	ebi-a-GCST005843	440328	34217	406111	European	0.266	98.5
Jiang L	SAH	GCST90043993	456348	832	455516	European	0.271	95.2
Malik R	Stroke	ebi-a-GCST005838	446696	40585	406111	European	0.266	98.5
Jiang L	TIA	GCST90044001	456348	2045	454303	European	0.269	96.8

$F \text{ statistic} = ((N-K-1) / K) * (R/(1-R))$ $R^2 = 2 * eaf * (1 - eaf) * \text{beta}^2$ **N:** Sample size of the exposure GWAS study. **K:** Number of SNPs. **beta:** Column containing the effect size for each SNP. **R²:** Proportion of variance in the exposure explained by the IVs. **eaf:** Column containing the effect allele frequency for each SNP.

ish individuals, encompassing low-frequency and high-impact variants (23). Stroke-related data of interest were selected, and summary statistics were downloaded from the FinnGen portal website.

To replicate the causal relationship between SLE and CVDs, data on SLE and CVD-related aspects of European populations were downloaded from the OpenGWAS API (13,18). The definitions of SLE, AN, ICH, ischemic stroke, SAH, stroke, and TIA, as well as the number of individuals in the experimental and control groups, are presented in Table I.

Statistical and Sensitivity Analyses

The statistical analysis for MR was performed via the two-sample MR, Mendelian randomization, and MR-PRESSO packages in R (version 4.2.3) (18,41). The primary approach applied is the inverse variance weighted (IVW) method, with additional analyses conducted using the MR Egger technique as secondary methods (4,5,7,17). The sensitivity tests include heterogeneity, multiplicative heterogeneity, and leave-one-out analysis (9,39). Heterogeneity was evaluated through IVW analysis and MR-Egger regression, with Cochran's Q test p values indicating the level of heterogeneity. To detect and correct for horizontal pleiotropy, the MR-PRESSO method is employed, identifying and adjusting outliers ($p < 0.05$) to compare estimates before and after correction. A leave-one-out test is conducted to verify the robustness of the MR analysis. The outcomes are reported as odds ratios (ORs) with 95% confidence intervals (CIs), along with beta coefficients and standard errors (se). P values less than 0.05 were considered statistically significant.

The positive results of UVMR analysis are expanded through MVMR. After adjusting for potential confounding factors such as smoking and type 2 diabetes (T2D), a direct causal relationship between SLE and stroke outcomes associated with UVMR was confirmed. For false discovery rate (FDR) correction in MVMR analysis, adjusted P values are calculated via the Benjamini-Hochberg procedure, which ranks the P values from smallest to largest and applies a correction factor on the basis of the number of tests performed. A significance threshold of $p < 0.05$ after FDR correction was used to identify statistically significant associations (26).

Meta-Analysis Approach

To validate the consistency and generalizability of our findings, a meta-analysis is conducted by synthesizing results from multiple independent datasets, including the UKB, FinnGen, and OpenGWAS datasets. To assess the robustness of the analysis, Cochran's Q test and the I^2 statistic were used to quantify between-study heterogeneity. A random-effects model is applied to account for potential variability across studies, minimizing bias and providing more conservative effect estimates.

IVW effect estimates for SLE on different types of CVDs are separately calculated using data from UKB, FinnGen, and OpenGWAS. These estimates are then combined in a random-effects meta-analysis (38). Dichotomous data with ORs and corresponding 95% CIs were used as effect measures.

Prediction intervals are employed to estimate the range of outcomes in future studies while considering interstudy variability and uncertainty. Heterogeneity was assessed via Cochran's Q test, with significance set at $p < 0.1$, and further quantified via the I^2 statistic. An I^2 value less than 50% indicates low heterogeneity, whereas values between 50% and 75% suggest high heterogeneity (10). The findings revealed a significant association between SLE and various types of stroke, with a bilateral $p < 0.05$ considered potentially significant. The meta-analysis was conducted via the meta package in R (1).

RESULTS

The study included individual data of European descent extracted from UKB, FinnGen, and other extensive cohort studies. Definitions and sources of disease diagnoses for SLE, AN, ICH, ischemic stroke, SAH, stroke, and TIA are provided in Table I. On the basis of the correlation between SLE and different CVDs, genetic markers were identified (Table II-III). The UVMR effects of genetic proxies for SLE on different types of CVDs were estimated separately in UKB, FinnGen and other large databases (Table III). After adjusting for confounders such as smoking and T2D, MVMR outcomes were analysed to validate the robustness of the outcomes (Table IV). The IVs and outcomes extracted from the reverse UVMR analysis are presented in Tables V-VI. The UVMR outcomes were then combined in a random-effects meta-analysis. All IVs demonstrated strong validity (F statistic greater than 10) (Table I). No significant abnormalities were observed in horizontal pleiotropy or heterogeneity tests for any of the MR analyses (Table III).

Associations Between SLE and the Risk of Different Types of CVDs

Univariate Mendelian Randomization

When the UKB was used as the primary exposure outcome, the results of univariate MR-IVW analysis suggested a genetic causal relationship between SLE and ischemic stroke. We observed a positive correlation between genetically predicted SLE and ischemic stroke (OR, 1.000367; 95% CI, 1.000074--1.00066; $p = 0.014$; Figure 2 and Table III). We further validated other types of CVDs in the UKB and found no evidence of a correlation between SLE and the risk of AN, ICH, SAH, stroke, or TIA (Table III). We conducted sensitivity analyses via MR-Egger mode. In the sensitivity analysis of SLE and stroke, only the MR-Egger results were contrary to those of the other methods. The results of the remaining sensitivity analyses were consistent with the direction of IVW. The scatter plots indicate that in all association analyses, the MR-Egger intercept did not significantly deviate from 0, and there was no evidence of pleiotropy (pleiotropy test > 0.05) (Figure 3 and Table III). Leave-one-out analysis was used to validate the reliability of the results (Figure 3).

We further validated in other cohort studies that there was no evidence of a correlation between SLE and the risk of ischemic stroke. In all cohorts, we found no evidence of a genetic causal relationship between SLE and AN, ICH, SAH, stroke, or TIA (Table III).

Table II: Identifying Robust Instrumental Variables for SLE

SNP	Sample size	p-value	Se	Beta	Effect allele	Other allele
rs6679677	14267	4.55E-13	0.046485	0.336472	A	C
rs4661543	14267	9.40E-11	0.042376	0.274437	G	T
rs10912578	14267	1.65E-15	0.030992	0.24686	A	G
rs17849501	14267	1.81E-59	0.049864	0.81093	T	C
rs6671847	14267	6.64E-12	0.028965	0.198851	A	G
rs4916215	14267	5.07E-11	0.033969	0.223144	T	C
rs12094036	14267	1.37E-08	0.05786	0.328504	T	C
rs13019891	14267	1.65E-83	0.029034	0.562119	G	T
rs2573219	14267	1.13E-42	0.042929	0.587787	C	A
rs10200680	14267	4.96E-09	0.042484	0.248461	C	T
rs268124	14267	8.60E-09	0.03237	0.18633	T	C
rs2459611	14267	7.62E-09	0.045245	0.261365	T	C
rs4274624	14267	9.73E-66	0.032679	0.559616	C	T
rs10048743	14267	2.04E-08	0.041206	0.231112	G	T
rs34703115	14267	4.08E-09	0.104778	0.616186	T	C
rs1464446	14267	2.79E-16	0.04015	0.328504	G	T
rs9852014	14267	2.26E-36	0.049273	0.620577	G	A
rs13136219	14267	3.50E-10	0.027787	0.174353	C	T
rs1078324	14267	7.11E-20	0.078167	0.71335	C	A
rs4388254	14267	3.71E-10	0.060398	0.378436	T	C
rs2431697	14267	2.60E-14	0.029296	0.223144	T	C
rs6889239	14267	2.19E-18	0.03174	0.277632	C	T
rs389884	14267	2.92E-102	0.043232	0.928219	G	A
rs9274357	14267	1.28E-38	0.035196	0.457425	T	C
rs7768653	14267	3.11E-12	0.029689	0.207014	C	T
rs12524498	14267	2.48E-08	0.120793	0.673345	G	T
rs58721818	14267	3.38E-18	0.075594	0.65752	T	C
rs150180633	14267	2.66E-41	0.068957	0.928219	T	C
rs35000415	14267	1.86E-45	0.041539	0.587787	T	C
rs2736332	14267	4.83E-18	0.032069	0.277632	C	G
rs7823055	14267	1.64E-34	0.028621	0.350657	G	T
rs7899626	14267	4.19E-08	0.033253	0.182322	T	C
rs7097397	14267	8.60E-11	0.028712	0.18633	G	A
rs58688157	14267	2.97E-11	0.033565	0.223144	A	G
rs353608	14267	2.93E-11	0.02802	0.18633	G	A
rs73050535	14267	9.11E-09	0.124134	0.71335	C	T
rs597808	14267	3.51E-08	0.029474	0.162519	A	G
rs1143679	14267	5.03E-48	0.039987	0.582216	A	G
rs13332649	14267	5.43E-17	0.037568	0.314711	A	G
rs143123127	14267	2.23E-08	0.084034	0.470004	A	G
rs35251378	14267	3.61E-13	0.032427	0.235722	G	A
rs73068668	14267	4.40E-08	0.05749	0.314711	G	A
rs3747093	14267	2.88E-14	0.034506	0.262364	A	G

Select genome-wide significant SNPs for SLE ($p < 5 \times 10^{-8}$), ensuring independence with an $r^2 < 0.001$ for linkage disequilibrium and a distance of 10,000 kb. **Se:** Standart error.

Table III: The Univariate Mendelian Randomization of Genetic Proxies for SLE on IS, AN, ICH, SAH, Stroke and TIA in the UK Biobank, FinnGen, IEU and GWAS Catalog Databases.

Outcomes	Method	SNPs	Beta	Se	p-value	Heterogeneity tests	Pleiotropy test
						Q p-value	p-value
UK Biobank							
Ischemic stroke	MR Egger	38	0.0004545	0.0003141	0.1565208	0.1330163	0.7524929
	IVW	38	0.000367	0.0001493	0.0139635*	0.1558752	
Cerebral aneurysm	MR Egger	33	-0.0001177	8.43E-05	0.1728961	0.2166895	0.2964794
	IVW	33	-0.0000389	4.02E-05	0.3332591	0.2089223	
Intracerebral hemorrhage	MR Egger	38	-0.0001262	0.0001247	0.3181248	0.2130197	0.7063034
	IVW	38	-0.0000846	0.0000587	0.1495237	0.2422703	
Subarachnoid hemorrhage	MR Egger	39	-0.0002222	0.0001236	0.0803506	0.6111911	0.1372706
	IVW	39	-0.0000579	0.0000598	0.3327382	0.5485976	
Stroke	MR Egger	40	-0.0000023	0.0001429	0.9870552	0.3077826	0.6064423
	IVW	40	0.0000626	0.0000685	0.3607582	0.3369019	
Transient ischemic attack	MR Egger	41	-0.0000751	0.0001927	0.6990531	0.1420934	0.6878885
	IVW	41	-0.0000069	0.0000929	0.9404493	0.1631692	
FinnGen							
Ischemic stroke	MR Egger	38	0.0268424	0.0500244	0.5948539	0.7928841	0.5810486
	IVW	38	0.0021593	0.0231927	0.9258213	0.8150444	
Cerebral aneurysm	MR Egger	41	0.0186737	0.0395707	0.6396221	0.1692403	0.9777643
	IVW	41	0.019656	0.0181996	0.2801319	0.1983929	
Intracerebral hemorrhage	MR Egger	41	-0.0503262	0.0323408	0.1277578	0.2055257	0.357942
	IVW	41	-0.02372	0.0150735	0.1155749	0.2076139	
Subarachnoid hemorrhage	MR Egger	39	0.0122422	0.0371933	0.743897	0.1014085	0.6470525
	IVW	39	0.0274719	0.0169944	0.105982	0.1171651	
Stroke	MR Egger	35	-0.0261687	0.0135192	0.0615134	0.2402225	0.1082091
	IVW	35	-0.006117	0.0060882	0.3150282	0.1761803	
Transient ischemic attack	MR Egger	39	-0.0133896	0.017999	0.4616303	0.1295774	0.3983252
	IVW	39	0.0004787	0.0077546	0.9507814	0.1339409	
IEU							
Ischemic stroke	MR Egger	38	-0.0033896	0.011596	0.7717279	0.5575338	0.781113
	IVW	38	-0.0004924	0.0052316	0.9250126	0.6003995	
Cerebral aneurysm	MR Egger	41	-0.0270455	0.0561382	0.6326646	0.7195153	0.680128
	IVW	41	-0.0064915	0.026518	0.8066129	0.7505296	
Intracerebral hemorrhage	MR Egger	41	0.0012602	0.0325245	0.9692916	0.3979051	0.8730485
	IVW	41	-0.0033626	0.0150381	0.8230633	0.4407831	
Subarachnoid hemorrhage	MR Egger	41	-0.0331494	0.0391241	0.4020033	0.0898489	0.4778944
	IVW	41	-0.0083868	0.018234	0.6455498	0.0973094	

Table III: Cont.

Outcomes	Method	SNPs	Beta	Se	p-value	Heterogeneity tests	Pleiotropy test
						Q p-value	p-value
Stroke	MR Egger	41	-0.0002526	0.0002999	0.4048778	0.3395831	0.2205481
	IVW	41	0.0000739	0.0001466	0.6142352	0.3157272	
Transient ischemic attack	MR Egger	37	0.0351295	0.0259391	0.1843189	0.4464989	0.4785699
	IVW	37	0.018841	0.0123974	0.1285717	0.4695658	
GWAS Catalog							
Ischemic stroke	MR Egger	39	-0.0022559	0.0121873	0.8541578	0.1933407	0.6194726
	IVW	39	0.0031688	0.0055303	0.5666545	0.2166684	
Intracerebral hemorrhage	MR Egger	37	-0.0879597	0.1449075	0.5477648	0.5056632	0.7689564
	IVW	37	-0.05069	0.0717484	0.479879	0.5492968	
Subarachnoid hemorrhage	MR Egger	41	-0.1075429	0.0588226	0.0751672	0.8832752	0.101926
	IVW	41	-0.0215335	0.0286975	0.4530363	0.824411	
Stroke	MR Egger	39	0.0022268	0.0113727	0.8458378	0.1922506	0.9264027
	IVW	39	0.0012885	0.0051804	0.8035746	0.2243507	
Transient ischemic attack	MR Egger	40	-0.0241888	0.0379735	0.5279504	0.4621167	0.8404686
	IVW	40	-0.0174683	0.0184679	0.3442112	0.5060334	

*, *p* value <0.05.**SNPs:** Single nucleotide polymorphisms; **Se:** Standard error; **IVW:** Inverse variance weighted.**Table IV:** The Multivariable Mendelian Randomization Effect of SLE on Ischemic Stroke After Adjusting for Smoking and Type 2 Diabetes

Exposure	Outcome	beta	Se	p-value	Adjusted p-values	F statistic	Q stat	Q p-value
Systemic lupus erythematosus	Ischemic stroke	0.000387	0.000141	0.00677	0.020311	23.55347	187.8418	0.065384
Diabetes Mellitus, Type 2	Ischemic stroke	0.000648	0.000384	0.09335	0.140025	56.39439	187.8418	0.065384
Tobacco Smoking, Current	Ischemic stroke	0.00959	0.006624	0.149605	0.149605	6.307108	187.8418	0.065384

Se: Standard error.**Table V.** Identifying Robust Instrumental Variables for Ischemic Stroke in UK Biobank

SNP	Sample size	p-value	Se	Beta	Effect allele	Other allele
rs116676869	361194	2.13539e-06	0.000447294	0.00212028	A	G
rs117184775	361194	2.67794e-06	0.00110861	0.00520402	A	G
rs118001501	361194	1.6788e-06	0.000668369	-0.00320066	G	T
rs12665721	361194	4.00247e-06	0.000230751	0.00106407	C	T
rs142726048	361194	4.56208e-06	0.000649805	0.00297874	A	G
rs149541600	361194	4.52765e-06	0.000936969	0.00429659	T	C
rs151319393	361194	1.84923e-06	0.000681006	0.00324793	T	A
rs16955419	361194	1.0722e-06	0.000487215	0.00237663	G	T
rs17336988	361194	5.91489e-07	0.000875933	0.00437447	A	G
rs35847387	361194	7.22471e-07	0.000410946	0.00203637	T	C

Table V. Cont.

SNP	Sample size	p-value	Se	Beta	Effect allele	Other allele
rs4307235	361194	1.13945e-06	0.000237493	0.00115564	T	C
rs6054662	361194	3.16397e-08	0.000317744	-0.00175783	T	C
rs62174635	361194	4.35309e-06	0.000789791	0.00362817	T	C
rs6564437	361194	3.95323e-06	0.000264794	-0.00122173	C	T
rs66961966	361194	4.42965e-06	0.000598503	0.00274725	G	C
rs7085903	361194	7.79616e-07	0.000273432	-0.00135089	T	C
rs72781382	361194	1.15692e-06	0.000980832	0.00476975	C	T
rs7501414	361194	3.23506e-06	0.000328134	-0.00152759	C	A
rs75238399	361194	4.01368e-06	0.000833806	0.00384447	A	G
rs75259736	361194	9.38906e-08	0.000285389	-0.00152349	A	T
rs75415430	361194	3.15976e-06	0.000576427	0.00268628	T	C
rs76307406	361194	2.58378e-06	0.000475683	0.00223641	A	C

Select genome-wide significant SNPs for SLE ($p < 5 \times 10^{-6}$), ensuring independence with an $r^2 < 0.001$ for linkage disequilibrium and a distance of 10,000 kb.

Table VI. The Univariate Mendelian Randomization of Genetic Proxies for IS on SLE in the UK Biobank

Outcomes	Method	SNPs	Beta	Se	p-value	Heterogeneity tests	Pleiotropy test
						Q p-value	p-value
UK Biobank							
Ischemic stroke	MR Egger	16	-6.4407259	16.11462417	0.695	0.7418789	0.80194265
	IVW	16	-7.2543813	7.1918339	0.313	0.8019426	

SNPs: Single nucleotide polymorphisms; Se: Standard error; IVW: Inverse variance weighted.

Reverse UVMR analyses revealed that the genome-wide significant SNPs ($p < 5 \times 10^{-6}$) for ischemic stroke provided by the UKB may not exhibit a causal association with systemic lupus erythematosus (SLE) ($p = 0.802$) (Tables V-VI).

Multivariable Mendelian Randomization

Within the MVMR framework, the positive results of UVMR analysis were extended via MVMR. After adjusting for potential confounders such as smoking and T2D, we validated a more direct causal relationship between SLE and ischemic stroke outcomes that was associated with UVMR (Table IV). We found that after adjusting for the effects of smoking and T2D, the causal relationship between SLE and ischemic stroke in the UKB remained stable (beta, 0.000387; se, 0.000141; $p = 0.007$). When the FDR method was used to correct for potential Type I errors, a positive association between SLE and ischemic stroke was observed ($P_{\text{adjust}} = 0.02$).

Meta-analysis

A meta-analysis of all outcomes between SLE and different types of CVDs revealed a positive causal association between SLE and ischemic stroke (OR, 1.00037; 95% CI, 1.00008-1.00067; Figure 4). There was no evidence of heterogeneity or

pleiotropy. In the meta-analysis of SLE patients with AN, ICH, SAH, stroke, and TIA outcomes, we found no evidence of a genetic causal relationship. Similarly, there was no evidence of heterogeneity or pleiotropy (Figure 5).

DISCUSSION

Previous observational studies and several recent MR analyses have provided inconsistent explanations regarding the associations between SLE and CVEs (12,16,21). Our study further provided genetic evidence supporting the association between SLE and ischemic stroke, as demonstrated through UVMR (OR, 1.000367; 95% CI, 1.000074--1.00066) and MVMR (beta, 0.000387; se, 0.000141; $p = 0.007$). Furthermore, a meta-analysis integrating data from various genetic levels indicated that SLE patients may have an elevated risk of ischemic stroke (OR, 1.00037; 95% CI, 1.00008-1.00067). Nevertheless, there is currently no evidence of a causal relationship between SLE and AS, ICH, SAH, stroke, or TIA. Reverse UVMR analysis indicated that ischemic stroke, as indicated by the UKB, may not be causally associated with SLE ($p = 0.802$). These findings suggest that there may be a unidirectional causal relationship between SLE and ischemic stroke.

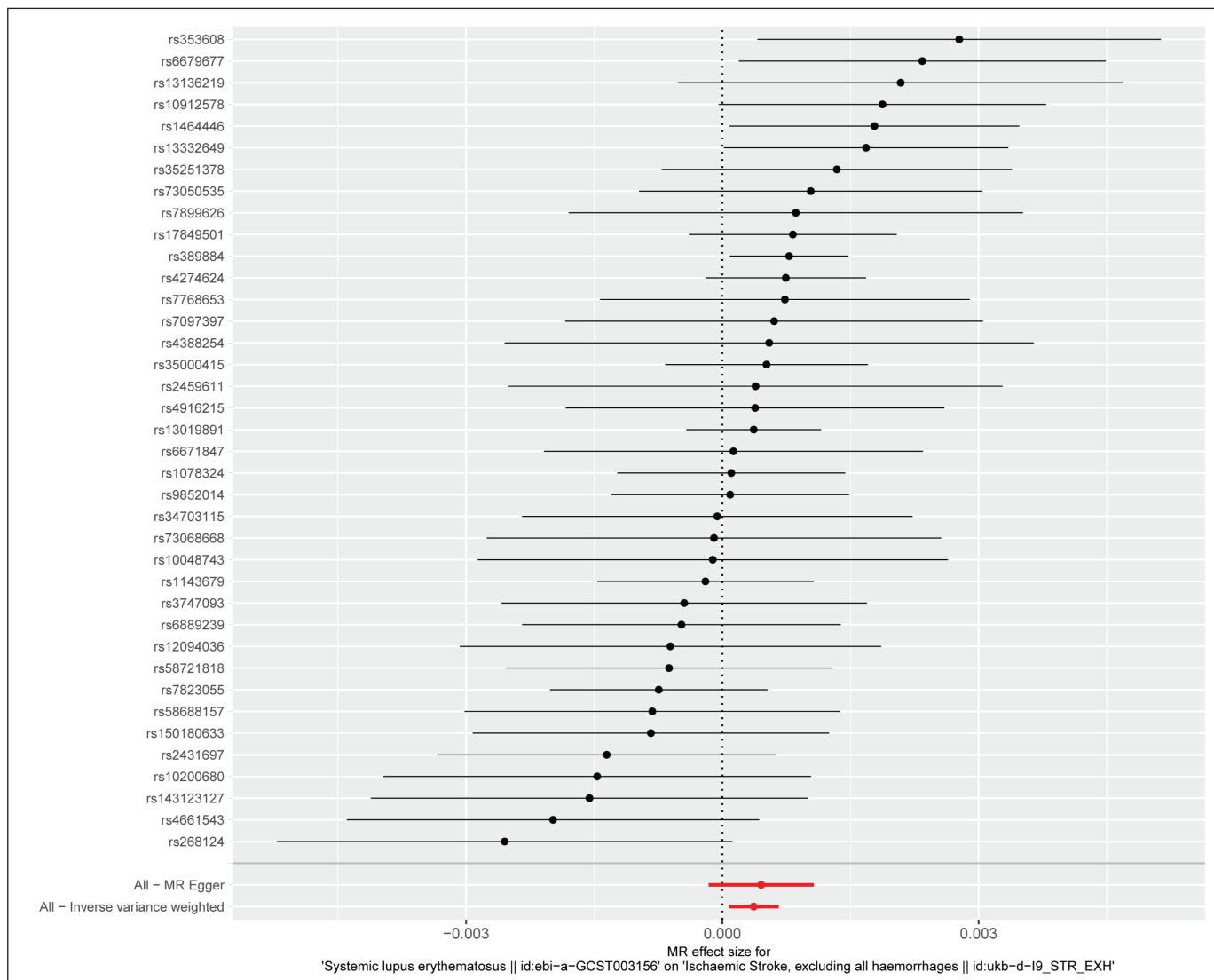


Figure 2: MR effect size for systemic lupus erythematosus on ischemic stroke.

Global Incidence and Risks in SLE

Recent studies have reported that approximately 3.4 million people worldwide are affected by SLE. Each year, 400,000 new cases of systemic lupus erythematosus are diagnosed globally (19,29). Observational studies have emphasized that SLE patients face an increased risk of cardiovascular and cerebrovascular diseases. However, researchers have objectively noted that most of the literature focuses on data from national registries, where significant discrepancies in the incidence and prevalence of SLE are observed. Additionally, the associations between SLE and various CVDs have not been well explained. Observational studies may have potential confounding or reverse causality biases (2,24). For example, hypertension or oral anticoagulants in SLE patients may influence CVDs, but such factors are difficult to control in clinical studies. MR, which is based on genetic variations assigned at birth, is not affected by drugs, the environment, or other factors and can be used to assess the correlation between

genetic markers of SLE and CVDs effectively. Unfortunately, recent MR analyses have not provided consistent evidence for a causal relationship between SLE and CVDs (16,21,34). The primary considerations are pleiotropy and heterogeneity between studies, as well as limitations in study populations. It is necessary to conduct larger MR analyses, combining outcomes from different databases and study populations.

Potential Problems

Our study effectively analysed the correlation between SLE genetic susceptibility and different cerebrovascular diseases via MR analysis. CVDs include ischemic CVDs and hemorrhagic CVDs, with the former being more common in SLE patients. Compared with that in non-SLE patients, the incidence of ischemic stroke in SLE patients is as high as 90%, whereas the incidence of nonischemic stroke is 63%. Additionally, the incidence of widespread cerebral infarction in SLE patients is significantly greater than that in non-SLE patients (69.4% vs. 18.7%) (37). Previous studies have shown that the risk of

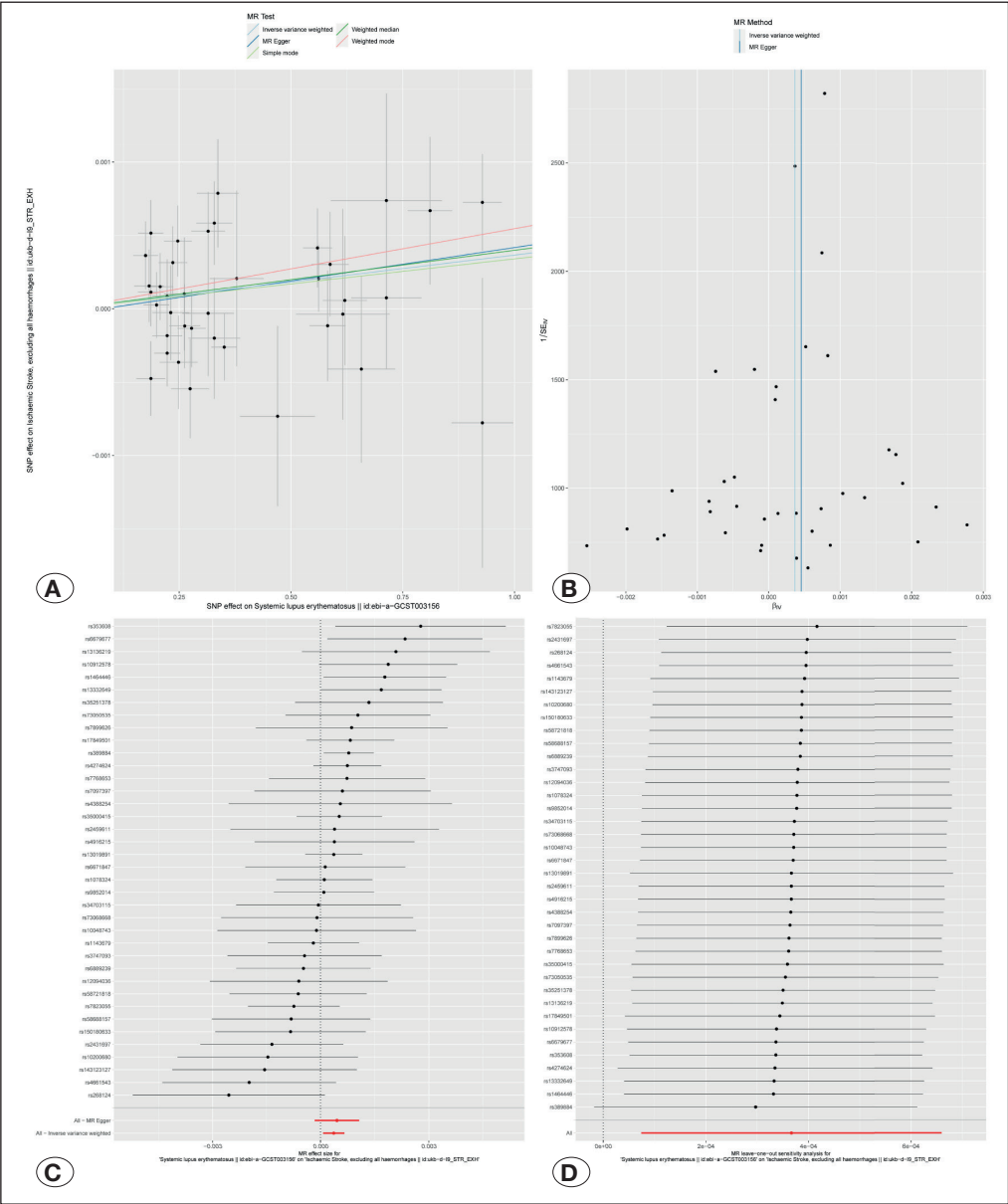


Figure 3: The UVMR effect of SLE-associated SNPs on ischemic stroke in the UKB.

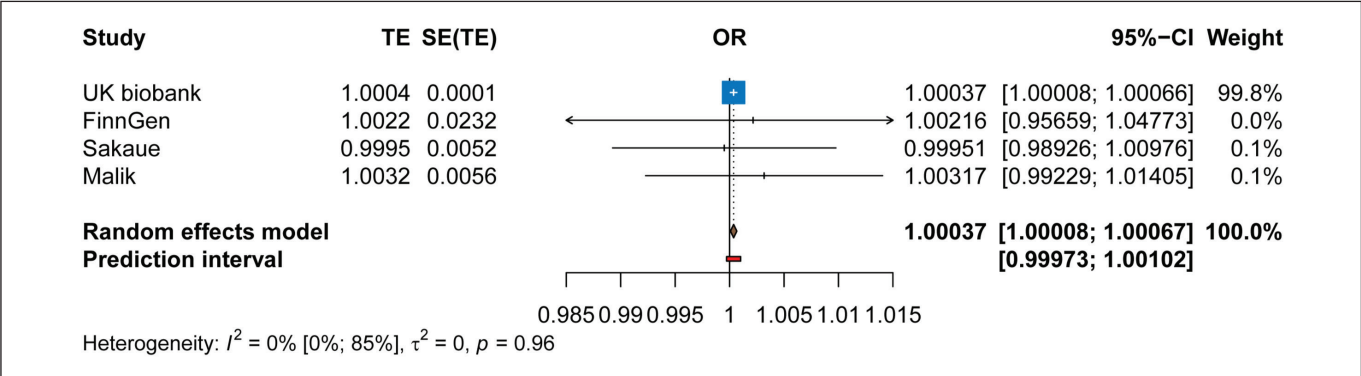
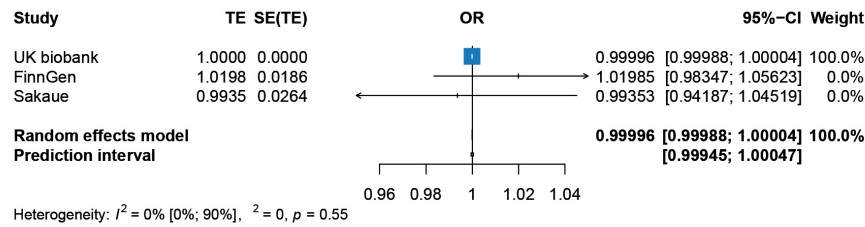
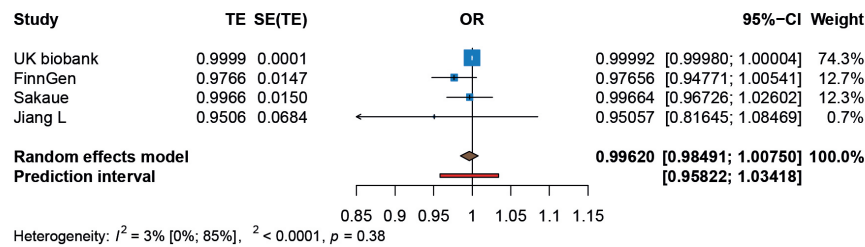


Figure 4: Combined random-effects model meta-analysis of the effect of SLE on ischemic stroke in the UK Biobank, FinnGen, IEU and GWAS Catalog.

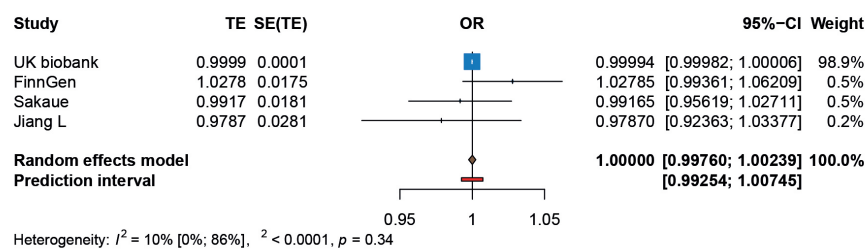
(A) Cerebral aneurysm



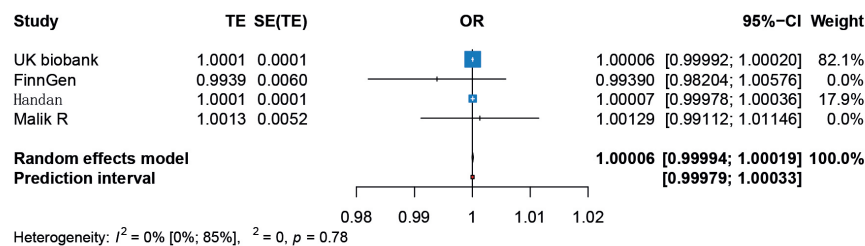
(B) Intracerebral hemorrhage



(C) Subarachnoid hemorrhage



(D) Stroke



(E) Transient ischemic attack

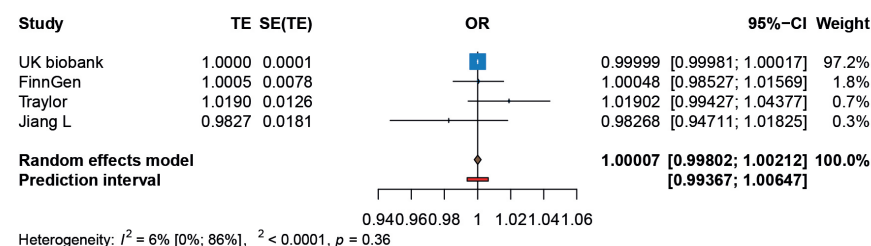


Figure 5: Combined random-effects model meta-analysis of the effect of SLE on AN, ICH, SAH, Stroke, and TIA in the UK Biobank, FinnGen, IEU and GWAS Catalog.

thrombosis persists throughout the course of SLE, accelerating atherosclerosis and vascular calcification and thereby increasing the risk of ischemic stroke. SLE patients often have other cardiovascular risk factors, such as smoking and diabetes, which further increase the risk of CVDs (28). Therefore, it is crucial to comprehensively assess and manage the impact of these comorbidities and validate the correlation between SLE and CVDs. We used MVMR to adjust for potential confounding factors such as smoking and type 2 diabetes, further validating the correlation between SLE genetic susceptibility and a high risk of ischemic stroke. Moreover, our MR analysis did not reveal a correlation between SLE genetic susceptibility and AN, ICH, SAH, overall stroke, or TIA. This finding does not align with the outcomes of observational studies, and the underlying mechanisms are currently unclear. The mechanisms of AN, ICH, SAH, overall stroke, and TIA are closely related to the structural integrity of the vascular wall, blood pressure control, and endothelial function, and these pathological processes may not be directly influenced by SLE-related genes. SLE genetic susceptibility may be related to immune system abnormalities (such as the production of autoantibodies and complement system activation), and these factors may have limited direct effects on vascular lesions. For example, chronic immune activation in SLE, characterized by elevated levels of autoantibodies and inflammatory cytokines such as TNF- α and IL-6, has been associated with endothelial dysfunction and plaque formation in cerebral arteries (40). These immune-mediated processes can disrupt vascular homeostasis, promote atherosclerosis and increase the risk of ischemic stroke. Additionally, complement activation, a hallmark of SLE, has been linked to vascular injury and an increased risk of thromboembolic events, potentially contributing to the pathogenesis of ischemic stroke (6). The deposition of immune complexes and the generation of complement-derived anaphylatoxins can further exacerbate endothelial damage and microvascular thrombosis, creating a pro-thrombotic environment that predisposes SLE patients to cerebrovascular events (20). MR analysis relies on the validity of the selected instrumental variables, specifically whether these genetic variations affect the risk of AN, ICH, and TIA by influencing SLE risk. If the instrumental variables do not fully meet this assumption (e.g., they also affect vascular health through other pathways), the study results may be biased, making it difficult to detect significant associations. We included data from several large databases, all of which involved European populations (Table I), to minimize the interference caused by population stratification features such as race and geography (32). Of course, we acknowledge that we cannot fully control for confounding factors related to population stratification. Therefore, we conducted heterogeneity tests to assess the degree of heterogeneity and further evaluate the reliability of the outcomes (42,43).

Influence on Clinicians

In our study, we further optimized the MR analysis by ensuring the selection of robust instrumental variables. Additionally, we applied various sensitivity analysis methods and combined meta-analyses to verify the stability of the outcomes. However, further studies with larger sample sizes and multicenter

studies are still needed. A longitudinal study design combined with MR analysis was used to track the occurrence of cardiovascular events in SLE patients over time (35). The associations between SLE populations with different characteristics, such as sex or age, and various CVD subgroups should be investigated, confounding factors should be reduced, and genetic associations should be further elucidated (34). While our MR analysis suggested a genetic causal relationship between SLE and ischemic stroke, it was important to recognize the inherent limitations of MR in establishing causality. While robust, MR findings are ultimately observational in nature and require experimental validation to confirm causality. Future studies should aim to validate these genetic associations through experimental approaches, such as animal models or in vitro studies, to directly assess the impact of SLE-related genetic variants on vascular pathology and stroke risk. Additionally, clinical trials targeting specific pathways identified in this study (e.g., immune system activation or complement regulation) could provide further insights into the causal mechanisms linking SLE to ischemic stroke (19).

Limitations

Our study revealed a causal association between SLE genetic susceptibility and CVDs, but it is important to acknowledge the limitations of the methodology and data sources.

1) Sample population limitations: The genetic data analysed in this study were predominantly derived from European populations, limiting the generalizability of our findings to non-European cohorts. Furthermore, a systematic review of the literature revealed no large-scale genetic studies investigating SLE-CVDs relationships in non-European populations, underscoring the reliance on Eurocentric datasets and the uncertain applicability of our conclusions to ethnically diverse cohorts.

2) Selection of instrumental variables: Although we used stringent criteria to screen instrumental variables ($p < 5 \times 10^{-8}$, LD $r^2 < 0.001$), there remains the possibility that instrumental variables may not have completely eliminated potential bias. Specifically, instrumental variables might influence stroke risk through pathways other than SLE, which could lead to biased results.

3) Limitations of genetic data sources: Although we used multiple large databases (e.g., UKB, FinnGen, and OpenGWAS) for data analysis, the coverage and accuracy of certain genetic variants in these databases may be limited, potentially affecting the robustness of the study results.

4) Unmeasured confounding factors: We acknowledge that unmeasured confounding factors, such as diet, physical activity, or other environmental exposures, could still bias our results. Furthermore, while our sensitivity analyses provided some reassurance against horizontal pleiotropy, they cannot entirely rule out its presence, particularly if pleiotropic effects are correlated with IV-exposure associations.

5) Limitations of the study design: Although MR analysis partially avoids reverse causation and confounding bias, it relies on the assumption of a gene-phenotype association, which may make it difficult to fully capture the impact of SLE on stroke risk under certain complex biological

mechanisms. While we employed robust sensitivity analyses (e.g., MR-Egger, MR-PRESSO) to address these issues, residual biases may still exist. Furthermore, MR findings are inherently observational and cannot replace experimental evidence. Therefore, our results should be interpreted as suggestive of a causal relationship, with further validation through experimental and clinical studies. Future research should incorporate longitudinal study designs to assess the incidence of CVDs in SLE patients more comprehensively. These limitations highlight the caution needed when interpreting the association between SLE and CVDs in this study and provide directions for further improvements in future research.

CONCLUSION

This study utilized MR analysis to explore the potential causal associations between SLE and multiple CVDs. Our findings present novel genetic evidence supporting a causal link between SLE and ischemic stroke. However, no significant genetic causal associations were identified between SLE and other types of CVDs. These results highlight the necessity of further investigations to validate and expand our findings.

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Declarations

Funding: This research was conducted in the absence of any commercial or financial relationships that could be construed as potential conflicts of interest.

Availability of data and materials: The datasets generated and/or analyzed during the current study are available from the corresponding author by reasonable request.

Disclosure: The authors declare no competing interests.

AUTHORSHIP CONTRIBUTION

Study conception and design: WL, YG

Data collection: YG, YX, MC, CL, HZ, WL

Analysis and interpretation of results: YG, YX, MC, WL

Draft manuscript preparation: YG, YX, MC, WL

Critical revision of the article: YG, YX, MC, WL

Other (study supervision, fundings, materials, etc...): YG, YX, MC, WL

All authors (YG, YX, CL, MC, HZ, WL) reviewed the results and approved the final version of the manuscript.

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