Turk Neurosurg, 2026
**DOI:** 10.5137/1019-5149.JTN.48929-25.1

*Original Investigation*

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Received: 16.04.2025
Accepted: 03.06.2025
Published Online: 16.01.2026

# Genetic Association Between Systemic Lupus Erythematosus and Cerebrovascular Disorders

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## 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

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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 Mendelian randomization packages for robust computational processing (18).

### 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 ($p<5\times10^{-8}$) 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 nonrandom 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 Finnish 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.

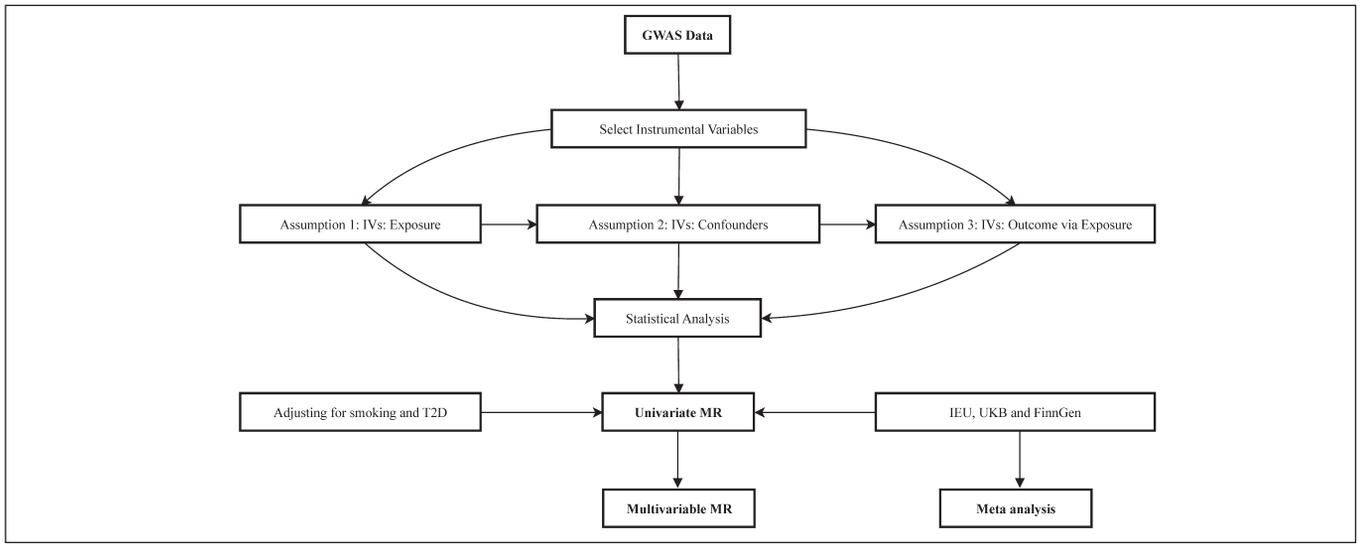


**Figure 1:** A diagram of the study workflow.

**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 statistic= ((N-K-1) / K) * (R/(1-R)) $R^2$ = 2 * eaf * (1 - eaf) * **beta² N:** Sample size of the exposure GWAS study. **K:** Number of SNPs. **beta:** Column containing the effect size for each SNP. **$R^2$:** Proportion of variance in the exposure explained by the IVs. **eaf:** Column containing the effect allele frequency for each SNP.*

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).

Reverse UVMR analyses revealed that the genome-wide significant SNPs ($p<5\times10^{-6}$) for ischemic stroke provided by the UKB may not exhibit a causal association with systemic lupus erythematosus (SLE) (p=0.802) (Tables V-VI).

**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 ($p<5\times10-8$), 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<5×10−6), 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.*

### *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-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 CEVs (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.

### 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

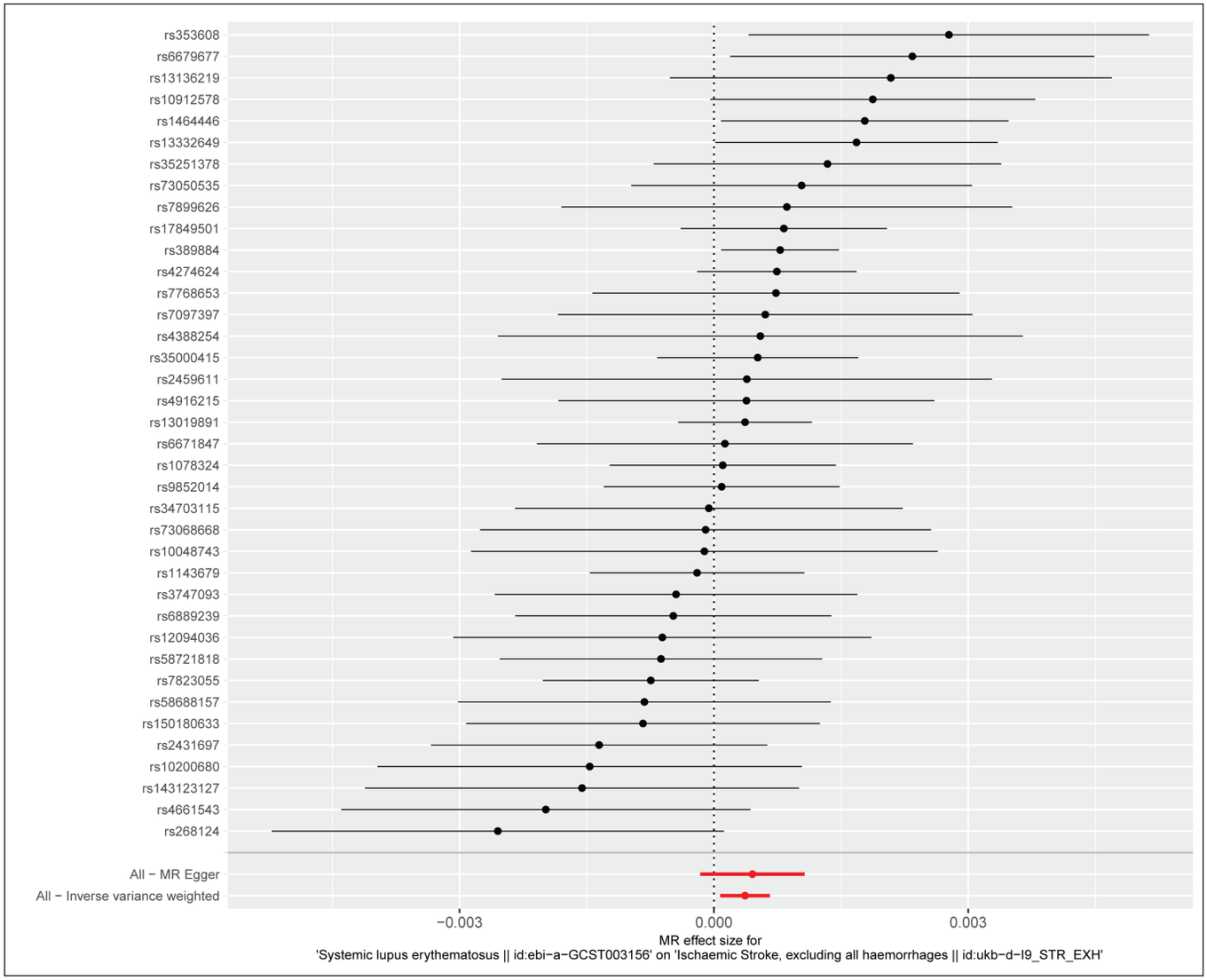


**Figure 2:** MR effect size for systemic lupus erythematosus on ischemic stroke.

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.

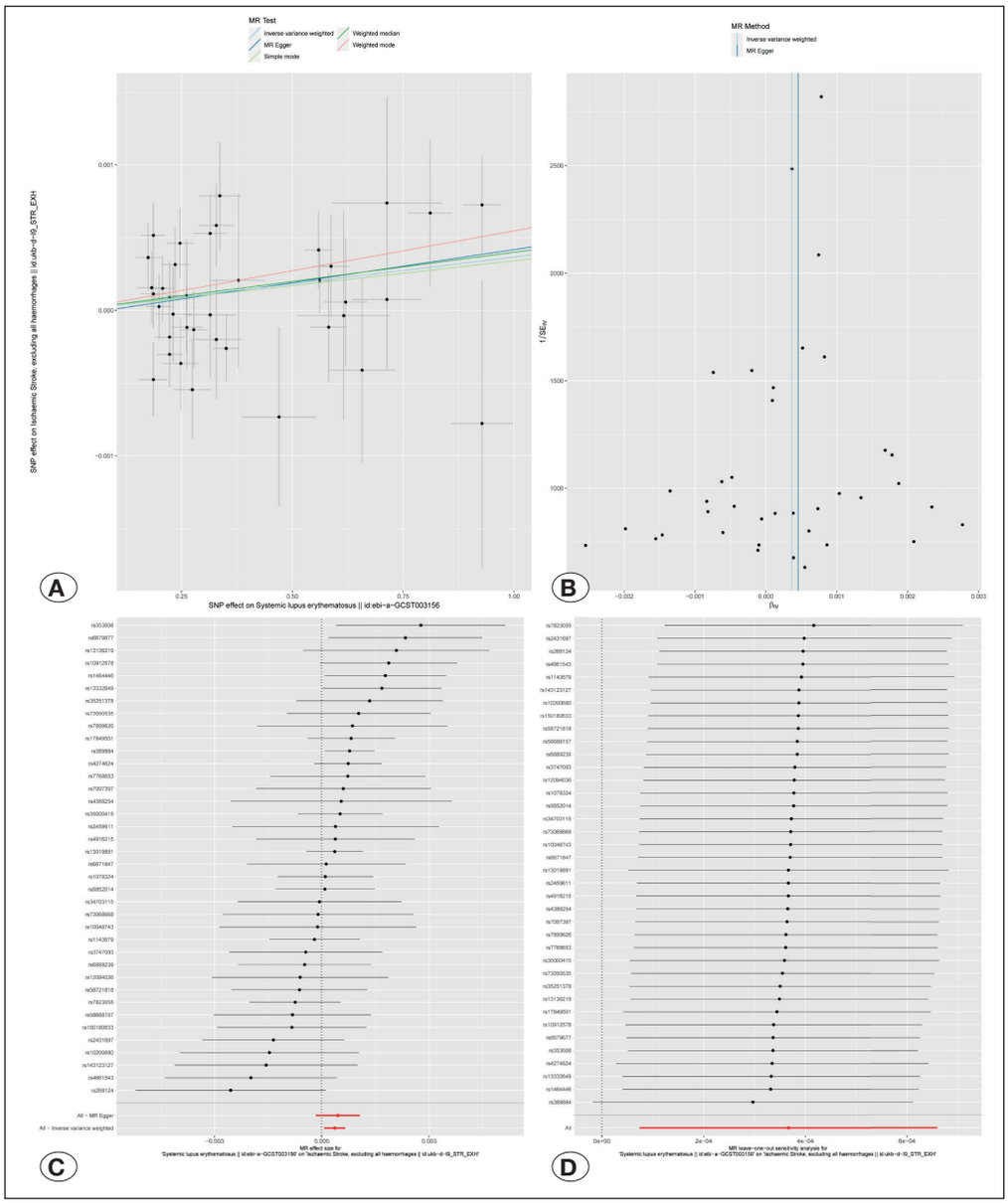


**Figure 3:** The UVMR effect of SLE-associated SNPs on ischemic stroke in the UKB.

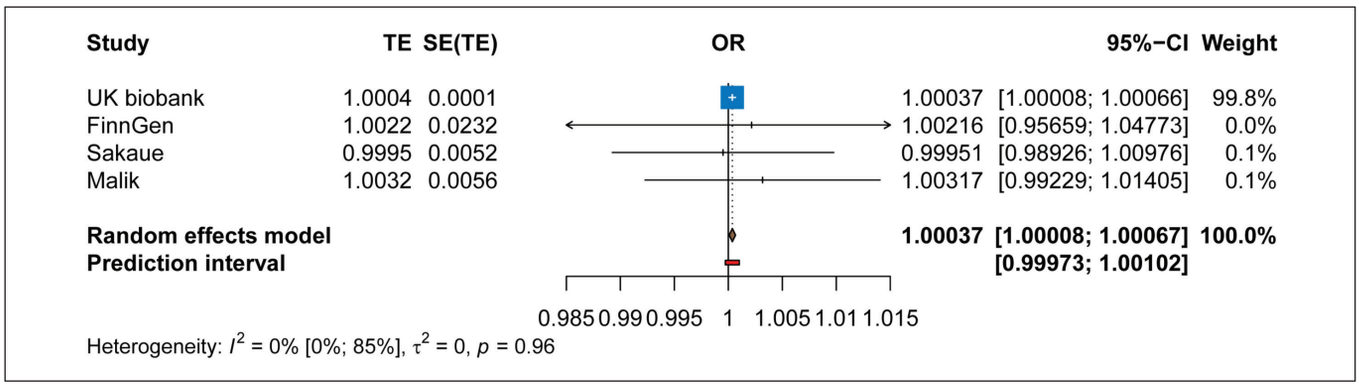


**Figure 4:** Combined random-effects model meta-analysis of the effect of SLE on ischemic stroke in the UK Biobank, FinnGen, IEU and GWAS Catalog.

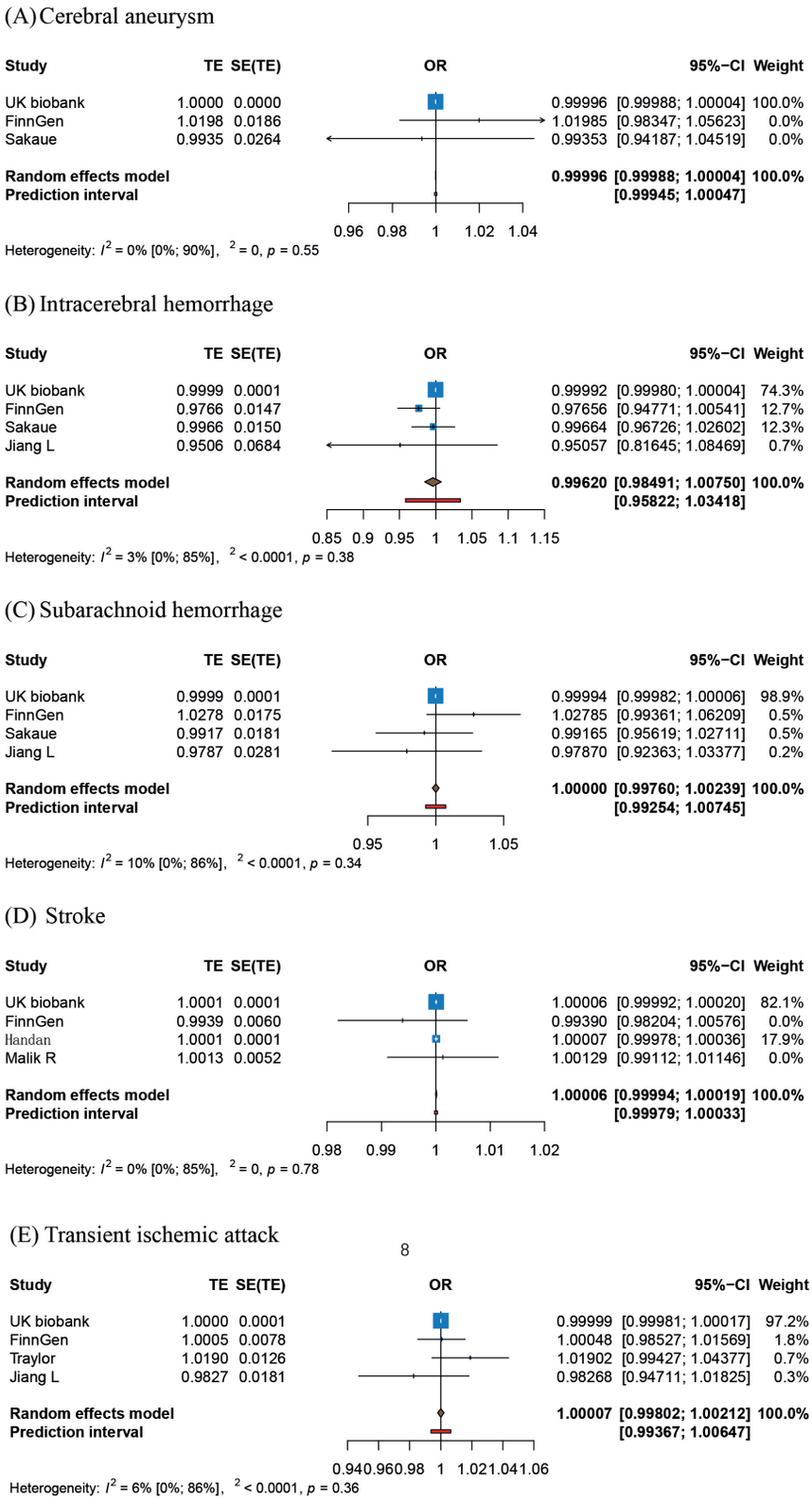


**Figure 5:** Combined random-effects model meta-analysis of the effect of SLE on AN, ICH, SAH, Stroke, and TIA in the UK Biobank, FinnGen, IEU and GWAS Catalog.

### 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 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 ($p<5\times10^{-8}$, 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 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.

## ACKNOWLEDGMENTS

We acknowledge the participants of the UK Biobank and FinnGen studies for their contributions to science. We also appreciate the IEU OpenGWAS and GWAS Catalog databases for providing the genome-wide association statistics.

**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.

**Ethics approval:** 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.

**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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