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Mediating factors in the association between educational attainment and stroke: A mendelian randomization study

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ABSTRACT

Background: Stroke is a common cardiovascular and cerebrovascular disease with high disability and mortality. Lower educational attainment has been reported to be associated with an increased risk of stroke, but it is unclear which pathways mediate this association.
Methods: Using genome-wide association studies (GWAS) based on European ancestry, we performed two-sample Mendelian randomization (MR) analyses to investigate the causal association of genetically estimated educational attainment with stroke and its subtypes. Then, we used mediation analyses to assess the extent to which seven cardiometabolic risk factors alone and in combination explain their effects.
Results: Genetically estimated educational attainment was negatively associated with the risk of any stroke (AS), any ischemic stroke (AIS), ischemic stroke subtypes (large artery stroke [LAS], cardioembolic stroke [CES], and small vessel stroke [SVS]), and hemorrhagic stroke subtypes (cerebral hemorrhage [ICH] and subarachnoid hemorrhage [SAH]). For individual mediating effects, type 2 diabetes, hypertension, hyperlipidemia, and smoking mediated the impact of education on AS, AIS, and ischemic stroke subtypes, while obesity, NAFLD, and alcohol consumption played no role. For combined mediation, the proportion of the association that cardiometabolic mediators explained ranged from 4% (95% CI: 2.72%–5.27%) for SVS to 38.73% (95% CI: 37.42%–40.05%) for LAS. Nevertheless, they did not account for any of the estimates for hemorrhagic stroke subtypes.
Conclusion: Higher educational attainment would have a protective effect on stroke and its subtypes, and cardiometabolic risk factors mediated part proportion of this association. Hence, patients with low education should pay more attention to managing cardiometabolic diseases to prevent stroke.

1. Introduction

Stroke is a common cardiovascular disease (CVD) among the elderly especially in low-income countries, with a constantly increasing prevalence that has attracted global attention. In 2019, more than 100 million people were suffering from stroke, and 12 million new cases of stroke occurred worldwide (GBD 2019 Stroke Collaborators, 2021). Moreover, stroke remains the second leading cause of death and the third leading cause of disability globally (de Havenon et al., 2023; GBD 2016 Lifetime Risk of Stroke Collaborators et al., 2018), resulting in a significant disease burden. Given this, the prevention and control of stroke are necessary and urgent.

Socioeconomic status (SES), including education, income, and occupation, have long been recognized as key determinants of health outcomes, including stroke risk (Pantoja-Ruiz et al., n.d.). Previous studies have explored the roles of income levels and employment status as mediators between SES and health. For instance, Andersson et al. found that lower income levels were associated with higher stroke risk (Andersson et al., 2020), while Xia et al. observed the impact of employment status on cardiovascular health (Xia et al., 2024). These studies underscore the complexity of socioeconomic influences on health. In this context, educational attainment stands out due to its

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robustness and measurability, making it a reliable indicator of SES (Howe et al., 2012). The inverse association between years of schooling and stroke risk has been repeatedly observed in previous literature (Carter et al., 2019; Kuper et al., 2007; Ye et al., 2023). Education not only directly impacts health behaviors and access to healthcare but also influences other SES factors. Besides, education was the focus of the first large-scale GWAS of a social science phenotype (Lee et al., 2018), with subsequent studies demonstrating its broad utility across diverse fields of research (Belsky et al., 2019). However, improving the inequality of educational level among the global populations is a great challenge that requires early intervention. Hence, pinpointing modifiable mediators influenced by education that affect stroke risk is crucial for stroke prevention.

Conventional epidemiological studies have identified that cardiometabolic risk factors, including diseases (type 2 diabetes, hypertension, hyperlipidemia, obesity, and non-alcoholic fatty liver disease [NAFLD]) and unhealthy lifestyle factors (smoking and alcohol consumption), are closely related to stroke risk (Alexander et al., 2019; Alloubani et al., 2021; Global Burden of Metabolic Risk Factors for Chronic Diseases Collaboration (BMI Mediated Effects) et al., 2014; Jia et al., 2022; Li et al., 2022; Mosenzon et al., 2023), but it was unclear whether and to what extent these cardiometabolic traits account for differences in stroke risk associated with educational attainment. Understanding the distribution of these cardiometabolic factors across varying levels of education and quantifying their mediating role in the relationship between education and stroke can help develop targeted intervention strategies to reduce stroke risk, particularly among populations with lower educational attainment. However, traditional observational studies have several unavoidable limitations. First, due to flaws such as reverse causality, recall bias, and measurement errors, those type of studies are deemed capable of establishing associations but not inferring causal correlations. Secondly, educational attainment is often affected by social and environmental factors (such as school quality, income, and occupation), resulting in residual confounding effects that are difficult to eliminate (Brown et al., 2011; Jeong et al., 2022; Kim et al., 2021).

Mendelian randomization (MR) is an emerging and reliable approach for inferring causal relationships, using genetic variants that are strongly associated with exposure (e.g., educational attainment) to create genetically estimated measures of that exposure, which are then used as instrumental variables to assess its causal effect on outcomes (e.g., stroke risk) (Smith & Ebrahim, 2003). According to Mendel's genetic law, alleles from parents are randomly assigned to their offspring and unchanged throughout life, indicating that genetic variation is not influenced by traditional confounders such as environmental, social, or behavioral factors and avoids bias caused by reverse causation and providing a robust framework for causal inference (*Biosocial Surveys*, 2007). In recent years, only a limited number of studies have utilized MR analysis to examine the role of modifiable risk factors in mediating the associations between genetically estimated educational attainment and stroke (Harshfield et al., 2021; Wan et al., 2023; Zhang et al., 2024), with almost none investigating specific stroke subtypes. Furthermore, these studies mainly focused on mediators related to body measure indices, such as BMI, waist circumference, and blood pressure, and scarcely considered cardiometabolic-related disease states. Given the differences in underlying genetic factors between body measurements and disease states, the pathways through which cardiometabolic traits influence the effect of educational attainment on stroke, particularly stroke subtypes, require further investigation.

Building on the methodological drawbacks of observational research and the narrow focus of previous studies on specific mediators and stroke outcomes without addressing stroke subtypes, this study aimed to use MR analyses to clarify the causal effects of genetically estimated educational attainment on the risk of stroke and its subtypes, and evaluate the mediating role of cardiometabolic risk factors alone or in combination among their association.

2. Materials and methods

2.1. Study design

This study used two-sample MR to explore the causal relationship between educational attainment and stroke, including its subtypes. Mediation analyses were conducted using two-step MR and multivariable MR (MVMR) to evaluate the role of cardiometabolic traits individually and collectively. MR analyses rely on three core assumptions: (1) Relevance assumption, i.e., the genetic instruments are strongly associated with the exposure (educational attainment); (2) Independence assumption, i.e., the instruments are not associated with confounders of the relationship between exposure and outcome (stroke risk); and (3) Exclusivity assumption, i.e., the instruments influence the outcome only through exposure but not any other pathways (Fig. 1). Detailed methods related to these assumptions are provided in the Supplementary Materials. The analytic process followed the Strengthening the Reporting of Observational Studies in Epidemiology using Mendelian Randomization (STROBE-MR) guidelines (Skrivankova et al., 2021).

2.2. Data sources

Data on exposures, mediating factors, and outcomes were extracted based on summary-level statistics from genome-wide association studies (GWAS) in reliable consortia or studies (Table 1).

Exposures Genetic instruments for educational attainment were derived from a GWAS by Okbay et al. (Okbay et al., 2022). In that GWAS, educational level was measured as the years of schooling and was matched across different participating cohorts using the International Standard Classification of Education 1997 category. The mean (SD) level of education was 15.4 (3.4) years. The single nucleotide polymorphisms (SNPs) that met the following criteria were selected as instrumental variables. (1) For genome-wide significance, a statistically significant threshold ($P < 5 \times 10^{-8}$) was applied to ensure that SNPs were significantly correlated with educational attainment. (2) SNPs in linkage disequilibrium (LD) ($R^2 < 0.001$) within a 10,000 kb window were excluded by the clumping algorithm. (3) For each SNP, F-statistics were calculated to evaluate the explained potential weak instrument bias. SNPs with F-statistic parameters <10 were considered weak instruments and removed (Pierce et al., 2011).

Outcomes Genetic associations for any stroke (AS) regardless of subtype were derived from the MEGASTROKE Consortium (Malik et al., 2018), which released summary statistics for relevant genome-wide meta-analyses of association data. Any ischemic stroke (AIS) regardless of subtype, as well as its specific subtypes such as large artery stroke (LAS), cardioembolic stroke (CES), and small vessel stroke (SVS) were also extracted from the MEGASTROKE consortium. In addition, we also extracted GWAS for hemorrhagic stroke subtypes from a study by Sakaue et al. (Sakaue et al., 2021), which contains cerebral hemorrhage (ICH) and subarachnoid hemorrhage (SAH). Specific phenotype definitions related to all these summary genetic association estimates are accessible in their original publications.

Mediators This study identified five representative metabolism-related diseases and two modifiable lifestyles as mediators. Type 2 diabetes-related summary-level data originated from the DIAGRAM Consortium (Xue et al., 2018). The NAFLD-related summary-level data originated from a GWAS study by Ghodsian et al. (Ghodsian et al., 2021). Genetic associations for hypertension, hyperlipidemia, and obesity were extracted from a publicly available GWAS summary statistics database from the UK Biobank (Dönertaş et al., 2021; Jiang et al., 2021; Trinder et al., 2022). Genetically estimated smoking (per day) and alcohol consumption (per week) were obtained from the GSCAN Consortium (Liu et al., 2019). All metabolism-related diseases were binary, except for two lifestyle factors, which were analyzed as continuous variables.

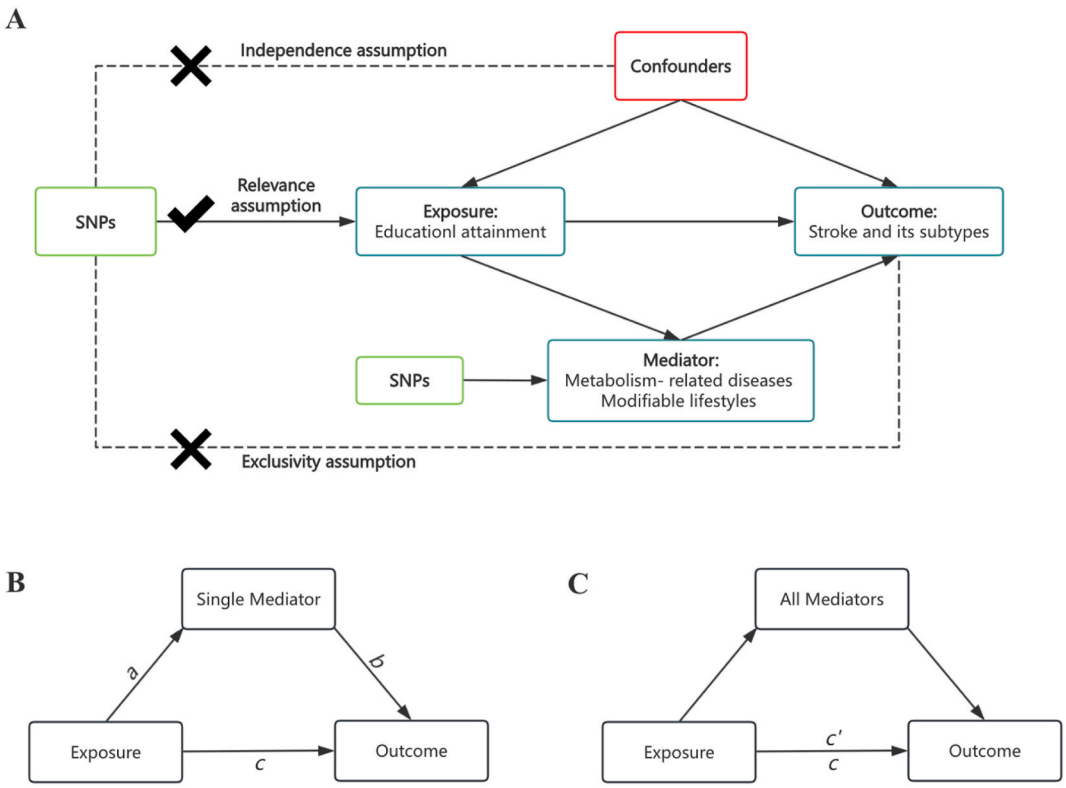

Fig. 1. Study design overview
(**A**) Three core assumptions of MR analysis. (**B**) Mediation analysis for single mediator. (**C**) Mediation analysis for all mediators combined. Single nucleotide polymorphisms, SNPs.

2.3. Statistical analysis

We used the inverse variance weighting (IVW) method as the main analysis and conducted the MR Egger regression, weighted median, and weighted mode as sensitivity analyses to explore the robustness of the primary findings. IVW estimates with $P < 0.05$ and supported by at least one sensitivity analysis were considered as providing robust causal evidence. Conversely, IVW estimates with $P < 0.05$ but not supported by any sensitivity analysis were considered to provide suggestive evidence of a causal effect. Additionally, heterogeneity was assessed using Cochran's Q statistic within IVW and MR-Egger models, while pleiotropy was evaluated using the MR-PRESSO and MR-Egger intercept analysis (van de Vegte et al., 2020; Verbanck et al., 2018).

For each mediator (Fig. 1B), two-step MR (Carter et al., 2021) was applied to evaluate the mediating effect. In the first step, we estimated the causal effect of education on each mediator (*a*), and in the second step, we estimated the causal effect of each mediator on stroke or each subtype (*b*). Mediating effects were calculated as *a*b*, and confidence intervals were estimated using the delta method (MacKinnon et al., 2002). For all mediated combined (Fig. 1C), the difference method was performed. The indirect effects were obtained by subtracting the direct effect from the total effect (*c*) where the direct effect was the effect of education on stroke after accounting for all mediators in MVMR model (*c'*). Confidence intervals were estimated using bootstraping. Last, the mediated proportion was quantified by dividing the indirect effect by the total effect.

Two-sided $P < 0.05$ indicated statistical significance. All of the analyses were conducted in R, version 4.3.2 (R Foundation for Statistical Computing) and using the R packages MendelianRandomization, TwoSampleMR, MVMR, and MR-PRESSO. The summary-level GWAS data used in this study was publicly accessible, and no specific ethical approval was required.

3. Results

3.1. Effect of educational attainment on stroke and stroke subtypes

We analyzed educational attainment for their associations with AS, AIS, subtypes of ischemic stroke (CES, LAS, and SVS), and subtypes of hemorrhagic stroke (ICH and SAH) (Fig. 2). According to genetically predicted causal associations, educational attainment was inversely associated with the risk of AS (odds ratio [OR] = 0.66, 95% CI: 0.61–0.72), AIS (OR = 0.67, 95% CI: 0.61–0.74), LAS (OR = 0.54, 95% CI: 0.43–0.68), CES (OR = 0.77, 95% CI: 0.65–0.92), SVS (OR = 0.58, 95% CI: 0.47–0.72), ICH (OR = 0.76, 95% CI: 0.60–0.97), and SAH (OR = 0.73, 95% CI: 0.57–0.94), implying that increased educational level was protective against any type of stroke. Sensitive analyses had reduced precision, but the general causal direction of estimates did not change (Table S1).

3.2. Effect of educational attainment on cardiometabolic mediators

There also was a protective association of educational attainment with the risk of most cardiometabolic mediators (Fig. 3). For the metabolism-related diseases considered, genetically estimated education had a significant inverse correlation with the risk of type 2 diabetes (OR = 0.56, 95% CI: 0.51–0.61), hypertension (OR = 0.97, 95% CI: 0.96–0.98), hyperlipidemia (OR = 0. 69, 95% CI: 0.63–0.75), obesity (OR = 0.25, 95% CI: 0.14–0.43), and NAFLD (OR = 0. 63, 95% CI: 0.55–0.74), respectively. For the lifestyle factors, genetically estimated education was negatively correlated with the number of smoking (β (se) = −0.21 (0.02)), but positively related to the quantity of alcohol consumption (β (se) = 0.04 (0.01)). These associations were supported by sensitivity analyses accounting for pleiotropy (Table S2).

Table 1
GWAS used as sources for two-sample mendelian randomization analyses.

Phenotype	Unit	Sample size (overall or case/control)	Cohort(s)	Ancestry	Source
Exposure					
Education level	1 s.d.	3,037,499	71 Cohorts, including UK Biobank and 23andMe	European	Okbay et al. (2022)
Outcomes					
AS	Event	40,585/406,111	17 Cohorts, including MEGASTROKE and deCODE	European	Malik et al. (2018)
AIS	Event	34,217/406,111			
Ischemic stroke					
LAS	Event	4,373/406,111	17 Cohorts, including MEGASTROKE and deCODE	European	Malik et al. (2018)
CES	Event	7,193/406,111			
SVS	Event	5,386/406,111			
Hemorrhagic stroke					
ICH	Event	1,935/471,578	UK Biobank and FinnGen	European	Sakaue et al. (2021)
SAH	Event	1,693/471,562			
Mediators					
Diseases					
T2D	Event	61,714/593,952	32 Cohorts, including deCODE and UK Biobank	European	Xue et al. (2018)
HTN	Event	129,909/354,689	UK Biobank	European	Dönertaş et al. (2021)
HLP	Event	39,961/309,261	UK Biobank	European	Trinder et al. (2022)
Obesity	Event	581/455,767	UK Biobank	European	Jiang et al. (2021)
NAFLD	Event	8,434/770,180	4 Cohorts, including UK Biobank and FinnGen	European	Ghodsian et al. (2021)
Lifestyle factors					
Smoking	1 s.d.	337,334	6 Cohorts, including UK Biobank and 23andMe	European	Liu et al. (2019)
Alcohol	1 s.d.	335,394			

AS, all stroke; AIS, any ischemic stroke; LAS, large artery stroke; CES, cardioembolic stroke; SVS, small vessel stroke; ICH, intracerebral hemorrhage; SAH, subarachnoid hemorrhage; T2D, type 2 diabetes; HTN, hypertension; HLP, hyperlipidemia; NAFLD, non-alcoholic fatty liver disease; and Alcohol, alcohol consumption.

3.3. Effect of cardiometabolic mediators on stroke and its subtypes

We analyzed each cardiometabolic mediator for their associations with stroke and its subtypes (Fig. 4). The result showed that genetically estimated higher liability of type 2 diabetes was associated with a statistically significant increase in the risk of AS (OR = 1.09, 95% CI: 1.06–1.12), AIS (OR = 1.11, 95% CI: 1.07–1.14), LAS (OR = 1.26, 95% CI: 1.17–1.36), and SVS (OR = 1.18, 95% CI: 1.10–1.25), respectively; hypertension significantly increased the risk of all kinds of stroke outcomes, ranging from the least strength of relationship with CES (OR = 2.93, 95% CI: 1.52–5.67) to the greatest strength of relationship with SAH (OR = 14.28, 95% CI: 7.30–27.95); hyperlipidemia, similar to type 2 diabetes, was associated with a statistically significant increase in the risk of AS (OR = 1.06, 95% CI: 1.03–1.09), AIS (OR = 1.06, 95% CI: 1.03–1.10), LAS (OR = 1.19, 95% CI: 1.09–1.29), and SVS (OR = 1.08, 95% CI: 1.01–1.15); while obesity was modestly associated with an increased risk of LAS (OR = 1.05, 95% CI: 1.00–1.09) and not with other outcomes. For lifestyle factors, genetically estimated smoking increased the risk of AS (OR = 1.21, 95% CI: 1.06–1.38) and AIS (OR = 1.20, 95% CI: 1.03–1.39); alcohol consumption only increased the risk of SAH (OR = 1.68, 95% CI: 1.15–2.47). Besides, there was no significant association of NAFLD with stroke or any stroke subtype. The sensitivity analyses supported this finding (Tables S3–9).

3.4. Mediating pathways between educational attainment and stroke outcomes

Our results show that type 2 diabetes, hypertension, hyperlipidemia, and smoking individually mediated the impact of education on AS (Fig. 5), with the decomposition of their mediated effects specifically shown in Fig. 6A–D. When accounting for all mediators, the mediation proportions were 16.77% (95% CI: 16.03%–17.52%) (Fig. 6E). AIS was similar to AS, the proportions of all mediators were 22.94% (95% CI: 22.11%–23.77%). In terms of LAS and SVS, hyperlipidemia did not play a separate mediating role but type 2 diabetes, hypertension, hyperlipidemia, and smoking played. After accounting for all combined, the mediating ratios were 38.73% (95% CI: 37.42%–40.05%) and 4% (95% CI: 2.72%–5.27%). Furthermore, only hypertension mediated the impact of education on the other three stroke subtypes. The combined proportion was 32.59% (95% CI: 29.14%–36.04%) for CES and almost zero for hemorrhagic stroke subtypes that ICH and SAH. The details were provided in Table S10. To further explore the socioeconomic determinants of stroke, we conducted parallel analyses using household income as an additional exposure in Tables S11–12.

4. Discussion

This two-sample MR study supported a potential causal association of genetically predicted educational attainment with stroke and its subtypes. For instance, each additional 3.4 years of genetically estimated schooling was linked to a one-third reduction in the risk of AS and approximately halved risks of LAS and SVS. Cardiometabolic risk factors mediated the association mentioned above, which accounted for 17% of estimates for AS and 23% of estimates for AIS, but did not account for any of the estimates for hemorrhagic stroke subtypes.

Educational attainment and risks of stroke and its subtypes

In this study, we observed a significant negative association between genetically estimated educational attainment and the risk of AS, AIS, and ischemic stroke subtypes (LAS, SVS) through two-sample MR analyses, which is consistent with current MR findings (Davies et al., 2023; Gill et al., 2019; Li et al., 2022; Lindmark et al., 2022). However, our research differed from Harshfield et al. (Harshfield et al., 2021) in that a significant association between education and CES risk was not observed in their study, but it was observed in our study. The educational attainment SNPs used in our study come from a more recent meta-analysis with a sample size nearly three times larger than that of Harshfield et al. (3,037,499 vs. 1,131,881), which may explain this difference (Lee et al., 2018). The larger sample size likely contributed to the significant results we observed, as it provides more reliable and accurate estimates, whereas the smaller sample size in their study may have limited its ability to detect the associations. For hemorrhagic stroke outcomes, Harshfield et al. (Harshfield et al., 2021) reported a significant association between educational attainment and hemorrhagic stroke subtype (ICH), while Wen et al. (Xiuyun et al., 2020) found no association between educational attainment and total hemorrhagic stroke, regardless of subtype (OR = 1.00, 95% CI: 0.99–1.00). The

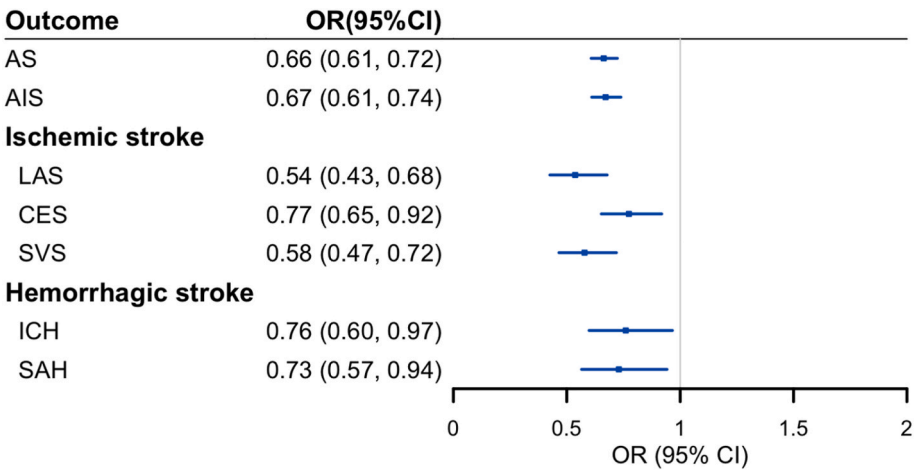

Fig. 2. Effect of educational attainment on stroke and its subtypes
Results of inverse variance–weighted two-sample MR analyses are shown. Estimates are odds ratios (ORs) for stroke and its subtypes. AS, all stroke; AIS, any ischemic stroke; LAS, large artery stroke; CES, cardioembolic stroke; SVS, small vessel stroke; ICH, intracerebral hemorrhage; and SAH, subarachnoid hemorrhage.

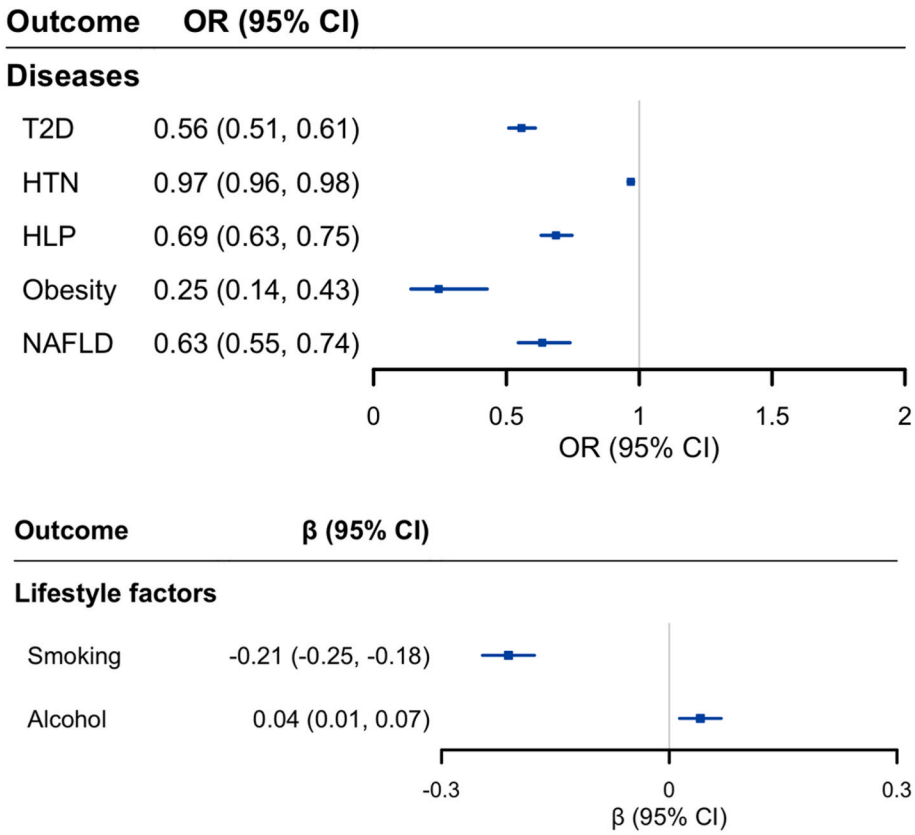

Fig. 3. Effect of educational attainment on cardiometabolic risk factors
Results of inverse variance–weighted two-sample MR analyses are shown. Estimates are the change in the cardiometabolic risk factors per 1-SD increase of genetically estimated years of education (3.4 years), and the risk factors are in log(odds) units for metabolic-related diseases and in SD units for lifestyle factors. T2D, type 2 diabetes; HTN, hypertension; HLP, hyperlipidemia; NAFLD, non-alcoholic fatty liver disease; and Alcohol, alcohol consumption.

different outcomes selected in these studies resulted in findings that are not comparable between them. Furthermore, in the Wen et al. study, the participants of exposure and outcome were from different populations (exposure from European descent, outcome from mixed descent). This mismatch may have introduced bias, as two-sample MR studies require consistent population sources to avoid genetic heterogeneity and ensure accurate estimates. Our findings suggest that higher education may reduce the risk of hemorrhagic stroke subtypes (ICH and SAH). In general, the evidence above suggests that low education level is associated with an increased risk of stroke, so we emphasize the importance of enhancing public education and addressing educational inequalities to minimize the social burden of stroke. Since it is challenging to modify an individual's educational level, identifying modifiable risk factors through which education influences stroke, such as cardiometabolic factors, may help develop effective interventions to reduce stroke risk.

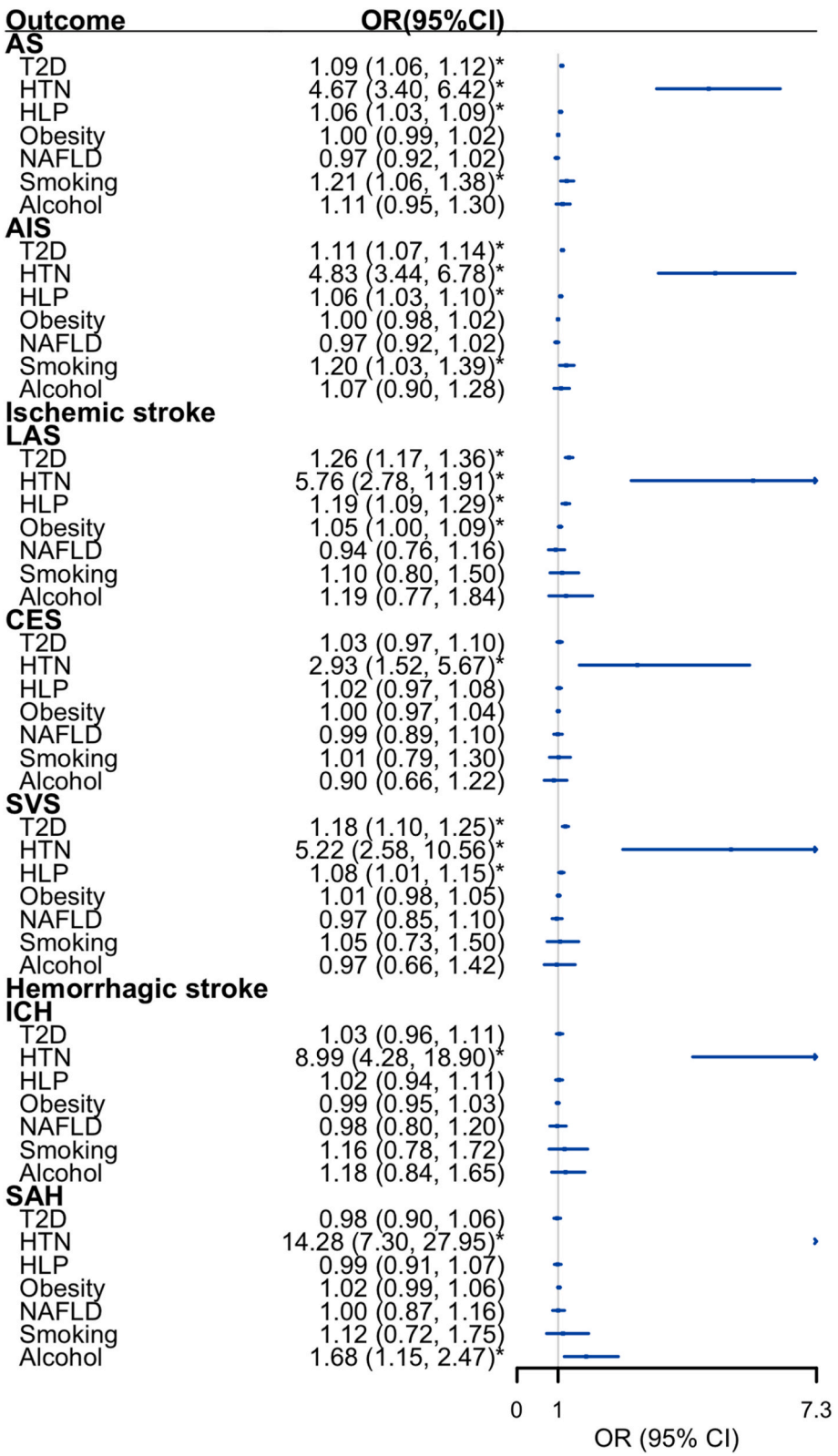

Fig. 4. Effect of cardiometabolic risk factors on stroke and its subtypes

Results of inverse variance–weighted two-sample MR analyses are shown. The symbol (*) is used to indicate statistical significance, $P < 0.05$. Estimates are odds ratios (ORs) for stroke and its subtypes. AS, all stroke; AIS, any ischemic stroke; LAS, large artery stroke; CES, cardioembolic stroke; SVS, small vessel stroke; ICH, intracerebral hemorrhage; SAH, subarachnoid hemorrhage; T2D, type 2 diabetes; HTN, hypertension; HLP, hyperlipidemia; NAFLD, non-alcoholic fatty liver disease; and Alcohol, alcohol consumption.

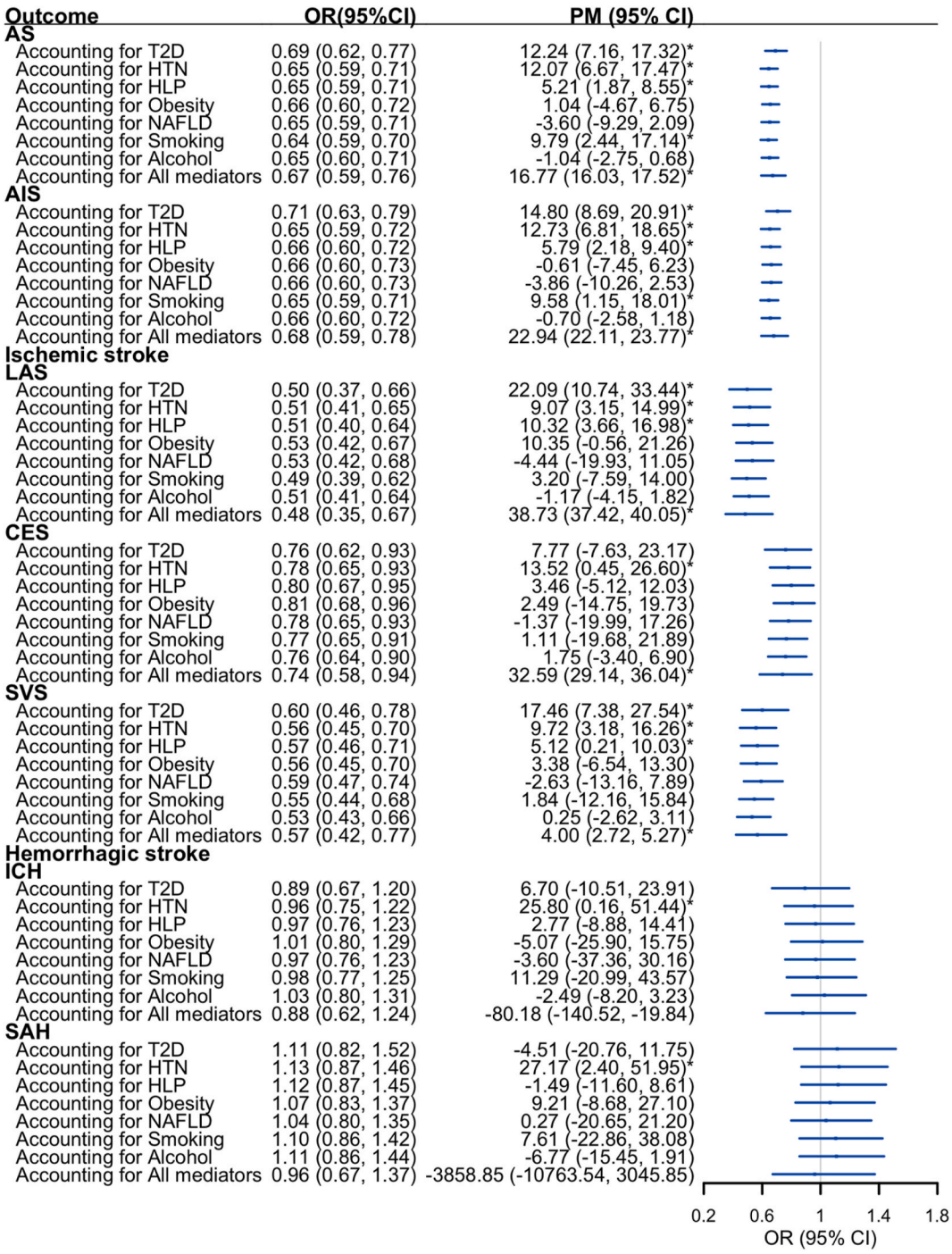

Fig. 5. Mediating pathways between educational attainment and stroke outcomes
Results of MR mediation analyses are shown. The OR (95% CI) indicates the direct correlation of education on stroke and its subtypes after adjusting for each cardiometabolic mediator alone and all combined. The symbol (*) is used to indicate statistical significance, $P < 0.05$. PM, the proportion of mediators; AS, all stroke; AIS, any ischemic stroke; LAS, large artery stroke; CES, cardioembolic stroke; SVS, small vessel stroke; ICH, intracerebral hemorrhage; SAH, subarachnoid hemorrhage; T2D, type 2 diabetes; HTN, hypertension; HLP, hyperlipidemia; NAFLD, non-alcoholic fatty liver disease; and Alcohol, alcohol consumption.

Mediating pathways between educational attainment and stroke outcomes

To the best of our knowledge, this is the first MR study to investigate cardiometabolic factors mediating the association between educational attainment and risk of specific stroke subtypes rather than just total stroke, total ischemic or hemorrhagic stroke, and the first study to include hyperlipidemia, obesity, and NAFLD as potential mediators. Previous observational research found that the incidence of stroke in diabetic patients was almost doubled, and even short-term remission of diabetes could reduce the risk of stroke (Saul et al., 2024; Zhang et al., 2023). A recent study using MR analysis demonstrated that type 2 diabetes mediated a causal relationship between genetically predicted education and stroke risk (Zhang et al., 2024), similar to our findings. In addition, Beltrán et al. (Beltrán-Sánchez & Andrade, 2016) confirmed that the incidence of hypertension varies among people with different educational levels. A study that carried out observational and genetic analyses showed that SBP explained 14.32% of the effect of genetically estimated educational level on stroke (Carter et al., 2019), while another

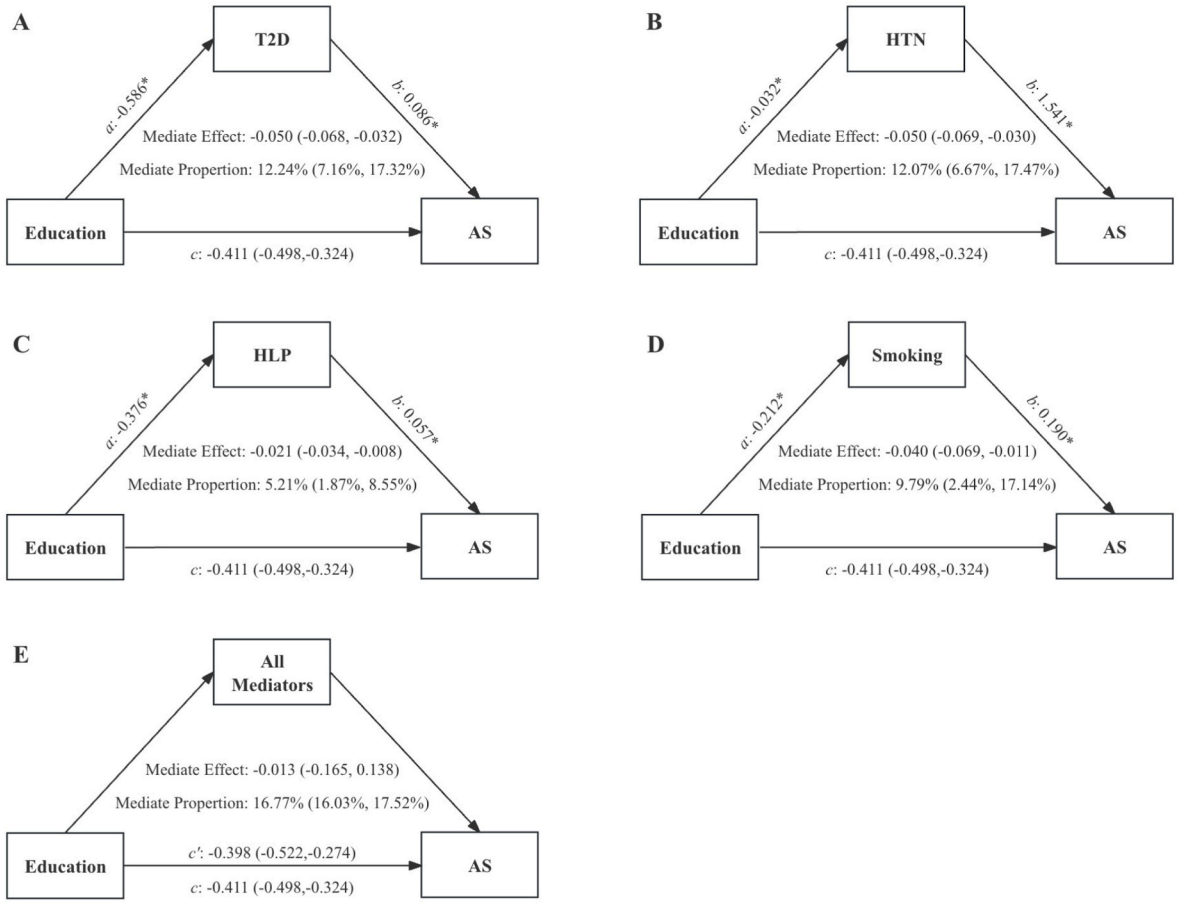

Fig. 6. The decomposition of mediated effects of education on AS

AS, all stroke; T2D, type 2 diabetes; HTN, hypertension; and HLP, hyperlipidemia. (A) *c*, the total effect of educational attainment on AS by univariable MR. The total effect was decomposed into: (i) indirect effect using a two-step approach (where *a* is the effect of education on T2D, and *b* is the effect of T2D on AS) and the product method ($a \times b$), and (ii) direct effect ($c - a \times b$). (B) The same process applied to the mediation analysis of HTN. (C) The same process applied to the mediation analysis of HLP. (D) The same process applied to the mediation analysis of smoking. (E) For all mediators combined, the indirect effect using the difference method ($c - c'$), and *c'* is the effect of education on AS adjusting for all mediators by multivariable MR. Mediate proportion was the indirect effect divided by the total effect.

network MR study (Wan et al., 2023) concluded that hypertension explained 47.35%. Our study supported this association and validated it in stroke subtypes. For hyperlipidemia, it was considered to promote extracranial atherosclerosis and the risk for stroke, even influencing stroke recovery (Amarenco, 2001). What has not been reported previously is that our results suggest a mediating role for hyperlipidemia in the effect of education on most ischemic strokes. This finding is consistent with research by Zhang et al. (Zhang et al., 2024), which identified a mediating role of LDL cholesterol in the relationship between education and stroke risk. This may be related to the fact that individuals with higher levels of education are more likely to adopt a healthy lifestyle (such as diet and physical activity) that affects lipid metabolism and indirectly reduces stroke risk (Han et al., 2023; Jensen et al., 2023). Besides, while BMI has previously been observed to mediate the causal effect of education and stroke (Wan et al., 2023; Zhang et al., 2024), we did not observe a corresponding effect of obesity. This discrepancy may be attributed to differences in the metabolic profiles or inflammatory pathways associated with obesity, which may influence stroke risk in more complex or indirect ways, and require further investigation to clarify these mechanisms. NAFLD was demonstrated to increase the development of cardiovascular disease (Tang et al., 2022), but we did not observe its potential mediating effect, suggesting that education may not influence stroke by this pathway. Moreover, both smoking and alcohol consumption were recognized as unhealthy lifestyle factors. Previous studies (Harshfield et al., 2021) showed that smoking, not alcohol consumption, was a mediator between educational level and stroke, which is similar to what we found. Accordingly, this study provides novel insights into the pathways through which educational attainment influences stroke risk, particularly its subtypes. Our findings highlight the critical need for targeted interventions addressing cardiometabolic risk factors, such as type 2 diabetes, hypertension, hyperlipidemia, and smoking, which are central to mitigating the impact of educational inequality on stroke risk. Specifically, accessible screening and management of hypertension and diabetes, along with smoking cessation and lipid control, should be prioritized in low-education communities. These targeted interventions have the potential to significantly reduce stroke incidence, particularly among populations with lower educational attainment, and promote more equitable health outcomes.

There are some strengths in this study. It utilized GWAS summary-level data from the latest and largest sample studies, allowing the most extensive possible genetic instruments for exposures to increase statistical power. Besides, the mediation MR analyses were conducted across two approaches to identify the mediated proportions of common cardiometabolic risk factors, which can be considered individually and all combined. However, there are still limitations that should be emphasized. First, while our study has incorporated common cardiometabolic risk factors to guide clinical practice, it does not cover all potential mediation pathways, particularly those involving non-heritable elements. Second, this study mainly focused on educational

attainment rather than other socioeconomic determinants such as income levels, employment status, or geographic location. Future studies could comprehensively explore the combined impact of these factors on stroke risk to provide a broader socioeconomic perspective. Moreover, as with many MR studies, it's unlikely to eliminate all instances of pleiotropy. Although we used methods like outlier removal and sensitivity analyses, some pleiotropy may still remain. Last, the GWAS summary data were derived from European populations, limiting the generalizability of our findings. If there are suitable public GWAS data from diverse ancestries and demographic information, we will continue to explore the mediating factors between education and stroke, validating our findings across other descents and conducting stratified analyses by key variables such as gender and age to better understand the heterogeneity in stroke risk.

In conclusion, this study supports a protective effect of genetically estimated educational attainment on the risk of stroke and its subtypes. Our results also suggest that interventions targeting the reduction of type 2 diabetes, hypertension, hyperlipidemia, and smoking would result in decreased cases of stroke associated with lower educational levels. Hence, patients with low education should more pay attention to managing cardiometabolic diseases to prevent stroke.

CRediT authorship contribution statement

Nuo Xu: Writing – original draft, Formal analysis, Conceptualization. **Yiwen Qiu:** Writing – review & editing, Methodology. **Diliyaer Ainiwan:** Methodology. **Boya Wang:** Methodology. **Xialidan Alifu:** Methodology. **Haibo Zhou:** Methodology, Formal analysis. **Haoyue Cheng:** Methodology. **Ye Huang:** Methodology. **Libi Zhang:** Methodology, Formal analysis. **Hui Liu:** Methodology. **Lina Yu:** Formal analysis, Writing – review & editing. **Yunxian Yu:** Writing – review & editing, Supervision.

Ethical statement

No applicable.

This is a Mendelian randomization study, and summary statistics are available from each consortium (details in Table 1) or via online website. Therefore, no additional ethical approval is required for this study.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ssmph.2025.101766.

List of abbreviations

Cardiovascular diseases, CVD; socioeconomic status, SES; non-alcoholic fatty liver disease, NAFLD; mendelian randomization, MR; body mass index, BMI; and systolic blood pressure, SBP; genome-wide association studies, GWAS; multi-variable MR, MVMR; single nucleotide polymorphisms, SNPs; all stroke, AS; any ischemic stroke, AIS; large artery stroke, LAS; cardioembolic stroke, CES; small vessel stroke, SVS; intracerebral hemorrhage, ICH; and subarachnoid hemorrhage, SAH.

Data availability

The datasets supporting the conclusions of this article are available on the GWAS catalog website (https://www.ebi.ac.uk/gwas/), UK Biobanks (https://www.ukbiobank.ac.uk/), MR-Base platform (https://gwas.mrcieu.ac.uk/), SSGAC Consortium (https://www.thessgac.org/), and MEGASTROKE Consortium (https://megastroke.org/).

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