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ORIGINAL ARTICLE

Genetic association between years of education and intracranial aneurysm: A two-sample Mendelian randomization study

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Abstract

OBJECTIVE: To investigate whether genetically proxied educational attainment influences the risk of intracranial aneurysm.
METHOD: We conducted a two-sample Mendelian randomization analysis using genome wide association study summary statistics from individuals of European ancestry. The inverse variance weighted method was the primary estimator, complemented by MR Egger, weighted median, weighted mode, and simple mode analyses, with years of schooling and college completion as educational exposures combined with intracranial aneurysm GWAS data.
RESULTS: We selected two groups of genes associated with genetic susceptibility to education as exposure factors. When using years of education from the UK Biobank based GWAS as the exposure, the inverse variance weighted method indicated an inverse association between genetically proxied longer schooling and intracranial aneurysm risk. MR Egger regression suggested that directional pleiotropy was unlikely to strongly bias the results and yielded an inverse association between years of schooling and intracranial aneurysm. The weighted median estimator yielded a similar direction and magnitude of effect. When using college completion as the exposure, the inverse variance weighted method also indicated an inverse association with intracranial aneurysm risk, and sensitivity analyses produced estimates of similar direction and magnitude. MR-Egger regression intercept testing did not provide evidence of substantial directional pleiotropy.
CONCLUSION: These Mendelian randomization findings are consistent with a potentially protective association of higher genetically proxied educational attainment with intracranial aneurysm risk in individuals of European ancestry.

INTRODUCTION

Socioeconomic status (SES) is commonly characterized by factors such as occupation, income, and educational attainment, with education frequently used as a quantifiable indicator of SES (Allen *et al.* 2017; Marmot, 2005). Research has indicated an association between higher levels of education and a reduced likelihood of intracranial aneurysm, although findings across studies have not always been consistent (Sun *et al.* 2022; Tian *et al.* 2022; Yechoor *et al.* 2024; Davies *et al.* 2018; Liu *et al.* 2024). From an aetiological perspective,

the underlying mechanisms linking educational attainment to the risk of intracranial aneurysm remain poorly understood. Nevertheless, several plausible mechanisms have been proposed to explain this association. Research has shown that the number of years of education an individual completes is largely influenced by environmental factors, with individual single nucleotide polymorphisms (SNPs) accounting for only a minimal portion of the variation. Educational level may indirectly influence the risk of intracranial aneurysms by affecting health behaviors such as smoking, alcohol consumption, and sedentary behavior. For example, higher educational attainment is often associated with healthier lifestyle choices, which may have a protective association against the risk of aneurysm (Cutler & Lleras-Muney, 2010; Vlak *et al.* 2011).

Over the past decade, genome-wide association studies (GWASs) have transformed the field of complex disease genetics by systematically analyzing millions of genetic variants across the genomes of large populations to identify associations between genotypes and phenotypes. GWASs provide an unbiased approach to investigating the genetic underpinnings of complex diseases, offering valuable insights into their etiology (Visscher *et al.* 2017). Mendelian randomisation (MR) serves as a technique designed to address issues inherent in traditional observational epidemiology, such as unmeasured confounding and reverse causality (Sanderson *et al.* 2022). The two-sample MR framework leverages summary statistics from independent genome-wide association studies (GWAS) to estimate causal effects by integrating SNP-exposure and SNP-outcome associations. The growing availability of large scale GWAS datasets has greatly improved the feasibility and statistical power of two sample MR analyses (Skrivankova *et al.* 2021). To our knowledge, this is the first two sample Mendelian randomization analysis to evaluate genetically proxied educational attainment as a determinant of intracranial aneurysm risk using large contemporary GWAS datasets. By focusing specifically on aneurysm and leveraging two distinct educational exposures (years of schooling and college completion), our study aims to clarify whether previously observed associations are consistent with a causal relationship.

MATERIALS

Study design

To evaluate the potential causal effect of years of education on the risk of intracranial aneurysm, we conducted two sample Mendelian randomization analyses using years of schooling and college completion as exposures and intracranial aneurysm as the outcome. The data for this study were derived from GWASs. The overall structure of the MR framework is depicted in Figure 1. Ethical approval and informed consent were not required for this study, as the MR analyses were conducted using publicly available summary statistics in a two-sample approach. The study was reported in accordance with the STROBE-MR guidelines (Skrivankova *et al.* 2021). For valid Mendelian randomization analyses, three assumptions must be satisfied: (i) relevance, meaning the genetic instruments are strongly associated with the exposure; (ii) independence, meaning they are not associated with confounders of the exposure–outcome relationship; and (iii) exclusion restriction, meaning they influence the outcome only through the exposure (Xu *et al.* 2021).

Data sources for TN

The outcome was intracranial aneurysm as defined in the GWAS Catalog (hereafter referred to as intracranial

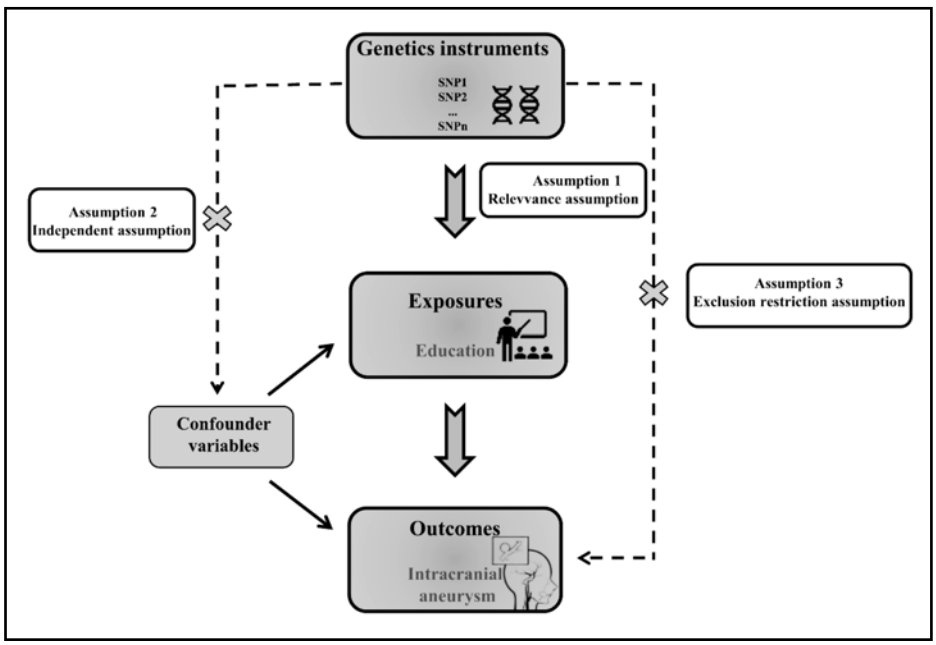

Fig. 1. Conceptual framework of the two sample Mendelian randomization design for educational attainment and intracranial aneurysm. Schematic diagram of the two sample Mendelian randomization (MR) framework assessing the causal effect of genetically proxied educational attainment (years of schooling and college completion) on intracranial aneurysm risk, using genome wide significant SNPs from large European ancestry GWAS.

Tab. 1. Overview of genome wide association study datasets for educational attainment and intracranial aneurysm

Trait	GWAS ID	Sample size	Number of variants	Population	Sex	Year
Years of schooling	ieu-a-1239	766,345	10,101,242	European	Male and female	2018
Educational attainment (college completion)	ebi-a-GCST90029012	470,941	11,972,619	European	Not reported	2018
Intracranial aneurysm	ebi-a-GCST90018815	473,683	24,191,145	European	Not reported	2021

The table summarizes the GWAS identifiers, sample sizes, number of genetic variants, population ancestry, sex distribution, and publication year for each trait. Years of schooling and college completion served as exposures, and intracranial aneurysm as the outcome in the two sample Mendelian randomization analyses.
Abbreviations: GWAS, genome-wide association study. Sample size and number of variants are reported as in the original summary statistics for each GWAS.

aneurysm throughout this manuscript). Summary statistics for intracranial aneurysm were sourced from the GWAS Catalog. This database, maintained by the European Bioinformatics Institute (EBI), archives and disseminates results from GWAS. It includes data from 473,683 participants of European ancestry. Further details are provided in Table 1.

Selection of genetic variants

Years of education were extracted as two sets of exposure data from the IEU Open GWAS Database and the GWAS Catalog, respectively, both derived from European populations (Lee *et al.* 2018; Loh *et al.* 2018). To satisfy the first MR assumption—that genetic instruments are strongly associated with the exposure—we selected SNPs associated with years of education at genome-wide significance ($p < 5\times10^{-8}$) and applied linkage disequilibrium clumping ($r^2 < 0.001$, *clumping distance = 10,000 kb*) to obtain independent instruments. Furthermore, to address the second MR assumption (i.e., genetic variants are independent of potential confounders), we systematically queried the PhenoScanner database *(http://www.phenoscanner.medschl.cam.ac.uk/)* to evaluate whether the selected SNPs were linked to known confounding factors.

Since all SNPs in the GWAS on educational attainment reached genome-wide significance, we selected 301 SNPs and 201 SNPs respectively for subsequent analyses. The strength of instrumental variables was assessed by calculating the *F*-statistic ($F = \beta^2/SE^2$, where β denotes the exposure-associated SNP's beta coefficient and SE its standard error). An *F*-statistic threshold >10 was applied to evaluate potential weak instrument bias, with values exceeding this threshold indicating robust instrument strength (Sanderson *et al.* 2021).

Statistical analysis

To evaluate the causal effect between educational attainment and intracranial aneurysm risk, we implemented a two-sample Mendelian randomization framework. This approach leverages GWAS summary statistics to estimate the putative causal effect of education duration on cerebrovascular outcomes through rigorously selected genetic instruments.

Genetic associations for the exposure and outcome were harmonized so that all effect estimates corresponded to the same effect allele. Palindromic SNPs with ambiguous strand orientation (minor allele frequency close to 0.5) were excluded, whereas non ambiguous palindromic variants were retained after alignment. SNPs that could not be reliably harmonized were removed from the analysis.

We conducted Mendelian randomization analyses using inverse variance weighted (IVW) estimation as the primary method, complemented by MR-Egger regression, weighted median, and simple and weighted mode estimators. Horizontal pleiotropy can bias causal estimates if genetic instruments influence the outcome through pathways other than the exposure, thereby violating the exclusion restriction assumption. To address this, we applied robust approaches: the weighted median estimator, which yields consistent estimates when up to 50% of the total instrument weight comes from invalid variants, and MR Egger regression, which provides a pleiotropy adjusted effect estimate and tests for directional pleiotropy via its intercept under the Instrument Strength Independent of Direct Effect (InSIDE) assumption (Sanderson *et al.* 2022; Bowden *et al.* 2016; Burgess & Thompson, 2017). Analyses were conducted using the Mendelian Randomization R package (version 0.6.0) for summary-level MR, with all genetic associations derived from consortium-grade GWAS summary statistics. Statistical significance was determined through two tailed testing at $\alpha = 0.05$, consistent with conventional epidemiological thresholds.

Heterogeneity and sensitivity test

These diagnostic procedures collectively constitute a tripartite verification system addressing the three principal threats to MR validity: (i) genetic variant heterogeneity (Q-test), (ii) influential observations (leave-one-out), and (iii) systematic pleiotropy (Egger intercept), as per the STROBE-MR reporting guidelines. Individual SNP contributions to Cochran's Q heterogeneity statistics were quantified, with outliers identified using a Bonferroni-adjusted significance threshold ($\alpha = 0.05$/number of variants) (Skrivankova

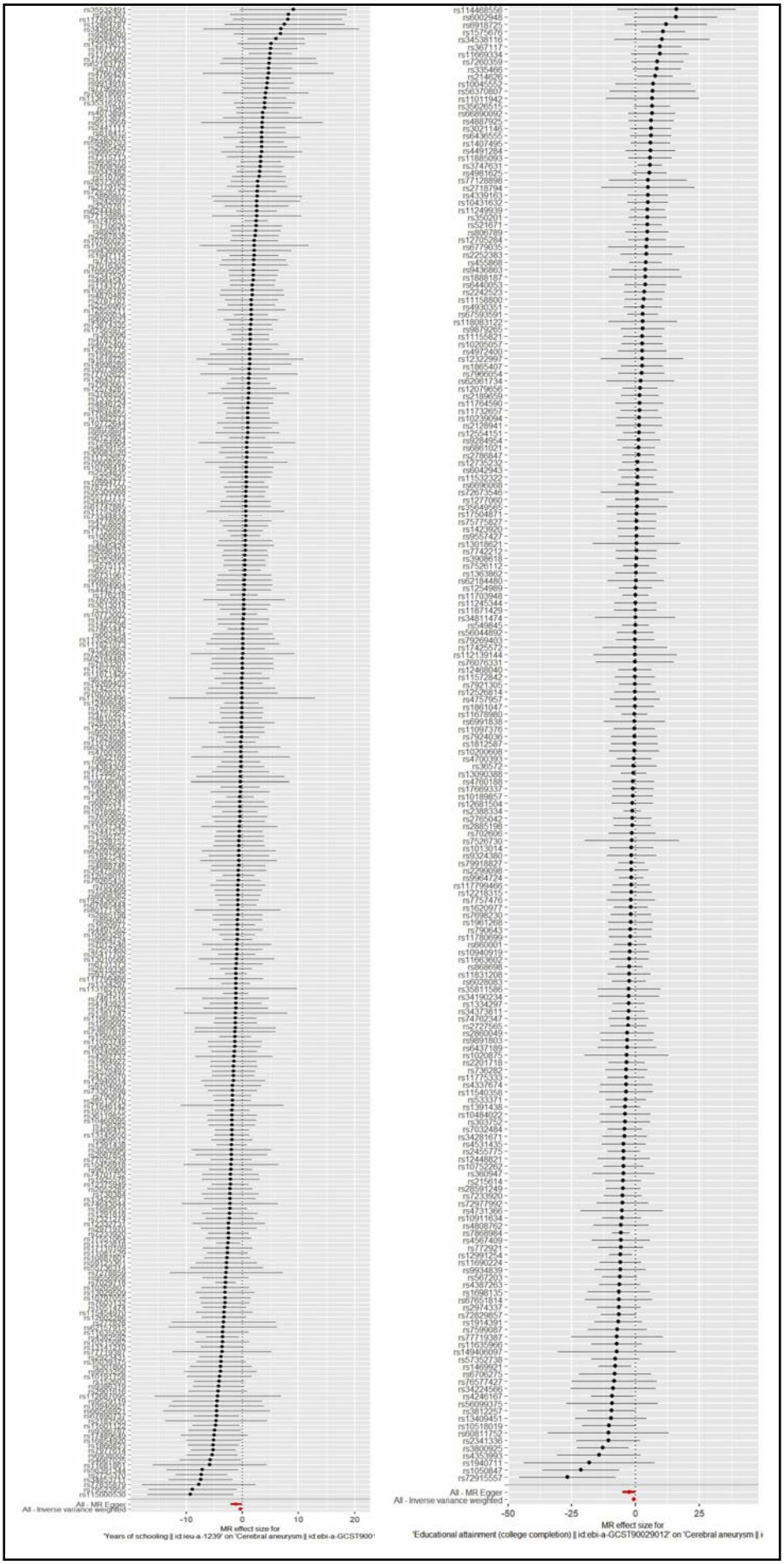

Fig. 2. Single variant Mendelian randomization estimates for educational ttainment–associated SNPs and intracranial aneurysm risk. Forest plot of single variant Mendelian randomization estimates for the association between educational attainment–associated SNPs and intracranial aneurysm risk. Each point represents the causal effect estimate for an individual SNP on aneurysm risk per genetically predicted unit increase in education, with horizontal lines indicating 95% confidence intervals. Panels A and B correspond to instruments derived from the years of schooling GWAS (ieu a 1239) and the college completion GWAS (ebi a GCST90029012), respectively. IVW, inverse variance weighted.

et al. 2021). The MR-PRESSO framework (v1.0) was subsequently implemented to iteratively remove pleiotropic outliers and generate bias-corrected causal estimates through distortion testing. Statistical power calculations were performed using the mRnd platform (available at http://cnsgenomics.com/shiny/mRnd/), incorporating parameters for instrument strength and expected effect sizes. All analyses were conducted in R 4.3.3 utilizing: TwoSampleMR package (v0.5.7) for core Mendelian randomization analyses MR-PRESSO (v1.0) for systematic pleiotropy detection.

RESULTS

Instrumental variable determination and weak instrumental variable bias determination

A represents ieu-a-1239 and B represents ebi-a-GCST90029012 in each figure, and 301 and 201 education-related SNPs were extracted as IVs, respectively, after excluding IVs with chain imbalance from the GWAS study (r^2 < 0. 001, $p < 5\times10^{-8}$, Clumping distance = 10000 kb). To estimate the adjusted results and to exclude abnormal SNPs (outliers), the 'MR-PRESSO outlier test' was used. The study's findings were determined to be valid as the $F > 10$ for the

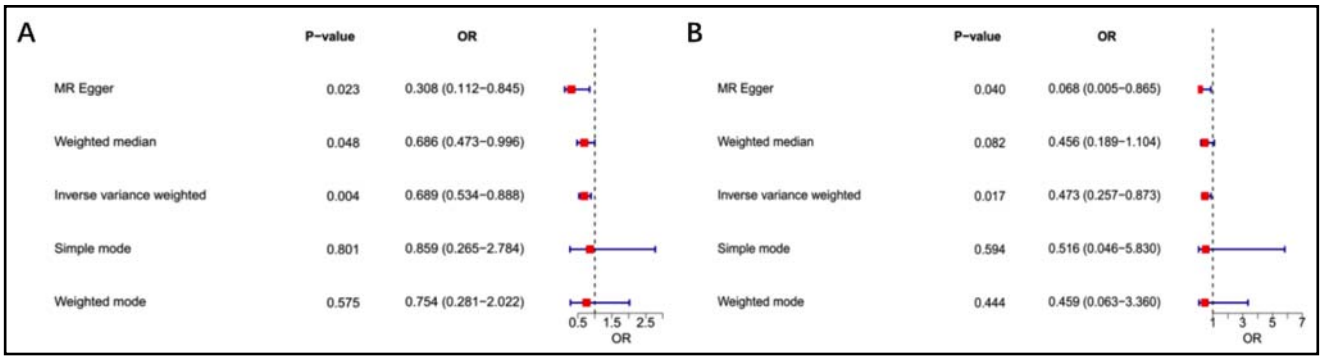

Fig. 3. Mendelian randomization estimates for the association between educational attainment and intracranial aneurysm across multiple methods.
Panel A presents results using genetically proxied years of schooling as the exposure, and Panel B presents results using college completion as the exposure. For each exposure, point estimates and 95% confidence intervals are shown for the inverse variance weighted (IVW), MR Egger, weighted median, weighted mode, and simple mode methods. Consistently inverse estimates across methods support a protective association of higher educational attainment with aneurysm risk.

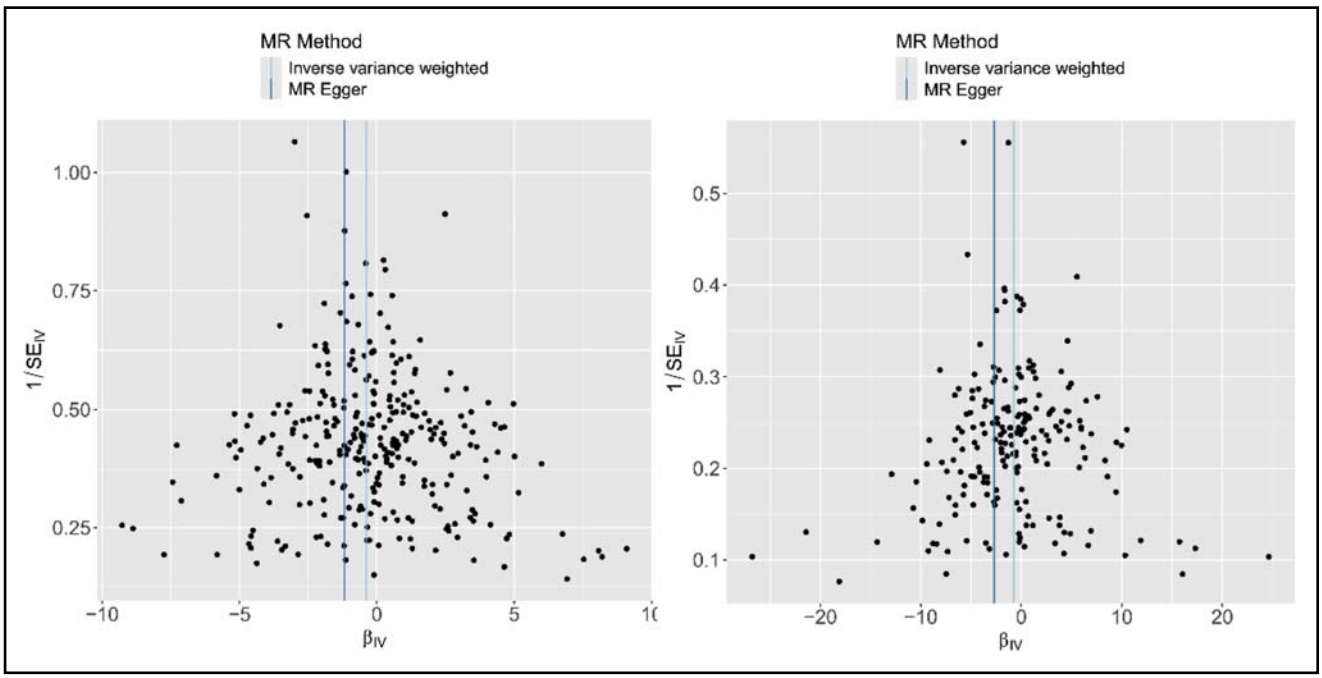

Fig. 5. Funnel plots assessing heterogeneity and directional pleiotropy in the education–aneurysm Mendelian randomization analyses.
Each point represents a single SNP instrument, plotted as its MR estimate (x axis) against the inverse of its standard error (y axis). Symmetry around the pooled estimate lines for the IVW (blue) and MR Egger (dark blue) methods suggests limited directional horizontal pleiotropy and supports the robustness of the causal estimates.

SNPs included in the analysis indicated that the results were not weakly skewed. The validity of these findings was further confirmed through two-sample MR. The impact of each SNP locus on intracranial aneurysm was established. The results are presented in Figure 2.

Results of MR

The inverse variance weighted method indicated an inverse association between genetically proxied years of schooling and intracranial aneurysm risk (β = −0.373, OR = 0.689, *95% CI*: 0.534–0.888, p = 0.004), such that higher genetically predicted schooling was associated with lower intracranial aneurysm risk. MR-Egger analysis suggested an inverse association between years of schooling and intracranial aneurysm (β = -1.178, *95% CI*: 0.112-0.845, p = 0.023), and the MR Egger regression did not provide evidence of substantial directional pleiotropy (intercept = 0.011; p = 0.107). The MR PRESSO global test did not detect significant horizontal pleiotropy (p = 0.296). Years of schooling and intracranial aneurysm were found to be causally associated using weighted median technique (β = -0.376, *95% CI*: 0.473-0.996, p = 0.048). The weighted median estimator preserves more precision in the estimates when compared to the simple method analysis (Bowden & Holmes, 2019). Although the simple and weighted mode estimates did not reach statistical significance, their point estimates indicated inverse associations of similar magnitude to the inverse variance weighted and weighted median results (Figure 3A and Figure 4A/B), supporting the overall pattern of a protective association. When using educational attainment (college completion) as the exposure, the IVW method also indicated an inverse association with intracranial aneurysm risk (β = -0.747, *95% CI*: 0.257–0.873, p = 0.017). The MR Egger intercept did not provide evidence of directional horizontal pleiotropy (intercept = 0.014, p = 0.125), suggesting that unbalanced pleiotropy is unlikely to strongly bias the results. MR-Egger yielded a negative point estimate for the association between educational attainment and intracranial aneurysm (β = -2.685, OR = 0.068, *95% CI*: 0.005–0.865, p = 0.040), but the wide confidence interval and lower precision mean this result should be interpreted cautiously. Although the simple mode and weighted mode estimates were not statistically significant, their directions of effect were similar to those of the other MR methods (Figure 3B and Figure 4B). The funnel plot (Figure 5) appeared symmetrical, which is consistent with limited directional horizontal pleiotropy. Taken together, these Mendelian randomization results support an inverse association between genetically proxied educational attainment and intracranial aneurysm risk that is compatible with a causal effect.

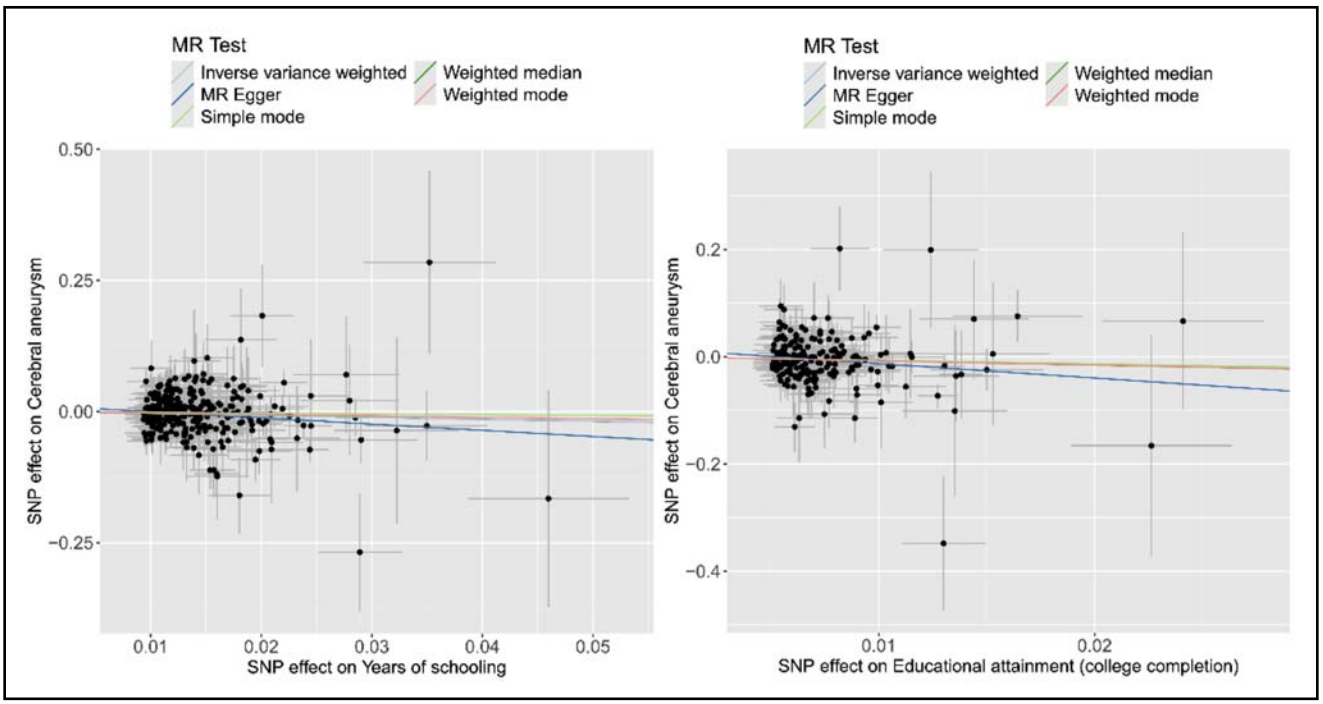

Fig. 4. Scatter plots of SNP–education and SNP–aneurysm associations in the Mendelian randomization analyses.
Scatter plots of genetic associations with educational attainment (x axis) versus genetic associations with intracranial aneurysm (y axis). Each point represents a single SNP instrument. The fitted regression lines correspond to different Mendelian randomization estimators: IVW (blue), weighted median (green), MR Egger (dark blue), weighted mode (red), and simple mode (light green). Panel A shows results for years of schooling, and Panel B shows results for college completion. The slope of each line represents the estimated causal effect of education on aneurysm risk for that method.

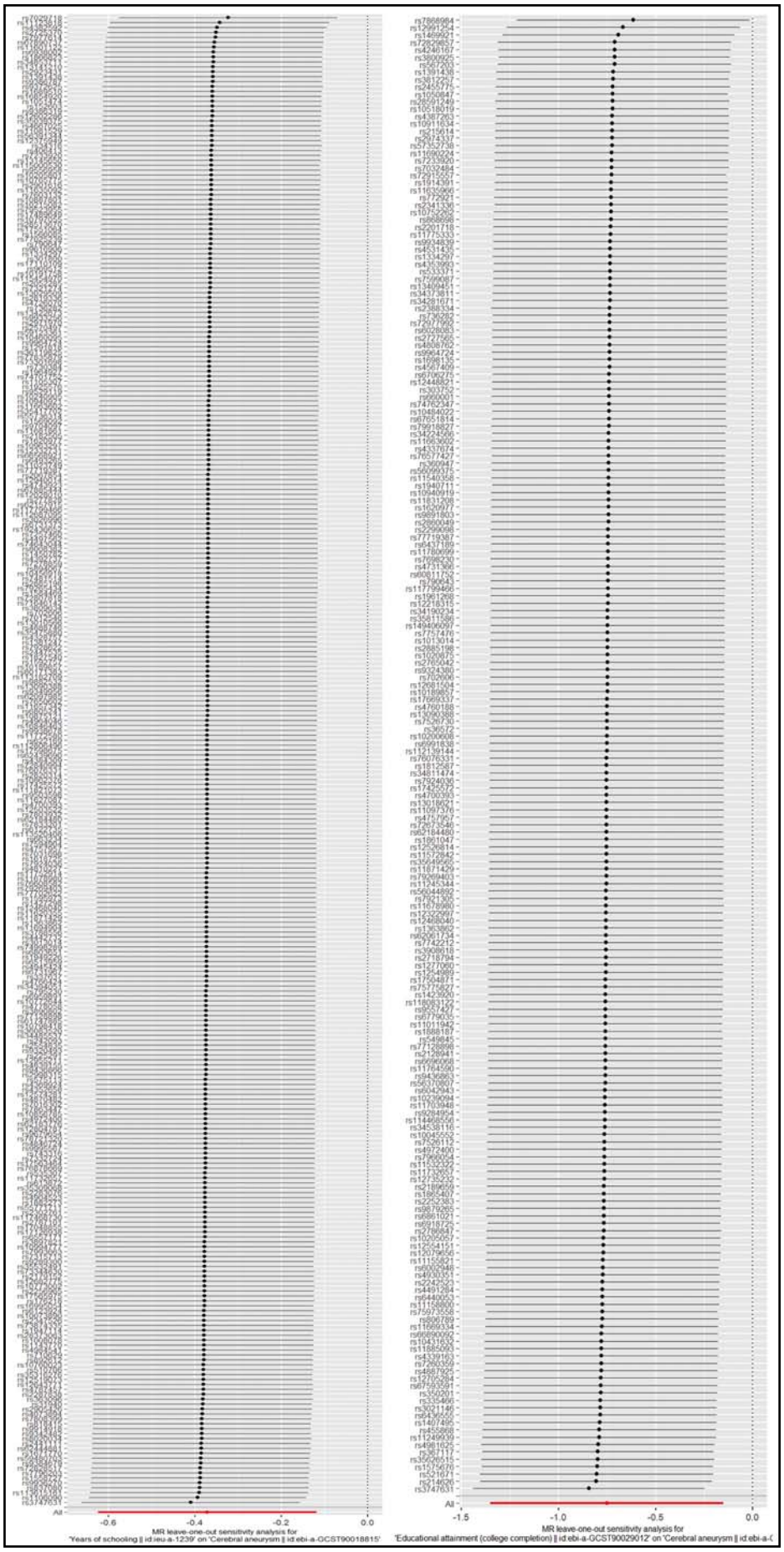

Fig. 6. Leave one out and pleiotropy diagnostics for the education–aneurysm Mendelian randomization analyses.
In the leave one out analysis, each point represents the IVW estimate obtained after excluding a single SNP, with horizontal lines indicating 95% confidence intervals. The stability of these estimates indicates that no individual SNP unduly drives the overall association. The MR Egger intercept test showed no strong evidence of directional horizontal pleiotropy, further supporting the validity of the instruments.

Tab. 2.

Outcome data	Exposure data	MR method	N of SNPs	β (log-OR)	SE	Association *p* value	Heterogeneity *p* value	Cochran Q statistic	OR	95% CI
Intracranial aneurysm (ebi-a-GCST90018815)	Years of schooling (ieu-a-1239)	IVW	301	-0.373	0.129	0.004	0.272	311.677	0.689	0.534–0.888
Intracranial aneurysm (ebi-a-GCST90018815)	Years of schooling (ieu-a-1239)	MR-Egger	301	-1.178	0.515	0.023	0.295	314.392	0.308	0.112–0.845
Intracranial aneurysm (ebi-a-GCST90018815)	Years of schooling (ieu-a-1239)	Weighted median	301	-0.376	0.190	0.048	–	–	0.686	0.473–0.996
Intracranial aneurysm (ebi-a-GCST90018815)	Educational attainment (college completion) (ebi-a-GCST90029012)	IVW	201	-0.747	0.311	0.017	0.113	224.411	0.473	0.257–0.873
Intracranial aneurysm (ebi-a-GCST90018815)	Educational attainment (college completion) (ebi-a-GCST90029012)	MR-Egger	201	-2.685	1.296	0.040	0.128	221.768	0.068	0.005–0.865

Mendelian randomization estimates for the association between educational duration and intracranial aneurysm risk across analytical methods. For each combination of exposure (years of schooling or college completion) and method, the table reports the number of SNP instruments.
Abbreviations: MR, Mendelian randomization; SNP, single nucleotide polymorphism; SE, standard error; OR, odds ratio; CI, confidence interval; IVW, inverse-variance weighted. β represents the log-odds ratio for cerebral aneurysm per genetically predicted unit increase in the education trait defined in the corresponding GWAS. Heterogeneity statistics (Cochran Q and heterogeneity *P* value) are reported for IVW and MR-Egger methods; they are not calculated for the weighted median estimator.

Heterogeneity and pleiotropy assessment

Heterogeneity, defined as the variability in causal effect estimates across individual SNPs (i.e., inconsistency in effect direction/magnitude), was formally evaluated. Cochran's *Q* test revealed no statistically significant heterogeneity between IV estimates derived from individual SNPs ($p > 0.05$; Table 2). Sensitivity analyses further supported the robustness of the findings: Leave-one-out analysis confirmed that no single SNP disproportionately influenced the pooled IVW estimate (Figure 6). Funnel plot symmetry and MR-Egger regression intercept test ($p > 0.05$ for intercept deviation) provided no evidence of directional horizontal pleiotropy—a potential source of bias in MR analyses due to unbalanced pleiotropic pathways.

DISCUSSION

Higher educational attainment has been hypothesized to protect against intracranial aneurysm, but the underlying causal mechanisms remain incompletely understood. To investigate this association within a causal inference framework, we used Mendelian randomization, a genetic epidemiological approach that utilizes instrumental variables to reduce confounding and clarify directional relationships. We systematically selected two distinct genetic exposure factors strongly associated with educational duration from large-scale GWAS, ensuring both relevance and independence assumptions were met for valid MR analysis.

Some studies suggest that education may play a protective role by improving management of cardiovascular risk factors (e.g., hypertension control, reducing aneurysm related complications), promoting healthier lifestyles (such as smoking cessation and reduced alcohol use), and enhancing access to healthcare resources (Zhang *et al.* 2021; Foster *et al.* 2023). Emerging evidence from a Mendelian randomization study has identified six modifiable risk factors causally linked to hypertension—low educational attainment, alcohol dependence, insomnia, obesity (body mass index), reduced HDL C levels, and elevated triglycerides—highlighting plausible biological and behavioral pathways through which education may influence vascular risk (van Oort *et al.* 2020). Notably, lower educational attainment appears to increase hypertension risk, potentially mediated by limited health literacy, psychosocial stress, and socioeconomic barriers to preventive care (van Oort *et al.* 2020). Hypertension is a critical driver of aneurysm formation and progression due to sustained hemodynamic stress on arterial walls. Elevated blood pressure exacerbates vascular remodeling, weakening structural proteins (e.g., collagen/elastin) and promoting inflammation (Wermer *et al.* 2005).

MR reduces, but does not eliminate, the risk of confounding and reverse causation compared with conventional observational studies by leveraging genetic

variants as instrumental variables. These genetic proxies, which are randomly allocated during gamete formation and remain fixed throughout life, reduce confounding and reverse causation compared with conventional observational studies. Our findings support an inverse association between genetically proxied higher educational attainment and intracranial aneurysm risk that is compatible with a protective causal effect. This approach reduces susceptibility to environmental confounding and measurement errors that typically distort observational associations, thereby enabling more robust causal inference about modifiable exposures (e.g., education) and health outcomes (e.g., intracranial aneurysm). By addressing key limitations of conventional observational designs, Mendelian randomization can strengthen causal inference while preserving the practicality of population level analyses (Ancira-Moreno *et al.* 2022). Genetic variants in MR studies may exhibit pleiotropy by influencing multiple phenotypes, necessitating sensitivity analyses to validate causal conclusions (Sanderson *et al.* 2021). To address this bias, we employed two robust methods: a weighted median estimator capable of maintaining validity even if 50% of SNPs are invalid instruments (Bowden *et al.* 2016), complemented by MR-Egger regression to detect and adjust for directional pleiotropic effects. Our findings support a potential causal effect of higher educational attainment on reduced risk of intracranial aneurysm.

This study has several notable limitations. Primarily, this investigation of intracranial aneurysm pathogenesis was conducted in cohorts exclusively composed of individuals of European descent. Given the potential influence of genetic and environmental factors linked to ethnicity on disease mechanisms and causal relationships, future investigations should incorporate more ethnically diverse cohorts to validate and extend these genetic associations across different ancestral populations. Second, the selected SNPs for years of education may have pleiotropic effects unrelated to education (for example, via socioeconomic status, cognition, or lifestyle), which could influence intracranial aneurysm risk through alternative pathways. Although we used MR Egger, weighted median, and MR PRESSO to probe and mitigate such bias, residual pleiotropy cannot be entirely ruled out. Third, education related genetic variants may capture dynastic effects, assortative mating, and subtle population structure that are not fully accounted for in GWAS analyses and may influence our estimates. Finally, methodological choices and model assumptions can yield divergent Mendelian randomization results, and statistical significance alone should not be interpreted as definitive proof of causality.

Our two-sample Mendelian randomization analyses provide evidence consistent with a potentially protective association between higher genetically proxied educational attainment and intracranial aneurysm risk in individuals of European ancestry, although these findings should be interpreted in the context of the underlying assumptions and potential residual bias.

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Conflict of interest: We declare that we have no conflicts of interest related to this research.

Author contribution: Yicheng Cui: Data collection, statistical analysis, conceptualization, and manuscript writing. Zhipeng Xiao, Meihua Li, Shangsong Yang: Data collection and analysis of imaging data and conceptualization of the paper. Wenqiang Xin: Conceptualization and manuscript writing.

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Ethics Approval: All analyses were based on previously published studies; therefore, no ethical approval or patient consent was required.

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