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ORIGINAL COMMUNICATION

Major depression and small vessel stroke: a Mendelian randomization analysis

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Abstract

Background and purpose Although observational studies have reported a positive association between depression and ischemic stroke, causality remains inconclusive. We aimed to assess the causal relationship of major depressive disorder (MDD) with ischemic stroke, especially with the small vessel stroke (SVS) subtype.

Methods We used 72 independent single-nucleotide polymorphisms associated with MDD in a genome-wide association study (GWAS) from the Psychiatric Genetics Consortium as instrumental variables. The corresponding data for ischemic stroke and its subtypes of European ancestry were available from the MEGASTROKE consortium of 34,217 ischemic stroke cases and 406,111 controls. Primary Mendelian randomization estimates were calculated with inverse-variance weighted method, and several alternate methods and multiple sensitivity analyses were also performed.

Results We found that genetic predisposition to higher risk of MDD was associated with higher risk of SVS, with an odds ratio of 1.33 (95% confidence interval, 1.08–1.65; $p=0.009$) per log-odds increment in MDD risk, but not with large artery stroke (OR, 1.08; 95% CI 0.83–1.41; $p=0.559$), cardioembolic stroke (OR, 0.98; 95% CI 0.80–1.20; $p=0.833$), or all ischemic stroke (OR, 1.03; 95% CI 0.92–1.15; $p=0.633$). The association of MDD with SVS was overall robust to sensitivity analyses.

Conclusions We provided evidence for a possible causal effect of MDD on increased risk of SVS. Future researches are required to investigate whether rational intervention on depression may help to reduce societal burden of SVS.

Keywords Major depression · Small vessel stroke · Ischemic stroke · Mendelian randomization · Single-nucleotide polymorphism

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Introduction

Stroke is a leading cause of disability and death worldwide with a high societal burden [1]. In the vigorous and effective control of traditional risk factors, such as hypertension, type 2 diabetes, smoking, and hypercholesterolemia, the incidence of stroke is notably declined over the past decade around the world [2–5]. However, in low-income and middle-income countries such as China, the burden of stroke is high and increasing [6]. To further reduce the stroke occurrence, more attention needs to be paid to non-traditional risk factors [7].

Depression, as a common psychiatric disorder worldwide, is an important risk factor for stroke and is one of the 10 risk factors that are associated with 90% of stroke risk [8]. The relationship between depression and ischemic stroke has received much attention in recent years [9–13], but the causality remains largely unknown due to the inherent limitations in observational studies of confounding and reverse causation. Moreover, most studies assessed the effect of depression on overall stroke only, and few have examined on specific subtypes. Considering the etiologically distinct pathogenesis, it is necessary to clarify the effects of depression on different stroke subtypes. A genetic study showed that polygenic risk score for depression was associated with a higher risk of small vessel stroke (SVS) than other ischemic stroke subtypes in European ancestry [14, 15].

Mendelian randomization (MR) has been widely used to make causal inference, using genetic variants as an instrument for the exposure. Because genetic variants are allocated randomly at conception, the MR design is largely free from confounding and reverse causation. Here, we applied two-sample MR to explore the potential causal association of major depressive disorder (MDD) with the risk of ischemic stroke, as well as specific stroke subtypes.

Materials and methods

All summary-level genomic data used for this work have been made publicly available online (Supplementary Table 1). All data sources were approved by relevant institutional review boards from original studies, and all participants were given informed consent. Details of the sample recruitment and genetic data quality control are described elsewhere [16, 17].

Date source and single-nucleotide polymorphism selection

Summary statistics data for ischemic stroke and its subtypes were derived from the largest published genome-wide association study (GWAS) meta-analysis by the MEGASTROKE consortium [16]. We restricted the data for ischemic stroke to European-descent individuals only to minimize potential bias from population stratification, including up to 34,217 ischemic stroke cases confirmed by clinical and imaging criteria and 406,111 stroke-free controls. Ischemic stroke cases were subdivided into large artery stroke (LAS) ($n = 4{,}373$), SVS ($n = 5{,}386$), and cardioembolic stroke (CES) ($n = 7{,}193$) based on the Trial of Org 10,172 in Acute Stroke Treatment criteria [18]. The study included differently sized control sets for stroke subtypes (LAS: 146,392 controls, SVS: 192,662 controls, CES: 204,570 controls).

We selected associated single-nucleotide polymorphisms (SNPs) for MDD in the hitherto largest GWAS meta-analysis of 7 cohorts (PGC29, deCODE, GenScotland, GERA, iPSYCH, UK Biobank, and 23andMe) in European populations from the MDD Working Group of the Psychiatric Genomics Consortium (PGC) (135,458 cases and 344,901 controls) [17]. A lifetime diagnosis of MDD was ascertained primarily via structured assessments by trained interviewers, clinician-administered checklists, or medical record review. To include more SNPs that contribute to MDD risk, we selected variants meeting a more relaxed threshold ($p < 1 \times 10^{-6}$) to allow for a sufficient number of SNPs to be included in the analysis, which has been used in psychiatric MR research [19]. In addition, we also repeated our analysis using a genome-wide significant threshold (5×10^{-8}) to check for consistency in the direction and magnitude with the relaxed threshold. Where the specified SNPs were not available in the outcome data set, we replaced them with proxy SNPs ($r^2 \geq 0.8$). We clumped SNPs for independence excluding those with $r^2 > 0.001$ in a reference panel of European from the 1000 Genomes and retained SNPs with the lowest p value. Then, we harmonized the effect sizes for the SNPs on the exposure (MDD) and the outcome (ischemic stroke and subtypes) data, and removed palindromic SNPs with minor allele frequency higher than 0.3. For one SNP (rs116755193) associated with MDD, no proxy was found for the MEGASTROKE consortium. Characteristics of the MDD-associated SNPs are presented in Supplementary Table 2.

Statistical analyses

The random-effect inverse-variance weighted (IVW) method was used as the primary analyses, which can provide an accurate estimate in the absence of directional pleiotropy [20].

We then performed several robust MR methods for sensitivity tests. Weighted median estimate (WME) permits up to 50% invalid instrument variables [21]. MR-Egger method can control for bias from directional pleiotropic effect, at the cost of reduced power [22]. In addition, two recently proposed approaches were carried out: (1) MR-Robust Adjusted Profile Score (MR.RAPS), a method provides unbiased estimates when many weak instruments and is robust to systematic and idiosyncratic pleiotropy [23] and (2) MR-Pleiotropy Residual Sum and Outlier (MR-PRESSO), a method to identify and correct for potential outliers [24].

Heterogeneity of individual genetic variants was evaluated by Cochran's Q test. The NOME assumption (no measurement error in the SNP-exposure associations) was assessed for MR-Egger via an I^2_{GX} statistic. If the statistic was lower than 90%, a simulation extrapolation (SIMEX) correction was performed to adjust the dilution bias [25]. We also provided scatter plots, forest plots, funnel plots and leave-one-out plots for further interpretation. To avoid the possibility of reverse causation, we made Steiger analyses to verify the directionality [26].

Bonferroni corrected p value threshold for 4 outcomes ($p < 0.013$) was used to indicate statistical significance for the primary analysis. A threshold of $p < 0.05$ was used in all sensitivity analyses. We considered as causal results that were concordant in direction and magnitude across multiple MR approaches, pass nominal significance in IVW MR. All statistical analyses were done by the TwoSampleMR [27] and MR-PRESSO [24] packages in R version 3.5.3.

Assessment of pleiotropy

We conducted two methods to detect possible pleiotropy, which was a primary violation of MR assumptions. First, we tested whether the intercept term from MR-Egger regression differed from zero, which provided evidence of directional pleiotropy. Second, we looked up PhenoScanner database [28] for potential associations ($p < 1 \times 10^{-5}$) of all SNPs in our study with the following SVS-related risk factors: systolic and diastolic blood pressure [29], smoking [29], type 2 diabetes [30], high-density lipoprotein cholesterol [31], and triglycerides [32].

Results

Associations of genetically determined risk of MDD with ischemic stroke and its subtypes using multiple MR methods are reflected in Fig. 1. Causal estimates are displayed as an odds ratio (OR) and 95% confidence interval (CI) per log-odds increment in genetically determined risk of MDD. We found evidence of a detrimental causal effect of MDD

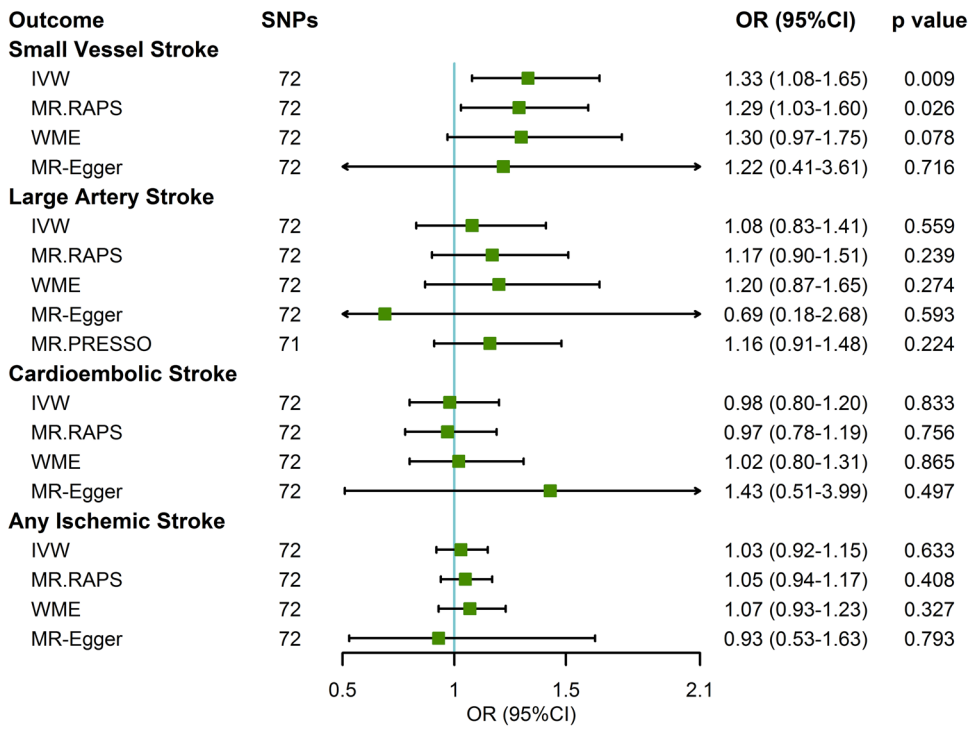

Fig. 1 Mendelian randomization (MR) estimates of major depressive disorder (MDD) with ischemic stroke and ischemic stroke subtypes from the primary analysis (IVW) and sensitivity analysis (MR.RAPS, WME, MR-Egger, and MR-PRESSO). For MR-PRESSO, outcomes of the outlier-corrected analysis are presented if outliers were detected, otherwise, MR-PRESSO results are not presented. Data are displayed as odds ratio (OR) and 95% confidence interval (CI) per log-odds increment in MDD risk. *SNP* single-nucleotide polymorphism, *IVW* inverse-variance weighted method, *WME* weighted median estimate, *MR.RAPS* MR-Robust Adjusted Profile Score, *MR-PRESSO* MR-Pleiotropy Residual Sum and Outlier

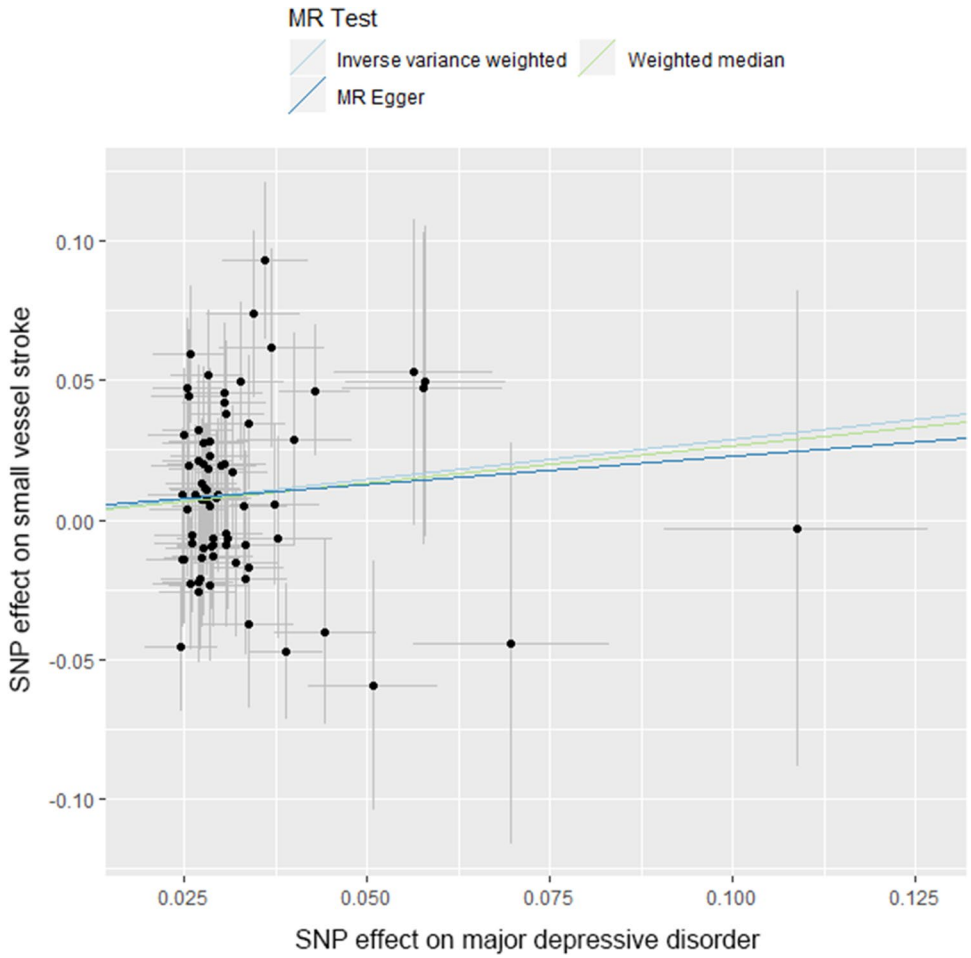

Fig. 2 Scatterplot of SNP potential effects on MDD vs small vessel stroke, with the slope of each line corresponding to estimated MR effect per method

on SVS in the primary analysis (IVW OR, 1.33 for SVS per log-odds increment in MDD risk, 95% CI 1.08–1.65; $p=0.009$; Fig. 2), with 72 SNPs meeting the relaxed threshold. The MR estimate was not statistically significant using the genome-wide significant threshold (IVW OR, 1.34, 95% CI 0.98–1.82; $p=0.063$), but was consistent in the direction and magnitude with the relaxed approach. With the 72 SNPs, WME MR and MR-Egger yielded the same pattern of effects as the primary analysis, although with broader CIs due to the lower statistical power. Likewise, the association persisted in the MR.RAPS (OR, 1.29; 95% CI 1.03–1.60; $p=0.026$). MR-PRESSO outlier test did not identify potential SNP outlier. The forest plot, funnel plot, and leave-one-out plot provided additional support that no single SNP drove the overall association with SVS (Supplementary Figs. 1–3). Accordingly, no heterogeneity was observed among individual SNPs (Cochran's Q test: $Q=82.39$; $p=0.167$; Table 1). The I^2_{GX} index was 96.9% (Table 1), suggesting low risk of dilution bias and no need to perform SIMEX correction. There was no evidence of directional pleiotropy detected by the MR-Egger intercepts (p for intercept $=0.875$; Table 1). To further exclude SNPs with pleiotropic effects, we looked up the PhenoScanner database and identified 6 of 72 SNPs for MDD nominally associated with SVS-relevant traits

Table 1 Heterogeneity tests, dilution bias evaluation, and MR-Egger intercept of major depressive disorder causally linked to ischemic stroke and its subtypes

Outcome	Cochran's Q	p value[a]	I^2_{GX} (%)	Intercept	p value[b]
Small vessel stroke	82.39	0.167	96.9	0.003	0.875
Large artery stroke	107.77	0.003	96.9	0.014	0.510
Cardioembolic stroke	104.23	0.006	96.9	− 0.012	0.463
Any ischemic stroke	118.50	3.50×10^{-4}	96.9	0.003	0.716

[a]p value for heterogeneity tests

[b]p value for MR-Egger intercept

(Supplementary Table 3). However, exclusion of these SNPs did not appreciably change the result for MDD and SVS (IVW OR, 1.32; 95% CI 1.05–1.65; $p = 0.019$).

Conversely, MDD was not causally related to LAS, CES, or all ischemic stroke (Fig. 1). The ORs of LAS, CES, and all ischemic stroke per log-odds increment in genetically determined risk of MDD in the primary analyses were 1.08 (95% CI 0.83–1.41; $p = 0.559$), 0.98 (95% CI 0.80–1.20; $p = 0.833$), and 1.03 (95% CI 0.92–1.15; $p = 0.633$), respectively. The lack of causal association remained in all sensitivity analyses (Fig. 1). The Cochran's Q test revealed moderate heterogeneity, but there was no clear evidence of directional pleiotropy (all p for intercept ≥ 0.46; Table 1). The relationship between MDD and LAS did not change after the exclusion of the outlier in *FADS2* (rs174594) detected by the MR-PRESSO. Furthermore, Steiger tests showed no statistically significant evidence that ischemic stroke and its subtypes contributed to MDD (Supplementary Table 4).

Discussion

We applied a two-sample MR approach to comprehensively evaluate the causal relationships between MDD and ischemic stroke and its subtypes in genomic data. The primary MR analysis showed that genetic predisposition to higher risk of MDD was associated with higher risk of SVS, but not associated with LAS, CES, or all ischemic stroke. The results were overall robust to sensitivity analyses.

Control of conventional risk factors is the cornerstone of stroke prevention, resulting in a notable decline in the incidence of stroke worldwide [2–5]. However, further reduction in stroke occurrence needs identification and control of nontraditional risk factors [7]. Depression, as a common psychiatric disorder [33] and a nontraditional risk factor for stroke, is one of the 10 factors that are associated with 90% of stroke risk in the INTERSTROKE study [8]. Previous observational studies have extensively reported the relevance of MDD or depression symptoms and ischemic stroke across diverse ancestries [9–13]. A recent large-scale meta-analysis including 103,586 subjects showed that depression was associated with subsequent stroke with a hazard ratio of 1.95 (95% CI 1.63–2.30) [12]. However, given that the use of antidepressant medications has also been a potential risk factor of stroke [34], and that observational studies are susceptible to bias due to various confounders, the causality between MDD and stroke remains largely uncertain.

MR is considered nature's randomized controlled trial and is widely used to assess causality of an observed association. While this manuscript was under revision, a MR research suggested a possible detrimental effect of genetically determined risk of depression on functional outcome after ischemic stroke [35]. In contrast, the study did not provide MR evidence of a causal association of risk of depression with risk of ischemic stroke [35], which was in line with our results. However, the study did not examine the effect on specific ischemic stroke subtypes. Given the biological plausibility of differential effects on different ischemic stroke subtypes, it is necessary to clarify the effects of MDD on etiologically distinct stroke subtypes. Our work extends prior MR study by directly assessing the casual effect of MDD on different subtypes of ischemic stroke, including a large sample of over 5000 SVS cases. We discovered that the relationship with MDD was specific to SVS, but not LAS, CES, or all ischemic stroke. Per log-odds increment of MDD risk accounts for an approximately 33% increase in odds of SVS risk. Our findings were supported by a previous study by the SiGN consortium, which also reported that higher polygenic risk score for MDD was associated with increased risk of ischemic stroke, particularly of the SVS subtype in those of European ancestry [14, 15]. It suggested a shared genetic basis between MDD and stroke. To avoid the possibility of reverse causation, we made Steiger analyses and showed no evidence that ischemic stroke and its subtypes contributed to MDD.

The underlying mechanisms linking MDD with SVS are unclear. One potential mechanism involves shared risk factors for both disease. A meta-analysis comprised 22,367 participants found that depression increased the risk of hypertension incidence [36], which is also a well-known risk factor of SVS. In addition, evidence from prospective and cross-sectional studies showed that psychological disorders and diabetes may exacerbate each other [37], which could partly explain the link between depression and SVS. Other possible mechanisms including systemic chronic inflammation [38], hypothalamic-pituitary-adrenocortical axis dysfunction [38], cerebrovascular dysregulation [39], and endothelial dysfunction [38].

One strength of our study is the MR design which largely minimizes confounding and reduces reverse causality. Another strength is the application of the most recent and comprehensive database for MDD and largest GWAS meta-analysis for stroke, which provided a possibility to evaluate the associations with ischemic stroke subtypes. Our MR study also has limitations. First, since a small number of genome-wide significant SNPs were identified, we selected MDD-associated SNPs at a more relaxed threshold ($p < 1 \times 10^{-6}$). This relaxed approach has been confirmed by other MR studies [19, 40]. Second, we restricted our study populations to European-descent individuals only to minimize population stratification, which might limit the generalizability to other ethnic groups. Consistently, a genetic study found that polygenic risk score for depression was associated with elevated risk of SVS in European ancestry only [14, 15]. Further studies expanding our findings by including

diverse ethnic populations may be important. One deficit in two-sample MR is sample overlap. We carefully reviewed the original cohorts in the PGC and MEGASTROKE data set, and found that sample overlap was negligible. In addition, residual pleiotropy might remain, despite a range of sensitivity analyses conducted to explore and account for pleiotropy. However, our main findings for MDD and SVS remained after the exclusion of pleiotropic SNPs associated with SVS-related risk factors, and no directional pleiotropy was observed.

Conclusions

In conclusion, our MR study suggested a possible causal effect of MDD on increased risk of SVS, and this effect might be specific to the SVS subtype. Future researches are required to investigate whether rational intervention on depression may help to reduce societal burden of SVS.

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Compliance with ethical standards

Conflicts of interest The author declares that they have no competing interest.

Ethics approval All data sources were approved by relevant institutional review boards from original studies (MEGASTROKE and PGC consortia).

Informed consent All participants were given informed consent from original studies (MEGASTROKE and PGC consortia).

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