

# Genetically Determined Risk of Depression and Functional Outcome After Ischemic Stroke

## Mendelian Randomization Study

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**Background and Purpose**—Psychosocial factors can have implications for ischemic stroke risk and recovery. This study investigated the effect of genetically determined risk of depression on these outcomes using the Mendelian randomization (MR) framework.

**Methods**—Genetic instruments for risk of depression were identified in a discovery genome-wide association study of 246 363 cases and 561 190 controls and further replicated in a separate population of 474 574 cases and 1 032 579 controls. Corresponding genetic association estimates for risk of ischemic stroke were taken from 60 341 cases and 454 450 controls, with those for functional outcome 3 months after ischemic stroke taken from an analysis of 6021 patients. Following statistical power calculation, inverse-variance weighted MR was performed to pool estimates across different instruments. The Cochran *Q* heterogeneity test, weighted median MR, and MR pleiotropy residual sum and outlier were used to explore possible bias relating to inclusion of pleiotropic variants.

**Results**—There was no MR evidence for an effect of genetically determined risk of depression on ischemic stroke risk. Although suffering low statistical power, the main inverse-variance weighted MR analysis was suggestive of a detrimental effect of genetically determined risk of depression on functional outcome after ischemic stroke (odds ratio of poor outcome [modified Rankin Scale,  $\geq 3$ ] per 1-SD increase in genetically determined risk of depression, 1.81; 95% CI, 0.98–3.35;  $P=0.06$ ). There was no evidence of heterogeneity between MR estimates produced by different instruments ( $Q\ P=0.26$ ). Comparable MR estimates were obtained with weighted median MR (odds ratio, 2.57; 95% CI, 1.05–6.25;  $P=0.04$ ) and MR pleiotropy residual sum and outlier (odds ratio, 1.81; 95% CI, 0.95–3.46;  $P=0.08$ ).

**Conclusions**—We found no MR evidence of genetically determined risk of depression affecting ischemic stroke risk but did find consistent MR evidence suggestive of a possible effect on functional outcome after ischemic stroke. Given the widespread prevalence of depression-related morbidity, these findings could have implications for prognostication and personalized rehabilitation after stroke. (*Stroke*. 2019;50:2219–2222. DOI: 10.1161/STROKEAHA.119.026089.)

**Key Words:** depression ■ morbidity ■ stroke

Functional outcome following stroke can vary considerably, ranging from complete resolution of symptoms to death. Psychosocial factors have implications for stroke

recovery, and predisposition toward depression in particular can affect both physiological and psychological mechanisms.<sup>1</sup> While observational studies can offer insight in this regard,

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they are often limited in inferring causality because of difficulty unraveling spurious associations related to confounding factors or reverse causation.

The Mendelian randomization (MR) technique uses genetic variants to evaluate the effect of varying an exposure on an outcome.<sup>2</sup> The random allocation of such variants at conception means that they are not associated with confounding factors or affected by reverse causation. Although this statistical approach has been extensively used to understand the factors that cause stroke, a scarcity of genetic data had prevented its utilization for investigating functional outcome after stroke. However, the recent publication of the GISCOME (Genetics of Ischemic Stroke Functional Outcome) genome-wide association study has now made implementation of MR in this context feasible.<sup>3</sup>

In this study, we perform MR analyses investigating the causal effect of genetically determined risk of depression on ischemic stroke risk and consequent functional outcome. By incorporating a range of analyses using distinct models, we present results that are robust to potential violations of the requisite assumptions.

## Methods

All data supporting this work are available within the article itself and its [online-only Data Supplement](#). These data were obtained from published studies that individually obtained appropriate ethical approval and participant consent, and no further ethical approval was required.

### Genetic Association Estimates

Details of the studies from which genetic association estimates for MR analyses were obtained are provided in Methods in the [online-only Data Supplement](#).

### Power Calculations

MR power calculations were based on the available sample sizes for the respective outcomes (Methods in the [online-only Data Supplement](#))<sup>3,4</sup> and the genetic risk of depression instruments explaining  $\approx 1.2\%$  of the variance in this exposure.<sup>5,6</sup>

### MR Analysis

The ratio method was used to calculate MR estimates for individual single-nucleotide polymorphisms (SNPs), using second-order weights for the standard errors.<sup>2</sup> Fixed-effects inverse-variance weighted meta-analysis was used to pool MR estimates across different instrument SNPs in the main analyses.<sup>2</sup> Methods in the [online-only Data Supplement](#) details sensitivity analyses that were performed to investigate the presence of pleiotropy, where the genetic instruments affect the outcome independently of genetically determined risk of depression, to bias the MR estimate.<sup>2</sup>

All analysis undertaken in this study used R, version 3.4.1 (The R Foundation for Statistical Computing).

## Results

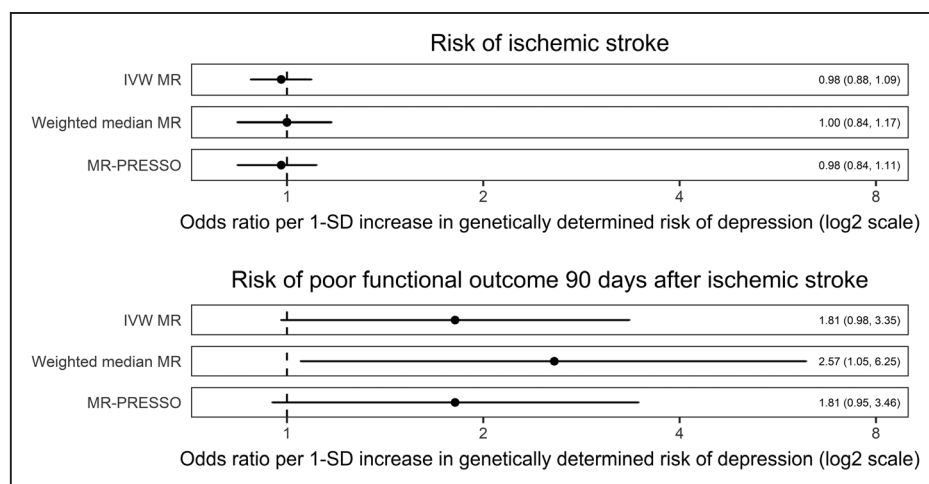
The 56 risk of depression instrument SNPs had F statistics ranging from 31 to 131 (Table II in the [online-only Data Supplement](#)), thus representing appropriate strength for MR analysis.<sup>2</sup> Performing power calculations for risk of ischemic stroke, we found that 80% statistical power would be achieved with a minimum detectable odds ratio (OR) of 1.11 per SD increase in genetically determined risk of depression.<sup>5</sup> For functional outcome after ischemic stroke, 80% statistical power

would be achieved with a minimum detectable OR of 1.85 for a modified Rankin Scale score  $\geq 3$  per SD increase in genetically determined risk of depression.<sup>5</sup>

There was no MR evidence that genetically determined risk of depression affects risk of ischemic stroke in any of the MR models considered (Figure). The main inverse-variance weighted MR analysis showed OR of 0.98 (95% CI, 0.88–1.09;  $P=0.69$ ), although the Cochran  $Q$  test did identify heterogeneity in the MR estimates produced by different SNPs ( $P=4\times 10^{-3}$ ). Similar results were obtained in the weighted median (OR, 1.00; 95% CI, 0.84–1.17;  $P=0.96$ ) and MR pleiotropy residual sum and outlier (OR, 0.98; 95% CI, 0.84–1.11;  $P=0.75$ ; 2 outliers detected and after removing these, OR, 0.98; 95% CI, 0.86–1.11;  $P=0.70$ ) sensitivity analyses. In contrast, MR evidence suggested that genetically determined risk of depression is associated with worse functional outcome after ischemic stroke. The main inverse-variance weighted MR analysis showed OR of 1.81 (95% CI, 0.98–3.35;  $P=0.06$ ), and Cochran  $Q$  test did not identify heterogeneity in the MR estimates produced by different SNPs ( $P=0.26$ ). Similar results were obtained in the weighted median (OR, 2.57; 95% CI, 1.05–6.25;  $P=0.04$ ) and MR pleiotropy residual sum and outlier (OR, 1.81; 95% CI, 0.95–3.46;  $P=0.08$ ; no outliers detected) sensitivity analyses. Forest, radial, and funnel plots depicting the ratio method MR estimates produced by individual SNPs for this analysis are provided in Figures I through III in the [online-only Data Supplement](#).

## Discussion

This MR study overcomes environmental confounding and reverse causation to find no evidence of an effect of genetically determined risk of depression on risk of ischemic stroke but did find evidence suggestive of a possible effect on functional outcome after ischemic stroke. This work represents the first MR study to investigate functional outcome after stroke. The lack of association with ischemic stroke risk suggests that collider bias is unlikely to affect our analysis of functional outcome,<sup>7</sup> and our sensitivity analyses did not reveal any evidence of pleiotropic variants biasing the MR estimates. Furthermore, by using a 2-sample MR approach, we were able to maximize the data available for analyses. Despite this, statistical power for the analysis of functional outcome was restricted, with wide 95% CIs and borderline statistical significance for the observed magnitude of effect. Use of distinct study populations for exposure and outcome genetic association estimates may also have introduced bias related to differences in the underlying populations and discrepancies in the analytical models used. Variation in the time that baseline National Institutes of Health Stroke Scale was measured when obtaining genetic association estimates for functional outcome may have introduced measurement error, thus also potentially reducing statistical power. Additional limitations include the use of genetic variants to evaluate risk of depression as a proxy for predisposition to depression.<sup>8</sup> The results should, therefore, not be directly extrapolated to estimate the effect of a clinical intervention for treating or preventing depression, either before or after stroke.



**Figure.** Forest plot summarizing the results of the Mendelian randomization (MR) analyses, measured in odds ratio of ischemic stroke and poor functional outcome (modified Rankin Scale,  $\geq 3$ ), respectively, per 1-SD increase in genetically determined risk of depression. IVW MR indicates inverse-variance weighted Mendelian randomization; and PRESSO, pleiotropy residual sum and outlier.

The lack of association of risk of depression with risk of stroke contradicts the findings from some previous observational studies (Table IV in the [online-only Data Supplement](#)). Indeed, observational analyses can be biased by reverse causation and confounding biases, and this may also explain the discrepancies between previous observational studies (Table IV in the [online-only Data Supplement](#)) and indeed the findings of our current MR analysis that largely overcomes such limitations. Depressive disorders and related tendencies are widespread and have implications for ischemic stroke patients.<sup>1</sup> Recovery may be affected through reduced motivation, engagement with rehabilitation, and cognitive function.<sup>1</sup> A recent randomized controlled trial of 3127 patients with stroke did not identify any benefit of the antidepressant fluoxetine on functional outcome at 6 months, although incidence of poststroke depression was reduced.<sup>9</sup> The research question addressed in this trial differs markedly from our current study aim, which is concerned with the effect of predisposition to depression before ischemic stroke event on functional recovery at 3 months. Further work is warranted to replicate our findings in a larger dataset, consider distinct patient subgroups (including different ethnic groups and those with and without recurrent stroke), and explore whether a history of depressive tendencies before stroke may be used to predict outcome or influence rehabilitation strategies after stroke.

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### Disclosures

Dr Lindgren reports personal fees for advisory board, speech, and seminar participation from Bayer, Astra Zeneca, Boehringer Ingelheim, Bristol-Myers Squibb-Pfizer, and Reneuron. The other authors report no conflicts.

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