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Diabetes Mellitus, Glycemic Traits, and Cerebrovascular Disease

A Mendelian Randomization Study

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Study Question

How do genetic predisposition to type 2 diabetes (T2D), hyperglycemia, insulin resistance, and pancreatic β-cell dysfunction influence the risks of stroke and other cerebrovascular diseases?

What Is Known and What This Paper Adds

Observational studies suggest that T2D, hyperglycemia, insulin resistance, and β-cell dysfunction independently contribute to the risk of cerebrovascular disease. This investigation's results indicate that genetic predisposition to T2D and hyperglycemia increase the risks of large artery and small vessel stroke.

Methods

For this 2-sample Mendelian randomization (MR) study, the investigators used data from multiple genome-wide association studies of individuals of European ancestry to identify single-nucleotide polymorphisms (SNPs) that predicted T2D risk (n = 74,124 cases and 824,006 controls), HbA1c levels (n = 421,923 people), fasting glucose levels (n = 133,010 people), insulin resistance (n = 108,557 people), or β-cell dysfunction (n = 16,378 people). The investigators then calculated MR estimates for the effects of those SNPs on the risks of ischemic stroke (IS; n = 60,341 cases and 454,450 controls) and intracerebral hemorrhage (ICH; n = 1,545 cases and 1,481 controls). They then pooled the individual MR estimates with random-effects inverse-variance–weighted meta-analyses. The pooled MR estimates were the primary outcomes.

Results and Study Limitations

Genetic predispositions to T2D and higher HbA1c levels predicted greater risks of any IS and of large artery stroke and small vessel stroke in particular. Genetic predispositions to insulin resistance predicted greater risks of large artery and small vessel stroke, and genetic predispositions to β-cell dysfunction predicted greater risks of small vessel stroke and ICH. These findings are Class II evidence that genetic predispositions to T2D and higher HbA1c levels predict elevated risks of large artery and small vessel IS. A limitation of the present study is that MR analyses quantify the effects of lifetime exposures to traits of interest, and this complicates efforts to draw implications concerning the effects of clinical interventions. The reliance on data from people of European ancestry may limit generalizability.

Table Effects of Genetic Predisposition to T2D and Higher HbA1c

Stroke subtype	OR (95% CI) for stroke subtype per 1-log-increment in genetically predicted odds for T2D	OR (95% CI) for stroke subtype per 1%-increment in genetically predicted HbA1c levels
Any IS	1.11 (1.08–1.13)	1.36 (1.21–1.53)
Large artery IS	1.22 (1.17–1.28)	2.06 (1.60–2.66)
Cardioembolic stroke	1.05 (1.01–1.09)	1.25 (1.02–1.52)
Small vessel IS	1.18 (1.13–1.23)	1.85 (1.50–2.27)
ICH	1.09 (0.97–1.23)	0.92 (0.52–1.64)

Study Funding and Competing Interests

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