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DOI: <https://doi.org/10.1212/WNL.0000000000011557>

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ZORA URL: <https://doi.org/10.5167/uzh-210370>

Journal Article

Accepted Version

Originally published at:

Arnold, Markus; Gill, Dipender; Katan, Mira (2021). A Good Start to Shed More Light on the Relationship Between Glycemic Traits, Diabetes Mellitus, and Cerebrovascular Disease. *Neurology*, 96(13):602-603.

DOI: <https://doi.org/10.1212/WNL.0000000000011557>

A good start to shed more light on the relationship between glycemic traits, diabetes mellitus and cerebrovascular disease

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Word count: 962

Number of references: 9

Author Contribution: MA, MK, DG: Drafting/revising the manuscript

Disclosures: DG is employed part-time by Novo Nordisk, outside of this work. The remaining authors have no conflicts of interest to declare.

Ischemic stroke is a heterogeneous disease with numerous underlying pathologies contributing to its pathogenesis. The association between diabetes mellitus and ischemic stroke is well-established. Population based studies suggest that diabetes is one of the most important modifiable risk-factor for stroke. Having type 2 diabetes mellitus (T2DM) alone increases the risk of stroke 1.5 to ~~4-fold~~[4-fold](#) and is associated with unfavorable clinical outcomes ¹. On the other hand, individuals presenting with ischemic stroke are more likely to have diabetes with a prevalence reaching nearly 30% ². The relative contribution of diabetes to the risk of different ischemic stroke subtypes is however less well known. Further, there is conflicting evidence on the association of hyperglycemia in the pre-diabetic range with an elevated stroke risk ^{3,4}. Whether, ~~other~~[other](#) metabolic markers of pathogenic states such as insulin resistance or beta cell dysfunction alone can be considered as risk-factors for ischemic stroke is still a matter of debate.

Using observational studies to disentangle the causal effect of diabetes and pre-diabetic metabolic disorders on stroke risk is challenging. Diabetes is highly correlated with other cerebrovascular risk factors, such as hypertension, dyslipidemia and obesity, and thus, the results from ~~population based~~[population-based](#) studies are prone to possible confounding ⁵. Mendelian randomization (MR) can help to overcome the problem of confounding by using genetic variant as instrumental variables to explore the effects of modifiable exposures on disease outcomes. MR is based on the principle that these genetic variants are randomly allocated at conception, thus their distribution is unrelated to factors that may bias observational associations, such as environmental confounding factors. However, as with any method, MR also carries limitations, and challenges in interpretation may occur. Factors such as pleiotropy (if for example the studied variants have effects on the outcomes that are unrelated to the exposure) may hamper the interpretation of results. Furthermore, genetic

variants proxy the lifelong effects of modifying an exposure, which may not mimic a clinical intervention.

In this issue of *NEUROLOGY*, Georgakis, et al. investigated the effect of genetic predisposition to T2DM, elevated HbA1c and higher fasting glucose levels as well as predisposition to insulin resistance and beta-cell dysfunction with risk of ischemic stroke. More importantly, the authors included additional analysis ~~in regards to~~in regard to etiological stroke subtypes assessed by the TOAST criteria (i.e. large artery arteriosclerosis (LAA), small vessel disease (SVD) and cardioembolism (CE)). Further, they also assessed possible causal effects on phenotypes corresponding to different etiological subgroups of stroke, including carotid atherosclerosis, imaging markers of cerebral white matter integrity and brain atrophy.⁶

The authors performed two-sample Mendelian randomization, which used data from genome-wide association studies (GWAS) that were performed by different consortia to obtain genetic association estimates for the considered exposures and outcomes. Genetic proxies were obtained for liability to T2DM, HbA1c, fasting glucose, insulin resistance and beta-cell dysfunction, and their association with risk of ischemic stroke and related traits was studied. Importantly, the authors performed multiple sensitivity ~~analysis~~analyses to test the validity of their MR assumptions, including weighted median MR, MR-Egger and outlier-corrected MR-PRESSO.

As a key finding of the analysis, they provide high-level evidence for a causal relationship between liability to T2DM and risk of any ischemic stroke and specific ischemic stroke subtypes, namely large artery arteriosclerosis (LAA) stroke and small vessel stroke (SMD).

Further, the authors showed that genetic predisposition to higher HbA1c levels was associated with LAA and SVD stroke among diabetes-free individuals. Additional analysis confirmed a causal relationship of liability to T2DM and elevated HbA1c with specific stroke-

related phenotypes (carotid plaque, and grey matter and total brain volume reduction), further strengthening the internal validity of the findings. Of interest are the result regarding the association of genetic predisposition to higher HbA1c levels with an elevated stroke risk, as they suggest that improved glycemic control may reduce stroke risk. However, these results are contrary to findings from several large randomized trials testing intensive glucose lowering therapies in patients with diabetes, which failed to provide clear evidence of a reduction in stroke risk ⁷. This discrepancy may be related to the speed and means of glycemic control. Current ADA guidelines recommend maintaining HbA1c < 7.0% in most adults (a target which is mainly based on studies showing risk reduction in microvascular complications, not for major cardiovascular events) ⁸. It remains to be determined if lower HbA1c levels may be beneficial for specific subgroups of patients.

In a second part of the manuscript, the authors demonstrated that a genetic predisposition to insulin resistance and beta-cell dysfunction, both pathologic states which may induce hyperglycemia at some point in time, are differentially associated with stroke subtypes. They showed that instruments for insulin resistance were associated with a higher risk for LAA and SVD stroke, while instruments for beta-cell dysfunction were only associated with a higher risk for SVD stroke. These findings are especially interesting because they may contribute to a deeper understanding of the underlying mechanisms leading to an elevated stroke risk in patients with diabetes and/or a pre-diabetic metabolic state. This could help in hypothesis formation in regard to different effects on risk of different subtypes of stroke of antidiabetic medications specifically targeting those mechanisms. Most recently, a meta-analysis of newer antidiabetic drugs suggested that pioglitazone as well as the GLP-1RA class drugs may reduce stroke risk in patients with diabetes or insulin resistance by mechanisms not directly dependent on glucose-lowering. ⁹ These findings should prompt more research in regard to

differential effects of antidiabetic drugs on risk of different stroke subtypes. In summary, there are still significant knowledge gaps regarding diabetes or pre-diabetic metabolic disorders and risk of stroke that need further investigation. The use of human genetics can help clarify the causal effects of long-term exposure to subtle changes of modifiable risk factors and thus, may contribute to filling those gaps.

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