Background and aims: Chronic kidney disease (CKD) increases the risk of stroke, but the extent through which this association is mediated by hypertension is unknown. We leveraged large-scale genetic data to explore causal relationships between CKD, hypertension and cerebrovascular disease phenotypes.
Methods: We used data from genome-wide association studies (GWAS) of European ancestry to identify genetic proxies for kidney function (CKD diagnosis, estimated glomerular filtration rate [eGFR], and urinary albumin-to-creatinine ratio [UACR]), systolic blood pressure (SBP), and cerebrovascular disease (ischaemic stroke and its subtypes, and intracerebral haemorrhage [ICH). We then conducted univariable, multivariable and mediation Mendelian randomization (MR) analyses to investigate the effect of kidney function on stroke risk and the proportion of this effect mediated through hypertension.
Results: Univariable MR analysis revealed associations between both lower eGFR (OR per 1-log decrement=2.10; 95% CI, 1.25-3.53) and higher UACR (OR per 1-log increment=2.34, 1.11-4.94) and risk of large artery stroke (LAS), as well as between higher UACR and risk of ICH (OR=5.19, 1.02-26.29). The associations between lower eGFR and LAS (OR=2.51, 1.53-4.13) and between higher UACR and ICH (OR=3.78, 1.39-10.32) remained significant in multivariable MR analysis with only a small proportion of the total effects mediated by SBP (1.8% and 7.8%, respectively). However, a large proportion of the other relationships between renal function and ischaemic subtypes were mediated by SBP.
Conclusions: Our results demonstrate an independent causal effect of impaired kidney function, as assessed by decreased eGFR and increased UACR, on LAS and ICH risk, even when controlled for SBP.
Disclosure: No

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Scientific Communications 14 - Genetics, Omics and Biomarkers

THE GUT MICROBIOME INFLUENCES THE RISK OF ACUTE ISCHEMIC STROKE: A MENDELIAN RANDOMIZATION STUDY

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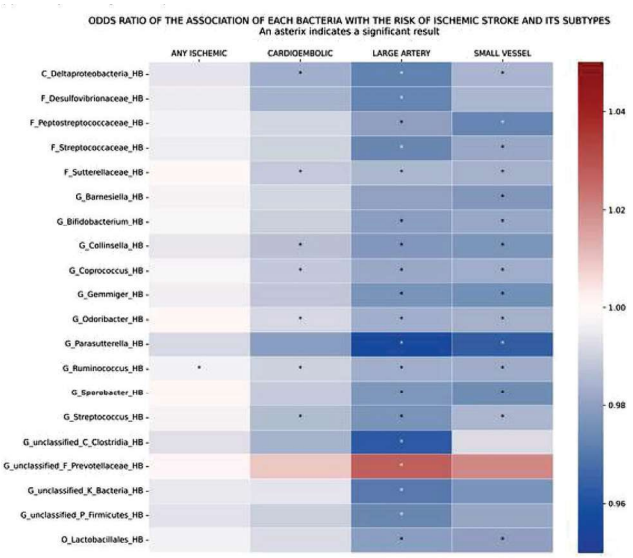
Background and aims: Recent evidence suggests that gut bacteria influence brain function through microbial compounds, metabolites, and endotoxins. However, the relationship between the gut flora and cerebrovascular disease remains understudied. We conducted a genetic study to assess the relationship between the concentration of gut bacteria and the risk of acute ischemic stroke.
Methods: We performed a two-sample Mendelian Randomization (MR) study using summary statistics from the Flemish Gut Flora Project and the MEGASTROKE consortium. We constructed 95 genetic instruments using single-nucleotide polymorphisms (SNPs) associated with microbial traits in the largest microbiome-wide GWAS. We then conducted summary statistics-based MR to test the association between each of these microbial traits and the risk of ischemic stroke or any of its subtypes: cardioembolic, large artery, and small vessel stroke. We used Bonferroni correction, adjusting for the 95 exposures x 4 traits = 380 tests performed.
Results: Our primary analysis using the inverse-variance weighted MR method identified 20 microbial traits significantly associated with the risk of developing at least one ischemic stroke subtype (Figure). Of these, G_Ruminococcus was associated with all four outcomes. Most of these associations were supported by other more conservative MR methods in secondary analyses.
Conclusions: Genetic analyses show that the gut microbiome influences the risk of developing an ischemic stroke. Further analyses are needed to validate these results and identify the mediating mechanisms. Because the gut microbiota can be easily modified with well-tolerated interventions, this avenue of research offers an appealing opportunity to design novel preventive treatments for stroke.



Disclosure: No

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Scientific Communications 14 - Genetics, Omics and Biomarkers

GENETICALLY PREDICTED ON-STATIN LDL RESPONSE IS ASSOCIATED WITH HIGHER RISK OF INTRACEREBRAL HEMORRHAGE

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Background and aims: It remains unclear whether stain-induced LDL lowering influences risk of intracerebral hemorrhage (ICH). We explored whether genetically predicted LDL response to statins is associated with ICH risk.
Methods: Utilizing genomic data from randomized trials, we derived a 35-SNP score of on-statin LDL response and tested it in the population-based UK Biobank (UKB). We extracted statin drug and dose data from primary care data on a subset of UKB participants covering a 29 year period (224,974 individuals). We validated the effects of the genetic score on longitudinal LDL measurements with generalized mixed models and explored associations with incident ICH using Cox regression analysis.
Results: Statins were prescribed at least once to 70,693 (31%) of the cohort (mean 57 years, 55% females). Among statin users, mean LDL decreased by 3.0 mg/dl per year (95% CI: [-3.02, -2.97]) over follow-up. A higher genetic score of statin response (one SD increment) was associated with significant reductions in LDL levels (-0.09 mg/dl per year, [-0.13, -0.05]) and showed concordant effects on other lipid traits as statin use. Over a 14-year follow-up period, a higher genetically predicted statin response among statin users associated with higher ICH risk (HR per one SD increment 1.19, 95% CI [1.06, 1.33]) even after adjusting for statin dose. Among statin non-users, there was no association with ICH risk (p=0.89).
Conclusions: On-statin genetically predicted LDL response is associated with ICH, thus providing further support for the hypothesis that larger LDL declines are causally associated with ICH risk.
Disclosure: No