Stroke

BRIEF REPORT

Metabolic Traits and Stroke Risk in Individuals of African Ancestry

Mendelian Randomization Analysis

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BACKGROUND AND PURPOSE: Metabolic traits affect ischemic stroke (IS) risk, but the degree to which this varies across different ethnic ancestries is not known. Our aim was to apply Mendelian randomization to investigate the causal effects of type 2 diabetes (T2D) liability and lipid traits on IS risk in African ancestry individuals, and to compare them to estimates obtained in European ancestry individuals.

METHODS: For African ancestry individuals, genetic proxies for T2D liability and circulating lipids were obtained from a meta-analysis of the African Partnership for Chronic Disease Research study, the UK Biobank, and the Million Veteran Program (total N=77 061). Genetic association estimates for IS risk were obtained from the Consortium of Minority Population Genome-Wide Association Studies of Stroke (3734 cases and 18 317 controls). For European ancestry individuals, genetic proxies for the same metabolic traits were obtained from Million Veteran Program (lipids N=297 626, T2D N=148 726 cases, and 965 732 controls), and genetic association estimates for IS risk were obtained from the MEGASTROKE study (34 217 cases and 406 111 controls). Random-effects inverse-variance weighted Mendelian randomization was used as the main method, complemented with sensitivity analyses more robust to pleiotropy.

RESULTS: Higher genetically proxied T2D liability, LDL-C (low-density lipoprotein cholesterol), total cholesterol and lower genetically proxied HDL-C (high-density lipoprotein cholesterol) were associated with increased risk of IS in African ancestry individuals (odds ratio per doubling the odds of T2D liability [95% CI], 1.09 [1.07–1.11]; per standard-deviation increase in LDL-C, 1.12 [1.04–1.21]; total cholesterol: 1.23 [1.06–1.43]; HDL-C, 0.93 [0.89–0.99]). There was no evidence for differences in these estimates when performing analyses in European ancestry individuals.

CONCLUSIONS: Our analyses support a causal effect of T2D liability and lipid traits on IS risk in African ancestry individuals, with Mendelian randomization estimates similar to those obtained in European ancestry individuals.

Key Words: cholesterol ■ ischemic stroke ■ lipid ■ mortality ■ risk factor

Stroke is a major contributor to morbidity and mortality globally, responsible for over 5.5 million deaths per year.[1] The global burden of stroke disproportionately affects low and middle-income countries, with over 85% of all stroke deaths occurring in these nations.[2] Although stroke was historically seen as a disease

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Nonstandard Abbreviations and Acronyms

COMPASS	Consortium of Minority Population Genome-Wide Association Studies of Stroke
HDL-C	high-density lipoprotein cholesterol
IS	ischemic stroke
LDL-C	low-density lipoprotein cholesterol
MR	Mendelian randomization
T2D	type 2 diabetes

affecting affluent regions, Africa now reports the highest incidence of stroke and the highest case fatality in the world.[3] There is thus a growing need to understand the risk factors for stroke in African ancestry individuals.

Large multinational observational studies have established metabolic traits, such as dyslipidemia and type 2 diabetes (T2D), as risk factors for stroke.[4] However, it is not clear how the effects of these risk factors vary between individuals of different genetic ancestries. Ethnic variation in stroke risk factors has previously been explored in observational studies, but these are liable to confounding and reverse causation, limiting the ability to make causal inferences.[5]

To address these issues, Mendelian randomization (MR) employs genetic variants as proxies for an exposure to study its effect on an outcome.[6] MR is analogous to a randomized controlled trial with individuals being randomly assigned genetic variants at conception, minimizing confounding and reverse causality. MR has been widely used to examine risk factors for stroke in European populations.[7–9] However, similar studies in other ethnic groups have not been undertaken, largely due to paucity of genetic data on individuals of non-European populations. The publication of the COMPASS (Consortium of Minority Population Genome-Wide Association Studies of Stroke)[10] provides an opportunity to conduct MR studies in people of African ancestry.

Here, we used MR to investigate the causal effect of lipid traits and T2D liability on ischemic stroke (IS) risk in African ancestry populations and compared estimates to those obtained in individuals of European ancestry.

METHODS

Ethical Approval, Data Availability, and Reporting

We used summary data from published studies that obtained relevant ethical approval and participant consent. These data are available on request to the original studies. The analysis codes are available on request to the corresponding author, and all results are presented in the main article or its Data Supplement.

Genetic Association Estimates

We used 2-sample MR to investigate the associations of genetically proxied levels of five metabolic traits with IS risk: T2D liability, HDL-C (high-density lipoprotein cholesterol), LDL-C (low-density lipoprotein cholesterol), total cholesterol, and triglycerides. Genetic association estimates were obtained from publicly available summary statistics of genome-wide association studies (GWAS) detailed in Methods in the Data Supplement. Briefly, genetic associations for metabolic traits in African ancestry individuals were obtained from a meta-analysis of the African Partnership for Chronic Disease Research, self-reported Black participants in the UK Biobank, and African ancestry individuals in the Million Veteran Program, with a total of ≈77 000 participants. The genetic associations with the risk of IS were obtained from COMPASS, a GWAS meta-analysis of 3734 cases and 18 317 controls of African ancestry from 13 cohorts.[10]

For European ancestry individuals, genetic associations for the metabolic traits were obtained from the Million Veteran Program (T2D liability, 148 726 cases, 965 732 controls; lipids N=297 626) via database of Genotypes and Phenotypes.[11,12] The genetic associations with the risk of IS were obtained from the MEGASTROKE consortium (34 217 cases, 406 111 controls, Methods in the Data Supplement).[13] All genetic associations for both ancestries were adjusted for age, sex, and population stratification.

Mendelian Randomization Analysis

For each exposure, we identified ancestry-specific instrumental variables for MR, based on GWAS on the exposure in the relevant ethnic group: variants that associated with the exposure at $P<5\times10^{-8}$ and were available in the outcome dataset were clumped at $r^2<0.01$ within ±500 kb, using the corresponding reference ancestry in 1000 Genomes Project. The remaining variants were used as instrumental variables for MR.

To measure instrument strength, we calculated the variance explained and F statistics for the individual variants. To evaluate statistical power, we calculated the minimum detectable odds ratio (OR) for each exposure at power=0.8, given the exposure GWAS sample size, total variance explained by the genetic instruments (calculated as the sum of the variances explained by each individual instrument), and type I error rate=0.05.[14]

The main analyses estimating the association of genetically proxied levels of each exposure with risk of IS were performed using the random-effects inverse-variance weighted method.[15] We examined the differences in the MR estimates between populations of European and African ancestries using the propagation of error method. Further sensitivity analyses—namely MR-Egger, weighted median, weighted mode, and contamination mixture method—were conducted to assess the robustness of the results to violations in instrumental variable assumptions (Methods in the Data Supplement).[15] MR effect estimates are expressed as ORs per SD increase in genetically predicted levels of the exposure for continuous traits, and per doubling the odds (log-OR per unit change in exposure log-odds multiplied by $\log_e[2]$) in the exposure for T2D.

RESULTS

The demographics for African ancestry individuals in UK Biobank are given in Table 1, and the demographics for

Table 1. Demographics for African Ancestry Individuals in UKBiobank, N=6614

Variable	Median (interquartile range) or percentage
Age at recruitment in years	51.6 (46.3–58.9)
Female sex	59.0%
Type 2 diabetes	9.0%
Body mass index in kg/m^2	28.8 (25.9–32.4)
Low-density lipoprotein cholesterol in mmol/L	3.3 (2.7–3.8)
High-density lipoprotein cholesterol in mmol/L	1.4 (1.2–1.7)
Triglycerides in mmol/L	1.0 (0.7–1.4)
Total cholesterol in mmol/L	5.2 (4.5–5.9)

other considered populations can be found in their original publications.[10–13,16] Table 2 provides minimum detectable ORs for MR analyses, and the association estimates for the variants used as instrumental variables and their individual *F* statistics are given in Table I in the Data Supplement.

In the MR analysis of African ancestry populations, higher genetically proxied T2D liability, LDL-C, and total cholesterol and lower genetically proxied HDL-C were associated with increased risk of IS (Figure; Table II in the Data Supplement). The MR estimate for triglycerides was similar in magnitude to the estimates for total cholesterol, LDL-C, and inversely to HDL-C, however with 95% CI for OR overlapping the null.

In European ancestry individuals, higher genetically proxied T2D liability, LDL-C, and lower genetically proxied HDL-C were associated with increased risk of IS (Figure; Table II in the Data Supplement). The effect estimate for genetically proxied total cholesterol was similar in the absolute value to other traits, however, with 95% CI for the OR marginally overlapping the null.

The comparison of MR estimates between European and African ancestry populations showed no strong evidence for differences in the MR estimates. The point estimates were marginally larger in African ancestry individuals for all traits (Table III in the Data Supplement). The associations between genetically proxied metabolic traits with the risk of IS were mostly consistent in the sensitivity analysis, apart from the estimates for HDL-C and triglycerides in European ancestry populations which were shrunk towards the null in the sensitivity analyses, implying some degree of horizontal pleiotropy (Table II and Figures I through VI in the Data Supplement).

DISCUSSION

This MR study found evidence for causal effects of lipid traits and T2D liability on IS risk for African ancestry individuals. When compared with the estimates obtained in European ancestry individuals, there was no evidence for marked differences in the effects.

These findings are of direct clinical relevance, as they support that optimization of these risk factors will be of benefit in reducing IS for all individuals, irrespective of ethnic background. However, although the effect of dyslipidemia and T2D on IS risk may be similar, it is also important to appreciate that the prevalence of these metabolic traits does vary considerably between different ethnic groups,[17] resulting in marked differences in the proportion of stroke that can be attributed to these risk factors.[18]

By leveraging large-scale genetic association data from African and European populations, we were able to investigate the comparative effects of T2D liability and lipid traits on stroke risk in these ethnic groups. The use of genetically proxied metabolic traits in MR approach offers robustness against environmental confounding and reverse causation that can hinder causal inference in observational studies. The findings were mostly

Table 2. Exposure Summary Data and Statistical Power Calculations

Ancestry	Trait	Sample size	Variants (N)	Variance explained, %	Detectable odds ratio*
African	Type 2 diabetes	24 646 cases, 31 446 controls	22	NA†	NA†
	High-density lipoprotein cholesterol	77 060	41	9.9	0.85
	Low-density lipoprotein cholesterol	77 060	71	21.4	1.11
	Total cholesterol	77 061	70	16.2	1.13
	Triglycerides	77 061	27	7.3	1.20
European	Type 2 diabetes	148 726 cases, 965 732 controls	557	NA†	NA†
	High-density lipoprotein cholesterol	215 551	225	12.4	0.96
	Low-density lipoprotein cholesterol	215 551	145	10.4	1.05
	Total cholesterol	215 551	161	8.5	1.06
	Triglycerides	215 551	200	11.9	1.05

The sources for the summary data are detailed in the Data Supplement. NA indicates not applicable.
*Minimum detectable odds ratio per 1 SD change in the exposure, at 80% power and type I error rate=0.05.
†Variance explained and the minimal detectable odds ratio not estimated for type 2 diabetes because it is a binary exposure.

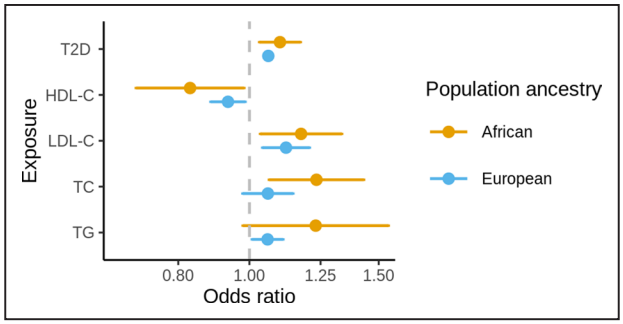

Figure. Forest plot showing the main Mendelian randomization estimates for the association between genetically proxied lipid traits and type 2 diabetes (T2D) liability with risk of ischemic stroke in African and European ancestry populations.

Estimates represent odds ratios and their 95% CIs for ischemic stroke risk per 1 SD increase in genetically predicted levels of the exposure. HDL-C indicates high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TC, total cholesterol; and TG, triglycerides.

consistent in sensitivity analyses more robust to the inclusion of pleiotropic variants, suggesting that this is unlikely to be a major source of bias.

The limitations of this work should be acknowledged. The statistical power may have been insufficient to identify small differences in the MR estimates between European and African ancestry populations. The binary categorization of individuals as either of European or African ancestry is an over-simplification and will not capture the wider genetic diversity of individuals within each group. Furthermore, there may also be a population effect that impacts the genetic associations for individuals of the same ancestry when considered in different contexts.[19] Genetic association estimates were pooled from studies of heterogeneous populations with varying demographics. Despite the adjustments for age, sex, and population stratification, population heterogeneity may introduce bias to the MR estimates. Summary statistics for the Million Veteran Program data were publicly available via database of Genotypes and Phenotypes only for variants with $P<10^{-4}$, and therefore, we were not able to conduct multivariable MR to investigate the mutually adjusted, direct effect of each considered cardiometabolic trait. Similarly, nor could we perform bidirectional MR to explore for reverse causality. We could not expand our analyses to other cardiometabolic traits, such as blood pressure or obesity, as sufficiently large GWAS summary statistics on these traits in African ancestry populations were not available to us. Finally, we were not able to examine the associations across different stroke subtypes, as subtype-specific GWAS summary statistics were not available in COMPASS.

In conclusion, our results are consistent with T2D liability and lipid traits having a similar effect on IS risk in both African and European ancestry populations. Optimization of these risk factors will be of benefit for reducing the population burden of IS.

ARTICLE INFORMATION

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Supplemental Materials

Expanded Methods
Online Tables I–III
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