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RESEARCH LETTER

Genetically Predicted Lipid Traits, Diabetes Liability, and Carotid Intima-Media Thickness in African Ancestry Individuals: A Mendelian Randomization Study

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Carotid intima-media thickness (cIMT) is a measure of atherosclerosis used to predict cardiovascular disease.[1] Lipid traits and type 2 diabetes (T2D) have been implicated in the pathogenesis of cIMT. Statins, which reduce low-density lipoprotein cholesterol (LDL-C), have been shown in a meta-analysis of randomized trials to slow cIMT growth or even reduce cIMT. However, most research into cIMT has been conducted in European ancestry individuals, and little is known about whether the same causal risk factors apply for African ancestry populations.

In this study, we investigated the relationship between lipid parameters and T2D with cIMT using inverse-variance weighted 2-sample Mendelian randomization (MR) analysis.[2] This method uses genetic variants as instrumental variables to study the effect of modifying an exposure. The random allocation of genetic variants at conception means that MR is less susceptible to the environmental confounding and reverse causation that can hinder causal inference in traditional epidemiological studies. Since the standard MR method can suffer from pleiotropy, we also perform 2 sensitivity analyses, the MR-Egger and weighted median methods. Since the lipid traits are correlated, we also performed a multivariable MR analysis. This analysis uses genetic variants associated with any of the lipid exposures to estimate the independent effect of each lipid exposure on the outcome.

All data and code used in this study are available upon reasonable request from the corresponding author. Only summary data were used, and ethical approval had been obtained in the original studies. Genetic association estimates for lipid traits and T2D were obtained from published data from the Million Veterans Program for both African (N=53 503–57 280) and European ancestry (N=210 967–1 042 540) individuals.[3,4] For cIMT, we used the study by Boua and colleagues for genetic association estimates of cIMT in African ancestry individuals (N=7894; we use mean-max cIMT; the average of the maximum cIMT from the left and right carotid arteries converted to micrometers), and replicated the genome-wide association study analysis by Boua and colleagues in UK Biobank for European ancestry individuals (N=35 175) using data fields 22 672, 22 675, 22 678, and 22 681, which are measures of cIMT at 2 different angles across the left and right carotid arteries (right 150°, right 120°, left 210°, and left 240°). The outcome genome-wide association studies are corrected for age, sex, and the first 8 principal components. We selected ancestry-specific independent (pair-wise linkage disequilibrium $r^2<0.01$ using the corresponding reference ancestry from the 1000 Genomes Project) genome-wide significant ($P<5\times10^{-8}$) genetic variants for high-density lipoprotein cholesterol, LDL-C, triglycerides, and T2D. There was no participant overlap anticipated in the exposure and outcome data.

Key Words: ancestry ■ cardiovascular disease ■ carotid intima-media thickness ■ diabetes ■ ethnicity ■ lipids ■ Mendelian randomization

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Nonstandard Abbreviations and Acronyms

cIMT	carotid intima-media thickness
LDL-C	low-density lipoprotein cholesterol
MR	Mendelian randomization
T2D	type 2 diabetes

In the univariate analyses, genetically predicted LDL-C levels are significantly associated with cIMT in both African and European individuals (Figure). Genetically predicted levels of high-density lipoprotein cholesterol are significantly associated with cIMT in Europeans, but not in the African ancestry analysis. For triglycerides, we do not see a significant association with cIMT for either ancestry. For T2D liability, we observe a significant association with cIMT

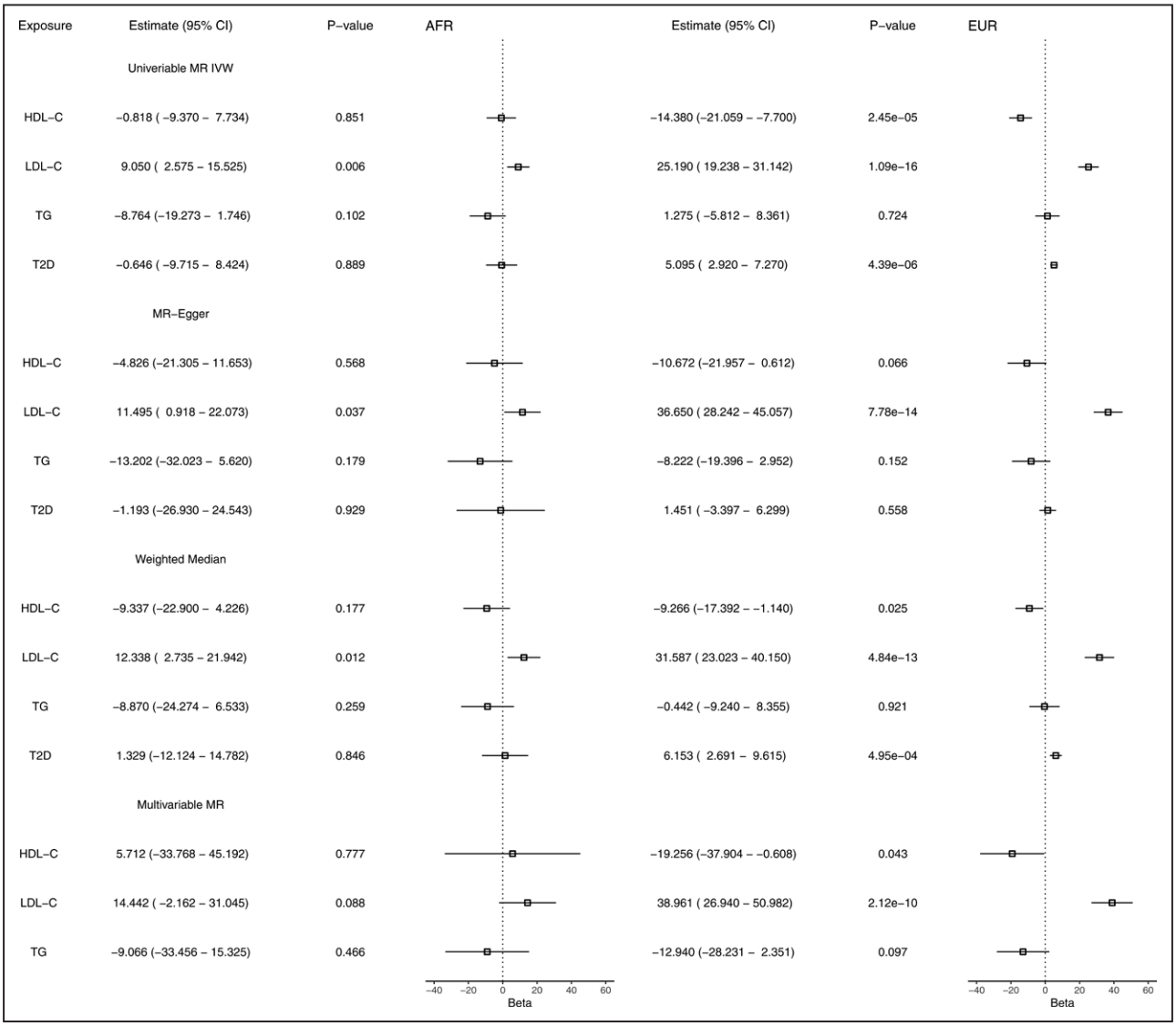

Figure. Associations between genetically predicted lipid traits, type 2 diabetes liability, and carotid intima-media thickness from univariable and multivariable Mendelian randomization analyses in African and European ancestry individuals. Estimates (95% CI) represent the estimated increase in carotid intima-media thickness (measured in micrometers) per SD increase in genetically predicted levels of the lipid trait or per unit increase in log odds of type 2 diabetes. For African individuals, the genetic variants explained 13.2% of the variance in LDL-C, 8.4% in HDL-C, and 7.8% in TG. For European individuals, the corresponding values were 7.4% for LDL-C, 9.0% for HDL-C, and 5.5% for TG. The shared SNPs across both ancestries explained 0.18% of the variance in HDL, 0.19% in LDL, and 0.01% in TG for European ancestry individuals, while the corresponding values for Africans were 0.19% for HDL, 0.16% for LDL, and 0.02% for TG. Number of SNPs=150 (HDL-C), 113 (LDL-C), 133 (TG), and 412 (T2D) in Europeans while in Africans number of SNPs=55 (HDL-C), 74 (LDL-C), 32 (TG), and 21 (T2D). No proxy SNPs were used. Estimated using univariable MR IVW, MR-Egger, Weighted median and Multivariable MR. The genetic variants used in the analyses are available at https://zenodo.org/record/7229645. AFR indicates African; EUR, European; HDL-C, high-density lipoprotein cholesterol; IVW, inverse-variance weighted; LDL-C, low-density lipoprotein cholesterol; MR, Mendelian randomization; TG, triglycerides; and T2D, type 2 diabetes.

in Europeans, but not in Africans. The sensitivity analyses using MR-Egger and the weighted median provide consistent results. MR-Egger showed no evidence of pleiotropic bias (intercept $P>0.05$). In the multivariable MR analyses, we observe that genetically predicted LDL-C levels are significantly associated with cIMT in European individuals. In African ancestry individuals, the multivariable MR results for LDL-C identify an association in the same direction, although not reaching conventional significance levels.

Limitations of our study were that we used different sources for our outcome data, with different imaging software. This, combined with the fact that cIMT tends to be larger on average in African ancestry individuals makes the comparison of effect size estimates difficult across ancestries. There may be differences in the allele frequencies and linkage disequilibirum between the exposure and outcome populations, as the exposure data contains an admixed population. However, given that most African-Americans are of West-African origin, this differences might not be significant enough to bias the estimate. Another potential issue is a lack of power, especially in the African ancestry individuals, as represented by the wider CIs of the MR estimates. This may explain the discrepancy in significant associations identified between European and African ancestry populations.

This MR study provides evidence to support that LDL-C is a causal risk factor for cIMT in both European and African ancestry individuals. It also provides evidence that T2D is a risk factor for cIMT in Europeans, although we did not find evidence to support this in African ancestry individuals. This discrepancy may in part be attributable to limited statistical power. We found no evidence that there is a difference between European and African ancestry individuals in the role of lipid traits and T2D liability in affecting cIMT. These data are consistent with the risk factor optimization strategies used to tackle atherosclerosis in European ancestry populations equally applying to African ancestry populations.

ARTICLE INFORMATION

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Disclosures

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