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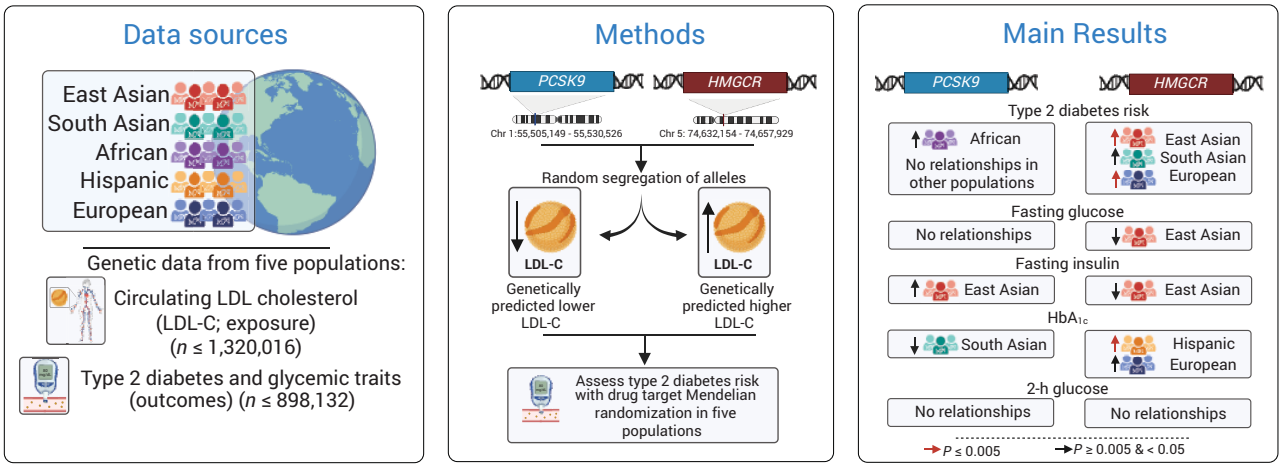
Diabetes 2025;74(1):120–130 | https://doi.org/10.2337/db24-0451



Multiomic Mendelian Randomization Study Investigating the Impact of PCSK9 and HMGCR Inhibition on Type 2 Diabetes Across Five Populations

Daniel B. Rosoff,[1–3] Josephin Wagner,[1] Jeesun Jung,[1] Pal Pacher,[4] Constantinos Christodoulides,[2] George Davey Smith,[3] David Ray,[2,5] and Falk W. Lohoff[1]

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The prevalence of type 2 diabetes (T2D) varies among populations of different races/ethnicities. The influence of genetically proxied LDL cholesterol lowering through proprotein convertase subtilisin/kexin 9 (PCSK9) and HMG-CoA reductase (HMGCR) on T2D in non-European populations is not well established. A drug target Mendelian randomization approach was used to assess the effects of PCSK9 and HMGCR inhibition on T2D risk and glycemic traits in five populations: East Asian (EAS), South Asian (SAS), Hispanic (HISP), African (AFR), and Europe (EUR). Our study did not find relationships between genetically proxied PCSK9 inhibition and T2D risk in the EAS (odds ratio [OR] 1.02; 95% CI 0.95–1.10), SAS (1.05; 0.97–1.14), HISP (1.03; 0.94–1.12), or EUR population (1.04; 0.98–1.11). However, in the AFR population, primary analyses suggested an increased risk of T2D resulting from PCSK9 inhibition (OR 1.53; 95% CI 1.058–2.22; $P = 0.024$), although this was not supported in sensitivity analyses. Genetically proxied HMGCR inhibition was associated with an increased risk of T2D in SAS (OR 1.44; 95% CI 1.30–1.61; $P = 9.8 \times 10^{-12}$), EAS (1.36; 1.22–1.51; $P = 4.2 \times 10^{-10}$), and EUR populations (1.52; 1.21–1.90; $P = 3.3 \times 10^{-4}$). These results were consistent across various sensitivity analyses, including colocalization, indicating a robust finding. The findings indicate a neutral impact of long-term PCSK9 inhibition on T2D and glycemic markers in most non-EUR populations, with a potential increased risk in AFR cohorts. By contrast, HMGCR inhibition increased the risk of T2D in SAS, EAS, and EUR cohorts, underscoring the need to consider diversity in genetic research on metabolic diseases.

ARTICLE HIGHLIGHTS

- This study investigates the impact of lipid-lowering therapies, specifically proprotein convertase subtilisin/kexin 9 (PCSK9) and HMG-CoA reductase (HMGCR) inhibition, on type 2 diabetes (T2D) risk across diverse populations using Mendelian randomization analyses.
- We found no adverse effect of PCSK9 inhibition on T2D risk in the East Asian, South Asian, Hispanic, or European population, although weak evidence of increased risk was seen in the African population, which was not robust in sensitivity analyses.
- HMGCR inhibition was associated with a slight increase in T2D risk, consistent with previous findings, but the cardiovascular benefits of statin therapy likely outweigh this risk.

Type 2 diabetes (T2D) affects ∼410 million people worldwide (1), with prevalence differing significantly by region and race and ethnicity (2). For example, in the U.S., T2D prevalence in the Hispanic (HISP) population is nearly double that in the European (EUR) population (2). These differences highlight the need for a deeper understanding

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Received 29 May 2024 and accepted 9 October 2024

This article contains supplementary material online at https://doi.org/10.2337/figshare.27236181.

of T2D risk factors, molecular mechanisms, and treatment strategies across diverse populations (3).

T2D often coexists with cardiovascular disease (CVD), the leading cause of death in patients with T2D (4). Preventing CVD through lipid-lowering therapies, such as statins and proprotein convertase subtilisin/kexin 9 (PCSK9) inhibitors, is crucial in T2D management (5). Although statins have been linked to a modestly increased T2D risk in recent meta-analyses (6–8), the relationship between PCSK9 inhibition and T2D is less clear. Randomized controlled trial (RCT) data failed to find evidence of an adverse impact on T2D risk (9), and long-term efficacy and safety data are currently not available. Early drug target Mendelian randomization (MR) studies suggested that PCSK9 variants lower LDL cholesterol (LDL-C) but increase T2D risk (7), although more recent MR studies have not confirmed this (7). Most studies have focused on the EUR population, leaving the long-term effects of statin and PCSK9 inhibition on T2D in non-EUR populations unknown.

To address long-term safety concerns in non-EUR populations, we used summary-level genome-wide association study (GWAS) data from East Asian (EAS), South Asian (SAS), African (AFR), HISP, and EUR populations, performing drug target MR analyses to assess the impact of LDL-C lowering via PCSK9 variants on T2D risk and glycemic traits. We compared these estimates with those for LDL-C lowering by the statin target HMG-CoA reductase (HMGCR) (8). A multiomic approach was applied, using PCSK9 instruments based on LDL-C levels (10), circulating PCSK9 protein levels (10), and liver PCSK9 expression data (11) to model the effects of anti-PCSK9 monoclonal antibodies and inclisiran (12). Given preclinical findings suggesting pancreatic PCSK9 may influence β-cell LDLR expression and insulin secretion (13), we also analyzed the glycemic impact of pancreatic PCSK9 expression. These results will enhance our understanding of the long-term safety of PCSK9 and HMGCR inhibition in diverse populations and their efficacy for CVD management in the context of T2D, addressing health disparities caused by the underrepresentation of non-EUR populations in studies (14).

RESEARCH DESIGN AND METHODS

Figure 1 provides an overview of the study, which follows the STROBE guideline (STROBE checklist).

Data Sources

This study used only preexisting deidentified publicly accessible summary-level GWAS data. Details regarding sex, age, and other demographic groupings for these data sets are provided in the respective GWAS publications referenced in the manuscript (with links provided in Supplementary Table 1). Sex was not considered a factor in the statistical analysis. Furthermore, all contributing GWAS studies received institutional review board approval and informed consent from participants, in line with the Declaration of Helsinki.

For our exposure LDL-C data, we used GWASs of LDL-C levels from the 2021 Global Lipid Genetics Consortium (GLGC) LDL-C population-specific meta-analyses of AFR ($n \leq 94{,}623$), EAS ($n \leq 82{,}587$), SAS ($n \leq 40{,}472$), HISP ($n \leq 46{,}039$), and EUR populations ($n \leq 1{,}320{,}016$) (15). For T2D in EAS, SAS, and EUR populations, we used the Diabetes Meta-Analysis of Trans-Ethnic association studies (DIAMANTE) population-specific meta-analyses (EAS n = 433,540; SAS n = 49,492; EUR n = 898,132) (16). HISP and AFR data were not available in the DIAMANTE cohorts, and we used HISP T2D data (n = 10,106) from the Population Architecture using Genomics and Epidemiology study (17). Because a recent MR study evaluated the impact of lipids and lipid-lowering drug targets on T2D in the AFR population using results from the Million Veteran Program cohort (18), we used another independent AFR GWAS of T2D (N = 4,347) (19). We used GWAS data from the Meta-Analyses of Glucose and Insulin-Related Traits (MAGIC) Consortium (20) to evaluate the glycemic impact of lipid-lowering targets on HbA_{1c}, fasting glucose, fasting insulin, and 2-h glucose levels across five populations (2-h glucose data were unavailable for the SAS population). We also assessed the impact on insulin-stimulated glucose uptake in the EUR cohort using GWASs of the modified Stumvoll insulin sensitivity index (ISI) and insulin fold change (IFC) (21).

Instrumentation

To construct the PCSK9 and HMGCR instruments, we selected genetic variants within 100 kb on either side of gene boundaries that were associated with LDL-C levels (genome-wide significance $P < 5 \times 10^{-8}$) to proxy the primary physiologic response to pharmacologic inhibition of these targets (9). We clumped the *PCSK9* and *HMGCR* variants at linkage disequilibrium (LD) $r^2 \leq 0.2$ using a 250-kb window and the respective population-specific 1000 Genomes Project (1000G) reference panels (22). That is, for each population-specific analysis, we applied the corresponding reference panels from the 1000G: the EAS panel for EAS analyses, the SAS panel for SAS analyses, the AFR panel for AFR analyses, the HISP panel for HISP analyses, and the EUR panel for EUR analyses. For PCSK9, we also created instruments composed only of functional variants (the gain-of-function *R46L* [rs505151] and the loss-of-function *E670G* [rs11591147] (23)). Both *E670G* and *R46L* data were available for analysis in SAS, AFR, HISP, and EUR populations, whereas only *R46L* data were available in the EAS population because *E670G* information was not present in the EAS LDL-C GWAS data. Detailed information for each drug target instrument is shown in Supplementary Tables 2 and 3.

To further explore the impact of PCSK9 inhibition on T2D and glycemic traits, we conducted drug target MR analyses using expression quantitative trait loci (eQTL)

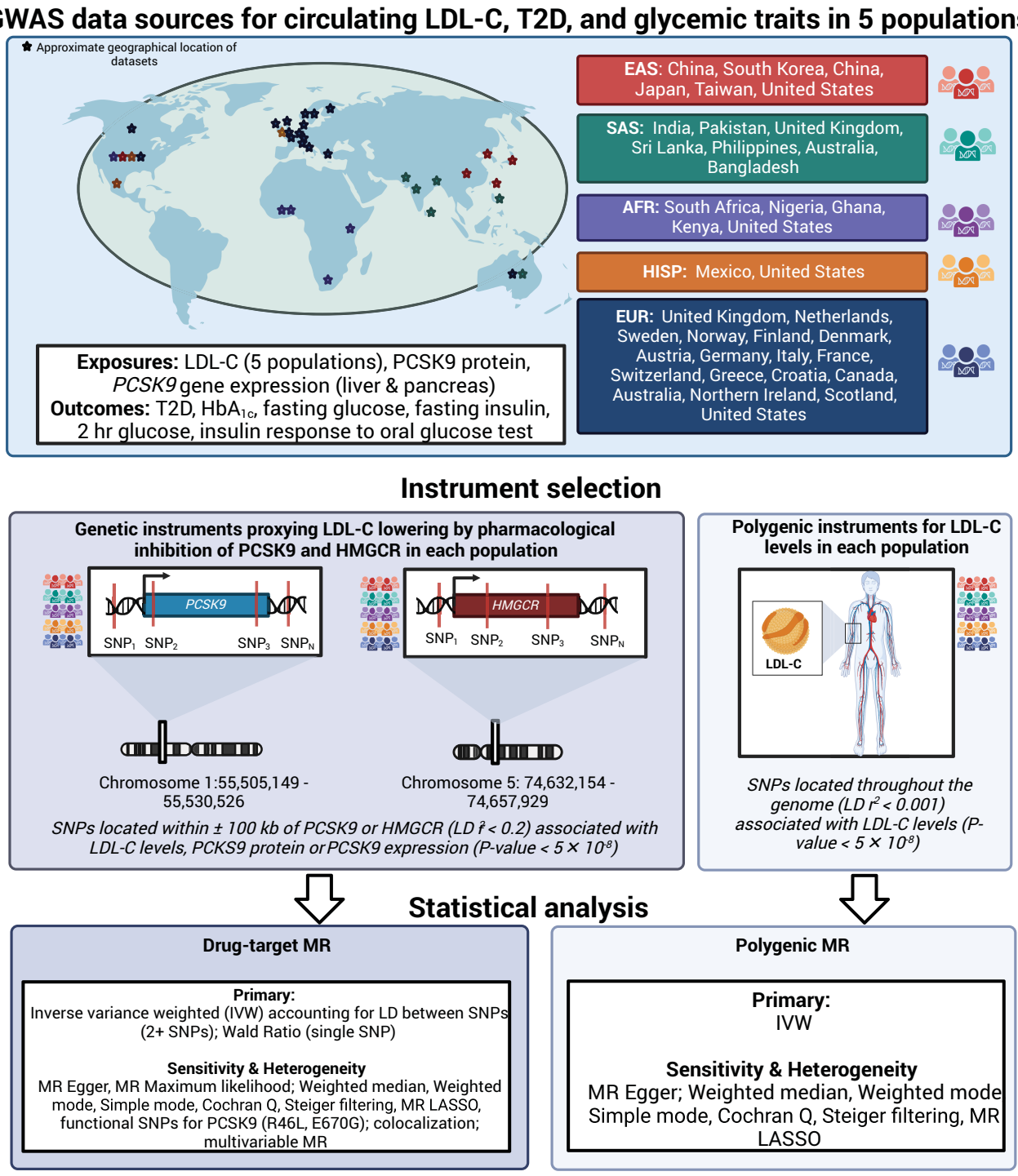

Figure 1—Study overview. Presented are details outlining instrument selection, data sources, and analysis plan. Top panel describes populations included in the study and the countries of origin for each data set (stars reflect the approximate geographic locations of the data sets included in the publicly available GWAS data). We constructed genetic instruments for PCSK9 and HMGCR extracting variants at the gene target locus (±100 kb) from population-specific summary-level GWAS data of circulating LDL-C levels (2021 GLGC meta-analysis GWAS for EAS, SAS, AFR, HISP, and EUR populations). For PCSK9, we also constructed alternative instruments composed of previously identified functional variants (*R46L*, *E670G*). Similarly, we constructed polygenic LDL-C instruments using conventionally genome-wide statistically significant ($P < 5 \times 10^{-8}$) variants across the genome that were conditionally independent at LD $r^2 < 0.001$. We obtained GWAS summary statistics for T2D and glycemic markers from each population and harmonized the exposure and outcome before performing MR. Additional information regarding GWAS data sources is presented in Supplementary Table 1. For the drug target MR genetically proxying LDL-C lowering via the PCSK9 and HMGCR loci, we used the IVW random effects method accounting for the correlation between the genetic variants, for 2+ SNP instruments, and for single SNP instruments, the Wald ratio, as main methods. We performed colocalization under the single- and multiple-variant models for exposure-outcome pairs that had MR estimates with P values <0.05.

from GTEx (version 8) and protein QTL (pQTL) from deCODE (N = 35,559) (10). We created tissue-specific *PCSK9* expression instruments using liver eQTL (n = 178) and pancreatic eQTLs (n = 243) (11). *cis-PCSK9* variants were selected and clumped using the same criteria as for LDL-C data-derived PCSK9 instruments. PCSK9 protein levels were measured in normalized units (10), and eQTL data were in transcripts per million (11). Because pQTL and eQTL data for non-EUR cohorts were unavailable, these analyses were limited to EUR T2D data and glycemic markers.

Change in LDL-C levels is the primary biomarker measured to assess the physiologic response to PCSK9 inhibition and statin therapy (24,25), and dyslipidemia has also been associated with T2D risk (20). Therefore, we investigated the relationships of circulating LDL-C and both T2D and glycemic traits in the five populations using polygenic LDL-C instruments. For the polygenic LDL-C instruments, we identified variants associated in respective population-specific 2021 GLGC GWASs of LDL-C levels at conventional genome-wide significance ($P < 5 \times 10^{-8}$) located throughout the genome. We clumped the variants at LD $r^2 \leq 0.001$ (10,000-kb window) using the appropriate 1000G reference panel (22). Information for polygenic LDL-C instruments is provided in Supplementary Table 2.

Statistical Analyses

The assumptions of MR also apply to drug target MR. These assumptions (Supplementary Fig. 1) include *1*) relevance (MR instruments must be associated with the exposure) *2*) exchangeability (MR instruments should not influence outcomes through pathways other than the exposure of interest), and *3*) exclusion restriction (instruments should not affect the outcome via an exposure-independent mechanism or influence another trait that could affect the outcome [no horizontal pleiotropy]) (26). To assess the relevance assumption, we calculated F statistics and R^2 for each population-specific variant, retaining only strong instruments (F statistic >10) (26). Complementary MR methods and alternative instruments were used to assess adherence to the exchangeability and exclusion restriction assumptions (26). For single-variant instruments, we used the Wald ratio. For instruments with two or more variants, we applied inverse-variance weighting (IVW) MR, MR Egger, and maximum likelihood methods, incorporating correlation matrices from the 1000G to account for LD between variants (27). These methods assessed the relationship of PCSK9 and HMGCR with outcomes and checked for potential MR assumption violations (26,27). Consistency across methods indicates unbiased estimates (26). For polygenic LDL-C and PCSK9 instruments (*R46L* and *E670G* variants), IVW was the main method for multi–single nucleotide polymorphism (SNP) instruments, with Wald ratio for single-SNP instruments. Complementary methods (MR Egger, weighted median, and weighted mode) were used as sensitivity analyses to ensure robustness and evaluate MR assumption violations, such as horizontal pleiotropy (26,27). We also conducted the MR Egger intercept test, Cochran Q test for heterogeneity, and MR Steiger test to check the causal direction (27). The MR LASSO method was used to remove outliers in polygenic LDL-C analyses.

Sensitivity Analyses: Multivariable MR With BMI

The MAGIC GWAS glycemic trait data were adjusted for BMI, which can introduce bias into the SNP associations and MR effect estimates (28). Multivariable MR (MVMR), which estimates the direct effect of multiple exposures on an outcome, can reduce this bias by incorporating the heritable covariate (BMI) used in the GWAS (29). To assess the robustness of glycemic trait analyses, we performed MVMR incorporating BMI genetics into the PCSK9, HMGCR, and polygenic LDL-C models using GWAS BMI data available for all populations (30–33). MVMR instruments were constructed using the same instrumentation strategies as outlined for the drug target and single-variable MR methods described above. We could not construct an MVMR instrument for PCSK9 in the SAS population to confirm the HbA_{1c} finding because the PCSK9 SAS instrument contained only a single SNP, making it impossible to perform these analyses.

Interpretation of MR Results

We report MR 95% CIs as odds ratios (ORs) for T2D risk and effect estimates for continuous glycemic traits, aligning estimates with the physiologic effects of PCSK9 inhibitors and statins by converting MR estimates to an SD lowering in LDL-C. Although we advise caution in relying solely on P values (34), we used a Bonferroni-corrected threshold of 0.005 (0.05/5 outcomes × two targets) to define strong evidence for a genetics-based relationship. Findings with P values between 0.005 and 0.05 were considered weak evidence. For MVMR sensitivity analyses, we used P = 0.05 and assessed consistency through overlapping CIs across MR methods.

Colocalization Analyses

For drug target estimates with $P < 0.05$, we performed colocalization analyses to assess shared causal variants between exposure and outcome in the *PCSK9* or *HMGCR* locus, evaluating the exclusion restriction MR assumption (35). The primary method involved testing for single or multiple causal variants using the coloc.abf function in the coloc R package. This function estimates posterior probabilities for five configurations of association between two traits, assuming one causal variant per trait: *1*) H0 (no association for either trait), *2*) H1 (association for trait 1), *3*) H2 (association for trait 2), *4*) H3 (both traits are associated with different variants) and *5*) H4 (both traits share a causal variant) (35). We included variants within ±100 kb of the loci and used default coloc priors (p_1, $p_2 = 1 \times 10^{-4}$ and $p_{12} = 1 \times 10^{-5}$). Low H3 and H4 probabilities with high H1 indicated underpowered analyses, possibly because of weak genetic signals (35). An alternative H4 was calculated by dividing H4 by the sum of H3 and H4, as used in

other drug target MR studies (35). If H3 >0.6 suggested multiple causal variants, we used SuSiE regression colocalization to confirm multiple shared variants (36). Colocalization evidence was defined by H4 or alternate H4 >0.60.

Data and Resource Availability

This study was conducted using publicly available data and codes that are accessible in public databases and open for public access. Links to GWAS sources and the lipid-lowering drug targets and polygenic lipid instruments are available in Supplementary Table 1. All analyses were completed with existing software packages. This study uses the TwoSampleMR (https://mrcieu.github.io/TwoSampleMR/), MendelianRandomization (https://cran.r-project.org/web/packages/MendelianRandomization/index.html) (37,38), and coloc R (https://github.com/chr1swallace/coloc) packages, with R software (version 4.0.3). BioRender.com was used to assist with figure generation. Inquiries can be directed to the corresponding author.

RESULTS

Instrument Strength

F statistics for PCSK9 and HMGCR drug target instruments in each population were strong (Supplementary Table 2). The average F statistics for LDL-C lowering ranged from 40.13 (SAS) to 279 (EUR) for *PCSK9* variants and from 55.3 (AFR) to 241.3 (EUR) for *HMGCR* variants. Alternate PCSK9 instruments (Supplementary Tables 3 and 4) were similarly robust, suggesting minimal weak instrument bias (39) (Supplementary Table 5). PCSK9 instruments explained an average of 1.5% of LDL-C variance (3.9% in EAS and 0.5% in SAS), whereas HMGCR instruments explained 0.36% on average (0.12% in AFR and 0.62% in EAS). Polygenic LDL-C instruments were also strong (Supplementary Table 2).

Impact of LDL-C Lowering by PCSK9 and HMGCR on T2D

Estimates of genetically proxied PCSK9 inhibition and T2D risk in SAS, EAS, HISP, and EUR populations included the null (Fig. 2 and Supplementary Table 6), aligning with results using functional variants (*R46L* and *E670G* in SAS, HISP, and EUR and *R46L* in EAS) (Supplementary Table 7). In the AFR population, there was weak evidence that LDL-C lowering via PCSK9 variants increased T2D risk (OR 1.53; 95% CI 1.058–2.22; P = 0.024), but this was inconsistent across instruments. In contrast, strong evidence in EAS and EUR populations indicated HMGCR inhibition increased T2D risk, with SAS showing weak evidence (OR 1.698; 95% CI 1.051–2.743; P = 0.031) (Fig. 2). HMGCR estimates were generally consistent across MR methods, with no evidence of pleiotropy from MR Egger intercept estimates. Regarding colocalization of the T2D results with

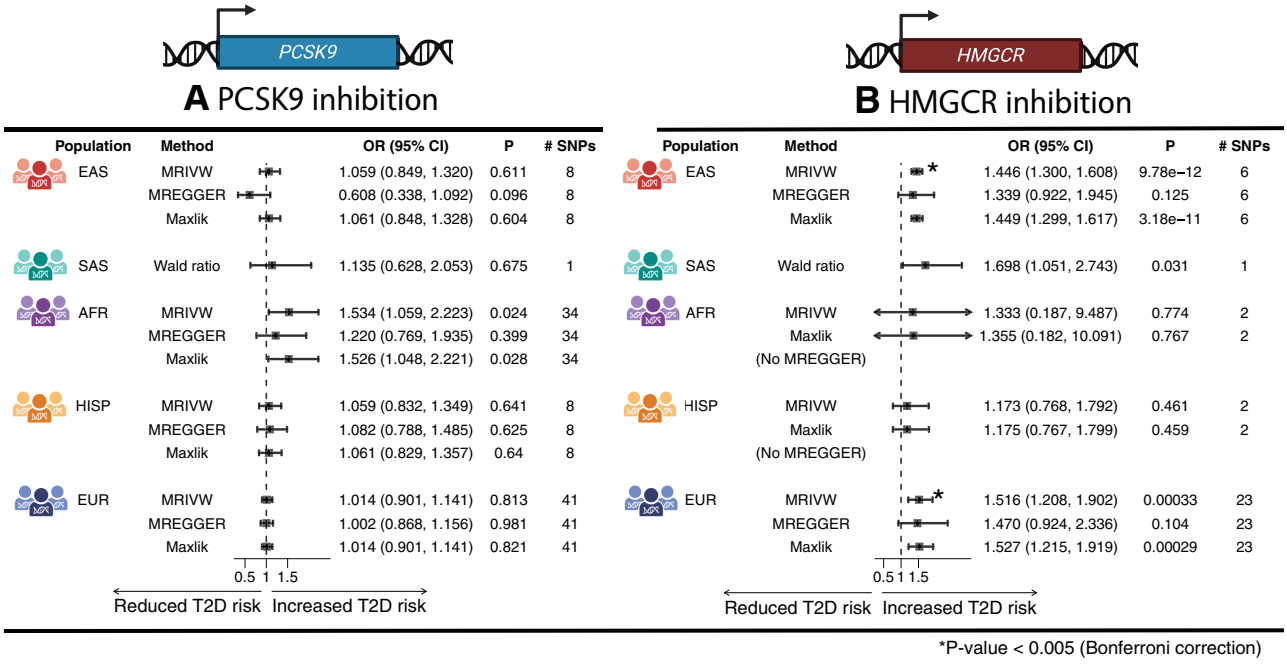

Figure 2—MR results of the impact of PCSK9 (*A*) and HMGCR (*B*) inhibition on T2D risk. Results report the IVW estimates from MR analyses that incorporated correlation between SNPs. Because there were only two SNPs in the AFR and HISP HMGCR instruments, the MR Egger method was not performed (requires 3+ SNPs). Results for T2D are reported as OR change (with 95% CI) in T2D risk per SD decrease in LDL-C levels via variants within the *PCSK9* and *HMGCR* genomic loci. IVW MR estimates surpassing correction for multiple comparisons ($P < 0.005$ [0.05/10 tests performed per population]) are indicated with an asterisk. Number of SNPs is the number of genetic variants used in the drug target MR analysis.

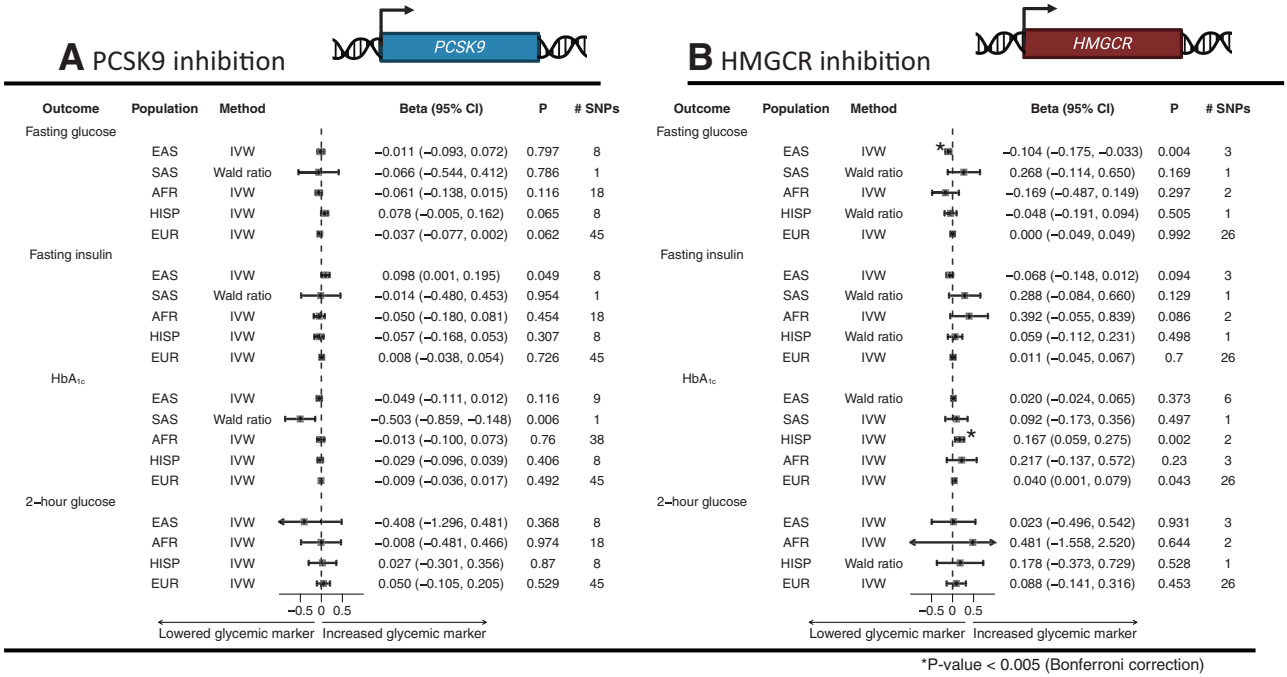

Figure 3— MR results of PCSK9 (*A*) and HMGCR (*B*) inhibition on glycemic markers. Presented are MR results of the impact of PCSK9 and HMGCR inhibition on glycemic traits; results are reported with the IVW or Wald ratio estimates from MR analyses; 2-h glucose levels were not available for SAS. Results for the glycemic markers are reported as the regression coefficient (β; with 95% CI) in the respective glycemic marker per SD decrease in the LDL-C levels via variants within the *PCSK9* and *HMGCR* genomic loci. MR estimates surpassing correction for multiple comparisons ($P < 0.005$ [0.05/10 tests performed per population]) are indicated with an asterisk. Number of SNPs is the number of genetic variants used in the drug target MR analysis.

P values <0.05, we observed evidence of a shared causal variant between LDL-C and T2D in the EAS, EUR, and SAS populations (Supplementary Table 8). The PCSK9 T2D finding in the AFR population did not colocalize (H4 0.033). However, we observed evidence of a single shared causal variant between LDL-C and T2D in *HMGCR* for both EAS and SAS populations (EAS H4 0.682; SAS H4 0.813), whereas SuSiE colocalization confirmed evidence of shared multiple causal variants between LDL-C and T2D in the *HMGCR* locus in the EUR population (SuSiE H4 0.76) (Supplementary Table 8).

Impact of LDL-C Lowering by PCSK9 and HMGCR on Glycemic Markers

IVW and Wald ratio results from the primary drug target MR analyses on LDL-C lowering via *PCSK9* and *HMGCR* loci and glycemic markers are presented in Fig. 3. Although no PCSK9 estimates surpassed the multiple comparisons threshold, we found weak evidence for reduced HbA_{1c} in the SAS population and increased fasting insulin in the EAS population (Fig. 3 and Supplementary Table 6), with the latter being robust and directionally consistent in MVMR adjusting for BMI (Supplementary Tables 9–13). The PCSK9 HbA_{1c} finding in the SAS population was supported by colocalization (H4 0.835) (Supplementary Table 8), whereas the EAS population showed some evidence for colocalization (H4 0.537), although below the study threshold. Estimates using *PCSK9* functional variants (*R46L* and *E670G*) spanned the null (Supplementary Table 7).

For HMGCR, we found strong evidence that genetically proxied inhibition increased HbA_{1c} in the HISP population (β = 0.167; 95% CI 0.059–0.275; *P* = 0.002), supported by colocalization (H4 0.813) (Supplementary Table 8) and robust after BMI adjustment (Supplementary Table 12), with weaker evidence in the EUR population (β = 0.040; 0.001–0.0979; *P* = 0.043), although not robust in MVMR (Supplementary Table 13). No colocalization was observed for other glycemic traits in the *HMGCR* locus with MR estimate *P* values <0.05. Estimates for insulin resistance measures in the EUR population indicated weak evidence that a 1-SD reduction in LDL-C via PCSK9 variants increased IFC (β = 0.14; 95% CI 0.03–0.34; *P* = 0.009) but not ISI (β = −0.07; −0.16 to 0.012; *P* = 0.092), whereas *HMGCR* variants showed weak evidence for reduced ISI (β = −0.16; −0.28 to −0.03; *P* = 0.013) (Table 14). These MR estimates were consistent with results using *PCSK9* functional variants across populations (Supplementary Tables 3 and 7).

Impact of Circulating PCSK9 Protein and Tissue Expression

Given the mechanisms of approved PCSK9 inhibitors (anti-PCSK9 antibodies lowering circulating PCSK9 protein and inclisiran inhibiting hepatic PCSK9 expression)

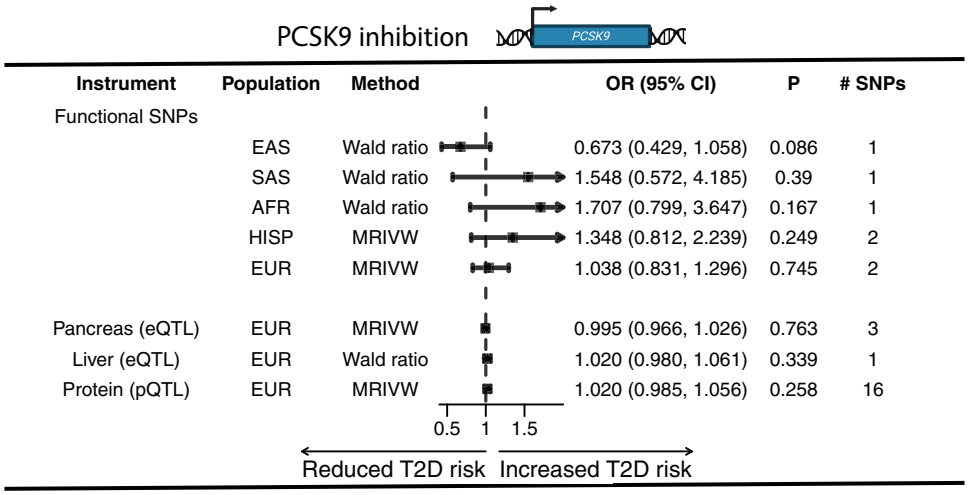

Figure 4—MR results of additional PCSK9 instruments (functional variants and QTL) on T2D risk. Presented are MR results (either IVW or Wald ratio depending on number of *cis*-variants in the instrument) of the impact of the additional PCSK9 instruments (functional variants lowering LDL-C, tissue-specific *PCSK9* expression, and circulating PCSK9 protein levels) on T2D risk. Results for T2D are reported as the OR (with 95% CI) in the respective glycemic marker per SD decrease in either LDL-C, circulating PCSK9 protein levels, or transcripts per million in pancreas and liver *PCSK9* expression. Number of SNPs is the number of genetic variants used in the drug target MR analysis.

(10,40), we investigated the impact of genetically lowered circulating, hepatic, and pancreatic PCSK9 on T2D and glycemic markers. Results aligned with LDL-C lowering via PCSK9 variants (Figs. 4 and 5 and Supplementary Table 15). We found weak evidence linking genetically lowered circulating PCSK9 protein with reduced HbA_{1c} and 2-h glucose, but no associations with other glycemic markers, and the HbA_{1c} finding was not replicated with hepatic/pancreatic PCSK9 instruments. In IFC and ISI analyses, PCSK9 pQTL instruments showed weak evidence of increased IFC (β = 0.04; 95% CI 0.009–0.078; P = 0.013) (Supplementary Table 15).

Polygenic LDL-C Results

Full results of the polygenic lipid instrument are presented in Supplementary Table 10. Before interpretation, we aligned each polygenic LDL-C estimate to correspond to the expected physiologic response to pharmacologic lipid-lowering therapy (i.e., a change in T2D risk or glycemic marker level per unit SD lowering in LDL-C). In line with the results observed using *HMGCR* variants, we observed strong evidence that lower LDL-C levels increased risk of T2D in SAS (OR 1.34; 95% CI 1.166–1.529; $P = 2.81 \times 10^{-5}$) and EUR populations (1.056; 1.013–1.101; P = 0.001). Polygenic LDL-C estimates in the other populations included the null.

DISCUSSION

We used drug target MR to compare the relationships of genetic LDL-C lowering via *PCSK9* and *HMGCR* inhibition with T2D and glycemic markers using data from five populations. We found a neutral safety profile for PCSK9 inhibition on T2D in SAS, EAS, HISP, and EUR populations, adding to the growing body of genetics-based literature finding generally safe adverse effect profiles of long-term PCSK9 lowering (41–44). Sensitivity analyses using functional *PCSK9* variant *R46L*, PCSK9 protein levels, and both hepatic and pancreatic *PCSK9* gene expression similarly yielded null results. Our assessment of the genetic PCSK9 T2D relationships across cohorts representing five populations using complementary MR methods, sensitivity analyses based upon functional *PCSK9* variants, and analyses using multiomic PCSK9 instruments, along with other lines of evidence failing to find an adverse increase in T2D risk by PCSK9 inhibition (18), further strengthens our inference of the neutral adverse effect profile and should be reassuring for any concerns regarding T2D diabetes risk from pharmacologic PCSK9 inhibition. Importantly, although global T2D prevalence is high, it varies widely across geographic regions and by race and ethnicity (2), and epidemiologic data suggest that certain populations may have higher or lower risk of developing T2D (2). Nevertheless, despite the need for more diversity in all clinical trials and genetics-based studies (14), apart from a recent study investigating the relationships of lipids, lipid-lowering targets, and T2D risk among African Americans (18), the existing PCSK9 T2D literature is based primarily on analysis of individuals in the EUR population, highlighting the need for population-specific work to inform our understanding of PCSK9 inhibition and the risk of T2D. Finally, our polygenic LDL-C findings aligned with previous observational and genetics-based work finding that lower levels of circulating LDL-C are linked with higher T2D risk (Supplementary Discussion).

We found weak evidence ($P < 0.05$) indicating PCSK9 inhibition was associated with increased T2D risk in the AFR population; however, the result was not robust to our sensitivity analyses using functional *PCSK9* variants

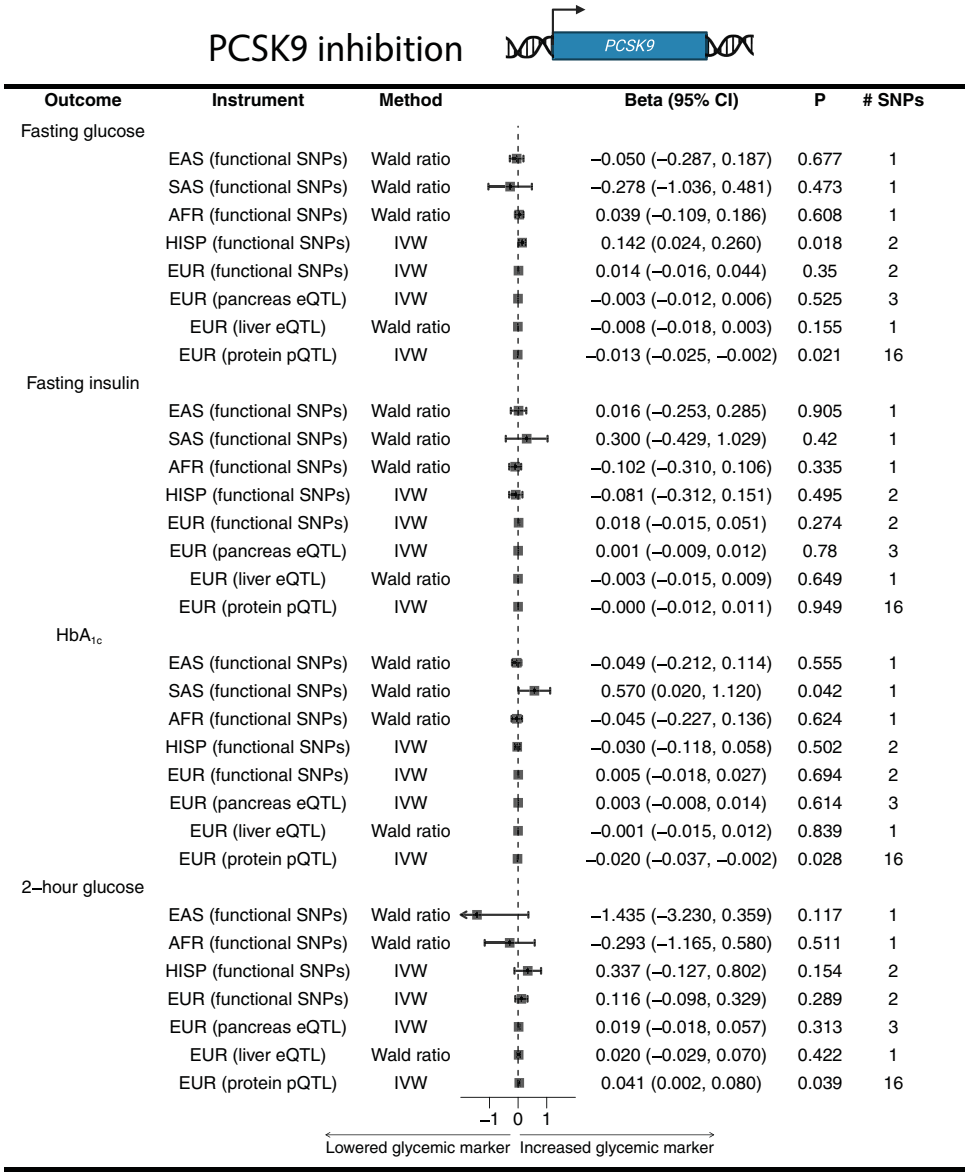

Figure 5—MR results of additional PCSK9 instruments (functional variants and QTL) on glycemic traits. Presented are MR results (either IVW or Wald ratio depending on number of *cis*-variants in the instrument) of the impact of the additional PCSK9 instruments (functional variants lowering LDL-C, tissue-specific *PCSK9* expression, and circulating PCSK9 protein levels) for glycemic traits. Glycemic traits results are reported as the regression coefficient (β; with 95% CI) per SD decrease in either LDL-C, circulating PCSK9 protein levels, or transcripts per million in pancreas and liver *PCSK9* expression. Note that 2-h glucose levels were not available for SAS. Number of SNPs is the number of genetic variants used in the drug target MR analysis.

as instruments. In addition, we did not find a relationship between HMGCR and T2D risk in the AFR data. Our AFR T2D results were based on cohorts from continental Africa, and neither the PCSK9 nor the HMGCR finding aligned with the recent MR study by Soremekun et al. (18) assessing the impact of LDL-C lowering by PCSK9 and HMGCR inhibition on T2D risk among African Americans in the Million Veteran Program. Soremekun et al. (18) found that HMGCR inhibition increased T2D risk, but PCKS9 inhibition did not. These discrepancies may also reflect the impact of genetic admixture, the mixing of different ancestral populations (45), which can influence genetic associations by introducing variability in allele frequencies and genetic backgrounds across populations (45). In the context of genetic studies, admixture can lead to confounding effects, where associations identified in one population may not hold true in another because of differences in genetic architecture (45). This variability can obscure or inflate the true effects of genetic variants on traits such as T2D risk. For example, in populations with a high degree of admixture, such as the African American population (46), the presence of alleles from different ancestral backgrounds may alter the expression and impact of genes targeted by therapies such as HMGCR inhibitors or PCSK9

inhibitors. Therefore, the observed genetic associations in a more genetically homogenous population may differ when studied in an admixed population, leading to discrepancies in the findings. Moreover, Africans possess more genetic and linguistic diversity, with >3,000 indigenous languages, largely shaped by geography. However, >90% of these ethnolinguistic groups lack genetic data (14). Focusing on the African diaspora overlooks Africa's genetic diversity, perpetuating imbalances and health disparities (14), underscoring the importance of future investigation and replication with these populations.

For HMGCR inhibition, our results replicate and extend reports of increased T2D risk from RCTs evaluating statin use and MR analyses using variants in the *HMGCR* region as proxies for long-term HMGCR inhibition (6–8), by also finding adverse relationships between HMGCR and T2D risk in EAS (having strong genetic evidence with drug target MR estimates surpassing correction for multiple comparisons and also demonstrating evidence of colocalization) and SAS populations (weak evidence with a less precise MR estimate, but evidence of colocalization). They also extend recent population genetic work in diverse populations that applied a clustering-based method to a GWAS of T2D along with other cardiometabolic diseases and glycemic markers to develop genetic signatures underlying subtypes of T2D using GWAS data from EUR and non-EUR cohorts (47). We did not find corresponding evidence for adverse effects of HMGCR inhibition on glycemic traits in either the EAS or SAS population (in fact, HMGCR inhibition reduced fasting glucose in the EAS population, and this result was robust in MVMR to correct bias for the BMI adjustment in the fasting glucose GWAS data, suggesting some potential glycemic benefits); it is possible that the adverse impact on T2D may be via potential pathways that have been previously reported (e.g., statin-related weight gain) (48).

Because the heterogenous HMGCR findings suggested adverse relationships in three of five study populations, suggesting potential population specificity and biologic mechanisms, it is possible that the observed differences in the estimates reflect differing allele frequencies of the *HMGCR* variants across the populations; however, the R^2 values for HMGCR instruments were generally comparable across populations, and the variants used for population-specific instruments were largely distinct, likely capturing the genetic architecture of the *HMGCR* locus specific to each population. Furthermore, MR studies may be biased by population differences, which include differences in allele frequencies, between the exposure and outcome data (49). Although we matched populations between the exposure and outcome pairs, we cannot eliminate the possibility that there is remaining population stratification present between the GLGC LDL-C, DIAMANTE T2D, and MAGIC glycemic trait cohorts that may influence HMGCR T2D and other findings in our study. Therefore, future studies are necessary with additional data sources to replicate and confirm the suggested population-level differences in lifelong HMGCR inhibition. We emphasize, as previous studies have, that the modest increase in T2D risk with statin therapy does not outweigh its significant cardiovascular benefits (7). Although the drug target MR design cannot explore mechanisms, it has been suggested that statins may increase T2D risk by impairing pancreatic insulin secretion and reducing insulin sensitivity in adipose tissue (50). The genetic risk of long-term HMGCR inhibition may not match that of shorter statin therapy. Exploratory analyses showed no link between HMGCR inhibition and fasting insulin or postprandial insulin resistance (21), indicating the T2D risk is not due to increased insulin resistance. In contrast, PCSK9 inhibition was associated with reduced insulin resistance, because lower PCSK9 was linked to increased IFC. These findings were consistent across several PCSK9 instruments, suggesting a potential beneficial effect of PCSK9 inhibition on insulin secretion, warranting further study.

There are study limitations. First, although participants from five populations across 34 countries and four continents improve our understanding of lipid-lowering therapies and T2D risk, the results may not apply to unrepresented populations or geographically distinct groups within included populations. We were unable to evaluate country-specific heterogeneity or ethnolinguistic differences within populations. Causal inference requires triangulating study designs (51), and although increased diversity in genetic studies is important, long-term RCTs across diverse populations are needed to further understand lipid-lowering therapy and T2D relationships. Some population-based estimates showed heterogeneity, possibly reflecting differences in health care access and glycemic control. For example, in the HISP cohort, HMGCR inhibition was linked with increased HbA_{1c}, whereas PCSK9 inhibition was not, potentially because of health care challenges in this population (52). Recent work found that HISP patients who preferred Spanish had poorer HbA_{1c} control than those who preferred English (53), highlighting the need for programs to address organizational barriers to glycemic control in the HISP population (53). Other limitations of the drug target MR framework include the inability to assess off-target effects of PCSK9 and HMGCR inhibition beyond their lipid-lowering mechanisms. Future non-EUR MR studies will be essential as more data becomes available. Although *cis*-instruments reduce MR assumption violations compared with polygenic MR, confounding or pleiotropy bias cannot be fully ruled out (26). The Supplementary Discussion lists study strengths.

In conclusion, our study finds no adverse impact of genetically proxied LDL-C lowering by PCSK9 variants on T2D or glycemic markers in EAS, SAS, HISP, and EUR cohorts. We observed an adverse relationship in the AFR population, but this was not robust in sensitivity analyses and conflicts with recent findings from African American data using U.S.-based data, highlighting the need for further research. For HMGCR, we confirm a slight increase

in T2D risk, although this is likely outweighed by the cardiovascular benefits of statin therapy. These findings should guide clinicians and patients concerned about T2D risk when considering lipid-lowering therapies.

Acknowledgments. The authors thank the contributing GWASs and the participants and investigators in those studies, without whom this effort would not be possible. The graphical abstract, Fig. 1, and the drug target icons in the forest plots were made using BioRender.com.

Funding. This work was supported by National Institutes of Health intramural funding (ZIA-AA000242 to F.W.L) and the Division of Intramural Clinical and Biological Research, National Institute on Alcohol Abuse and Alcoholism.

Duality of Interest. No potential conflicts of interest relevant to this article were reported.

Author Contributions. D.B.R. analyzed the data and wrote the first manuscript draft. D.B.R. and F.W.L. designed the study. J.W., J.J., P.P., C.C., G.D.S., D.R., and F.W.L. provided critical revision of the manuscript for important intellectual content. D.B.R. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Prior Presentation. Parts of this study were presented in abstract form at the 9th Meeting of the Study Group on Genetics of Diabetes, Exeter, U.K., 17–19 April 2024.

References

1. International Diabetes Federation. IDF Diabetes Atlas, 7th ed. Accessed 4 August 2017. Available from https://www.diabetesatlas.org/
2. Barroso I. The importance of increasing population diversity in genetic studies of type 2 diabetes and related glycaemic traits. Diabetologia 2021;64:2653–2664
3. Cusi K, Ocampo GL. Unmet needs in Hispanic/Latino patients with type 2 diabetes mellitus. Am J Med 2011;124(Suppl.10):S2–S9
4. Chatterjee S, Khunti K, Davies MJ. Type 2 diabetes. Lancet 2017;389:2239–2251
5. Elnaem MH, Mohamed MHN, Huri HZ, Azarisman SM, Elkalmi RM. Statin therapy prescribing for patients with type 2 diabetes mellitus: a review of current evidence and challenges. J Pharm Bioallied Sci 2017;9:80–87
6. Preiss D, Seshasai SRK, Welsh P, et al. Risk of incident diabetes with intensive-dose compared with moderate-dose statin therapy: a meta-analysis. JAMA 2011;305:2556–2564
7. Schmidt AF, Swerdlow DI, Holmes MV, et al.; UCLEB Consortium. PCSK9 genetic variants and risk of type 2 diabetes: a mendelian randomisation study. Lancet Diabetes Endocrinol 2017;5:97–105
8. Ference BA, Robinson JG, Brook RD, et al. Variation in PCSK9 and HMGCR and risk of cardiovascular disease and diabetes. N Engl J Med 2016;375:2144–2153
9. Sabatine MS, Leiter LA, Wiviott SD, et al. Cardiovascular safety and efficacy of the PCSK9 inhibitor evolocumab in patients with and without diabetes and the effect of evolocumab on glycaemia and risk of new-onset diabetes: a prespecified analysis of the FOURIER randomised controlled trial. Lancet Diabetes Endocrinol 2017;5:941–950
10. Ferkingstad E, Sulem P, Atlason BA, et al. Large-scale integration of the plasma proteome with genetics and disease. Nat Genet 2021;53:1712–1721
11. Aguet F, Anand S, Ardlie KG, et al.; GTEx Consortium. The GTEx Consortium atlas of genetic regulatory effects across human tissues. Science 2020;369:1318–1330
12. Ray KK, Wright RS, Kallend D, et al.; ORION-10 and ORION-11 investigators. Two phase 3 trials of inclisiran in patients with elevated LDL cholesterol. N Engl J Med 2020;382:1507–1519
13. Da Dalt L, Ruscica M, Bonacina F, et al. PCSK9 deficiency reduces insulin secretion and promotes glucose intolerance: the role of the low-density lipoprotein receptor. Eur Heart J 2019;40:357–368
14. Fatumo S, Chikowore T, Choudhury A, Ayub M, Martin AR, Kuchenbaecker K. A roadmap to increase diversity in genomic studies. Nat Med 2022;28:243–250
15. Graham SE, Clarke SL, Wu K-HH, et al.; Global Lipids Genetics Consortium. The power of genetic diversity in genome-wide association studies of lipids. Nature 2021;600:675–679
16. Mahajan A, Spracklen CN, Zhang W, et al.; eMERGE Consortium. Multi-ancestry genetic study of type 2 diabetes highlights the power of diverse populations for discovery and translation. Nat Genet 2022;54:560–572
17. Wojcik GL, Graff M, Nishimura KK, et al. Genetic analyses of diverse populations improves discovery for complex traits. Nature 2019;570:514–518
18. Soremekun O, Karhunen V, He Y, et al. Lipid traits and type 2 diabetes risk in African ancestry individuals: a Mendelian randomization study. eBioMedicine 2022;78:103953
19. Chen J, Sun M, Adeyemo A, et al. Genome-wide association study of type 2 diabetes in Africa. Diabetologia 2019;62:1204–1211
20. Mooradian AD. Dyslipidemia in type 2 diabetes mellitus. Nat Clin Pract Endocrinol Metab 2009;5:150–159
21. Williamson A, Norris DM, Yin X, et al.; Meta-Analysis of Glucose and Insulin-Related Traits Consortium (MAGIC). Genome-wide association study and functional characterization identifies candidate genes for insulin-stimulated glucose uptake. Nat Genet 2023;55:973–983
22. Auton A, Brooks LD, Durbin RM, et al.; 1000 Genomes Project Consortium. A global reference for human genetic variation. Nature 2015;526:68–74
23. Qiu C, Zeng P, Li X, et al. What is the impact of PCSK9 rs505151 and rs11591147 polymorphisms on serum lipids level and cardiovascular risk: a meta-analysis. Lipids Health Dis 2017;16:111
24. Sabatine MS. PCSK9 inhibitors: clinical evidence and implementation. Nat Rev Cardiol 2019;16:155–165
25. Mihaylova B, Emberson J, Blackwell L, et al.; Cholesterol Treatment Trialists' (CTT) collaborators. The effects of lowering LDL cholesterol with statin therapy in people at low risk of vascular disease: meta-analysis of individual data from 27 randomised trials. Lancet 2012;380:581–590
26. Sanderson E, Glymour MM, Holmes MV, et al. Mendelian randomization. Nat Rev Methods Primers 2022;2:6
27. Burgess S, Mason AM, Grant AJ, et al. Using genetic association data to guide drug discovery and development: review of methods and applications. Am J Hum Genet 2023;110:195–214
28. Hartwig FP, Tilling K, Davey Smith G, Lawlor DA, Borges MC. Bias in two-sample Mendelian randomization when using heritable covariable-adjusted summary associations. Int J Epidemiol 2021;50:1639–1650
29. Sanderson E. Multivariable Mendelian randomization and mediation. Cold Spring Harb Perspect Med 2021;11:a038984
30. Chen C-Y, Chen T-T, Feng Y-CA, et al. Analysis across Taiwan Biobank, Biobank Japan, and UK Biobank identifies hundreds of novel loci for 36 quantitative traits. Cell Genom 2023;3:100436
31. Neale Lab. UK Biobank GWAS. Accessed 30 June 2019. Available from https://www.nealelab.is/uk-biobank/
32. Fernández-Rhodes L, Graff M, Buchanan VL, et al. Ancestral diversity improves discovery and fine-mapping of genetic loci for anthropometric traits: The Hispanic/Latino Anthropometry Consortium. HGG Adv 2022;3:100099
33. Pulit SL, Stoneman C, Morris AP, et al.; GIANT Consortium. Meta-analysis of genome-wide association studies for body fat distribution in 694 649 individuals of European ancestry. Hum Mol Genet 2019;28:166–174
34. Amrhein V, Greenland S, McShane B. Scientists rise up against statistical significance. Nature 2019;567:305–307
35. Zuber V, Grinberg NF, Gill D, et al. Combining evidence from Mendelian randomization and colocalization: review and comparison of approaches. Am J Hum Genet 2022;109:767–782

36. Wallace C. A more accurate method for colocalisation analysis allowing for multiple causal variants. PLoS Genet 2021;17:e1009440
37. Hemani G, Zheng J, Elsworth B, et al. The MR-Base platform supports systematic causal inference across the human phenome. Elife 2018;7: e34408
38. Yavorska OO, Burgess S. MendelianRandomization: an R package for performing Mendelian randomization analyses using summarized data. Int J Epidemiol 2017;46:1734–1739
39. Hemani G, Tilling K, Davey Smith G. Orienting the causal relationship between imprecisely measured traits using GWAS summary data. PLoS Genet 2017;13:e1007081
40. Lonsdale J, Thomas J, Salvatore M, et al. The Genotype-Tissue Expression (GTEx) project. Nat Genet 2013;45:580–585
41. Rosoff DB, Bell AS, Wagner J, et al. Assessing the Impact of PCSK9 and HMGCR inhibition on liver function: drug-target Mendelian randomization analyses in four ancestries. Cell Mol Gastroenterol Hepatol 2024;17:29–40
42. Rosoff DB, Bell AS, Jung J, Wagner J, Mavromatis LA, Lohoff FW. Mendelian randomization study of PCSK9 and HMG-CoA reductase inhibition and cognitive function. J Am Coll Cardiol 2022;80:653–662
43. Bell AS, Wagner J, Rosoff DB, Lohoff FW. Proprotein convertase subtilisin/ kexin type 9 (PCSK9) in the central nervous system. Neurosci Biobehav Rev 2023;149:105155
44. Rao AS, Lindholm D, Rivas MA, Knowles JW, Montgomery SB, Ingelsson E. Large-scale phenome-wide association study of PCSK9 variants demonstrates protection against ischemic stroke. Circ Genom Precis Med 2018;11:e002162
45. Korunes KL, Goldberg A. Human genetic admixture. PLoS Genet 2021;17: e1009374
46. Zakharia F, Basu A, Absher D, et al. Characterizing the admixed African ancestry of African Americans. Genome Biol 2009;10:R141
47. Bowden J, Davey Smith G, Haycock PC, Burgess S. Consistent estimation in Mendelian randomization with some invalid instruments using a weighted median estimator. Genet Epidemiol 2016;40:304–314
48. Redberg RF. Statins and weight gain. JAMA Intern Med 2014;174: 1046–1046
49. Lawlor DA, Harbord RM, Sterne JAC, Timpson N, Davey Smith G. Mendelian randomization: using genes as instruments for making causal inferences in epidemiology. Stat Med 2008;27:1133–1163
50. Yu Q, Chen Y, Xu C-B. Statins and new-onset diabetes mellitus: LDL receptor may provide a key link. Front Pharmacol 2017;8:372
51. Hammerton G, Munafò MR. Causal inference with observational data: the need for triangulation of evidence. Psychol Med 2021;51:563–578
52. Fortmann AL, Gallo LC, Philis-Tsimikas A. Glycemic control among Latinos with type 2 diabetes: the role of social-environmental support resources. Health Psychol 2011;30:251–258
53. Aceves B, Ezekiel-Herrera D, Marino M, et al. Disparities in HbA1c testing between aging US Latino and non-Latino white primary care patients. Prev Med Rep 2022;26:101739