The causal effects of lipid traits on kidney function in Africans: bidirectional and multivariable Mendelian-randomization study

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Abstract

Background: Observational studies have investigated the effect of serum lipids on kidney function, but these findings are limited by confounding, reverse causation and have reported conflicting results. Mendelian randomization (MR) studies address this confounding problem. However, they have been conducted mostly in European ancestry individuals. We, therefore, set out to investigate the effect of lipid traits on the estimated glomerular filtration rate (eGFR) based on serum creatinine in individuals of African ancestry.

Methods: We used the two-sample and multivariable Mendelian randomization (MVMR) approaches; in which instrument variables (IVs) for the predictor (lipid traits) were derived from summary-level data of a meta-analyzed African lipid GWAS (MALG, n=24,215) from the African Partnership for Chronic Disease Research (APCDR) (n = 13,612) & the Africa Wits-IN-DEPTH partnership for Genomics studies (AWI-Gen) dataset (n=10,603). The outcome IV's were computed from the eGFR summary-level data of African-ancestry individuals within the Million Veteran Program (n=57,336). A random-effects inverse variance method was used in our primary analysis, and pleiotropy was adjusted for using robust and penalized sensitivity testing. The lipid predictors for the MVMR were high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol, and triglycerides (TG).

Results: We found a significant causal association between genetically predicted low-density lipoprotein (LDL) cholesterol and eGFR in African ancestry individuals β = 1.1 (95% CI [0.411-1.788]; p=0.002). Similarly, total cholesterol (TC) showed a significant causal effect on eGFR β = 1.619 (95% CI [0.412-2.826]; p=0.009). However, the IVW estimate showed that genetically predicted HDL-C β = -0.164, (95% CI = [-1.329-1.00]; p = 0.782), and TG β = -0.934 (CI = [-2.815-0.947]; p = 0.33) were not significantly causally associated with the risk of eGFR. In the multivariable analysis inverse-variance weighted (MVIVW) method, there was evidence for a causal association between LDL and eGFR β = 1.228 (CI = [0.477-1.979]; p=0.001). A significant causal effect of Triglycerides (TG)

on eGFR in the MVIVW analysis β = -1.283 (95% CI = [-2.605-0.038]; p=0.057) was observed as well. HDL showed no evidence of a significant causal association with eGFR in the MVIVW method (β = -0.117 (95% CI [-1.252-0.018]; p=0.840). We found no evidence of a reverse causal impact of eGFR on serum lipids. All our sensitivity analyses indicated no strong evidence of pleiotropy or heterogeneity between our instrumental variables.

Interpretation: In this African ancestry population, genetically predicted higher LDL-C and TC are causally associated with higher eGFR levels, which may suggest that the relationship between LDL, TC and kidney function may be U-shaped. And as such, lowering LDL_C does not necessarily improve risk of kidney disease. This may also imply the reason why LDL_C is seen to be a poorer predictor of kidney function compared to HDL. In addition, this further supports that more work is warranted to confirm the potential association between lipid traits and risk of kidney disease in individuals of African Ancestry.

Keywords: Serum lipids; eGFR; Chronic Kidney Disease; Kidney function; Two-sample Mendelian Randomization

Introduction

Chronic kidney disease (CKD) is defined as a reduction in kidney function indicated by estimated glomerular filtration rate (eGFR) <60 ml/min per 1.73 m2 or kidney damage markers or both that persist for at least three months[1]. It has a significant impact worldwide, with an estimated prevalence of 10-15% globally as a direct cause of mortality, morbidity, and comorbidity in other complex traits[2]. The prevalence of CKD in Africa is equally high with most sub-Saharan African countries showing generally a >10% prevalence. Managing CKD in its advanced stages requires huge amounts of resources, and this is quite cumbersome on most sub-Saharan Africa (SSA) economies.

Serum lipids: high-density lipoprotein (HDL) and low-density lipoprotein (LDL) cholesterol, rank among the highest commonly measured biomarkers in clinical medicine[3]. Most epidemiological studies have reported an association between these lipids and kidney function, indicating that low HDL cholesterol is associated with poor kidney function and CKD progression[4-6]. In a well-powered study of 2 million United States veterans who were followed up for a median of 9 years, Bowe *et al.,* [7] reported on the association between HDL cholesterol concentrations and various CKD end points. The authors reported individuals with low HDL cholesterol concentrations (<30 mg/dL) have the highest risk for CKD or CKD progression [5]. Other studies have found that higher levels of blood total cholesterol (TC), LDL, TC: HDL ratio, TG: HDL ratio, and lower levels of blood HDL cholesterol, are associated with a higher risk of incident CKD [8]. However, evidence from these epidemiological and observational studies is limited by its inability to demonstrate a causal relationship and inconsistencies between several studies [9-12]. Further still, most of such high-powered studies have not only been limited by sample selection bias towards majorly European ancestries, but also confounding from environmental factors.

Mendelian randomization studies can enable us to conduct causal inferences by dealing better with environmental confounding and reverse causation[3, 13, 14].[15]. However, similar to observational studies, the association of serum lipids and eGFR has been conflicted, even in the MR studies. Studies like that by Coassin *et al.*, indicated that HDL

cholesterol does not influence eGFR, and they further proposed pleiotropic effects on eGFR for some of the associated SNPs [8]. Other findings elsewhere conflicted these findings and reported a genetically higher HDL concentration being associated with higher eGFR[16, 17]. Such studies, however, have been subject to sample selection bias due to the lack of ethnic diversity in the Genome-Wide Association Studies (GWASs) used which are primarily based on European ancestry individuals[18, 19]. A two-sample Mendelian randomization analysis of data from the most extensive lipid and CKD cohorts supported genetically higher HDL cholesterol concentration as causally associated with better kidney function[20]. This analysis and several others were performed on European ancestry individuals, and the results cannot be confidently generalized to non-European ancestry individuals.

In this study, therefore, we set out to use bi-directional and multivariable MR methods to investigate the causal relationship between serum lipids profile and kidney function using estimated glomerular filtration rate based on serum creatinine (eGFRcrea) as a marker among individuals of African-ancestry selected from the Million veteran program (MVP) and Meta-analysed of continental African Lipid GWASs (APCDR and AWI-Gen), which we called MALG (n=24,215).

Methods

GWAS data sources

We selected eGFR instruments from GWAS summary statistics of all individuals of African ancestry within the U.S. Veteran's Administration million veteran program, MVP (N=57336) [21]. Genetic instruments for lipid traits were obtained from summary statistics of MALG (n=24,215) - 13,612 African-ancestry participants from the African Partnership for Chronic Disease Research (APCDR) & the Africa Wits-IN-DEPTH partnership for Genomics studies (AWI-Gen) [22]. More information about the African cohorts (AWI-Gen+APCDR) from which the lipids instrumental variables were obtained are detailed elsewhere [21-23].

Univariable Mendelian Randomization

After instrument harmonization and selection, the inverse-weighted variance (IVW) method was used to perform the bi-directional MR analysis. In the absence of directional pleiotropy and heterogeneity between exposure and outcome, the estimates from this method have been reported to be reasonably accurate [23]. We checked for the possible presence of horizontal pleiotropy between instrumental variables by including the MR-Egger regression method and MR-PRESSO. Evidence of horizontal pleiotropy was based on the MR-Egger intercept value deviating significantly from zero with a P-value ≤ 0.05 [23, 24]. The weighted median method was used as the method of choice in case of observed pleiotropy [25].

Multivariable Mendelian Randomization

The Multivariable Mendelian Randomization method can be applied for multiple genetic instruments regardless of their association with the exposure [26]. In this MVMR method, the instrumental variables may be associated with more than one risk factor but they must fulfill the equivalent instrumental-variable assumptions [27]. Thus, we applied this method by considering all the instrumental variables for HDL, LDL, and TG to determine their independent effects on eGFR.

Sensitivity analyses

We performed a sensitivity analysis using the penalization method in which the contribution of some of the instrumental variables (e.g., heterogeneous or outlying IVs) to the analysis is down-weighted (or penalized) [25]. We performed the systematic leave-one-out approach to determine potential pleiotropy per SNP. The resultant effect was assessed using the robust penalized IVW estimate. The change in results before and after SNP removal was then assessed. We also checked for heterogeneity between instrumental variables determined by Q statistics at P-value ≤ 0.05.

Ethics statement

The parent studies; MVP, and MALG obtained participant consent with respective ethical approvals, and consequently, this work is exempt from seeking further ethics approval.

Statistical analysis

We performed the MR analyses using the two-sample random-effects inverse-variance weighted (IVW) method implemented in the Mendelian Randomization R package [28]. This method determines the causal estimates for instruments that meet the instrumental variable assumptions reported elsewhere [14]. To account for the documented horizontal pleiotropy between lipids, we conducted a multivariable MR (MVMR) including instrumental variables from HDL, LDL, and TG at $P < 5 \times 10^{-8}$. We further checked for reverse causality by conducting an MR analysis considering eGFRcrea from MVP as exposure and lipid traits from MALG as outcome. The genetic instruments included in this study for all analyses were selected as those significantly associated with the risk of lipid traits at $p < 5X10^{-8}$ in the MALG dataset with clumping at 500kb. We controlled for the false discovery rate in multiple testing using the Bonferroni method [29]. Statistical significance for causal associations was considered at p-value < 0.005. All analyses were performed using Mendelian Randomization packages in R.

Role of funding source

Funding sources had no role in the conduct or reporting of the research.

Results

The bi-directional MR analysis was performed as shown in **figure1**. Further details on the instrumental variables chosen can be found in **supplementary data**.

Association of estimated glomerular filtration rate with lipid levels

Univariable MR

The associations between genetically predicted lipid traits and eGFR are shown in **Table1, figure 2, supplementary figure s2**. We found no evidence of a statistically significant causal association between genetically predicted HDL-C and eGFR (β = -0.164, 95% CI = -1.329-1.00; p = 0.782). The effect estimates (β) [95% confidence intervals (CIs)] for the other lipid traits on eGFR were 1.1([0.411-1.788]; 0.002), 1.619([0.412-2.826]; 0.009) and -0.934([-2.815-0.947]; 0.33) for LDL, TC, and TG respectively. There was evidence of a significant causal association between genetically predicted LDL cholesterol and eGFR. Similarly, TC showed a significant causal effect on eGFR **(Figure 2)**. Genetically predicted Triglycerides (TG) were not significantly associated with eGFR as well.

The reverse MR analysis showed no significant causal association between eGFR and all four lipid traits, as shown in the **supplementary figure S1 & Table S1**. For the reverse MR, the effect estimate ([95% CI]) for HDL, LDL, TC, and TG was 0.01([-0.011-0.012]; p=0.873), 0.007([-0.005-0.018]; p=0.265), 0.008([-0.005-0.021]; p=0.225) and 0.00([-0.011-0.011]; p=0.984) respectively. eGFR showed no evidence of a reverse causal effect on this population's genetically predicted lipid traits.

Multivariable MR

The MVMR analysis showed statistically significant causal associations for genetically predicted lipid traits; LDL and TG on eGFR **(figure 3; supplementary TableS2).** LDL cholesterol had a significant positive causal effect on eGFR, consistent with that observed in the forward univariable analysis (β = 1.228([0.477-1.979]; p=0.001). There was evidence of a significant causal effect of genetically predicted TG on eGFR ((β = -1.3([-2.533—0.067]; p=0.039). HDL was not significantly associated with eGFR, just like in prior analyses.

Sensitivity analyses

We accounted for the pleiotropic effects between instrumental variables using MR-Egger, penalized robust MREgger, leave-one-out analysis, simple median, and weighted median analyses. We found no evidence of horizontal pleiotropy between IVs using the MR-Egger regression intercept analysis. All associations had p-values > 0.005 for the MR-Egger intercept, as shown in **figure s2**. We further estimated any horizontal pleiotropy using the leave-one-out approach and found no evidence of any confounding due to pleiotropy between SNPs with all p-value > 0.05 **(Table2)**.

Discussion

In this African-ancestry MR study, we investigated the causal effect of genetically predicted lipid traits on eGFRcrea using a two-sample and multivariable MR approach. In the primary MR-IVW forward analysis, LDL-C and TC showed evidence of a significant causal association with eGFR. Therefore, we report significant evidence that genetically predicted lipids; LDL and TC are causally associated with eGFRcrea in this African population. However, the reverse MR-IVW analysis indicated a non-significant causal association between eGFRcrea and either of the genetically predicted lipids.

Our findings in the main analysis on HDL and TC differ from those reported on MR analyses in European ancestry cohorts by Lanktree *et al*. and other groups[16, 17, 30]. They reported a significant association between higher HDL levels with higher eGFR. Here, we report no evidence of association between genetically-proxied HDL cholesterol and better kidney function in this African cohort. However, our findings tally with those from another study based on European ancestry individuals using GLCG and CKDGen consortium datasets which reported a non-significant effect of HDL on eGFR levels [8]. Notably, elevated HDL has been shown to lower the mortality rate of CKD within observed ranges [31].

Our causal association between LDL and eGFR differs with findings from elsewhere [4, 10]. The Chronic Renal Insufficiency Cohort Study reported no association between LDL-C levels and the change rate of eGFR in low proteinuria individuals at baseline [32]. We, therefore, suggest better powered future studies within the same African ancestry to

clarify the true association between serum lipids and kidney function as measured by eGFR in this ancestry.

The reverse univariable analysis showed no evidence of a significant causal association between eGFR and lipid traits. Our findings from the reverse association between eGFR and serum lipids are consistent with findings elsewhere[33].

In the main univariable analysis, we report that high LDL and TC levels had a strong significant causal effect on eGFR levels. In the multivariable MR analysis, low TG levels had a protective effect on eGFR. Unlike TC, genetically predicted low TG levels showed a consistent causal effect on eGFR between the MVMR and the main forward univariable analysis, showing significance in the latter. Findings from other studies have reported a conflicting association between TG and eGFR, but these have been based on European ancestry populations [16, 33-35]. Evidence from observational studies supports a greater triglyceride to HDL cholesterol ratio as associated with a decline in eGFR [20, 36]. These observational studies are, however, limited by confounding and inability to determine direction of effect.

The respective directions of effect from the MVMR analysis were quite similar to those observed in the forward univariable MR analysis. In this MVMR analysis, both LDL and TG had protective causal effects on eGFR. The un-expected direction of effect of genetically predicted LDL and TG on eGFR reported in this study might be due to the low statistical power in this study. Noteworthy, a recent study reported an inconsistent evidence between higher atherogenic lipids including LDL-C, TG, and Apo B and weak increase in eGFR [33]. A higher eGFR association with higher LDL-C and TG has been previously associated with glomerular hyperfiltration rates that occur in individuals with cardiometabolic conditions [37]. We couldn't verify the role of underlying cardiometabolic conditions towards the observations in this study. We recommend a more powered study on African-ancestry individuals, accounting for such clinical parameters to further clarify our findings.

Our study strengths were in the use of continental African-derived GWAS summary statistics (MALG) and assessing a possibility for a reverse causation between eGFR and serum lipids. We also performed sensitivity analyses including multi-variable MR-Egger to determine reliability of our instrumental variables as detailed under the methods section.

Study limitations

The study was limited by a lack of access to individual-level data as we only had access to GWAS summary statistics. This meant that the strength of the instruments used couldn't be measured directly. Therefore, we couldn't measure a possible bias caused by weak instruments. In our case, weak instruments would lead to an estimate of the causal effect that is biased toward the observational effect estimate. The study was also limited by power, and we also didn't correct for sample overlap. We also did not assess for ancestral differences in the instrumental variables with other ancestries, as suggested by Graham et al. [38].

Conclusions

This Mendelian Randomization study suggests a causal association between LDL cholesterol and higher eGFR, but not HDL cholesterol. We report that genetically elevated LDL cholesterol levels are associated with developing higher eGFR. Our findings suggest that the relationship between non-HDL cholesterol and kidney function may be U-shaped. This may be a reason why LDL is seen to be a poor predictor of renal function compared to HDL, and as such lowering LDL does not necessarily improve risk of kidney disease. Therefore, our findings highlight the need for bigger MR studies focused on African ancestry individuals to accurately determine the association between serum lipid traits and kidney function measured by eGFRcrea in continental Africans.

Data sharing statement

All scripts for the analysis are available from the authors upon request.

Contributors

SF conceptualised the study. CK performed the analyses. OS verified the underlying data. CK, OS, TC and SF wrote the first draft of the manuscript. All authors read and approved the final version of the manuscript.

Declaration of interests

DG is employed part-time by Novo Nordisk and has received consultancy fees from Policy Wisdom. No potential conflicts of interest relevant to this article were reported by all other authors.

Acknowledgements

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Dr. Segun Fatumo 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.

Tables and figures

Tables

Table1: **Univariable IVW Mendelian Randomization results**. LDL-C: low-density lipoprotein cholesterol; HDL-C: high-density lipoprotein cholesterol; TC: Total Cholesterol; TG: Triglycerides; IVW: Inverse Variance Weighted; SE, standard error. *statistically significant ($p < 0.05$)

Exposure	Outcome	BETA	SE	95%CI	P-value
HDL	eGFR	-0.164	0.594	-1.329-1	0.782
LDL	eGFR	1.1	0.351	0.411-1.788	0.002*
TC	eGFR	1.619	0.616	0.412-2.826	0.009*
TG	eGFR	-0.934	0.96	-2.815-0.947	0.33

Table2: Leave-one-out sensitivity analyses for all SNPs in the Multivariable MR

SNP	MR-Egger intercept	SE	95% CI	P-value
rs1800588	-0.058	0.084	-0.222-0.107	0.493
rs17111732	-0.038	0.098	-0.229-0.153	0.698
rs116513376	-0.061	0.085	-0.227-0.106	0.476
rs59523416	-0.056	0.084	-0.220-0.108	0.503
rs12740374	-0.028	0.073	-0.171-0.115	0.703
rs143375141	-0.070	0.085	-0.236-0.097	0.413
rs35804417	-0.057	0.084	-0.221-0.107	0.497
rs75143493	-0.073	0.075	-0.220-0.075	0.334
rs73015020	-0.095	0.079	-0.250-0.060	0.229
rs10416720	-0.076	0.089	-0.251-0.099	0.393
rs7412	-0.084	0.095	-0.271-0.102	0.375
rs3810308	-0.107	0.083	-0.270-0.056	0.199
rs326	-0.073	0.088	-0.246-0.100	0.406
rs2070895	-0.054	0.088	-0.227-0.119	0.538

rs12721054	-0.035	0.069	-0.170-0.101	0.613
rs114139997	-0.054	0.077	-0.204-0.096	0.477

Supplementary material

Supplementary tables

Table S1: **Reverse Mendelian Randomization results**. *LDL: low-density lipoprotein cholesterol; HDL: High-density lipoprotein cholesterol; TC: Total Cholesterol; TG: Triglycerides

Exposure	Outcome	BETA	SE	95%CI	P
eGFR	HDL	0.001	0.006	-0.011-0.012	0.873
eGFR	LDL	0.007	0.006	-0.005-0.018	0.265
eGFR	TC	0.008	0.007	-0.005-0.21	0.225
eGFR	TG	0	0.006	-0.011-0.011	0.984

Table S2: **Multivariable Mendelian Randomization results**. *LDL: low-density lipoprotein cholesterol; HDL: High-density lipoprotein cholesterol; TG: Triglycerides; SE: standard error; CI: confidence interval

Exposure Trait	Outcome	BETA	SE	95%CI	P
HDL	eGFRcrea	-0.117	0.579	-1.252-0.018	0.84
LDL	eGFRcrea	1.228	0.383	0.477-1.979	0.001
TG	eGFRcrea	-1.3	0.629	-2.533-0.067	0.039

Table S3: Heterogeneity Tests. LDL: low-density lipoprotein cholesterol; HDL: High-density lipoprotein cholesterol; TG: Triglycerides; TC: total cholesterol

Exposure trait	Cochran's Q	I^2(%)	p-value
HDL	2.3129	56.8	0.1283
LDL	11.5815	22.3	0.2379
TC	9.5642	47.7	0.0886
TG	7.4009	59.5	0.0602

Figures

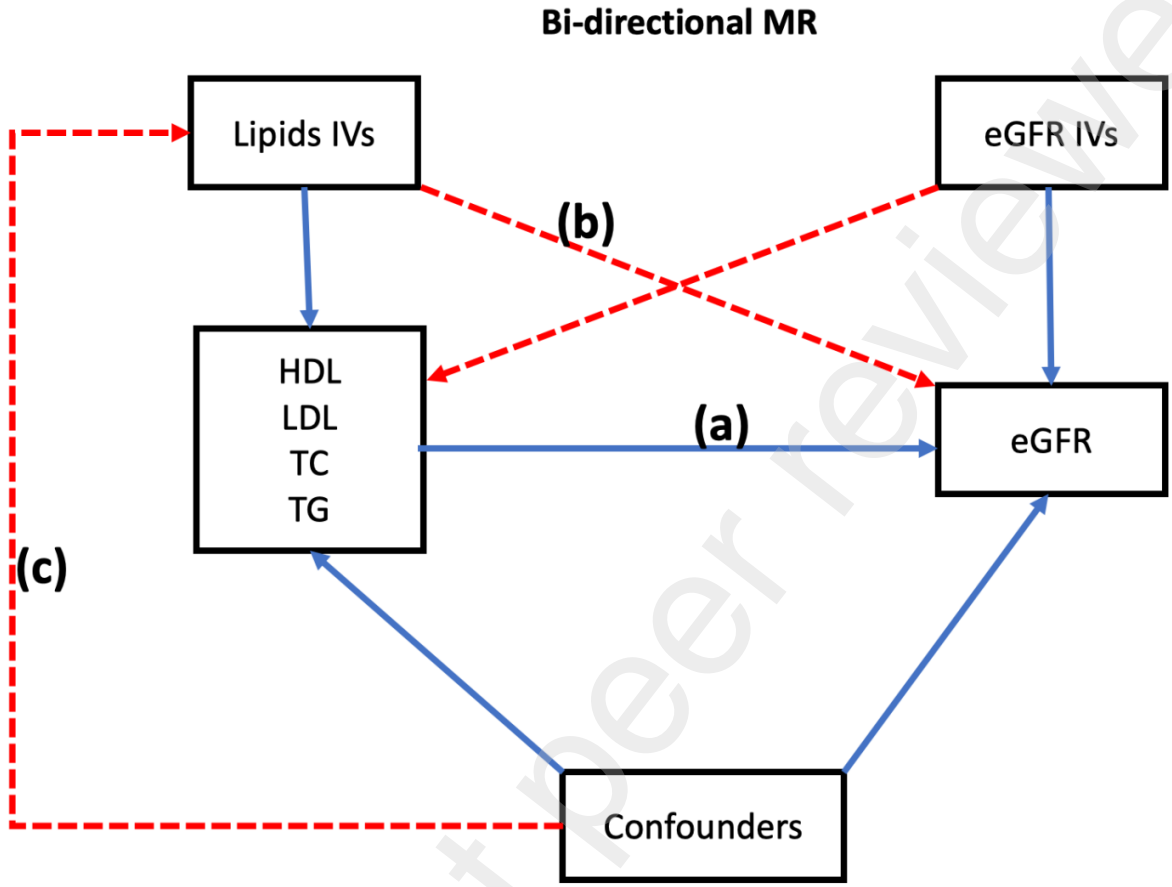


Figure 1: A schematic representation of bi-directional MR analyses: (a) Forward univariable MR; (b) IVs for lipid traits should not have an association with eGFR; (c) IVs for lipid traits are not related to measured or unmeasured confounding. HDL, high-density lipoprotein; LDL, low-density lipoprotein; TG, triglycerides; eGFR, estimated glomerular filtration rate; SNP, single-nucleotide polymorphism; MR, Mendelian Randomization; F/R, Forward/Reverse; IVs, Instrumental variables.

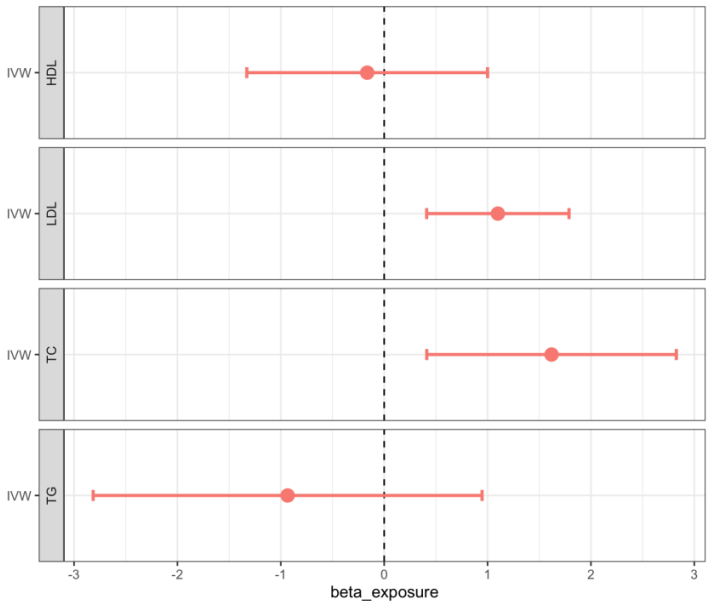


Figure2: Forest plot of the beta estimates and their 95% confidence intervals between genetically predicted lipid traits and eGFR using the IVW univaribale MR method. IVW, inverse-variance weighted; HDL, high-density lipoprotein cholesterol; LDL, low-density lipoprotein cholesterol, TC: total cholesterol

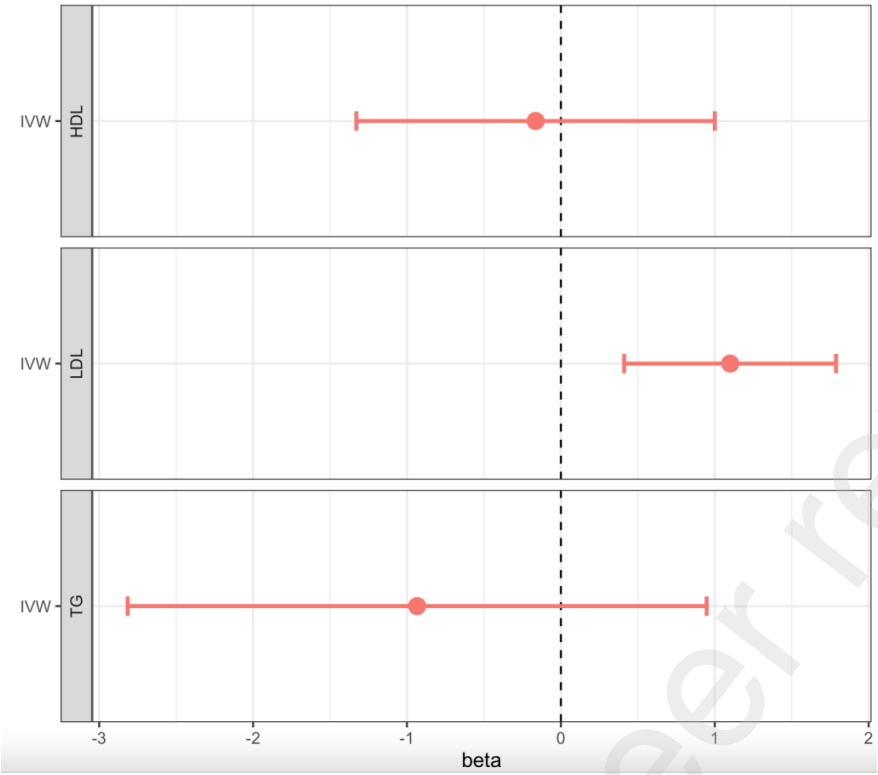


Figure 3: Forest plot showing the beta estimates and 95% confidence intervals of Multivariate MR of lipids vs eGFR traits. HDL-C: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol; TG: Triglycerides

Supplementary figures

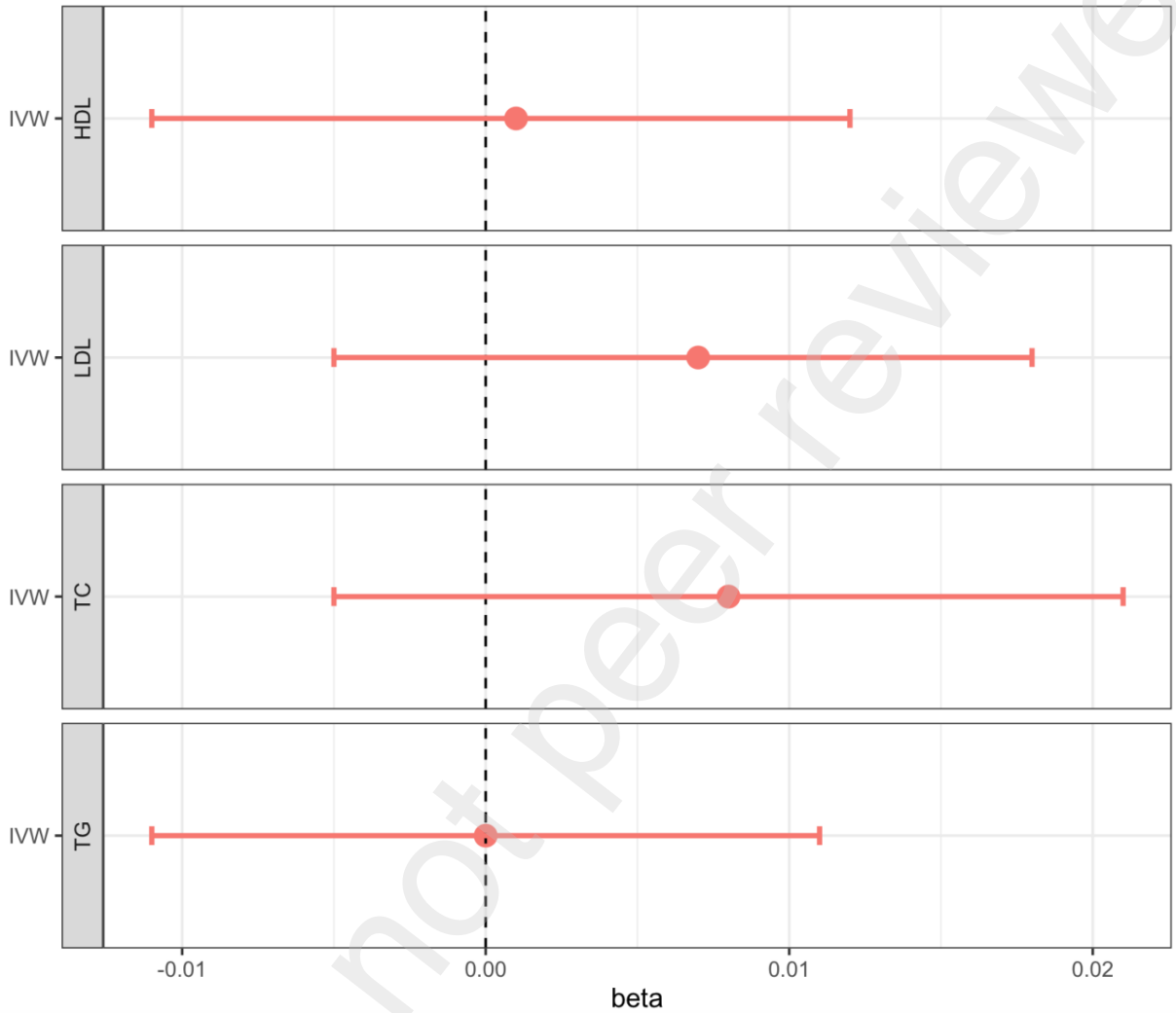
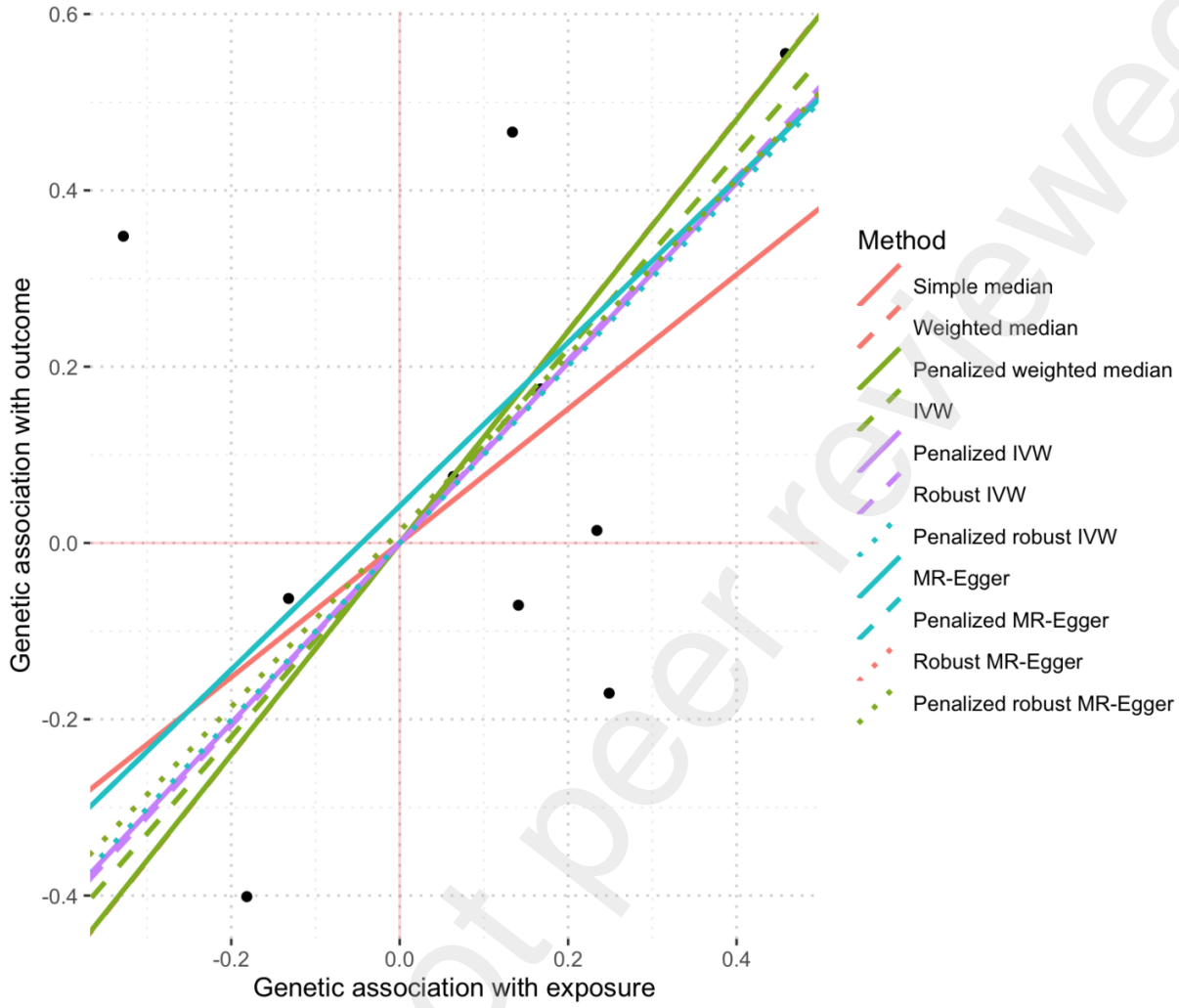
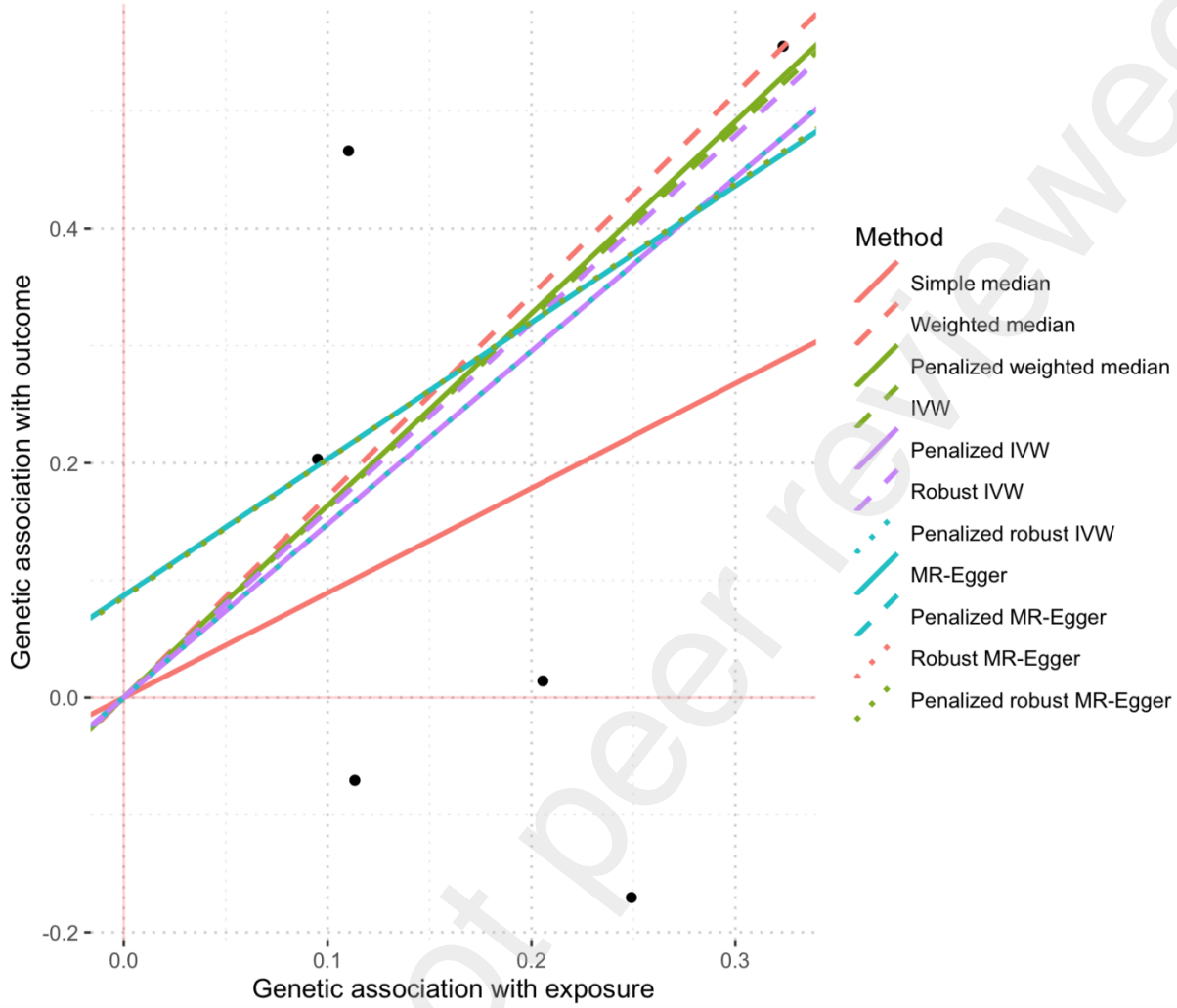


Figure S1: Forest plot showing the beta estimates and their 95% confidence intervals of reverse MR of eGFRcrea vs lipid traits. HDL-C: high-density lipoprotein cholesterol; IVW: inverse-variance weighted; LDL-C: low-density lipoprotein cholesterol; Total C: total cholesterol; TG: Triglycerides



(a)



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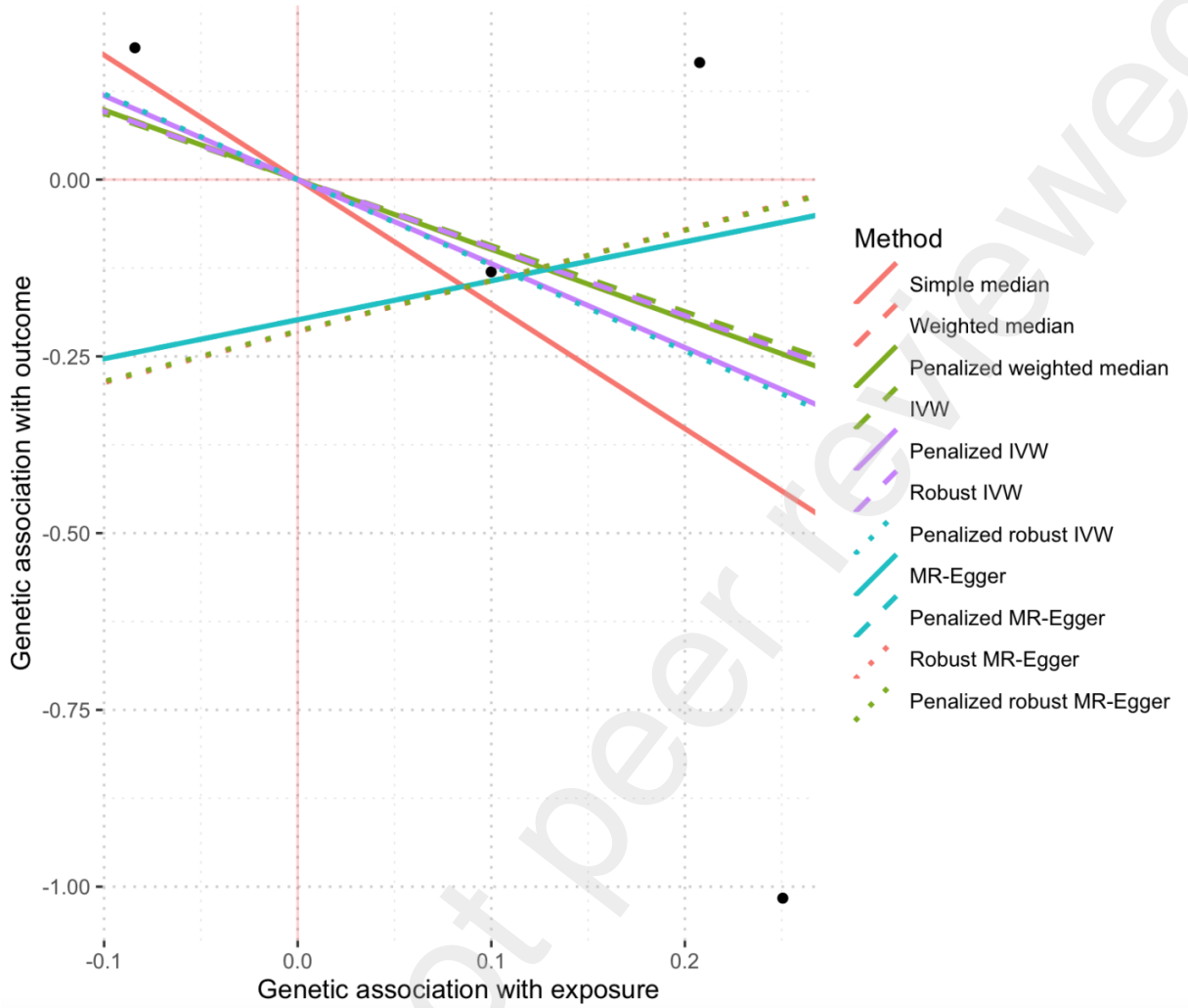

(c)

Figure S2: Estimated causal effects of lipids on eGFR using univariable MR assessed using different MR methods: (a) Causal estimates for LDL, (b) Causal estimates for TC (c) causal estimates for TG. LDL-C, low-density lipoprotein; TG, triglycerides; eGFRcrea, estimated glomerular filtration rate based on creatinine measurements; IVW, inverse variance-weighted

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