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Association of Lipid Fractions With Risks for Coronary Artery Disease and Diabetes

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Editorial page 631

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IMPORTANCE Low-density lipoprotein cholesterol (LDL-C) is causally related to coronary artery disease (CAD), but the relevance of high-density lipoprotein cholesterol (HDL-C) and triglycerides (TGs) is uncertain. Lowering of LDL-C levels by statin therapy modestly increases the risk of type 2 diabetes, but it is unknown whether this effect is specific to statins.

OBJECTIVE To investigate the associations of 3 routinely measured lipid fractions with CAD and diabetes through mendelian randomization (MR) using conventional MR and making use of newer approaches, such as multivariate MR and MR-Egger, that address the pleiotropy of genetic instruments where relevant.

DESIGN, SETTING, AND PARTICIPANTS Published data from genome-wide association studies were used to construct genetic instruments and then applied to investigate associations between lipid fractions and the risk of CAD and diabetes using MR approaches that took into account pleiotropy of genetic instruments. The study was conducted from March 12 to December 31, 2015.

MAIN OUTCOMES AND MEASURES Coronary artery disease and diabetes.

RESULTS Genetic instruments composed of 130 single-nucleotide polymorphisms (SNPs) were used for LDL-C (explaining 7.9% of its variance), 140 SNPs for HDL-C (6.6% of variance), and 140 SNPs for TGs (5.9% of variance). A 1-SD genetically instrumented elevation in LDL-C levels (equivalent to 38 mg/dL) and TG levels (equivalent to 89 mg/dL) was associated with higher CAD risk; odds ratios (ORs) were 1.68 (95% CI, 1.51-1.87) for LDL-C and 1.28 (95% CI, 1.13-1.45) for TGs. The corresponding OR for HDL-C (equivalent to a 16-mg/dL increase) was 0.95 (95% CI, 0.85-1.06). All 3 lipid traits were associated with a lower risk of type 2 diabetes. The ORs were 0.79 (95% CI, 0.71-0.88) for LDL-C and 0.83 (95% CI, 0.76-0.90) for HDL-C per 1-SD elevation. For TG, the MR estimates for diabetes were inconsistent, with MR-Egger giving an OR of 0.83 (95%CI, 0.72-0.95) per 1-SD elevation.

CONCLUSIONS AND RELEVANCE Routinely measured lipid fractions exhibit contrasting associations with the risk of CAD and diabetes. Increased LDL-C, HDL-C, and possibly TG levels are associated with a lower risk of diabetes. This information will be relevant to the design of clinical trials of lipid-modifying agents, which should carefully monitor participants for dysglycemia and the incidence of diabetes.

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Understanding the interplay between circulating lipids and the risk of type 2 diabetes and coronary artery disease (CAD) is of emerging public health importance and has implications for drug development for cardiovascular disease prevention.[1,2] For example, a causal influence of low-density lipoprotein cholesterol (LDL-C) on CAD is widely accepted[3-5] and the proposed causal role of triglycerides (TGs) in CAD is gaining acceptance.[6,7] In contrast, the role of high-density lipoprotein cholesterol (HDL-C) in CAD remains in doubt.[7-9]

However, evidence has emerged that LDL-C reduction with statin therapy results in a modest increase in risk of type 2 diabetes[10,11] (outweighed by the benefit of statins in protection from CAD).[12] Whether this diabetogenic effect is a general consequence of LDL-C lowering or whether it is specific to inhibition of hydroxymethylglutaryl coenzyme A reductase remains unclear.[13] Moreover, the role of TGs and HDL-C in the development of diabetes remains uncertain.[14]

Residual confounding and reverse causality can limit causal inference from observational studies. When a genetic instrument can be used as an instrument for an exposure, mendelian randomization (MR) generates unbiased, unconfounded effect estimates that are sometimes taken as evidence of a causal role. This interpretation is because genotype is not modifiable by disease and the random allocation of alleles at gametogenesis helps to avoid bias in studies arising due to reverse causality and confounding, respectively.

A critical assumption of the MR paradigm is that the genetic instrument influences disease risk exclusively through the exposure of interest. However, genetic variants used to proxy the exposure of interest can also associate with other traits, a phenomenon termed *pleiotropy*. When pleiotropy arises as a downstream consequence of genetic perturbation of the biomarker of interest, it is referred to as *vertical* pleiotropy and the MR assumption is preserved.[15] However, when pleiotropy arises because of the association of genetic variants with additional phenotypes in alternative disease pathways (termed *horizontal* pleiotropy), the assumption is compromised. When MR analysis is based on multiple single-nucleotide polymorphisms (SNPs) drawn from different regions of the genome selected systematically for their association with the biomarker of interest, additional nonsystematic effects on any other biomarkers might be balanced and the MR effect estimate could still be valid. However, if horizontal pleiotropy is unbalanced, as might occur when the set of biomarkers concerned comes from closely connected pathways, MR estimates may become systematically biased (termed *unbalanced* or *directional* pleiotropy[16]), resulting in invalid effect estimates (**Figure 1**).

Recent methodologic advances in MR analysis, including multivariate MR[17] and MR-Egger,[16] provide new approaches for dealing with pleiotropic genetic instruments. In multivariate MR, adjustment is made for genetic associations with measured traits but may not fully account for unbalanced pleiotropy.[18] In contrast, MR-Egger can detect and correct for unbalanced pleiotropy of the genetic instrument, even when unbalanced pleiotropy is mediated through unmeasured or unknown traits; a disadvantage being a reduction in power.

Key Points

Question Are levels of routinely measured lipids associated with the risk of cardiometabolic disease?

Findings In this mendelian randomization analysis, a lifelong higher low-density lipoprotein cholesterol (LDL-C) and triglyceride (TG) levels was found to be associated with higher risk of coronary artery disease. In contrast, higher levels of all 3 lipid traits (LDL-C, high-density lipoprotein cholesterol, and TGs) was associated with a reduced risk of diabetes.

Meaning Lower LDL-C and TG levels may increase risk of diabetes; clinical trials of lipid-modifying agents should carefully monitor for the incidence of diabetes.

We used summary data from multiple major cardiometabolic genome-wide association studies to investigate the underlying associations between lipid levels, diabetes, and CAD using 3 MR approaches: (1) conventional MR, which does not account for pleiotropy; (2) multivariate MR, which adjusts for traits that may mediate unbalanced pleiotropy; and (3) MR-Egger, which more fully accounts for unbalanced pleiotropy.

Methods

Data Sources

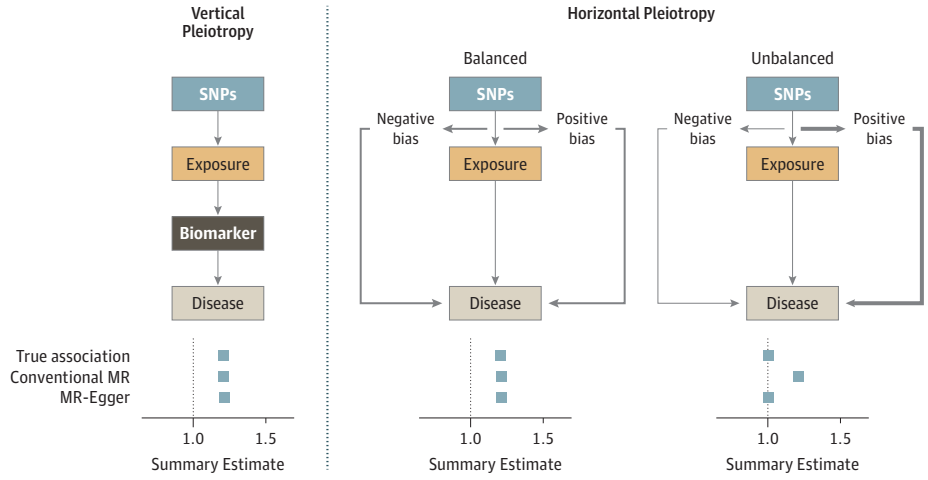
We used summary-level data for lipids from the Global Lipids Genetics Consortium,[19] diabetes data from the Diabetes Genetics Replication and Meta-analysis,[20] and CAD data from the Coronary Artery Disease Genome-wide Replication and Meta-analysis plus Coronary Artery Disease Genetics.[21] Details of the consortia are provided in the **Table**. All data sets were limited to individuals of European ancestry; β coefficients and SEs were obtained for the per-allele association of each SNP with all exposures and outcomes from these data sources. If SNPs were not present in a data set, we used proxies ($R^2 > 0.9$) as indicated in **Figure 2**. The study was conducted from March 12 to December 31, 2015.

Because this report used published genome-wide association studies data available in the public domain, specific ethical review and/or consent from study participants was not sought (and had been obtained in the original studies).

Selection of SNPs

We used 185 lipid-associated SNPs identified by Willer et al[19] to generate a series of genetic instruments for each of the exposures: LDL-C, HDL-C, and TGs. This process was conducted by first restricting to a set of SNPs in low linkage disequilibrium (pairwise $R^2<0.2$). We then organized these SNPs by descending order of proportional variance (R^2, estimated from the summary statistics using the gtx package in R [https://www.r-project.org/]) between SNPs with the corresponding lipid exposure to generate a range of instruments from 5 to 150 SNPs. The process used to determine the final tally of SNPs for inclusion in a genetic instrument for each lipid trait is described below.

Figure 1. Pleiotropy and the Validity of Estimates Derived From Mendelian Randomization



Single-nucleotide polymorphisms (SNPs) are used in a genetic instrument for an exposure to assess the association with risk of disease. For each exposure there is a true association, which we try to approximate from mendelian randomization (MR). For the purposes of simplicity, conventional MR is compared with MR-Egger. Vertical pleiotropy explains where the genetic instrument associates with biomarkers (other than the exposure) that are on the causal pathway from exposure through disease. Horizontal pleiotropy is where the genetic instrument associates with additional traits not on the causal pathway of the exposure of interest. When horizontal pleiotropy is balanced, there should be no bias in the effect derived from MR. In this scenario, the estimate obtained from conventional MR is similar to that from MR-Egger. When horizontal pleiotropy is unbalanced (also termed directional pleiotropy), the pleiotropy systematically biases the estimate (which can be exaggerated or diminished) in a naive analysis using conventional MR. In the example given in this figure, the unbalanced pleiotropy exaggerates the magnitude of the association. Conventional MR will derive a biased estimate, whereas MR-Egger, correcting for unbalanced pleiotropy, should yield a valid estimate. An example of unbalanced horizontal pleiotropy is the association between high-density lipoprotein cholesterol (HDL-C) and risk of coronary artery disease (CAD); the association derived from conventional MR is different from that of MR-Egger, with the latter indicating that, once unbalanced pleiotropy is accounted for, there is no effect of HDL-C on risk of CAD.

Table. Details of the Consortia

Consortium	Trait/Disease	No. of Participants	Data Source
GLGC[19]	LDL-C, HDL-C, TGs	188 577	http://www.sph.umich.edu/csg/abecasis/public/lipids2013
DIAGRAM[20]	Diabetes	Diabetes, 34 840; controls, 114 981	http://diagram-consortium.org (version 3 data set)
CARDIoGRAMplusC4D[21]	CAD	CAD, 63 746; controls, 130 681	http://www.cardiogramplusc4d.org

Abbreviations: CAD, coronary artery disease; CARIoGRAMplusC4D, Coronary Artery Disease Genome-wide Replication and Meta-analysis plus Coronary Artery Disease Genetics; DIAGRAM, Diabetes Genetics Replication and Meta-analysis; GLGC, Global Lipids Genetic Consortium; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TGs, triglycerides.

Handling of SNPs

We matched SNPs across the data sources by aligning them to the same effect allele. Effect allele frequencies were checked for concordance.

MR Analyses

We used 3 MR approaches. First, we conducted conventional 2-sample instrumental variable analyses, which do not make any allowance for pleiotropy. Basing our approach on the method first proposed by Johnson,[22] we incorporated the bootstrap suggested by Bowden et al[16] as a way to incorporate the error in the published estimates of SNP effect on both exposure and outcome.

Second, we conducted multivariate MR analyses, which statistically adjust for pleiotropy with additional phenotypes measured in the data set.[23] Multivariate MR is an extension of the conventional weighted regression in which the β values for additional phenotypes are included as covariates. In this case we used all 3 lipid traits in the model (eg, for the HDL-C instrument, we included LDL-C and TGs, thereby adjusting for them).

Third, we used MR-Egger,[16] which accounts for unbalanced pleiotropy of a genetic instrument. MR-Egger is a linear regression of estimated SNP effects (for the exposure-raising allele) on exposure against the corresponding estimates of SNP on outcome weighted by the inverse variance of the SNP on outcome effect estimates. This approach differs from conventional 2-sample MR in that the regression line is not forced through the origin. Bowden et al[16] showed that the MR-Egger estimate is unaffected by net pleiotropic effects of the instrument and that the presence of unbalanced pleiotropy can be inferred if the intercept term is not zero.

For all 3 approaches (conventional MR, multivariate MR, and MR-Egger), we conducted 10 000 bootstraps, and our effect estimate is the mean of the bootstraps with the CI deter-

mined empirically and set to Bonferroni-adjusted (for 6 tests) 95% (ie, 99.2%).

Quantifying the Proportion of Variance Explained by the Genetic Instruments

R Trend

The proportion of variance (R^2) of the trait explained by the genetic instrument will rise with the addition of more SNPs. However, the improvement beyond the optimum number of SNPs in the instrument will occur increasingly as a result of model overspecification. We examined the ratio of R^2 for the current instrument to R^2 for an instrument comprising 30 more SNPs (we term this the *R* trend). The trend in the ratio gives an indication of the transition from useful additional information to overspecification since it becomes asymptotic when each new SNP adds the same amount of information than the last. We judged the beginning of the asymptotic phase of the line to mark the largest useful instrument obtainable from the available data. The 30-SNP window was chosen empirically because it emphasizes trend; a smaller window gave a more erratic line, obscuring the trend. Calculation and use of the *R* trend effectively limited the analysis to instruments comprising 155 or fewer SNPs, further restricted to 150 for presentational purposes.

Gain From Adding a SNP to the Instrument

We estimated the benefit to R^2 from adding the current SNP to the previous instrument by bootstrapping the summary statistics and calculating R^2 values for the instruments with n and (n − 1) SNPs. While performing 10 000 bootstraps, we noted the number of occasions when the current instrument gave higher R^2 than the previous instrument. This value was summarized as a percentage; the point at which the current instrument was no better than the previous instrument was when 50% of the runs showed a benefit.

Selection of Optimal Number of SNPs

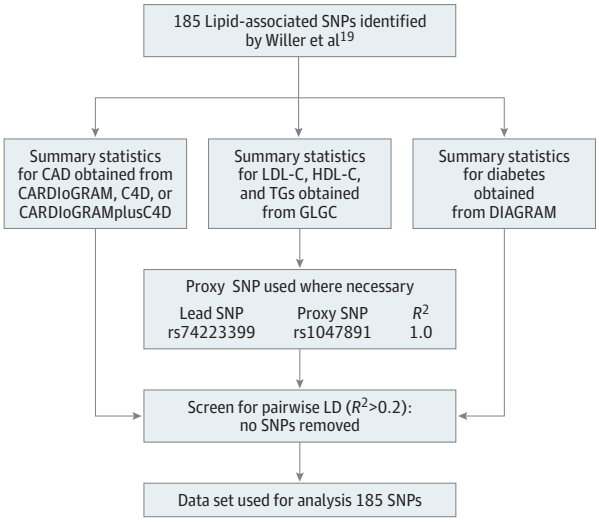
The optimum number of SNPs was chosen by consideration of the *R* trend and the gain from adding the current SNP when presented graphically (eFigures 1-6 in the Supplement). The optimum instrument was identified when both estimates of R^2 gain were asymptotic. As discussed below, the exact point (±20 SNPs) makes little difference to the conclusions. After independent consideration, 2 investigators (J.W. and M.V.H.) reached a consensus as to the number of SNPs to include for each genetic instrument for each lipid trait.

Selection of MR Model to Derive Estimates of the Underlying Association

Once we determined the optimal number of SNPs to incorporate in each instrument, we used the following decision tree to select the MR approach to derive the estimate:

1. if there was no evidence of unbalanced pleiotropy using the intercept derived from MR-Egger, we selected the conventional MR instrumental variable estimate as the most reliable indicator to the underlying association since it retains maximal power and makes the fewest assumptions;
2. if there was evidence of unbalanced pleiotropy, we used the estimate from MR-Egger; and
3. in cases of discordance between conventional MR and MR-Egger, we used multivariate MR to inform whether differences could arise from pathways shared between the 3 lipid traits.

Figure 2. Pipeline for Derivation of the Data Set Used for Mendelian Randomization Analyses of Lipid Subtypes With Risk of Coronary Artery Disease (CAD) and Diabetes



CARDIoGRAM indicates Coronary Artery Disease Genome-wide Replication and Meta-analysis; C4D, Coronary Artery Disease Genetics; DIAGRAM, Diabetes Genetics Replication and Meta-analysis; GLGC, Global Lipids Genetics Consortium; HDL-C, high-density lipoprotein cholesterol; LD, linkage disequilibrium; LDL-C, low-density lipoprotein cholesterol; SNP, single-nucleotide polymorphism; and TGs, triglycerides.

The inSIDE Assumption

Because the underlying models assume a linear dose response, instrumental variable effect estimates must be independent of the exposure effect in MR analysis (ie, the Instrument Strength Independent of Direct Effect [inSIDE] rule).[16] We tested the null hypothesis that the instrumental variable effect (derived from the ratio of outcome to exposure) estimates for the SNPs in an instrument were independent of the exposure (lipid) effect estimates for the same SNPs for both CAD and diabetes. In all scenarios, the inSIDE assumption was satisfied (eTable 1 in the Supplement).

Power

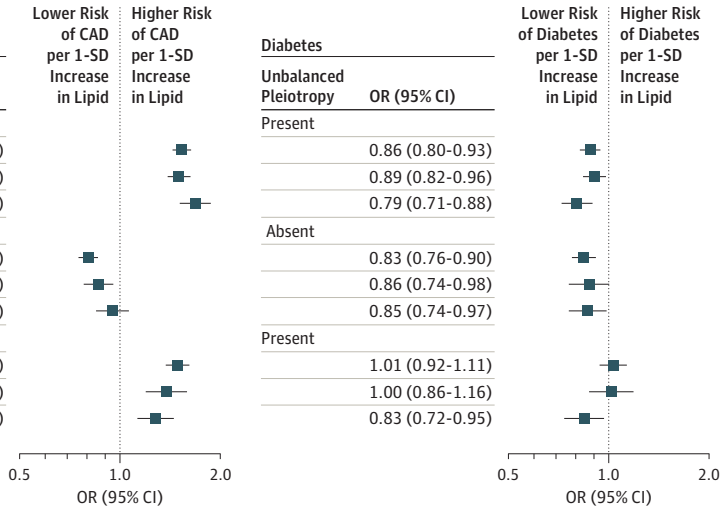
We followed the method of Brion et al[24] (http://cnsgenomics.com/shiny/mRnd/). Using the mean number of individuals and estimated R^2 for the instrument together with the reported proportion of cases, we adjusted the estimate of the true effect of exposure on outcome to obtain the value for which we had 80% power at a Bonferroni-adjusted α value of .05/6.

Results

The pooled data set included 188 577 individuals with measures of blood lipids, 63 158 CAD cases, and 34 840 diabetes

Figure 3. Associations of Routinely Measured Lipids With Risk of Coronary Artery Disease (CAD) and Diabetes From Mendelian Randomization (MR) Analyses

Lipid, MR Model	No. of SNPs	R^2	Coronary Artery Disease: Unbalanced Pleiotropy	Coronary Artery Disease: OR (95% CI)	Diabetes: Unbalanced Pleiotropy	Diabetes: OR (95% CI)
LDL-C (per 1-SD [38-mg/dL] increase)			Present		Present	
Conventional	130	0.08		1.53 (1.44-1.64)		0.86 (0.80-0.93)
MVMR	130	0.08		1.50 (1.39-1.63)		0.89 (0.82-0.96)
MR-Egger	130	0.08		1.68 (1.51-1.87)		0.79 (0.71-0.88)
HDL-C (per 1-SD [16-mg/dL] increase)			Present		Absent	
Conventional	140	0.07		0.80 (0.75-0.86)		0.83 (0.76-0.90)
MVMR	140	0.07		0.86 (0.78-0.96)		0.86 (0.74-0.98)
MR-Egger	140	0.07		0.95 (0.85-1.06)		0.85 (0.74-0.97)
TG (per 1-SD [89-mg/dL] increase)			Present		Present	
Conventional	140	0.06		1.49 (1.37-1.62)		1.01 (0.92-1.11)
MVMR	140	0.06		1.38 (1.19-1.59)		1.00 (0.86-1.16)
MR-Egger	140	0.06		1.28 (1.13-1.45)		0.83 (0.72-0.95)



A description of the 3 mendelian randomization models is provided in the Methods section. Estimates for conventional MR were derived from 2-sample MR that forces the slope through the origin, thereby not accounting for pleiotropy. Multivariate MR statistically adjusts for other lipid traits, and MR-Egger adjusts for unbalanced pleiotropy. R^2 refers to the proportion of variance of lipid traits explained by the genetic instrument; 95% CIs are Bonferroni-adjusted. To convert high-density lipoprotein cholesterol (HDL-C) and low-density lipoprotein cholesterol (LDL-C) to millimoles per liter, multiply by 0.0259; to convert triglycerides (TGs) to millimoles per liter, multiply by 0.0113. OR indicates odds ratio; SNPs, single-nucleotide polymorphisms.

cases. The optimal number of SNPs for each lipid trait was 130 for LDL-C (explaining 7.9% of its variance), 140 for HDL-C (6.6% of the variance), and 140 for TG (5.9% of the variance) (eFigures 1-6 in the Supplement).

Low-Density Lipoprotein Cholesterol

The genetic instrument for LDL-C showed unbalanced pleiotropy for CAD and diabetes. For CAD, the estimate derived from MR-Egger was an OR of 1.68 (95% CI, 1.51-1.87) per 1-SD (equivalent to 38 mg/dL [to convert to millimoles per liter, multiply by 0.0259]) genetically instrumented higher LDL-C. This was of greater magnitude but directionally consistent with conventional and multivariate MR estimates (**Figure 3** and eFigure 1 in the Supplement). For diabetes, the OR was 0.79 (95% CI, 0.71-0.88) per 1-SD higher LDL-C from MR-Egger, which was again of greater magnitude yet directionally consistent with conventional and multivariate MR estimates (Figure 3 and eFigure 2 in the Supplement).

High-Density Lipoprotein Cholesterol

A 1-SD genetically instrumented elevation in HDL-C (equivalent to 16 mg/dL [to convert to millimoles per liter, multiply by 0.0259]) did not provide conclusive evidence of an association between HDL-C and risk of CAD. There was evidence of unbalanced pleiotropy of the HDL-C genetic instrument, and the estimate for CAD from MR-Egger was an OR of 0.95 (95% CI, 0.85-1.06). There was a stepwise weakening of the effect toward the null from conventional MR (OR, 0.80; 95% CI, 0.75-0.86) through adjusting for LDL-C and TGs in multivariate MR (OR, 0.86; 95% CI, 0.78-0.96) to the MR-Egger estimate (Figure 3 and eFigure 3 in the Supplement).

For diabetes, there was no evidence of unbalanced pleiotropy of the genetic instrument comprising 140 SNPs. The conventional MR provided an estimate consistent with estimates from both multivariate MR and MR-Egger (OR, 0.83; 95% CI, 0.76-0.90) (Figure 3 and eFigure 4 in the Supplement).

Triglycerides

The TG genetic instrument showed unbalanced pleiotropy for both CAD and diabetes. A 1-SD genetically instrumented increase in TG (equivalent to 89 mg/dL [to convert to millimoles per liter, multiply by 0.0113]) yielded an OR for CAD from MR-Egger of 1.28 (95% CI, 1.13-1.45), which was weaker than the multivariate MR estimate (OR, 1.38; 95% CI, 1.19-1.59) and roughly half the magnitude of the conventional MR estimate (OR, 1.49; 95% CI, 1.37-1.62) (Figure 3 and eFigure 5 in the Supplement).

Triglycerides were associated with reduced risk of diabetes (OR, 0.83; 95% CI, 0.72-0.95 from MR-Egger). This was dissimilar to both conventional and multivariate MR estimates (Figure 3). The scatterplot identified that the intercept of the MR-Egger slope was positive (eFigure 6 in the Supplement).

Power

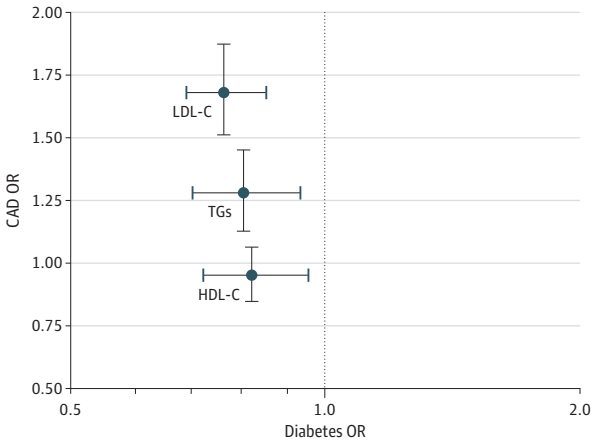
There was adequate power to detect the reported estimates (eTable 2 in the Supplement). The level of power made it unlikely that associations arose from chance.

Putting the Pieces Together: Framework of Associations

Our findings demonstrate that elevations in LDL-C, TG, and HDL-C levels are associated with a reduced risk of diabetes,

with the magnitude (per 1-SD increase) being greatest for LDL-C, then TG followed by HDL-C (although the 95% CI for the effect on diabetes for the 3 lipids overlap) (**Figure 4**). In contrast, only LDL-C and TG levels were associated with an increased risk of CAD (with the magnitude again stronger for LDL-C vs TG).

Figure 4. Crosshair Plot of a 1-SD Increase in Lipids and Risk of Coronary Artery Disease (CAD) and Diabetes



All estimates derived from mendelian randomization-Egger. Error bars represent 95% CIs that are Bonferroni-adjusted. HDL-C indicates high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; OR, odds ratio; and TGs, triglycerides.

Discussion

We exploited data from multiple genome-wide association studies to conduct MR analyses exploring the associations between lipids and risk of diabetes and CAD. Our findings reveal a series of associations that will help inform potential downstream consequences of pharmacologic modification of lipid levels.

Although all 3 lipids were associated with reduced risk of diabetes, it does not necessarily follow that lowering of LDL-C or TG levels through use of drugs that target specific proteins (eg, PCSK9) will alter the risk of diabetes. Large-scale genetic and clinical investigations are needed to clarify the effects of pharmacologic lowering of LDL-C and TG levels to gauge dysglycemic associations.[25,26]

Our findings are complementary to those from a study by Fall et al[13] that, to address pleiotropy, excluded SNPs showing strong associations with diabetes, glycemia-related traits, or potential confounders, such as adiposity. This manual pruning weakened the associations, yielding inconsistent conclusions. In our study, we applied novel approaches for SNP selection (to optimize the SNPs in each genetic instrument) and MR (using MR-Egger, obviating the need to manually prune SNPs); these approaches collectively allow us to make more robust conclusions about the role of lipids in diabetes.

To our knowledge, the protective effect of TGs in the risk of diabetes that we describe is novel, yet potentially counterintuitive. Observational studies[27] report that increases in TG levels are associated with an increase in the risk of diabetes; however, insulin resistance results in perturbations in TG metabolism,[28] meaning that the direction of the causal association is not clear. Although our data (suggesting that TGs may provide protection from diabetes) should be interpreted with caution, especially given that effect estimates from the 3 MR approaches were not consistent with one another, the findings are consistent with those of recent genetic studies[29,30] in both Europeans and African Americans. Further investigations are needed to identify which TG pathways, if any, may lead to a reduction in the risk of diabetes.

The effects of LDL-C and TGs on the risk of CAD were robust; however, the evidence on HDL-C was far less convincing, with the estimate from MR-Egger failing to identify an effect. This finding is in keeping with prior MR studies,[7,8] including that of Voight et al,[8] that manually pruned pleiotropic SNPs. However, choosing only nonpleiotropic SNPs could introduce selection bias in the genetic instrument by focusing on a subset of SNPs that is not representative of any meaningful proxy of HDL-C, with the removal of potentially informative HDL-C–related pathways. Our data show that adjusting for TGs and LDL-C in multivariate MR does not fully account for the unbalanced pleiotropy of the HDL-C genetic instrument. Use of MR-Egger identifies the likely underlying association is a genetically determined higher HDL-C that does not result in a reduced risk of CAD. Although these findings are consistent with those of recent trials of therapeutics targeting HDL-C,[9,31] the results do not preclude the possibility that a drug modifying HDL-C (or HDL particles) could reduce the risk of CAD or other outcomes, such as stroke.

The association of TGs with CAD recapitulates findings from prior MR and genetic studies.[6,7] The MR-Egger estimate for TG levels was less than half the magnitude for an equivalent increase in LDL-C levels (OR [95% CI], 1.28 [1.13-1.45]; and 1.68 [1.51-1.87] for TGs and LDL-C, respectively, per 1-SD increment). Specific TG-lowering approaches have had, at best, modest efficacy, whereas statin trials have had consistently positive results.[32,33] Our data suggest that pharmacologic lowering of TG levels should translate into CAD benefit.

The present study has several advantages. First, we used the most up-to-date data available for lipids to generate the most comprehensive genetic instruments available. Second, MR-Egger enabled inclusion of genome-wide association study–identified lipid-related SNPs in the genetic instruments regardless of the presence of unbalanced pleiotropy. Third, use of summary-level data from different sources represents an efficient study design to facilitate original investigations such as these without the cost or need for de novo phenotyping or genotyping.

The study also has some limitations. First, estimates could be sensitive to SNPs that were included in the genetic instruments. However, MR estimates were stable at the point at which we selected the genetic instrument. Second, our MR analyses pertain to biomarkers rather than specific drug targets. Mendelian randomization for validating individual targets is best achieved using SNPs in genes encoding the drug target of

interest.[34] Third, patients targeted for lipid modification may be at risk for other diseases, such as heart failure or atrial fibrillation; the relevance and direction of effects on these and other end points could be important but were not evaluated in this study. Fourth, we are not able to account for statin treatment in the analyses; given that we detected the protective effect of LDL-C on the risk of diabetes (the scenario that statins are most likely to confound), major bias is unlikely to arise in this setting. Finally, although our data cast further doubt on the relevance of HDL-C in development of CAD, it remains possible that individual HDL lipoproteins and/or lipid compositions could play an important role. New methods, such as hydrogen 1 nuclear magnetic resonance metabolomics,[35] that quantify lipoprotein subclasses and lipid compositions are likely to facilitate future MR studies of HDL subclasses.

Conclusions

Our comprehensive MR investigations identify distinct associations between major lipid subfractions and the risk of CAD and diabetes. Increased LDL-C and TG levels increase the risk of CAD. In contrast, an increase in LDL-C and HDL-C levels is likely to provide protection from diabetes, with new evidence suggesting that TGs may also play a protective role. Although further studies are needed to examine whether specific pathways or lipid subtypes are implicated, our findings inform potential expected downstream consequences of interventions affecting lipid traits and provide cautionary evidence that therapeutics that lower LDL-C and TG levels may have dysglycemic effects.

ARTICLE INFORMATION

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Author Contributions: Dr White 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.
Study concept and design: White, Hingorani, Holmes.
Acquisition, analysis, or interpretation of data: All authors.
Drafting of the manuscript: White, Holmes.
Critical revision of the manuscript for important intellectual content: Swerdlow, Preiss, Fairhurst-Hunter, Keating, Asselbergs, Sattar, Humphries, Hingorani, Holmes.
Statistical analysis: White, Holmes.
Administrative, technical, or material support: Keating.
Study supervision: Hingorani, Holmes.

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