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Association of Triglyceride-Lowering LPL Variants and LDL-C-Lowering LDLR Variants With Risk of Coronary Heart Disease

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IMPORTANCE Triglycerides and cholesterol are both carried in plasma by apolipoprotein B (ApoB)–containing lipoprotein particles. It is unknown whether lowering plasma triglyceride levels reduces the risk of cardiovascular events to the same extent as lowering low-density lipoprotein cholesterol (LDL-C) levels.

OBJECTIVE To compare the association of triglyceride-lowering variants in the lipoprotein lipase (LPL) gene and LDL-C–lowering variants in the LDL receptor gene (LDLR) with the risk of cardiovascular disease per unit change in ApoB.

DESIGN, SETTING, AND PARTICIPANTS Mendelian randomization analyses evaluating the associations of genetic scores composed of triglyceride-lowering variants in the LPL gene and LDL-C–lowering variants in the LDLR gene, respectively, with the risk of cardiovascular events among participants enrolled in 63 cohort or case-control studies conducted in North America or Europe between 1948 and 2017.

EXPOSURES Differences in plasma triglyceride, LDL-C, and ApoB levels associated with the LPL and LDLR genetic scores.

MAIN OUTCOMES AND MEASURES Odds ratio (OR) for coronary heart disease (CHD)—defined as coronary death, myocardial infarction, or coronary revascularization—per 10-mg/dL lower concentration of ApoB-containing lipoproteins.

RESULTS A total of 654,783 participants, including 91,129 cases of CHD, were included (mean age, 62.7 years; 51.4% women). For each 10-mg/dL lower level of ApoB-containing lipoproteins, the LPL score was associated with 69.9-mg/dL (95% CI, 68.1-71.6; \( P = 7.1 \times 10^{-1363} \)) lower triglyceride levels and 0.7-mg/dL (95% CI, 0.03-1.4; \( P = .04 \)) higher LDL-C levels; while the LDLR score was associated with 14.2-mg/dL (95% CI, 13.6-14.8; \( P = 1.4 \times 10^{-465} \)) lower LDL-C and 1.9-mg/dL (95% CI, 0.1-3.9; \( P = .04 \)) lower triglyceride levels. Despite these differences in associated lipid levels, the LPL and LDLR scores were associated with similar lower risk of CHD per 10-mg/dL lower level of ApoB-containing lipoproteins (OR, 0.771 [95% CI, 0.741-0.802]; \( P = 3.9 \times 10^{-38} \) and OR, 0.773 [95% CI, 0.747-0.801]; \( P = 1.1 \times 10^{-46} \), respectively). In multivariable mendelian randomization analyses, the associations between triglyceride and LDL-C levels with the risk of CHD became null after adjusting for differences in ApoB (triglycerides: OR, 1.014 [95% CI, 0.965-1.065], \( P = .19 \); LDL-C: OR, 1.010 [95% CI, 0.967-1.055], \( P = .19 \); ApoB: OR, 0.76 [95% CI, 0.723-0.798], \( P = 7.51 \times 10^{-20} \)).

CONCLUSIONS AND RELEVANCE Triglyceride-lowering LPL variants and LDL-C-lowering LDLR variants were associated with similar lower risk of CHD per unit difference in ApoB. Therefore, the clinical benefit of lowering triglyceride and LDL-C levels may be proportional to the absolute change in ApoB.
All major clinical guidelines recommend treatment to lower plasma low-density lipoprotein cholesterol (LDL-C) because numerous randomized trials have demonstrated that therapies that lower LDL-C levels by reducing LDL particles through upregulation of the LDL receptor (LDL-R) reduce the risk of cardiovascular events.\textsuperscript{1-5} By contrast, the guidelines do not recommend treatment to lower plasma triglyceride levels because randomized trials have not provided consistent evidence that lowering plasma triglyceride levels reduces the risk of cardiovascular events.\textsuperscript{1,2}

Several novel therapies that potently reduce triglyceride levels are currently in development.\textsuperscript{6-8} The development of these therapies has been motivated in part by the observation that rare loss-of-function mutations in the lipoprotein lipase (LPL) gene are associated with higher plasma triglyceride levels and a higher risk of cardiovascular disease; while rare, loss-of-function mutations in the\textit{APOC3},\textit{ANGPTL3}, and\textit{ANGPTL4} genes, which encode for natural inhibitors of LPL, are associated with lower triglyceride levels and a corresponding lower risk of cardiovascular disease.\textsuperscript{9-13} However, it is unknown whether lowering plasma triglyceride levels by targeting the LPL pathway will reduce the risk of cardiovascular events.

Both triglycerides and cholesterol are carried in plasma by apolipoprotein B (ApoB)-containing lipoprotein particles. Because all ApoB-containing lipoproteins, including triglyceride-rich lipoprotein particles and LDL particles, have a single ApoB molecule the clinical benefit of lowering triglyceride levels can be compared with the clinical benefit of lowering LDL-C levels by estimating their effects per unit change in ApoB. Therefore, the objective of this study was to use mendelian randomization to compare the association of triglyceride-lowering\textit{LPL} variants and LDL-C-lowering\textit{LDLR} variants with the risk of cardiovascular disease per unit difference in ApoB to make inferences about the potential clinical benefit of lowering plasma triglyceride levels as compared with lowering LDL-C levels.

### Methods

#### Study Population

The study included individual participant data from 367,641 participants enrolled in the UK Biobank study, individual participant data from 102,837 participants enrolled in 1 of 14 prospective cohort or case-control studies that reported data on cardiovascular outcomes in the US National Center for Biotechnology Information Database of Genotypes and Phenotypes program (dbGaP), and summary-level data from 184,305 participants enrolled in 1 of 48 prospective cohort, case-control, or cross-sectional studies included in the Coronary Artery Disease Genomewide Replication and Meta-Analysis plus the Coronary Artery Disease (CARDioGRAMplusC4D) Consortium.\textsuperscript{14-16} Participants of European descent in the UK Biobank, and all racial/ethnic groups for which cardiovascular data were reported in the dbGaP and CARDioGRAMplusC4D Consortium studies, were included in the analysis. In each included study, race/ethnicity was self-identified using a study-specific fixed-category questionnaire and was recorded to allow assessment of potential heterogeneity of effect estimates by ethnicity.

Contributing studies received ethical approval from their respective institutional review boards, and written informed consent was obtained from all participants. A description of the included studies and the genotyping platforms used in each study is provided in eTable 1 in the Supplement.

#### Genetic Instruments

The\textit{LPL}\ genetic score was constructed by combining all variants within 100kb on either side of the\textit{LPL} gene that were associated with plasma triglyceride levels at genome-wide level of significance ($P < 5.0 \times 10^{-8}$) as reported by the Global Lipids Genetics Consortium and that were in low linkage disequilibrium ($r^2 < 0.3$) with all other variants included in the score.\textsuperscript{17,18} The\textit{LDLR} genetic score was constructed similarly by combining all variants within 100kb on either side of the\textit{LDLR} gene that were associated with plasma LDL-C levels at genome-wide level of significance and that were in low linkage disequilibrium ($r^2 < 0.3$) with all other variants included in the score. The exposure allele for each\textit{LPL} variant was defined as the allele associated with lower plasma triglyceride levels, and the exposure allele for each\textit{LDLR} variant was defined as the allele associated with lower LDL-C levels.\textsuperscript{17,18} For each participant, an\textit{LPL} genetic score was calculated by summing the number of triglyceride-lowering alleles that participants inherited at each variant included in the\textit{LPL} score and an\textit{LDLR} score was calculated by summing the number of LDL-C-lowering alleles that participants inherited at each variant included in the\textit{LDLR} score. Participants were excluded if they had missing data for 1 or more variants included in either genetic score.

#### Study Outcomes

The primary clinical outcome was coronary heart disease (CHD) defined as a composite of prevalent or the first incident occurrence of myocardial infarction (MI), coronary revascularization, or coronary death. For analyses involving individual participant data, the primary clinical outcome was harmonized across all included studies. For analyses involving summary-level data, the definition of CHD was defined by each study included in the CARDioGRAMplusC4D consortium, which included CHD death, MI, and coronary revascularization but...
in some studies also included chronic stable angina or more than 50% stenosis in a major epicardial coronary artery.16

**Study Design and Statistical Analysis**

A description of the study design, analyses performed, and data used for each analysis is provided in eFigures 1-3 in the Supplement. The association of each genetic score with plasma triglycerides, LDL-C, and ApoB was evaluated using linear regression and with CHD risk using logistic regression. All regression analyses were performed separately in each of the included studies adjusting for age, sex, and the first 5 principal components of ancestry. To directly compare the clinical benefit of lower triglyceride levels due to the LPL score with lower LDL-C levels due to the LDLR genetic score, the associations of each score with risk of CHD was scaled for a common 10-mg/dL lower level of ApoB-containing lipoproteins. For individual participant data, the scaled point estimates were obtained by weighting each variant included in either genetic score by its associated change in ApoB. For summary-level data, the scaled associations were obtained by dividing the reported point estimate (and standard error) for an outcome by the reported point estimate for ApoB (measured in mg/dL). The scaled summary point estimates for all variants included in a score were then combined in a fixed-effect inverse variance-weighted meta-analysis to estimate the association between that genetic score generated using summary data and the outcome for a 10-mg/dL lower level of ApoB-containing lipoproteins.

The point estimates derived from the individual participant data and the summary data were then combined across studies in a fixed-effect inverse variance-weighted meta-analysis to produce an overall summary point estimate using a previously reported method that accounts for correlation between variants.19

Effect modification between lowering triglyceride levels through the LPL pathway and lower LDL-C levels through the LDL receptor pathway was assessed by comparing the associations of each genetic score with the risk of CHD stratified by the other genetic score. The association of combined exposure to triglyceride-lowering LPL variants and LDL-C-lowering LDLR variants with the risk of CHD was evaluated in a 2 × 2 factorial mendelian randomization analysis.20-23 For both the stratified and factorial analyses, associations with the risk of CHD were necessarily restricted to participants with individual data and associations with changes in triglycerides, LDL-C, and ApoB were necessarily restricted to participants with individual data for whom 1 or more lipid measurements were available.

**Sensitivity Analyses**

To compare the potential clinical benefit of pharmacologically lowering triglyceride and LDL-C levels, the associations of the LDLR and LPL scores with the risk of CHD per unit difference in ApoB were compared with variants in the genes that encode the targets of current therapies that lower LDL-C through the LDL receptor pathway; variants in the genes that encode the targets of potential therapies that lower triglycerides through the LPL pathway; and variants in the APOB gene. To compare the association of triglyceride and LDL-C levels with the risk of CHD per unit difference in ApoB not related to the LPL and LDLR genes, several additional genetic scores were constructed using up to 178 genetic variants associated with either triglycerides, LDL-C, or both at genome-wide significance as reported by the Global Lipids Genetics Consortium.17,18

To further assess the independent associations of lower triglycerides, lower LDL-C, and lower ApoB on the risk of CHD, a multivariable mendelian randomization analysis was performed using these 178 genetic variants combined with the LPL and LDLR variants. This analysis was performed using meta-regression analyses in which the dependent variable was the associated log-odds for the risk of CHD, and the independent variables were the reported differences in plasma triglycerides, LDL-C, and ApoB for each variant included in the analysis, weighted by the inverse of the squared standard error for the association of each variant with CHD and forced to pass through the origin.

All analyses were performed using Stata (version 14.2; StataCorp), R (version 3.2.2; R Project for Statistical Computing), or Golden Helix SNP & Variation Suite software (version 8.1.4). A 2-tailed P value less than .05 was considered statistically significant. A detailed description is provided in eMethods in the Supplement.

**Results**

**Participant Characteristics**

A total of 654,783 participants, including 91,129 cases of CHD, were included in the analysis (mean age, 62.7 years; 51.4% women). Individual participant data were available for 470,478 participants including 30,328 cases of CHD (Table I). Summary-level data were available for a further 184,305 participants, including 60,801 cases of CHD.

**LPL and LDLR Genetic Scores**

A total of 5 independently inherited variants were included in the LPL score (eTables 2 and 3 in the Supplement) and 3 independently inherited variants were included in the LDLR score (eTables 4 and 5 in the Supplement). Each exposure allele in the LPL score was associated with an inverse variance-weighted mean of 11.64-mg/dL (95% CI, 10.38-10.90; P = 8.3 × 10−1365) lower plasma triglyceride level (to convert to mmol/L, multiply by 0.0113). 0.11-mg/dL (95% CI, 0.00-0.21; P = .04) higher plasma LDL-C level (to convert to mmol/L, multiply by 0.0259, and a 1.72-mg/dL (95% CI, 1.30-2.14; P = 5.5 × 10−16) lower level of ApoB-containing lipoproteins. By contrast, each exposure allele in the LDLR score was associated with an inverse variance-weighted mean of 3.42-mg/dL (95% CI, 3.27-3.57; P = 2.3 × 10−466) lower plasma LDL-C level, 0.48-mg/dL (95% CI, 0.30-0.93; P = .04) lower plasma triglyceride level, and a 2.40-mg/dL (95% CI, 2.02-2.79; P = 3.9 × 10−34) lower level of ApoB-containing lipoproteins.

**Association of Genetic Scores With Lipids and CHD per Unit Change in ApoB**

For each 10-mg/dL lower level of ApoB-containing lipoproteins, the LPL score was associated with 69.9-mg/dL (95% CI, 68.1-71.6; P = 7.1 × 10−1365) lower plasma triglyceride levels and...
0.7-mg/dL (95% CI, 0.031-1.4; P = .04) higher plasma LDL-C level (Figure 1). By contrast, for the same 10-mg/dL lower level of ApoB-containing lipoproteins, the LDLR score was associated with 14.2-mg/dL (95% CI, 13.6-14.8; P = 1.4 × 10^{-46}) lower plasma LDL-C level and 1.9-mg/dL (95% CI, 0.1-3.9; P = .04) lower plasma triglyceride level. Despite these differences in associated lipid levels, the LPL and LDLR scores were associated with similar lower risk of CHD per 10-mg/dL lower level of ApoB-containing lipoproteins (odds ratio [OR], 0.771 [95% CI, 0.747-0.802]) that was proportional to their associated absolute lower level of ApoB—i.e., 14.2-mg/dL (95% CI, 13.6-14.8; P = 1.4 × 10^{-46}) for the LPL score and OR, 0.773 [95% CI, 0.747-0.801], P = 1.1 × 10^{-46} for the LDLR score). The associations of the LPL and LDLR scores with the risk of CHD per unit lower ApoB was consistent between studies that contributed individual participant data and studies that contributed summary data (eTable 6 in the Supplement).

In stratified analyses, the associations of the LPL and LDLR scores with plasma lipids, lipoproteins, and the risk of CHD appeared to be independent of each other (LPL score OR for CHD per 10-mg/dL lower ApoB, 0.771 [95% CI, 0.714-0.832] for participants with LDLR scores below the median and 0.769 [95% CI, 0.709-0.834] for participants with LDLR scores above the median) (eFigure 4 in the Supplement). In a 2 × 2 factorial mendelian randomization analysis, combined exposure to both the LPL and LDLR genetic scores was associated with linearly additive lower levels of triglycerides (LPL score alone: −20.1 mg/dL [95% CI, −28.8 to −13.3]; LDLR score alone: −3.8 mg/dL [95% CI, −5.1 to 7.3]; combined exposure to both scores: −24.3 mg/dL [95% CI, −32.4 to −16.2]), LDL-C levels (LPL score alone: −0.1 mg/dL [95% CI, −0.5 to 0.3]; LDLR score alone: −4.8 mg/dL [95% CI, −7.6 to −2.0]; combined exposure to both scores: −4.9 mg/dL [95% CI, −7.7 to −2.1]), and ApoB (LPL score alone: −3.0 mg/dL [95% CI, −4.9 to −1.2]; LDLR score alone: −3.4 mg/dL [95% CI, −5.2 to −1.5]; combined exposure to both scores: −6.4 mg/dL [95% CI, −8.5 to −4.4]), as well as a log-linearly additive decreases in the risk of CHD (LPL score alone: OR, 0.924 [95% CI, 0.889-0.960]; LDLR score alone: OR, 0.921 [95% CI: 0.885-0.958]; combined exposure to both scores: OR, 0.842 [95% CI, 0.811-0.874]) that was proportional to the absolute difference in ApoB but not to differences in either triglycerides or LDL-C (eFigure 5 in the Supplement).

### Sensitivity Analyses

In additional analyses, variants in the genes that encode the targets for several potential therapies that lower triglycerides through the LPL pathway, and variants in the genes that encode the targets of several current therapies that lower LDL-C through the LDLR pathway, were also associated with similar lower risk of CHD per unit difference in ApoB as compared with the LPL and LDLR scores and as compared with an APOB score composed of 8 independently inherited variants in the APOB gene (Figure 2). Furthermore, the associated lower CHD risk for each of these variants and genetic scores was log-linearly proportional to their associated absolute lower level of ApoB-containing lipoproteins (Figure 3).

Several additional genetic scores consisting of other variants associated with triglycerides or LDL-C at genome-wide level of significance (excluding variants in the LPL and LDLR genes)—including scores consisting of variants associated with either triglycerides or LDL-C, triglycerides but not LDL-C, LDL-C but not triglycerides; both triglycerides and LDL-C with the same direction of effect; and both triglycerides and LDL-C with opposite directions of effect—were also associated with similar lower risk of CHD per 10-mg/dL lower level of ApoB-containing lipoproteins (Table 2). In multivariable mendelian randomization analyses that included both triglycerides and LDL-C in the same model, the associations between plasma triglycerides and LDL-C with the risk of CHD were independent and genome-wide significant. However, when changes in ApoB were included in these analyses, the associations between both plasma triglycerides and LDL-C with the risk of CHD became null (triglycerides: OR, 1.014 [95% CI, 0.965-1.065], P = .19;
Triglycerides are carried in plasma by ApoB-containing triglyceride-rich lipoproteins while cholesterol is carried predominantly by ApoB-containing low-density lipoproteins. Changes in plasma triglycerides and LDL-C concentration are thus markers of the corresponding changes in the concentration of the ApoB-containing lipoproteins that transport these lipids. Variants in the LPL gene that increase LPL activity are associated with lower triglycerides and a corresponding lower ApoB concentration, while variants in the LDLR gene that increase activity of the LDL receptor are associated with lower LDL-C and a corresponding lower ApoB. The figure shows that for each 10-mg/dL lower plasma ApoB concentration associated with variants in the LPL score, there is a corresponding 69.9-mg/dL lower triglyceride level, no change in LDL-C, and a lower risk of CHD (odds ratio, 0.771 [95% CI, 0.741-0.802]). By contrast, for the same 10-mg/dL lower plasma ApoB concentration associated with variants in the LDLR score, there is a corresponding 141-mg/dL lower LDL-C level, no change in triglycerides, and a similar lower risk of CHD (odds ratio, 0.773 [95% CI, 0.747-0.801]). Therefore, despite being associated with changes in different lipids, the LPL and LDLR scores were associated with similar lower risk of CHD for the same lower plasma ApoB concentration. The data presented are for the associations of the LPL and LDLR genetic scores with risk of CHD per 10-mg/dL decrease in ApoB-containing lipoproteins in all 654,783 participants included in the study. The associations of either score with changes in triglycerides and LDL-C per 10-mg/dL lower level of ApoB-containing lipoproteins are from up to 305,699 participants enrolled in the Global Lipid Genetics Consortium. Boxes represent effect size estimates and lines represent 95% CIs.

LDL-C: OR, 1.010 [95% CI, 0.967-1.055], P = .19; and ApoB: OR, 0.761 [95% CI, 0.723-0.798], P = 7.51 × 10^{-25} (Table 3; eTable 8 in the Supplement).

Discussion
In this study, triglyceride-lowering LPL variants and LDL-C-lowering LDLR variants were associated with similar lower CHD risk per unit lower level of ApoB-containing lipoproteins. The associations between lower triglyceride level and lower LDL-C level with risk of CHD due to these variants appeared to be independent, additive, and proportional to the absolute change in ApoB. In addition, numerous variants in the genes that encode the targets of potential therapies that lower triglyceride levels through the LPL pathway and current therapies that lower LDL-C levels through the LDLR pathway were also associated with similar lower CHD risk per unit lower plasma ApoB levels. Furthermore, multiple genetic scores composed of other variants associated with either triglycerides, LDL-C, or both were also associated with similar lower risk of CHD per unit lower level of ApoB-containing particles, even when the associated changes in triglyceride and LDL-C levels were in opposite directions. In multivariable mendelian randomization analyses, the independent and genome-wide significant associations between triglycerides and LDL-C with the risk of CHD became null after adjusting for changes in ApoB.

The results of this study suggest that the clinical benefit of lowering triglyceride levels is similar to the clinical benefit of lowering LDL-C levels per unit change in ApoB and is proportional to the net absolute reduction in ApoB-containing lipoproteins. The results of this study therefore suggest that all ApoB-containing lipoprotein particles, including triglyceride-rich very-low-density lipoprotein (VLDL) particles and their metabolic remnants as well as LDL particles, have approximately the same effect on the risk of cardiovascular disease per particle. As a result, the clinical benefit of lowering triglyceride levels, lowering LDL-C levels, or lowering both may be proportional to the absolute change in ApoB-containing lipoproteins, regardless of the observed changes in plasma triglycerides or LDL-C.

The results of this study are consistent with the current understanding of the biology of lipids and atherosclerosis. Both triglycerides and cholesterol are carried in plasma by ApoB-containing lipoprotein particles. These particles are secreted by the liver as VLDL particles, which principally contain triglycerides, some cholesterol, and 1 molecule of ApoB. Lipoprotein lipase removes most of the triglycerides from these particles to convert the triglyceride-rich VLDL particles into triglyceride-depleted cholesterol-carrying LDL particles, which are then removed from plasma by hepatic LDL receptors. All ApoB-containing lipoproteins less than 70 nm in diameter, including triglyceride-rich VLDL remnants and LDL particles, freely flux across the endothelial barrier where they can become retained in the artery wall.24 The cholesterol, and perhaps triglyceride, content of the ApoB particles retained in the artery wall provokes an inflammatory response that leads to the initiation and progression of atherosclerotic plaque.25 The results of this study suggest that the effect of ApoB-containing particles on the risk of atherosclerotic cardiovascular disease appears to be determined largely by the concentration of circulating ApoB particles, which in turn determines the number of particles that become retained in the artery wall, regardless of whether those particles principally contain cholesterol or triglycerides. The present findings and interpretations based on mendelian randomization confirm and extend the initial findings and interpretations in 1980 of Sniderman and colleagues,26 which were based on cross-sectional coronary angiographic studies.

The results of this study are also consistent with prior mendelian randomization studies demonstrating that triglyceride-rich ApoB-containing remnant particles appear to be causally
Figure 2. Association of Genetic Variants and Genetics Scores With Triglycerides, Low-Density Lipoprotein Cholesterol (LDL-C), and Risk of Coronary Heart Disease (CHD) per 10-mg/dL Lower Concentration of Apolipoprotein B (ApoB)–Containing Lipoproteins

<table>
<thead>
<tr>
<th>Gene</th>
<th>Genetic Variant</th>
<th>Functional Consequence</th>
<th>Therapy</th>
<th>Δ Triglycerides (95% CI)</th>
<th>Δ Low-Density Lipoprotein Cholesterol (95% CI)</th>
<th>Odds Ratio (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>LDLR</td>
<td>rs3846662</td>
<td>Intron</td>
<td>Statin</td>
<td>-7.4 (-13.0 to -0.8)</td>
<td>-9.1 (-15.4 to -2.8)</td>
<td>0.719 (0.600-0.870)</td>
<td>1.1 x 10^-4</td>
</tr>
<tr>
<td>NPC1L1</td>
<td>rs217386</td>
<td>Intron</td>
<td>Ezetimibe</td>
<td>-7.6 (-12.0 to -3.2)</td>
<td>-10.1 (-16.9 to -3.3)</td>
<td>0.531 (0.421-0.676)</td>
<td>1.9 x 10^-9</td>
</tr>
<tr>
<td>PCSK9</td>
<td>rs1206510</td>
<td>Intergenic</td>
<td>PCSK9 inhibitor</td>
<td>-3.1 (-6.9 to 0.7)</td>
<td>-4.1 (-8.3 to 0.1)</td>
<td>0.743 (0.602-0.914)</td>
<td>2.6 x 10^-12</td>
</tr>
<tr>
<td>ABCG5/G8</td>
<td>rs245791</td>
<td>Intron</td>
<td>Bile resin</td>
<td>-11.5 (-18.4 to -4.6)</td>
<td>-12.6 (-18.2 to -7.0)</td>
<td>0.743 (0.614-0.901)</td>
<td>6.7 x 10^-12</td>
</tr>
<tr>
<td>CETP</td>
<td>rs5880</td>
<td>Ala139Phe</td>
<td>CETP inhibitor</td>
<td>-3.4 (-6.2 to 0.0)</td>
<td>-4.1 (-6.9 to 1.2)</td>
<td>0.719 (0.532-0.960)</td>
<td>0.04</td>
</tr>
</tbody>
</table>

Furthermore, for the same 10-mg/dL lower plasma ApoB concentration associated with variants in the APOB gene, for example, each 10-mg/dL lower plasma ApoB concentration associated with the partial loss-of-function rs11591147 variant in the PCSK9 gene was associated with a corresponding 18.0-mg/dL lower LDL-C level, no change in triglycerides, and a lower risk of CHD odds ratio, 0.778 [95% CI, 0.737-0.821]. Despite a range of associated changes in triglyceride levels, LDL-C, or both, all genetic variants and genetic scores were associated with similar lower risk of CHD for the same 10-mg/dL lower plasma ApoB concentration. The ApoB score is composed of the 8 independently inherited variants in the APOB gene listed in the figure. Boxes represent effect size estimates and lines represent 95% CIs. Associations with CHD per 10-mg/dL lower ApoB were measured in all 654 783 participants included in the study; associations with changes in triglycerides and LDL-C per 10-mg/dL lower ApoB were measured in up to 305 699 participants from the Global Lipid Genetics Consortium.
Figure 3. Log-Linear Association Between Absolute Differences in Apolipoprotein B (ApoB) and Lower Risk of Coronary Heart Disease (CHD)

The associations of each genetic variant with ApoB concentration is plotted against its unadjusted association with CHD, expressed as a proportional lower risk (calculated as \[1-\text{OR}_{\text{CHD}}\times100\]). Variants in the genes that encode the targets of therapies that lower triglycerides through the LPL pathway are marked with blue labels, and variants in the genes that encode the targets of therapies that lower LDL-C through upregulation of the LDL receptor are marked with red labels. Circles represent the associated absolute change in ApoB concentration in ApoB-containing lipoproteins. However, the mean reduction in plasma triglyceride concentration in the fibrate trials was only 20 mg/dL to 50 mg/dL, a fraction of what would be needed to significantly reduce the risk of major vascular events within a short-term trial. Therefore, the results of the fibrate trials appear to be explained by the modest reductions in triglyceride level and therefore the modest corresponding reductions in ApoB-containing lipoproteins observed in these studies. Future randomized trials evaluating novel therapies that lower plasma triglyceride levels should be designed based on the net absolute reductions in ApoB-containing lipoproteins that can be achieved with those therapies, rather than on the corresponding therapeutic changes in triglycerides or LDL-C, particularly for therapies that alter plasma concentrations of both triglycerides and LDL-C either in the same or competing directions.

Limitations

This study has several limitations. First, this study compared triglyceride- and LDL-C-lowering genetic variants not lipid-lowering therapies. Second, genetic variants reflect the effect of lifelong changes in ApoB-containing lipoproteins on the risk of cardiovascular disease, which appear to be cumulative over time. As a result, the lower risk associated with lower triglycerides, LDL-C, and ApoB reported in this study is much larger than what have been reported for lipid-lowering therapies in randomized trials. However, having first established that the association between lifetime exposure to lower triglycerides and LDL-C on the risk of cardiovascular disease is approximately the same per unit lower level of ApoB-containing particles, it is reasonable to
Abbreviations: ApoB, apolipoprotein B; CHD, coronary heart disease; LDL-C, low-density lipoprotein cholesterol.

Table 2. Association of Additional Genetic Scores With Triglycerides, LDL-C, and Risk of CHD per 10-mg/dL Lower Concentration of ApoB-Containing Lipoproteins a

<table>
<thead>
<tr>
<th>Composition of Genetic Score</th>
<th>Δ Triglycerides (95% CI)</th>
<th>Δ LDL-C (95% CI)</th>
<th>Odds Ratio for CHD (95% CI) per 10-mg/dL Lower ApoB</th>
</tr>
</thead>
<tbody>
<tr>
<td>51 Variants associated with triglycerides at P &lt; 5.0×10^{-8}, but not LDL-C (P &gt; .001)</td>
<td>−43.1 (−44.5 to −41.7)</td>
<td>−2.1 (−2.6 to −1.6)</td>
<td>0.762 (0.724 to 0.803)</td>
</tr>
<tr>
<td>59 Variants associated with LDL-C at P &lt; 5.0×10^{-8}, but not triglycerides (P &gt; .001)</td>
<td>−2.1 (−3.0 to −1.1)</td>
<td>−15.5 (−15.8 to −15.1)</td>
<td>0.774 (0.748 to 0.800)</td>
</tr>
<tr>
<td>168 Variants associated with either triglycerides or LDL-C at P &lt; 5.0×10^{-8}</td>
<td>−21.6 (−22.1 to −21.1)</td>
<td>−11.8 (−12.0 to −11.6)</td>
<td>0.770 (0.757 to 0.783)</td>
</tr>
<tr>
<td>91 Variants associated with triglycerides at P &lt; 5.0×10^{-8}</td>
<td>−35.3 (−35.9 to −34.6)</td>
<td>−9.3 (−9.6 to −9.1)</td>
<td>0.776 (0.758 to 0.795)</td>
</tr>
<tr>
<td>100 Variants associated with LDL-C at P &lt; 5.0×10^{-8}</td>
<td>−17.5 (−18.0 to −17.0)</td>
<td>−13.5 (−13.7 to −13.3)</td>
<td>0.776 (0.762 to 0.791)</td>
</tr>
<tr>
<td>23 Variants associated with both triglycerides and LDL-C, both at P &lt; 5.0×10^{-8}, in same direction of effect</td>
<td>−32.3 (−33.0 to −31.5)</td>
<td>−12.0 (−12.3 to −11.7)</td>
<td>0.793 (0.771 to 0.815)</td>
</tr>
<tr>
<td>10 Variants associated with both triglycerides and LDL-C, both at P &lt; 5.0×10^{-8}, with opposite directions of effect</td>
<td>17.2 (16.0 to 18.4)</td>
<td>−22.5 (−23.0 to −22.1)</td>
<td>0.798 (0.767 to 0.830)</td>
</tr>
<tr>
<td>9 Variants associated with both triglycerides and LDL-C, both at P &lt; 5.0×10^{-8}, with opposite directions of effect (excluding APOE variant rs7412)</td>
<td>26.0 (23.7 to 28.3)</td>
<td>−20.3 (−21.2 to −19.4)</td>
<td>0.770 (0.711 to 0.833)</td>
</tr>
</tbody>
</table>

Abbreviations: ApoB, apolipoprotein B; CHD, coronary heart disease; LDL-C, low-density lipoprotein cholesterol; OR, odds ratio.

a To compare the association of triglycerides and LDL-C with the risk of CHD for the same lower concentration of ApoB-containing lipoproteins not related to the LPL and LDLR genes, several additional genetic scores were constructed using up to 178 genetic variants associated with either triglycerides, LDL-C, or both at genome-wide significance as reported by the Global Lipids Genetics Consortium (GLGC). The data presented are for the associations of each genetic score with changes in triglycerides and LDL-C per 10-mg/dL lower ApoB in up to 305,699 participants in the GLGC and with the risk of CHD per 10-mg/dL lower ApoB in all 654,783 participants included in this study. For example, for each 10-mg/dL lower plasma ApoB concentration associated with a genetic score consisting of 51 variants associated with triglycerides but not LDL-C at genome-wide level of significance, there was a corresponding 41.3-mg/dL lower triglyceride level, 2.1-mg/dL lower LDL-C level, and a lower risk of CHD (odds ratio [OR], 0.762 [95% CI, 0.724-0.803]). By contrast, for the same 10-mg/dL lower plasma ApoB concentration associated with a genetic score consisting of 59 variants associated with LDL-C but not triglycerides at genome-wide level of significance, there was a corresponding 15.5-mg/dL lower LDL-C level, 2.1-mg/dL lower triglyceride level, and a similar lower risk of CHD (OR, 0.774 [95% CI, 0.748-0.800]). Furthermore, for the same 10-mg/dL lower plasma ApoB concentration associated with a genetic score consisting of 168 variants associated with either triglycerides or LDL-C at genome-wide level of significance, there was a corresponding 21.6-mg/dL lower triglyceride level, an 11.8-mg/dL lower LDL-C level, and a similar lower risk of CHD (OR, 0.770 [95% CI, 0.757-0.783]). Despite being associated with different changes in lipids, all genetic scores were associated with similar lower risk of CHD for the same 10-mg/dL lower plasma ApoB concentration. The unadjusted associations with triglycerides, LDL-C, ApoB, and CHD for each variant included in the genetic scores are provided in Table 7 in the Supplement.

Table 3. Multivariable Mendelian Randomization Analysis of the Association Between Plasma Triglycerides, LDL-C, and ApoB With the Risk of CHD a

<table>
<thead>
<tr>
<th>Analysis</th>
<th>Variables</th>
<th>Odds Ratio for CHD (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Association of 10-mg/dL lower ApoB with risk of CHD</td>
<td>ApoB</td>
<td>0.770 (0.760-0.781)</td>
<td>1.42E-170</td>
</tr>
<tr>
<td>Association of 10-mg/dL lower LDL-C with risk of CHD</td>
<td>LDL-C</td>
<td>0.846 (0.833-0.858)</td>
<td>8.16E-77</td>
</tr>
<tr>
<td>Association of 50-mg/dL lower triglycerides with risk of CHD</td>
<td>Triglycerides</td>
<td>0.815 (0.785-0.846)</td>
<td>1.37E-18</td>
</tr>
<tr>
<td>Association of 10-mg/dL lower LDL-C and 50-mg/dL lower triglycerides with risk of CHD included in same model</td>
<td>LDL-C</td>
<td>0.862 (0.849-0.875)</td>
<td>6.92E-65</td>
</tr>
<tr>
<td></td>
<td>Triglycerides</td>
<td>0.876 (0.850-0.902)</td>
<td>1.36E-14</td>
</tr>
<tr>
<td>Association of 10-mg/dL lower LDL-C, 50-mg/dL lower triglycerides, and 10-mg/dL lower ApoB with risk of CHD included in same model</td>
<td>ApoB</td>
<td>0.761 (0.723-0.798)</td>
<td>7.51E-20</td>
</tr>
<tr>
<td></td>
<td>LDL-C</td>
<td>1.010 (0.967-1.055)</td>
<td>.19</td>
</tr>
<tr>
<td></td>
<td>Triglycerides</td>
<td>1.014 (0.965-1.065)</td>
<td>.19</td>
</tr>
</tbody>
</table>

Abbreviations: ApoB, apolipoprotein B; CHD, coronary heart disease; LDL-C, low-density lipoprotein cholesterol; OR, odds ratio.

a Data presented are derived from a multivariable meta-regression analysis of 186 genetic variants, including the 5 variants included in the LPL score, 3 variants included in the LDLR score, and 178 variants associated with either triglycerides, LDL-C, or both at genome-wide significance as reported by the Global Lipids Genetics Consortium. Effect sizes for the associated risk of CHD are reported per 10-mg/dL lower ApoB concentration, per 10-mg/dL lower LDL-C level, or per 50-mg/dL lower triglyceride level (because dividing triglyceride concentration by 5 estimates the cholesterol content carried by triglyceride-rich ApoB-containing lipoproteins as estimated by the Friedewald formula). In these analyses, the dependent variable was the effect estimate for risk of CHD in all 654,783 participants included in the study for each variant and the independent variables were the effect estimates for the associated changes in plasma triglycerides, LDL-C, and ApoB, measured in up to 305,699 participants in Global Lipids Genetics Consortium for each variant. The analysis was weighted by the inverse squared standard error of the associated risk of CHD for each variant and forced to pass through the origin. For example, in multivariable mendelian randomization analyses involving these 186 genetic variants, both triglycerides (odds ratio [OR], 0.876 per 50-mg/dL lower triglycerides) and LDL-C (OR, 0.862 per 10-mg/dL lower LDL-C) were independently associated with a lower risk of CHD at genome-wide level of significance. By contrast, when ApoB was included in the multivariable mendelian randomization analyses, the associations with CHD for both triglycerides (OR, 1.014 per 50-mg/dL lower triglycerides) and LDL-C (OR, 1.010 per 10-mg/dL lower LDL-C) became null, but the association per 10-mg/dL lower ApoB remained unchanged (OR, 0.761 per 10-mg/dL lower ApoB). The unadjusted associations with triglycerides, LDL-C, ApoB, and CHD for each variant included in the analysis are provided in eTable 7 in the Supplement. Additional multivariable meta-regression analyses for various combinations of these variants is provided in eTable 8 in the Supplement.
then anticipate that short-term pharmacologic reductions in plasma triglyceride and LDL-C levels will be associated with the same lower risk of cardiovascular events per unit change in ApoB. Third, this study specifically estimates the clinical benefit of the lipid-lowering effect of therapies that reduce plasma triglycerides, LDL-C, or both, but not the other potential pleiotropic effects that a therapy may have on the risk of cardiovascular disease. Indeed, the reported reductions in cardiovascular events in the JELIS and REDUCE-IT trials were far greater than what would have been expected from the modest observed changes in plasma lipid levels, thus suggesting that the observed clinical benefit of the omega-3 fatty acid eicosapentaenoic acid may be largely due to its non-lipid-related effects.

Conclusions

Triglyceride-lowering LPL variants and LDL-C-lowering LDLR variants were associated with similar lower risk of CHD per unit difference in ApoB. Therefore, the clinical benefit of lowering triglyceride and LDL-C levels may be proportional to the absolute change in ApoB.

ARTICLE INFORMATION

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Concept and design: Ference, Laufs, Catapano.

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