Association of triglyceride-lowering *LPL* variants and LDL-C lowering *LDLR* variants with risk of coronary heart disease

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Word count (text only, not including abstract, tables, figures, or references): 3412

Date of revision: 30 November 2018

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Key Points

Question

What is the clinical benefit of lowering plasma triglycerides as compared to lowering low-density lipoprotein cholesterol?

Findings

In Mendelian randomization analyses involving 654,783 participants, triglyceride-lowering variants in the lipoprotein lipase gene and LDL-C lowering variants in the LDL receptor gene were associated with similar reductions in the risk of coronary heart disease per 10 mg/dl decrease in apoB-containing lipoproteins (odds ratios [ORs] of 0.771 and 0.773, respectively).

Meaning

The clinical benefit of lowering triglycerides was similar to the clinical benefit of lowering LDL-C per unit change in apoB and may be related to the absolute reduction in apoB-containing lipoprotein particles.

ABSTRACT

IMPORTANCE: Triglycerides and cholesterol are both carried in plasma by apolipoprotein B (apoB)-containing lipoprotein particles. Whether lowering plasma triglycerides reduces the risk of cardiovascular events to the same extent as lowering low-density lipoprotein cholesterol (LDL-C) is unknown.

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 triglycerides, 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 decrease in 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 decrease in apoB-containing lipoproteins, the *LPL* score was associated with 69.9 (95%CI:68.1-71.6;p=7.1×10^{-1363}) mg/dl lower triglycerides and 0.7 (95%CI:0.03-1.4;p=0.039) mg/dl higher LDL-C; while the *LDLR* score was associated with 14.2 (95%CI:13.6-14.8;p=1.4×10^{-465}) mg/dl lower LDL-C and 1.9 (95%CI:0.1-3.9;p=0.036) mg/dl lower triglycerides. Despite these differences in associated lipid changes, the *LPL* and *LDLR* scores were associated with very similar reductions in the risk of CHD per 10 mg/dl decrease in apoB-containing lipoproteins (OR: 0.771,

95%CI:0.741-0.802,p=3.9x10^{-38}; OR: 0.773, 95%CI:0.747-0.801,p=1.1x10^{-46}, respectively). In multivariable Mendelian randomization analyses, the associations between triglycerides and LDL-C with the risk of CHD became null after adjusting for changes in apoB (triglycerides OR:1.014, 95%:0.965-1.065,p=0.189; LDL-C OR:1.010, 95%:0.967-1.055,p=0.186; apoB OR:0.761, 95%CI:0.723-0.798,p=7.51x10^{-20}).

CONCLUSIONS AND RELEVANCE: Triglyceride-lowering *LPL* variants and LDL-C lowering *LDLR* variants were associated with similar reductions in the risk of CHD per unit change in apoB. Therefore, the clinical benefit of lowering triglycerides and LDL-C may be proportional to the absolute change in apoB.

INTRODUCTION

All major clinical guidelines recommend treatment to lower plasma LDL cholesterol (LDL-C) because numerous randomized trials have demonstrated that therapies that lower LDL-C by reducing LDL particles through up-regulation of the LDL receptor (LDLR) reduce the risk of cardiovascular events.[1-5] By contrast, the guidelines do not recommend treatment to lower plasma triglycerides because randomized trials have not provided consistent evidence that lowering plasma triglycerides reduces the risk of cardiovascular events.[1,2]

Several novel therapies that potently reduce triglycerides are currently in development.[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 triglycerides and a higher risk of cardiovascular disease; while rare loss-of-function mutations in the *APOC3*, *ANGPTL3*, and *ANGPTL4* genes, which encode for natural inhibitors of LPL, are associated with lower triglycerides and a corresponding lower risk of cardiovascular disease.[9-13] However, whether lowering plasma triglycerides by targeting the LPL pathway will reduce the risk of cardiovascular events is unknown.

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 triglycerides can be compared with the clinical benefit of lowering LDL-C 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 *LPL* variants and LDL-C lowering *LDLR* variants with the risk of cardiovascular disease per unit change in apoB, to make inferences about the potential clinical benefit of lowering plasma triglycerides as compared to lowering LDL-C.

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 one 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 one of 48 prospective cohort, case-control or cross-sectional studies included the Coronary Artery Disease Genomewide Replication and Meta-Analysis plus the Coronary Artery Disease (CARDIoGRAMplusC4D) consortium.[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.

GENETIC INSTRUMENTS

The *LPL* genetic score was constructed by combining all variants within 100kb on either side of the *LPL* gene that were associated with plasma triglyceride levels at genome wide level of significance ($P<5.0\times10^{-8}$) 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.[17,18] The *LDLR* genetic score was constructed similarly by combining all variants within 100kb on either side of the *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 *LPL* variant was defined as the allele associated with lower plasma triglycerides, and the exposure allele for each *LDLR* variant was defined as the allele associated with lower LDL cholesterol levels.[17,18] For each participant, an *LPL* genetic score was calculated by summing the number of triglyceride-lowering alleles that participants inherited at each variant included in the *LPL* score; and an *LDLR* score was calculated by summing the number of LDL cholesterol-lowering alleles that participant inherited at each variant included in the *LDLR* score. Participants were excluded if they had missing data for one 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 coronary heart disease (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 > 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 eFigure 1. 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, gender and the first five principal components of ancestry. To directly compare the clinical benefit of lower triglycerides due to

the *LPL* score with lower LDL-C due to the *LDLR* genetic score, the associations of each score with risk of CHD was scaled for a common 10 mg/dl mg/dL decrease in 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 change in 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.[23]

Effect modification between lowering triglycerides through the LPL pathway and lowering LDL-C 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 2x2 factorial Mendelian randomization analysis.[19-22] For both the stratified and factorial analyses, associations with the risk of CHD was 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 one or more lipid measurements were available.

SENSITIVITY ANALYSES

To compare the potential clinical benefit of pharmacologically lowering triglycerides and lowering LDL-C, the associations of the *LDLR* and *LPL* scores with the risk of CHD per unit change 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 triglycerides and LDL-C with the risk of CHD per unit change in apoB not related to the *LPL* and *LDLR* genes, several additional genetic scores were constructed using up to 183 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 183 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 changes 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), R (version 3.2.2), 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 of the methods is provided 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 was available for 470,478 participants including 30,328 cases of CHD (Table 1). Summary level data was 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); and 3 independently inherited variants were included in the *LDLR* score (eTables 4 and 5). Each exposure allele in the *LPL* score was associated with an inverse variance-weighted mean of 11.64 (95% CI: 10.38-10.90; $p=8.3x10^{-1365}$) mg/dl lower plasma triglycerides, 0.11 (95% CI: 0.00-0.21, p=0.039) mg/dl higher plasma LDL-C, and a 1.72 (95% CI: 1.30-2.14; $p=5.5x10^{-16}$) mg/dl decrease in apoB-containing lipoproteins. By contrast, each exposure allele in the *LDLR* score was associated with an inverse variance-weighted mean of 3.42 (95% CI: 3.27-3.57; $p=2.3x10^{-464}$) mg/dl lower plasma LDL-C, 0.48 (95% CI: 0.03-0.93; p=0.036) mg/dl lower plasma triglycerides, and a 2.40 (95% CI: 2.02-2.79, $p=3.9x10^{-34}$) mg/dl decrease in apoB-containing lipoproteins.

ASSOCIATION OF GENETIC SCORES WITH LIPIDS AND CHD PER UNIT CHANGE IN APOB

For each 10 mg/dl decrease in apoB-containing lipoproteins, the *LPL* score was associated with 69.9 (95% CI: 68.1-71.6; $p=7.1x10^{-1363}$) mg/dl lower plasma triglycerides, and 0.7 (95% CI: 0.0-1.4; p=0.039) mg/dl higher plasma LDL-C level (Figure 2). By contrast, for the same 10 mg/dl decrease in apoB-containing lipoproteins, the *LDLR* score was associated with 14.2 (95% CI: 13.6-14.8; $p=1.4x10^{-465}$) mg/dl lower plasma LDL-C, and 1.9 (95% CI: 0.1-3.9; p=0.036) mg/dl lower plasma triglycerides. Despite these

differences in associated lipid changes, the *LPL* and *LDLR* scores were associated with very similar reductions in the risk of CHD per 10 mg/dl decrease in apoB-containing lipoproteins (OR: 0.771, 95% CI: 0.741-0.802, $p=3.9x10^{-38}$ for the *LPL* score; OR: 0.773, 95% CI: 0.747-0.801, $p=1.1x10^{-46}$ for the *LDLR* score). The associations of the *LPL* and *LDLR* scores with the risk of CHD per unit change in apoB was consistent between studies that contributed individual participant data and studies that contributed summary data (eTable 6).

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_{CHD} per 10 mg/dl lower apoB: 0.771 (95%CI: 0.714-0.832) for participants with *LDLR* scores below the median; 0.769 (95%CI: 0.709-0.834) for participants with *LDLR* scores above the median) (eFigure 4). In a 2x2 factorial Mendelian randomization analysis, combined exposure to both the *LPL* and *LDLR* genetic scores was associated with linearly additive decreases in triglycerides (*LPL* score alone: -20.1 mg/dl [95%CI: -13.3, -28.8]; *LDLR* score alone: -3.8 mg/dl [95%CI: -15.1, +7.3]; combined exposure to both scores: -24.3 mg/dl [95%CI: -32.4, -16.2]), LDL-C (*LPL* score alone: -0.1 mg/dl [95%CI: -0.5, +0.3]; *LDLR* score alone: -4.8 mg/dl [95%CI: -7.6, -2.0]; combined exposure to both scores: -4.9 mg/dl [95%CI: -7.7, -2.1]), and apoB (*LPL* score alone: -3.0 mg/dl [95%CI: -4.9, -1.2]; *LDLR* score alone: -3.4 mg/dl [95%CI: -5.2, -1.5]; combined exposure to both scores: -6.4 mg/dl [95%CI: -8.5, -4.4]); and a log-linearly additive decrease 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 change in apoB but not to changes in either triglycerides or LDL-C (eFigue 5).

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 very similar reductions in the risk of CHD per unit change in apoB as compared to the *LPL* and *LDLR* scores; and as compared to an *APOB* score composed of 8 independently inherited variants in the *APOB* gene (Figure 2A). Furthermore, the associated reduction in CHD risk for each of these variants and genetic scores was log-linearly proportional to their associated absolute reduction in apoB-containing lipoproteins (Figure 2B).

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 very similar reductions in the risk of CHD per 10 mg/dL decrease in 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%:0.965-1.065,p=0.189; LDL-C OR:1.010, 95%:0.967-1.055,p=0.186; apoB OR:0.761, 95%CI:0.723-0.798,p=7.51×10^{-20}) (Table 3, eTable 8).

DISCUSSSION

In this study, triglyceride lowering *LPL* variants and LDL-C lowering *LDLR* variants were associated with very similar reductions in CHD risk per unit change in apoB-containing lipoproteins. The associations between lower triglycerides and lower LDL-C 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 triglycerides through the LPL pathway and current therapies that lower LDL-C through the LDLR pathway were also associated with very similar reductions in CHD risk per unit change in apoB. Furthermore, multiple genetic scores composed of other variants associated with either triglycerides, LDL-C or both, were also associated with very similar reductions in the risk of CHD per unit change in apoB, even when the associated changes in triglycerides and LDL-C 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 triglycerides is very similar to the clinical benefit of lowering LDL-C 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 lipoproteins particles, including triglyceride-rich 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 triglycerides, lowering LDL-C 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 the apoB-containing lipoprotein particles. These particles are secreted by the liver as VLDL particles which principally contain triglycerides, some cholesterol and one 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. Indeed, the present findings and interpretations based on Mendelian randomization confirm and extend the initial findings and interpretations in 1980 of Sniderman, Kwiterovich and their colleagues, which were based on cross-sectional coronary angiographic studies.[26]

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 associated with the risk of cardiovascular disease.[27,28] The results of the current study extend those findings by suggesting that triglyceride-rich remnant particles have approximately the same effect on the risk of cardiovascular disease as LDL particles. Furthermore, the results of this study are consistent with a recent Mendelian randomization study that demonstrated that the causal effect of LDL particles on the risk of

cardiovascular disease appears to be determined by the concentration of circulating LDL particles as measured by apoB rather than by the mass of cholesterol carried by those particles as measured by LDL-C.[22] The results of the current study confirm and extend those findings by suggesting that the causal effect of all apoB-containing lipoprotein particles on the risk of cardiovascular disease appears to be determined by the circulating concentration of those particles rather than by the mass of cholesterol or triglyceride that they carry.

The results of this study may also help to explain why prior randomized trials evaluating fibrates, which lower plasma triglycerides at least partially through the LPL pathway, have failed to consistently demonstrate that lowering triglycerides reduces the risk of cardiovascular events.[29-33] The concentration of triglyceride-rich lipoproteins can be estimated by dividing plasma triglyceride concentration by 5 (on the milligram per decilitre scale). Therefore, if all apoB-containing particles have approximately the same atherogenic effect as suggested by this study, then to reduce the risk of cardiovascular events by 20% as can be achieved by lowering LDL-C by 40-mg/dL,[3,4] triglycerides must be reduced by 5-fold this quantity, or approximately 200 mg/dL, to achieve the same corresponding reduction 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 failure of the fibrate trials appears to be explained by the modest reduction in triglycerides and therefore the modest reductions in apoB-containing lipoproteins observed in these studies. Future randomized trials evaluating novel therapies that lower plasma triglycerides 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.[5,34] As a result, the reductions in risk associated with lower triglycerides, LDL-C and apoB reported in this study are 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 change apoB, it is reasonable to then anticipate that short-term pharmacologic reductions in plasma triglycerides and LDL-C will be associated with the same reduction the risk of cardiovascular events per unit change in apoB.[20] 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 reduction 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.[35,36]

CONCLUSIONS

Triglyceride-lowering *LPL* variants and LDL-C lowering *LDLR* variants were associated with very similar reductions in the risk of CHD per unit change in apoB, suggesting that the clinical benefit of lowering triglycerides and is very similar the clinical benefit of lowering LDL-C for the same change in apoB-

containing lipoproteins. Therefore, the clinical benefit of lowering triglycerides, LDL-C or both may be proportional to the absolute change in apoB.

ACKNOWLEDGEMENTS

Funding/Support:

Dr. Ference is supported by the National Institute for Health Research Cambridge Biomedical Research Centre at the Cambridge University Hospitals NHS Foundation Trust. Dr. Clare Oliver-Williams is supported by Homerton College, University of Cambridge. Dr. Butterworth is supported by the European Research Council. Dr Danesh is supported by the Medical Research Council, British Heart Foundation, and the National Institute for Health Research.

Conflict of Interest Disclosures

All authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Dr. Ference reported receiving personal fees from Merck & Co., Amgen, Regeneron, Sanofi, Pfizer, CiVi BioPhama, and KrKA Phamaceuticals, and grants from Merck & Co., Amgen, Novartis and Esperion Therapeutics. Dr. Kastelein reported receiving personal fees from Merck & Co., Lilly, Roche, Pfizer, and Dezima. . Dr. Ray reported receiving personal fees from Sanofi, Amgen, Regeneron, Lilly, Medicines Company, Astra Zeneca, Pfizer, Kowa, Algorithm, IONIS, Esperion, Novo Nordisk, Takeda, Boehringer Ingelheim, Resverlogix, and Abbvie; and grants from Merck & Co., Sanofi, Regeneron, Pfizer, and Amgen. Dr. Ginsberg reported receiving personal fees and grants from Merck & Co, Sanofi-Regeneron, and Amgen. Dr. Chapman reported receiving personal fees from Akcea, Alexion, Amarin, Amgen, Daiichi-Sankyo, Kowa, Merck & Co, Pfizer, Sanofi, Regeneron, and Unilever; and grants from Amgen, CSL, Kowa, Merck & Co, and Pfizer. Dr. Packard reported receiving personal fees from Merck & Co., Amgen, Pfizer, Sanofi, Regeneron, and Daiichi-Sankyo. Dr. Laufs reported receiving personal fees Merck & Co., Amgen, Pfizer, and Sanofi. Dr. Butterworth reported receiving grants from Pfizer, Merck & Co., Novartis, Biogen, and the European Research Council. Dr Danesh reported receiving personal fees from Merck & Co., Novartis, Pfizer, and Sanofi; nonfinancial support from diaDexus; and grants from the

British Heart Foundation, Bupa Foundation, diaDexus, European Research Council, European Union, Evelyn Trust, Fogarty International Center, GlaxoSmithKline, Merck & Co., National Heart, Lung, and Blood Institute, National Institute for Health Research, National Institute of Neurological Disorders and Stroke, NHS Blood and Transplant, Novartis, Pfizer, UK Medical Research Council, Wellcome Trust, and the UK Biobank. Dr. Nicholls reported receiving personal fees from Eli Lilly, AstraZeneca, Amgen, Novartis, Resverlogix, Sanofi-Regeneron, Merck, Boehringer Ingelheim, CSL Behring, and Roche; and grants from Eli Lilly, AstraZeneca, Amgen, Novartis, Resverlogix, Sanofi-Regeneron, Cerenis, Esperion, Merck & Co., and The Medicines Company. Dr. Bhatt reports grants from Amarin, during the conduct of the study; grants from Amarin, grants from AstraZeneca, grants from Bristol-Myers Squibb, grants from Eisai, grants from Ethicon, grants from Medtronic, grants from sanofi aventis, grants from The Medicines Company, other from FlowCo, other from PLx Pharma, other from Takeda, personal fees from Duke Clinical Research Institute, personal fees from Mayo Clinic, personal fees from Population Health Research Institute, personal fees and non-financial support from American College of Cardiology, personal fees from Belvoir Publications, personal fees from Slack Publications, personal fees from WebMD, personal fees from Elsevier, other from Medscape Cardiology, other from Regado Biosciences, other from Boston VA Research Institute, personal fees and non-financial support from Society of Cardiovascular Patient Care, non-financial support from American Heart Association, personal fees from HMP Global, grants from Roche, personal fees from Harvard Clinical Research Institute (now Baim Institute for Clinical Research), other from Clinical Cardiology, personal fees from Journal of the American College of Cardiology, other from VA, grants from Pfizer, grants from Forest Laboratories/AstraZeneca, grants from Ischemix, other from St. Jude Medical (now Abbott), other from Biotronik, other from Cardax, other from American College of Cardiology, other from Boston Scientific, grants from Amgen, grants from Lilly, grants from Chiesi, grants from Ironwood, personal fees from Cleveland Clinic, personal fees from Mount Sinai School of Medicine, other from Merck, grants from

Abbott, grants from Regeneron, other from Svelte, grants from PhaseBio, grants from Idorsia, grants from Synaptic, personal fees from TobeSoft, personal fees and other from Boehringer Ingelheim, personal fees from Bayer, outside the submitted work. Dr. Sabatine reported receiving personal fees from Amgen, AstraZeneca, Intarcia, Merck & Co., Janssen Research Development, MedImmune, Alnylam, CVS Caremark, Ionis, Cubist, Esperion, Medicines Company, MyoKardia, and Zeus Scientific; and grants from Abbott Laboratories, Amgen, AstraZeneca, Clinical Diagnostics, Daiichi-Sankyo, Gilead, GlaxoSmithKline, Intarcia, Merck & Co., Roche Diagnostics, Takeda, Novartis, Poxel, Janssen Research Development, MedImmune, Eisai, Genzyme, and Pfizer. Dr. Catapano reported receiving personal fees from Astrazeneca, Amgen, Aegerion, Genzyme, Sanofi, Merck & Co., and Pfizer; and grants from Amgen, Ely-Lilly, Genzyme, Mediolanum, Sanofi, Merck & Co., Pfizer, Rottapharm, Recordati, and Sigma tau. All other authors have no disclosures to report.

Role of Funder/Sponsor

No funders or sponsors were involved in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; or the decision to submit the manuscript for publication.

Dr Ference 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.

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TABLES:

Table 1: Baseline characteristics of included participants

Baseline Characteristics	No. participants with available data	Participant Summary
Sample Size, No.	654,783	654,783
CHD cases, No.	654,783	91,129
Age, mean (SD), y	654,783	62.7 (± 8.1)
Women, No. (%)	654,783	336,462 (51.4%)
Systolic Blood Pressure, mean (SD), mmHg	470,478	132.1 (± 18.2)
Diastolic Blood pressure, mean (SD), mmHg	470,478	80.9 (± 9.3)
Body mass index, mean (SD), kg/m2	470,478	27.5 (± 4.9)
Prevalent Diabetes, No. (%)	470,478	21,642 (4.6%)
Current smoker, No. (%)	470,478	43,284 (9.2%)
Total cholesterol, mean (SD), mg/dl	31,221	206.6 (± 39.4)
Low-density lipoprotein cholesterol, mean (SD), mg/dl	31,221	129.7 (± 32.1)
High-density lipoprotein cholesterol, mean (SD), mg/dl	31,221	52.0 (± 15.4)
Triglycerides, median (IQR), mg/dl	31,221	117.6 (84.1 – 163.3)
Apolipoprotein B, mean (SD), mg/dl	31,221	101.4 (± 27.3)
Non-high-density lipoprotein cholesterol (Total cholesterol – HDL-C), mg/dl	31,221	154.9 (± 38.3)
Remnant cholesterol, (total cholesterol – HDL-C – LDL-C), mg/dl	31,221	23.9 (15.9 – 32.8)

Table 1 Legend: Data for age and gender were available for all 654,783 participants included in the primary analysis. Data for other non-lipid baseline characteristics were available for 470,478 participants with individual level data enrolled in the UK Biobank or one of the 14 case-control or cohort studies that reported cardiovascular outcomes in the database of genotypes and phenotypes program (dbGAP). Data for baseline lipid measurements were available for 31,221 participants with individual data enrolled in one of the dbGAP studies and for whom lipid measurements were available (the UK Biobank has not yet released lipid measurements of enrolled participants). Non-HDL-C and remnant

cholesterol are calculated values. LDL-C is low-density lipoprotein cholesterol; HDL-C is high-density lipoprotein cholesterol; SD is standard deviation; IQR is interquartile range.

Table 2: Association of additional genetic scores with triglycerides, LDL-C and risk of coronary heart disease per 10 mg/dl decrease in apoB-containing lipoproteins

Composition of Genetic score	**Δ triglycerides (95% CI)**	**Δ LDL-C (95% CI)**	**OR_{CHD} (95% CI)**
51 variants associated with triglycerides at $p < 5.0x10^{-8}$; but not LDL-C ($p > 0.001$)	-43.1 (-44.5, -41.7)	-2.1 (-2.6, -1.6)	0.762 (0.724 - 0.803)
59 variants associated with LDL-C at $p < 5.0x10^{-8}$; but not triglycerides ($p > 0.001$)	-2.1 (-3.0, -1.1)	-15.5 (-15.8, -15.1)	0.774 (0.748 - 0.800)
173 variants associated with either triglycerides or LDL-C at $p < 5.0x10^{-8}$	-21.6 (-22.1, -21.1)	-11.8 (-12.0, -11.6)	0.770 (0.757 - 0.783)
91 variants associated with triglycerides at $p < 5.0x10^{-8}$	-35.3 (-35.9, -34.6)	-9.3 (-9.6, -9.1)	0.776 (0.758 - 0.795)
100 variants associated with LDL-C at $p < 5.0x10^{-8}$	-17.5 (-18.0, -17.0)	-13.5 (-13.7, -13.3)	0.776 (0.762 - 0.791)
23 variants associated with triglycerides and LDL-C, both at $p < 5.0x10^{-8}$; in same direction of effect	-32.3 (-33.0, -31.5)	-12.0 (-12.3, -11.7)	0.793 (0.771, 0.815)
10 variants associated with triglycerides and LDL-C, both at $p < 5.0x10^{-8}$; with opposite directions of effect	+17.2 (+16.0, +18.4)	-22.5 (-23.0, -22.1)	0.798 (0.767 - 0.830)
9 variants associated with triglycerides and LDL-C, both at $p < 5.0x10^{-8}$; with opposite directions of effect (excluding APOE variant rs7412)	+26.0 (+23.7, +28.3)	-20.3 (-21.2, -19.4)	0.770 (0.711 - 0.833)

Table 2 Legend: To compare the association of triglycerides and LDL-C with the risk of CHD for the same decrease in the concentration of apoB-containing lipoproteins not related to the *LPL* and *LDLR* genes, several additional genetic scores were constructed using up to 173 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 decrease in apoB in up to 305,699 participants in GLGC; and with the risk of CHD per 10 mg/dl decrease in apoB in all 654,783 participants included in this study. For example, for each 10 mg/dL decrease in 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 decrease in triglycerides, 2.1 mg/dl decrease in LDL-C and a lower risk of CHD (OR: 0.76, 95%CI: 0.72-0.80). By contrast, for the same 10 mg/dl decrease in 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 decrease in LDL-C, 2.1 mg/dl decrease in triglycerides and a similar lower risk of CHD (OR: 0.77, 95%CI: 0.75-0.80). Furthermore, for the same 10 mg/dl decrease in plasma apoB concentration associated with a genetic score consisting of 173 variants associated with either triglycerides or LDL-C at genome-wide level of significance, there was a corresponding 21.6 mg/dl decrease in triglycerides, an 11.8 mg/dl decrease in LDL-C, and a similar lower risk of CHD (OR: 0.77, 95%CI: 0.76-0.78). Despite being associated with different changes in lipids, all genetic scores were associated with similar reductions in the risk of CHD for the same 10 mg/dl decrease in plasma apoB concentration. Boxes represent effect size estimates and lines represent 95% confidence intervals. The unadjusted associations with triglycerides, LDL-C, apoB and coronary heart disease for each variant included in the genetic scores are provided in eTable 7.

Table 3: Multivariable Mendelian randomization analysis of the association between plasma triglycerides, LDL-C and apoB with the risk of coronary heart disease

Analysis	variables	**OR_{CHD} (95% CI)**	**p value**
Association of 10 mg/dl lower apoB with risk of CHD	apoB	0.770 (0.760 - 0.781)	1.42E-170
Association of 10 mg/dl lower LDL-C with risk of CHD	LDL-C	0.846 (0.833 - 0.858)	8.16E-77
Association of 50 mg/dl lower triglycerides with risk of CHD	Triglycerides	0.815 (0.785 - 0.846)	1.37E-18
Association of 10 mg/dl lower LDL-C and 50 mg/dl lower triglycerides with risk of CHD included in same model	LDL-C	0.862 (0.849 - 0.875)	6.92E-65
	Triglycerides	0.876 (0.850 - 0.902)	1.36E-14
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	apoB	0.761 (0.723 - 0.798)	7.51E-20
	LDL-C	1.010 (0.967 - 1.055)	0.186
	Triglycerides	1.014 (0.965 - 1.065)	0.189

Table 3 Legend: Data presented are derived from a multivariable meta-regression analysis of 191 genetic variants, including the 5 variants included in the LPL score, 3 variants included in the LDLR score, and 183 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 coronary heart disease are reported per 10 mg/dl decrease in apoB; per 10 mg/dl decrease in LDL-C, or per 50 mg/dl decrease in triglycerides (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 coronary heart disease 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 191

genetic variants, both triglycerides (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 with apoB remained unchanged (OR: 0.761 per 10 mg/dl lower apoB). The unadjusted associations with triglycerides, LDL-C, apoB and coronary heart disease for each variant included in the analysis are provided in eTable 7. Additional multivariable meta-regression analyses for various combinations of these variants is provided in eTable 8.

FIGURES:

Figure 1: Associations between the LPL and LDLR genetic scores with triglycerides, LDL-C and risk of coronary heart disease per 10 mg/dl decrease in apoB-containing lipoproteins

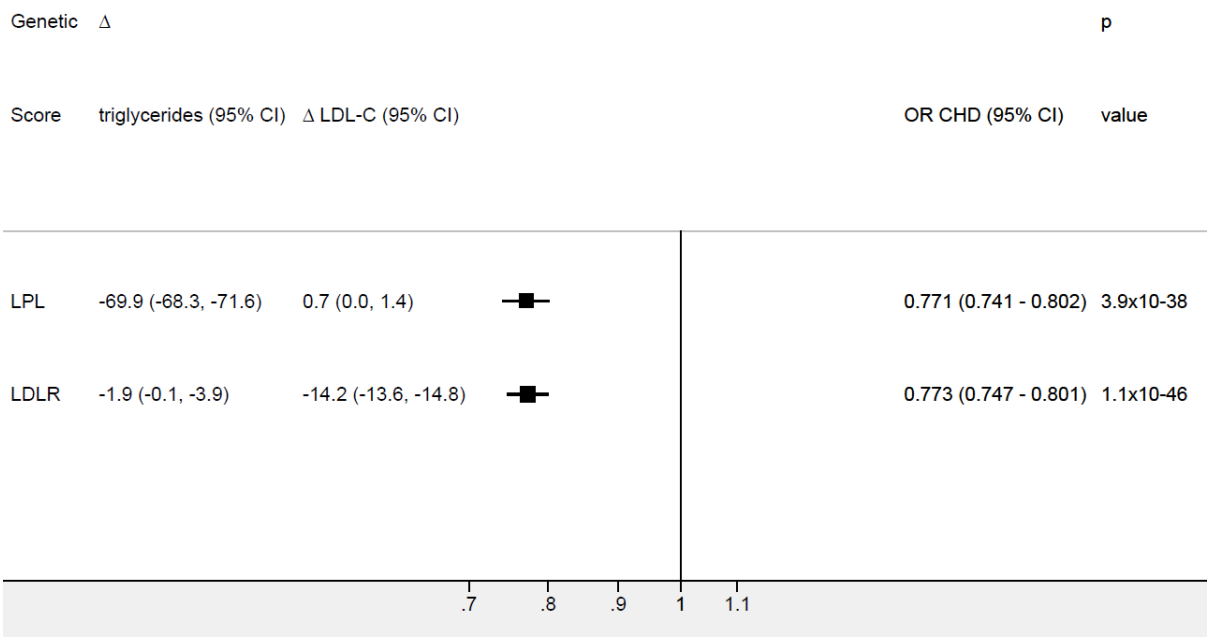
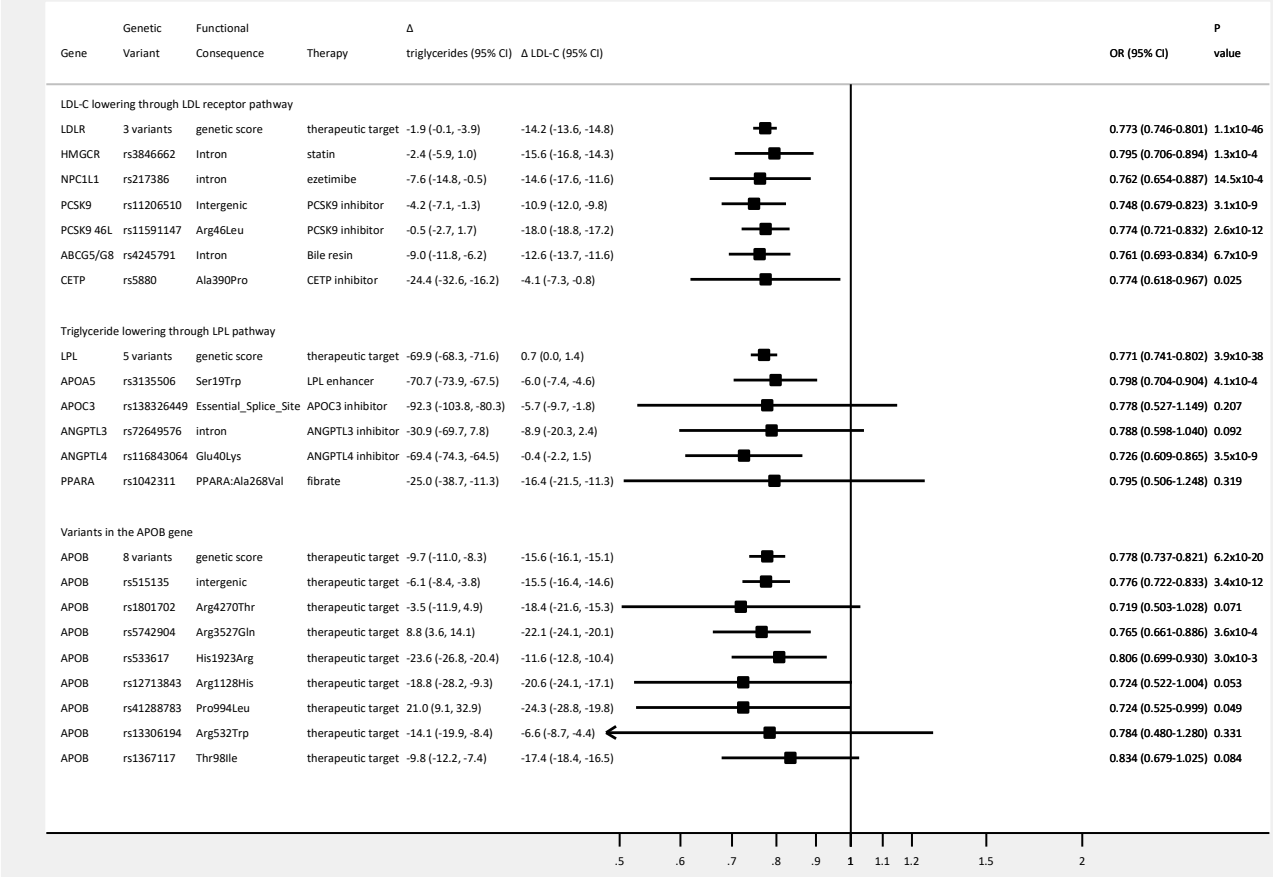


Figure 1 legend: Triglycerides are carried in plasma by apoB-containing triglyceride-rich lipoproteins while cholesterol is carried predominantly by apoB-containing low-density lipoproteins. Changes in plasma triglycerides and LDL-C concentration are thus markers of the corresponding changes in the concentration 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 decrease in plasma apoB concentration associated with variants in the *LPL* score, there is a corresponding 69.9 mg/dl decrease in triglycerides, no change in LDL-C and a lower risk of CHD (OR: 0.77, 95%CI: 0.74-0.80). By contrast, for the same 10 mg/dl decrease in plasma apoB concentration associated with variants in

the *LDLR* score, there is a corresponding 14.1 mg/dl decrease in LDL-C, no change in triglycerides, and a similar lower risk of CHD (OR: 0.77, 95%CI: 0.75-0.80). Therefore, despite being associated with changes in different lipids, the *LPL* and *LDLR* scores were associated with similar reductions in the risk of CHD for the same decrease in 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 decrease in 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% confidence intervals.

Figure 2: Associations between variants in the genes that encode the targets of lipid lowering therapies with triglycerides, LDL-C and risk of coronary heart disease

A. Association of genetic variants and genetics scores with triglycerides, LDL-C and risk of coronary heart disease per 10 mg/dl decrease in apoB-containing lipoproteins



Gene	Genetic Variant	Functional Consequence	Therapy	Δ triglycerides (95% CI)	Δ LDL-C (95% CI)	OR (95% CI)	P value
LDL-C lowering through LDL receptor pathway							
LDLR	3 variants	genetic score	therapeutic target	-1.9 (-0.1, -3.9)	-14.2 (-13.6, -14.8)	**0.773 (0.746-0.801)**	**1.1x10-46**
HMGCR	rs3846662	Intron	statin	-2.4 (-5.9, 1.0)	-15.6 (-16.8, -14.3)	**0.795 (0.706-0.894)**	**1.3x10-4**
NPC1L1	rs217386	intron	ezetimibe	-7.6 (-14.8, -0.5)	-14.6 (-17.6, -11.6)	**0.762 (0.654-0.887)**	**14.5x10-4**
PCSK9	rs11206510	Intergenic	PCSK9 inhibitor	-4.2 (-7.1, -1.3)	-10.9 (-12.0, -9.8)	**0.748 (0.679-0.823)**	**3.1x10-9**
PCSK9 46L	rs11591147	Arg46Leu	PCSK9 inhibitor	-0.5 (-2.7, 1.7)	-18.0 (-18.8, -17.2)	**0.774 (0.721-0.832)**	**2.6x10-12**
ABCG5/G8	rs4245791	Intron	Bile resin	-9.0 (-11.8, -6.2)	-12.6 (-13.7, -11.6)	**0.761 (0.693-0.834)**	**6.7x10-9**
CETP	rs5880	Ala390Pro	CETP inhibitor	-24.4 (-32.6, -16.2)	-4.1 (-7.3, -0.8)	**0.774 (0.618-0.967)**	**0.025**
Triglyceride lowering through LPL pathway							
LPL	5 variants	genetic score	therapeutic target	-69.9 (-68.3, -71.6)	0.7 (0.0, 1.4)	**0.771 (0.741-0.802)**	**3.9x10-38**
APOA5	rs3135506	Ser19Trp	LPL enhancer	-70.7 (-73.9, -67.5)	-6.0 (-7.4, -4.6)	**0.798 (0.704-0.904)**	**4.1x10-4**
APOC3	rs138326449	Essential_Splice_Site	APOC3 inhibitor	-92.3 (-103.8, -80.3)	-5.7 (-9.7, -1.8)	**0.778 (0.527-1.149)**	**0.207**
ANGPTL3	rs72649576	intron	ANGPTL3 inhibitor	-30.9 (-69.7, 7.8)	-8.9 (-20.3, 2.4)	**0.788 (0.598-1.040)**	**0.092**
ANGPTL4	rs116843064	Glu40Lys	ANGPTL4 inhibitor	-69.4 (-74.3, -64.5)	-0.4 (-2.2, 1.5)	**0.726 (0.609-0.865)**	**3.5x10-9**
PPARA	rs1042311	PPARA:Ala268Val	fibrate	-25.0 (-38.7, -11.3)	-16.4 (-21.5, -11.3)	**0.795 (0.506-1.248)**	**0.319**
Variants in the APOB gene							
APOB	8 variants	genetic score	therapeutic target	-9.7 (-11.0, -8.3)	-15.6 (-16.1, -15.1)	**0.778 (0.737-0.821)**	**6.2x10-20**
APOB	rs515135	intergenic	therapeutic target	-6.1 (-8.4, -3.8)	-15.5 (-16.4, -14.6)	**0.776 (0.722-0.833)**	**3.4x10-12**
APOB	rs1801702	Arg4270Thr	therapeutic target	-3.5 (-11.9, 4.9)	-18.4 (-21.6, -15.3)	**0.719 (0.503-1.028)**	**0.071**
APOB	rs5742904	Arg3527Gln	therapeutic target	8.8 (3.6, 14.1)	-22.1 (-24.1, -20.1)	**0.765 (0.661-0.886)**	**3.6x10-4**
APOB	rs533617	His1923Arg	therapeutic target	-23.6 (-26.8, -20.4)	-11.6 (-12.8, -10.4)	**0.806 (0.699-0.930)**	**3.0x10-3**
APOB	rs12713843	Arg1128His	therapeutic target	-18.8 (-28.2, -9.3)	-20.6 (-24.1, -17.1)	**0.724 (0.522-1.004)**	**0.053**
APOB	rs41288783	Pro994Leu	therapeutic target	21.0 (9.1, 32.9)	-24.3 (-28.8, -19.8)	**0.724 (0.525-0.999)**	**0.049**
APOB	rs13306194	Arg532Trp	therapeutic target	-14.1 (-19.9, -8.4)	-6.6 (-8.7, -4.4)	**0.784 (0.480-1.280)**	**0.331**
APOB	rs1367117	Thr98Ile	therapeutic target	-9.8 (-12.2, -7.4)	-17.4 (-18.4, -16.5)	**0.834 (0.679-1.025)**	**0.084**

B. Log-linear association between absolute changes in apoB and reduction in risk of CHD

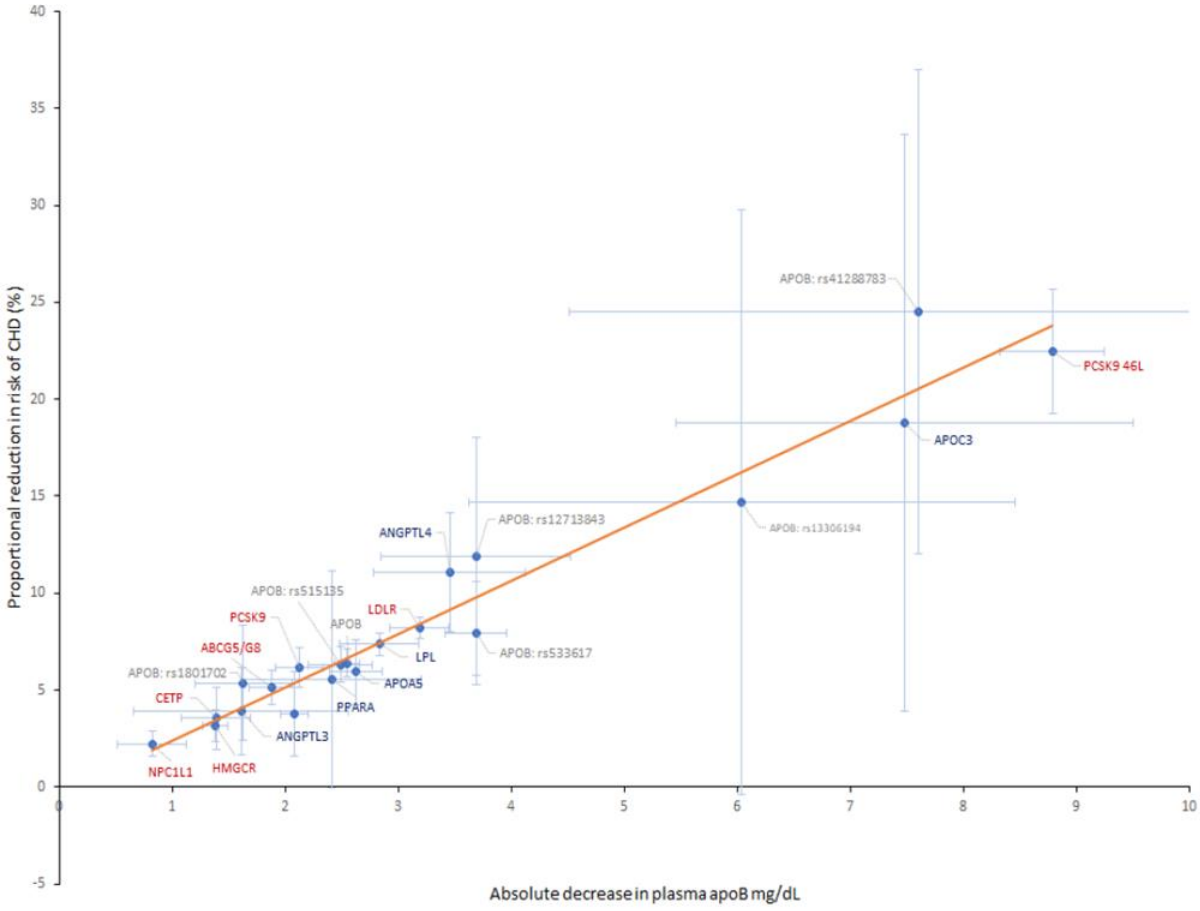


Figure 2 legend: The Figure shows the associations with triglycerides, LDL-C and risk of CHD for the same 10 mg/dl decrease in apoB-containing lipoprotein concentration for variants in the *LPL* and *LDLR* scores as compared to variants in the genes that encode the targets of current therapies that decrease 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. For example, each 10 mg/dL decrease in 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

decrease in LDL-C, no change in triglycerides and a lower risk of CHD (OR: 0.77, 95%CI: 0.72-0.83). By contrast, for the same 10 mg/dL decrease in plasma apoB concentration associated with the functional rs116843064 variant in the *ANGPTL4* gene, there was a corresponding 69.4 mg/dl decrease in triglycerides, no change in LDL-C and a similar lower risk of CHD (OR: 0.73, 95%CI: 0.61-0.86). Furthermore, for the same 10 mg/dL decrease in plasma apoB concentration associated with variants in the *APOB* gene score, there was a corresponding 9.7 mg/dl decrease in triglycerides, 15.6 mg/dl decrease in LDL-C and a similar lower risk of CHD (OR: 0.78, 95%CI: 0.74-0.82). Despite a range of associated changes in triglycerides, LDL-C or both, all genetic variants and genetic scores were associated with similar reductions in the risk of CHD for the same 10 mg/dL decrease in plasma apoB concentration. In Panel A, 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% confidence intervals. In panel B, the associations of each genetic variant with apoB concentration is plotted against its unadjusted association with CHD, expressed as a proportional reduction in risk (calculated as $[1\text{-}OR_{CHD}]*100$). 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 up-regulation of the LDL receptor are marked by red labels. Circles represent the associated absolute change in apoB and corresponding proportional risk reduction for each variant. The horizontal lines through each circle represents ± 1 standard errors for the associated absolute change in apoB for each variant; and the vertical line through each circle represents ± 1 standard errors for the associated proportional risk reduction. In both panels, associations with CHD per 10 mg/dl lower apoB were measured in all 654,783 participants included in the study; and in Panel A 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.

Supplementary Online Content

Ference BA, Kastelein JJP, Ray, KK, et al. Association of triglyceride-lowering *LPL* variants and LDL-C lowering *LDLR* variants with risk of coronary heart disease

eMethods

eReferences

eMethods:

I. Constructing the genetic scores

All approximately independently inherited variants in the *LPL* gene that are conditionally independently associated with plasma triglyceride levels at genome-wide level of statistical significance ($p < 5x10^{-8}$) were combined to create an *LPL* genetic score, and all approximately independently inherited variants in the *LDLR* gene that are conditionally independently associated with plasma LDL-C levels at genome-wide level of statistical significance were combined to create to create an *LDLR* genetic score. These genetic scores are instruments of randomization that reflect the combined effect of the variants included in the respective score on plasma lipid and lipoprotein levels. As a result, each score has a much larger effect on plasma lipid and lipoprotein levels than any individual variant included in the respective score.

To select variants for inclusion in the *LPL* genetic score, the following protocol was used. First, the association of each variant within a 100 KB window of the *LPL* gene was tested in a linear regression model where the dependent variable was triglycerides (the major lipid effect of lipoprotein lipase) and the independent variables were age, sex, study sample, and 5 principal components of ancestry to select the variant that was most strongly associated with plasma triglyceride levels in up to 54,837 participants enrolled in one of the dbGAP studies who were free of cardiovascular disease at baseline and for whom one or more measurements of plasma lipids and lipoproteins was available. Next, we iteratively tested the association of each remaining variant in the same linear model where the dependent variable was triglyceride level and the independent variables were age, sex, study sample, 5 principal components of ancestry, plus all variants selected in a previous step of the algorithm. The variant that was associated with triglycerides in this conditional analysis with the lowest p-value below a threshold of 5×10^{-8} was added to the set of selected variants. Once a variant was included in the analysis, all other variants that were correlated with the selected variant at $r^2 > 0.3$ were removed from the set of candidate variants.[1,2] We then iteratively repeated this process until all variants were either selected, removed due to linkage disequilibrium with a selected variant, or were not strongly associated ($p < 5 \times 10^{-8}$) with plasma triglycerides in the conditional analysis. To select variants for inclusion in the *LDLR* genetic score, we used the same protocol except that the dependent variable was plasma LDL-C level (the major lipid effect of the LDL receptor) in all regression models. This approach selected the variants in the *LPL* gene most strongly associated with triglycerides, and the variants in the *LDLR* gene most strongly associated with LDL-C.

We defined the exposure allele for each variant included in the *LPL* score as the allele associated with lower plasma triglyceride levels; and the exposure allele for each variant included in the *LDLR* score as the allele associated with lower plasma LDL-C levels as reported by the Global Lipid Genetics Consortium (GLGC).[3,4]

Both triglycerides and cholesterol are carried in plasma by apoB-containing lipoproteins, which can become retained in the artery wall leading to the initiation and progression of atherosclerotic plaque. Furthermore, all apolipoprotein B containing lipoproteins synthesized by the liver (including triglyceride-rich VLDL particles, VLDL remnant particles, and LDL particles) contain a single apoB-100 molecule the association of the *LPL* and *LDLR* genetic scores on lipids, lipoprotein levels and the risk of CHD can be compared directly per apoB-containing lipoprotein particle by comparing the associations of these genetic scores per unit change in plasma apoB levels. Thus, to directly compare the effect of the *LPL* and *LDLR* scores, each exposure allele included in either genetic score was weighted by its effect on apoB. To measure the association of each variant included in the *LPL* score on apoB levels conditional on the presence of all other variants included in the *LPL* score, the association of each variant with apoB was measured in a linear regression model where the dependent variable was plasma apoB level and the independent variables were age, sex, study sample, the first 5 principal components of ancestry, and all variants included in the *LPL* score selected using the algorithm described above. Similarly, to measure the association of each variant included in the *LDLR* score on apoB levels conditional on the presence of all other variants included in the *LDLR* score, the association of each variant with apoB was measured in a linear regression model where the dependent variable was plasma apoB level and the independent variables were age, sex, study sample, the first 5 principal components of ancestry, and all variants included in the *LDLR* score selected using the algorithm described above. The conditional apoB analyses were performed in an independent external sample including up to 63,890 participants with available measurements of plasma apoB levels from the MAGNETIC NMR GWAS consortium and INTERVAL Bioresource studies.[5,6] All studies used the same NMR platform to measure the plasma concentration of apoB using the same protocol.

To calculate the *LPL* genetic score for each participant weighted by apoB, the number of exposure alleles that a participant inherited at each variant included in the *LPL* score was multiplied by the conditional effect of that variant on plasma apoB concentration measured in mg/dL. These values were then

summed to create a weighted *LPL* genetic score for each participant. Similarly, the *LDLR* genetic score for each participant weighted by apoB was calculated by multiplying the number of exposure alleles that a participant inherited at each variant included in the *LDLR* score by the conditional effect of that variant on plasma apoB concentration measured in mg/dL, and then summed.

II. Allocation into exposure groups for stratified and 2x2 factorial Mendelian randomization analysis

Because all variants included in either genetic score are inherited approximately randomly at the time of conception in a process sometimes referred to as Mendelian randomization,[7] and because each variant is inherited approximately independently of the other polymorphisms included in the score by virtue of low linkage disequilibrium as defined by the construction of the score, the number of exposure alleles that a person inherits in either score should also be random.

To perform the stratified analyses, each genetic score was first dichotomized as having a value above or below the median score for participants in the population under study. Because the number of exposure alleles that a person inherits in either score should be random, dichotomizing the genetic score as above and below the median should therefore randomly allocate participants under study into two approximately equal sized groups. The association between each score and changes in plasma triglyceride, plasma LDL-C levels, and the risk of CHD was then measured separately among participants with scores less than or equal to the median and greater than the median value for the other score., and effect estimates were compared using a z statistic to assess for heterogeneity of effect estimates.

To conduct the 2x2 factorial analyses, study participants were first randomly allocated into two groups based on whether their *LDLR* genetic score was above or below the median value. Participants in either of these two groups were then randomly allocated into two further groups based on whether their *LPL* genetic score was above or below the median value. Because all variants included in either score are inherited approximately randomly and approximately independently of each other due to low linkage disequilibrium; and because *LPL* and *LDLR* variants are located on different chromosomes and therefore inherited independently of the other, this process should randomly allocate participants into 4 approximately equal-sized groups: the reference group with both scores equal to or below the median, a group with *LPL* scores above the median but *LDLR* scores equal to or below the median (i.e. a group with lower TG but not lower LDL-C compared to the reference group), a group with *LDLR* scores above the median but *LPL* scores equal to or below the median (i.e. a group with lower LDL-C but not lower TG

compared to the reference group), and a group with both scores above the median (i.e. a group with lower LDL-C but not lower TG compared to the reference group).[8,9]

The success of the naturally random allocation scheme was assessed by comparing baseline characteristics among persons in each group being compared. Continuous variables were compared using a t-test, dichotomous (and ordinal) variables were compared using a chi-square test, and non-normally distributed variables were compared using non-parametric rank tests or empirical resampling.

III. Harmonized definition of cardiovascular outcome events

The primary outcome for the study was CHD, defined as a composite of the first occurrence of non-fatal MI, coronary revascularization or coronary death. Both prevalent and incident cases of MI were included in the primary composite to meet the definition of "first occurrence" (understanding that all coronary deaths during follow-up were necessarily incident events) in the cohort studies. Therefore, the primary cardiovascular outcome is a composite of prevalent MI or prevalent coronary revascularization; or the first occurrence of incident MI, incident coronary revascularization or coronary death.

For participants enrolled in the dbGAP studies, the definition of all cardiovascular-related outcome was first harmonized as previously described.[10-18] Individual level data was then coded for each study participant as necessary to satisfy the harmonized variable definitions to the extent possible, as described below.

In general, and where possible, only the outcomes of coronary heart disease death (as adjudicated by the individual studies); "definite" myocardial infarction (excluding "silent MI", "possible MI", "probable MI", "ECG-detected prior MI" and "resuscitated cardiac arrest"); and coronary revascularization (defined as "angioplasty", "percutaneous coronary intervention" or "coronary artery bypass grafting") were included. New reconciled study outcome variables were created in each data set using the definitions described above.

We did not recode the "case" definition for the case-control studies. In the six (6) Myocardial Infarction Genetics (MIGEN) Consortium case-control studies, all "cases" were MI.[18] Therefore, because MI is a component of the primary outcome, these "cases" were included in the primary composite outcome.

In the Wellcome Trust Case-Control Consortium (WTCCC) study, "cases" had a history of either myocardial infarction or coronary revascularization before the age of 66 years, and a family history of coronary artery disease.[19] Of the 1,926 WTCCC "cases", 1,377 had MI (71.5%) and the remaining 549 had coronary revascularization (202 PCI; 347 CABG) as the case ascertainment event. Therefore all "cases" in the WTCCC met the criteria for a primary composite outcome event and were included in the analyses.

In the UK Biobank, data for each of components of the primary composite outcome was available for all participants enrolled in the study.[19] These outcomes included nonfatal MI [UK Biobank's algorithmically defined myocardial infarction (ICD9: 410.X, 411.0.X, 412.X, 429.79; ICD10: I21.X, I22.X, I23.X, I24.1, I25.2; self-report 20002: 1075)]; PTCA or CABG (self-report 20004: 1070, 1095, 1523; Procedures (OPCS): K50.1, K40.X, K41.X, K42.X, K43.X, K44.X); and CHD death (Death 40001, 40002: I21.X, I22.X, I23.X, I24.X, I25.1, I25.2, I25.3, I25.5, I25.6, I25.6, I25.8, I25.9).

The definition of CHD in studies that provided summary level data was defined by the individual studies included in the CARDIoGRAMplusC4D consortium (www.CARDIOGRAMPLUSC4D.org).[20]
Case status was defined in these studies by an inclusive CHD diagnosis (e.g. MI, acute coronary syndrome, chronic stable angina, PCI or coronary stenosis >50%). Approximately 70% of total number of CHD cases in the CARDIoGRAMplusC4D consortium studies were defined by a reported history of MI.

IV. Analytic methods

In studies with individual participant data, the association between each weighted genetic score and plasma lipid levels was evaluated using linear regression, and the association with CHD was evaluated using logistic regression (for combined prevalent and incident outcomes) or proportional hazards models (for incident events). All analyses were adjusted for age, gender and the first five principal components of ancestry.

In the main analysis, the associations for each score were adjusted for a standardized decrement of 10 mg/dl lower plasma apoB concentration. In the stratified analyses, the associations for either genetic score was calculated separately among participants with values of the other score equal to or below the median value for that score; and among participants with values of the other score above the median. In the 2x2 factorial analysis, the group with both the *LPL* and *LDLR* scores below the median was used as

the reference group. The associations with changes in lipid levels and the risk of CHD for each group was compared to the reference group.

To calculate association of the *LPL* and *LDLR* genetic scores on plasma lipid levels scaled for a given change in apoB-containing lipoproteins in studies with summary level data, the reported association was looked-up between each variant included in the *LPL* and *LDLR* score, respectively, with plasma triglycerides and LDL-C in up to 316,391 participants as reported by the Global Lipids Genetic Consortium (GLGC).[2,3] The reported lipid effect size (and the corresponding standard error) was then adjusted by the conditional effect of that variant on apoB (measured in mg/dl) using the usual ratio of effect estimates method (i.e. dividing the effect of each variant on plasma triglycerides and LDL-C by the effect of that allele on apoB). The adjusted effect estimates for each *LPL* variant was then combined in a fixed-effect inverse-variance weighted meta-analysis to measure the association between the *LPL* genetic score and plasma lipid levels per unit lower apoB. Similarly, the adjusted effect estimates for each *LDLR* variant was combined in a fixed-effect inverse-variance weighted meta-analysis to measure the association between the *LDLR* genetic score and plasma lipid levels per unit lower apoB.

To calculate association of the *LPL* and *LDLR* genetic scores on the risk of CHD scaled for a given change in apoB-containing lipoproteins in studies with summary level data, the association was looked-up between each variant included in the *LPL* and *LDLR* score, respectively, with the risk of CHD as reported by the CARDIoGRAMplusC4D consortium (www.CARDIOGRAMPLUSC4D.org).[20] The reported CHD effect sizes in natural log units (and the corresponding standard error) were then adjusted by the effect of each variant on apoB (measured in mg/dl)) using the usual ratio of effect estimates method (i.e. dividing the effect of each variant on the risk of CHD in natural log units by the effect of that allele on apoB). The adjusted effect estimates for the *LPL* variants were then combined in a fixed-effect inverse-variance weighted meta-analysis to measure the association between the *LPL* genetic score and the risk of CHD per unit lower apoB; and the adjusted effect estimates for the *LDLR* variants were combined in a fixed-effects inverse-variance weighted meta-analysis to measure the association between the *LDLR* genetic score and the risk of CHD per unit lower apoB.

All analyses were conducted in separately in each study using individual participant data (or each consortium using summary level data) and then combined across all studies to produce overall summary estimates of effect using a generalized linear regression model that takes into account partial correlation

due to low linkage disequilibrium between variants included in either score.[21] If variants were uncorrelated, this method would be equivalent to combining the variant-specific causal estimates in an inverse-variance weighted meta-analysis (or combining the variants into a single genetic score variable and calculating the Mendelian randomization ratio estimate using this score).

To combine study specific effect estimates across studies, a matrix of genetic correlations between variants included in each score, respectively, was estimated in participants not having a previous CHD event at baseline only. The regression model was:

$$\beta_Y = \theta\, \beta_X + \varepsilon, \qquad \varepsilon \sim N(0, \Omega)$$

where θ is the Mendelian randomization causal estimate, β_X is a vector of the genetic associations (beta-coefficients) with the risk factor, β_Y is a vector of the genetic associations with the outcome, and the weighting matrix Ω has terms $\Omega_{j_1 j_2} = \sigma_{Y j_1}\sigma_{Y j_2}\rho_{j_1 j_2}$, where $\sigma_{Y j}$ is the standard error of the genetic association with the outcome for the *j*th variant, and $\rho_{j_1 j_2}$ is the correlation between the j_1th and j_2th variants. The causal estimate from this weighted generalized linear regression is $({\beta_X}^T \Omega^{-1} \beta_X)^{-1} {\beta_X}^T \Omega^{-1} \beta_Y$, and the standard error is $\sigma\sqrt{({\beta_X}^T \Omega^{-1} \beta_X)^{-1}}$, where ^{T} is a matrix transpose, and σ is the maximum of the residual standard error from the regression model and 1. This is equivalent to assuming a multiplicative random-effects model on the variant-specific causal effect estimates. By fixing σ to be no lower than 1, we ensure that the random-effects analysis is no more precise than a fixed-effect analysis would be. This method has been described previously and was implemented using the Mendelian Randomization package in R (available for download at https://cran.r-project.org/web/packages/MendelianRandomization/). When run as a fixed-effect analysis, it is equivalent to the commonly-used two-stage least squares method that requires individual-level data.

Data Sources and Acknowledgements

UK Biobank (UK BB) [10]

UK Biobank is a population-based cohort of over 500,000 people aged between 40-69 years who were recruited in 2006-2010 from several centers across the United Kingdom. This research has been conducted using the UK Biobank Resource under Application Number 11193.
http://www.ukbiobank.ac.uk/

ARIC Atherosclerosis Risk in Communities Study (ARIC) [11]

DbGaP dataset reference: The datasets used for the analyses described in this manuscript were obtained from dbGaP at http://www.ncbi.nlm.nih.gov/sites/entrez?db=gap through dbGaP Study Accession: phs000280.v2.p1

The research reported in this article was supported by contract numbers HHSN268201100006C, HHSN268201100007C, HHSN268201100008C, HHSN268201100009C, HHSN268201100010C, HHSN268201100011C, and HHSN268201100012C; all from the National Heart, Lung, and Blood Institute; National Institutes of Health; Bethesda, MD, USA. A full list of principal ARIC investigators and institutions can be found at https://www2.cscc.unc.edu/aric/. This manuscript was not prepared in collaboration with ARIC investigators and does not necessarily reflect the opinions or views of ARIC, or the NHLBI.

Candidate Gene Association Resource (CARe) - Support for the genotyping through the CARe Study was provided by NHLBI Contract N01-HC-65226.

GENEVA (Gene-Environment Association Studies) - Support for the genotyping through the GENEVA Study was provided by the NIH GEI U01HG004438, U01HG04424, and HHSN268200782096C

Cardiovascular Health Study (CHS) [12]

DbGaP dataset reference: The datasets used for the analyses described in this manuscript were obtained from dbGaP at http://www.ncbi.nlm.nih.gov/sites/entrez?db=gap through dbGaP Study Accession: phs000287.v4.p1

The research reported in this article was supported by contract numbers N01-HC-

85079, N01-HC-85080, N01-HC-85081, N01-HC-85082, N01-HC-85083, N01-HC-85084, N01-HC-85085, N01-HC-85086, N01-HC-35129, N01 HC-15103, N01 HC-55222, N01-HC-75150, N01-HC-45133, N01-HC-85239 and HHSN268201200036C; grant numbers U01 HL080295 from the National Heart, Lung, and Blood Institute and R01 AG-023629 from the National Institute on Aging, with additional contribution from the National Institute of Neurological Disorders and Stroke. A full list of principal CHS investigators and institutions can be found at http://www.chs-nhlbi.org/pi.htm. This manuscript was not prepared in collaboration with CHS investigators and does not necessarily reflect the opinions or views of CHS, or the NHLBI.

CHS Candidate gene Association Resource (CARe): Support for the genotyping through the CARe Study was provided by NHLBI Contract N01-HC-65226.

Support for the Cardiovascular Health Study Whole Genome Study was provided by NHLBI grant HL087652. Additional support for infrastructure was provided by HL105756 and additional genotyping among the African-American cohort was supported in part by HL085251.
DNA handling and genotyping at Cedars-Sinai Medical Center was supported in part by National Center for Research Resources grant UL1RR033176, now at the National Center for Advancing Translational Technologies CTSI grant UL1TR000124; in addition to the National Institute of Diabetes and Digestive and Kidney Diseases grant DK063491 to the Southern California Diabetes Endocrinology Research Center.

The Framingham Heart Study (FHS) [13,14]

DbGaP dataset reference: The datasets used for the analyses described in this manuscript were obtained from dbGaP at http://www.ncbi.nlm.nih.gov/sites/entrez?db=gap through dbGaP Study Accession: phs000007.v23.p8

The Framingham Heart Study is conducted and supported by the National Heart, Lung, and Blood Institute (NHLBI) in collaboration with Boston University (Contract No. N01-HC-25195). This manuscript was not prepared in collaboration with investigators of the Framingham Heart Study and does not necessarily reflect the opinions or views of the Framingham Heart Study, Boston University, or NHLBI.

FHS SNP Health Association Resource (SHARe): Funding for SHARe Affymetrix genotyping was provided by NHLBI Contract N02-HL-64278. SHARe Illumina genotyping was provided under an agreement between Illumina and Boston University.

Candidate gene Association Resource (CARe): Funding for CARe genotyping was provided by NHLBI Contract N01-HC-65226.

Multi-Ethnic Study of Atherosclerosis (MESA) [15]

DbGaP dataset reference: The datasets used for the analyses described in this manuscript were obtained from dbGaP at http://www.ncbi.nlm.nih.gov/sites/entrez?db=gap through dbGaP Study Accession: phs000209.v12.p3

MESA and the MESA SHARe project are conducted and supported by the National Heart, Lung, and Blood Institute (NHLBI) in collaboration with MESA investigators. Support for MESA is provided by contracts N01-HC-95159, N01-HC-95160, N01-HC-95161, N01-HC-95162, N01-HC-95163, N01-HC-95164, N01-HC-95165, N01-HC-95166, N01-HC-95167, N01-HC-95168, N01-HC-95169 and CTSA UL1-RR-024156.

MESA SNP Health Association Resource (SHARe): Funding for SHARe genotyping was provided by NHLBI Contract N02-HL-64278. Genotyping was performed at Affymetrix (Santa Clara, California, USA) and the Broad Institute of Harvard and MIT (Boston, Massachusetts, USA) using the Affymetric Genome-Wide Human SNP Array 6.0.

Candidate gene Association Resource (CARe): The MESA CARe data used for the analyses described in this manuscript were obtained through dbGaP (accession numbers). Funding for CARe genotyping was provided by NHLBI Contract N01-HC-65226.

Coronary Artery Risk Development in Young Adults (CARDIA) [16]

DbGaP dataset reference: The datasets used for the analyses described in this manuscript were obtained from dbGaP at http://www.ncbi.nlm.nih.gov/sites/entrez?db=gap through dbGaP Study Accession: phs000285.v3.p2

The research reported in this article was supported by contract numbers HHSN268201100006C, HHSN268201100007C, HHSN268201100008C, HHSN268201100009C, HHSN268201100010C, HHSN268201100011C, and HHSN268201100012C; all from the National Heart, Lung, and Blood Institute; National Institutes of Health; Bethesda, MD, USA. A full list of principal ARIC investigators and institutions can be found at http://www.cardia.dopm.uab.edu/. This manuscript was not prepared in collaboration with CARDIA investigators and does not necessarily reflect the opinions or views of CARDIA, or the NHLBI.

Candidate Gene Association Resource (CARe) - Support for the genotyping through the CARe Study was provided by NHLBI Contract N01-HC-65226.

GENEVA (Gene-Environment Association Studies) - Support for the genotyping through the GENEVA Study was provided by the NIH GEI U01HG004438, U01HG04424, and HHSN268200782096C

Women's Health Initiative (WHI) [17]

DbGaP dataset reference: The datasets used for the analyses described in this manuscript were obtained from dbGaP at http://www.ncbi.nlm.nih.gov/sites/entrez?db=gap through dbGaP Study Accession: phs000200.v9.p3

The WHI program is funded by the National Heart, Lung, and Blood Institute, National Institutes of Health, U.S. Department of Health and Human Services through contracts N01WH22110, 24152, 32100-2, 32105-6, 32108-9, 32111-13, 32115, 32118-32119, 32122, 42107-26, 42129-32, and 44221. This manuscript was not prepared in collaboration with investigators of the WHI, has not been reviewed and/or approved by the Women's Health Initiative (WHI), and does not necessarily reflect the opinions of the WHI investigators or the NHLBI.

PAGE: WHI PAGE is funded through the NHGRI Population Architecture Using Genomics and Epidemiology (PAGE) network (Grant Number U01 HG004790). Assistance with phenotype harmonization, SNP selection, data cleaning, meta-analyses, data management and dissemination, and general study coordination, was provided by the PAGE Coordinating Center (U01HG004801-01).

GARNET: Funding support for WHI GARNET was provided through the NHGRI Genomics and Randomized Trials Network (GARNET) (Grant Number U01 HG005152). Assistance with phenotype harmonization and

genotype cleaning, as well as with general study coordination, was provided by the GARNET Coordinating Center (U01 HG005157). Assistance with data cleaning was provided by the National Center for Biotechnology Information. Funding support for genotyping, which was performed at the Broad Institute of MIT and Harvard, was provided by the NIH Genes, Environment and Health Initiative [GEI] (U01 HG004424).

SHARe: Funding for WHI SNP Health Association Resource (SHARe) genotyping was provided by NHLBI Contract N02-HL-64278.

Myocardial Infarction Genetics Consortium (MIGen) [18]

DbGaP dataset reference: The datasets used for the analyses described in this manuscript were obtained from dbGaP at http://www.ncbi.nlm.nih.gov/sites/entrez?db=gap through dbGaP Study Accession: phs000294.v1.p1 Funding Source: R01 HL087676. National Institutes of Health, Bethesda, MD, USA

Wellcome Trust Case Control Consortium (WTCCC) [19]

The principal funder of this project was the Wellcome Trust. Case collections were funded by: Arthritis Research Campaign, BDA Research, British Heart Foundation, British Hypertension Society, Diabetes UK, Glaxo-Smith Kline Research and Development, Juvenile Diabetes Research Foundation, National Association for Colitis and Crohn's disease, SHERT (The Scottish Hospitals Endowment Research Trust), St Bartholomew's and The Royal London Charitable Foundation, UK Medical Research Council, UK NHS R&D and the Wellcome Trust.

Global Lipid Genetic Consortium (GLGC) [3,4]

Data on coronary artery disease / myocardial infarction have been contributed by Global Lipids Genetics Consortium investigators and have been downloaded from: www.sph.umich.edu/csg/abecasis/public/lipids2013/

CARDIoGRAMplusC4D Consortium [20]

CARDIoGRAMplusC4D 1000 Genomes-based GWAS is a meta-analysis of GWAS studies of mainly European, South Asian, and East Asian, descent imputed using the 1000 Genomes phase 1 v3 training set with 38 million variants. The study interrogated 9.4 million variants and involved 60,801 CAD cases

and 123,504 controls. Data on coronary artery disease / myocardial infarction have been contributed by CARDIoGRAMplusC4D investigators and have been downloaded from www.CARDIOGRAMPLUSC4D.ORG

MAGNETIC NMR GWAS [5]

External validation data from a genome-wide association study of 39 million genetic markers and 233 human blood lipid and metabolite concentrations, including the lipid concentrations and composition of 14 lipoprotein subclasses, quantified by automated high-throughput serum NMR metabolomics platform in 14 genotyped data sets derived from ten European studies for up to 24,925 individuals was provided by: http://www.computationalmedicine.fi/data/NMR_GWAS/

INTERVAL Bioresource [6]

External validation data from a genome-wide association study of 39 million genetic markers and 233 human blood lipid and metabolite concentrations quantified by automated high-throughput serum NMR metabolomics platform in up to 40,904 participants enrolled in the INTERVL trial, a randomised trial assessing how often blood donors can safely give whole blood. Data provided by the Cardiovascular Epidemiology Unit, University of Cambridge.

Additional Data Sources:

Data on SNP annotation, proxy search and estimates of pairwise linkage disequilibrium metrics were obtained using LDlink, a suite of web-based applications designed to easily and efficiently interrogate linkage disequilibrium in population groups. All population genotype data originates from Phase 3 (Version 5) of the 1000 Genomes Project and variant RS numbers are indexed based on dbSNP build 142. Where coordinates are specified, GRCh37/hg19 is used. LDlink was developed by Mitchell Machiela in collaboration with NCI's Center for Biomedical Informatics and Information Technology (CBIIT). Support comes from the Division of Cancer Epidemiology and Genetics Informatics Tool Challenge.[1,2]

Data on genotyping platform specific SNP identification was obtained from NCBI dbSNP Human Build 141: http://www.ncbi.nlm.nih.gov/SNP/

eTable 1: Included studies and genotyping platforms

Study	Total No. Participants	No. Primary CV Events	Follow-up (Years)	Included Genetic Sub-studies	Genotyping Platforms
UK Biobank	367,641	18,154	7	n/a	UK Biobank Axiom array
Atherosclerosis Risk in Communities Study (ARIC) [15]	15,347	2,114	16	phs000090 GENEVA_ARIC phs000557 ARIC_CARe	Affymetrix AFFY_6.0 Illumina CVDSNP55v1_A
Cardiovascular Health Study (CHS) [16]	5,583	1,614	14	phs000377 CARe Cardiovascular Health Study phs000226 STAMPEED: Cardiovascular Health Study	Illumina CVDSNP55v1_A Illumina HumanOmni1-Quad_v1-0_B
The Framingham Heart Study (FHS): Original Cohort [17] Offspring Cohort [18]	 5,209 5,124	 428 527	 54 32	phs000342 Framingham SHARe phs000282 Framingham CARe	Affymetrix HuGeneFocused 50K_Affy Affymetrix 500K Set (Mapping250K_Nsp and Mapping250K_Sty Arrays) Illumina CVDSNP55v1_A
Multi-Ethnic Study of Atherosclerosis (MESA) [19]	7,674	423	10	phs000420 MESA SHARe phs000283 MESA CARe	Affymetrix AFFY_6.0 Illumina CVDSNP55v1_A
Coronary Artery Risk Development in Young Adults (CARDIA) [20]	3,622	21	15	phs000309 GENEVA_CARDIA phs000613 CARDIA_CARe	Affymetrix AFFY_6.0 Illumina CVDSNP55v1_A
Women's Health Initiative (WHI) [21]	49,234	2154	16	phs000386 WHI SHARe phs000315 WHI GARNET phs000227 PAGE WHI	Affymetrix AFFY_6.0 Illumina HumanOmni1-Quad_v1-0_B Illumina Cardio-Metabo_Chip_11395247_A
Myocardial Infarction Genetics Consortium (MIGen) [7] ATVB FINRISK HARPS MALMO MGH-PCOD REGICOR	 3,361 339 1,064 185 464 629	 1,693 167 505 86 204 312	 Case-control Case-control Case-control Case-control Case-control Case-control	phs000294 STAMPEED: Myocardial Infarction Genetics Consortium (MIGen)	Affymetrix AFFY_6.0
Wellcome Trust Case Control Consortium (WTCCC) [8]	5,002	1926	Case-control	1958 British Birth Cohort controls (1504) UK National Blood Service controls (1500) Coronary Artery Disease (CAD) cases (1998)	Affymetrix 500K (Mapping250K_Nsp and Mapping250K_Sty Arrays)
CARDIoGRAMplusC4D Consortium	184,305	60,801	Meta-analysis of 48 studies	1000 Genomes-based GWAS	imputed using the 1000 Genomes phase 1 v3 training set with 38 million variants. The study interrogated 9.4 million variants.

eTable 2: *LPL* variants included in *LPL* score and associations with plasma triglycerides and LDL-C in Global Lipids Genetics Consortium

SNP	Effect Allele	Effect Allele frequency	Sample Size (n)	TG (mg/dl)	TG SE	P	LDL-C (mg/dl)	LDL-C SE	P
rs1801177	G	0.987	304,596	-15.013	0.906	1.97E-61	-0.296	0.333	0.374
rs268	A	0.982	290,452	-18.798	0.788	9.60E-126	-0.592	0.332	0.074
rs301	C	0.237	305,699	-9.143	0.233	2.08E-336	0.109	0.101	0.273
rs326	G	0.305	305,699	-14.913	0.354	3.80E-388	0.015	0.093	0.867
rs328	G	0.098	305,699	-9.365	0.308	1.97E-203	0.402	0.142	0.005

eTable 2 Legend: Plasma triglyceride and LDL-C effect sizes measured in mg/dl. For each variant, the exposure allele is the allele associated with lower triglycerides. The range of the unweighted LPL score was 1 – 10, with a mean of 5.2 and standard deviation of 1.5. The range of the LPL score weighted by the association of each exposure allele with apoB was 6.75 -33.57, with a mean of 23.35 and standard deviation 3.11.

eTable 3: Linkage disequilibrium matrix for variants included in the *LPL* genetic score

***LPL* variant**	**rs1801177**	**rs268**	**rs301**	**rs326**	**rs328**
rs1801177	1.0	0.0	0.005	0.004	0.001
rs268	0.0	1.0	0.0	0.0	0.001
rs301	0.005	0.0	1.0	0.281	0.161
rs326	0.004	0.0	0.281	1.0	0.19
rs328	0.001	0.001	0.161	0.19	1.0

eTable 3 Legend: Values represent r^2 values, a measure of linkage disequilibrium. r^2 values range from 0 to 1; with 0 representing complete equilibrium (no evidence for linkage disequilibrium) and 1 representing complete disequilibrium. Variants were included in the score if they had an r^2 value < 0.3 with all other variants included in the score using the conditional forward step-wise procedure described in the eMethods.

eTable 4: *LDLR* variants included in *LDLR* genetic score and their and associations with plasma triglycerides and LDL-C in Global Lipids Genetics Consortium

SNP	Effect Allele	Effect Allele frequency	Sample Size (n)	TG (mg/dl)	TG SE	P	LDL-C (mg/dl)	LDL-C SE	P
rs6511720	T	0.1086	295,826	-3.1213	2.0551	0.128	-6.7657	0.1362	3.69E-538
rs1122608	T	0.2266	262,102	-1.6781	0.6923	0.015	-2.1179	0.1075	2.02E-86
rs688	C	0.5586	166,792	-0.2937	0.2436	0.229	-1.728	0.1184	3.04E-48

eTable 4 Legend: Plasma triglyceride and LDL-C effect sizes measured in mg/dl. For each variant, the exposure allele is the allele associated with lower LDL-C. The range of the unweighted *LDLR* score was 1 – 6, with a mean of 1.8 and standard deviation of 1.2. The range of the *LDLR* score weighted by the association of each exposure allele with apoB was 0 -18.33, with a mean of 4.04 and standard deviation 3.54.

eTable 5: Linkage disequilibrium matrix for variants included in the *LDLR* genetic score

***LDLR* variant**	**rs1122608**	**rs6511720**	**rs688**
rs1122608	1.0	0.064	0.003
rs6511720	0.064	1.0	0.0
rs688	0.003	0.0	1.0

eTable 5 Legend: Values represent r^2 values, a measure of linkage disequilibrium. r^2 values range from 0 to 1; with 0 representing complete equilibrium (no evidence for linkage disequilibrium) and 1 representing complete disequilibrium. Variants were included in the score if they had an r^2 value < 0.3 with all other variants included in the score using the conditional forward step-wise procedure described in the eMethods.

eTable 6: Association of LPL and LDLR scores with CHD risk per 10 mg/dl lower apoB among studies contributing individual participant data and summary level data

Study sample	sample size (n)	no. CHD events	genetic score	OR (95% CI)
All studies	654,783	91,129	*LPL*	0.771 (0.741 - 0.802)
(IPD and summary data)			*LDLR*	0.773 (0.747 - 0.801)
Studies with individual participant data	470,478	30,328	*LPL*	0.761 (0.715 - 0.809)
(UK Biobank and dbGAP studies)			*LDLR*	0.767 (0.722 - 0.815)
Studies with summary level data	184,305	60,801	*LPL*	0.780 (0.738 - 0.824)
(CARDIoGRAMplusC4D)			*LDLR*	0.776 (0.744 - 0.810)

eTable 6 Legend: OR is odds ratio for each genetic score scaled per 10 mg/dl lower apoB. The main analysis of all studies involved a total of 654,783 participants, including 91,129 cases of CHD. Analyses of studies with individual data involved 470,478 participants, including 30,328 cases of CHD. Analyses of studies with summary level data involved 184,305 participants, including 60,801 cases of CHD.

eTable 7: variants associated with triglycerides or LDL-C in the Global Lipids Genetics Consortium

position	rsid	annotation	EA	EAF	TG	TG SE	LDL-C	LDL-C SE	apoB	apoB SE	CHD	CHD SE
1:109818530	rs646776	CELSR2:Intergenic	C	0.23	-1.128	0.286	-5.281	0.109	-3.502	0.224	-0.110	0.010
1:150958836	rs267733	ANXA9:Asp166Gly	G	0.14	-0.469	0.331	-0.825	0.129	-0.204	0.102	0.001	0.012
1:172346548	rs1011731	DNM3:Intron	A	0.56	-1.302	0.234	-0.125	0.089	-0.461	0.157	-0.017	0.008
1:183094547	rs20558	LAMC1:Leu888Pro	T	0.44	0.046	0.226	-0.495	0.089	-0.377	0.216	-0.015	0.008
1:219687432	rs2785990	LYPLAL1:Intergenic	C	0.31	-1.389	0.243	-0.314	0.096	-0.284	0.144	-0.003	0.008
1:221057646	rs2738755	HLX:Pro356Leu	T	0.33	0.373	0.243	-0.495	0.092	-0.359	0.162	0.008	0.008
1:230304988	rs10489615	GALNT2:Intron	G	0.56	-3.385	0.234	-0.069	0.089	-0.696	0.176	-0.027	0.008
1:23766233	rs1077514	ASAP3:Intron	C	0.18	-1.649	0.304	-0.495	0.116	-0.452	0.241	-0.016	0.011
1:25768937	rs10903129	TMEM57:Intron	A	0.48	-0.660	0.226	-0.924	0.089	-0.474	0.089	-0.011	0.008
1:27138393	rs12748152	PIGV:Intergenic	C	0.928	-2.691	0.434	-1.023	0.168	-1.077	0.245	-0.023	0.012
1:39797055	rs16826069	MACF1:Ile39Val	A	0.79	-2.171	0.278	0.015	0.109	-0.450	0.275	-0.014	0.009
1:55496039	rs11206510	PCSK9:Intergenic	C	0.17	-0.868	0.304	-2.309	0.119	-2.122	0.209	-0.062	0.010
1:55504650	rs2479409	PCSK9:Intergenic	A	0.66	-0.174	0.234	-1.551	0.092	-1.095	0.171	-0.026	0.009
1:55505647	rs11591147	PCSK9:Arg46Leu	T	0.015	-0.425	0.955	-15.84	0.363	-8.787	0.462	-0.225	0.032
1:55529187	rs505151	PCSK9:Gly670Glu	A	0.95	-0.573	0.529	-2.968	0.205	-1.671	0.325	-0.059	0.022
1:63118196	rs10889353	DOCK7:Intron	C	0.33	-6.684	0.243	-1.485	0.092	-1.132	0.121	-0.012	0.008
2:118835841	rs10490626	MTOR:Intergenic	A	0.068	-0.955	0.469	-1.749	0.182	-1.151	0.224	-0.018	0.015
2:165528876	rs13389219	FLG:Intergenic	T	0.4	-3.212	0.243	-0.314	0.096	-0.601	0.148	-0.020	0.009
2:169830155	rs2287623	ABCB11:Intron	A	0.59	-0.694	0.234	-0.693	0.089	-0.566	0.132	-0.006	0.008
2:202122995	rs3769823	CASP8:Lys14Arg	A	0.31	-1.476	0.243	-0.043	0.096	-0.029	0.203	-0.007	0.009
2:20396122	rs6749689	EPHA2:Intergenic	C	0.57	-1.389	0.226	-0.363	0.086	-0.506	0.141	-0.013	0.008
2:21225485	rs1801702	APOB:Arg4270Thr	G	0.028	-0.556	0.686	-3.003	0.264	-1.630	0.432	-0.054	0.030
2:21229160	rs5742904	APOB:Arg3527Gln	C	0.99962	19.096	5.816	-48.84	2.244	-22.085	5.991	-0.590	0.165
2:21233972	rs533617	APOB:His1923Arg	C	0.039	-8.506	0.582	-4.289	0.224	-3.686	0.274	-0.079	0.027
2:21238367	rs12713843	APOB:Arg1128His	T	0.0044	-6.769	1.736	-7.590	0.661	-3.686	0.838	-0.119	0.061
2:21242613	rs41288783	APOB:Pro994Leu	G	0.99937	15.624	4.514	-18.48	1.749	-7.602	3.093	-0.245	0.125
2:21252534	rs13306194	APOB:Arg532Trp	A	0.0052	-8.333	1.736	-3.958	0.659	-6.038	2.418	-0.147	0.151
2:21263900	rs1367117	APOB:Thr98Ile	G	0.72	-1.996	0.252	-3.629	0.099	-2.083	0.122	-0.038	0.022
2:21294975	rs541041	TNFSF4:Intergenic	G	0.19	-1.562	0.295	-3.963	0.112	-2.339	0.161	-0.058	0.011
2:219555262	rs1344642	STK36:Arg583Gln	A	0.44	-1.302	0.226	-0.254	0.089	-0.303	0.131	-0.003	0.008
2:227093745	rs2943641	ALDH4A1:Intergenic	T	0.34	-2.864	0.243	-0.221	0.092	-0.618	0.204	-0.036	0.009
2:234668570	rs887829	UGT1A10:Intron	T	0.34	-0.625	0.243	-0.726	0.092	-0.307	0.145	-0.002	0.009
2:27730940	rs1260326	GCKR:Leu446Pro	C	0.63	-10.416	0.234	-0.759	0.092	-1.225	0.108	-0.022	0.009
2:44028013	rs11556157	DYNC2LI1:Ile230Leu	A	0.74	-0.694	0.261	-0.825	0.099	-0.316	0.168	-0.021	0.011
2:44074431	rs4245791	ABCG8:Intron	T	0.72	-1.649	0.259	-2.376	0.102	-1.881	0.201	-0.051	0.009
2:62871225	rs11125936	TCEB3:Intergenic	C	0.1	-1.389	0.373	-0.924	0.145	-0.667	0.202	-0.018	0.014
3:12393125	rs1801282	PPARG:Pro12Ala	G	0.12	-1.996	0.347	-0.109	0.135	-0.097	0.096	-0.002	0.012
3:12628920	rs2290159	RAF1:Intron	C	0.2	-0.955	0.331	-0.693	0.129	-0.461	0.168	-0.006	0.010
3:135926622	rs645040	RFX5:Intergenic	G	0.22	-1.996	0.269	-0.363	0.106	-0.663	0.178	-0.032	0.010
3:32533010	rs7640978	CMTM6:Intron	T	0.092	-0.312	0.391	-1.089	0.152	-0.583	0.288	-0.014	0.015
3:52532118	rs13326165	STAB1:Intron	A	0.19	-1.736	0.286	-0.109	0.112	-0.351	0.343	-0.017	0.011

position	rsid	annotation	EA	EAF	TG	TG SE	LDL-C	LDL-C SE	apoB	apoB SE	CHD	CHD SE
3:52584787	rs2251219	PBRM1:Pro1466Pro	T	0.62	0.075	0.234	-0.528	0.092	-0.430	0.242	-0.009	0.008
3:57528503	rs9311651	DNAH12:Val32Ala	G	0.17	-1.823	0.312	-0.069	0.119	-0.304	0.476	-0.026	0.013
3:58381287	rs13315871	PXK:Intron	A	0.085	-0.217	0.417	-1.254	0.162	-0.761	0.249	-0.024	0.015
4:100045616	rs1126673	ADH4:Val374Ile	C	0.28	-1.476	0.252	-0.185	0.099	-0.229	0.166	-0.003	0.009
4:100504664	rs3816873	MTTP:Ile128Thr	C	0.26	-0.295	0.262	-0.561	0.099	-0.596	0.168	-0.038	0.009
4:103188709	rs13107325	SLC39A8:Ala391Thr	T	0.051	2.951	0.521	-1.155	0.201	-0.531	0.363	-0.009	0.016
4:3446091	rs3748034	HGFAC:Ala218Ser	G	0.86	-3.038	0.365	-0.627	0.142	-0.881	0.251	-0.025	0.012
4:3449652	rs16844401	HGFAC:Arg509His	G	0.934	-2.604	0.477	-0.661	0.185	-0.761	0.351	-0.044	0.016
4:3473139	rs6831256	DOK7:Intron	A	0.56	-1.823	0.226	-0.429	0.089	-0.569	0.258	-0.024	0.008
4:69343287	rs976002	TMPRSS11E:Tyr303Cys	A	0.77	-1.302	0.278	-0.759	0.109	-0.685	0.255	-0.017	0.010
4:88030261	rs442177	AFF1:Intron	G	0.43	-2.691	0.226	-0.281	0.089	-0.442	0.122	0.012	0.008
4:89740128	rs13133548	FAM13A:Intron	G	0.52	-1.215	0.226	-0.122	0.086	-0.338	0.177	-0.021	0.011
5:122855416	rs4530754	CSNK1G3:Intron	G	0.45	0.252	0.234	-0.561	0.092	-0.486	0.171	-0.015	0.008
5:131008194	rs26008	FNIP1:Gln620Arg	C	0.92	-2.432	0.417	0.089	0.158	-0.502	0.314	-0.029	0.015
5:131744574	rs1016988	CD101:Intergenic	C	0.22	0.764	0.269	-0.663	0.106	-0.291	0.124	0.003	0.011
5:156390297	rs6882076	TIMD4:Upstream	T	0.37	-3.298	0.234	-1.287	0.089	-1.018	0.117	-0.029	0.009
5:176520243	rs351855	FGFR4:Gly388Arg	A	0.29	-0.712	0.278	-0.594	0.109	-0.369	0.138	-0.012	0.012
5:53300662	rs4311394	ARL15:Intron	A	0.73	-1.562	0.252	-0.129	0.099	-0.511	0.407	-0.028	0.012
5:55861786	rs9686661	ASPM:Intergenic	C	0.81	-3.646	0.286	-0.314	0.112	-0.802	0.185	-0.037	0.011
5:67714246	rs4976033	IGFN1:Intergenic	A	0.58	-1.562	0.226	-0.096	0.089	-0.324	0.288	-0.012	0.009
5:74651084	rs3846662	HMGCR:Intron	A	0.52	-0.331	0.234	-2.145	0.089	-1.378	0.113	-0.032	0.008
6:116387134	rs1999930	SLC16A4:Intergenic	T	0.25	0.165	0.278	-0.594	0.106	-0.601	0.143	-0.007	0.008
6:127452935	rs2745353	RSPO3:Intron	C	0.47	-1.736	0.226	-0.099	0.086	-0.583	0.159	-0.016	0.008
6:135411228	rs9376090	VPS13D:Intergenic	C	0.24	-0.259	0.269	-0.825	0.106	-0.725	0.242	-0.022	0.012
6:135418635	rs7775698	VPS13D:Intergenic	T	0.25	-0.278	0.262	-0.858	0.102	-0.737	0.296	-0.024	0.011
6:139839423	rs643381	TXNIP:Intergenic	A	0.5	-1.996	0.226	-0.198	0.089	-0.771	0.217	-0.024	0.008
6:160543148	rs12208357	SLC22A1:Arg61Cys	C	0.938	-2.778	0.469	-1.914	0.182	-1.501	0.251	-0.006	0.016
6:160578860	rs1564348	SLC22A1:Intron	T	0.85	-1.736	0.312	-1.551	0.122	-0.607	0.226	-0.038	0.014
6:16145325	rs9370867	MYLIP:Asn342Ser	G	0.53	-0.131	0.234	-1.089	0.089	-0.595	0.103	-0.014	0.008
6:26093141	rs1800562	HFE:Cys102Tyr	A	0.048	0.703	0.538	-1.452	0.208	-1.171	0.371	-0.032	0.018
6:31262169	rs3873379	BLZF1:Intergenic	T	0.68	-2.429	0.252	-0.294	0.096	-0.706	0.197	-0.017	0.010
6:31379109	rs1051794	MICA:Glu196Lys	G	0.7	-0.261	0.269	-0.693	0.102	-0.531	0.140	-0.001	0.011
6:31440082	rs1055569	HCG26:Exon	C	0.66	-0.781	0.262	-0.627	0.099	-0.375	0.151	-0.009	0.009
6:31564821	rs2844480	F5:Intergenic	C	0.8	-1.996	0.286	-0.312	0.112	-0.642	0.175	-0.009	0.011
6:32052444	rs61995676	TNXB:Arg1064His	C	0.979	-8.072	0.816	-0.759	0.314	-0.501	1.136	-0.017	0.031
6:32261252	rs7775397	C6orf10:Glu317Ala	G	0.085	-3.125	0.434	-0.561	0.168	-0.202	0.243	-0.002	0.016
6:32586854	rs9271366	PADI4:Intergenic	G	0.15	-2.083	0.33	-0.594	0.125	-0.840	0.271	-0.028	0.012
6:32671103	rs13192471	ASTN1:Intergenic	T	0.84	-1.476	0.321	-1.254	0.122	-0.653	0.218	-0.003	0.013
6:32813279	rs1057373	TAP1:Utr3	C	0.903	-2.604	0.399	-0.168	0.152	-0.293	0.230	-0.004	0.012
6:43758873	rs6905288	SH2D5:Intergenic	G	0.41	-2.864	0.234	-0.317	0.089	-0.964	0.226	-0.039	0.011
6:43811762	rs9472138	SH2D5:Intergenic	T	0.27	-1.736	0.263	-0.267	0.102	-0.565	0.171	-0.012	0.009
6:52453220	rs2239619	HSPG2:Intergenic	C	0.38	-0.085	0.234	-0.594	0.092	-0.367	0.128	-0.005	0.009
7:116358044	rs38855	MET:Intron	G	0.46	-1.215	0.226	-0.116	0.089	-0.256	0.112	-0.006	0.008
7:130433384	rs4731702	SNX27:Intergenic	T	0.46	-2.344	0.234	-0.218	0.089	-0.519	0.134	-0.020	0.010

position	rsid	annotation	EA	EAF	TG	TG SE	LDL-C	LDL-C SE	apoB	apoB SE	CHD	CHD SE
7:17284577	rs4410790	NCSTN:Intergenic	T	0.41	-1.302	0.234	-0.182	0.089	-0.606	0.166	-0.021	0.011
7:21607352	rs12670798	DNAH11:Intron	T	0.75	-1.128	0.269	-1.089	0.106	-1.177	0.133	-0.028	0.008
7:25991826	rs4722551	HMCN1:Intergenic	T	0.84	2.257	0.321	-1.321	0.125	-0.455	0.188	-0.008	0.012
7:44444122	rs11550029	NUDCD3:Arg235Cys	G	0.83	-1.128	0.304	-0.661	0.116	-0.745	0.213	-0.017	0.011
7:73012042	rs35332062	MLXIPL:Ala358Val	A	0.12	-10.416	0.356	0.462	0.135	-0.765	0.207	-0.022	0.013
8:10683929	rs11776767	PINX1:Intron	G	0.63	-1.913	0.243	0.195	0.092	-0.139	0.081	0.008	0.010
8:116599199	rs2293889	TRPS1:Intron	G	0.62	-0.356	0.234	-0.495	0.089	-0.189	0.453	-0.005	0.009
8:116648565	rs2737229	TRPS1:Intron	C	0.34	-1.128	0.243	-0.726	0.096	-0.318	0.081	-0.005	0.009
8:11702375	rs3947	CTSB:Utr3	G	0.77	-2.083	0.295	0.053	0.112	-0.172	0.161	-0.004	0.011
8:126490972	rs2954029	AMPD1:Intergenic	T	0.45	-6.944	0.226	-1.584	0.089	-1.812	0.141	-0.049	0.008
8:145058986	rs11136343	PARP10:Leu395Pro	A	0.62	-0.321	0.234	-0.957	0.092	-0.567	0.111	-0.002	0.009
8:18272881	rs1495741	PGLYRP4:Intergenic	A	0.75	-3.038	0.262	-0.726	0.102	-0.668	0.204	-0.028	0.011
8:55421614	rs10102164	CRP:Intergenic	G	0.8	-1.302	0.278	-1.023	0.109	-0.799	0.16	-0.024	0.010
8:59388565	rs2081687	IGSF9:Intergenic	C	0.66	-1.649	0.234	-0.924	0.092	-0.535	0.094	-0.007	0.009
8:9183596	rs4841132	NECAP2:Intergenic	A	0.09	3.038	0.382	-1.881	0.149	-0.641	0.161	-0.011	0.015
9:107664301	rs1883025	ABCA1:Intron	T	0.26	-1.911	0.252	-0.792	0.099	-0.876	0.197	-0.028	0.011
9:136155000	rs635634	IL6R:Intergenic	C	0.81	0.955	0.295	-2.541	0.116	-1.579	0.182	-0.061	0.015
9:139368953	rs3812594	SEC16A:Arg1039Cys	A	0.24	0.564	0.269	-0.594	0.102	-0.306	0.167	-0.011	0.012
9:16887366	rs3927680	OR6P1:Intergenic	A	0.52	-1.562	0.234	-0.429	0.089	-0.670	0.146	-0.021	0.008
9:19376255	rs67710536	RPS6:Utr3	A	0.89	-0.347	0.382	-0.924	0.149	-1.112	0.377	-0.030	0.015
9:2640759	rs3780181	VLDLR:Intron	G	0.074	0.521	0.425	-1.221	0.165	-0.862	0.341	-0.008	0.016
10:113940329	rs2792751	GPAM:Ile43Val	C	0.73	1.736	0.252	-0.924	0.099	-0.507	0.246	-0.012	0.009
10:124610027	rs1891110	FAM24B:Pro2Leu	G	0.45	-0.269	0.226	-0.693	0.086	-0.162	0.061	-0.003	0.008
10:64927823	rs1935	JMJD1C:Glu2299Asp	C	0.52	2.517	0.226	-0.594	0.089	-0.141	0.209	-0.012	0.008
10:94839642	rs2068888	C1orf106:Intergenic	A	0.47	-2.778	0.226	-0.528	0.089	-0.649	0.116	-0.018	0.008
11:116639104	rs10790162	BUD13:Intron	G	0.92	-22.568	0.408	-1.089	0.162	-3.059	0.252	-0.060	0.015
11:116662407	rs3135506	APOA5:Ser19Trp	G	0.941	-18.532	0.424	-1.573	0.187	-2.62	0.234	-0.059	0.017
11:116701353	rs76353203	APOC3:Arg19Stp	T	0.00045	-105.896	5.642	-4.291	2.178	-2.889	5.347	-0.174	0.230
11:116701354	rs138326449	APOC3:Essential_Splice_Site	A	0.0018	-68.870	4.485	-4.290	1.518	-7.482	2.020	-0.188	0.149
11:116896155	rs10892063	SIK3:Intron	C	0.58	-5.034	0.261	-0.208	0.099	-0.542	0.115	-0.013	0.009
11:126160826	rs8177399	TIRAP:Arg13Trp	C	0.982	-1.911	0.842	-2.013	0.327	-1.697	0.591	-0.076	0.029
11:126243952	rs11220462	ST3GAL4:Intron	G	0.86	-0.495	0.391	-1.419	0.149	-1.023	0.201	-0.018	0.014
11:18645843	rs11024739	SPTY2D1:Intron	C	0.32	-0.764	0.261	-0.825	0.099	-0.498	0.137	-0.014	0.008
11:47270255	rs2167079	ACP2:Arg29Gln	T	0.35	-1.736	0.243	-0.033	0.096	-0.336	0.116	-0.003	0.009
11:61569830	rs174546	FADS1:Utr3	T	0.31	4.514	0.252	-1.749	0.096	-0.772	0.152	-0.023	0.009
11:64031241	rs35169799	PLCB3:Ser778Leu	C	0.941	-3.298	0.477	-0.191	0.185	-0.719	0.299	-0.032	0.016
11:65391317	rs12801636	PCNXL3:Intron	A	0.23	-1.562	0.269	0.251	0.102	-0.308	0.165	-0.045	0.011
11:66297363	rs3816492	BBS1:Leu472Leu	T	0.23	-0.339	0.278	-0.594	0.109	-0.479	0.197	-0.008	0.011
12:107174646	rs10861661	RIC8B:Intron	A	0.77	-1.649	0.278	-0.028	0.106	-0.481	0.161	-0.012	0.009
12:121416650	rs1169288	HNF1A:Ile27Leu	A	0.67	-0.202	0.252	-1.221	0.096	-0.474	0.168	-0.042	0.009
12:124427306	rs11057401	CCDC92:Ser70Cys	A	0.3	-2.432	0.243	-0.195	0.096	-0.521	0.142	-0.042	0.009
12:125307053	rs11057830	SCARB1:Intron	G	0.85	-1.302	0.329	-0.759	0.125	-0.977	0.284	-0.063	0.011
12:21331549	rs4149056	SLCO1B1:Val174Ala	T	0.86	-2.517	0.330	0.271	0.129	-0.140	0.198	0.030	0.011
12:57809456	rs1106766	CFH:Intergenic	T	0.21	-2.604	0.278	-0.429	0.106	-0.601	0.157	-0.036	0.009

position	rsid	annotation	EA	EAF	TG	TG SE	LDL-C	LDL-C SE	apoB	apoB SE	CHD	CHD SE
13:32953388	rs4942486	BRCA2:Intron	C	0.52	-0.738	0.226	-0.726	0.089	-0.658	0.153	-0.018	0.008
14:24883887	rs8017377	NYNRIN:Ala978Thr	G	0.58	-0.321	0.234	-0.759	0.089	-0.433	0.164	-0.004	0.008
14:64235556	rs7157785	NPR1:Intergenic	G	0.82	-1.996	0.321	-0.363	0.125	-0.470	0.199	-0.002	0.012
14:71096344	rs9646133	FLAD1:Intergenic	T	0.33	-0.037	0.243	-0.627	0.092	-0.484	0.166	-0.015	0.009
14:74250126	rs13379043	C14orf43:Intron	C	0.31	-0.746	0.252	-0.594	0.099	-0.363	0.182	-0.020	0.009
14:94844947	rs28929474	SERPINA1:Glu366Lys	C	0.985	-1.823	0.955	-2.673	0.363	-1.765	0.342	0.125	0.033
15:40751555	rs3803357	BAHD1:Gln298Lys	A	0.54	-1.476	0.226	0.014	0.089	-0.171	0.116	-0.002	0.009
15:43820717	rs55707100	MAP1A:Pro2349Leu	C	0.976	-11.284	0.738	-0.244	0.284	-2.314	0.441	0.002	0.027
15:58678512	rs10468017	SNX27:Intergenic	C	0.73	-2.951	0.252	-0.109	0.099	-0.894	0.146	-0.014	0.009
15:58723675	rs1800588	SNX27:Intergenic	C	0.76	-4.082	0.259	-0.032	0.102	-1.296	0.155	-0.015	0.012
16:15129970	rs7200543	PDXDC1:Leu736Leu	A	0.69	-2.083	0.252	0.011	0.099	-0.241	0.192	-0.011	0.011
16:56989590	rs247616	OR10K2:Intergenic	T	0.31	-3.125	0.243	-1.056	0.096	-0.911	0.124	-0.042	0.009
16:57015091	rs5880	CETP:Ala390Pro	G	0.952	-3.385	0.582	-0.561	0.228	-1.386	0.304	-0.036	0.021
16:72108093	rs2000999	HPR:Intron	G	0.8	-1.823	0.304	-2.079	0.116	-1.387	0.178	-0.042	0.012
16:81534790	rs2925979	CMIP:Intron	C	0.7	-2.517	0.243	-0.099	0.096	-0.111	0.341	0.000	0.019
17:17409560	rs7946	PEMT:Val212Met	T	0.67	-1.389	0.252	-0.238	0.096	-0.304	0.161	-0.012	0.009
17:26694861	rs704	VTN:Thr400Met	G	0.51	0.547	0.226	-0.693	0.086	-0.196	0.128	-0.005	0.008
17:29629326	rs11080150	NF1:Intron	G	0.33	-0.217	0.243	-0.627	0.092	-0.368	0.101	-0.009	0.008
17:41926126	rs72836561	CD300LG:Arg82Cys	C	0.972	-11.284	0.686	0.891	0.264	-1.246	0.357	-0.061	0.024
17:41931375	rs12453522	CD300LG:Thr194Ala	A	0.82	-1.823	0.295	0.017	0.116	0.326	0.249	-0.011	0.011
17:45732774	rs11871606	KPNB1:Intron	A	0.5	1.389	0.226	-0.891	0.086	-0.526	0.141	-0.018	0.008
17:64210580	rs1801689	APOH:Cys325Gly	A	0.973	4.081	0.694	-3.303	0.271	-1.481	0.543	-0.059	0.024
17:67081278	rs77542162	ABCA6:Cys1359Arg	A	0.985	3.212	1.128	-6.271	0.429	-2.868	0.571	-0.033	0.035
17:7091650	rs314253	CRB1:Intergenic	C	0.35	-0.486	0.234	-0.659	0.092	-0.331	0.197	-0.011	0.009
17:73782191	rs2125345	UNK:Intron	C	0.31	-0.955	0.252	-0.792	0.099	-0.595	0.138	-0.024	0.009
17:76395430	rs2292642	PGS1:Gly172Gly	T	0.61	-1.736	0.226	0.429	0.089	-0.177	0.137	-0.001	0.009
19:11275139	rs7188	KANK2:Utr3	A	0.68	-0.955	0.243	-1.584	0.092	-1.468	0.146	-0.032	0.009
19:19379549	rs58542926	TM6SF2:Glu167Lys	T	0.074	-10.416	0.434	-3.304	0.165	-2.645	0.233	-0.045	0.016
19:45316588	rs28399654	BCAM:Val196Ile	A	0.027	6.336	0.712	-8.910	0.277	-4.694	0.372	-0.113	0.024
19:45395266	rs157580	TOMM40:Intron	G	0.37	-4.081	0.234	-2.376	0.089	-2.081	0.122	-0.039	0.009
19:45410002	rs769449	APOE:Intron	G	0.89	-5.729	0.365	-6.27	0.139	-3.637	0.170	-0.090	0.013
19:45412079	rs7412	APOE:Arg176Cys	T	0.075	10.416	0.564	-17.82	0.211	-7.636	0.212	-0.163	0.018
19:46181392	rs1800437	GIPR:Glu354Gln	C	0.2	0.477	0.278	-0.627	0.109	-0.306	0.161	-0.008	0.011
19:49206417	rs492602	FUT2:Ala69Ala	A	0.55	-1.562	0.243	-0.924	0.092	-0.581	0.173	-0.017	0.008
19:50000009	rs2280401	RPS11:Intron	A	0.15	-1.736	0.312	-0.528	0.119	-0.579	0.156	-0.015	0.011
20:12962718	rs364585	DBT:Intergenic	A	0.36	1.042	0.243	-0.627	0.092	-0.504	0.192	-0.013	0.009
20:17596155	rs1132274	RRBP1:Arg891Leu	C	0.83	-0.295	0.304	-0.627	0.116	-0.544	0.252	-0.041	0.011
20:34116282	rs7261862	C20orf173:Lys194Glu	C	0.18	-1.128	0.295	-0.792	0.116	-0.699	0.353	-0.012	0.011
20:39154095	rs6016373	SLC27A3:Intergenic	G	0.39	-0.746	0.234	-0.792	0.089	-0.807	0.161	-0.021	0.008
20:39672618	rs6029526	TOP1:Intron	T	0.49	-1.128	0.234	-1.155	0.089	-0.685	0.144	-0.022	0.008
20:43042364	rs1800961	HNF4A:Thr117Ile	T	0.031	0.373	0.651	-1.782	0.251	-0.839	0.325	-0.019	0.024
20:44576502	rs7679	PCIF1:Utr3	T	0.83	-4.604	0.304	-0.363	0.116	0.477	0.164	0.018	0.016
20:62695931	rs6062343	TCEA2:Intron	A	0.43	-1.562	0.234	-0.462	0.089	-0.482	0.159	-0.025	0.009
22:35660875	rs1053593	HMGXB4:Gly165Val	T	0.61	-0.582	0.252	-0.528	0.096	-0.244	0.151	-0.004	0.009

position	rsid	annotation	EA	EAF	TG	TG SE	LDL-C	LDL-C SE	apoB	apoB SE	CHD	CHD SE
22:38569006	rs738322	PLA2G6:Intron	G	0.49	-1.736	0.226	-0.053	0.089	-0.214	0.121	-0.002	0.008
22:39100128	rs5757251	NPR1:Intergenic	G	0.61	-1.389	0.252	-0.142	0.099	-0.063	0.137	0.014	0.009
22:41170063	rs2076674	SLC25A17:Intron	T	0.65	0.174	0.243	-0.594	0.092	-0.384	0.178	-0.014	0.009
22:44324727	rs738409	PNPLA3:Ile149Met	G	0.23	-1.562	0.269	-0.594	0.102	-0.706	0.229	-0.028	0.014
22:45996298	rs13268	FBLN1:His695Arg	G	0.021	-0.056	0.781	-1.749	0.301	-0.763	0.355	-0.011	0.027
22:46627780	rs1042311	PPARA:Ala268Val	C	0.9951	-5.902	1.649	-3.960	0.627	-2.417	0.790	-0.055	0.056

eTable 7 Legend: EA is effect allele, EAF is effect allele frequency; TG is triglycerides, SE is standard error.

eTable 8: Additional multivariable Mendelian randomization analyses for the association between changes in triglycerides, LDL-C, apoB and the risk of coronary heart disease

A. 183 variants associated with either TG or LDL-C ($p < 5.0x10^{-8}$) not including *LPL* or *LDLR* variants

Model	Included variables	OR_{CHD} (95% CI)	p value
1	LDL-C	0.845 (0.832 - 0.858)	2.75E-75
2	Triglycerides	0.826 (0.792 - 0.861)	6.48E-16
3	apoB	0.771 (0.759 - 0.781)	1.26E-163
4	LDL-C	0.860 (0.847 - 0.873)	8.86E-64
	Triglycerides	0.877 (0.849 - 0.906)	1.79E-12
5	**apoB**	**0.762 (0.724 - 0.802)**	**6.11E-19**
	LDL-C	**1.014 (0.971 - 1.059)**	**0.183**
	Triglycerides	**1.003 (0.955 - 1.054)**	**0.177**

B. 51 variants associated with TG at p < 5.0x10-8); but not LDL-C (p > 0.001)

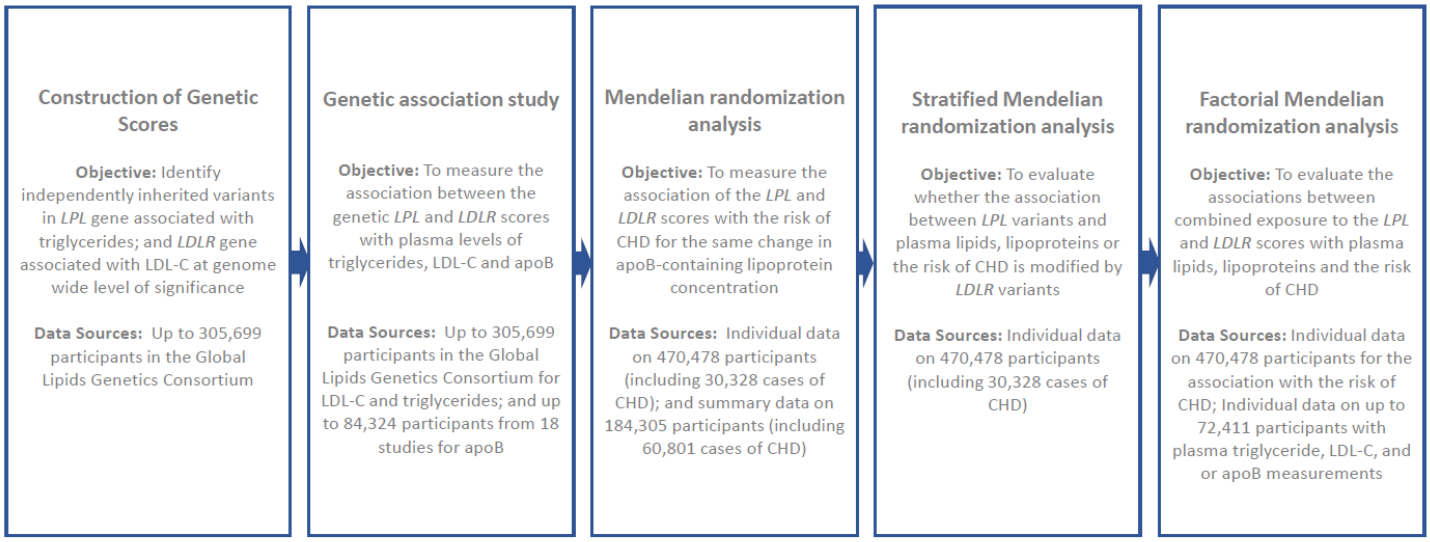
Model	Included variables	OR_{CHD} (95% CI)	p value
1	LDL-C	0.626 (0.543 - 0.721)	5.35E-05
2	Triglycerides	0.823 (0.782 - 0.865)	4.38E-10
3	apoB	0.765 (0.730 - 0.802)	1.60E-17
4	LDL-C	0.879 (0.703 - 1.101)	0.322
	Triglycerides	0.842 (0.789 - 0.899)	1.42E-05
5	**apoB**	**0.778 (0.711 - 0.851)**	**1.79E-05**
	LDL-C	**0.971 (0.776 - 1.213)**	**0.795**
	Triglycerides	**0.989 (0.892 - 1.097)**	**0.841**

C. 59 variants associated with LDL-C at p < 5.0x10-8; but not TG (p > 0.001)

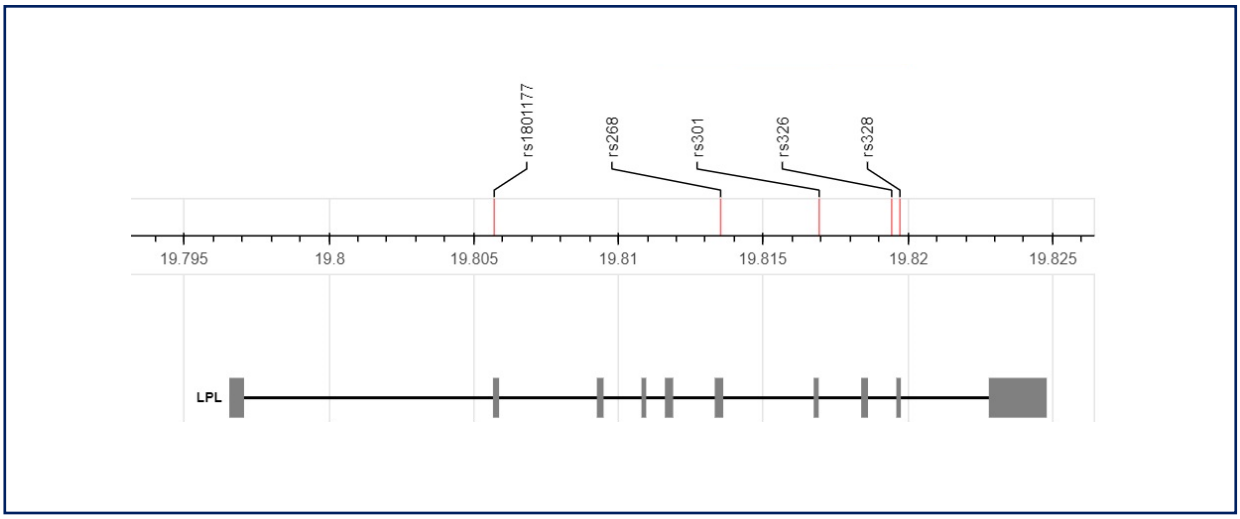
Model	Included variables	OR_{CHD} (95% CI)	p value
1	LDL-C	0.859 (0.844 - 0.876)	1.56E-41
2	Triglycerides	1.017 (0.545 - 1.897)	0.285
3	apoB	0.774 (0.754 - 0.794)	3.45E-51
4	LDL-C	0.861 (0.845 - 0.878)	2.65E-40
	Triglycerides	0.827 (0.671 - 1.021)	0.142
5	**apoB**	**0.770 (0.689 - 0.861)**	**3.85E-04**
	LDL-C	**1.003 (0.919 - 1.095)**	**0.944**
	Triglycerides	**0.999 (0.769 - 1.298)**	**0.992**

eTable 8 Legend: Data are from genetic variants associated with either triglycerides, LDL-C or both at genome-wide significance as reported by the updated Global Lipids Genetics Consortium and listed in eTable 6. Effect sizes for the associated risk of coronary heart disease are per 10 mg/dl decrease in apoB; 10 mg/dl decrease in LDL-C, or a 50 mg/dl decrease in triglycerides (because dividing triglyceride concentration by 5 estimates the cholesterol content carried by triglyceride-rich apoB-containing lipoproteins as estimated by the Friedewald formula). The results are derived from a multivariable meta-regression analysis where the dependent variable is the effect estimate for risk of coronary heart disease, and the independent variables are the effect estimates for the associated changes in plasma triglycerides, LDL-C and apoB, 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.

eFigure 1: Study design and analyses



eFigure 2: Plot of *LPL* variants included in *LPL* score



eFigure 3: Plot of *LDLR* variants included in *LDLR* score

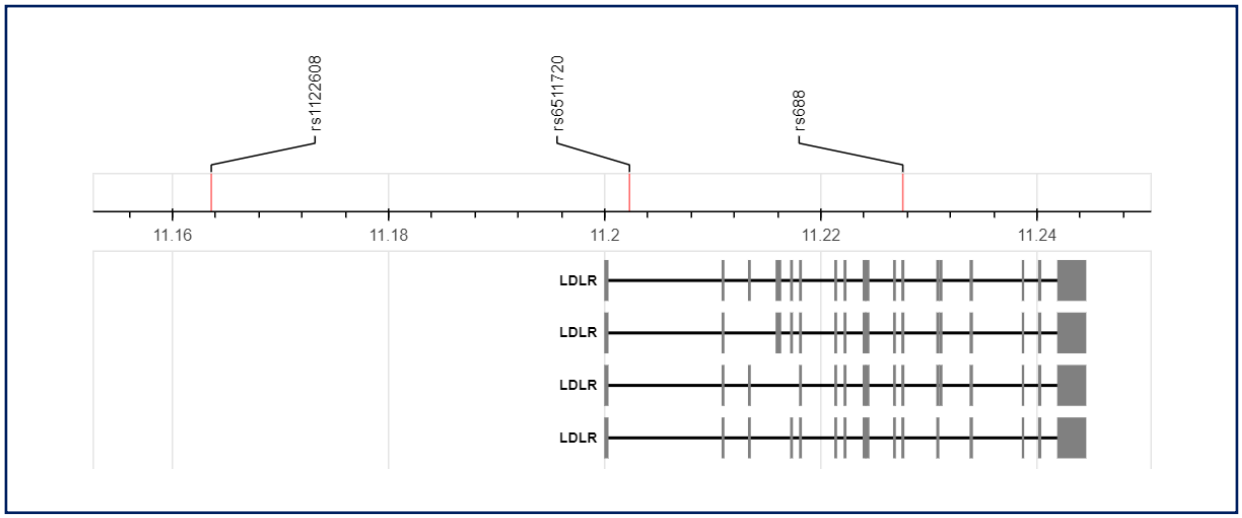
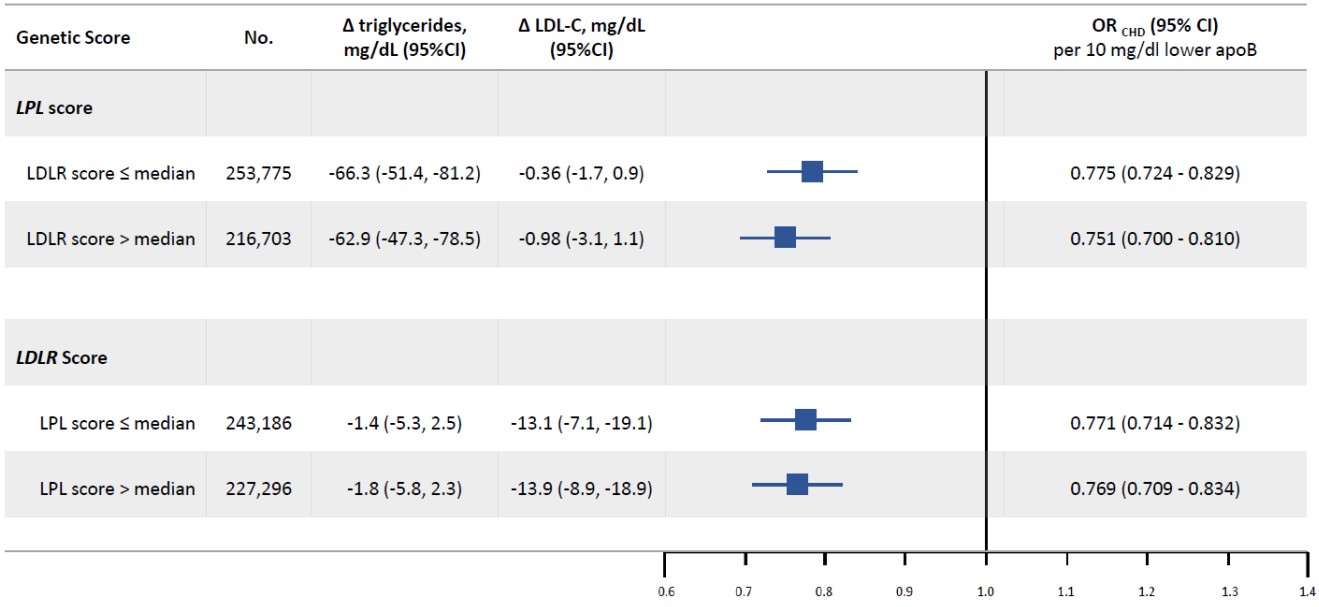


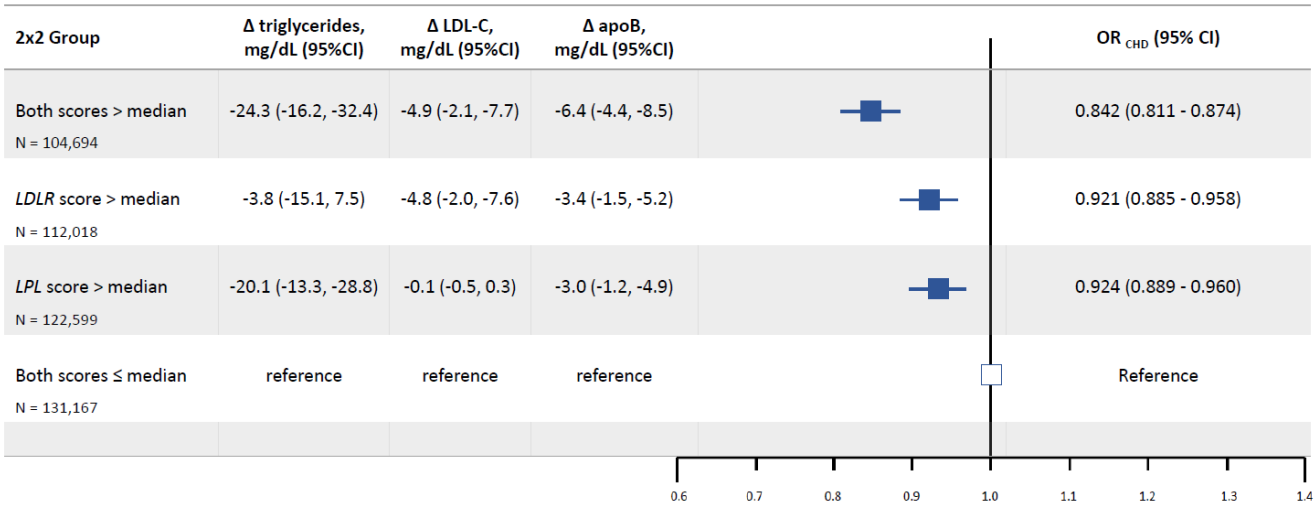
Figure 4: Associations of the *LPL* and *LDLR* scores with plasma lipid levels and risk of coronary heart disease for the same change in plasma concentration of apoB-containing lipoproteins stratified by the other score



eFigure 4 Legend: Data are from analyses of 470,478 participants with individual participant data including 30,328 cases of CHD. Changes in lipid levels were obtained from up 72,411 participants with individual participant data for whom one or more lipid measurements were available. Boxes represent point estimates of effect. Lines represent 95% error bars.

eFigure 5: 2x2 Factorial Mendelian randomization analysis evaluating the separate and combined effects of the LPL and LDLR scores on plasma lipids, lipoproteins, and risk of coronary heart disease

A. Unadjusted Associations



B. Associations with CHD adjusted per 10 mg/dl lower apoB

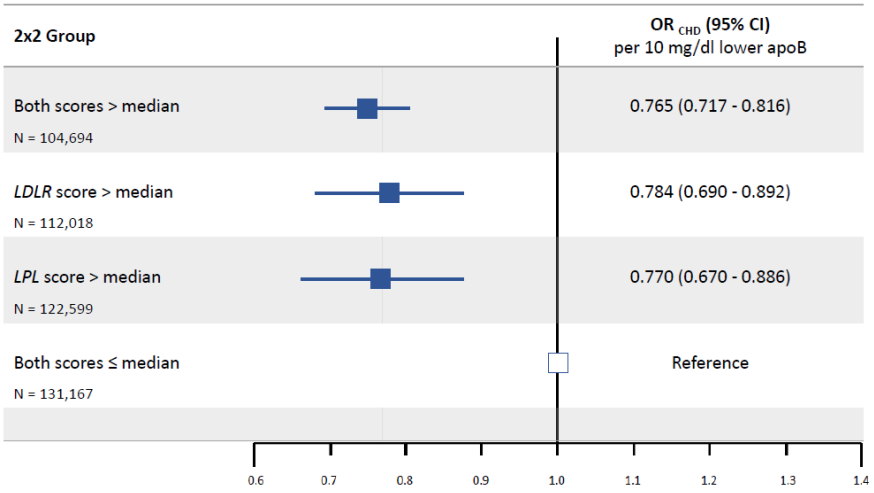


Figure 3 Legend: Data are from analyses of 470,478 participants with individual participant data including 30,328 cases of CHD. Changes in lipid levels were obtained from up 72,411 participants with individual participant data for whom one or more lipid measurements were available. Boxes represent point estimates of effect. Lines represent 95% confidence intervals.

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