Common variants associated with plasma triglycerides and risk for coronary artery disease

Triglycerides are transported in plasma by specific triglyceride-rich lipoproteins; in epidemiological studies, increased triglyceride levels correlate with higher risk for coronary artery disease (CAD). However, it is unclear whether this association reflects causal processes. We used 185 common variants recently mapped for plasma lipids ($P < 5 \times 10^{-8}$ for each) to examine the role of triglycerides in risk for CAD. First, we highlight loci associated with both low-density lipoprotein cholesterol (LDL-C) and triglyceride levels, and we show that the direction and magnitude of the associations with both traits are factors in determining CAD risk. Second, we consider loci with only a strong association with triglycerides and show that these loci are also associated with CAD. Finally, in a model accounting for effects on LDL-C and/or high-density lipoprotein cholesterol (HDL-C) levels, the strength of a polymorphism's effect on triglyceride levels is correlated with the magnitude of its effect on CAD risk. These results suggest that triglyceride-rich lipoproteins causally influence risk for CAD.

CAD is one of the leading causes of death and infirmity worldwide[1]. Plasma lipids such as cholesterol and triglycerides are associated with risk for CAD. Cholesterol is mostly carried in either LDL or HDL, whereas triglycerides are mostly transported in very-low-density lipoprotein (VLDL), chylomicrons and remnants of their metabolism.

In observational epidemiological studies, increased triglyceride levels, increased LDL-C levels and decreased HDL-C levels in the plasma are associated with increased risk for CAD[2,3]. However, it is difficult to establish causal inference in observational epidemiology[4], especially given the correlations among triglycerides, LDL-C and HDL-C[3].

SNPs can be used as instruments to test whether a biomarker is causally related to disease risk[5,6]. Because genotypes are randomly assigned at meiosis and are fixed throughout life, a genetic association may overcome some limitations of observational epidemiology such as confounding and reverse causation[7,8]. Using gene variants that exclusively affect a biomarker of interest (i.e., that do not have pleiotropic effects on other factors), investigators have confirmed LDL-C as a causal risk factor for CAD[9] and have cast doubt on whether HDL-C directly influences risk for CAD[10–15].

So far, however, it has been challenging to use a similar approach to define whether plasma triglyceride levels reflect processes that are causal in CAD. In contrast to variants associated with LDL-C and HDL-C, nearly all SNPs identified so far for plasma triglycerides have additional effects on either plasma LDL-C or HDL-C levels[16–18], violating the 'no pleiotropy' assumption of instrumental variable analysis[8,19].

Here we use common variants and develop a statistical framework to dissect causal influences among a set of correlated biomarkers. As this approach requires a large set of SNPs for which precise measurements of effects on the levels of triglycerides, LDL-C and HDL-C and on CAD risk are simultaneously available, we leveraged (i) 185 common SNPs all representing independent loci that are associated with at least 1 lipid trait at genome-wide levels of significance; (ii) estimates of the effect of each SNP on plasma triglyceride, LDL-C and HDL-C levels in a sample exceeding 180,000 individuals; and (iii) estimates of the effect of each SNP on CAD in a sample exceeding 86,000 individuals (22,233 cases and 64,762 controls).

We studied 185 SNPs at 157 1-Mb intervals with association $P < 5 \times 10^{-8}$ for triglyceride, LDL-C or HDL-C levels in a meta-analysis involving 188,577 genotyped individuals (see the companion manuscript; ref. 20). For each SNP, we obtained effect estimates for

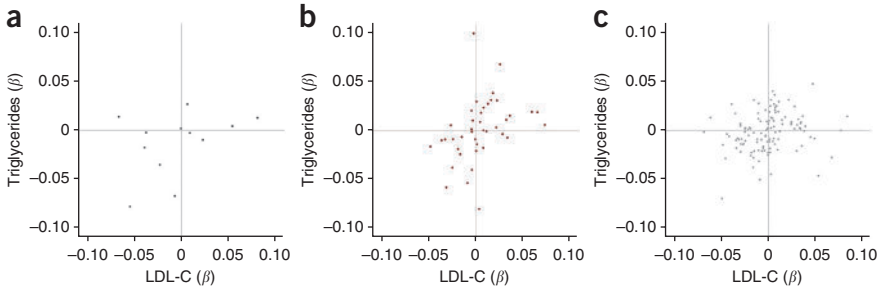

Figure 1 Effect of a SNP on the levels of triglycerides and LDL-C and on risk for CAD. (**a**) Black dots represent SNPs with $P_{CAD} < 0.001$. (**b**) Red dots represent SNPs with $0.01 < P_{CAD} < 0.001$. (**c**) Gray dots represent SNPs with $P_{CAD} > 0.10$. Loci strongly associated with CAD tend to have consistent directions of effect for both triglyceride and LDL-C levels (bottom left and top right quadrants). In contrast to the gray dots, the black and red dots are concentrated in the bottom left and top right quadrants. β values are in s.d. SNPs with $-0.10 < \beta_{LDL\text{-}C} < 0.10$ and $-0.10 < \beta_{triglycerides} < 0.10$ are shown.

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Table 1 SNPs with consistent direction of genetic effects on LDL-C and triglyceride levels and their relationship to risk for CAD

			LDL-C		Triglycerides		CAD	
Locus	rs ID	A1	$\beta_{LDL\text{-}C}$	*P*	$\beta_{triglycerides}$	*P*	β_{CAD}	*P*
ANGPTL3	rs4587594	A	−0.049	3×10^{-37}	−0.069	3×10^{-87}	0.017	0.26
APOB	rs1367117	A	0.12	2×10^{-196}	0.025	3×10^{-12}	0.035	0.02
GCKR	rs3817588	T	0.026	3×10^{-8}	0.067	7×10^{-58}	0.034	0.08
TIMD4	rs6882076	T	−0.046	5×10^{-33}	−0.029	1×10^{-16}	−0.021	0.15
HLA-B	rs2247056	T	−0.025	6×10^{-9}	−0.038	2×10^{-22}	−0.030	0.06
TRIB1	rs2980885	A	−0.031	4×10^{-12}	−0.058	5×10^{-45}	−0.041	0.02
TRIB1	rs2954022	A	−0.055	4×10^{-51}	−0.078	2×10^{-124}	−0.056	6×10^{-5}
ABCA1	rs1883025	T	−0.030	1×10^{-11}	−0.022	3×10^{-8}	−0.014	0.41
APOA1	rs10790162	A	0.076	3×10^{-26}	0.23	1×10^{-276}	0.13	2×10^{-6}
CETP	rs9989419	A	0.028	8×10^{-13}	0.024	3×10^{-12}	0.010	0.61
CILP2	rs10401969	T	0.12	2×10^{-60}	0.12	3×10^{-76}	0.11	2×10^{-4}

Shown are SNPs that have strong association with both LDL-C and triglyceride levels ($P < 5 \times 10^{-8}$ for each), have consistent direction of effect size for LDL-C and triglycerides, and have a ratio of magnitude of effect size of LDL-C to triglycerides within a factor of 5. Five loci confer risk for CAD ($P < 0.05$), and 10 of the 11 loci show consistent direction of effect for both lipid traits with the effect of CAD. All β estimates were calculated with respect to the A1 allele.

triglycerides ($\beta_{triglycerides}$), LDL-C ($\beta_{LDL\text{-}C}$) and HDL-C ($\beta_{HDL\text{-}C}$) (in s.d., estimated using inverse normal transformed residuals of lipid levels after adjusting for covariates; see **Supplementary Fig. 1** for study design). We also estimated the effect of each SNP on CAD risk (β_{CAD}) using data from a recently published genome-wide association study (GWAS) involving 86,995 individuals (the CARDIoGRAM study)[21]. For the 185 SNPs, effect sizes (β values) and *P* values for triglycerides, LDL-C, HDL-C and CAD are shown in **Supplementary Table 1**.

We considered several analytical approaches to investigate whether plasma triglyceride levels reflect processes that are causal in CAD. First, we evaluated the direction and magnitude of $\beta_{LDL\text{-}C}$ and $\beta_{triglycerides}$ in combination and then compared these values to β_{CAD} (**Fig. 1** and **Supplementary Fig. 2**). Second, to isolate the effects of triglycerides for the 185 SNPs, we restricted analysis to loci that had moderate to strong effects on triglyceride levels (large $\beta_{triglycerides}$) but minimal effects on LDL-C levels (small $\beta_{LDL\text{-}C}$). Finally, across the 185 SNPs, we formally developed and applied a statistical framework to test whether the effect size of a SNP on triglyceride levels was linearly related to its effect size on CAD, before and after accounting for the potential effect of the same SNP on plasma LDL-C and/or HDL-C levels.

For each of the 185 independent lipid-associated SNPs, we evaluated joint patterns of associations for triglyceride and LDL-C levels by examining SNPs that had strong associations with both triglycerides and LDL-C ($P < 5 \times 10^{-8}$ for each). Among these, we examined SNPs with the same direction and a similar magnitude of association for both lipid traits (within a factor of 5 of each other). We observed 11 loci with this pattern of association. Five loci conferred risk for CAD ($P < 0.05$), and 10 of the 11 loci showed a direction of effect that was consistent between the lipid traits and CAD (**Table 1**). For example, the A allele at rs2954022 in the *TRIB1* gene was strongly associated with lower triglyceride levels ($\beta_{triglycerides} = -0.078$; $P = 2 \times 10^{-124}$) and lower LDL-C levels ($\beta_{LDL\text{-}C} = -0.055$; $P = 4 \times 10^{-51}$) and showed the expected association with lower CAD risk ($\beta_{CAD} = -0.056$; $P = 6 \times 10^{-5}$).

Next, we identified SNPs that had strong associations with both triglyceride and LDL-C levels ($P < 5 \times 10^{-8}$ for each) but had opposite directions for $\beta_{triglycerides}$ and $\beta_{LDL\text{-}C}$ (within a factor of 5 of each other; **Table 2**). Four SNPs showed this pattern, and none of these showed significant association with CAD (all $P > 0.05$). For example, the A allele at rs2255141 in the *GPAM* gene was associated with lower triglyceride levels ($\beta_{triglycerides} = -0.021$; $P = 1 \times 10^{-8}$) and higher LDL-C levels ($\beta_{LDL\text{-}C} = 0.030$; $P = 7 \times 10^{-14}$) but had no discernible effect on CAD risk ($\beta_{CAD} = -0.0076$; $P = 0.63$).

Second, we considered a subset of the 185 SNPs that had moderate to strong effects on triglyceride levels but minimal effect on LDL-C levels ($n = 44$ SNPs, all SNPs had large $\beta_{triglycerides}$ (>0.01 or <−0.01) but small $\beta_{LDL\text{-}C}$ (between −0.01 and 0.01)). In regression analysis, we confirmed that $\beta_{LDL\text{-}C}$ was not associated with β_{CAD} for this set of SNPs ($P = 0.68$; **Supplementary Table 2**). However, we observed a significant association between $\beta_{triglycerides}$ and β_{CAD} ($P = 3 \times 10^{-5}$; **Supplementary Table 3**). These observations suggest that the direction and magnitude of the effects of a SNP on both triglyceride and LDL-C levels affect risk for CAD.

To formally investigate whether the strength of a SNP's association with triglyceride levels predicts CAD risk, we devised a statistical framework that controls for pleiotropic effects on secondary lipid traits. This approach is particularly important because SNP association signals with triglyceride, LDL-C and/or HDL-C levels ($\beta_{triglycerides}$, $\beta_{LDL\text{-}C}$ and $\beta_{HDL\text{-}C}$, respectively) are correlated (**Supplementary Fig. 3** and **Supplementary Table 4**).

We tested the role of triglyceride levels in CAD by first calculating residuals of β_{CAD} after including $\beta_{LDL\text{-}C}$ and $\beta_{HDL\text{-}C}$ as covariates in our regression model (**Supplementary Fig. 1**). We then tested the association of $\beta_{triglycerides}$ with β_{CAD} residuals. Similar models were created to assess the independent roles of LDL-C and HDL-C levels.

We observed that, across the 185 SNPs, $\beta_{LDL\text{-}C}$ was strongly associated with β_{CAD}, after adjusting for either $\beta_{triglycerides}$ individually, $\beta_{HDL\text{-}C}$ individually, or both $\beta_{triglycerides}$ and $\beta_{HDL\text{-}C}$ (all $P < 1 \times 10^{-18}$; **Table 3**). The pattern for $\beta_{HDL\text{-}C}$ was different. Across the 185 SNPs, $\beta_{HDL\text{-}C}$ was associated with β_{CAD}, after adjusting for $\beta_{LDL\text{-}C}$ ($P = 0.005$); however, this association was greatly attenuated after adjusting for $\beta_{triglycerides}$ individually ($P = 0.057$) and was rendered non-significant after accounting for both $\beta_{triglycerides}$ and $\beta_{LDL\text{-}C}$ ($P = 0.35$; **Table 3**).

The results for triglycerides were similar to those observed for LDL-C. Across the 185 SNPs, $\beta_{triglycerides}$ was strongly associated with β_{CAD}, after adjusting for both $\beta_{LDL\text{-}C}$ and $\beta_{HDL\text{-}C}$ ($P = 1 \times 10^{-9}$; **Table 3**).

Table 2 SNPs with opposite direction of genetic effects on LDL-C and triglyceride levels and their relationship to risk for CAD

			LDL-C		Triglycerides		CAD	
Locus	rs ID	A1	$\beta_{LDL\text{-}C}$	*P*	$\beta_{triglycerides}$	*P*	β_{CAD}	*P*
MIR148A	rs4722551	T	−0.039	7×10^{-16}	0.027	2×10^{-9}	−0.033	0.23
GPAM	rs2255141	A	0.030	7×10^{-14}	−0.021	1×10^{-8}	−0.0076	0.63
FADS1-2-3	rs1535	A	0.053	3×10^{-43}	−0.046	1×10^{-40}	0.0019	0.90
APOE	rs7254892	A	−0.49	8×10^{-365}	0.12	4×10^{-31}	−0.14	0.09

Shown are SNPs that have strong association with both LDL-C and triglyceride levels ($P < 5 \times 10^{-8}$ for each) but have opposite directions of effect for LDL-C and triglycerides and have a ratio of magnitude of effect size of LDL-C to triglycerides within a factor of 5. Four SNPs displayed this pattern, and none showed significant association with CAD (all $P > 0.05$). All β estimates were calculated with respect to the A1 allele.

Table 3 Association of the strength of a SNP's effect on plasma lipid levels with its strength of effect on CAD risk

Outcome	Predictor	Covariate	β	s.e.m.	P
		–	0.41	0.039	4×10^{-20}
β_{CAD}	$\beta_{LDL\text{-}C}$	$\beta_{HDL\text{-}C}$	0.38	0.039	9×10^{-19}
		$\beta_{triglycerides}$	0.40	0.034	1×10^{-23}
		$\beta_{HDL\text{-}C}$, $\beta_{triglycerides}$	0.38	0.034	2×10^{-22}
		–	–0.18	0.052	0.0006
β_{CAD}	$\beta_{HDL\text{-}C}$	$\beta_{LDL\text{-}C}$	–0.12	0.041	0.005
		$\beta_{triglycerides}$	–0.09	0.048	0.057
		$\beta_{LDL\text{-}C}$, $\beta_{triglycerides}$	–0.04	0.037	0.35
		–	0.44	0.074	2×10^{-8}
β_{CAD}	$\beta_{triglycerides}$	$\beta_{LDL\text{-}C}$	0.42	0.057	5×10^{-12}
		$\beta_{HDL\text{-}C}$	0.36	0.074	3×10^{-6}
		$\beta_{LDL\text{-}C}$, $\beta_{HDL\text{-}C}$	0.36	0.057	1×10^{-9}

Residuals for β_{CAD} were calculated after adjustment of a SNP's effect on the denoted lipid trait. A total of 185 SNPs identified from GWAS for LDL-C, HDL-C and triglycerides were included in regression analysis. $\beta_{LDL\text{-}C}$, $\beta_{HDL\text{-}C}$ and $\beta_{triglycerides}$ represent the effect sizes for a SNP on LDL-C, HDL-C and triglycerides, respectively, in the GWAS meta-analysis for lipids. Regression was performed with the predictor variable of the effect size on lipid traits (β estimate from predictor column) and the outcome variable of residual CAD effect size after adjusting for covariates.

As an alternative to this approach using residuals, we also tested a single model with the outcome variable of β_{CAD} and predictor variables of $\beta_{triglycerides}$, $\beta_{LDL\text{-}C}$ and $\beta_{HDL\text{-}C}$ considered jointly (**Supplementary Table 5**). Results were similar, with $\beta_{triglycerides}$ and $\beta_{LDL\text{-}C}$ showing association with β_{CAD} ($P = 2 \times 10^{-10}$ and 1×10^{-22}, respectively), but with $\beta_{HDL\text{-}C}$ failing to show association ($P = 0.32$).

In summary, we have demonstrated that (i) SNPs with the same direction and a similar magnitude of association for both triglycerides and LDL-C tend to associate with CAD risk; (ii) loci that have an exclusive effect on triglycerides are also associated with CAD; and (iii) the strength of a SNP's effect on triglyceride levels is correlated with the magnitude of its effect on CAD risk, even after accounting for the same SNP's effect on LDL-C and/or HDL-C levels.

Using an analytical approach that accounts for the potential pleiotropic effects of a SNP on triglyceride, LDL-C and/or HDL-C levels, we provide evidence that plasma triglyceride levels likely reflect processes that are causal in CAD. This finding, based on data at 185 common SNPs, is in line with recent reports of specific genes predominantly related to triglyceride levels also affecting risk for CAD. A SNP in the promoter of the *APOA5* gene[22], a common SNP upstream of the *TRIB1* gene[23] and a nonsense polymorphism in the *APOC3* gene[24] all predominantly associate with plasma triglyceride levels, and each SNP has been convincingly related to clinical CAD[18,25] or subclinical atherosclerosis[24].

Our results raise several questions. First, if plasma triglyceride levels reflect causal processes, what are the specific mechanistic direct links to atherosclerosis? Triglycerides are carried in plasma, mostly in VLDL, chylomicrons and remnants of their metabolism, and, as such, triglycerides capture several physiological processes that may promote atherosclerosis. One potential link is postprandial cholesterol metabolism. Plasma triglyceride levels are highly correlated with the amount of cholesterol in remnant lipoproteins (i.e., VLDL and chylomicron particles after interaction with lipoprotein lipase), and a variety of evidence, ranging from the human mendelian disorder of type III hyperlipoproteinemia to experimental evidence in cell culture and animal models, suggests that cholesterol-rich remnant particles have proatherogenic properties similar to LDL (reviewed in ref. 26). Another process reflected by plasma triglyceride levels is the activity of lipoprotein lipase, a key enzyme that hydrolyzes triglycerides within triglyceride-rich lipoproteins. Higher enzymatic activity of lipoprotein lipase in the circulation leads to lower plasma triglyceride levels; a gain-of-function nonsense polymorphism in the *LPL* gene has been shown to not only reduce plasma triglyceride levels but also to lower risk for CAD[27].

Second, why are plasma triglyceride levels not significantly associated with CAD in observational epidemiological studies when multiple risk factors are considered jointly to predict risk for future CAD (ref. 2)? Multivariate models have known limitations in assessing the etiological relevance of a given exposure. For example, an exposure may be rendered non-significant after multivariate adjustment because of less precise measurement or greater biological variability compared with other factors. Plasma triglyceride measurements are more variable than those of other plasma lipids such as HDL-C[26]. Alternatively, downstream effects of an exposure may more completely capture the risk conferred. For example, body mass index does not predict CAD risk in the Framingham model after accounting for blood pressure and type 2 diabetes, despite the accepted causal influence of weight on blood pressure and type 2 diabetes[28]. Our approach using SNPs as proxies overcomes these limitations of observational epidemiology.

Finally, what are the implications of these data for the development of drugs aimed at lowering plasma triglyceride levels with the hope of reducing CAD risk? Several recent randomized controlled trials have tested whether the lowering of plasma triglyceride levels with fish oils[29] or with fibrates[30–32] will decrease risk for CAD, and, in many cases, treatment did not reduce risk[29,31,32]. Possible explanations for failed trials are the use of an incorrect study population, an incorrect mechanism of lowering triglyceride levels, an insufficient degree by which triglyceride levels are lowered and limited statistical power.

Our study has several limitations. SNPs associated with triglyceride levels are also related to other lipid traits and, thus, are not ideal instruments for mendelian randomization analysis. Given that the plasma triglyceride levels measured in blood represent the end product of several metabolic processes, it is not surprising that triglyceride-related SNPs affect at least one other lipid trait. We have attempted to address this complexity through our statistical approach.

We are unable to distinguish whether only specific mechanisms of altering triglyceride levels affect risk for CAD. Of note, there is strong evidence that at least three mechanisms that robustly influence triglycerides—loss of APOA5 function, loss of TRIB1 function and gain of APOC3 function—increase risk for CAD.

In summary, we use common polymorphisms and employ a statistical framework to dissect causal influences among a set of correlated biomarkers. By applying this framework to a correlated set of plasma lipid measures and CAD risk, we suggest a causal role of triglyceride-rich lipoproteins in the development of CAD.

METHODS

Methods and any associated references are available in the online version of the paper.

Accession codes. Transcript sequences are available in GenBank for *ANGPTL3* (NM_014495), *APOB* (NM_000384), *GCKR* (NM_001486), *TIMD4* (NM_138379), *HLA-B* (NM_005514), *TRIB1* (NM_025195), *ABCA1* (NM_005502), *APOA1* (NM_000039), *CETP* (NM_000078), *CILP2* (NM_153221), *MIR148A* (NR_029597), *GPAM* (NM_020918), *FADS1*, *FADS2* and *FADS3* (NM_013402, NM_004265 and NM_021727, respectively), *APOE* (NM_000041), *APOA5* (NM_052968) and *APOC3* (NM_000040).

Note: Any Supplementary Information and Source Data files are available in the online version of the paper.

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AUTHOR CONTRIBUTIONS

R.D. carried out primary data analyses and prepared the supplementary information. R.D. and C. Gao prepared figures and tables. C.J.W., E.M.S., S. Sengupta, S.S.R. and G.R.A. contributed meta-analysis results. J.C. and M.L.B. performed bioinformatic analyses. R.D., M.J.D., B.M.N. and S. Kathiresan contributed to the design and conduct of the study. R.D., M.J.D., B.M.N. and S. Kathiresan wrote the manuscript.

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The authors declare competing financial interests: details are available in the online version of the paper.

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ONLINE METHODS

For the association of a given SNP with a plasma lipid trait, we obtained estimates of the effect size ($\beta_{triglycerides}$, $\beta_{LDL\text{-}C}$ and $\beta_{HDL\text{-}C}$) and strength of association (*P* value) from a meta-analysis of association results from genome-wide and custom-array genotyping—the Global Lipids Genetics Consortium (GLGC) Metabochip study (described in a companion manuscript published in this issue; ref. 20). All effect sizes are in s.d. from inverse normal transformed residuals of lipids after adjusting for covariates. This analysis included up to 188,577 individuals from 60 studies. For the association of a given SNP with CAD, we obtained estimates of the effect size (β_{CAD}) and strength of association (*P* value) from a published GWAS for CAD—the CARDIoGRAM study[21]. This study included 22,233 cases and 64,762 controls.

We selected independent SNPs associated with plasma lipid levels using the following criteria. First, we restricted to SNPs with association with at least one of the three lipid traits (triglyceride, LDL-C or HDL-C levels) at a genome-wide significance level of $P < 5 \times 10^{-8}$. For each lipid-associated locus, defined as a region of the genome that has a cluster of associated SNPs within 1 Mb of each other, we selected the strongest associated SNP (lead SNP). For loci with multiple associated SNPs, we calculated pairwise linkage disequilibrium (LD) estimates (r^2) for these SNPs using whole-genome sequencing data from 85 Utah residents of Northern and Western European ancestry (CEU) samples from the 1000 Genomes Project[33] and selected a second SNP if there was very low LD ($r^2 < 0.05$) with the lead SNP. In total, we selected 185 SNPs that met these criteria. These criteria yield a conservative estimate of the number of independent lipid-associated SNPs. A list of effect sizes and *P* values for the levels of triglycerides, LDL-C and HDL-C and for CAD for the 185 selected SNPs is shown in **Supplementary Table 1**.

To formally investigate whether the strength of a SNP's association with triglyceride levels predicts CAD risk, we performed linear regression on the effect sizes of each SNP for triglycerides ($\beta_{triglycerides}$), LDL-C ($\beta_{LDL\text{-}C}$) and HDL-C ($\beta_{HDL\text{-}C}$) as predictor variables and the effect sizes of CAD (β_{CAD}) as the outcome variable. To control for pleiotropic effects, we first calculated the residuals of β_{CAD} after adjusting for covariates of $\beta_{triglycerides}$, $\beta_{LDL\text{-}C}$ and/or $\beta_{HDL\text{-}C}$. We then performed linear regression analysis in a second model on the effect size of the primary lipid trait ($\beta_{triglycerides}$, $\beta_{LDL\text{-}C}$ or $\beta_{HDL\text{-}C}$) with the residuals of β_{CAD}. For example, to test for the role of LDL-C levels in CAD, we first calculated residuals of β_{CAD} after including as covariates $\beta_{triglycerides}$ and $\beta_{HDL\text{-}C}$ in our regression model. In a second regression model, we then performed association of residual β_{CAD} with $\beta_{LDL\text{-}C}$. All possible combinations of linear regression analysis were performed for $\beta_{triglycerides}$, $\beta_{LDL\text{-}C}$ or $\beta_{HDL\text{-}C}$ and β_{CAD} (**Table 3**).

As an alternative to this residuals approach, we also tested a single model in which the outcome variable of β_{CAD} was tested with the predictor variables of $\beta_{triglycerides}$, $\beta_{LDL\text{-}C}$ and $\beta_{HDL\text{-}C}$ jointly considered (**Supplementary Table 5**). We also performed several sensitivity analyses to test for the effect of using different thresholds of $\beta_{triglycerides}$ and $\beta_{LDL\text{-}C}$ when highlighting loci with associations with both triglyceride and LDL-C levels (**Supplementary Tables 6–8**). We used thresholds that yielded the highest number of SNPs for each statistical analysis (factor threshold of five in **Tables 1** and **2**; β cutoff value of 0.01 in **Supplementary Tables 2** and **3**). Furthermore, we assessed the effect of extreme influential outliers using Cook's *D* statistic[34] (**Supplementary Fig. 4** and **Supplementary Table 9**) on our conditional regression models (**Table 3**). A list of the number of SNPs included in each of the different analyses is shown in **Supplementary Table 10**.

33. 1000 Genomes Project Consortium. A map of human genome variation from population-scale sequencing. *Nature* **467**, 1061–1073 (2010).
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Supplementary Information

Common variants associated with plasma triglycerides and risk for coronary artery disease

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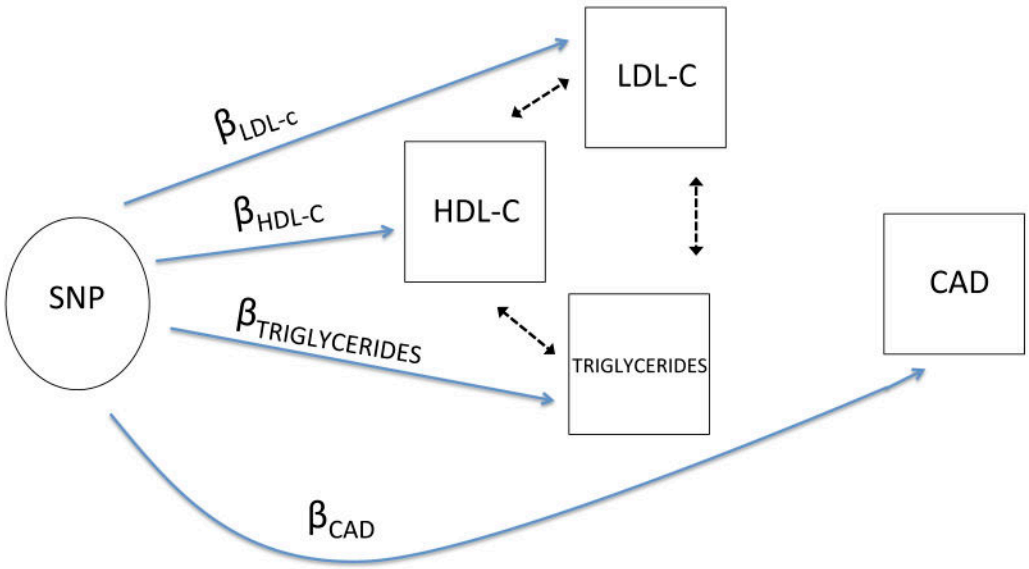
Supplementary Figure 1. Schematic to evaluate the effect of a SNP on three lipid fractions and coronary artery disease.



Dotted arrows indicate phenotypic correlations among plasma LDL-C, HDL-C and triglycerides. Blue arrows indicate the regression model performed between the independent variable (SNPs) and outcome variable (lipid trait or CAD). Betas (β) are the observed effect size of the independent variable in the association model. In total, 12 regression models were tested for association of the strength of effect of a SNP on plasma lipids (predictor variable) with its strength of effect on CAD (outcome variable), after accounting for a SNP's potential effects on other lipid traits (covariate) (**Table 3**).

SNP: Single nucleotide polymorphism; LDL-C: Low-density lipoprotein cholesterol; HDL-C: High-density lipoprotein cholesterol; CAD: Coronary artery disease.

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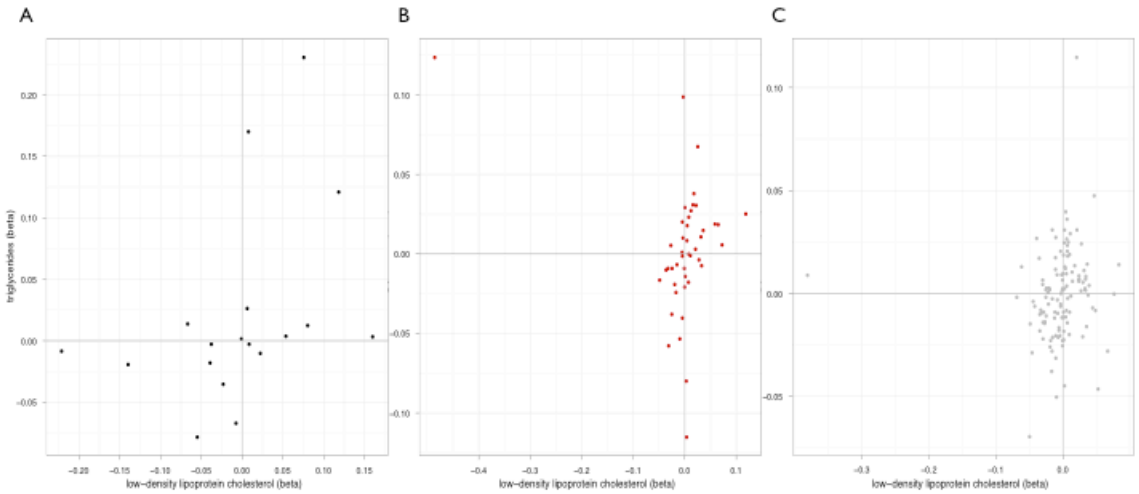
Supplementary Figure 2. Effect of a SNP on triglycerides, LDL-C, and risk for coronary artery disease.



A. Black dots represent SNPs with CAD $P<0.001$; B. Red dots represent SNPs with $0.01 <$ CAD $P <0.001$; C. Grey dots represent CAD $P>0.10$). Loci strongly associated with CAD tend to have consistent directions for both triglycerides and LDL-C (bottom left and top right quadrants). In contrast to the grey points, the black and red points are concentrated in the bottom left and top right quadrants. Betas are in standard deviation units. All SNPs are shown.

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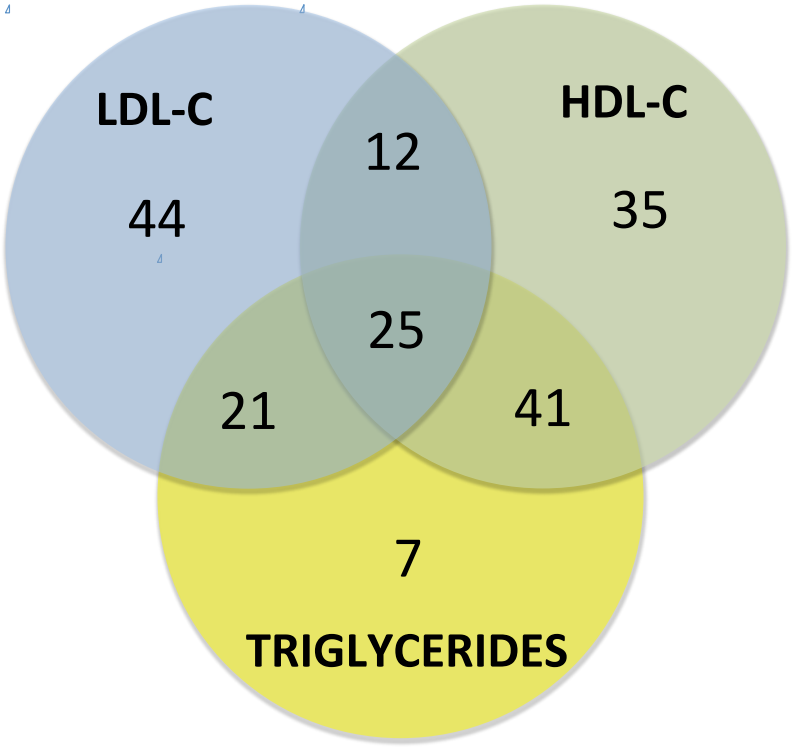
Supplementary Figure 3. Overlap between SNPs associated with triglycerides, LDL-C and HDL-C.



Number of SNPs associated with triglycerides, low-density lipoprotein cholesterol (LDL-C) and/or high-density lipoprotein cholesterol (HDL-C) (P<0.001) are shown. The results show that many SNPs have associations with more than one lipid trait.

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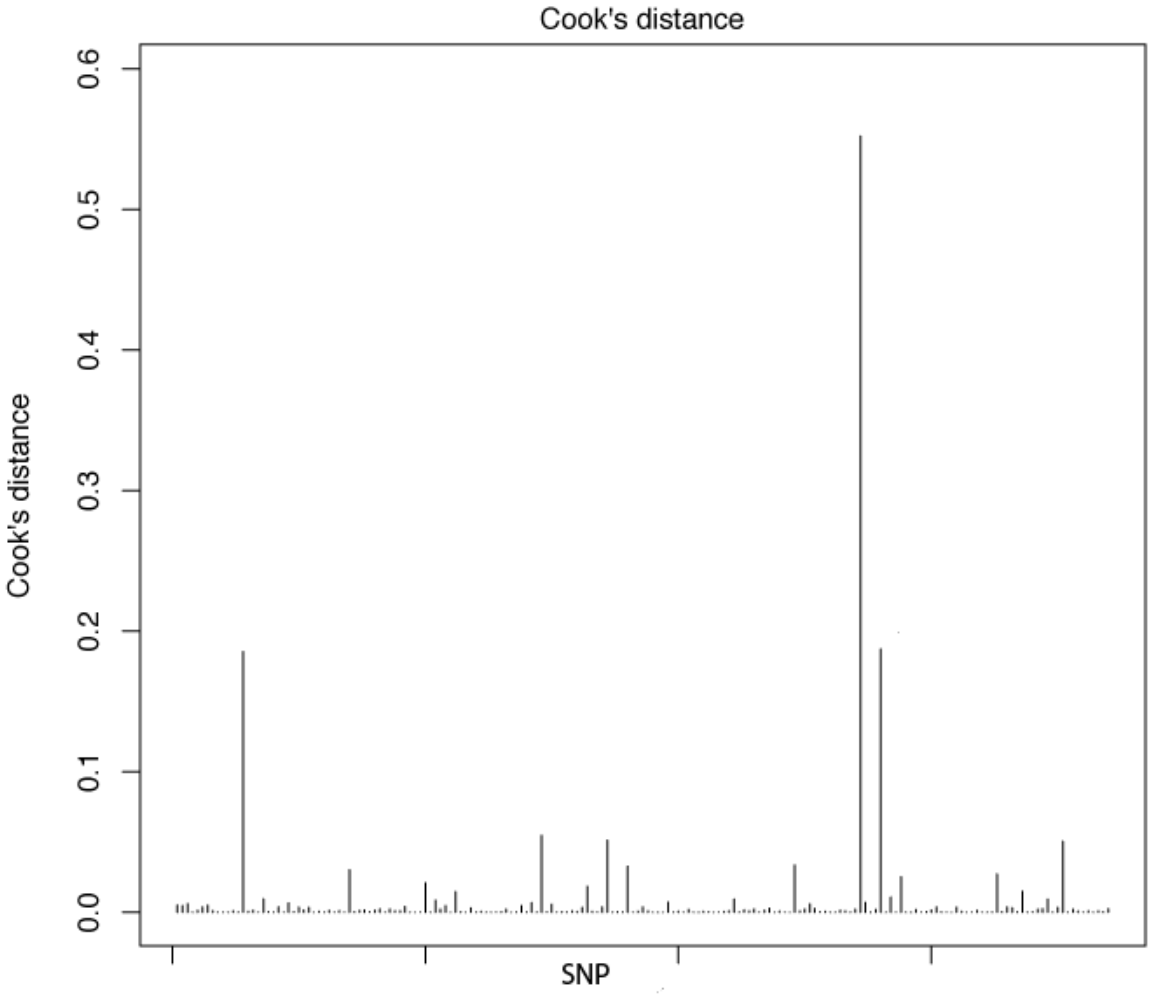
Supplementary Figure 4. Distribution of Cook's D statistic for 185 SNPs.



The distribution of influential observations using Cook's D statistic[1] for the association of the magnitude of a SNP's effect on a lipid fraction with its magnitude of effect on CAD risk when jointly considered in a multiple linear regression model are shown (**Supplementary Table 5**). The results show that there are only a few extreme outliers.

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Supplementary Table 1. Effect sizes and *P*-values for LDL-C, HDL-C, triglycerides and CAD for all 185 lipid SNPs.

					LDL-C		HDL-C		Triglycerides		CAD	
rs ID	chr	pos	a1	a2	beta	*P*-value	beta	*P*-value	beta	*P*-value	beta	*P*-value
rs10903129	1	25641524	A	G	-0.033	$4x10^{-19}$	-0.0009	0.79	-0.008	0.017	-0.012	0.38
rs4660293	1	39800767	A	G	-0.011	0.014	0.035	$7x10^{-19}$	-0.02	$1x10^{-7}$	-0.011	0.48
rs1998013	1	55730618	T	C	-0.38	$4x10^{-67}$	0.035	0.077	0.0089	0.66	-0.15	0.12
rs10493326	1	62725961	A	G	0.021	$6x10^{-7}$	-0.0013	0.74	0.031	$1x10^{-15}$	-0.0087	0.65
rs4587594	1	62906518	A	G	-0.049	$3x10^{-37}$	-0.015	$5x10^{-5}$	-0.069	$3x10^{-87}$	0.017	0.26
rs6603981	1	92766395	T	C	0.034	$2x10^{-14}$	0.0039	0.35	0.0072	0.076	0.012	0.48
rs12133576	1	93588988	A	G	0.01	0.006	0.024	$6x10^{-12}$	-0.009	0.0088	0.0058	0.69
rs646776	1	109620053	T	C	0.16	$1x10^{-292}$	-0.034	$9x10^{-17}$	0.0034	0.39	0.094	$5x10^{-8}$
rs1010167	1	110000250	C	G	-0.025	$3x10^{-10}$	0.0044	0.23	-0.0016	0.66	-0.028	0.14
rs267733	1	149225460	A	G	0.033	$5x10^{-10}$	-0.016	0.0012	0.0025	0.61	0.0027	0.9
rs12145743	1	154967275	T	G	0.0042	0.29	-0.02	$2x10^{-8}$	0.012	$6x10^{-4}$	-0.0092	0.55
rs4650994	1	176781935	A	G	0.0027	0.45	-0.021	$6x10^{-10}$	0.0024	0.47	0.0082	0.55
rs1689797	1	180417601	A	C	0.014	0.00022	-0.036	$2x10^{-23}$	0.011	0.0025	0.0098	0.51
rs2642438	1	219036651	A	G	-0.035	$4x10^{-17}$	-0.03	$5x10^{-15}$	0.017	$5x10^{-6}$	-0.02	0.22
rs903319	1	219052434	T	C	-0.027	$8x10^{-11}$	-0.01	0.0067	0.0054	0.15	0.031	0.047
rs4846914	1	228362314	A	G	-0.0043	0.25	0.048	$6x10^{-44}$	-0.04	$7x10^{-33}$	-0.029	0.041
rs6680658	1	228485967	A	G	-0.0055	0.22	0.023	$2x10^{-8}$	-0.017	$4x10^{-5}$	-0.0096	0.58
rs2587534	1	232915962	A	G	0.039	$3x10^{-26}$	0.0093	0.0065	0.0041	0.22	-0.00064	0.96
rs1367117	2	21117405	A	G	0.12	$2x10^{-196}$	-0.022	$2x10^{-9}$	0.025	$3x10^{-12}$	0.035	0.023
rs515135	2	21139562	T	C	-0.14	$1x10^{-188}$	0.011	0.014	-0.019	$1x10^{-5}$	-0.064	$9x10^{-4}$
rs1260326	2	27584444	T	C	0.021	$3x10^{-8}$	-0.011	0.001	0.11	$2x10^{-254}$	0.024	0.1
rs3817588	2	27584716	T	C	0.026	$3x10^{-8}$	-0.0049	0.26	0.067	$7x10^{-58}$	0.034	0.077
rs6544713	2	43927385	T	C	0.081	$6x10^{-85}$	-0.003	0.43	0.013	$7x10^{-4}$	0.061	$2x10^{-4}$
rs4148218	2	43953086	A	G	-0.044	$3x10^{-21}$	0.0029	0.51	-0.0037	0.38	-0.026	0.23

rs2710642	2	63003061	A	G	0.024	$3x10^{-10}$	-0.0096	0.0068	0.0065	0.06	0.017	0.26
rs17508045	2	118293189	T	C	0.049	$9x10^{-14}$	-0.0085	0.16	-0.0083	0.16	0.032	0.21
rs2030746	2	121025958	T	C	0.021	$2x10^{-8}$	-0.0025	0.49	0.0031	0.38	0.028	0.087
rs16831243	2	135478814	T	C	0.038	$8x10^{-12}$	0.011	0.027	-0.0006	0.91	-0.012	0.58
rs7607980	2	165259447	T	C	0.0065	0.24	-0.045	$1x10^{-17}$	0.036	$7x10^{-13}$	0.012	0.57
rs355838	2	165327409	T	G	0.018	$2x10^{-6}$	-0.019	$4x10^{-8}$	0.014	$8x10^{-5}$	0.019	0.20
rs2287623	2	169538401	A	G	-0.022	$7x10^{-9}$	-0.011	0.0012	0.0006	0.87	0.0073	0.60
rs7422339	2	211248752	A	C	0.0079	0.06	-0.027	$5x10^{-12}$	0	1	-0.047	0.013
rs1250229	2	216012629	T	C	-0.024	$8x10^{-9}$	0.0034	0.39	-0.0089	0.019	0.034	0.067
rs1515110	2	226830460	T	G	0.0063	0.089	-0.032	$2x10^{-20}$	0.027	$5x10^{-15}$	0.048	$8x10^{-4}$
rs11563251	2	234344123	T	C	0.035	$2x10^{-8}$	0.0058	0.31	0.0083	0.14	0.0016	0.95
rs9875338	3	12271469	A	G	-0.027	$3x10^{-13}$	-0.0073	0.034	-0.014	$2x10^{-5}$	-0.018	0.21
rs7640978	3	32508014	T	C	-0.039	$1x10^{-8}$	0.0003	0.96	-0.018	0.0044	-0.093	$4x10^{-4}$
rs2290547	3	47036187	A	G	0.0006	0.90	-0.03	$8x10^{-11}$	0.0096	0.03	-0.039	0.15
rs2240327	3	50088038	A	G	-0.0005	0.88	-0.024	$9x10^{-13}$	0.0017	0.61	0.055	$7x10^{-5}$
rs13326165	3	52507158	A	G	-0.0042	0.36	0.029	$2x10^{-11}$	-0.021	$9x10^{-7}$	-0.021	0.24
rs6805251	3	121043296	T	C	0.012	0.0013	0.02	$8x10^{-9}$	-0.0011	0.75	0.0069	0.62
rs17345563	3	133691893	A	G	0.036	$3x10^{-10}$	-0.014	0.007	0.015	0.0038	0.066	0.0026
rs687339	3	137415049	T	C	0.011	0.014	-0.032	$3x10^{-14}$	0.029	$6x10^{-13}$	0.024	0.16
rs1482852	3	158280988	A	G	0.0029	0.45	-0.021	$3x10^{-9}$	0.013	$2x10^{-4}$	0.027	0.11
rs10513688	3	172209912	A	G	0.022	$3x10^{-4}$	-0.0049	0.38	0.031	$4x10^{-8}$	0.048	0.046
rs6831256	4	3442937	A	G	-0.019	$1x10^{-6}$	0.013	$3x10^{-4}$	-0.026	$9x10^{-14}$	-0.026	0.2
rs10019888	4	25672088	A	G	-0.018	$3x10^{-4}$	0.027	$6x10^{-9}$	-0.023	$5x10^{-7}$	-0.0097	0.61
rs442177	4	88249285	T	G	0.016	$2x10^{-5}$	-0.022	$3x10^{-10}$	0.031	$3x10^{-20}$	0.028	0.046
rs10029254	4	88379164	T	C	0.0058	0.18	-0.0085	0.037	0.027	$1x10^{-11}$	-0.0082	0.63
rs3822072	4	89960292	A	G	0.0074	0.046	-0.025	$3x10^{-13}$	0.018	$6x10^{-8}$	0.015	0.3
rs2602836	4	100233828	A	G	-0.0007	0.84	0.019	$2x10^{-8}$	-0.009	0.007	0.028	0.049
rs13107325	4	103407732	T	C	-0.016	0.061	-0.071	$8x10^{-20}$	0.031	$6x10^{-5}$	0.0049	0.91

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rs6450176	5	53333782	A	G	0.01	0.013	-0.025	$1x10^{-10}$	0.019	$6x10^{-7}$	0.024	0.14
rs9686661	5	55897543	T	C	0.018	$2x10^{-4}$	-0.028	$2x10^{-10}$	0.038	$3x10^{-18}$	0.054	0.0032
rs4976033	5	67750002	A	G	0.001	0.79	0.022	$9x10^{-9}$	-0.014	$1x10^{-4}$	-0.067	0.0055
rs7703051	5	74661243	A	C	0.073	$5x10^{-85}$	0.002	0.56	0.0057	0.093	0.033	0.02
rs4530754	5	122883315	A	G	0.028	$4x10^{-14}$	0.0008	0.81	0.0015	0.64	-0.0075	0.59
rs6882076	5	156322875	T	C	-0.046	$5x10^{-33}$	-0.0015	0.67	-0.029	$1x10^{-16}$	-0.021	0.15
rs2294261	6	16217142	A	C	0.033	$5x10^{-19}$	-0.0085	0.015	0.0021	0.54	-0.0038	0.81
rs1800562	6	26201120	A	G	-0.062	$2x10^{-14}$	-0.0074	0.32	0.013	0.072	-0.026	0.38
rs2247056	6	31373469	T	C	-0.025	$6x10^{-9}$	-0.012	0.0023	-0.038	$2x10^{-22}$	-0.03	0.058
rs205262	6	34671142	A	G	0.0088	0.034	0.028	$2x10^{-13}$	-0.0028	0.45	-0.061	$1x10^{-4}$
rs998584	6	43865874	A	C	0.0005	0.9	-0.026	$4x10^{-12}$	0.029	$2x10^{-15}$	0.048	0.009
rs17789218	6	100706818	T	C	0.024	$3x10^{-8}$	-0.0041	0.31	0.0061	0.12	-0.01	0.54
rs868943	6	116444196	A	G	-0.026	$1x10^{-12}$	-0.0075	0.029	-0.014	$5x10^{-5}$	-0.019	0.17
rs9491696	6	127494332	C	G	-0.0057	0.12	0.02	$3x10^{-9}$	-0.018	$9x10^{-8}$	-0.0098	0.48
rs634869	6	139873450	T	C	0.013	$6x10^{-4}$	-0.023	$8x10^{-12}$	0.027	$4x10^{-16}$	0.038	0.0072
rs12525163	6	152081984	T	C	0.0043	0.29	-0.022	$9x10^{-9}$	0.0086	0.018	-0.043	0.0054
rs2297374	6	160495975	T	C	-0.033	$6x10^{-18}$	0.0056	0.11	-0.0091	0.0077	-0.029	0.058
rs1564348	6	160498850	T	C	-0.048	$3x10^{-22}$	0.0077	0.098	-0.016	$3x10^{-4}$	-0.061	0.0013
rs702485	7	6415797	A	G	-0.001	0.79	-0.024	$1x10^{-12}$	0.0016	0.64	0.0063	0.66
rs17286602	7	16118699	A	T	-0.0032	0.38	0.021	$8x10^{-10}$	-0.006	0.07	-0.007	0.62
rs10282707	7	17877563	T	C	-0.0084	0.025	-0.025	$8x10^{-13}$	0.0092	0.0072	-0.0016	0.91
rs12670798	7	21573877	T	C	-0.034	$7x10^{-16}$	0.0014	0.73	-0.01	0.0089	0.0074	0.66
rs4722551	7	25958351	T	C	-0.039	$7x10^{-16}$	-0.01	0.027	0.027	$2x10^{-9}$	-0.033	0.23
rs2073547	7	44548856	A	G	-0.049	$5x10^{-23}$	0.0049	0.28	-0.015	$9x10^{-4}$	-0.021	0.43
rs217386	7	44567220	A	G	-0.036	$8x10^{-22}$	0.0013	0.71	-0.01	0.0031	-0.025	0.087
rs4917014	7	50276409	T	G	-0.0047	0.23	-0.022	$8x10^{-10}$	0.0012	0.74	0.026	0.078
rs17145738	7	72620810	T	C	0.0039	0.50	0.041	$1x10^{-14}$	-0.11	$2x10^{-103}$	0.042	0.057
rs799160	7	72697942	T	C	0.0045	0.25	-0.013	0.0004	0.04	$7x10^{-29}$	-0.011	0.61

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rs38855	7	116145280	A	G	0.001	0.78	-0.015	$2x10^{-5}$	0.019	$2x10^{-8}$	0.02	0.15
rs3996352	7	130095474	A	G	0.0053	0.14	-0.03	$4x10^{-18}$	0.018	$7x10^{-8}$	0.04	0.0039
rs17173637	7	150160382	T	C	-0.0069	0.26	0.036	$2x10^{-10}$	-0.021	$2x10^{-4}$	-0.0076	0.77
rs4240624	8	9221641	A	G	0.067	$7x10^{-27}$	0.082	$3x10^{-45}$	-0.028	$1x10^{-6}$	0.021	0.4
rs9693857	8	9304527	T	C	-0.0046	0.21	-0.0037	0.28	0.02	$3x10^{-9}$	-0.026	0.072
rs4332136	8	15844224	C	G	-0.043	0.66	0.48	$1x10^{-13}$	0.024	0.65	0.0032	0.97
rs4921914	8	18316718	T	C	-0.023	$2x10^{-7}$	-0.0019	0.65	-0.035	$8x10^{-19}$	-0.075	$9x10^{-6}$
rs12678919	8	19888502	A	G	0.008	0.19	-0.16	$5x10^{-165}$	0.17	$2x10^{-206}$	0.087	$3x10^{-4}$
rs894210	8	19910123	A	G	-0.0071	0.054	0.069	$1x10^{-90}$	-0.067	$5x10^{-90}$	-0.06	$7x10^{-5}$
rs10102164	8	55584167	A	G	0.032	$3x10^{-12}$	-0.0005	0.9	0.011	0.0054	0.012	0.47
rs2326077	8	59548473	T	C	-0.034	$2x10^{-19}$	-0.0043	0.22	-0.018	$2x10^{-7}$	0.0055	0.71
rs2293889	8	116668374	T	G	0.015	0.00011	-0.031	$1x10^{-18}$	0.0062	0.071	-0.012	0.4
rs2737252	8	116733072	A	G	-0.031	$1x10^{-14}$	-0.013	$9x10^{-4}$	-0.0092	0.013	0.0079	0.61
rs4871137	8	121937732	T	G	-0.0043	0.28	-0.021	$1x10^{-8}$	-0.0013	0.72	-0.026	0.083
rs2980885	8	126543488	A	G	-0.031	$4x10^{-12}$	0.035	$4x10^{-17}$	-0.058	$5x10^{-45}$	-0.041	0.016
rs2954022	8	126551803	A	C	-0.055	$4x10^{-51}$	0.04	$2x10^{-32}$	-0.078	$2x10^{-124}$	-0.056	$6x10^{-5}$
rs4075205	8	144356084	T	C	-0.012	0.0016	0.022	$2x10^{-10}$	-0.009	0.0083	-0.00094	0.96
rs7832643	8	145094645	T	G	0.034	$7x10^{-19}$	-0.001	0.77	0.0017	0.62	-0.011	0.44
rs3780181	9	2630759	A	G	0.045	$1x10^{-9}$	0.0038	0.58	-0.0069	0.30	0.035	0.18
rs686030	9	15294782	A	C	0.0085	0.11	0.055	$3x10^{-29}$	0.025	$2x10^{-7}$	0.027	0.19
rs7033354	9	16894846	T	C	-0.019	$5x10^{-7}$	0.015	$1x10^{-5}$	-0.019	$3x10^{-8}$	-0.034	0.021
rs1883025	9	106704122	T	C	-0.03	$1x10^{-11}$	-0.07	$6x10^{-66}$	-0.022	$3x10^{-8}$	-0.014	0.41
rs2472509	9	106724051	T	G	-0.0004	0.91	-0.023	$7x10^{-10}$	0.0024	0.51	0.025	0.25
rs8176720	9	135122694	T	C	0.033	$6x10^{-18}$	0.0005	0.88	-0.0073	0.037	0.027	0.06
rs579459	9	135143989	T	C	-0.067	$3x10^{-49}$	-0.015	0.00052	0.014	$9x10^{-4}$	-0.098	$1x10^{-7}$
rs1781930	10	5186273	A	G	-0.01	0.035	-0.0018	0.69	-0.031	$5x10^{-13}$	0.019	0.3
rs970548	10	45333283	A	C	-0.016	$2x10^{-4}$	-0.026	$2x10^{-11}$	-0.0025	0.51	0.022	0.19
rs7897379	10	64971731	T	C	-0.01	$5x10^{-3}$	-0.019	$1x10^{-8}$	0.027	$2x10^{-16}$	-0.016	0.26

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rs2068888	10	94829632	A	G	-0.017	$1x10^{-5}$	0.019	$5x10^{-8}$	-0.024	$2x10^{-12}$	-0.033	0.099
rs2255141	10	113923876	A	G	0.03	$7x10^{-14}$	0.034	$1x10^{-19}$	-0.021	$1x10^{-8}$	-0.0076	0.63
rs2923084	11	10345358	A	G	-0.012	0.013	0.026	$2x10^{-8}$	-0.012	0.0071	0.01	0.58
rs2303975	11	14233575	A	G	-0.0013	0.81	0.028	$1x10^{-8}$	-0.012	0.016	0.015	0.46
rs10832962	11	18612847	T	C	0.032	$2x10^{-15}$	0.0043	0.25	0.011	0.0028	0.044	0.0049
rs326214	11	47254936	A	G	0.0071	0.14	-0.061	$3x10^{-42}$	0.024	$2x10^{-8}$	0.0055	0.73
rs17788930	11	47709351	A	G	0.0046	0.23	0.036	$1x10^{-23}$	-0.011	0.0013	-0.008	0.58
rs11246602	11	51368666	T	C	-0.0019	0.73	-0.034	$6x10^{-11}$	0.0091	0.079	-0.0032	0.88
rs12226802	11	55080884	A	G	-0.0002	0.97	-0.033	$2x10^{-11}$	0.0067	0.18	-0.013	0.51
rs174532	11	61305450	A	G	0.035	$5x10^{-17}$	0.021	$8x10^{-8}$	-0.016	$3x10^{-5}$	0.0097	0.67
rs1535	11	61354548	A	G	0.053	$3x10^{-43}$	0.039	$5x10^{-28}$	-0.046	$1x10^{-40}$	0.0019	0.9
rs12801636	11	65147893	A	G	0.0078	0.079	0.024	$2x10^{-8}$	-0.018	$1x10^{-5}$	-0.038	0.038
rs499974	11	75132669	A	C	0.0012	0.79	-0.026	$2x10^{-9}$	-0.009	0.034	-0.017	0.35
rs10790162	11	116144314	A	G	0.076	$3x10^{-26}$	-0.095	$3x10^{-46}$	0.23	$1x10^{-276}$	0.13	$2x10^{-6}$
rs603446	11	116159645	T	C	-0.0092	0.013	0.0018	0.60	-0.05	$2x10^{-50}$	-0.0089	0.52
rs7117842	11	122039714	T	C	-0.019	$3x10^{-7}$	-0.027	$6x10^{-15}$	0.002	0.56	-0.017	0.24
rs11220462	11	125749162	A	G	0.059	$3x10^{-23}$	-0.016	0.004	0.019	$4x10^{-4}$	0.053	0.015
rs11045163	12	20354793	A	G	0.0055	0.14	-0.022	$3x10^{-10}$	0.0097	0.004	0.0056	0.7
rs3741414	12	56130316	T	C	-0.016	$3x10^{-4}$	0.03	$2x10^{-13}$	-0.028	$8x10^{-13}$	-0.0019	0.92
rs10861661	12	105698776	A	C	-0.0004	0.93	0.022	$2x10^{-7}$	-0.023	$3x10^{-8}$	0.0052	0.78
rs2241210	12	108434527	A	G	-0.0078	0.035	-0.033	$3x10^{-21}$	-0.0029	0.38	0.0058	0.68
rs653178	12	110492139	T	C	0.023	$2x10^{-9}$	0.026	$1x10^{-13}$	-0.0099	0.004	-0.077	$2x10^{-6}$
rs6489818	12	110794963	A	G	0.028	$6x10^{-9}$	-0.0004	0.93	-0.0036	0.41	-0.055	0.0017
rs1186380	12	119860799	T	C	-0.024	$1x10^{-8}$	-0.0002	0.96	0.0026	0.50	0.0035	0.84
rs1169288	12	119901033	A	C	-0.038	$9x10^{-21}$	-0.0096	$1x10^{-2}$	-0.0025	0.49	-0.07	$3x10^{-6}$
rs838876	12	123825841	A	G	-0.003	0.47	0.049	$5x10^{-36}$	-0.0052	0.16	0.0036	0.84
rs10773105	12	123849719	T	C	0.0058	0.12	-0.036	$1x10^{-25}$	0.0037	0.28	-0.012	0.42
rs4942486	13	31851388	T	C	0.024	$3x10^{-11}$	-0.014	$6x10^{-5}$	0.0071	0.031	0	1

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rs1341267	13	94082981	A	C	0.0016	0.67	0.0023	0.50	-0.018	$4x10^{-8}$	-0.02	0.15
rs8017377	14	23953727	A	G	0.03	$3x10^{-15}$	-0.0037	0.30	0.0056	0.11	-0.018	0.36
rs4983559	14	104348254	A	G	-0.0026	0.5	-0.02	$4x10^{-8}$	0.0001	0.98	-0.023	0.24
rs2412710	15	40471079	A	G	-0.0024	0.87	-0.084	$1x10^{-9}$	0.099	$8x10^{-14}$	0.14	0.0052
rs492571	15	41998565	T	C	0.0033	0.73	0.066	$2x10^{-13}$	-0.08	$2x10^{-19}$	-0.081	0.019
rs1532085	15	56470658	A	G	0.0026	0.48	0.11	$2x10^{-209}$	0.031	$5x10^{-20}$	0.0067	0.65
rs261342	15	56518445	C	G	0.0026	0.69	-0.11	$6x10^{-71}$	-0.045	$4x10^{-14}$	-0.014	0.42
rs2652834	15	61183920	A	G	0.0019	0.68	-0.029	$4x10^{-11}$	0.025	$4x10^{-9}$	0.013	0.48
rs1035744	15	70353669	T	C	0.0069	0.095	-0.0055	0.15	0.021	$4x10^{-8}$	0.019	0.23
rs3198697	16	15037441	T	C	0.0096	0.01	0.016	$3x10^{-6}$	-0.02	$4x10^{-9}$	-0.017	0.23
rs749671	16	30995848	A	G	-0.015	$4x10^{-5}$	0.0071	0.041	-0.021	$4x10^{-10}$	-0.0054	0.7
rs9930333	16	52357478	T	G	0.0002	0.96	0.02	$1x10^{-7}$	-0.021	$1x10^{-8}$	-0.04	0.005
rs9989419	16	55542640	A	G	0.028	$8x10^{-13}$	-0.15	$8x10^{-373}$	0.024	$3x10^{-12}$	0.01	0.61
rs5880	16	55572592	C	G	0.047	$9x10^{-7}$	-0.31	$4x10^{-257}$	0.048	$3x10^{-8}$	0.023	0.62
rs16942887	16	66485543	A	G	0.0011	0.84	0.083	$1x10^{-60}$	-0.012	0.020	-0.027	0.21
rs2288002	16	70614783	A	G	-0.029	$5x10^{-14}$	-0.0069	0.050	-0.0089	0.009	-0.022	0.11
rs2000999	16	70665594	A	G	0.065	$1x10^{-45}$	0.0023	0.59	0.019	$9x10^{-6}$	0.04	0.03
rs2925979	16	80092291	T	C	-0.0031	0.44	-0.035	$4x10^{-21}$	0.021	$2x10^{-8}$	0.026	0.11
rs314253	17	7032374	T	C	0.024	$2x10^{-10}$	-0.003	0.4	0.0086	0.012	0.01	0.49
rs4791641	17	8101874	T	C	-0.02	$4x10^{-8}$	-0.0041	0.23	0.0028	0.4	-0.02	0.15
rs931992	17	35074961	T	G	0.0055	0.15	0.034	$3x10^{-21}$	-0.0083	0.018	-0.0045	0.76
rs8077889	17	39233692	A	C	-0.0005	0.91	0.021	$2x10^{-6}$	-0.025	$2x10^{-9}$	0.03	0.1
rs7225700	17	42746803	T	C	-0.03	$8x10^{-15}$	-0.0098	0.006	0.0046	0.19	-0.015	0.33
rs4148005	17	64394061	T	G	-0.015	$1x10^{-5}$	0.028	$6x10^{-15}$	-0.0066	0.063	-0.042	0.0052
rs4969178	17	73899797	A	G	-0.011	0.0033	-0.026	$4x10^{-14}$	0.018	$3x10^{-7}$	-0.0068	0.63
rs4939883	18	45421212	T	C	-0.021	$1x10^{-5}$	-0.08	$1x10^{-71}$	-0.0052	0.23	-0.0057	0.75
rs11660468	18	45463141	T	C	0.011	0.0028	0.039	$9x10^{-30}$	-0.0008	0.82	0.025	0.08
rs952044	18	55949090	T	C	-0.0033	0.41	-0.023	$3x10^{-10}$	0.01	0.0043	0.03	0.042

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rs2278236	19	8337581	A	G	0.0067	0.074	0.033	$7x10^{-21}$	-0.014	$4x10^{-5}$	-0.025	0.14
rs6511720	19	11063306	T	G	-0.22	$3x10^{-289}$	0.025	$1x10^{-5}$	-0.0084	0.13	-0.13	$2x10^{-4}$
rs688	19	11088602	T	C	0.054	$9x10^{-48}$	-0.011	$2x10^{-3}$	0.0041	0.22	0.056	$7x10^{-5}$
rs10401969	19	19268718	T	C	0.12	$2x10^{-60}$	-0.013	0.057	0.12	$3x10^{-76}$	0.11	$2x10^{-4}$
rs731839	19	38590905	A	G	0.0018	0.66	0.022	$2x10^{-9}$	-0.022	$5x10^{-10}$	-0.021	0.2
rs1688030	19	40248584	T	C	-0.016	0.031	-0.0085	0.22	-0.038	$3x10^{-8}$	0.0051	0.85
rs6859	19	50073874	A	G	0.084	$1x10^{-101}$	-0.018	$1x10^{-6}$	0.014	$6x10^{-5}$	0.019	0.35
rs7254892	19	50081436	A	G	-0.49	$8x10^{-365}$	0.053	$3x10^{-6}$	0.12	$4x10^{-31}$	-0.14	0.09
rs492602	19	53898229	A	G	-0.029	$3x10^{-14}$	0.0032	0.38	-0.014	$7x10^{-5}$	-0.001	0.95
rs17695224	19	57016028	A	G	-0.011	0.011	-0.029	$2x10^{-13}$	0.012	0.0021	0.015	0.36
rs103294	19	59489660	T	C	0.0073	0.12	0.052	$4x10^{-33}$	-0.0021	0.61	-0.013	0.51
rs364585	20	12910718	A	G	-0.025	$4x10^{-11}$	-0.0005	0.88	0.0018	0.6	-0.0072	0.61
rs2328223	20	17793921	A	C	-0.03	$2x10^{-9}$	0.0004	0.93	0.0066	0.14	0.0053	0.85
rs7264396	20	33618155	T	C	-0.025	$3x10^{-8}$	-0.0054	0.19	-0.011	$8x10^{-3}$	0.026	0.32
rs6016381	20	38613850	T	C	0.036	$6x10^{-22}$	-0.0084	0.016	0.014	$3x10^{-5}$	0.016	0.27
rs6065311	20	39157752	T	C	-0.042	$3x10^{-30}$	-0.0024	0.48	-0.0061	0.067	-0.019	0.17
rs1800961	20	42475778	T	C	-0.069	$1x10^{-10}$	-0.13	$7x10^{-38}$	-0.0017	0.86	0.030	0.49
rs4465830	20	44018827	A	G	-0.009	0.056	0.06	$4x10^{-42}$	-0.053	$5x10^{-36}$	0.039	0.027
rs181362	22	20262068	T	C	-0.0076	0.091	-0.038	$7x10^{-20}$	-0.0095	0.02	0.0015	0.93
rs5763662	22	28708703	T	C	0.077	$2x10^{-10}$	0.033	0.0031	-0.0001	0.99	-0.0097	0.85
rs3761445	22	36925357	A	G	0.0081	0.029	-0.016	$5x10^{-6}$	0.023	$7x10^{-12}$	-0.027	0.061

Effect size is with respect to allele1; a1: allele 1; a2: allele.

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Supplementary Table 2. For SNPs with moderate effect on triglycerides but minimal effect on LDL-C, the association of LDL-C effect size with CAD effect size.

Outcome	Predictor	Beta	SE	*P*
β_{CAD}	$\beta_{LDL\text{-}C}$	0.49	1.18	0.68

N=44 SNPs, ($-0.01<\beta_{LDL\text{-}C}<0.01$) and ($\beta_{TRIGLYCERIDES}<-0.01$ or $\beta_{TRIGLYCERIDES}>0.01$)

No association of $\beta_{LDL\text{-}C}$ on β_{CAD} is observed after restricting to SNPs with minimal effect on LDL-C but moderate to strong effect on triglycerides. SE: standard error.

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Supplementary Table 3. For SNPs with moderate effect on triglycerides but minimal effect on LDL-C, the association of triglyceride effect size with CAD effect size.

Outcome	Predictor	Beta	SE	*P*
β_{CAD}	$\beta_{TRIGLYCERIDES}$	0.51	0.11	$3x10^{-5}$

N=44 SNPs, ($-0.01<\beta_{LDL\text{-}C}<0.01$) and ($\beta_{TRIGLYCERIDES}<-0.01$ or $\beta_{TRIGLYCERIDES}>0.01$)

Significant association of $\beta_{TRIGLYCERIDES}$ on β_{CAD} is observed after restricting SNPs with minimal effect on LDL-C but moderate to strong effect on triglycerides. SE: standard error.

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Supplementary Table 4. For 185 SNPs, the correlation in effect sizes for LDL-C, HDL-C, triglycerides, and CAD.

	$\beta_{HDL\text{-}C}$	$\beta_{TRIGLYCERIDES}$	β_{CAD}
$\beta_{LDL\text{-}C}$	-0.14 (0.05)	0.031 (0.67)	0.61 (<0.0001)
$\beta_{HDL\text{-}C}$		-0.30 (<0.0001)	-0.25 (0.0006)
$\beta_{TRIGLYCERIDES}$			0.40 (<0.0001)

The correlation matrix shows that $\beta_{LDL\text{-}C}$, $\beta_{HDL\text{-}C}$, $\beta_{TRIGLYCERIDES}$ and β_{CAD} are correlated for 185 lipid SNPs. Pearson r values are shown. *P* value for each correlation is shown in parentheses.

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Supplementary Table 5. Association of the magnitude of a SNP's effect on a lipid fraction with its magnitude of effect on CAD risk when jointly considered in a multiple linear regression model.

Outcome	Predictor	Beta	SE	*P*
β_{CAD}	$\beta_{LDL\text{-}C}$	0.39	0.035	$1x10^{-22}$
	$\beta_{HDL\text{-}C}$	0.039	0.039	0.32
	$\beta_{TRIGLYCERIDES}$	0.40	0.060	$2x10^{-10}$

A total of 185 SNPs identified from GWAS for triglycerides, LDL-C, and HDL-C were included in regression analysis. $\beta_{TRIGLYCERIDES,}$ $\beta_{LDL\text{-}C}$ and $\beta_{HDL\text{-}C}$ represent the effect sizes for a SNP on triglycerides, LDL-C and HDL-C in a GWAS meta-analysis for lipids. Regression was performed with all three predictor variables of the effect size on lipid traits ($\beta_{TRIGLYCERIDES,}$ $\beta_{LDL\text{-}C}$ and $\beta_{HDL\text{-}C}$) and the outcome variable of CAD effect size (β_{CAD}) in a multiple linear regression model. SE: standard error.

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Supplementary Table 6. Number of SNPs with consistent direction of effects for both triglycerides and LDL-C for different factor thresholds.

Factor	Number of SNPs with CAD $P < 0.05$	Number of total SNPs
2	3	8
3	3	9
4	4	10
5	5	11

We show the number of SNPs with consistent direction of effects for both triglycerides and LDL-C for different factor thresholds. We observed similar results for the different factor thresholds.

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Supplementary Table 7. Number of SNPs with opposite direction of effects for both triglycerides and LDL-C for different factor thresholds.

Factor	Number of SNPs with CAD $P < 0.05$	Number of total SNPs
2	0	3
3	0	3
4	0	4
5	0	4

We show the number of SNPs with opposite direction of effects for both triglycerides and LDL-C for different factor thresholds. We observed similar results for the different factor thresholds.

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Supplementary Table 8. For SNPs with moderate effect on triglycerides but minimal effect on LDL-C, the association of LDL-C effect size and triglyceride effect size with CAD effect size at different cutoff values.

β cutoff value[1]	Predictor[2]	Beta	SE	*P*	Number of SNPs
0.005	$\beta_{\text{LDL-C}}$	-2.92	2.52	0.26	33
0.005	$\beta_{\text{TRIGLYCERIDES}}$	0.51	0.17	$6\text{x}10^{-3}$	33
0.01	$\beta_{\text{LDL-C}}$	0.49	1.18	0.68	44
0.01	$\beta_{\text{TRIGLYCERIDES}}$	0.51	0.11	$3\text{x}10^{-5}$	44
0.02	$\beta_{\text{LDL-C}}$	1.28	0.60	0.04	42
0.02	$\beta_{\text{TRIGLYCERIDES}}$	0.47	0.10	$4\text{x}10^{-5}$	42
0.03	$\beta_{\text{LDL-C}}$	1.27	0.70	0.08	23
0.03	$\beta_{\text{TRIGLYCERIDES}}$	0.45	0.13	$2\text{x}10^{-3}$	23

[1] β cutoff value refers to set of SNPs with large $\beta_{\text{TRIGLYCERIDES}}$ (greater than positive cutoff value or less than the negative cutoff value) but small $\beta_{\text{LDL-C}}$ (between negative and positive cutoff value)]. [2] Predictor refers to predictor variable tested in single linear regression model with β_{CAD}. Beta, SE, and *P* are results from single linear regression model with β_{CAD}. SE: standard error.

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Supplementary Table 9. Association of the strength of a SNP's effect on plasma lipids with its strength of effect on CAD risk, after removing three outliers for Cook's D statistic.

Outcome	Predictor	Covariate	Beta	SE	*P*
β_{CAD}	$\beta_{LDL\text{-}C}$	-	0.41	0.037	$6x10^{-22}$
β_{CAD}	$\beta_{LDL\text{-}C}$	$\beta_{HDL\text{-}C}$	0.38	0.035	$1x10^{-20}$
β_{CAD}	$\beta_{LDL\text{-}C}$	$\beta_{TRIGLYCERIDES}$	0.40	0.032	$1x10^{-25}$
β_{CAD}	$\beta_{LDL\text{-}C}$	$\beta_{HDL\text{-}C}$, $\beta_{TRIGLYCERIDES}$	0.38	0.032	$4x10^{-24}$
β_{CAD}	$\beta_{HDL\text{-}C}$	-	-0.30	0.065	$9x10^{-6}$
β_{CAD}	$\beta_{HDL\text{-}C}$	$\beta_{LDL\text{-}C}$	-0.21	0.051	$6x10^{-5}$
β_{CAD}	$\beta_{HDL\text{-}C}$	$\beta_{TRIGLYCERIDES}$	-0.14	0.062	0.023
β_{CAD}	$\beta_{HDL\text{-}C}$	$\beta_{LDL\text{-}C}$, $\beta_{TRIGLYCERIDES}$	-0.065	0.046	0.16
β_{CAD}	$\beta_{TRIGLYCERIDES}$	-	0.44	0.076	$2x10^{-8}$
β_{CAD}	$\beta_{TRIGLYCERIDES}$	$\beta_{LDL\text{-}C}$	0.42	0.056	$3x10^{-12}$
β_{CAD}	$\beta_{TRIGLYCERIDES}$	$\beta_{HDL\text{-}C}$	0.30	0.075	$1x10^{-4}$
β_{CAD}	$\beta_{TRIGLYCERIDES}$	$\beta_{LDL\text{-}C}$, $\beta_{HDL\text{-}C}$	0.31	0.056	$1x10^{-7}$

We tested conditional models in **Table 3** after removing the three most influential observations using Cook's D statistic[1]. Residuals for β_{CAD} were calculated after adjustment of a SNP's effect on the denoted lipid trait. SNPs identified from GWAS for LDL-C, HDL-C and triglycerides were included in regression analysis. $\beta_{LDL\text{-}C}$, $\beta_{HDL\text{-}C}$, and $\beta_{TRIGLYCERIDES}$ represent the effect sizes for a SNP on LDL-C, HDL-C and triglycerides in the GWAS meta-analysis for lipids. Regression was performed with the predictor variable of the effect size on lipid traits (β from predictor column) and the outcome variable of residual CAD effect size after adjusting for covariates. SE: standard error.

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Supplementary Table 10. Number of SNPs included for various analyses performed in the study.

Analyses performed in following figures/tables	Number of SNPs
Figure 1	174
Table 1	11
Table 2	4
Table 3	185
Supplementary Figure 2	185
Supplementary Figure 3	185
Supplementary Table 2	44
Supplementary Table 3	44
Supplementary Table 4	185
Supplementary Table 5	185
Supplementary Table 9	182

Shown are the number of SNPs included for various analyses performed in the various figures and tables.

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