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

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Abstract

Triglycerides are transported in plasma by specific triglyceride-rich lipoproteins; in epidemiologic 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 ($P<5\times10^{-8}$ for each) to examine the role of triglycerides on risk for CAD. First, we highlight loci associated with both low-density lipoprotein cholesterol (LDL-C) and triglycerides, and show that the direction and magnitude of both are factors in determining CAD risk. Second, we consider loci with only a strong magnitude of 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, a polymorphism's strength of effect on triglycerides is correlated with the magnitude of its effect on CAD risk. These results suggest that triglyceride-rich lipoproteins causally influence risk for CAD.

Coronary artery disease (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 low-density lipoproteins (LDL) or high-density lipoproteins (HDL) whereas triglycerides are mostly transported in very low-density lipoproteins (VLDL), chylomicrons, and remnants of their metabolism.

In observational epidemiologic studies, plasma concentrations of increased triglycerides, increased LDL cholesterol (LDL-C), and decreased HDL cholesterol (HDL-C) are associated with increased risk for CAD[2,3]. However, it is difficult to establish causal inference from observational epidemiology[4], especially given the correlations among triglycerides, LDL-C, and HDL-C[3].

Single nucleotide polymorphisms (SNPs) can be used as instruments to test whether a biomarker causally relates to disease risk[5,6]. Because genotypes are randomly assigned at meiosis and fixed throughout lifetime, 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., no pleiotropic effects on other

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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].

However, to date, it has been challenging to utilize a similar approach to define if plasma triglycerides reflect processes causal for CAD. In contrast to LDL-C and HDL-C, nearly all SNPs identified to date for plasma triglycerides have additional effects on either plasma LDL-C or HDL-C[16-18], violating the "no pleiotropy" assumption of instrumental variable analysis[8,19].

Here, we utilize 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 where precise measurements of effect on triglycerides, LDL-C, HDL-C, and CAD risk are simultaneously available, we leveraged: 1) 185 common SNPs all representing independent loci that are associated with at least one lipid trait at genome-wide levels of significance; 2) estimates of effect of each SNP on plasma triglycerides, LDL-C, and HDL-C in a sample exceeding 180,000 individuals; and 3) estimates of 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 one megabase pair intervals with association $P<5\times10^{-8}$ for triglycerides, LDL-C, or HDL-C in a meta-analysis involving 188,578 genotyped individuals (see companion manuscript[20]). For each SNP, we obtained effect estimates for triglycerides ($\beta_{TRIGLYCERIDES}$), LDL-C ($\beta_{LDL\text{-}C}$), and HDL-C ($\beta_{HDL\text{-}C}$) (in standard deviation units and estimated using inverse normal transformed residuals of lipid levels after adjusting for covariates; see Supplementary Figure 1 for study design). We also estimated the effect of each SNP on CAD (β_{CAD}) from a recently published genome-wide association study (GWAS) involving 86,995 individuals (the CARDIoGRAM study)[21]. For the 185 SNPs, effect sizes (β) and *P*-values for triglycerides, LDL-C, HDL-C, and CAD are shown in Supplementary Table 1.

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

For each of the 185 independent lipid SNPs, we evaluated joint patterns of associations for triglycerides and LDL-C by examining SNPs that have strong association to both triglycerides and LDL-C ($P<5\times10^{-8}$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). We observed 11 loci with this pattern of association. Five loci confer risk for CAD ($P<0.05$) and ten of the eleven loci show a direction of effect consistent between the lipid traits and CAD (Table 1). For example, the A allele at rs2954022 in the *TRIB1* gene was

associated strongly with lower triglycerides ($\beta_{TRIGLYCERIDES}$=−0.078, P=2×10^{-124}) and lower LDL-C ($\beta_{LDL\text{-}C}$=−0.055, P=4×10^{-51}) and showed the expected association with lower CAD risk (β_{CAD}=−0.056, P=6×10^{-5}).

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

Secondly, we considered a subset of the 185 SNPs that have moderate to strong effects on triglycerides but minimal effect on LDL-C [n=44 SNPs, all SNPs have 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; see Supplementary Table 2). However, we observed a significant association of $\beta_{TRIGLYCERIDES}$ and β_{CAD} (P=3×10^{-5}; see Supplementary Table 3). These observations suggest that the direction and magnitude of effect of a SNP on both triglycerides and LDL-C impact risk for CAD.

To formally investigate whether the strength of a SNP's association with triglycerides 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 triglycerides, LDL-C, and/or HDL-C ($\beta_{TRIGLYCERIDES}$, $\beta_{LDL\text{-}C}$, and $\beta_{HDL\text{-}C}$) are correlated (Supplementary Figure 3 and Supplementary Table 4).

We tested the role of triglycerides on CAD by first calculating residuals of β_{CAD} after including as covariates $\beta_{LDL\text{-}C}$ and $\beta_{HDL\text{-}C}$ in our regression model (Supplementary Figure 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.

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 < 1×10^{-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 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 =1×10^{-9}, Table 3).

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} ($P=2\times10^{-10}$ and $P=1\times10^{-22}$, respectively) but $\beta_{HDL\text{-}C}$ failing to show association (P=0.32).

In summary, we have demonstrated that: 1) SNPs with the same direction and a similar magnitude of association for both triglycerides and LDL-C tend to associate with CAD risk; 2) loci that have an exclusive effect on triglycerides are also associated with CAD; and 3) the strength of a SNP's effect on triglycerides 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.

Using an analytical approach that accounts for the potential pleiotropic effects of a SNP on triglycerides, LDL-C, and/or HDL-C, we provide evidence that plasma triglycerides likely reflects processes causal for CAD. This finding based on 185 common SNPs is in line with recent reports of specific genes predominantly related to triglycerides also affecting risk for CAD. A promoter SNP in the *APOA5* gene[22], a common SNP upstream of the *TRIB1* gene[23], and a nonsense polymorphism at the *APOC3* gene[24] all predominantly associate with plasma triglycerides and each SNP has been convincingly related to clinical CAD[11,25] or subclinical atherosclerosis[24].

Our results raise several questions. First, if plasma triglycerides 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 physiologic processes that may promote atherosclerosis. One potential link is post-prandial cholesterol metabolism. Plasma triglycerides 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 pro-atherogenic properties similar to LDL (reviewed in [26]). Another process reflected by plasma triglycerides 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 triglycerides; a gain-of-function nonsense polymorphism in the *LPL* gene has been shown to not only reduce plasma triglyceride levels but also lower risk for CAD[27].

Second, why are plasma triglycerides not significantly associated with CAD in observational epidemiologic studies when multiple risk factors are considered jointly to predict risk for future CAD[2]? Multivariable models have known limitations for assessing the etiological relevance for a given exposure. For example, an exposure may be rendered non-significant after multivariable adjustment because of less precise measurement or greater biologic variability when compared with other factors. Plasma triglyceride measurements are more variable than 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 triglycerides with the hope of reducing CAD risk? Several recent randomized controlled trials have tested whether the lowering of plasma triglycerides 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 wrong study population, wrong mechanism of lowering triglycerides, insufficient degree of triglyceride-lowering, and limited statistical power.

Our study has several limitations. SNPs associated with triglycerides also relate to other lipid traits and thus, are not ideal instruments for Mendelian randomization analysis. Given that the plasma triglycerides measured in the blood is 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 if only specific mechanisms of altering triglycerides 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 utilize 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.

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 companion manuscript, Willer et al.[20]). All effect sizes are in standard deviation units from inverse normal transformed residuals of lipids after adjusting for covariates. This analysis included up to 188,578 individuals from 60 studies. For the association of a given SNP with coronary artery disease (CAD), we obtained estimates of the effect size (β_{CAD}) and strength of association (*P*-value) from a published GWAS study for CAD, the CARDIoGRAM study[21]. This study included 22,233 cases and 63,762 controls.

We selected independent SNPs associated with plasma lipids using the following criteria. First, we restricted to SNPs with association with at least one of the three lipid traits (triglycerides, LDL-C or HDL-C) at a genome-wide significance level of $P<5\times10^{-8}$. For each lipid locus – defined as a region of the genome that has a cluster of associated SNPs within one megabase from 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) of these SNPs using whole genome sequencing data from 85 Utah residents with ancestryfrom northern and western Europe (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 SNPs. A list of effect sizes and *P*-values for triglycerides, LDL-C, HDL-C and CAD for the 185 selected SNPs is shown in Supplementary Table 1.

To formally investigate whether the strength of a SNP's association with triglycerides predicts CAD risk, we performed linear regression on the effect sizes of each SNP for triglycerides ($\beta_{TRIGLYCERIDES}$), LDL-C ($\beta_{LDL\text{-}C}$), 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 on 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 was performed between $\beta_{TRIGLYCERIDES}$, $\beta_{LDL\text{-}C}$ or $\beta_{HDL\text{-}C}$ on β_{CAD} (see Table 3).

As an alternative to this residuals approach, we also tested a single model where 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 on $\beta_{TRIGLYCERIDES}$ and $\beta_{LDL\text{-}C}$ when highlighting loci with associations for both triglycerides and LDL-C (Supplementary Table 6, 7 and 8). We used thresholds that yielded the highest number of SNPs for each statistical analysis (factor threshold of 5 in Table 1 and Table 2, and β cutoff value of 0.01 in Supplementary Table 2 and 3). Furthermore, we assessed the effect of extreme influential outliers using Cook's D statistic[34] (Supplementary Figure 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 are shown in Supplementary Table 10.

Supplementary Material

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Disclosures

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

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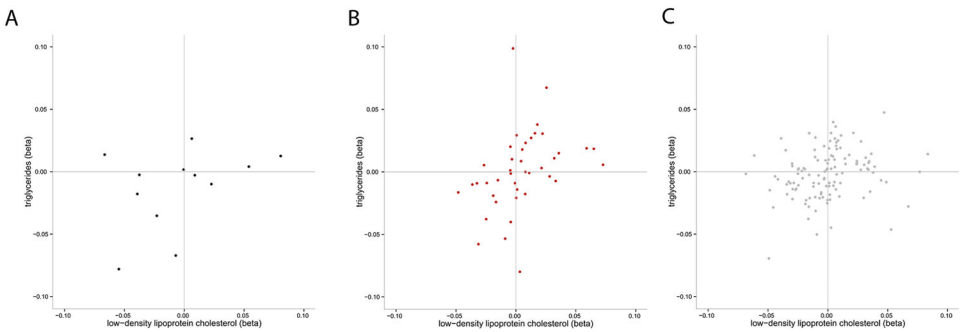

Figure 1. Effect of a single nucleotide polymorphism on triglycerides, low-density lipoprotein cholesterol, and risk for coronary artery disease

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. SNPs with $-0.10<\beta_{\text{LDL-C}}<0.10$ and $-0.10<\beta_{\text{TRIGLYCERIDES}}<0.10$ are shown.

Table 1

SNPs with consistent direction of genetic effects on LDL-C and triglycerides and their subsequent 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 triglycerides ($P<5\times10^{-8}$ 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 ten of the eleven loci show consistent direction of effect size for both lipid traits with the effect size of CAD.

A1: All beta estimates were calculated with respect to this allele.

Table 2

SNPs with opposite direction of genetic effects on LDL-C and triglycerides and their subsequent 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 triglycerides ($P<5\times10^{-8}$ for each), but have opposite 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. Four SNPs displayed this pattern and none showed significant association with CAD (all $P>0.05$).

A1: All beta estimates were calculated with respect to this allele.

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Table 3

Association of the strength of a SNP's effect on plasma lipids with its strength of effect on CAD risk.

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