The role of lipoprotein subfractions in coronary artery disease: A Mendelian randomization study

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Abstract

Lipoprotein subfractions and particle sizes are increasingly used in observational studies to predict the risk of cardiovascular diseases. However, the causal role of the different subfractions remain largely uncertain because the conventional study designs are subject to unmeasured confounding. We used Mendelian randomization and public GWAS summary data to estimate the effect of 82 lipoprotein subfraction and particle size traits on the occurrence of coronary artery disease and myocardial infarction. We found that, unlike LDL and VLDL subfractions, HDL subfraction traits appear to have heterogeneous effects on coronary artery disease according to particle size. The concentration of medium HDL particles may have a protective effect on coronary artery disease that is independent of traditional lipid factors.

Introduction

Lipoprotein subfractions have been increasingly used in epidemiological studies and even in clinical practice to predict the risk of cardiovascular diseases (CVD) (1–3). Some studies have identified potentially novel lipoprotein subfraction predictors for CVD (2,4–8) and demonstrated that the addition of lipoprotein subfraction measures can significantly improve the prediction of CVD (1,9–11). However, observational studies of lipoprotein subfractions have provided conflicting evidence. For example, several studies have suggested that small, dense LDL particles are more atherogenic (4,12), while others have found that larger LDL size is associated with CVD risk (13,14). Several recent observational studies found that the inverse association of CVD outcomes with smaller HDL particles is stronger than the association with larger HDL particles (6,11,15,16), but studies in different cohorts have reached contradictory conclusions (17,18).

Currently, the utility of lipoprotein subfractions in routine clinical practice remains controversial (14,19–21), there is a lack of intervention data showing that changing specific subfractions reduces CVD risk (21), and there is uncertainty around the causal relationship of subfractions to CVD. Mendelian randomization (MR) is an epidemiological method to investigate the causal role of risk exposures (22). MR uses genetic variation as instrumental variables (23) and asks if genetic predisposition to a higher level of the exposure (in this case, lipoprotein subfractions) is associated with higher occurrences of the disease outcome. A positive result suggests a causal relationship if the genetic variants satisfy the instrumental variable assumptions (23,24).

Because Mendelian randomization can potentially provide unbiased causal estimate even when there are unmeasured confounders, it is generally considered more credible than other non-randomized designs (25,26). MR has been used to estimate the association of several metabolites with CVD risk, although most prior studies are limited to one or a few risk exposures at a time (27,28). In this study we use MR to estimate the effect of 82 lipid and lipoprotein traits on the occurrence of coronary artery disease (CAD) and myocardial infarction (MI). This is to our knowledge the first comprehensive MR study to investigate the association of all lipoprotein subfractions with CAD.

In addition to complementing the existing observational epidemiology of lipoprotein subfractions, our study is also motivated by the inconclusive results about HDL-C in prior MR studies (29–32). An MR study of HDL subfractions can thus provide additional insights into the heterogeneous MR estimates and strong genetic correlation between HDL-C and CAD (32,33) reported in previous studies. We will discuss interpretations of this study in the Discussion section.

Materials and Methods

Lipoprotein particle measurements

We used GWAS summary data of 82 lipid and lipoprotein traits reported by two previous studies (34,35). In both studies, the circulating lipid and lipoprotein traits are measured using high-throughput nuclear magnetic resonance (NMR) spectroscopy (36). All the subfraction traits are named using three components separated by hyphen: the first indicates the size (XS, S, M, L, XL, XXL); the second indicates the category according to the lipoprotein density (VLDL, LDL, IDL, HDL); the third indicates the measurement (C for total cholesterol, CE for cholesterol esters, FC for free cholesterol, L for total lipids, P for particle concentration, PL for phospholipids, TG for triglycerides). For example, M-HDL-P means the concentration of medium HDL particles. Apart from the traditional lipid traits (TG, LDL-C, HDL-C), the

two studies also measured the average diameter of the fractions (VLDL-D, LDL-D, HDL-D) and the concentration of apoB and apoA1.

Mendelian randomization design

We employed a three-sample summary-data Mendelian randomization design in this study, in which one genome-wide association study (GWAS) was used to select independent SNPs that are associated with one or several lipoprotein measures. More specifically, the selection GWAS was used to create two sets of SNPs that are in linkage equilibrium in a reference panel ($r^2 < 0.001$): 1. a set of genome-wide significant SNPs (p-value $\leq 5 \times 10^{-8}$); 2. a full set of SNPs (p-value ≤ 1). The latter is called the "genome-wide Mendelian randomization" design and requires more advanced statistical methods to avoid weak instrument bias (32). The other two GWAS were then used to obtain summary associations of the selected SNPs with the exposure and the outcome, as in the commonly used two-sample MR design (37,38). To avoid the pitfall of statistical selection bias (aka winner's curse), we require that the other two GWAS used for estimation of causal effect to have non-overlapping sample set with the selection GWAS. More details about the three-sample Mendelian randomization design can be found elsewhere (32,39) and the Online Supplement.

GWAS datasets and instrument selection

Table 1 describes all GWAS summary datasets used in the present study, including two GWAS of the traditional lipid traits (40,41), two recent GWAS of circulating metabolites using nuclear magnetic resonance spectroscopy (34,35), and three GWAS of coronary artery disease or myocardial infarction (42–44).

Based on how the genetic instruments were selected, the MR designs we used can be categorized into three types:

1. **Traditional selection:** Traditional lipid traits were used to select SNPs for the Mendelian randomization of lipoprotein subfraction traits. That is, HDL-C was used to select SNPs for HDL subfraction traits, LDL-C for IDL and LDL subfraction traits, and TG for VLDL subfraction traits. The selected SNPs were then used to estimate the univariate effect of lipoprotein subfractions on CAD.
2. **Subfraction selection:** For each lipoprotein subfraction, the instrumental SNPs were selected using the same or closest lipoprotein subfraction in the selection GWAS. For example, if the target exposure is S-HDL-L but this is not measured in the selection GWAS, we use S-HDL-P in the selection GWAS. The selected SNPs are then used to estimate the univariate effects. Because we have two GWAS datasets for the lipoprotein subfractions, we used one for instrument selection and the other one for statistical inference and then swapped their roles.
3. **Multivariate Mendelian randomization:** In this design, the estimate of each lipoprotein subfraction was further adjusted for the traditional lipid traits (TG, LDL-C, HDL-C) of the other two lipoprotein classes (TG is treated as a traditional lipid trait of VLDL and IDL traits are treated as belonging to the LDL class). For example, M-HDL-P is further adjusted for LDL-C and TG; IDL-C and L-LDL-C are further adjusted for HDL-C and TG; S-VLDL-CE is further adjusted for HDL-C and LDL-C. In this multivariate MR, SNPs were selected as instruments if they were associated (p-value $\leq 10^{-4}$) with at least one of the three exposures (the subfraction trait under investigation and two other traditional lipids).

Statistical methods

For univariate MR (the first two types of instrument selection), we used three statistical methods: inverse-variance weighting (IVW) (45), weighted median (46), and robust adjusted profile score (RAPS) (32,47). All three methods require the exposure GWAS and outcome GWAS have non-overlapping samples. The last two methods can provide consistent estimate of the causal effect even when some of the genetic variants are not valid instruments, provided that the direct effects of the genetic variants are independent of the strength of their associations with the exposure (32,47). The last condition is called the Instrument Strength Independent of Direct Effect (InSIDE) assumption in the literature (46,48). RAPS is also robust to idiosyncratically large direct effects by using techniques from robust statistics (47). RAPS further increases the statistical power by exploiting weak genetic instruments and does not suffer from weak instrument bias (32). Because IVW and weighted median can be severely biased when there are many SNPs only weakly associated with the exposure (32,47), we only used them with the set of genome-wide significant SNPs.

For multivariate Mendelian randomization, we used an extension of RAPS called GRAPPLE (Genome-wide mendelian Randomization under Pervasive PLEiotropy) to obtain the statistical estimates (39). This method allows overlapping exposure and outcome GWAS.

We used Bonferroni's correction to adjust for multiple comparisons. In our main analysis using RAPS, we used 7 designs to investigate 82 lipoprotein traits, so the p-value threshold for significance level 0.05 is $0.05/7/82 = 8.7 \times 10^{-5}$.

Genetic correlations

Genetic correlation is a measure of association between the genetic determinants of two phenotypes. It is generally different from the epidemiological correlation estimated from cross-sectional data. To further explore whether any novel causal effect found by Mendelian randomization is independent of other subfraction exposures, we used the LD-score regression to estimate the genetic correlations of the lipoprotein subfraction traits (49). The two GWAS datasets of lipoprotein subfractions are used to obtain two independent estimates of the genetic correlations and are then combined using inverse-variance weighted average.

Results

Genetic correlations between lipoproteins

We first describe the genetic correlations between the lipoprotein subfraction concentrations and other parameters that are estimated by LD-score regression (Figure 2).**Error! Reference source not found.** Most LDL and VLDL subfractions were strongly correlated with each other as well as with ApoB. L-HDL-P, XL-HDL-P, HDL-C and HDL-D were negatively correlated with the VLDL subfractions. The concentrations of large and extra-large HDL particles (L-HDL-P and XL-HDL-P) were strongly correlated with ApoA1, HDL-C and HDL-D. The concentrations of small and medium HDL particles (S-HDL-P and M-HDL-P) had relatively few significant correlations with other subfractions. Finally, the triglyceride content in small HDL (S-HDL-TG) was strongly correlated with VLDL subfractions but not with S-HDL-P. The estimated genetic correlation using the individual GWAS can be found in Supplement D.

Mendelian randomization

The estimated associations of genetic determinants of selected lipoprotein subfractions with CAD or MI are reported in Table 2 and Figure 1**Error! Reference source not found.**. The full results are available in the Online Supplement.

Associations of genetically-determined apoB-containing lipoproteins with CAD/MI

As expected, in all MR analyses (univariate and multivariate), genetically-determined LDL-C, apoB and TG had strong positive association with CAD and MI (Table 2) and most of the results are statistically significant after Bonferroni's correction.

In univariate MR, genetically-determined VLDL and LDL subfractions had uniformly positive associations with CAD and MI. Within VLDL or LDL, the magnitude of the associations was very similar, though the associations of VLDL subfractions were smaller than of LDL subfractions. Most of the results were statistically significant after Bonferroni's correction for LDL subfractions, and only some were significant for VLDL subfractions. In multivariate MR that adjusted for LDL-C and TG, the associations of VLDL subfractions were attenuated and became non-significant. In contrast, after adjusting for HDL-C and TG, the associations of LDL subfractions were still strong and statistically significant.

Genetically-determined VLDL particle size (VLDL-D) showed weak negative associations with CAD and MI in univariate and multivariate MR. The associations are not statistically significant after adjusting for multiple comparisons. In comparison, genetically-determined LDL size (LDL-D) showed positive associations with CAD and in one study the association is statistically significant after Bonferroni's correction.

Associations of genetically-determined HDL measures and HDL subfractions with CAD/MI

In one univariate MR study, genetically-determined HDL-C showed significant association with CAD, but the diagnostic plot show evidence of horizontal pleiotropy that violates the InSIDE assumption (Supplement Figure F6). The magnitude of this association was much smaller than that of LDL-C or TG. In all other univariate and multivariate MR studies, HDL-C was not associated with CAD or MI. Genetically-determined apoA1, the major protein component of HDL particles, did not show a significant association with CAD or MI.

In contrast to the apoB lipoproteins, genetically-determined HDL subfractions showed highly heterogeneous associations with CAD and MI in univariate MR. The concentration and lipid contents of extra-large HDL particles were not associated with CAD or MI. The large HDL traits trended toward a negative association with CAD, but the associations were non-significant after Bonferroni's correction and were attenuated in multivariate MR. In contrast, the medium HDL traits (M-HDL-P, M-HDL-C, M-HDL-L) had *inverse* associations with CAD that remained statistically significant after adjusting for multiple comparisons. Among the small HDL traits, S-HDL-P and S-HDL-L had a trend toward inverse associations with CAD but were not statistically significant. Interestingly, S-HDL-TG had significantly positive association with CAD, possibly confounded by its strong genetic correlation with VLDL subfractions (Figure 2) that had similar positive associations with CAD.

Adjusting for LDL-C and TG in the multivariate MR did not change the results for HDL subfractions substantially. In particular, the inverse association between medium HDL traits and CAD were not attenuated but did become non-significant due to increased standard error.

Finally, genetically-determined HDL particle size (HDL-D) was not associated with CAD or MI.

Horizontal pleiotropy for M-HDL-P

We further evaluate the independence of M-HDL-P as a risk factor for CAD. By a meta-analysis (inverse-variance weighting) of the two GWAS of lipoprotein subfractions (34,35), we obtained 10 SNPs that are significantly associated with M-HDL-P (p-value $\leq 5 \times 10^{-8}$). Table 1 lists the associations of these 10 SNPs with HDL subfractions, HDL-C, LDL-C, TG and CAD. Although M-HDL-P was not genetically correlated with LDL-C or TG (Figure 2), several SNPs associated with M-HDL-P were also associated with LDL-C and/or TG, so there is potentially a large amount of horizontal pleiotropy in the univariate Mendelian randomization analysis of M-HDL-P. However, the associations of these 10 SNPs with LDL-C and TG did not exhibit any apparent pattern and are roughly balanced around the null. Therefore we did not find any evidence against the InSIDE condition, a crucial assumption for the validity of the weighted median and RAPS estimators (46,47). This observation is further illustrated in Figure 3, in which the SNP effects on CAD are plotted against the SNP effects on M-HDL-P. Figure 3 also demonstrates how adjusting for LDL-C and TG (red arrows) may affect the multivariate Mendelian randomization (adjusted effect on CAD = original effect on CAD – 0.45 * effect on LDL-C – 0.25 * effect on TG). After the adjustment, the associations of the genetic variants with CAD generally became closer to the straight line in red which corresponds to a Mendelian randomization estimate of -0.3.

Discussion

Because existing GWAS data for lipoprotein subfractions are much smaller than those for the traditional lipid traits, there are fewer genetic variants significantly associated with the subfraction traits. This limits the statistical power of a conventional MR analysis. We overcome this challenge by adopting a new statistical method, robust adjusted profile score (RAPS), that efficiently utilizes weak instruments (32,47). RAPS is also robust to certain violations of the instrumental variable assumptions, including horizontal pleiotropy that satisfies the InSIDE assumption. These methodological innovations allow us to obtain new insights into the role of lipoprotein subfractions.

Our study provides a comprehensive Mendelian randomization examination of the potential causal role of lipoprotein subfractions in CAD. To summarize, our results suggest that:

- LDL and VLDL subfractions appear to have nearly uniform effects on CAD across particle size. Therefore, the results do not support the hypothesis that small, dense LDL particles are more atherogenic. On the contrary, we found some evidence that larger LDL particle size might have positive effect on CAD.
- HDL subfractions appear to have heterogeneous effects on CAD. In particular, the concentration and lipid constituents of medium HDL particles appear to have a protective effect on CAD

occurrence. Moreover, this relationship is independent of traditional risk factors in the following sense:

- M-HDL-P was not genetically correlated with the traditional lipid traits (HDL-C, LDL-C and TG).
- The estimated effect of M-HDL-P (and other lipid measurements such as M-HDL-C) with CAD was not attenuated when adjusting for LDL-C and TG in multivariate MR analysis, although the effect became statistically non-significant after adjusting for multiple comparisons.
- The SNPs that are associated with M-HDL-P showed a balanced pattern of association with LDL-C and TG, which is consistent with the InSIDE assumption.

We investigated the effect of lipoprotein subfractions on CAD using multiple datasets, study designs and statistical methods. The MR estimates are overwhelming in agreement, which further strengthens our conclusions.

There has been a heated debate on the role of HDL in preventing CVD in recent years following the failure of several *CETP* trials (50–52). Observational epidemiology studies have long demonstrated strong inverse association between HDL-C and the risk of CAD or MI (53–55), but contradictory evidence was found in MR studies. In an influential study, Voight and collaborators found that genetic variants associated with HDL-C had varied associations with CAD and that all variants suggesting a significant protective effect of HDL-C on CAD also had pleiotropic effects on LDL cholesterol (LDL-C) or triglycerides (TG) (29). One single nucleotide polymorphism (SNP) in the *HNF4A* gene, when used as an instrumental variable, even suggested positive association of HDL-C with CAD. Another MR study found that HDL-C is negatively associated with CAD using 48 SNPs as instruments, but the association became statistically non-significant after restricting to the 19 SNPs that do not have pleiotropic association with LDL-C or TG (56). A similar finding was made in a subsequent study (31), where the negative effect of HDL-C on CAD found by conventional MR methods becomes statistically non-significant after using the "pleiotropy-robust" MR-Egger regression (48). A more recent study using the more powerful MR-RAPS found that the negative effect of HDL-C is statistically significant, although estimates of the magnitude of effect depend considerably on the strength of the instruments (32). To summarize, the failed *CETP* trials and previous MR studies have led to the broad conclusion that raising HDL-C may not causally reduce the risk of CAD, at least not in a uniform way. Our results for the HDL subfractions further support this conclusion, as their effects on CAD appear to be heterogeneous.

Our results may also be related to the HDL function hypothesis (57). Cholesterol efflux capacity, a measure of HDL function, has been documented as superior to HDL-C in predicting CVD risk (58,59). Recent epidemiologic studies found that HDL particle size is positively associated with cholesterol efflux capacity in post-menopausal women (60) and in an asymptomatic older cohort (61). However, mechanistic efflux studies showed that small HDL particles actually mediate more cholesterol efflux (62,63). A likely explanation of this seeming contradiction is that high concentrations of small HDL particles in the serum may mark a block in maturation of small HDL particles (61). This may also explain our finding that only the medium HDL traits have significant negative association with CAD in Mendelian randomization, as increased medium HDL may mark successful maturation of small HDL particles.

Our study should be viewed in the context of its limitations, in particular, the inherent limitations of the summary-data Mendelian randomization design. Any causal inference from non-experimental data

makes unverifiable assumptions, so does our study. Conventional MR studies assume the genetic variants are valid instrumental variables. The statistical methods we used, in particular MR-RAPS, make less stringent assumption---the causal inference is unbiased if, apart from a few instruments, most of the pleotropic effects satisfy the InSIDE assumption (47,48). The InSIDE assumption is unverifiable (64) but can be falsified (32). Figure 3 and scatterplots in the Online Supplement do not suggest evidence against the InSIDE assumption for medium HDL traits, but this does not completely eliminate the possibility that InSIDE is violated.

Our study did not adjust for other important risk factors such as body mass index, blood pressure, and smoking. Heterogeneous populations are used to obtain genetic associations with the exposures and the outcomes, which may introduce bias (65). Most of the genes strongly associated with the concentration of medium HDL particles are also associated with LDL-C and/or TG (Table 3). Although this does not necessarily bias the MR estimate (Figure 3), the lack of genetic variants exclusively associated with medium HDL particles means that medium HDL particles may only be a biomarker (instead of the causal mediator) in a mechanism that lowers CAD risk.

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Table 1 GWAS summary datasets used in this study.

Phenotype	Dataset Name	PubMed ID	Population	Sample size	Sample overlap with other datasets	URL to summary dataset
Traditional lipid traits	AGEN	28334899 (41)	Asian	69,414		https://blog.nus.edu.sg/agen/summary-statistics/
	GLGC	24097068 (40)	European	188,578	Kettunen, CARDIoGRAMplusC4D	http://csg.sph.umich.edu/abecasis/public/lipids2013/
Lipoprotein subfraction traits	Davis	29084231 (35)	Finnish	8,372		http://csg.sph.umich.edu/boehnke/public/metsim-2017-lipoproteins/
	Kettunen	27005778 (34)	European	24,925	GLGC, CARDIoGRAMplusC4D	http://www.computationalmedicine.fi/data#NMR_GWAS
Heart disease traits	CARDIoGRAMplusC4D (CAD)	26343387 (42)	Mostly European	185,000	GLGC, Kettunen	http://www.cardiogramplusc4d.org/data-downloads/
	CARDIoGRAMplusC4D + UK Biobank (CAD)	28714975 (43)	Mostly European			
	UK Biobank (MI)	Interim round 2 release (44)	European	360,420		http://www.nealelab.is/uk-biobank/

*Table 2 Estimated effects (in log odds ratio) of selected lipoprotein subfractions with CAD or MI. Significance level (p-value): . < 0.05, * < 0.001, ** < 0.0001 (Bonferroni correction: 0.05/82/6 = 0.0001). Full results can be found in Section D of the Online Supplement.*

Design						
	Traditional selection (univariate)	Subfraction selection (univariate)				Multivariate Mendelian randomization
Selection GWAS	GERA	Davis	Davis	Kettunen	Kettunen	GERA + DAVIS
Exposure GWAS	Davis	Kettunen	Kettunen	Davis	Davis	GLGC + Kettunen
OUTCOME GWAS	CARDIoGRAMplusC4D (CAD)	UK Biobank (MI)	UK BioBank (MI)	UK Biobank (MI)	UK Biobank (MI)	CARDIoGRAMplusC4D + UK Biobank (CAD)
Variants	All	All	p < 5e-8	All	p < 5e-8	p < 1e-4
Method	RAPS	RAPS	IVW	RAPS	IVW	RAPS (Multivariate)
VLDL traits						
TG	0.258 **			0.289 **	0.207 .	
VLDL-D	-0.099 .	-0.163 .	-0.083	-0.204 .	-0.083	-0.147 .
XS-VLDL-P	0.170 **	0.429 **	0.374 **	0.338 **	0.373 **	0.072
S-VLDL-P	0.226 **	0.359 **	0.266 .	0.271 .	0.331 .	-0.079
M-VLDL-P	0.250 **	0.293 *	0.322 *	0.269 **	0.268 *	-0.035
L-VLDL-P	0.268 **	0.219 .	0.332 .	0.255 .	0.247 .	-0.069
XL-VLDL-P	0.270 **	0.404 *	0.346	0.251 .	0.245 .	-0.196 .
XXL-VLDL-P	0.308 **	0.320 .	-0.120	0.227 .	0.006	-0.119
IDL and LDL traits						
LDL-C	0.523 **	0.435 **	0.416 **	0.464 **	0.422 **	0.320 **
ApoB	0.605 **	0.610 **	0.636 **	0.613 **	0.569 **	0.367 **
LDL-D	0.271	0.328 **	0.309 .	0.201 *	0.211 .	0.208 *
S-LDL-P	0.621 **	0.459 **	0.490 *	0.546 **	0.588 **	0.368 **
M-LDL-P	0.638 **	0.472 **	0.413 *	0.460 **	0.439 **	0.381 **
L-LDL-P	0.606 **	0.484 **	0.413 **	0.494 **	0.424 **	0.337 **
IDL-C	0.596 **	0.511 **	0.439 **	0.423 **	0.422 **	0.324 **
HDL Traits						
HDL-C	-0.117 **	-0.045	-0.082	-0.108 .	-0.015	-0.066
ApoA1	-0.119 .	0.075	0.001	-0.130	0.066	-0.06
HDL-D	-0.008	0.067	0.073	0.007	0.074	-0.002
S-HDL-L		-0.037	-0.033			-0.302 .
S-HDL-P	-0.265 .	-0.053	-0.033	-0.08	-0.115	-0.301 .
S-HDL-TG	0.354 **	0.351 **	0.334 *	0.283 *	0.286	0.306 **
M-HDL-C	-0.323 **	-0.460 **	-0.423 .	-0.434 **	-0.390 .	-0.250 .
M-HDL-P	-0.298 **	-0.565 **	-0.386	-0.307 **	-0.180	-0.255 .
L-HDL-P	-0.071 .	-0.083	0.009	-0.100 .	0.025	-0.017
XL-HDL-P	0.038	0.083	0.103	0.023	0.135	0.044

*Table 3 GWAS associations with HDL subfractions, traditional lipid traits and CAD of 10 SNPs that are significantly associated with M-HDL-P. Significance level (p-value): . < 0.05, * < 0.001, ** < 0.0001, *** < 5×10^{-8}.*

SNP	GENE	M-HDL-P	S-HDL-P	L-HDL-P	XL-HDL-P	HDL-C	LDL-C	TG	CAD
RS11208004	DOCK7	0.075 ***	0.039 **	0.015	-0.002	0.015 **	0.050 ***	0.069 ***	0.012
RS4846913	GALNT2	0.061 ***	0.000	0.062 ***	0.023 .	0.055 ***	-0.006	-0.044 ***	-0.025 .
RS2126259	LOC157273	0.082 ***	0.066 ***	0.063 **	0.025 .	0.075 ***	0.063 ***	-0.016 .	-0.004
RS2083637	LPL	0.058 ***	-0.001	0.092 ***	0.053 **	0.105 ***	-0.008	-0.108 ***	-0.047 **
RS10468017	ALDH1A2/LIPC	0.060 ***	-0.096 ***	0.209 ***	0.202 ***	0.118 ***	0.002	0.038 ***	0.013
RS247616	CETP	0.121 ***	0.058 ***	0.198 ***	0.129 ***	0.243 ***	-0.055 ***	-0.039 ***	-0.044 **
RS1943973	LIPG	0.108 ***	0.022	0.104 ***	0.078 ***	0.077 ***	0.024 **	0.009	-0.016
RS737337	DOCK6	0.087 ***	0.047 .	0.081 **	0.058 *	0.056 ***	0.007	-0.011	-0.038 .
RS769449	APOE	0.078 ***	-0.016	0.071 ***	-0.015	0.064 ***	-0.214 ***	-0.042 ***	-0.085 ***
RS7679	PCIF1/PLTP	0.071 ***	0.188 ***	-0.129 ***	-0.152 ***	-0.059 ***	0.009	0.051 ***	-0.025 .

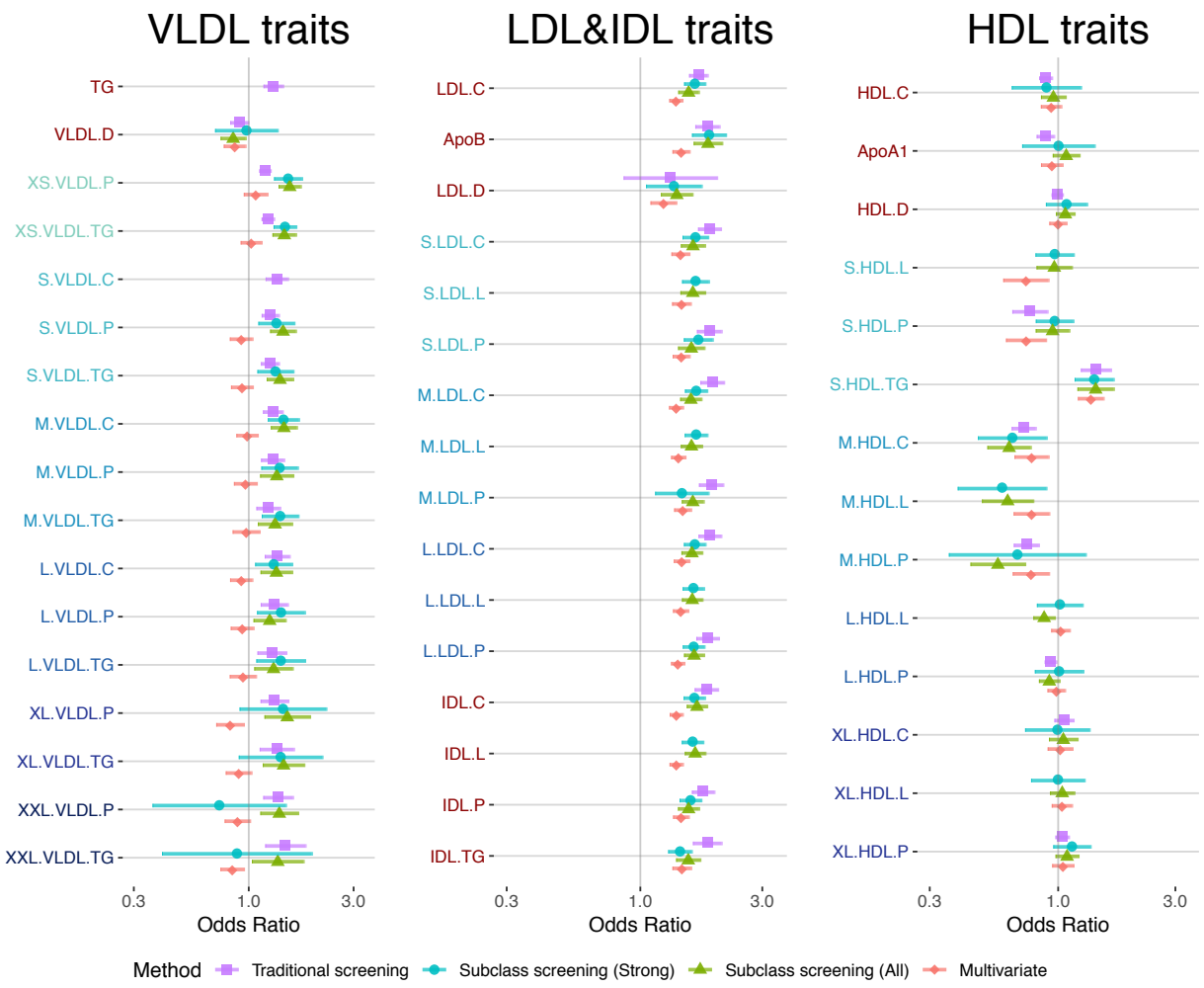

Figure 1 Estimated odds ratio of selected lipoprotein subfraction traits with CAD or MI using MR-RAPS and four different strategies of selecting instruments (see Online Supplement).

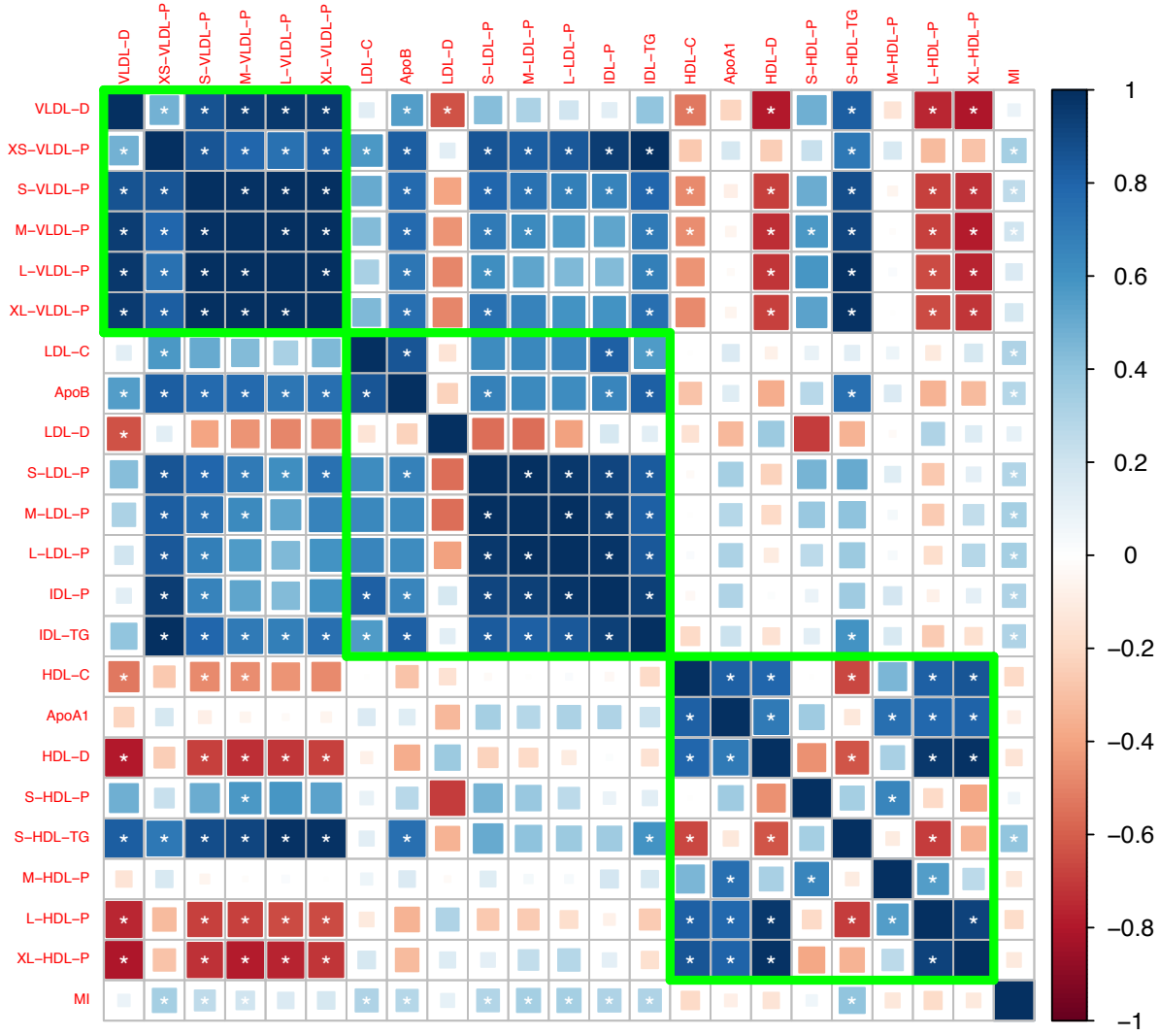

Figure 2 Genetic correlations of lipoprotein subfraction traits. White asterisk indicates the correlation is statistically significant after Bonferroni correction for multiple comparisons.

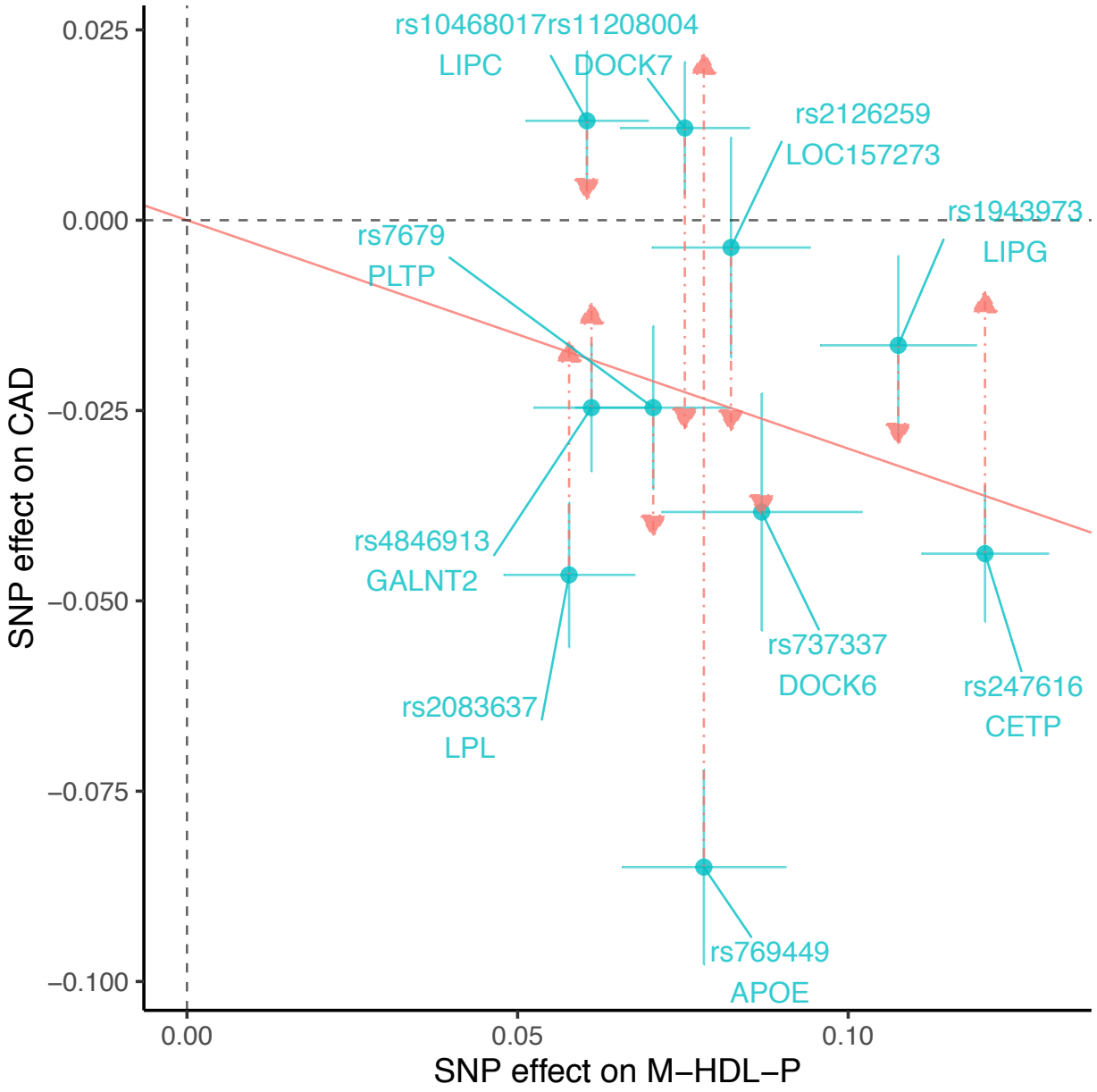

Figure 3 Blue: Scatter-plot of SNP effects on CAD versus M-HDL-P. Red: Adjusting the effects on CAD for LDL-C and TG. Slope of the red line across the origin is -0.3.

Supplement to "The role of lipoprotein subfractions in coronary artery disease: A Mendelian randomization study"

Contents

A Methods

A.1 Study design

A.1.1 Univeraite Mendelian randomization

For univariate Mendelian randomization we follow the three-sample summary-data design as described in [5]. This design requires three non-overlapping GWAS summary datasets which will be referred to as the selection, exposure, and outcome datasets. The selection and exposure datasets are two non-overlapping GWAS for the same (or similar) phenotypes. After obtaining the GWAS summary datasets, we preprocessed the data to select genetic instruments for the statistical analysis. We first removed SNPs that do not coappear in all three datasets. Then we used the remaining selection dataset to find independent SNPs (distance $\geq$ 10 megabase pairs, linkage disequilibrium $r^2 \leq 0.001$) that are most associated with the exposure phenotype. This was done in a greedy fashion using the linkage-disequilibrium (LD) clumping function in the PLINK software [3]. We created two sets of SNPs, one set with genome-wide significant association (p-value $\leq 5 \times 10^{-8}$) in the selection dataset, and one set without any restriction on the p-value. For this study, the former set usually consisted of a few (if the selection dataset is Kettunen or Davis) to a few dozen (if the selection dataset is GERA) SNPs, while the latter set typically contained about 1000 independent SNPs across the entire genome. We then obtained the associations of these selected SNPs with the exposure (some lipoprotein subfraction trait) and the outcome (CAD or MI) using the other two GWAS summary datasets.

Because we had multiple GWAS datasets for the lipoprotein subfractions and CAD/MI (Table 1), whenever possible we swapped the role of each GWAS in the three-sample Mendelian randomization design to obtain multiple statistical estimates. In total we conducted five different univariate Mendelian randomization studies which are summarized in Table A1. Some of the Mendelian randomization results (selected designs and phenotypes) are reported in the main paper. The full results are reported in Supplement D below.

Type	Selection	Exposure	Outcome	Reported in
Traditional selection (univariate)	GERA	Davis	CAD	Table 2; Figure 2 (all SNPs)
	GERA	Davis	UK Biobank	
	GERA	Kettunen	UK Biobank	
Subclass selection (univariate)	Kettunen	Davis	UK Biobank	Table 2 (significant and all SNPs)
	Davis	Kettunen	UK Biobank	Table 2, Figure 2 (significant and all SNPs)
Multivariate MR	GERA + Davis	GLGC + Kettunen	CAD + UK Biobank	Table 2, Figure 2
	GLGC + Kettunen	GERA + Davis	UK Biobank	

Table A1: List of all Mendelian randomization studies in this paper. The results of 4 studies are reported in the main paper. Note that the dataset name CARIDoGRAMplusC4D is abbreviated as CAD.

A.1.2 Multivariate Mendelian randomization

As described in **(author?)** [4], the multivariate Mendelian randomization was designed similarly to the univariate studies, where GWAS summary datasets were also used for one of the three puroposes: selecting SNPs, obtaining marginal effects of the selected SNPs on the exposure, obtaining marginal effects of the selected SNPs on the outcome. Some key distinctions are

- Both traditional lipid traits and subclass trait were used in the SNP selection. For example, in the multivariate Mendelian randomization study of M-HDL-P, the Davis GWAS (for M-HDL-P) and GERA GWAS (for HDL-C, LDL-C, TG) were used to select SNPs. Significance of each SNP was defined as the smallest of its four p-values (with M-HDL-P, HDL-C, LDL-C, TG), which were used as input to LD-clumping to select independent SNPs. For each lipoprotein subclass, we created one set of SNPs whose smallest p-value is less than 10^{-4}.

- The SNP-exposure association is now a vector of length 4 (instead of a scalar), containing its associations with the lipoprotein subclass under study (for example M-HDL-P) and HDL-C, LDL-C, TG.
- We no longer require the selection, exposure, outcome datasets to be completely non-overlapping. More specifically, we still require the selection dataset (in our 1st multivariate MR study, GERA and Davis) to be independent of the other datasets (GLGC, Kettunen, CARDIoGRAM, UK Biobank), but we don't require the exposure (GLGC + Kettunen) and outcome (CAD + UK Biobank) datasets to be non-overlapping. This means that the SNP-exposure and SNP-outcome associations are not independent because some samples are used to compute both associations. Fortunately, **(author?)** [4] shows that the correlation between the SNP-exposure and SNP-outcome marginal effect estimates does not depend on the SNPs and can be estimated using the GWAS summary data.

A.2 Statistical methods

For univariate Mendelian randomization, we applied three statistical methods: inverse-variance weighting (IVW), weighted median, and robust adjusted profile score (RAPS). For IVW and weighted median we used the implementation in the `TwoSampleMR` software package in R [2]. Because IVW and weighted median estimates are biased towards 0 when there are weak instruments [1, 6], we only use these methods with the set of SNPs that are genome-wide significant in the selection dataset. For RAPS we used the implementastion in the `mr.raps` package (`https://github.com/qingyuanzhao/mr.raps`), using the empirical partially Bayes estimator with Huber's loss function as described in [5]. RAPS does not suffer from weak instrument bias as long as the average instrument strength is not too weak [6], so we applied RAPS to both sets of SNPs.

For multivariate Mendelian randomization, we applied the multivariate extension to RAPS (aka GRAPPLE) that is briefly described below. For SNP j, we assume the estimated association with the K exposures $\hat{\boldsymbol{\gamma}}_j \in \mathbb{R}^K$ and the outcome $\hat{\Gamma}_j$ follow a multivariate normal distribution:

$$\begin{pmatrix} \hat{\Gamma}_j \\ \hat{\boldsymbol{\gamma}}_j \end{pmatrix} \sim \mathrm{N}\left(\begin{pmatrix} \Gamma_j \\ \boldsymbol{\gamma}_j \end{pmatrix}, \boldsymbol{S}_j \boldsymbol{\Sigma} \boldsymbol{S}_j \right), \ \boldsymbol{S}_j = \begin{pmatrix} \sigma_{Y_j} & & & \\ & \sigma_{X_{j1}} & & \\ & & \ddots & \\ & & & \sigma_{X_{jK}} \end{pmatrix},$$

where the mean vector $(\Gamma_j, \boldsymbol{\gamma}_j)$ is unknown, the diagonal matrix $\boldsymbol{S}_j$ contains the standard errors of the GWAS summary coefficients, and $\boldsymbol{\Sigma}$ is the correlation matrix due to sample-overlap of the GWAS that is shared between the SNPs. The setting considered in [6] assuming no sample overlap is a special case of this model with $K = 1$ and $\boldsymbol{\Sigma} = \boldsymbol{I}_2$. In the more general setting, we estimate $\boldsymbol{\Sigma}$ using sample correlation of the GWAS coefficients for the non-significant SNPs (e.g. p-value ≥ 0.5 in the selection GWAS). Let the estimate be $\hat{\boldsymbol{\Sigma}}$. We further assume the causal effect $\boldsymbol{\beta}$ (a vector because we have multiple exposures) satisfies the InSIDE assumption, $\alpha_j = \Gamma_j - \boldsymbol{\gamma}_j^T \boldsymbol{\beta} \perp \gamma_j$, for most SNPs j. The direct effect α_j is assumed to satisfy a random effects model, $\alpha_j \sim \mathrm{N}(0, \tau^2)$.

To estimate the causasl effect $\boldsymbol{\beta}$, define

$$t_j(\beta, \tau^2) = \frac{\hat{\Gamma}_j - \hat{\gamma}_j^T \beta}{\sqrt{\sigma_{Y_j}^2 + \beta^T \Sigma_{X_j} \beta - 2\beta^T \Sigma_{X_j Y_j} + \tau^2}} \tag{1}$$

where Σ_{X_j} is the variance of $\hat{\gamma}_j$ and $\Sigma_{X_j Y_j}$ is the covariance between $\hat{\gamma}_j$ and $\hat{\Gamma}_j$ in our model, replacing $\boldsymbol{\Sigma}$ with $\hat{\boldsymbol{\Sigma}}$. The GRAPPLE estimates $\boldsymbol{\beta}$ and τ^2 by solving the following estimating equations:

$$\frac{\partial}{\partial \boldsymbol{\beta}} \sum_{j=1}^{p} \rho(t_j(\boldsymbol{\beta}, \tau^2)) = 0,$$
$$\frac{1}{p} \sum_{j=1}^{p} \rho(t_j(\boldsymbol{\beta}, \tau^2)) = \delta,$$

where ρ is some robust loss function (we used Huber's loss function) and $\delta = \mathbb{E}[\rho(Z)]$ for $Z \sim \mathrm{N}(0, 1)$. Standard errors for $\boldsymbol{\beta}$ and τ^2 are computed using the delta method. More details about GRAPPLE can be found in a forthcoming paper [4].

A.3 Lipid and lipoprotein traits

A full list of lipid and lipoprotein traits used in this study can be found in Table A2.

Table A2: All 82 traits included in this study and whether they are measured in the Kettunen and Davis GWAS (NA means not available).

Trait	Description	Kettunen	Davis
VLDL traits			
TG	Total triglycerides	NA	
VLDL-D	VLDL diameter		
XS-VLDL-L	Total lipids in very small VLDL		NA
XS-VLDL-P	Concentration of very small VLDL particles		
XS-VLDL-PL	Phospholipids in very small VLDL		
XS-VLDL-TG	Triglycerides in very small VLDL		
S-VLDL-C	Total cholesterol in small VLDL	NA	
S-VLDL-FC	Free cholesterol in small VLDL		
S-VLDL-L	Total lipids in small VLDL		NA
S-VLDL-P	Concentration of small VLDL particles		
S-VLDL-PL	Phospholipids in small VLDL		
S-VLDL-TG	Triglycerides in small VLDL		
M-VLDL-C	Total cholesterol in medium VLDL		
M-VLDL-CE	Cholesterol esters in medium VLDL		
M-VLDL-FC	Free cholesterol in medium VLDL		
M-VLDL-L	Total lipids in medium VLDL		NA
M-VLDL-P	Concentration of medium VLDL particles		
M-VLDL-PL	Phospholipids in medium VLDL		
M-VLDL-TG	Triglycerides in medium VLDL		
L-VLDL-C	Total cholesterol in large VLDL		
L-VLDL-CE	Cholesterol esters in large VLDL		
L-VLDL-FC	Free cholesterol in large VLDL		
L-VLDL-L	Total lipids in large VLDL		NA
L-VLDL-P	Concentration of large VLDL particles		
L-VLDL-PL	Phospholipids in large VLDL		
L-VLDL-TG	Triglycerides in large VLDL		
XL-VLDL-L	Total lipids in very large VLDL		NA
XL-VLDL-P	Concentration of very large VLDL particles		
XL-VLDL-PL	Phospholipids in very large VLDL		
XL-VLDL-TG	Triglycerides in very large VLDL		
XXL-VLDL-L	Total lipids in chylomicrons and extremely very large VLDL		NA
XXL-VLDL-P	Concentration of chylomicrons and extremely very large VLDL particles		
XXL-VLDL-PL	Phospholipids in chylomicrons and extremely very large		
XXL-VLDL-TG	Triglycerides in chylomicrons and extremely very large		
LDL/IDL traits			
LDL-C	Total cholesterol in LDL		
ApoB	Apolipoprotein B		
LDL-D	LDL diameter		
S-LDL-C	Total cholesterol in small LDL		

Table A2: All 82 traits included in this study and whether they are measured in the Kettunen and Davis GWAS (NA means not available).

Trait	Description	Kettunen	Davis
S-LDL-L	Total lipids in small LDL		NA
S-LDL-P	Phospholipids in small LDL		
M-LDL-C	Total cholesterol in medium LDL		
M-LDL-CE	Cholesterol esters in medium LDL		
M-LDL-L	Total lipids in medium LDL		NA
M-LDL-P	Concentration of medium LDL particles		
M-LDL-PL	Phospholipids in medium LDL		
L-LDL-C	Total cholesterol in large LDL		
L-LDL-CE	Cholesterol esters in large LDL		
L-LDL-FC	Free cholesterol in large LDL		
L-LDL-L	Total lipids in large LDL		NA
L-LDL-P	Concentration of large LDL particles		
L-LDL-PL	Phospholipids in large LDL		
IDL-C	Total cholesterol in IDL		
IDL-FC	Free cholesterol in IDL		
IDL-L	Total lipids in IDL		NA
IDL-P	Concentration of IDL particles		
IDL-PL	Phospholipids in IDL		
IDL-TG	Triglycerides in IDL		
HDL traits			
HDL-C	Total cholesterol in HDL		
ApoA1	Apolipoprotein A1		
HDL-D	HDL diameter		
S-HDL-L	Total lipids in small HDL		NA
S-HDL-P	Concentration of small HDL particles		
S-HDL-TG	Triglycerides in small HDL		
M-HDL-C	Total cholesterol in medium HDL		
M-HDL-CE	Cholesterol esters in medium HDL		
M-HDL-FC	Free cholesterol in medium HDL		
M-HDL-L	Total lipids in medium HDL		NA
M-HDL-P	Concentration of medium HDL particles		
M-HDL-PL	Phospholipids in medium HDL		
L-HDL-C	Total cholesterol in large HDL		
L-HDL-CE	Cholesterol esters in large HDL		
L-HDL-FC	Free cholesterol in large HDL		
L-HDL-L	Total lipids in large HDL		NA
L-HDL-P	Concentration of large HDL particles		
L-HDL-PL	Phospholipids in large HDL		
XL-HDL-C	Total cholesterol in very large HDL		
XL-HDL-CE	Cholesterol esters in very large HDL		
XL-HDL-FC	Free cholesterol in very large HDL		
XL-HDL-L	Total lipids in very large HDL		NA
XL-HDL-P	Concentration of very large HDL particles		

Table A2: All 82 traits included in this study and whether they are measured in the Kettunen and Davis GWAS (NA means not available).

Trait	Description	Kettunen	Davis
XL-HDL-PL	Phospholipids in very large HDL		
XL-HDL-TG	Triglycerides in very large HDL		

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B SNPs associated with M-HDL-P and S-HDL-P

Table B3: SNPs associated with M-HDL-P.

SNP	Chr	Gene	S-HDL-P	M-HDL-P	L-HDL-P	XL-HDL-P	HDL-C	LDL-C	TG	CAD
rs11208004	1	DOCK7	0.039 **	0.075 ***	0.015	-0.002	0.015 **	0.050 ***	0.069 ***	0.012
rs4846913	1	GALNT2	0.000	0.061 ***	0.062 ***	0.023 .	0.055 ***	-0.006	-0.044 ***	-0.025 .
rs2126259	8	LOC157273	0.066 ***	0.082 ***	0.063 **	0.025 .	0.075 ***	0.063 ***	-0.016 .	-0.004
rs2083637	8	LPL	-0.001	0.058 ***	0.092 ***	0.053 **	0.105 ***	-0.008	-0.108 ***	-0.047 **
rs10468017	15	ALDH1A2/LIPC	-0.096 ***	0.060 ***	0.209 ***	0.202 ***	0.118 ***	0.002	0.038 ***	0.013
rs247616	16	CETP	0.058 ***	0.121 ***	0.198 ***	0.129 ***	0.243 ***	-0.055 ***	-0.039 ***	-0.044 **
rs1943973	18	LIPG	0.022	0.108 ***	0.104 ***	0.078 ***	0.077 ***	0.024 **	0.009	-0.016
rs737337	19	DOCK6	0.047 .	0.087 ***	0.081 **	0.058 *	0.056 ***	0.007	-0.011	-0.038 .
rs769449	19	APOE	-0.016	0.078 ***	0.071 ***	-0.015	0.064 ***	-0.214 ***	-0.042 ***	-0.085 ***
rs7679	20	PCIF1/PLTP	0.188 ***	0.071 ***	-0.129 ***	-0.152 ***	-0.059 ***	0.009	0.051 ***	-0.025 .

Table B4: SNPs associated with S-HDL-P.

SNP	Chr	Gene	S-HDL-P	M-HDL-P	L-HDL-P	XL-HDL-P	HDL-C	LDL-C	TG	CAD
rs780094	2	GCKR	0.074 ***	0.034 *	-0.04 **	-0.034 *	-0.011 .	0.021 **	0.110 ***	0.005
rs10935473	3	ST3GAL6-AS1	0.052 ***	0.014	-0.029 .	-0.031 *	-0.009 .	0.003	0.005	-0.007
rs4936363	11	SIK3	0.064 ***	0.046 **	0.019	0.006	0.034 **	0.018 .	0.043 ***	0.022
rs2043085	15	ALDH1A2/LIPC	0.092 ***	-0.056 ***	-0.202 ***	-0.197 ***	-0.106 ***	-0.003	-0.033 ***	-0.008
rs1800588	15	ALDH1A2/LIPC	0.106 ***	-0.050 **	-0.215 ***	-0.212 ***	-0.114 ***	0.002	-0.044 ***	-0.015
rs289714	16	CETP	0.077 ***	0.122 ***	0.162 ***	0.102 ***	0.214 ***	-0.036 ***	-0.035 ***	-0.012
rs6065904	20	PLTP	0.171 ***	0.060 ***	-0.127 ***	-0.149 ***	-0.052 ***	0.008	0.040 ***	-0.022 .

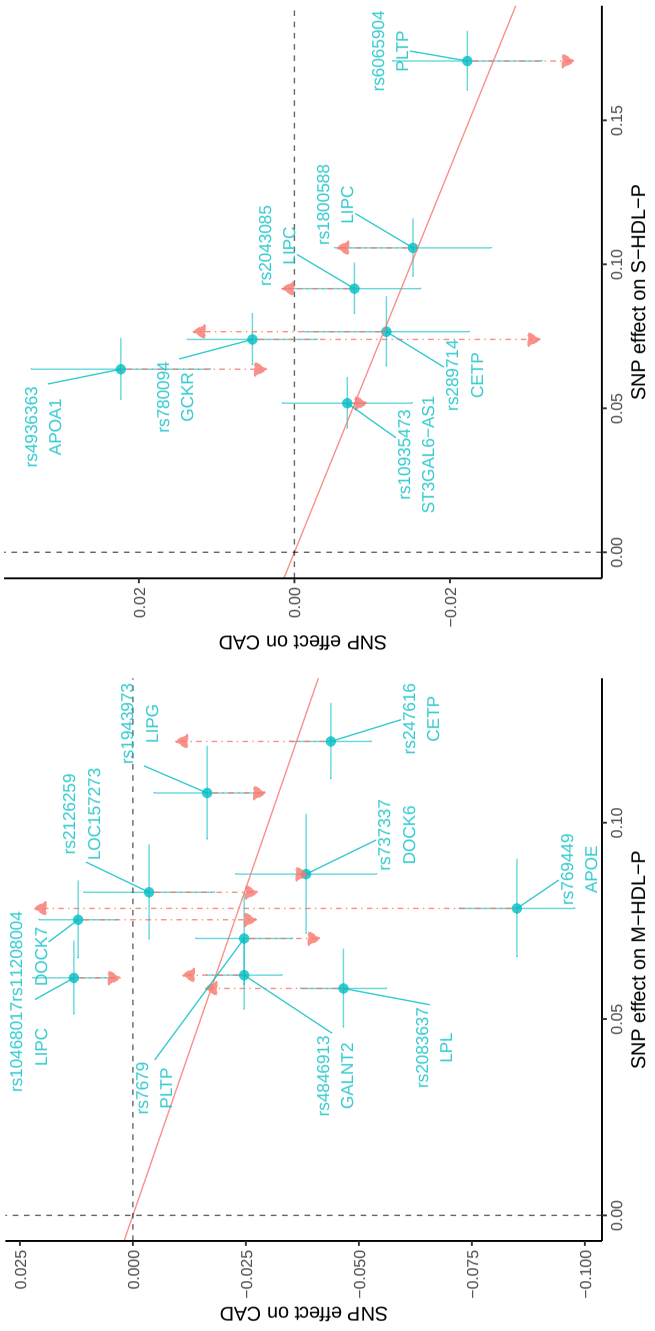

Figure B1: Scatter-plots for M-HDL-P (left) and S-HDL-P (right).

C Genetic Correlations

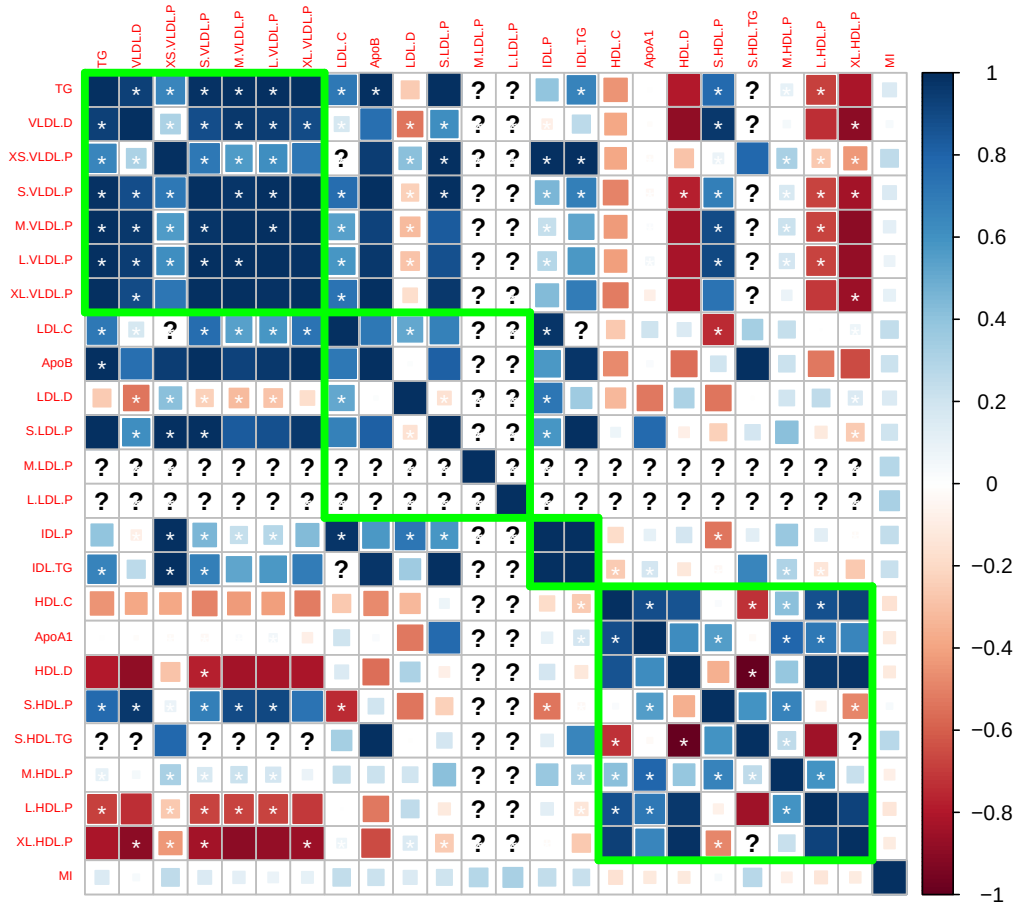

Figure C2: Genetic correlations computed using the Davis et al. (2017) GWAS summary dataset.

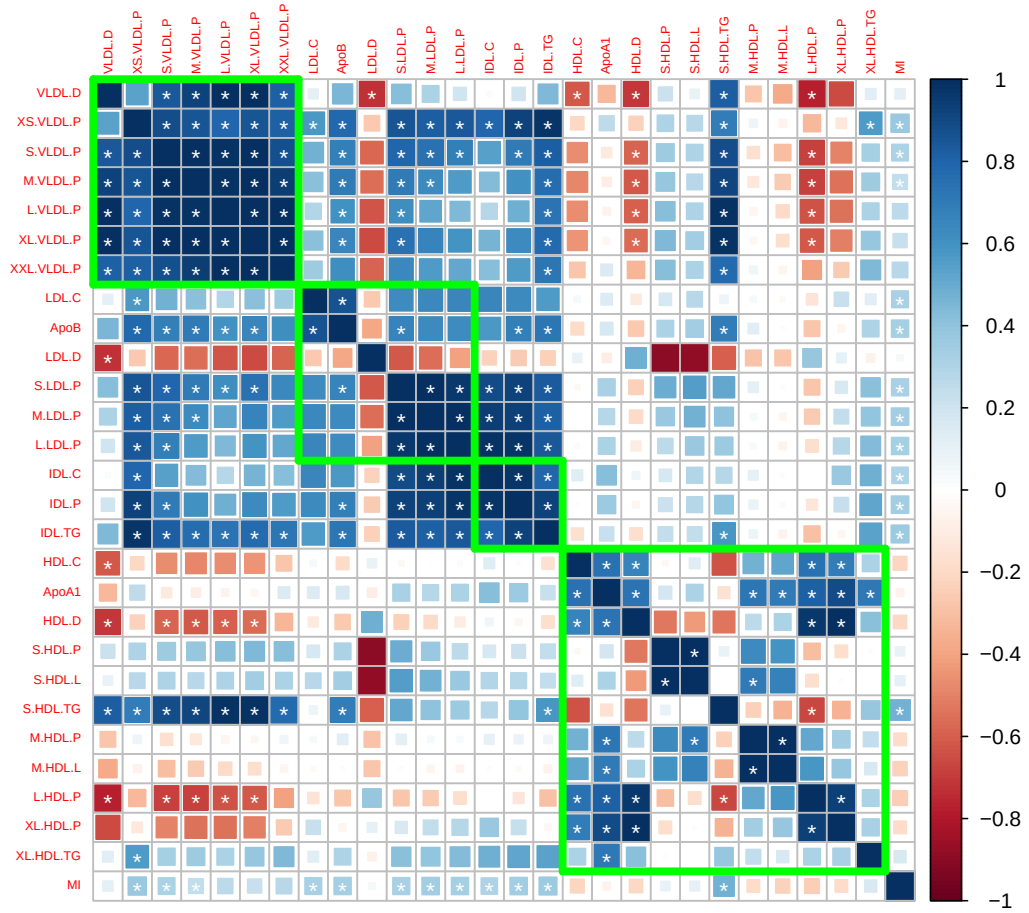

Figure C3: Genetic correlations computed using the Kettunen et al. (2016) GWAS summary dataset.

D Full Mendelian randomization results

See Tables D5 to D7 below. Red indicates p-value is significant (at level 0.05) after Bonferroni correction for all the results in the corresponding table and blue indicates p-value ≤ 0.05

Table D5: Mendelian randomization results using all SNPs and robust adjusted profile score (RAPS).

	Method: RAPS + Strong SNPs							
Screening	GERA	GERA	GERA	GLGC	Davis	Kettunen	Kettunen + GLGC	GERA + Davis
Exposure	Davis	Davis	Kettunen	Davis	Kettunen	Davis	GERA + Davis	GLGC + Kettunen
Outcome	CAD	UKB	UKB	UKB	UKB	UKB	UKB	CAD + UKB
VLDL traits								
TG	.258 (.053)	.296 (.075)	NA	.262 (.06)	NA	.289 (.068)	.112 (.073)	NA
VLDL.D	-.099 (.049)	.028 (.074)	.072 (.073)	.116 (.065)	-.163 (.067)	-.204 (.071)	-.056 (.092)	-.147 (.058)
XS.VLDL.L	NA	NA	.368 (.064)	NA	.429 (.059)	NA	NA	.076 (.064)
XS.VLDL.P	.17 (.031)	.26 (.048)	.367 (.065)	.248 (.047)	.429 (.06)	.338 (.056)	.218 (.071)	.072 (.064)
XS.VLDL.PL	.191 (.034)	.284 (.055)	.386 (.069)	.278 (.052)	.449 (.049)	.435 (.049)	.253 (.099)	.183 (.087)
XS.VLDL.TG	.201 (.034)	.3 (.053)	.388 (.068)	.283 (.046)	.372 (.063)	.326 (.055)	.167 (.066)	.025 (.056)
S.VLDL.C	.294 (.06)	.343 (.076)	NA	.322 (.063)	NA	.424 (.094)	.051 (.11)	NA
S.VLDL.FC	.243 (.051)	.303 (.068)	.389 (.079)	.286 (.056)	.489 (.071)	.416 (.074)	.095 (.089)	-.096 (.075)
S.VLDL.L	NA	NA	.356 (.075)	NA	.376 (.072)	NA	NA	-.088 (.064)
S.VLDL.P	.226 (.047)	.288 (.068)	.343 (.074)	.261 (.054)	.359 (.069)	.271 (.094)	.081 (.081)	-.079 (.061)
S.VLDL.PL	.228 (.047)	.294 (.067)	.372 (.074)	.273 (.054)	.365 (.066)	.336 (.063)	.091 (.084)	.017 (.071)
S.VLDL.TG	.223 (.049)	.283 (.071)	.323 (.073)	.25 (.055)	.327 (.071)	.275 (.067)	.061 (.079)	-.071 (.059)
M.VLDL.C	.253 (.053)	.304 (.078)	.327 (.074)	.276 (.06)	.368 (.07)	.312 (.079)	.045 (.08)	-.017 (.057)
M.VLDL.CE	.248 (.051)	.309 (.074)	.344 (.077)	.285 (.058)	.369 (.073)	.295 (.069)	.106 (.08)	-.044 (.058)
M.VLDL.FC	.245 (.058)	.283 (.082)	.31 (.076)	.259 (.063)	.341 (.069)	.341 (.068)	.033 (.083)	-.042 (.063)
M.VLDL.L	NA	NA	.311 (.079)	NA	.358 (.078)	NA	NA	-.035 (.06)
M.VLDL.P	.25 (.062)	.282 (.083)	.305 (.081)	.247 (.065)	.293 (.089)	.269 (.065)	.041 (.084)	-.035 (.061)
M.VLDL.PL	.248 (.056)	.295 (.077)	.318 (.075)	.259 (.06)	.351 (.071)	.31 (.063)	.041 (.08)	-.029 (.061)
M.VLDL.TG	.205 (.064)	.248 (.087)	.3 (.082)	.224 (.067)	.275 (.092)	.246 (.074)	.006 (.085)	-.027 (.072)
L.VLDL.C	.299 (.067)	.304 (.1)	.297 (.081)	.291 (.077)	.289 (.085)	.317 (.077)	.051 (.09)	-.079 (.06)
L.VLDL.CE	.247 (.061)	.282 (.088)	.282 (.082)	.282 (.072)	.285 (.082)	.3 (.112)	.114 (.093)	-.095 (.063)
L.VLDL.FC	.316 (.076)	.294 (.108)	.311 (.083)	.287 (.081)	.351 (.087)	.298 (.078)	.051 (.092)	-.099 (.06)
L.VLDL.L	NA	NA	.36 (.096)	NA	.32 (.102)	NA	NA	-.084 (.066)

Table D5: Mendelian randomization results using all SNPs and robust adjusted profile score (RAPS).

	Method: RAPS + Strong SNPs							
Screening	GERA	GERA	GERA	GLGC	Davis	Kettunen	Kettunen + GLGC	GERA + Davis
Exposure	Davis	Davis	Kettunen	Davis	Kettunen	Davis	GERA + Davis	GLGC + Kettunen
Outcome	CAD	UKB	UKB	UKB	UKB	UKB	UKB	CAD + UKB
L.VLDL.P	.268 (.073)	.287 (.103)	.281 (.085)	.262 (.075)	.219 (.086)	.255 (.082)	.031 (.093)	-.069 (.061)
L.VLDL.PL	.322 (.071)	.318 (.102)	.346 (.089)	.283 (.077)	.397 (.101)	.351 (.076)	.003 (.092)	-.062 (.067)
L.VLDL.TG	.243 (.077)	.238 (.104)	.332 (.094)	.246 (.08)	.26 (.103)	.324 (.082)	.028 (.101)	-.061 (.07)
XL.VLDL.L	NA	NA	.289 (.098)	NA	.435 (.14)	NA	NA	-.122 (.07)
XL.VLDL.P	.27 (.074)	.262 (.099)	.281 (.093)	.279 (.084)	.404 (.122)	.251 (.084)	.024 (.104)	-.196 (.074)
XL.VLDL.PL	.446 (.09)	.344 (.13)	.31 (.093)	.361 (.118)	.375 (.12)	.408 (.102)	.042 (.112)	-.14 (.068)
XL.VLDL.TG	.294 (.092)	.229 (.109)	.261 (.094)	.284 (.095)	.365 (.111)	.319 (.093)	.022 (.113)	-.106 (.069)
XXL.VLDL.L	NA	NA	.397 (.108)	NA	.312 (.108)	NA	NA	-.164 (.079)
XXL.VLDL.P	.308 (.08)	.327 (.096)	.378 (.097)	.297 (.088)	.32 (.101)	.227 (.073)	.147 (.091)	-.119 (.068)
XXL.VLDL.PL	.338 (.091)	.346 (.103)	.342 (.103)	.351 (.103)	.282 (.114)	.317 (.086)	.094 (.105)	-.149 (.069)
XXL.VLDL.TG	.384 (.108)	.374 (.124)	.348 (.1)	.433 (.121)	.304 (.138)	.359 (.18)	.119 (.115)	-.173 (.063)
IDL/LDL traits								
LDL.C	.523 (.043)	.512 (.053)	.514 (.042)	.473 (.055)	.435 (.048)	.464 (.048)	.358 (.056)	.32 (.031)
ApoB	.605 (.056)	.55 (.062)	.551 (.052)	.543 (.069)	.61 (.066)	.613 (.06)	.45 (.082)	.367 (.04)
LDL.D	.271 (.215)	.452 (.299)	2.064 (.233)	.831 (.684)	.328 (.073)	.201 (.055)	.375 (.09)	.208 (.06)
S.LDL.C	.624 (.053)	.589 (.061)	.539 (.048)	.537 (.067)	.474 (.056)	.48 (.05)	.341 (.064)	.361 (.042)
S.LDL.L	NA	NA	.561 (.047)	NA	.473 (.057)	NA	NA	.371 (.043)
S.LDL.P	.621 (.057)	.581 (.065)	.56 (.049)	.558 (.073)	.459 (.061)	.546 (.063)	.351 (.069)	.368 (.039)
M.LDL.C	.648 (.055)	.607 (.062)	.545 (.044)	.545 (.068)	.455 (.049)	.557 (.054)	.347 (.063)	.322 (.033)
M.LDL.CE	.643 (.056)	.601 (.062)	.564 (.042)	.545 (.069)	.467 (.05)	.55 (.055)	.347 (.064)	.337 (.032)
M.LDL.L	NA	NA	.559 (.042)	NA	.461 (.049)	NA	NA	.342 (.033)
M.LDL.P	.638 (.056)	.597 (.062)	.557 (.043)	.54 (.069)	.472 (.051)	.46 (.05)	.345 (.063)	.381 (.039)
M.LDL.PL	.658 (.063)	.605 (.067)	.556 (.047)	.571 (.077)	.506 (.053)	.559 (.057)	.388 (.075)	.38 (.042)
L.LDL.C	.627 (.053)	.577 (.059)	.515 (.042)	.504 (.063)	.465 (.048)	.488 (.052)	.35 (.059)	.372 (.036)
L.LDL.CE	.638 (.055)	.589 (.06)	.555 (.041)	.514 (.065)	.463 (.049)	.493 (.054)	.379 (.064)	.372 (.036)
L.LDL.FC	.609 (.051)	.557 (.057)	.503 (.041)	.491 (.06)	.468 (.047)	.457 (.052)	.361 (.057)	.34 (.03)
L.LDL.L	NA	NA	.543 (.04)	NA	.468 (.047)	NA	NA	.363 (.035)
L.LDL.P	.606 (.052)	.559 (.058)	.545 (.041)	.49 (.062)	.484 (.046)	.494 (.048)	.364 (.059)	.337 (.031)

Table D5: Mendelian randomization results using all SNPs and robust adjusted profile score (RAPS).

	Method: RAPS + Strong SNPs							
Screening	GERA	GERA	GERA	GLGC	Davis	Kettunen	Kettunen + GLGC	GERA + Davis
Exposure	Davis	Davis	Kettunen	Davis	Kettunen	Davis	GERA + Davis	GLGC + Kettunen
Outcome	CAD	UKB	UKB	UKB	UKB	UKB	UKB	CAD + UKB
L.LDL.PL	.61 (.053)	.558 (.058)	.515 (.043)	.492 (.063)	.528 (.048)	.502 (.052)	.364 (.062)	.354 (.032)
IDL.C	.596 (.054)	.55 (.059)	.562 (.042)	.481 (.064)	.511 (.047)	.423 (.051)	.425 (.06)	.324 (.03)
IDL.FC	.586 (.054)	.539 (.059)	.525 (.044)	.494 (.063)	.44 (.044)	.402 (.05)	.444 (.058)	.337 (.03)
IDL.L	NA	NA	.57 (.043)	NA	.494 (.048)	NA	NA	.323 (.031)
IDL.P	.566 (.052)	.536 (.059)	.575 (.044)	.488 (.065)	.434 (.049)	.412 (.051)	.426 (.06)	.366 (.036)
IDL.PL	.583 (.052)	.533 (.058)	.532 (.045)	.489 (.064)	.471 (.047)	.396 (.05)	.416 (.059)	.326 (.031)
IDL.TG	.603 (.066)	.595 (.075)	.658 (.063)	.567 (.085)	.432 (.056)	.315 (.053)	.382 (.07)	.374 (.043)
HDL traits								
HDL.C	-.117 (.031)	-.199 (.045)	-.136 (.055)	-.317 (.052)	-.045 (.059)	-.108 (.05)	-.106 (.06)	-.066 (.049)
ApoA1	-.119 (.042)	-.193 (.06)	.023 (.058)	-.264 (.071)	.075 (.064)	-.13 (.068)	-.153 (.073)	-.06 (.052)
HDL.D	-.008 (.027)	-.124 (.041)	.004 (.046)	-.092 (.048)	.067 (.045)	.007 (.041)	-.003 (.06)	-.002 (.041)
S.HDL.L	NA	NA	-.098 (.095)	NA	-.037 (.085)	NA	NA	-.302 (.108)
S.HDL.P	-.265 (.084)	-.362 (.113)	-.13 (.092)	-.317 (.119)	-.053 (.081)	-.08 (.094)	-.61 (.148)	-.301 (.096)
S.HDL.TG	.354 (.072)	.386 (.088)	.65 (.089)	.475 (.097)	.351 (.087)	.283 (.073)	-.195 (.208)	.306 (.062)
M.HDL.C	-.323 (.058)	-.43 (.079)	-.364 (.085)	-.376 (.091)	-.46 (.104)	-.434 (.075)	-.337 (.119)	-.25 (.082)
M.HDL.CE	-.333 (.058)	-.458 (.078)	-.372 (.09)	-.385 (.087)	-.542 (.105)	-.443 (.071)	-.345 (.12)	-.235 (.092)
M.HDL.FC	-.275 (.065)	-.319 (.08)	-.262 (.083)	-.313 (.092)	-.313 (.094)	-.409 (.082)	-.288 (.111)	-.205 (.076)
M.HDL.L	NA	NA	-.311 (.095)	NA	-.474 (.123)	NA	NA	-.25 (.085)
M.HDL.P	-.298 (.06)	-.394 (.086)	-.273 (.101)	-.373 (.1)	-.565 (.131)	-.307 (.079)	-.321 (.107)	-.255 (.087)
M.HDL.PL	-.265 (.058)	-.346 (.083)	-.25 (.09)	-.335 (.096)	-.358 (.104)	-.3 (.072)	-.304 (.114)	-.247 (.078)
L.HDL.C	-.067 (.03)	-.144 (.044)	-.139 (.051)	-.144 (.05)	-.147 (.052)	-.049 (.045)	-.067 (.065)	.014 (.047)
L.HDL.CE	-.063 (.03)	-.144 (.044)	-.116 (.051)	-.149 (.051)	-.134 (.051)	-.094 (.047)	-.007 (.064)	.011 (.047)
L.HDL.FC	-.082 (.03)	-.144 (.045)	-.114 (.053)	-.128 (.053)	-.13 (.051)	-.03 (.047)	-.028 (.076)	.001 (.047)
L.HDL.L	NA	NA	-.108 (.05)	NA	-.132 (.052)	NA	NA	.022 (.045)
L.HDL.P	-.071 (.028)	-.146 (.042)	-.111 (.05)	-.13 (.049)	-.083 (.05)	-.1 (.043)	-.042 (.063)	-.017 (.042)
L.HDL.PL	-.087 (.029)	-.161 (.043)	-.141 (.051)	-.142 (.051)	-.105 (.053)	-.092 (.044)	-.064 (.071)	.02 (.046)
XL.HDL.C	.055 (.046)	-.013 (.068)	.11 (.066)	.064 (.073)	.048 (.069)	.112 (.068)	.044 (.096)	.018 (.06)
XL.HDL.CE	.064 (.044)	.006 (.066)	.129 (.066)	.08 (.07)	.057 (.068)	.046 (.075)	.043 (.091)	.006 (.058)

Table D5: Mendelian randomization results using all SNPs and robust adjusted profile score (RAPS).

	Method: RAPS + Strong SNPs							
Screening	GERA	GERA	GERA	GLGC	Davis	Kettunen	Kettunen + GLGC	GERA + Davis
Exposure	Davis	Davis	Kettunen	Davis	Kettunen	Davis	GERA + Davis	GLGC + Kettunen
Outcome	CAD	UKB	UKB	UKB	UKB	UKB	UKB	CAD + UKB
XL.HDL.FC	.009 (.039)	-.05 (.059)	.066 (.058)	-.026 (.067)	.102 (.06)	.049 (.066)	.01 (.088)	.037 (.051)
XL.HDL.L	NA	NA	.073 (.055)	NA	.038 (.058)	NA	NA	.035 (.049)
XL.HDL.P	.038 (.033)	-.022 (.049)	.112 (.057)	.017 (.056)	.083 (.055)	.023 (.057)	.013 (.071)	.044 (.051)
XL.HDL.PL	.029 (.031)	-.031 (.046)	.037 (.05)	.005 (.055)	.038 (.052)	.013 (.046)	.023 (.071)	.047 (.044)
XL.HDL.TG	.092 (.027)	.112 (.041)	.14 (.047)	.135 (.047)	.191 (.042)	.136 (.039)	.048 (.055)	.037 (.043)

Table D6: Mendelian randomization results using genome-wide significant SNPs and inverse variance weighted (IVW) estimator.

	Method: IVW + Significant SNPs					
Selection	GERA	GERA	GERA	GLGC	Davis	Kettunen
Exposure	Davis	Davis	Kettunen	Davis	Kettunen	Davis
Outcome	CAD	UKB	UKB	UKB	UKB	UKB
VLDL traits						
TG	.184 (.051)	.278 (.076)	NA	.309 (.074)	NA	.207 (.064)
VLDL-D	.044 (.06)	.052 (.09)	.038 (.102)	.118 (.091)	-.083 (.16)	-.083 (.138)
XS-VLDL-L	NA	NA	.353 (.08)	NA	.372 (.083)	NA
XS-VLDL-P	.162 (.04)	.256 (.059)	.352 (.081)	.273 (.063)	.374 (.084)	.373 (.095)
XS-VLDL-PL	.165 (.046)	.262 (.069)	.37 (.088)	.27 (.075)	.443 (.048)	.401 (.07)
XS-VLDL-TG	.179 (.041)	.277 (.061)	.362 (.082)	.288 (.062)	.335 (.076)	.314 (.08)
S-VLDL-C	.237 (.053)	.343 (.08)	NA	.339 (.083)	NA	.443 (.116)
S-VLDL-FC	.21 (.05)	.307 (.076)	.344 (.098)	.314 (.076)	.262 (.122)	.397 (.116)
S-VLDL-L	NA	NA	.318 (.095)	NA	.27 (.106)	NA
S-VLDL-P	.188 (.049)	.274 (.074)	.311 (.093)	.29 (.072)	.266 (.103)	.331 (.142)
S-VLDL-PL	.198 (.048)	.291 (.072)	.342 (.091)	.3 (.072)	.281 (.089)	.331 (.125)
S-VLDL-TG	.174 (.051)	.255 (.076)	.296 (.094)	.28 (.073)	.261 (.102)	.262 (.093)
M-VLDL-C	.188 (.053)	.265 (.08)	.305 (.096)	.287 (.077)	.361 (.078)	.32 (.134)
M-VLDL-CE	.203 (.051)	.285 (.077)	.32 (.098)	.295 (.076)	.264 (.094)	.291 (.125)
M-VLDL-FC	.165 (.056)	.233 (.084)	.292 (.098)	.27 (.08)	.3 (.084)	.303 (.104)
M-VLDL-L	NA	NA	.265 (.104)	NA	.357 (.096)	NA
M-VLDL-P	.153 (.056)	.214 (.085)	.276 (.104)	.258 (.081)	.322 (.092)	.268 (.074)
M-VLDL-PL	.163 (.054)	.23 (.082)	.296 (.097)	.266 (.078)	.302 (.084)	.289 (.095)
M-VLDL-TG	.14 (.058)	.196 (.087)	.268 (.107)	.247 (.083)	.327 (.093)	.245 (.091)
L-VLDL-C	.177 (.06)	.24 (.091)	.288 (.106)	.286 (.089)	.108 (.223)	.31 (.084)
L-VLDL-CE	.178 (.057)	.245 (.087)	.262 (.105)	.279 (.086)	.182 (.187)	.299 (.077)
L-VLDL-FC	.176 (.063)	.242 (.094)	.295 (.108)	.298 (.091)	.321 (.101)	.314 (.082)
L-VLDL-L	NA	NA	.291 (.119)	NA	.125 (.232)	NA
L-VLDL-P	.164 (.062)	.227 (.093)	.269 (.108)	.275 (.09)	.332 (.127)	.247 (.076)
L-VLDL-PL	.173 (.061)	.23 (.092)	.308 (.115)	.284 (.088)	.32 (.127)	.302 (.079)
L-VLDL-TG	.149 (.063)	.202 (.095)	.268 (.118)	.267 (.092)	.33 (.131)	.302 (.08)
XL-VLDL-L	NA	NA	.263 (.123)	NA	.365 (.286)	NA

Table D6: Mendelian randomization results using genome-wide significant SNPs and inverse variance weighted (IVW) estimator.

	Method: IVW + Significant SNPs					
Selection	GERA	GERA	GERA	GLGC	Davis	Kettunen
Exposure	Davis	Davis	Kettunen	Davis	Kettunen	Davis
Outcome	CAD	UKB	UKB	UKB	UKB	UKB
XL-VLDL-P	.149 (.063)	.206 (.095)	.247 (.122)	.268 (.096)	.346 (.28)	.245 (.077)
XL-VLDL-PL	.176 (.067)	.243 (.101)	.292 (.119)	.323 (.101)	.333 (.265)	.344 (.133)
XL-VLDL-TG	.151 (.066)	.205 (.1)	.241 (.12)	.282 (.1)	.323 (.272)	.249 (.081)
XXL-VLDL-L	NA	NA	.356 (.127)	NA	-.165 (.425)	NA
XXL-VLDL-P	.228 (.067)	.35 (.099)	.372 (.119)	.376 (.098)	-.12 (.389)	.006 (.153)
XXL-VLDL-PL	.211 (.07)	.31 (.105)	.275 (.125)	.399 (.107)	-.145 (.395)	.071 (.191)
XXL-VLDL-TG	.221 (.067)	.3 (.102)	.292 (.126)	.415 (.104)	.09 (.36)	.349 (.303)
IDL/LDL traits						
LDL-C	.427 (.049)	.431 (.054)	.409 (.077)	.409 (.054)	.416 (.099)	.422 (.063)
ApoB	.506 (.058)	.525 (.065)	.474 (.093)	.473 (.064)	.636 (.092)	.569 (.071)
LDL-D	.217 (.151)	.423 (.161)	1.121 (.178)	.271 (.143)	.309 (.126)	.211 (.081)
S-LDL-C	.481 (.056)	.467 (.063)	.445 (.087)	.438 (.063)	.44 (.128)	.436 (.076)
S-LDL-L	NA	NA	.44 (.09)	NA	.456 (.132)	NA
S-LDL-P	.501 (.059)	.494 (.068)	.449 (.093)	.472 (.067)	.49 (.139)	.588 (.097)
M-LDL-C	.475 (.057)	.457 (.064)	.426 (.08)	.427 (.064)	.418 (.111)	.436 (.087)
M-LDL-CE	.485 (.058)	.47 (.065)	.432 (.078)	.436 (.064)	.43 (.107)	.444 (.085)
M-LDL-L	NA	NA	.43 (.08)	NA	.43 (.11)	NA
M-LDL-P	.479 (.057)	.465 (.064)	.437 (.081)	.44 (.064)	.413 (.122)	.439 (.093)
M-LDL-PL	.5 (.063)	.49 (.071)	.437 (.087)	.464 (.07)	.443 (.132)	.497 (.099)
L-LDL-C	.449 (.055)	.436 (.061)	.432 (.076)	.411 (.061)	.409 (.106)	.417 (.076)
L-LDL-CE	.464 (.056)	.451 (.062)	.426 (.075)	.422 (.062)	.416 (.102)	.433 (.077)
L-LDL-FC	.425 (.054)	.411 (.059)	.424 (.074)	.393 (.059)	.387 (.105)	.394 (.078)
L-LDL-L	NA	NA	.427 (.074)	NA	.407 (.103)	NA
L-LDL-P	.448 (.054)	.442 (.06)	.435 (.075)	.421 (.059)	.413 (.104)	.424 (.075)
L-LDL-PL	.444 (.056)	.438 (.061)	.441 (.078)	.423 (.061)	.42 (.109)	.429 (.076)
IDL-C	.447 (.055)	.455 (.059)	.451 (.075)	.433 (.06)	.439 (.085)	.422 (.07)
IDL-FC	.429 (.055)	.439 (.059)	.468 (.075)	.414 (.059)	.431 (.081)	.402 (.074)
IDL-L	NA	NA	.467 (.075)	NA	.445 (.085)	NA

Table D6: Mendelian randomization results using genome-wide significant SNPs and inverse variance weighted (IVW) estimator.

	Method: IVW + Significant SNPs					
Selection	GERA	GERA	GERA	GLGC	Davis	Kettunen
Exposure	Davis	Davis	Kettunen	Davis	Kettunen	Davis
Outcome	CAD	UKB	UKB	UKB	UKB	UKB
IDL-P	.443 (.055)	.467 (.06)	.48 (.077)	.45 (.059)	.446 (.088)	.426 (.071)
IDL-PL	.429 (.055)	.443 (.059)	.473 (.078)	.427 (.059)	.435 (.092)	.407 (.069)
IDL-TG	.461 (.07)	.518 (.076)	.625 (.098)	.494 (.073)	.342 (.085)	.34 (.123)
HDL traits						
HDL-C	-.085 (.044)	-.156 (.057)	-.146 (.085)	-.195 (.06)	-.082 (.159)	-.015 (.109)
ApoA1	-.072 (.054)	-.155 (.071)	-.036 (.09)	-.194 (.074)	.001 (.192)	.066 (.158)
HDL-D	-.027 (.042)	-.071 (.058)	-.052 (.073)	-.092 (.063)	.073 (.098)	.074 (.074)
S-HDL-L	NA	NA	-.064 (.148)	NA	-.033 (.092)	NA
S-HDL-P	-.117 (.087)	-.172 (.116)	-.13 (.146)	-.298 (.117)	-.033 (.09)	-.115 (.174)
S-HDL-TG	.224 (.063)	.317 (.082)	.496 (.107)	.344 (.085)	.334 (.096)	.286 (.17)
M-HDL-C	-.214 (.062)	-.327 (.078)	-.48 (.111)	-.39 (.079)	-.423 (.175)	-.39 (.159)
M-HDL-CE	-.227 (.062)	-.338 (.077)	-.497 (.111)	-.4 (.078)	-.435 (.194)	-.341 (.238)
M-HDL-FC	-.158 (.065)	-.272 (.084)	-.341 (.117)	-.337 (.085)	-.288 (.218)	-.278 (.144)
M-HDL-L	NA	NA	-.436 (.125)	NA	-.514 (.223)	NA
M-HDL-P	-.172 (.066)	-.292 (.087)	-.414 (.132)	-.361 (.089)	-.386 (.307)	-.18 (.118)
M-HDL-PL	-.161 (.064)	-.275 (.085)	-.38 (.126)	-.345 (.087)	-.419 (.301)	-.2 (.099)
L-HDL-C	-.047 (.044)	-.097 (.059)	-.124 (.08)	-.133 (.063)	.022 (.106)	.021 (.105)
L-HDL-CE	-.049 (.044)	-.098 (.059)	-.12 (.079)	-.137 (.063)	.023 (.112)	.004 (.106)
L-HDL-FC	-.044 (.046)	-.094 (.062)	-.106 (.082)	-.127 (.067)	.038 (.103)	.017 (.109)
L-HDL-L	NA	NA	-.106 (.077)	NA	.034 (.102)	NA
L-HDL-P	-.045 (.043)	-.097 (.058)	-.102 (.077)	-.125 (.063)	.009 (.111)	.025 (.11)
L-HDL-PL	-.054 (.044)	-.11 (.06)	-.115 (.079)	-.14 (.064)	.006 (.115)	.016 (.115)
XL-HDL-C	.03 (.06)	-.012 (.084)	.014 (.099)	-.05 (.088)	-.015 (.165)	.161 (.101)
XL-HDL-CE	.03 (.059)	-.009 (.081)	.025 (.098)	-.042 (.086)	-.001 (.166)	.221 (.107)
XL-HDL-FC	-.003 (.056)	-.05 (.076)	-.001 (.089)	-.077 (.081)	.072 (.11)	.057 (.092)
XL-HDL-L	NA	NA	.001 (.085)	NA	-.009 (.138)	NA
XL-HDL-P	.015 (.049)	-.021 (.067)	.013 (.088)	-.042 (.071)	.103 (.1)	.135 (.093)
XL-HDL-PL	0 (.047)	-.037 (.065)	-.026 (.079)	-.055 (.069)	.081 (.088)	.071 (.069)

Table D6: Mendelian randomization results using genome-wide significant SNPs and inverse variance weighted (IVW) estimator.

	Method: IVW + Significant SNPs					
Selection	GERA	GERA	GERA	GLGC	Davis	Kettunen
Exposure	Davis	Davis	Kettunen	Davis	Kettunen	Davis
Outcome	CAD	UKB	UKB	UKB	UKB	UKB
XL-HDL-TG	.086 (.041)	.103 (.059)	.14 (.075)	.13 (.063)	.165 (.043)	.126 (.051)

Table D7: Mendelian randomization results using genome-wide significant SNPs and the weighted median estimator.

	Method: Weighted median + Significant SNPs					
Selection	GERA	GERA	GERA	GLGC	Davis	Kettunen
Exposure	Davis	Davis	Kettunen	Davis	Kettunen	Davis
Outcome	CAD	UKB	UKB	UKB	UKB	UKB
VLDL traits						
TG	.042 (.055)	.191 (.072)	NA	.228 (.069)	NA	.195 (.077)
VLDL-D	-.098 (.052)	.039 (.095)	.057 (.11)	.058 (.093)	-.107 (.099)	-.052 (.115)
XS-VLDL-L	NA	NA	.312 (.076)	NA	.393 (.078)	NA
XS-VLDL-P	.101 (.037)	.23 (.052)	.303 (.079)	.229 (.052)	.409 (.08)	.253 (.059)
XS-VLDL-PL	.096 (.039)	.242 (.059)	.352 (.087)	.228 (.06)	.422 (.065)	.319 (.062)
XS-VLDL-TG	.125 (.041)	.266 (.057)	.287 (.079)	.221 (.056)	.361 (.084)	.306 (.069)
S-VLDL-C	.187 (.059)	.232 (.075)	NA	.256 (.074)	NA	.303 (.094)
S-VLDL-FC	.152 (.057)	.207 (.069)	.289 (.093)	.227 (.069)	.316 (.109)	.279 (.077)
S-VLDL-L	NA	NA	.282 (.083)	NA	.306 (.099)	NA
S-VLDL-P	.131 (.057)	.202 (.069)	.275 (.085)	.221 (.062)	.291 (.093)	.226 (.078)
S-VLDL-PL	.137 (.053)	.205 (.067)	.283 (.083)	.218 (.062)	.305 (.092)	.263 (.075)
S-VLDL-TG	.112 (.057)	.204 (.067)	.216 (.088)	.229 (.064)	.267 (.099)	.244 (.073)
M-VLDL-C	.12 (.058)	.2 (.07)	.255 (.088)	.213 (.066)	.303 (.099)	.224 (.081)
M-VLDL-CE	.144 (.054)	.207 (.071)	.262 (.087)	.207 (.068)	.301 (.098)	.209 (.072)
M-VLDL-FC	.081 (.058)	.188 (.074)	.221 (.087)	.218 (.068)	.272 (.102)	.231 (.08)
M-VLDL-L	NA	NA	.227 (.095)	NA	.275 (.109)	NA
M-VLDL-P	.047 (.06)	.191 (.072)	.221 (.096)	.226 (.069)	.31 (.104)	.257 (.079)
M-VLDL-PL	.103 (.056)	.197 (.071)	.228 (.089)	.217 (.064)	.29 (.104)	.231 (.078)
M-VLDL-TG	-.005 (.06)	.199 (.075)	.224 (.089)	.222 (.068)	.318 (.113)	.233 (.085)
L-VLDL-C	.109 (.068)	.2 (.078)	.237 (.093)	.231 (.075)	.242 (.122)	.262 (.088)
L-VLDL-CE	.147 (.063)	.211 (.079)	.249 (.09)	.253 (.073)	.281 (.11)	.286 (.081)
L-VLDL-FC	.045 (.065)	.199 (.085)	.225 (.093)	.224 (.077)	.252 (.125)	.228 (.089)
L-VLDL-L	NA	NA	.243 (.102)	NA	.261 (.122)	NA
L-VLDL-P	.041 (.064)	.209 (.082)	.224 (.092)	.21 (.079)	.289 (.122)	.223 (.086)
L-VLDL-PL	.08 (.063)	.201 (.08)	.244 (.101)	.224 (.077)	.278 (.123)	.247 (.092)
L-VLDL-TG	-.008 (.061)	.215 (.084)	.225 (.103)	.161 (.077)	.286 (.13)	.277 (.093)
XL-VLDL-L	NA	NA	.262 (.111)	NA	NA	NA

Table D7: Mendelian randomization results using genome-wide significant SNPs and the weighted median estimator.

	Method: Weighted median + Significant SNPs					
Selection	GERA	GERA	GERA	GLGC	Davis	Kettunen
Exposure	Davis	Davis	Kettunen	Davis	Kettunen	Davis
Outcome	CAD	UKB	UKB	UKB	UKB	UKB
XL-VLDL-P	-.026 (.063)	.207 (.091)	.289 (.102)	.192 (.088)	NA	.209 (.101)
XL-VLDL-PL	-.006 (.067)	.197 (.094)	.253 (.094)	.213 (.088)	NA	.24 (.101)
XL-VLDL-TG	-.026 (.064)	.214 (.092)	.229 (.102)	.191 (.088)	NA	.212 (.099)
XXL-VLDL-L	NA	NA	.316 (.114)	NA	-.156 (.22)	NA
XXL-VLDL-P	.091 (.071)	.236 (.089)	.267 (.1)	.263 (.088)	-.104 (.173)	.185 (.098)
XXL-VLDL-PL	.153 (.082)	.283 (.096)	.267 (.11)	.332 (.095)	-.139 (.178)	.126 (.124)
XXL-VLDL-TG	.126 (.078)	.266 (.096)	.244 (.108)	.339 (.097)	.227 (.171)	.23 (.123)
IDL/LDL traits						
LDL-C	.263 (.053)	.307 (.066)	.274 (.05)	.297 (.063)	.435 (.072)	.431 (.067)
ApoB	.365 (.073)	.472 (.078)	.381 (.063)	.375 (.081)	.624 (.08)	.565 (.094)
LDL-D	.306 (.09)	.413 (.157)	.467 (.163)	.271 (.142)	.294 (.075)	.193 (.06)
S-LDL-C	.271 (.058)	.342 (.073)	.343 (.056)	.273 (.068)	.498 (.08)	.274 (.083)
S-LDL-L	NA	NA	.354 (.061)	NA	.449 (.081)	NA
S-LDL-P	.355 (.063)	.366 (.078)	.397 (.069)	.329 (.08)	.49 (.089)	.581 (.098)
M-LDL-C	.283 (.055)	.313 (.073)	.299 (.05)	.244 (.07)	.474 (.074)	.297 (.074)
M-LDL-CE	.27 (.055)	.333 (.077)	.299 (.051)	.255 (.071)	.437 (.081)	.311 (.077)
M-LDL-L	NA	NA	.303 (.053)	NA	.432 (.079)	NA
M-LDL-P	.251 (.057)	.32 (.071)	.309 (.054)	.278 (.07)	.409 (.072)	.325 (.078)
M-LDL-PL	.343 (.063)	.337 (.081)	.316 (.055)	.318 (.078)	.457 (.074)	.353 (.085)
L-LDL-C	.251 (.052)	.29 (.067)	.303 (.048)	.231 (.063)	.45 (.075)	.309 (.071)
L-LDL-CE	.251 (.054)	.32 (.068)	.293 (.052)	.241 (.066)	.481 (.074)	.322 (.077)
L-LDL-FC	.251 (.048)	.214 (.061)	.301 (.049)	.214 (.062)	.427 (.068)	.289 (.065)
L-LDL-L	NA	NA	.289 (.051)	NA	.412 (.07)	NA
L-LDL-P	.281 (.053)	.321 (.067)	.29 (.053)	.244 (.066)	.42 (.072)	.351 (.072)
L-LDL-PL	.286 (.05)	.32 (.067)	.313 (.052)	.298 (.065)	.413 (.074)	.35 (.076)
IDL-C	.283 (.056)	.349 (.068)	.315 (.053)	.313 (.07)	.51 (.072)	.383 (.068)
IDL-FC	.283 (.053)	.334 (.066)	.337 (.053)	.314 (.065)	.422 (.067)	.367 (.064)
IDL-L	NA	NA	.329 (.056)	NA	.494 (.069)	NA

Table D7: Mendelian randomization results using genome-wide significant SNPs and the weighted median estimator.

	Method: Weighted median + Significant SNPs					
Selection	GERA	GERA	GERA	GLGC	Davis	Kettunen
Exposure	Davis	Davis	Kettunen	Davis	Kettunen	Davis
Outcome	CAD	UKB	UKB	UKB	UKB	UKB
IDL-P	.331 (.06)	.44 (.067)	.343 (.056)	.371 (.069)	.463 (.074)	.328 (.068)
IDL-PL	.265 (.055)	.332 (.066)	.344 (.056)	.316 (.066)	.451 (.072)	.359 (.066)
IDL-TG	.233 (.067)	.371 (.086)	.605 (.078)	.337 (.085)	.315 (.082)	.215 (.057)
HDL traits						
HDL-C	-.017 (.04)	-.167 (.058)	-.17 (.072)	-.167 (.058)	-.096 (.077)	-.085 (.07)
ApoA1	.094 (.049)	-.06 (.076)	-.069 (.087)	-.167 (.07)	.005 (.083)	-.051 (.121)
HDL-D	.079 (.034)	.062 (.061)	.102 (.064)	.088 (.061)	.099 (.061)	.096 (.058)
S-HDL-L	NA	NA	-.174 (.113)	NA	NA	NA
S-HDL-P	-.173 (.069)	.018 (.106)	-.171 (.109)	-.235 (.113)	NA	-.049 (.108)
S-HDL-TG	.157 (.061)	.238 (.085)	.312 (.105)	.228 (.086)	.327 (.105)	.229 (.076)
M-HDL-C	-.169 (.054)	-.236 (.082)	-.264 (.097)	-.241 (.077)	-.392 (.098)	-.266 (.084)
M-HDL-CE	-.166 (.053)	-.23 (.08)	-.271 (.099)	-.238 (.075)	-.394 (.103)	-.23 (.085)
M-HDL-FC	-.166 (.055)	-.254 (.086)	-.281 (.098)	-.282 (.087)	-.28 (.102)	-.22 (.1)
M-HDL-L	NA	NA	-.296 (.113)	NA	-.448 (.122)	NA
M-HDL-P	-.157 (.056)	-.199 (.09)	-.298 (.112)	-.231 (.086)	-.291 (.136)	-.165 (.131)
M-HDL-PL	-.143 (.058)	-.183 (.088)	-.285 (.108)	-.183 (.085)	-.321 (.114)	-.203 (.12)
L-HDL-C	.086 (.037)	-.009 (.066)	.031 (.083)	-.032 (.08)	.003 (.09)	.006 (.068)
L-HDL-CE	.086 (.038)	-.011 (.067)	.075 (.077)	-.037 (.076)	.015 (.091)	-.006 (.068)
L-HDL-FC	.09 (.039)	-.005 (.067)	.079 (.081)	-.019 (.076)	.041 (.078)	.027 (.074)
L-HDL-L	NA	NA	.074 (.077)	NA	.068 (.084)	NA
L-HDL-P	.081 (.036)	.046 (.062)	.075 (.074)	-.01 (.066)	.066 (.07)	.078 (.064)
L-HDL-PL	.084 (.039)	0 (.067)	.051 (.082)	-.021 (.071)	.054 (.075)	.074 (.071)
XL-HDL-C	.163 (.047)	.122 (.091)	.136 (.087)	.132 (.09)	.02 (.098)	.161 (.096)
XL-HDL-CE	.139 (.044)	.106 (.088)	.122 (.09)	.148 (.085)	.038 (.091)	.336 (.092)
XL-HDL-FC	.135 (.048)	.065 (.079)	.133 (.081)	.027 (.077)	.159 (.079)	.052 (.086)
XL-HDL-L	NA	NA	.119 (.075)	NA	.023 (.078)	NA
XL-HDL-P	.115 (.035)	.087 (.07)	.12 (.073)	.129 (.067)	.16 (.071)	.15 (.073)
XL-HDL-PL	.101 (.037)	.064 (.07)	.11 (.072)	.121 (.069)	.141 (.069)	.088 (.065)

Table D7: Mendelian randomization results using genome-wide significant SNPs and the weighted median estimator.

	Method: Weighted median + Significant SNPs					
Selection	GERA	GERA	GERA	GLGC	Davis	Kettunen
Exposure	Davis	Davis	Kettunen	Davis	Kettunen	Davis
Outcome	CAD	UKB	UKB	UKB	UKB	UKB
XL-HDL-TG	.074 (.027)	.107 (.047)	.126 (.051)	.118 (.042)	.156 (.05)	.114 (.045)

E Scatter-plots of marginal SNP effects for selected subfractions

This section of the Supplement reports the scatter-plots of marginal SNP effects on CAD/MI versus marginal effects on selected lipoprotein subfractions. Additional results can be found in Online Supplement 2.

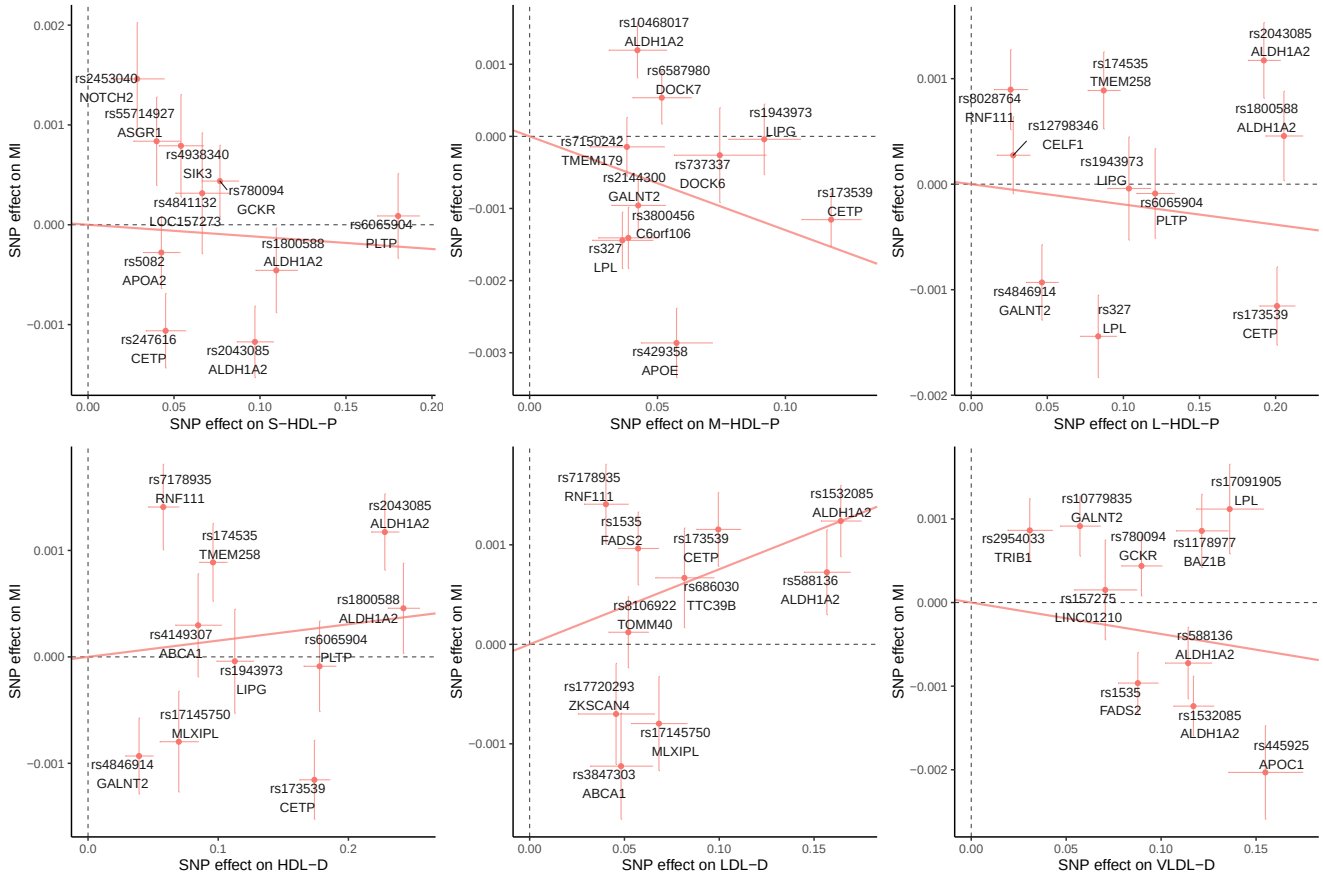

Figure E4: Selection: Davis; Exposure: Kettunen; Outcome: UK Biobank.

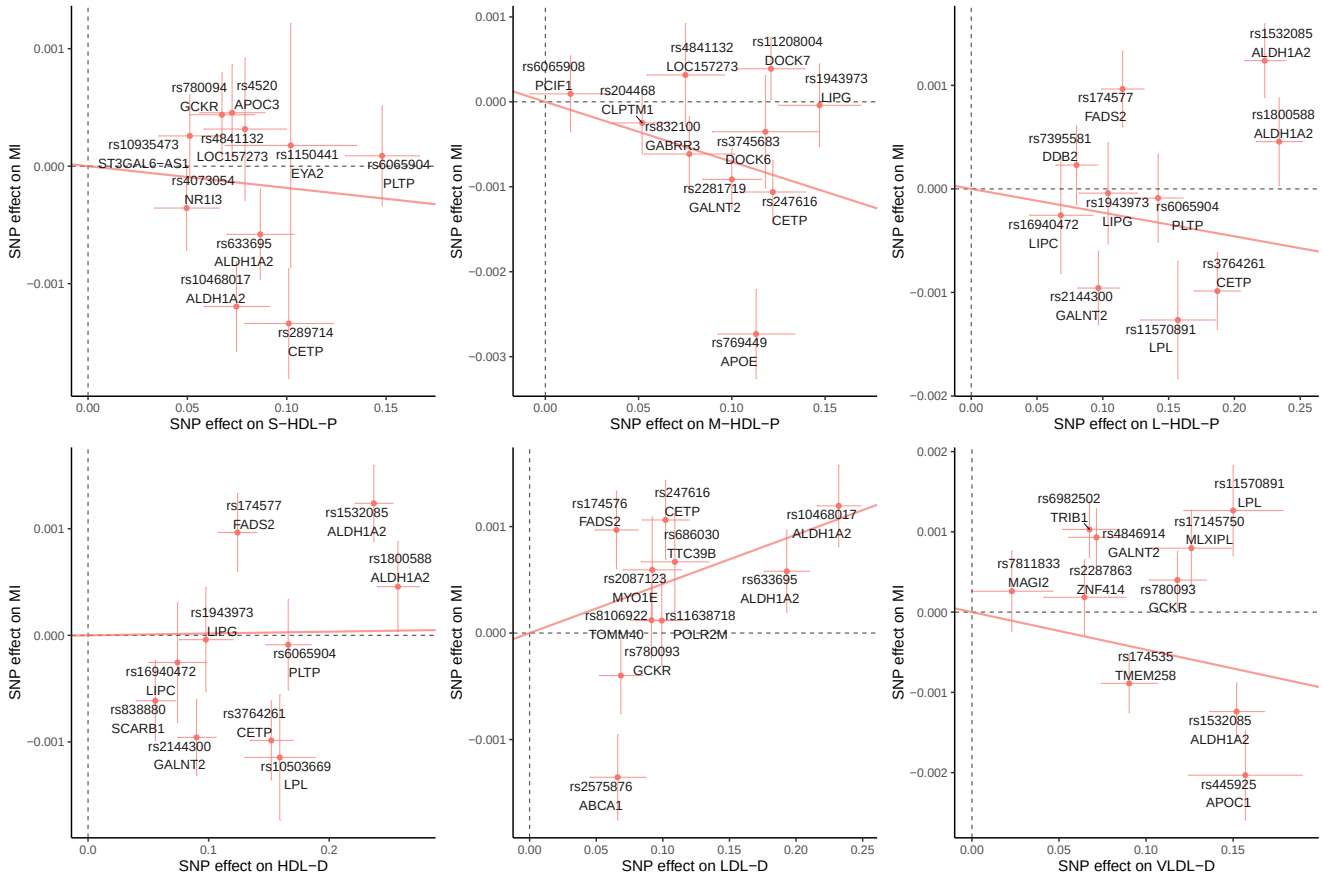

Figure E5: Selection: Davis; Exposure: Kettunen; Outcome: UK Biobank.

F Diagnostic plots of RAPS for HDL-C and M-HDL-P

Zhao et al. (2019) described two diagnostic plots for the modeling assumptions used by (univariate) RAPS. Here we report these plots for HDL-C and M-HDL-P in different studies.

F.1 HDL-C

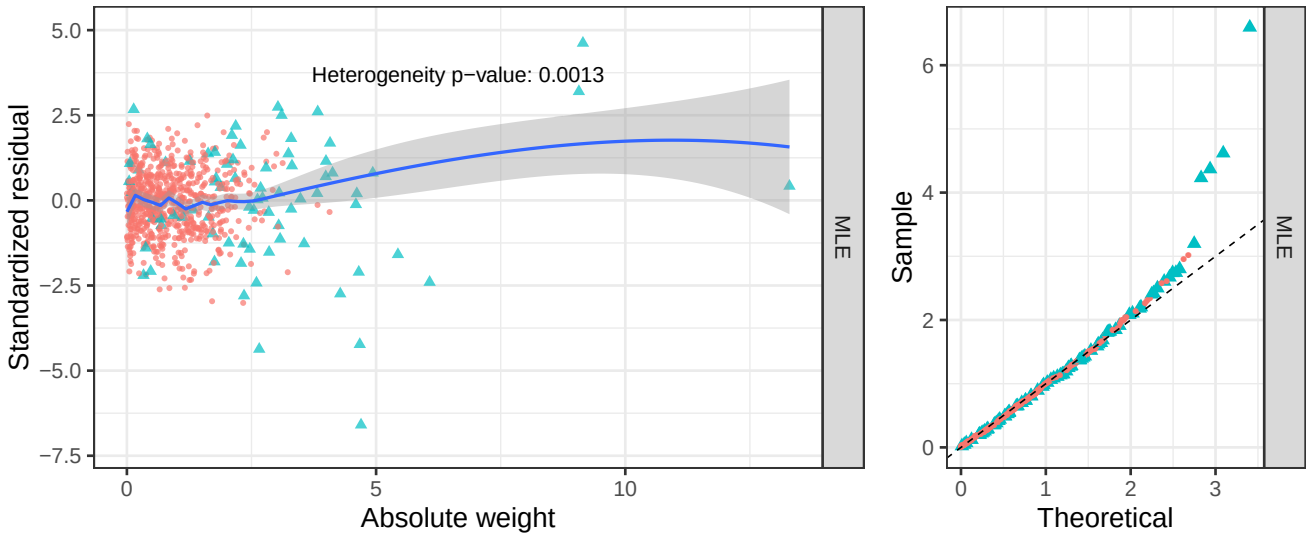

Figure F6: Selection: GERA; Exposure: Davis; Outcome: CAD.

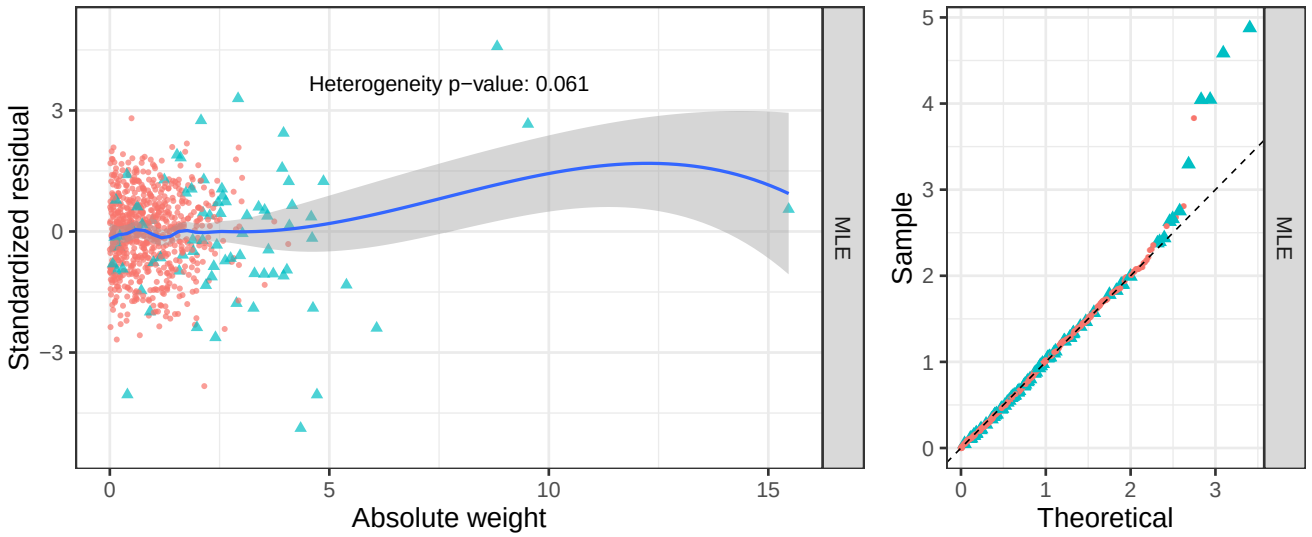

Figure F7: Selection: GERA; Exposure: Davis; Outcome: UKB.

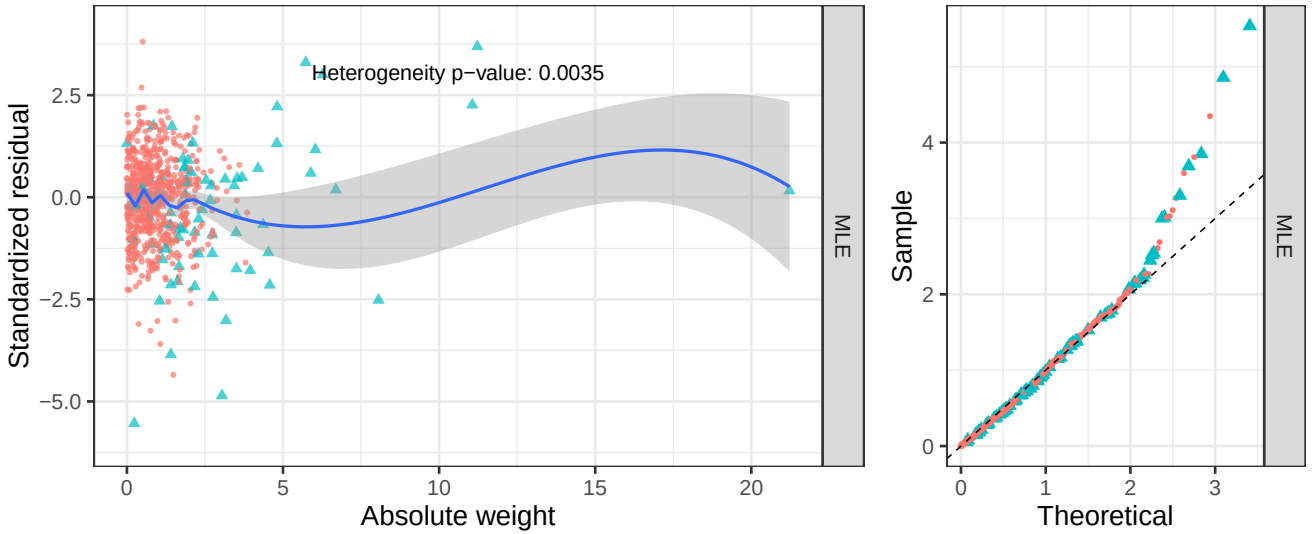

Figure F8: Selection: GERA; Exposure: Kettunen; Outcome: UKB.

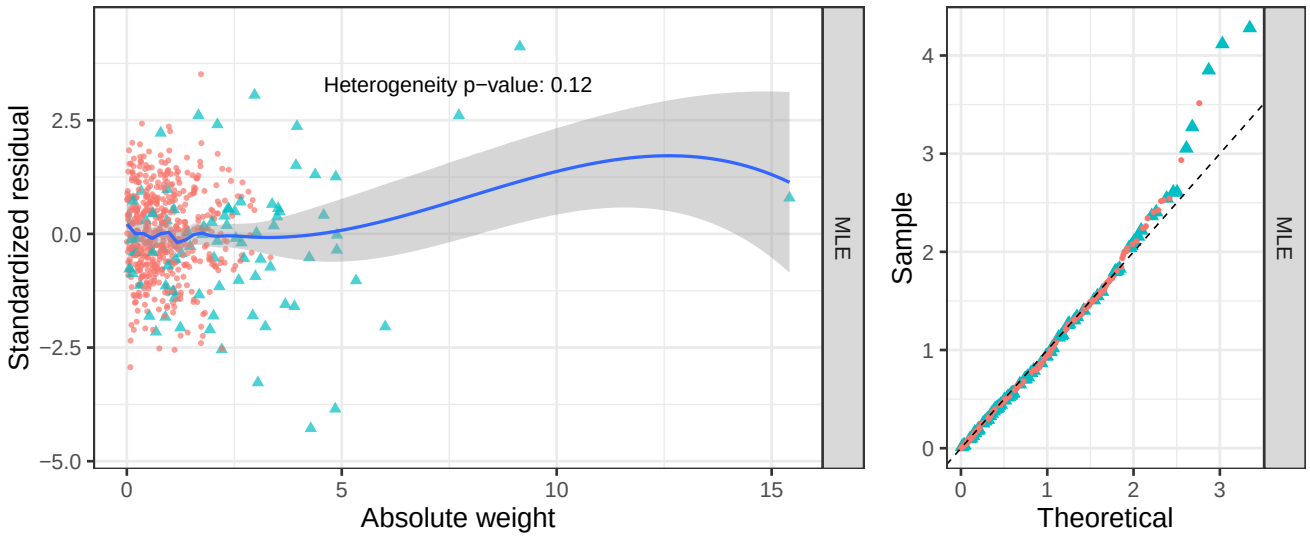

Figure F9: Selection: GLGC; Exposure: Davis; Outcome: UKB.

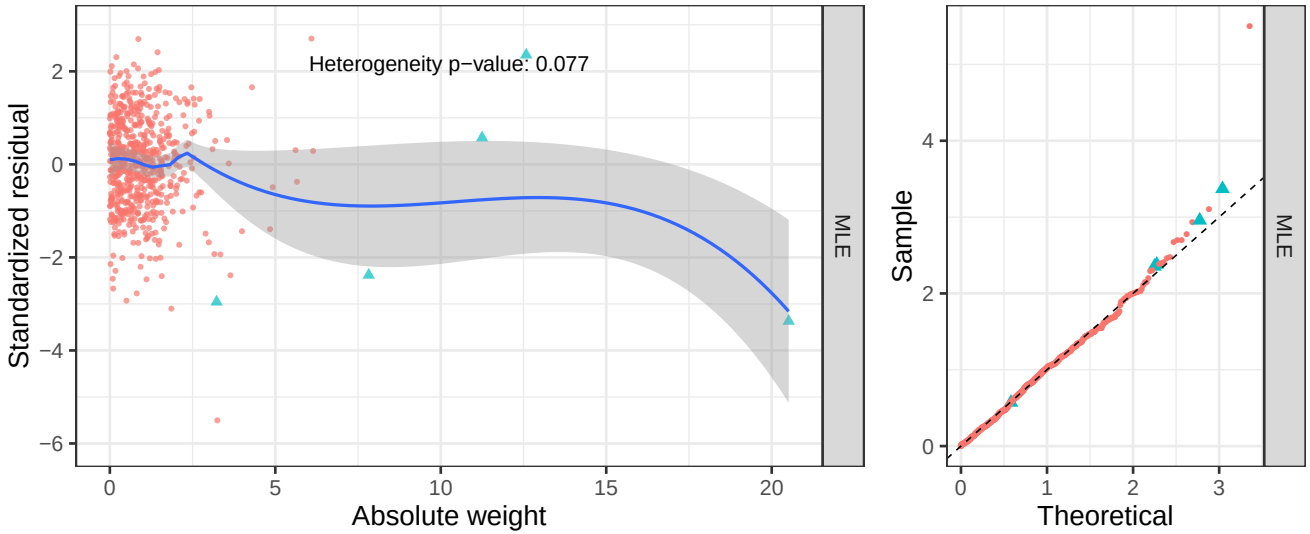

Figure F10: Selection: Davis; Exposure: Kettunen; Outcome: UKB.

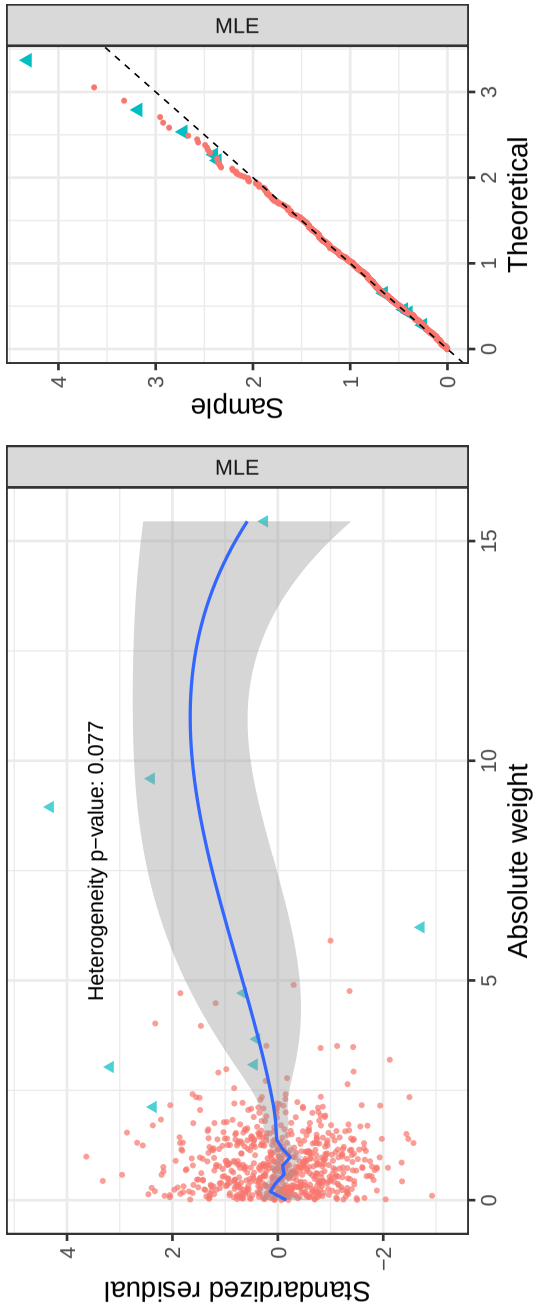

Figure F11: Selection: Kettunen; Exposure: Davis; Outcome: UKB.

F.2 M-HDL-P

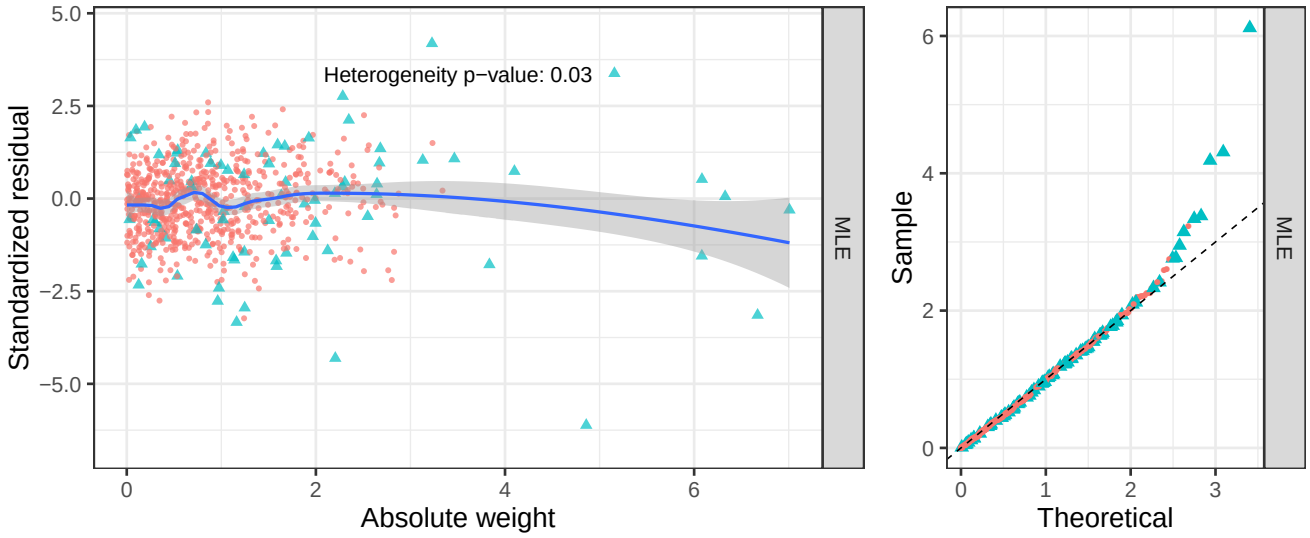

Figure F12: Selection: GERA; Exposure: Davis; Outcome: CAD.

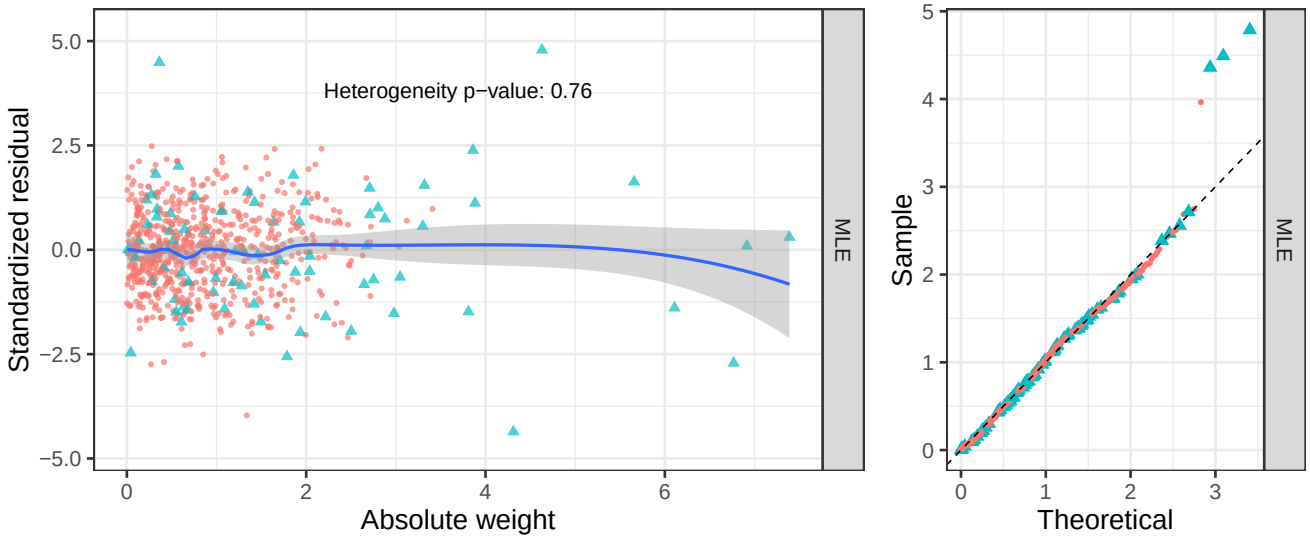

Figure F13: Selection: GERA; Exposure: Davis; Outcome: UKB.

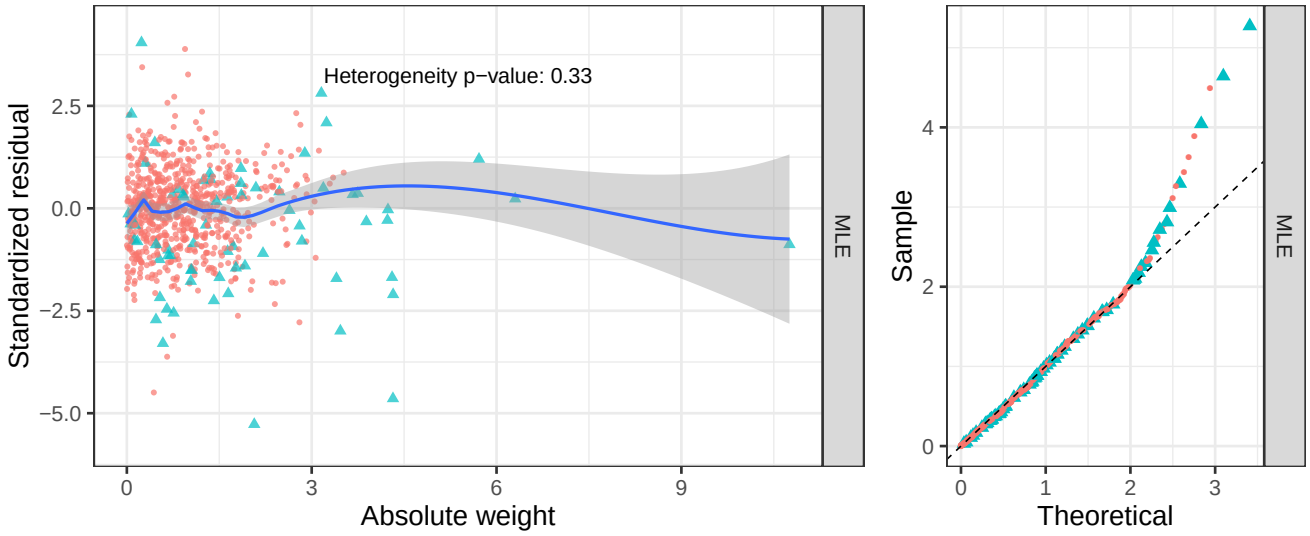

Figure F14: Selection: GERA; Exposure: Kettunen; Outcome: UKB.

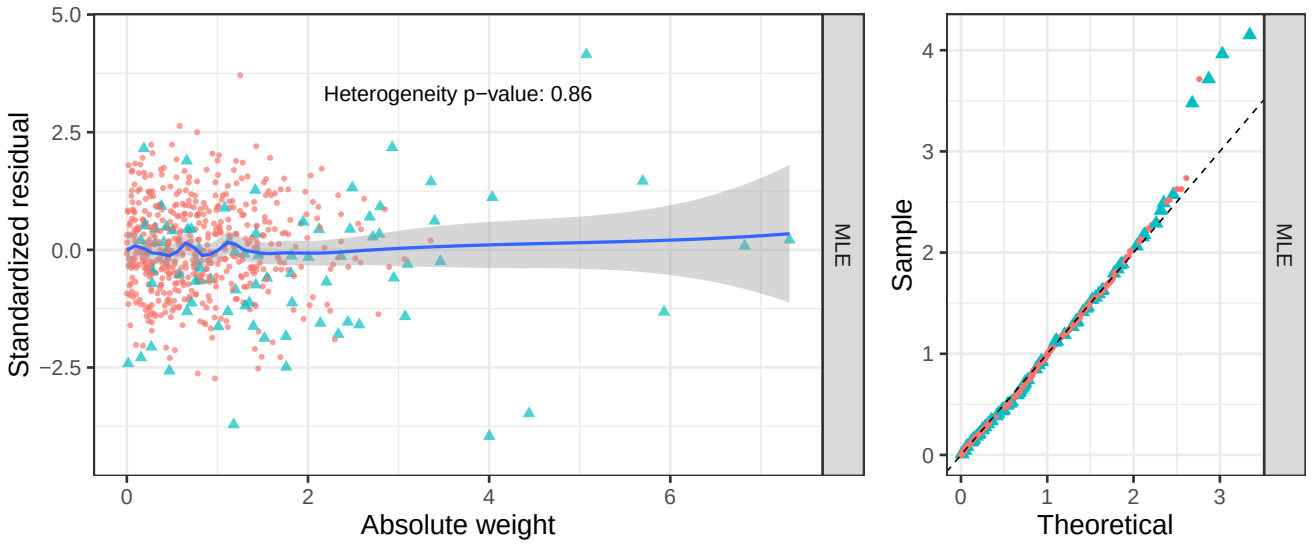

Figure F15: Selection: GLGC; Exposure: Davis; Outcome: UKB.

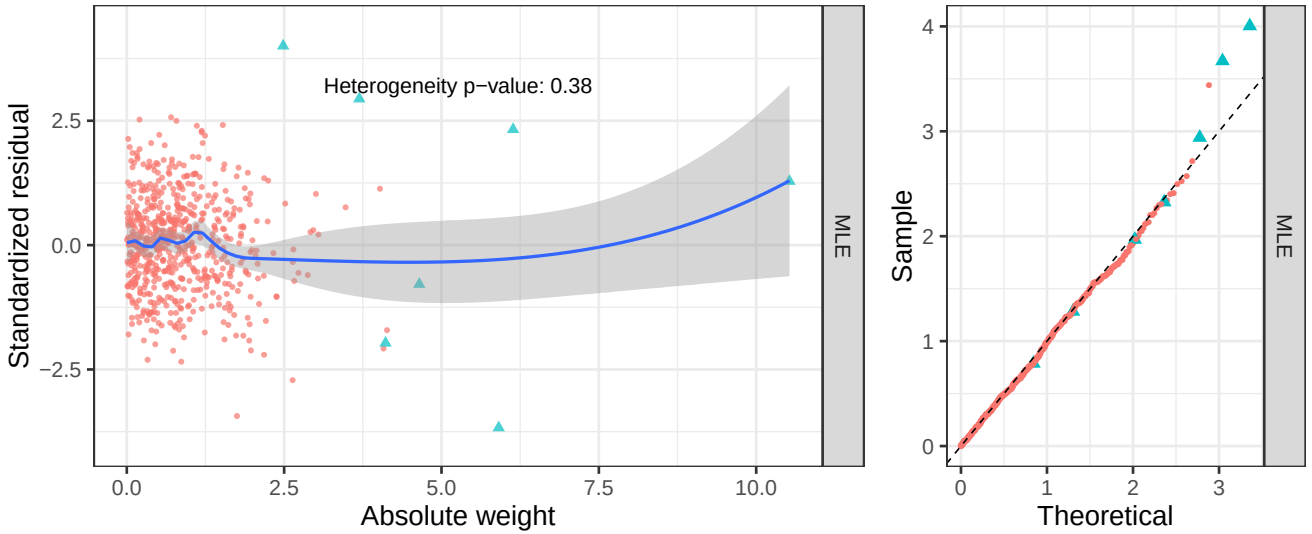

Figure F16: Selection: Davis; Exposure: Kettunen; Outcome: UKB.

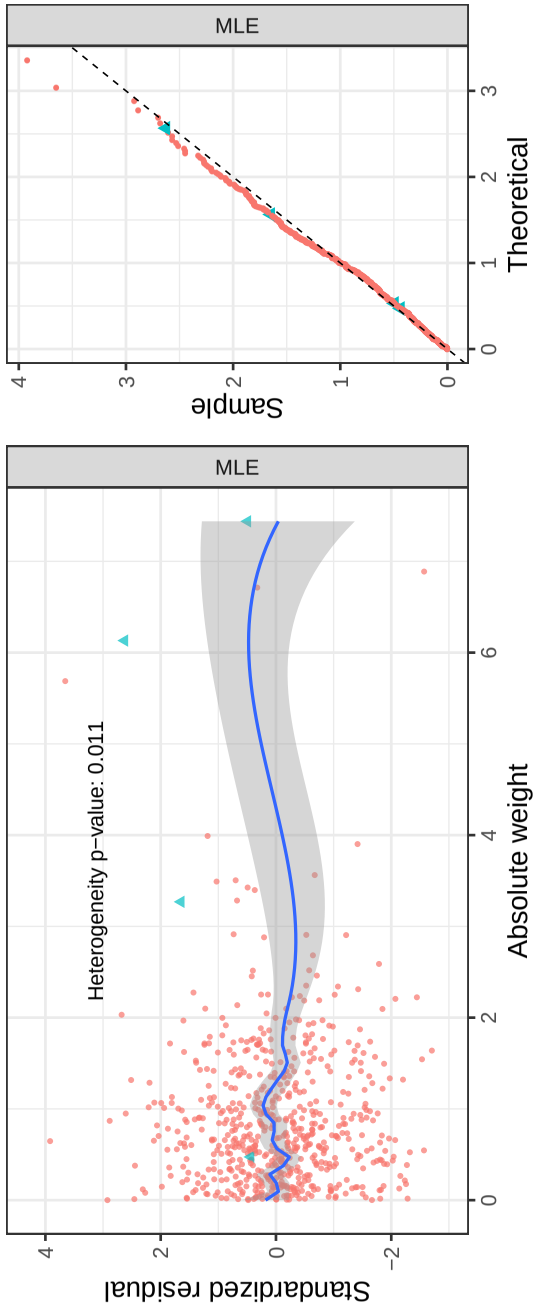

Figure F17: Selection: Kettunen; Exposure: Davis; Outcome: UKB.