The effect of lipids on the left ventricle: a Mendelian randomization study

Brief title: Lipids and the LV

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Funding
Dr Aung recognizes the National Institute for Health Research (NIHR) Integrated Academic Training programme which supports his Academic Clinical Lectureship post
Dr Sanghvi recognizes the National Institute for Health Research (NIHR) Integrated Academic Training programme which supports his Academic Clinical Fellowship post

Professor Piechnik acknowledges the British Heart Foundation for funding the manual analysis to create a cardiovascular magnetic resonance imaging reference standard for the UK Biobank imaging resource in 5000 CMR scans (PG/14/89/31194). Professor Piechnik is supported by the Oxford National Institute for Health Research Biomedical Research Centre and the Oxford British Heart Foundation Centre of Research Excellence.
Professor Neubauer acknowledges the British Heart Foundation for funding the manual analysis to create a cardiovascular magnetic resonance imaging reference standard for the UK Biobank imaging resource in 5000 CMR scans (PG/14/89/31194). Professor Neubauer is supported by the Oxford National Institute for Health Research Biomedical Research Centre and the Oxford British Heart Foundation Centre of Research Excellence.
Professor Munroe acknowledges support from the National Institute for Health Research Cardiovascular Biomedical Research Centre at Barts, Queen Mary University of London.
Professor Petersen acknowledges the British Heart Foundation for funding the manual analysis to create a cardiovascular magnetic resonance imaging reference standard for the UK Biobank imaging resource in 5000 CMR scans (PG/14/89/31194). Prof. Petersen also acknowledges support from the "SmartHeart" Engineering and Physical Sciences Research Council programme grant (EP/P001009/1) and from the National Institute for Health Research (NIHR) Cardiovascular Biomedical Research Centre at Barts.
He has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 825903 (euCanSHare project).

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Sample tweet:
@NayAungMD + @Sanghvi_M use Mendelian randomization to demonstrate LDL-chol and trigs may have causal effect on LV remodeling in addition to atherosclerosis.

Acknowledgments
This research has been conducted using the UK Biobank Resource under Application 2964. The authors wish to thank all UK Biobank participants and staff.

Abstract

Background

Cholesterol and triglycerides are amongst the most well-known risk factors for cardiovascular disease.

Objectives

This study investigates whether higher LDL cholesterol and triglyceride levels, and lower HDL cholesterol are causal risk factors for changes in prognostically-important left ventricular parameters.

Methods

One-sample Mendelian randomization (MR) of 17,311 European individuals from the UK Biobank with paired lipid and CMR data was performed. Two-sample MR was performed using summary level data from the Global Lipid Genetics Consortium (n = 188,577) and UK Biobank CMR sub-study (n = 16,923) for sensitivity analyses.

Results

In one-sample MR analysis, higher LDL cholesterol was causally associated with higher LV end-diastolic volume (b = 1.85 ml, CI = 0.59 to 3.14, p = 0.004) and higher LV mass (b = 0.81 g, CI = 0.11 to 1.51, p = 0.023) and triglycerides with higher LV mass (b = 1.37 g, CI = 0.45 to 2.3, p = 0.004). HDL cholesterol had no significant association with any LV parameter. Similar results were obtained using two-sample MR. Observational analyses were frequently discordant with those derived from MR.

Conclusions

Mendelian randomization analysis demonstrates that LDL cholesterol and triglycerides are associated with adverse changes in cardiac structure and function, in particular in relation to LV mass. These findings suggest that LDL cholesterol and triglycerides may have a causal effect in influencing cardiac morphology in addition to their established role in atherosclerosis.

Condensed abstract

This study investigates whether higher LDL cholesterol and triglyceride levels, and lower HDL cholesterol are causal risk factors for changes in prognostically-important left ventricular parameters. One-sample Mendelian randomization (MR) of 17,311 European individuals from the UK Biobank with paired lipid and CMR data was performed. Two-sample MR was performed using summary level data from the Global Lipid Genetics Consortium (n = 188,577) and UK Biobank CMR sub-study (n = 16,923). Mendelian randomization analysis demonstrates that LDL cholesterol and triglycerides may cause adverse changes in cardiac structure and function, in particular in relation to LV mass.

Key words:
Lipids, cholesterol, mendelian randomization, cardiovascular risk, cardiac remodeling

Abbreviations

CMR = cardiovascular magnetic resonance
EDV = end-diastolic volume
EF = ejection fraction
GRS = genetic risk score
HDL = high-density lipoprotein
LDL = low-density lipoprotein
LV = left ventricle
MR = Mendelian randomization
MR-PRESSO = Mendelian randomization pleiotropy residual sum and outlier

Introduction

Both the incidence and prevalence of ischemic heart disease, and its long-term sequelae such as heart failure, are on the rise (1, 2). Cardiac imaging is an important and widely-used tool in guiding the diagnosis and treatment of these patients (3). Left ventricular parameters derived from cardiac imaging modalities such as end-diastolic volume, ejection fraction and mass are known to be prognostically important with respect to subsequent major adverse cardiovascular events and cardiovascular death (4, 5). Low-density lipoprotein (LDL) cholesterol is one of the best publicized and most unequivocally implicated risk factors in the development of ischemic heart disease; its causal involvement in atherosclerotic plaque formation in the arterial system is well-elucidated (6). For triglycerides, a causal relationship with cardiovascular disease has also been demonstrated (7) whilst for high-density lipoprotein (HDL) cholesterol, low levels are associated with increased risk of cardiovascular disease but causality has not been established (8). No study, however, has established the causative impact of lipids on the structure and function of the LV.

Mendelian randomization (MR) is an analysis methodology whereby genetic variants associated with a proposed risk factor (e.g. raised LDL cholesterol) are utilized as surrogates in order to make causal inferences about the effect of that exposure on an outcome of interest (i.e. left ventricular phenotypes). Given that none of the landmark randomized controlled trials assessing the effect of statins on lipid lowering and cardiovascular outcomes included cardiac imaging in their protocols, examining the association between cholesterol and left ventricular parameters would traditionally be performed via an epidemiological observational study. Through adopting an MR approach, however, typical biases encountered in observational settings such as confounding and reverse causation are mitigated against. With the availability of genotype and cardiovascular magnetic resonance (CMR) data from the UK Biobank as well as large-scale genome wide association studies for lipids (9) and left

ventricular phenotypes (10), examining the causal relationship between lipid concentrations and prognostically-important and routinely-measured imaging phenotypes has been made possible.

This study investigates whether higher LDL cholesterol and triglycerides and lower HDL cholesterol are causal for changes in left ventricular parameters via individual-level instrumental variable analysis with subsequent sensitivity analysis using summary-level genome-wide association data, in order to gain further understanding of lipids as cardiovascular risk factors.

Methods

Study cohorts

The UK Biobank is a large population-based prospective cohort study of 500,000 individuals aged between 40 to 69 years at the time of initial recruitment between 2006 and 2010. It has collected information on health and lifestyle data, physical measurements, biological samples, genotype, and cardiac phenotypes derived from CMR.

The overall study protocol has been described in detail previously (11), as has the CMR protocol and reference ranges (12, 13). Genotypes called by the bespoke, closely related UK BiLEVE Axiom and UK Biobank Axiom microarrays (Affymetrix) were imputed using the Haplotype Reference Consortium and merged UK10K and 1000 Genomes phase 3 reference panels.

Biological samples for biochemical and genetic analysis were taken from participants at their initial baseline visit between 2006 and 2010. CMR examinations, as part of the UK Biobank imaging enhancement, have been performed from 2015 onwards.

This study was covered by the general ethical approval for UK Biobank studies from the NHS National Research Ethics Service (17th June 2011 [Ref 11/NW/0382]; extended on 10th May 2016 [Ref 16/NW/0274]).

Lipid measurements

Direct LDL cholesterol serum concentration was measured by enzymatic protective selection analysis on a Beckman Coulter AU5800 clinical chemistry analyzer (Beckman Coulter, Brea, California, USA). For participants where direct measurements were missing, LDL cholesterol concentration was derived using the Friedewald calculation as long as serum triglyceride concentration was ≤155 mg/dL (4 mmol/L) (14). Where participants had indicated they used lipid-lowering medications (UK Biobank field ID 20003), LDL cholesterol values were multiplied by a factor of 1.43 in order to estimate untreated LDL cholesterol serum concentration (15).

Serum HDL cholesterol concentration was measured by the enzyme immune-inhibition method and serum triglyceride concentration was measured using a series of coupled enzymatic reactions, both on a Beckman Coulter AU5800 clinical chemistry analyzer (Beckman Coulter).

Variant selection and genetic risk score construction

A weighted genetic risk score (GRS) for LDL cholesterol was built by using variants associated with LDL cholesterol attaining genome-wide significance ($p < 5 \times 10^{-8}$) reported in the data from the Global Lipids Genetic Consortium (GLGC) (9). Following linkage disequilibrium clumping (at $r^2 < 0.01$), 101 independent variants were included in the GRS. Equivalent processes were performed in the same dataset for HDL cholesterol and triglycerides yielding 125 and 73 variants, respectively (Supplementary Tables 1–3). The weighted GRS was calculated for each UK Biobank participant of European ancestry by summing the product of the effect sizes and the number of effect alleles across all selected variants. Variance explained by the weighted GRS was calculated by regressing the measured lipid values on their corresponding GRS. Correlation between the lipid genetic risk scores was assessed by Pearson's test.

Statistical analysis

Baseline data and observational analysis

Baseline data is presented in categorized fashion with participants grouped into unequal bins based on their serum LDL cholesterol percentile. To examine trend across the groups, Cuzick's extension of the Wilcoxon rank sum test was used for continuous variables whilst the chi-squared test for trend was used for ordinal variables. CMR parameters used as dependent variables were LV end-diastolic volume (LVEDV), LV mass and LV ejection fraction (LVEF). Non-European ancestries were excluded in order to improve homogeneity of the study population and align with the genetic analyses.

To observationally examine the association between phenotypic lipid concentration on important LV parameters, multivariable linear regression models were fitted for each dependent variable. Co-variates included age at recruitment, sex, log-transformed body mass index (BMI), body surface area (BSA, calculated via Dubois and Dubois equation), systolic blood pressure adjusted for anti-hypertensive medication use (by adding 15mmHg) (16), physical activity as determined by log-transformed total metabolic equivalent of task (MET) minutes per week, smoking status, log-transformed glycated hemoglobin (HbA1c) and presence of cardiovascular disease (defined as participants diagnosed or reporting myocardial infarction, angina, heart failure, arrhythmias [including atrial fibrillation], cardiomyopathy, stroke or peripheral vascular disease).

Instrumental variable analysis

MR was performed using the two-stage least squares method (one-sample MR) as implemented in the R package "ivpack". We included age, sex, BSA and the first five genetic principal components as covariates. Data are presented as the change in LV phenotype per 39 mg/dL (1 mmol/L) increment in lifetime LDL cholesterol and HDL cholesterol exposure and per 89 mg/dL (1 mmol/L) in lifetime triglyceride exposure. Significant causal associations

between each lipid GRS and the LV phenotype were additionally tested for the presence of an *independent* effect by including all three lipid genetic risk scores in the regression model. We assessed the presence of weak instrument bias (also known as violation of *relevance* assumption in MR) by calculating the F-statistic from the linear regression between GRS and LV phenotype. The Durbin-Wu-Hausman test of regressor endogeneity was performed to assess the consistency of the estimate of LV parameter change provided by the instrumental variable analysis compared to the observational analysis. Statistical power of instrumental variable analysis was estimated according to the method proposed by Brion (17). At our available sample size of ~17,000 individuals, our one-sample MR analyses were powered at 80% (alpha=0.05) to detect the minimum effect sizes of 0.39 to 0.53 ml for LVEDV, 0.16 to 0.24% for LVEF and 0.31 to 0.45 g for LV mass (Supplementary Figure 1).

Sensitivity analyses

As sensitivity analysis to examine the potential causal relationship between serum lipids and prognostically-important LV parameters, two-sample MR with summary-level genome-wide association data from the GLGC (n = 188,577) (9) and UK Biobank CMR sub-study (n = 16,923) (10) was performed. An MR effect estimate for each LV parameter was calculated by the inverse variance-weighted method with robust penalized regression to minimize the influence of genetic variants with outlying ratio estimates (18). Two-sample MR effect sizes are presented as the change in LV parameter per one standard deviation increase in LDL cholesterol (34 mg/dL [0.87 mmol/L]), HDL cholesterol (15 mg/dL [0.38 mmol/L]) and triglycerides (90 mg/dL [1.02 mmol/L]) respectively.

Additionally, we used the robust penalized MR-Egger, weighted median and weighted mode methods to evaluate the validity of genetic instruments (18, 19). We assessed the presence of directional horizontal pleiotropy by conducting the MR-Egger intercept test for which a p value <0.1 was considered as evidence of pleiotropic bias (20). We also

conducted the MR pleiotropy residual sum and outlier (MR-PRESSO) for further evaluation of horizontal pleiotropy. This test applies three procedures: (i) detection of horizontal pleiotropy with the global test; (ii) correction for horizontal pleiotropy by outlier removal known as the outlier test; and (iii) assessing significant differences in the causal estimates before and after correction for outliers using the distortion test. Additionally, we conducted multivariable MR in order to establish the potential causal effect on LV parameters independent of the effects of the other lipid fractions (21).

As further sensitivity analysis, we performed one-sample MR following additional adjustment for all co-variates (age at recruitment, sex, BMI, BSA, systolic blood pressure adjusted for anti-hypertensive medication use, physical activity, smoking status, HbA1c and presence of cardiovascular disease). We built models examining the association between lipid parameters and LV phenotypes using both phenotypic and genetically-determined lipid levels as co-variates to examine any attenuation effect. We also interrogated the GWAS Catalog database to identify the variants included in the lipid GRSs which were associated with other lipid and non-lipid traits at a genome-wide significance level. We manually examined this list and excluded the variants associated with traits (e.g. cardiovascular disease, cardiovascular risk factors) which might influence LV remodeling (Appendix 1) and performed the analysis using a restricted GRS.

We investigated the direction of causality by the MR-Steiger test which is based on the absolute correlations of the genetic variants with the exposure and outcome. The two-sample MR analyses were conducted using the "MendelianRandomization" and "TwoSampleMR" R packages.

Statin effect

To examine whether statin use modified the relationship of phenotypic (measured) LDL cholesterol and the LDL GRS, interaction analysis was performed using "statin use x

standardized genetic risk score" as an interaction term. For this analysis, we used the LDL cholesterol measurements unadjusted for statin use. We also investigated the effect modification by statin therapy on the association between the LDL GRS and LV parameters.

The causal effects were considered significant only if supported by both one-sample and two-sample MR analyses at $p < 0.05$. All analyses were conducted in the R (3.6.0) statistical computing environment.

Results

Demographic and clinical characteristics of study participants, as well as median CMR parameter values, are outlined in Table 1. There were 436,064 individuals for whom cholesterol data was available; of these, 17,311 had CMR examinations. Individuals in the top decile for phenotypic LDL cholesterol were older, predominantly female and had higher BMI, blood pressure and HbA1c measurements. The variances in lipid measurements explained by the corresponding genetic risk scores were 10.8% (F-statistic = 2492), 7.3% (F-statistic = 1811), and 5.0% (F-statistic = 925) for LDL cholesterol, HDL cholesterol and triglycerides, respectively. Large F-statistic values (>10) indicated that the MR analyses were unlikely to be affected by the weak instrument bias. The strength of correlations between lipid genetic risk scores was low (Pearson's r 0.1 to -0.26, $p > 0.1$, Supplementary Figure 2).

LDL cholesterol

In observational analysis (Table 2, Figure 1/Central Illustration), a 39 mg/dL (1 mmol/L) increase in LDL cholesterol levels were associated with lower LVEDV (b = -2.44 ml, confidence interval [CI] = -2.91 to -1.97, $p < 0.0001$), lower LV mass (b = -0.64 g, CI = -0.9 to -0.38, $p < 0.0001$) and higher LVEF (b = 0.13%, CI = 0.01 to 0.24, p = 0.03). In contrast, in one-sample MR analysis, a 39 mg/dL (1 mmol/L) increase in lifetime LDL cholesterol exposure was associated with higher LVEDV (b = 1.85 ml, CI = 0.59 to 3.14, p = 0.004), higher LV mass (b = 0.81 g, CI = 0.11 to 1.51, p = 0.023); there was no significant change in ejection fraction. Analyses controlling for HDL and triglycerides genetic

instruments did not change the significant results (Supplementary Table 4) indicating that the causal relationships between LDL cholesterol and LVEDV and LV mass were robust to confounding from other lipid fractions. One sample-MR was additionally performed following adjustment for all co-variates and yielded similar results (these are detailed, along with results for HDL and triglycerides, in Supplementary Table 5). Models examining the association between LV parameters and genetically determined lipid levels where phenotypic lipid levels were included as a co-variate demonstrated no significant attenuation of these associations indicating an independent effect (Supplementary Table 6). Sensitivity analysis performed using a restricted list of variants in the GRS following exclusion of potentially pleiotropic variants (69, 81 and 50 variants remained for LDL, HDL and triglycerides, respectively) yielded concordant results to the primary analysis (Supplementary Table 7).

In sensitivity analysis using two-sample MR (Table 3, Figure 1/Central Illustration), concordant associations were noted for LVEDV (inverse-variance weighted [IVW] b = 1.62 ml, CI 0.32 to 2.91, p = 0.014) and LV mass (IVW b = 0.66 g, CI 0.1 to 1.22, p = 0.021). Again, there was no association demonstrated for LVEF. These results were also confirmed using multivariable MR (Supplementary Table 8). Based on Egger intercept p-values, no directional horizontal pleiotropy was detected. Sensitivity analyses by MR-Egger, weighted median and weighted mode methods produced associations with concordant effect directions although the confidence intervals were much wider, as expected (Supplementary Table 9 and Supplementary Figure 3). The MR-PRESSO method found evidence of horizontal pleiotropy for the association between LDL cholesterol and LVEDV but upon removal of outlier variants, the effect estimates were not significantly changed as per the distortion tests (Supplementary Table 10). The MR-Steiger test suggested that the assumption of causal directionality for the relationships between the LDL GRS and the LV parameters was correct (Supplementary Table 11).

HDL cholesterol

In multivariate analysis, higher phenotypic HDL cholesterol levels were associated with higher LVEDV (b = 8.27 ml, CI = 7 to 9.53, p <0.0001) and higher LV mass (b = 1.34 g, CI = 0.64 to 2.04, p = 0.0002) with no association with LVEF. Associations demonstrated in observational analysis were not borne out in one-sample MR analysis with no association demonstrated between genetically higher lifetime exposure to HDL cholesterol and changes in LVEDV, LVEF or LV mass. This was further demonstrated using summary data in two-sample MR (Table 3, Figure 1/Central Illustration). These results were reproduced in sensitivity analyses with MR-Egger, weighted median and weighted mode methods (Supplementary Table 9 and Supplementary Figure 4).

Triglycerides

Examining the effect of triglycerides on CMR parameters, observational analysis indicated that an 89 mg/dL (1 mmol/L) increase in triglyceride concentration was associated with lower LVEDV (b = -3.98 ml, CI = -4.4 to -3.55, p <0.0001), higher LVEF (b = 0.12%, CI = 0.02 to 0.22, p = 0.024) and lower LV mass (b = -0.65 g, CI = -0.89 to -0.42, p = <0.0001). One-sample MR analysis demonstrated that there was no association with changes in LVEDV but an 89 mg/dL (1 mmol/L) increase in lifetime triglyceride exposure yielded a reduction in LVEF (b = -0.52%, CI = -0.92 to -0.13, p = 0.011) and higher LV mass (b = 1.37 g, CI = 0.45 to 2.3, p = 0.004). Additional adjustment for HDL and triglycerides genetic instruments produced similar results (Supplementary Table 4). Sensitivity analysis performed using a restricted list of variants in the GRS following exclusion of potentially pleiotropic variants yielded concordant results to the primary analysis (Supplementary Table 7).

Two-sample MR sensitivity analysis demonstrated no significant association between triglyceride concentration and LVEDV or LVEF; it showed concordant results for LV mass (IVW b = 0.61 g, CI 0.04 to 1.18, p = 0.036). Similar results were observed in multivariable

MR analysis (Supplementary Table 8). There was evidence of horizontal pleiotropy for the association between triglycerides and LVEDV but removal of the outlier variants did not significantly change the effect estimates as indicated by the distortion tests (Supplementary Table 10) . Sensitivity analysis examining the association of triglycerides and LV mass using MR-Egger, weighted median and weighted mode methods did not reach significance due to wider confidence interval although they showed concordant effect directions (Supplementary Table 9 and Supplementary Figure 5). The assessment of causal directionality using the MR Steiger test supported what this study's hypothesis has proposed (Supplementary Table 11).

Statin usage

To ascertain the effect of statin usage, the relationship between measured (phenotypic) LDL cholesterol and the standardized genetic risk score for LDL cholesterol was examined based on whether an individual was a statin user or not. Statin use significantly modified (p for interaction <0.0001) the relationship between measured (phenotypic) LDL cholesterol and the standardized genetic risk score for LDL cholesterol with statin users exhibiting a reduced measured LDL cholesterol for a given degree of genetic risk (Figure 2A). As demonstrated in Figure 2B, as genetic risk score percentile group increases, the relative increase in measured LDL cholesterol is greater in each group in non-statin users, compared to statin users. Examination of the effect modification of statin therapy on the relationships between genetically determined LDL and LV parameters did not yield any significant results (Supplementary Table 12).

Discussion

This study is the first to conduct MR analyses to examine the effect of lipids in the development of changes in prognostically-important LV parameters. Using instrumental variable analysis in 17,311 individuals with paired genotype and CMR data with subsequent sensitivity analysis using summary-level data, we demonstrate an association between

increased LDL cholesterol and higher LVEDV and LV mass, triglycerides with higher LV mass whilst HDL cholesterol does not result in any significant alterations in LV structure and function. Importantly, results derived from observational analysis were frequently discordant from those obtained via MR.

Lipids as a risk factor: beyond atherosclerosis

The substantial body of evidence indicating a continuous, positive and graded relationship between LDL cholesterol and cardiovascular mortality make cholesterol measurement and prescription of lipid-lowering therapy a cornerstone of primary and secondary prevention in cardiovascular disease (22). Left ventricular remodeling is a clinical characterization of the development and progression of morphological changes in the LV that result in ventricular dysfunction (23). These morphological changes have been shown to occur in association with exposure to other important risk factors, such as hypertension (24) or raised body mass index (25), and are frequently subclinical – present prior to any discrete clinical event.

In this study, MR analysis demonstrates that both LDL cholesterol and triglycerides have a potentially causal association with increased LV mass. The importance of LV mass as a biomarker in cardiovascular disease is demonstrated in studies where therapeutic interventions that result in a reduction in LV mass have decreased the number of cardiovascular events (26). Importantly, raised LV mass has also been shown to increase the risk of incident heart failure even in patients free of known ischemic heart disease or previous myocardial infarction – conditions which are atherosclerosis-driven (27). With LDL cholesterol and triglycerides appearing to be causative of myocardial remodeling by increasing LV mass, it suggests that they influence the development of cardiovascular disease not only by atherosclerosis but also by causing adverse alterations in cardiac structure and function.

An insight into the potential mechanistic pathways by which lipids might generate these alterations can be gleaned from work examining the pleiotropic effects of statins on the mevalonate pathway. The mevalonate pathway is an ubiquitous, negative feedback-controlled pathway responsible for cholesterol synthesis; statins act to inhibit cholesterol synthesis by preventing conversion of HMG-CoA to mevalonate. However, since mevalonate is not the immediate precursor of cholesterol and also acts as a precursor for several other molecules, its inhibition leads to pleiotropic effects being observed, particularly through inhibition of synthesis of isoprenoid intermediates of the mevalonate pathway such as farnesylpyrophosphate and geranylgernanylphosphate. An important function of these isoprenoids is the post-translational modification of many GTP-binding proteins of the Rho family (28) of signaling proteins. Rho proteins have been shown to mediate the development of cardiac hypertrophy via a number of mechanisms (29). For example, RhoA is involved in formation of actin stress fibers and focal adhesion complexes through Rho kinase activation and myosin light chain phosphorylation (30). Rac1 and Cdc42 regulate actin cytoskeletal processes called lamellipodia and filopodia, which are thought to contribute to morphological changes associated with LV hypertrophy (31, 32). Additionally, Rho proteins may regulate the hypertrophic process by activating downstream signaling molecules such as mitogen-activated protein (MAP) kinases (33). Additional work examining non-hypercholesterolemic transgenic rabbit models of hypertrophic cardiomyopathy demonstrated that simvastatin administration was associated with regression of cardiac hypertrophy and improvement of LV filling pressures (34). If lipid-lowering therapy has been shown to alter cardiac phenotypes, it is possible that the reverse effect may be true with increased cholesterol exposure.

A further aspect of this study is heightening the importance of raised serum triglycerides as a cardiovascular risk factor. Despite previous contention, triglycerides have

emerged as a recognized causal risk factor (7). Current American guidelines recommend intervention when triglycerides are >150 mg/dL (>1.7 mmol/L) (35) and European guidelines recommend the use of pharmacotherapy when triglycerides are >200 mg/dL (2.3 mmol/L) in high risk patients and when lifestyle measures have failed (36). By way of illustration, 40% of our cohort had a serum triglyceride measurement >150 mg/dL (1.7 mmol/L). Along with the recent data published by the REDUCE-IT investigators (37, 38), this study provides further evidence of the importance of triglycerides as a cardiovascular risk factor and perhaps will help in establishing a role for triglyceride reduction in a broader group of patients. In contrast, our findings of a lack of association with any LV remodeling parameter agree with the current narrative of HDL cholesterol not being associated with cardiovascular outcomes.

Observational analysis vs MR

A particularly interesting feature of this study is the discordance between the results produced from observational analysis compared to those derived from a MR approach. As examples, after adjusting for potential confounders, LDL cholesterol was shown to be observationally associated with significantly lower end-diastolic volume and LV mass. However, the directionality of association was reversed in one-sample and two-sample MR. Moreover, observationally HDL cholesterol was associated with higher end-diastolic volume and mass whereas no significant association was demonstrated using MR. The MR approach has gained much traction due its ability to permit experimental analysis free from the biases common to observational approaches. The results outlined above are tacit in highlighting the limitations of observational methods. Of particular note are the observational results for LDL cholesterol which *prima facie* suggest higher serum concentrations to be associated with ameliorative changes in the LV. This is in contrast to previous cross-sectional studies which have suggested adverse remodeling changes in association with non-HDL cholesterol and total cholesterol, respectively (39, 40). That this study, particularly with its large sample size

(n = 17,311), would deliver contrasting results in terms of both the previous literature and biological expectation is surprising. However, it may be instructive in characterizing a further challenge as biobank-based research becomes more common. As the degree of phenotyping undertaken by biobanks becomes more extensive, the temporal gap between different assessments will grow. For example, in this study, biochemistry samples for lipid quantification were drawn between 2006 and 2010 whereas CMR examinations have taken place since 2015. The observational analysis, therefore, is not strictly cross-sectional and it is possible that the LDL cholesterol results were confounded by modulating factors which occurred between the two time points. One particular and relevant confounding intervention would be the introduction/continuation of statin therapy during the period before CMR examination. Whilst it was reassuring that examination of the relationship of measured LDL and genetically-determined LDL demonstrated that statin use was consistently associated with relatively lower phenotypic LDL across the genetic LDL risk score range, a natural extension of this study would have been to investigate whether statins conferred any beneficial effect on LV parameters. Our examination of the effect modification by statin therapy on the association between the LDL GRS and LV parameters did not yield any significant results. However, a significant limitation is that data regarding commencement, duration, dosage and dosage change of pharmacological therapy (statins included) is not available in the UK Biobank.

Strengths and limitations

There are a number of strengths to this work, the first to investigate the potentially causal relationship between routinely measured lipid fractions and prognostically-important LV parameters. Firstly, the effect estimates for building the genetic risk scores for LDL cholesterol, HDL cholesterol and triglycerides were taken from an independent dataset (GLGC) which is one of the largest of its kind and has helped avoid circular inferences or

overestimation in our results. Secondly, this study has sufficient sample size as confirmed by power calculations performed *a priori* to its commencement. Finally, both one-sample and two-sample MR have been performed, providing an additional level of confidence concerning the results provided.

In addition to the lack of pharmacotherapy data explained above, whilst supporting data providing mechanistic insights has been outlined, this study is unable to determine the specific molecular mechanism(s) for the potentially causal relationship between LDL cholesterol and triglycerides and alterations in LV parameters, although it is hoped that the findings presented may prompt further basic science investigations. Additional limitations mostly pertain to the MR technique. It is acknowledged that MR assumptions of independence and exclusion restriction cannot be fully tested nor can residual horizontal pleiotropy be fully ruled out. However, as described, the MR-Egger intercepts did not deviate significantly from the origin. Bidirectional MR was not performed to determine whether LV genetic risk scores are causally associated with alterations in lipid measurements; this was because of the limited number of significant genome-wide variants for LV parameters. Nevertheless, MR-Steiger results suggested that assumptions of causal directionality were accurate. Finally, our study was restricted to Europeans because of the limited number of non-European participants in our CMR data. Thus, the insights gained cannot be extended to other ancestries. This limitation is likely be overcome in the near future by the ongoing UK Biobank CMR study with a target sample size of 100,000, as well as through collaboration with other maturing national biobanks, which will increase available data for other ethnicities.

Conclusion

By performing Mendelian randomization this study has investigated the association between lipids and CMR parameters. It provides evidence that exposure to higher levels of

LDL cholesterol and triglycerides are associated with changes in the left ventricle known to portend adverse prognosis. It improves our understanding of serum lipids as a risk factor for cardiovascular disease by demonstrating evidence of direct impact on cardiac structure and function.

Perspectives

Competency in medical knowledge 1: Mendelian randomization can be used as an approach to infer causation in situations were randomized control trials are unable to be performed.

Competency in medical knowledge 2: Mendelian randomization can overcome biases observed in observational studies. This is highlighted in this study where observational data and MR data for LDL cholesterol show discordant effects on LV phenotypes.

Translational Outlook 1:The role of lipids as a cardiovascular risk factor may extend further than their effects on atherogenesis to directly impacted on prognostically-important LV phenotypes.

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Figures

Figure 1 (Central Illustration):

Title: Change in LV parameter by lipid fraction in observational, one-sample MR and two-sample MR analysis.

Caption: There is a potentially causal association between increased LDL-cholesterol and higher LV end-diastolic volume and LV mass, and triglycerides with higher LV mass whilst HDL cholesterol does not result in any significant alterations in LV structure and function. Observational data is presented as change in LV parameter per 39 mg/dL (1 mmol/L) in LDL and HDL cholesterol and 89 mg/dL in triglycerides. One-sample Mendelian randomization (MR) data is presented as change in LV parameter per 39 mg/dL (1 mmol/L) for LDL and HDL cholesterol and 89 mg/dL for triglyceride increase in lifetime lipid parameter exposure. For two-sample MR, data is presented as the change in LV parameter per one standard deviation increase in LDL cholesterol (34 mg/dL [0.87 mmol/L]), HDL cholesterol (15 mg/dL [0.38 mmol/L]) and triglycerides (90 mg/dL [1.02 mmol/L]) respectively.

Figure 2:

Title: Relationship between genetic risk score for LDL cholesterol and phenotypic LDL cholesterol by statin usage.

Caption: Figure 2A: Statin use significantly modifies (p for interaction <0.0001) the relationship between measured (phenotypic) LDL cholesterol and the standardized genetic risk score for LDL cholesterol with statin users exhibiting a reduced measured LDL cholesterol for a given degree of genetic risk.

Figure 2B: As genetic risk score percentile group increases, the relative increase in measured LDL cholesterol is greater in each group in non-statin users, compared to statin users.

Table 1: Demographic data

Variable	Percentile group by serum LDL cholesterol concentration					P-value for trend
	0% - 50%	51% – 75%	76% – 90%	91% – 95%	96% – 100%	
n	215845	109763	66350	22204	21902	
LDL cholesterol* (mg/dL)	115 (20)	146 (19)	165 (22)	181 (25)	200 (33)	<0.001
HDL cholesterol* (mg/dL)	56 (15)	56 (14)	56 (13)	57 (13)	57 (13)	<0.001
Triglycerides* (mg/dL)	132 (82)	164 (89)	181 (93)	195 (96)	210 (101)	<0.001
Age (years)*	55.5 (8.4)	57.6 (7.6)	58.1 (7.3)	58.4 (7.1)	59.0 (6.9)	<0.001
Male (%)	99700 (46.2)	51742 (47.1)	29740 (44.8)	9482 (42.7)	8721 (39.8)	<0.001
Caucasian (%)	215845 (100.0)	109763 (100.0)	66350 (100.0)	22204 (100.0)	21902 (100.0)	
BMI† (kg/m^2)	26.1 [23.5, 29.3]	27.0 [24.5, 30.1]	27.4 [24.9, 30.4]	27.5 [25.1, 30.3]	27.7 [25.3, 30.7]	<0.001
Systolic BP† (mmHg)	133 [123, 147]	138 [127, 151]	140 [128, 152]	141 [129, 154]	142 [130, 155]	<0.001
On lipid-lowering medication (%)	31602 (14.6)	19081 (17.4)	13273 (20.0)	5286 (23.8)	8411 (38.4)	<0.001
On anti-hypertensive medications (%)	47173 (21.9)	25262 (23.0)	15148 (22.8)	5071 (22.8)	5691 (26.0)	<0.001
Diabetes mellitus (%)	13365 (6.2)	4424 (4.0)	2267 (3.4)	736 (3.3)	983 (4.5)	<0.001
HbA1c† (mmol/mol)	34.6 [32.1, 37.3]	35.3 [33.0, 37.9]	35.7 [33.5, 38.1]	36.1 [33.8, 38.5]	36.4 [34.1, 38.9]	<0.001
CMR parameters (n=17311)						
LV EDV† (ml)	146 [126, 171]	144 [123, 170]	142 [122, 167]	141 [120, 166]	139 [119, 161]	<0.001
LV ESV† (ml)	59 [49, 72]	58 [47, 72]	57 [46, 70]	56 [45, 68]	55 [44, 68]	<0.001
LV EF† (%)	59 [55, 63]	59 [56, 63]	60 [56, 64]	60 [56, 64]	60 [56, 63]	<0.001
LV mass† (g)	82 [69, 101]	84 [69, 103]	85 [70, 103]	83 [69, 101]	86 [69, 102]	0.015

** Denotes data presented as mean (standard deviation); † denotes data presented as median [interquartile range]; LDL = low-density lipoprotein, HDL = high-density lipoprotein, BMI = body mass index, BSA = body surface area, BP = blood pressure, LV = left ventricular, EDV = end-diastolic volume, ESV = end-systolic volume, EF = ejection fraction*

Table 2: Effect of phenotypic and genetically-determined lipid levels on LV parameters

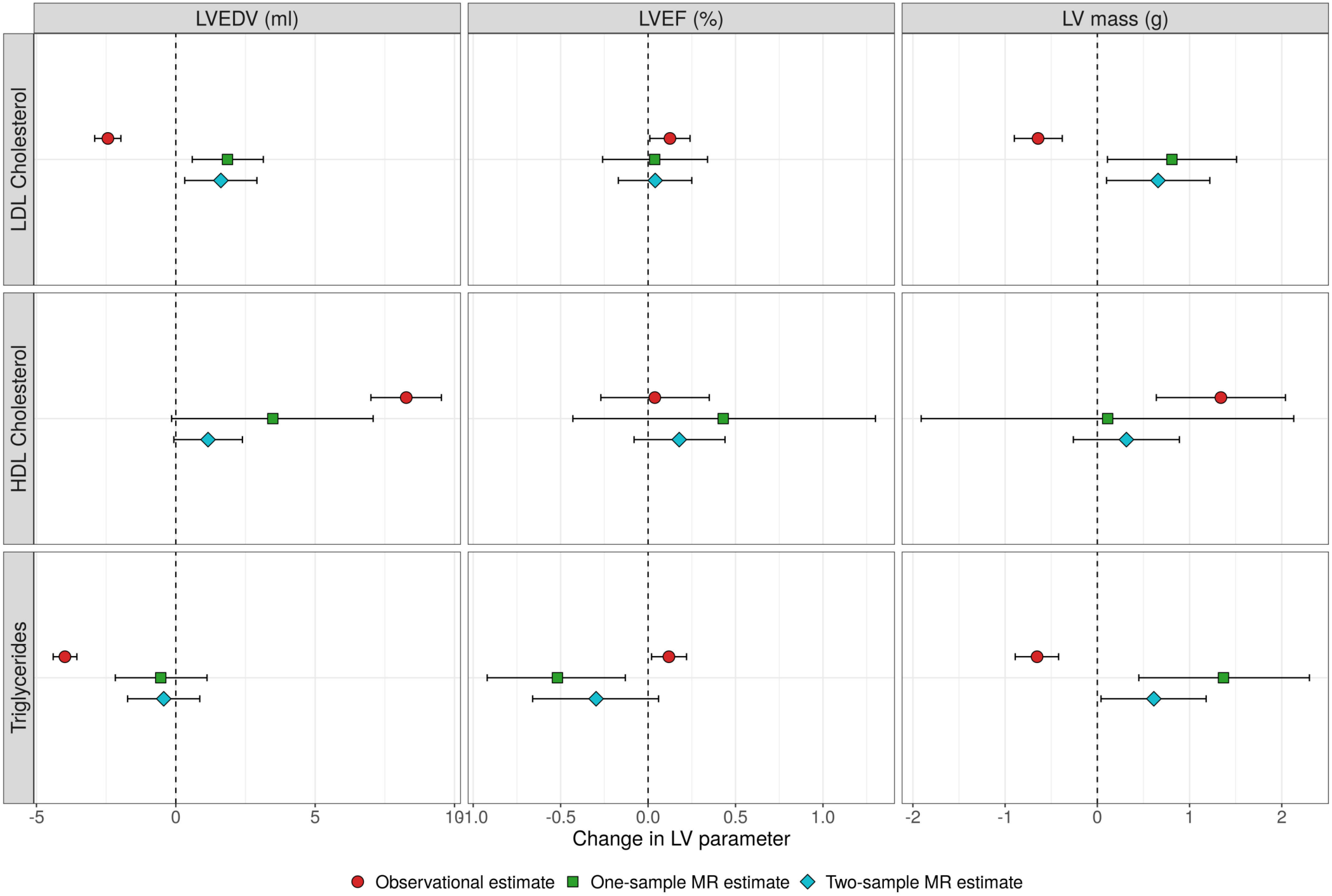
Lipid parameter	Phenotype	Observational effect size	Observational 95% CI	Observational p-value	MR effect size	MR 95% CI	MR p-value	Durbin-Wu -Hausman p-value	F-statistic
	LV EDV (ml)	-2.44	-2.91 to -1.97	<0.0001	1.85	0.59 to 3.14	0.004	<0.0001	2492.0
LDL Cholesterol	**LV EF (%)**	0.13	0.01 to 0.24	0.03	0.04	-0.26 to 0.34	0.8	0.22	2492.0
	LV mass (g)	-0.64	-0.90 to -0.38	<0.0001	0.81	0.11 to 1.51	0.023	0.0005	2492.0
	LV EDV (ml)	8.27	7.0 to 9.53	<0.0001	3.48	-0.15 to 7.08	0.056	<0.0001	1811.2
HDL Cholesterol	**LV EF (%)**	0.04	-0.27 to 0.35	0.806	0.43	-0.43 to 1.3	0.312	0.403	1811.2
	LV mass (g)	1.34	0.64 to 2.04	0.0002	0.11	-1.91 to 2.13	0.914	0.076	1811.2
	LV EDV (ml)	-3.98	-4.4 to -3.55	<0.0001	-0.54	-2.17 to 1.12	0.517	<0.0001	925.1
Triglycerides	**LV EF (%)**	0.12	0.02 to 0.22	0.024	-0.52	-0.92 to -0.13	0.011	0.0003	925.1
	LV mass (g)	-0.65	-0.89 to -0.42	<0.0001	1.37	0.45 to 2.3	0.004	0.0002	925.1

Observational data is adjusted for age at recruitment, sex, BMI, BSA, systolic blood pressure adjusted for anti-hypertensive medication use, physical activity, smoking status, HbA1c and presence of cardiovascular disease; data is presented for change in LV parameter per 39 mg/dL (1 mmol/L) in LDL and HDL cholesterol and 89 mg/dL in triglycerides.
One-sample Mendelian randomization (MR) data is adjusted for age, sex, BSA and the first five principal components and data is presented as change in LV parameter per 39 mg/dL (1 mmol/L) for LDL and HDL cholesterol and 89 mg/dL for triglyceride increase in lifetime lipid parameter exposure

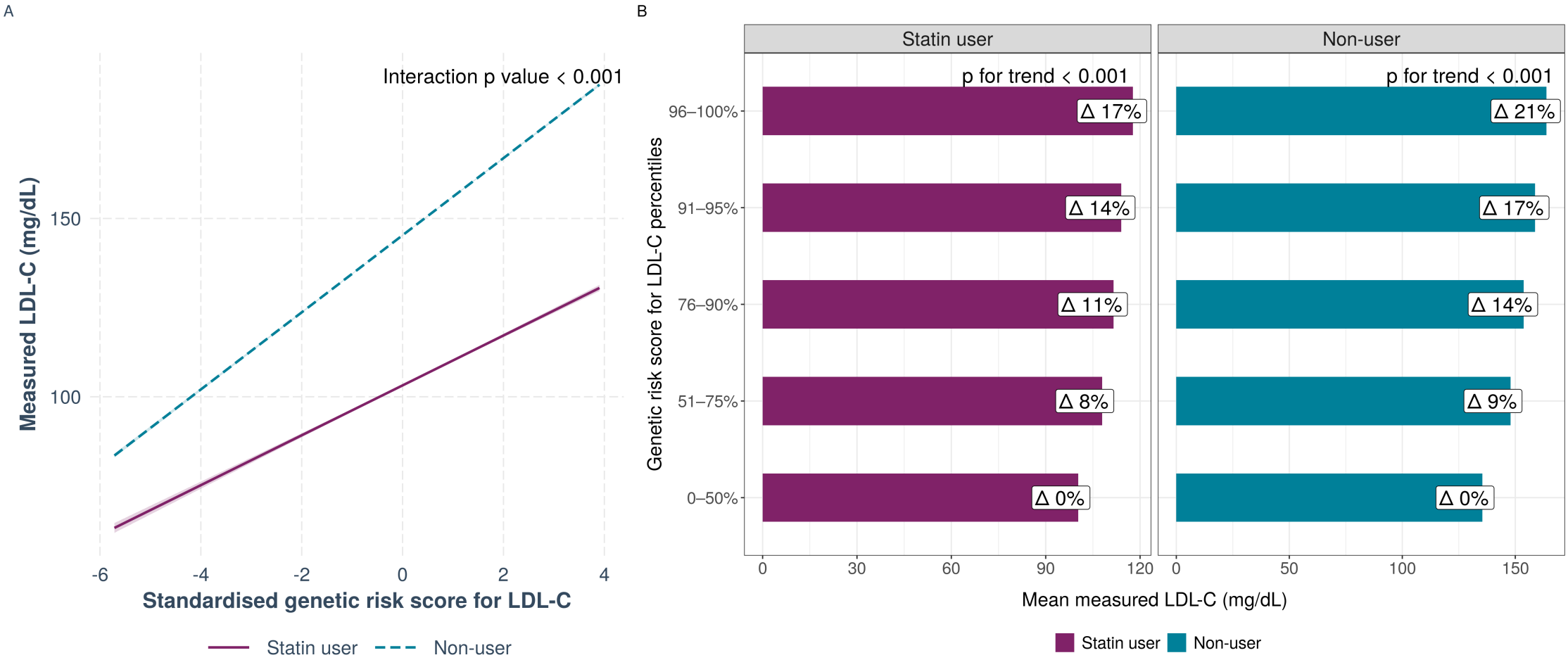
Table 3: Two-sample Mendelian randomization analysis using summary level data

Lipid parameter	Phenotype	IVW effect size	IVW confidence interval	IVW p-value	Egger intercept	Egger intercept p-value
LDL Cholesterol	**LV EDV (ml)**	1.62	0.32 to 2.91	0.014	-0.023	0.655
	LV EF (%)	0.04	-0.17 to 0.25	0.705	-0.007	0.490
	LV mass (g)	0.66	0.1 to 1.22	0.021	0.024	0.368
HDL Cholesterol	**LV EDV (ml)**	1.16	-0.07 to 2.39	0.065	0.013	0.820
	LV EF (%)	0.18	-0.08 to 0.44	0.184	-0.003	0.812
	LV mass (g)	0.32	-0.26 to 0.89	0.279	-0.029	0.296
Triglycerides	**LV EDV (ml)**	-0.43	-1.73 to 0.86	0.512	-0.039	0.504
	LV EF (%)	-0.30	-0.66 to 0.06	0.106	-0.002	0.889
	LV mass (g)	0.61	0.04 to 1.18	0.036	0.034	0.188

For two-sample MR the change in LV parameter reflects an increase per 34 mg/dL (0.87 mmol/L) 15 mg/dL (0.38 mmol/L) and 90 mg/dL (1.02 mmol/L) increase in LDL cholesterol, HDL cholesterol and triglycerides, respectively.



Mendelian randomization analysis demonstrates a potentially causal association between increased LDL-cholesterol and higher LV end-diastolic volume and LV mass, and triglycerides with higher LV mass.


A
Interaction p value < 0.001
Measured LDL-C (mg/dL)
150
100
-6
-4
-2
0
2
4
Standardised genetic risk score for LDL-C
Statin user
Non-user
B
Statin user
Non-user
p for trend < 0.001
p for trend < 0.001
Genetic risk score for LDL-C percentiles
96–100%
91–95%
76–90%
51–75%
0–50%
Δ 17%
Δ 14%
Δ 11%
Δ 8%
Δ 0%
Δ 21%
Δ 17%
Δ 14%
Δ 9%
Δ 0%
0
30
60
90
120
0
50
100
150
Mean measured LDL-C (mg/dL)
Statin user
Non-user

Supplementary Material

Supplementary Tables

Supplementary Table 1: 101 variants included in the genetic risk score for LDL cholesterol

Supplementary Table 2: 125 variants included in the genetic risk score for HDL cholesterol

Supplementary Table 3: 73 variants included in the genetic risk score for triglycerides

Supplementary Table 4. One-sample MR with a single instrument and additional adjustment for all three lipid instruments

Supplementary Table 5. One-sample MR adjusted for all potential confounders

Supplementary Table 6: Associations between LV parameters and lipid parameter with phenotypic and genetically-determined lipid level included as covariates

Supplementary Table 7: One-sample MR results using restricted list of variants in GRS

Supplementary Table 8: Two-sample single instrument and multivariable MR analysis using summary level data

Supplementary Table 9: Two-sample MR with MR-Egger, weighted median and weighted mode methods

Supplementary Table 10: MR pleiotropy residual sum and outlier (MR-PRESSO) analysis for horizontal pleiotropy

Supplementary Table 11: MR-Steiger analysis

Supplementary Table 12. Interaction analysis of the statin therapy on the relationships between the genetic risk score for LDL cholesterol and LV parameters

Supplementary Table 13: The variance of phenotypic LV parameters explained by observed lipid measurements and lipid genetic risk scores

Supplementary Figures

Supplementary Figure 1: Power analysis for one-sample MR

Supplementary Figure 2. Correlation between lipid genetic risk scores assessed by Pearson's test

Supplementary Figure 3. Forest plots for two-sample MR analysis of LDL cholesterol

Supplementary Figure 4. Forest plots for two-sample MR analysis of HDL cholesterol

Supplementary Figure 5. Forest plots for two-sample MR analysis of triglycerides

Supplementary Table 1: 101 variants included in the genetic risk score for LDL cholesterol

Variant ID	Effect allele	Other allele	Effect allele frequency	Beta	SE	P
rs2419604	A	G	0.3179	0.0302	0.004	7.49E-14
rs413380	C	T	0.9657	0.0861	0.0098	7.62E-17
rs4970834	C	T	0.8127	0.1503	0.0047	1.00E-200
rs9804646	C	T	0.91029	0.0454	0.007	8.60E-11
rs10893499	A	G	0.1438	0.0521	0.0053	3.86E-21
rs10832962	T	C	0.719	0.032	0.004	6.62E-14
rs267733	A	G	0.8628	0.0331	0.0053	5.29E-09
rs174583	C	T	0.6253	0.0522	0.0038	7.00E-41
rs3184504	C	T	0.5343	0.0268	0.0038	4.20E-12
rs1169288	C	A	0.3338	0.0375	0.004	6.45E-21
rs2642438	G	A	0.7454	0.0352	0.0042	7.32E-16
rs2587534	A	G	0.5277	0.0391	0.0037	8.06E-25
rs10903129	G	A	0.5369	0.0328	0.0037	3.03E-17
rs12748152	T	C	0.07124	0.0499	0.0066	3.21E-12
rs4942486	T	C	0.4617	0.0243	0.0037	2.26E-11
rs8017377	A	G	0.4591	0.0303	0.0038	2.52E-15
rs11206508	A	G	0.1319	0.0434	0.0055	2.26E-14
rs17111503	G	A	0.2414	0.0662	0.0045	1.39E-45
rs11591147	G	T	0.98285	0.497	0.018	8.60E-143
rs630431	A	G	0.6913	0.0351	0.0042	7.73E-17
rs11583974	A	G	0.03034	0.0646	0.0117	3.95E-09
rs2647281	G	A	0.05541	0.0589	0.0095	2.27E-09
rs207150	C	T	0.91821	0.0472	0.0065	2.00E-12
rs11485618	A	G	0.6913	0.05	0.0039	3.73E-33
rs247616	C	T	0.7071	0.0547	0.0041	2.57E-37
rs2000999	A	G	0.1847	0.065	0.0046	4.22E-41
rs6504872	T	C	0.4723	0.0274	0.0037	3.48E-13
rs1801689	C	A	0.03694	0.1028	0.0139	9.81E-12
rs2886232	T	C	0.1201	0.0451	0.0064	3.88E-11
rs314253	T	C	0.6649	0.0242	0.0038	3.44E-10
rs11669133	A	G	0.04222	0.0501	0.0098	4.80E-08
rs6511720	G	T	0.90237	0.2209	0.0061	1.00E-200
rs688	T	C	0.4472	0.054	0.0037	1.01E-43
rs6511727	T	G	0.3852	0.0266	0.0038	1.84E-11
rs376642	C	T	0.715	0.0233	0.004	4.67E-10
rs10401969	T	C	0.92876	0.1184	0.0072	2.65E-54
rs4970712	C	A	0.8061	0.0339	0.0044	2.46E-13
rs17800760	G	A	0.8681	0.0513	0.0053	8.87E-22
rs10460181	A	G	0.8127	0.0536	0.0046	2.25E-28
rs1531517	G	A	0.94855	0.2202	0.008	9.50E-163
rs7254892	G	A	0.96834	0.4853	0.0119	1.00E-200

rs2075650	G	A	0.1266	0.1767	0.0055	1.00E-200
rs75687619	T	G	0.02375	0.1735	0.0161	8.05E-24
rs2287019	C	T	0.81	0.0283	0.0048	8.36E-09
rs492602	G	A	0.4301	0.0293	0.0039	9.42E-14
rs364585	G	A	0.6332	0.0249	0.0038	4.28E-10
rs2328223	C	A	0.2493	0.0299	0.005	5.63E-09
rs7264396	C	T	0.781	0.0246	0.0045	4.41E-08
rs6016381	T	C	0.6398	0.0363	0.0038	6.85E-20
rs6065311	C	T	0.4604	0.0417	0.0036	1.66E-30
rs1800961	C	T	0.9657	0.0685	0.0106	6.03E-10
rs10490626	G	A	0.92084	0.0508	0.0069	1.70E-12
rs2030746	T	C	0.3984	0.0214	0.0038	8.61E-09
rs16831243	T	C	0.1807	0.0378	0.0055	9.06E-12
rs10195252	T	C	0.5818	0.0238	0.0039	3.81E-08
rs492399	G	A	0.03562	0.0629	0.0102	1.23E-09
rs13414987	A	C	0.2177	0.0308	0.0043	9.94E-12
rs1367117	A	G	0.2876	0.1186	0.004	9.50E-183
rs12471982	C	A	0.1359	0.0365	0.0054	3.93E-11
rs520861	G	A	0.7071	0.0843	0.0042	1.78E-84
rs1250229	C	T	0.7889	0.0243	0.0042	3.13E-08
rs5763662	T	C	0.02507	0.0767	0.0121	1.19E-08
rs11563251	T	C	0.1253	0.0345	0.0062	4.50E-08
rs4253776	G	A	0.124	0.0311	0.0059	3.35E-08
rs780093	T	C	0.4129	0.0223	0.0037	2.36E-08
rs1025447	C	T	0.1583	0.0418	0.0048	3.78E-16
rs6544713	T	C	0.2942	0.0806	0.0041	4.84E-83
rs6709904	A	G	0.8865	0.055	0.0085	4.58E-10
rs2710642	A	G	0.6187	0.0239	0.0038	6.09E-09
rs9875338	G	A	0.6121	0.027	0.0037	2.21E-11
rs17404153	G	T	0.8562	0.0336	0.0054	1.83E-09
rs7640978	C	T	0.8945	0.0392	0.0069	9.84E-09
rs6818397	T	G	0.4129	0.0224	0.004	1.68E-08
rs4530754	A	G	0.5818	0.0275	0.0036	3.58E-12
rs6882076	C	T	0.6662	0.0456	0.0038	3.31E-31
rs12916	C	T	0.4314	0.0733	0.0038	7.79E-78
rs6909746	C	T	0.6082	0.0263	0.0037	7.86E-11
rs1564348	C	T	0.1451	0.0481	0.005	2.76E-21
rs3125055	A	T	0.1398	0.0468	0.0055	5.92E-16
rs1510226	C	T	0.01319	0.1409	0.0214	1.71E-10
rs7770628	C	T	0.4485	0.0258	0.0037	3.17E-11
rs3757354	C	T	0.7902	0.0382	0.0044	2.09E-17
rs13206249	G	A	0.7836	0.0378	0.0062	4.53E-08
rs1800562	G	A	0.95383	0.0615	0.008	8.25E-14

rs2247056	C	T	0.7823	0.0248	0.0043	1.42E-08
rs10947332	A	G	0.1319	0.0504	0.0056	6.97E-18
rs12670798	C	T	0.2243	0.0344	0.0043	4.81E-14
rs4722551	C	T	0.1702	0.0391	0.0049	3.95E-14
rs2073547	G	A	0.1939	0.0485	0.0049	1.92E-21
rs2737252	G	A	0.7441	0.0314	0.0041	7.04E-14
rs2954029	A	T	0.5317	0.0564	0.0036	2.10E-50
rs7832643	T	G	0.405	0.0339	0.0038	2.67E-17
rs10102164	A	G	0.1741	0.0316	0.0045	3.74E-11
rs13277801	C	T	0.347	0.0338	0.0038	3.99E-17
rs9987289	G	A	0.9248	0.0714	0.0066	8.53E-24
rs1883025	C	T	0.7573	0.0296	0.0044	6.14E-11
rs8176722	C	A	0.8892	0.0473	0.006	1.85E-14
rs579459	C	T	0.215	0.0665	0.0045	2.42E-44
rs3780181	A	G	0.94723	0.0445	0.0074	1.76E-09
rs519113	C	G	0.786	0.0971	0.0066	1.61E-49
rs964184	G	C	0.162	0.0855	0.0078	2.01E-26

Supplementary Table 2: 125 variants included in the genetic risk score for HDL cholesterol

Variant ID	Effect allele	Other allele	Effect allele frequency	Beta	SE	P
rs2250802	G	A	0.3193	0.034	0.0038	2.02E-17
rs2148489	T	C	0.7757	0.0283	0.0041	1.41E-10
rs970548	C	A	0.277	0.0258	0.0039	1.71E-10
rs10761771	C	T	0.467	0.0198	0.0034	4.12E-09
rs12740374	T	G	0.2124	0.0343	0.0041	1.69E-15
rs333947	G	A	0.8536	0.0296	0.0047	3.17E-09
rs7943309	A	G	0.03958	0.0865	0.0088	1.18E-20
rs7117842	C	T	0.3892	0.0272	0.0035	1.06E-14
rs17135399	A	G	0.93404	0.0483	0.0077	4.26E-09
rs7128597	C	A	0.1715	0.0398	0.0065	1.82E-08
rs3847502	A	C	0.314	0.048	0.0036	3.31E-38
rs4752894	G	A	0.3984	0.0206	0.0035	1.89E-09
rs12145743	G	T	0.3311	0.0203	0.0036	1.80E-08
rs102275	T	C	0.628	0.0391	0.0035	6.40E-28
rs12801636	A	G	0.2243	0.0235	0.0042	3.15E-08
rs499974	C	A	0.8245	0.0263	0.0044	1.12E-08
rs4650994	G	A	0.5172	0.021	0.0034	6.70E-09
rs1689797	C	A	0.6979	0.0358	0.0036	2.85E-21
rs2241210	G	A	0.5528	0.0332	0.0035	2.49E-20
rs653178	T	C	0.5317	0.0263	0.0035	1.06E-12
rs2454722	G	A	0.1451	0.0351	0.0044	3.31E-14
rs11057397	T	C	0.3668	0.0282	0.0036	6.77E-14
rs863750	C	T	0.4195	0.0264	0.0035	4.71E-13
rs838876	A	G	0.3259	0.0493	0.0039	7.33E-33
rs7306660	G	A	0.6306	0.0345	0.0036	3.34E-19
rs7298751	G	A	0.1187	0.0434	0.0052	2.46E-16
rs2642438	G	A	0.7454	0.0303	0.0039	7.78E-14
rs11045163	G	A	0.4063	0.0217	0.0035	3.20E-09
rs4846914	A	G	0.5844	0.0479	0.0034	3.51E-41
rs3741414	T	C	0.1913	0.0296	0.004	6.10E-14
rs12748152	C	T	0.92876	0.0506	0.0062	9.74E-16
rs4660293	A	G	0.7639	0.0353	0.004	2.86E-18
rs4983559	G	A	0.3773	0.0197	0.0036	9.57E-09
rs492571	T	C	0.95778	0.0663	0.009	1.27E-12
rs2899624	A	G	0.8456	0.0714	0.0049	1.39E-40
rs185481	C	T	0.529	0.0366	0.0035	1.40E-23
rs16940147	A	G	0.04617	0.0514	0.008	2.45E-10
rs10468017	T	C	0.2757	0.1179	0.0038	1.20E-188
rs1077834	C	T	0.2111	0.1253	0.0041	7.80E-180
rs424346	T	C	0.04881	0.0679	0.0113	4.84E-08

rs1007076	C	T	0.7296	0.0247	0.0041	4.43E-09
rs1121980	G	A	0.5528	0.0196	0.0034	6.79E-09
rs3790106	C	G	0.81	0.0374	0.0052	3.27E-11
rs4784659	T	C	0.1847	0.0274	0.0049	1.02E-08
rs13336936	T	C	0.03562	0.0717	0.0104	6.98E-11
rs7193072	A	G	0.2375	0.0498	0.0038	1.40E-34
rs1138429	A	T	0.90237	0.1156	0.0065	9.52E-66
rs9989419	G	A	0.595	0.1473	0.0036	1.00E-200
rs4783961	A	G	0.4855	0.0997	0.0036	5.70E-162
rs289745	A	C	0.6029	0.0276	0.0041	2.28E-20
rs291040	T	C	0.6623	0.0305	0.0037	8.21E-17
rs16942887	A	G	0.1332	0.0831	0.0051	8.28E-54
rs4986970	A	T	0.96702	0.0792	0.0099	1.09E-15
rs2925979	C	T	0.7045	0.0351	0.0037	1.32E-19
rs1877031	A	G	0.6755	0.0336	0.0036	1.20E-19
rs4148005	T	G	0.7005	0.0283	0.0036	5.74E-14
rs4969178	G	A	0.6266	0.0263	0.0035	1.53E-12
rs8093249	A	G	0.8404	0.0384	0.0051	1.80E-13
rs9955201	A	G	0.06069	0.0638	0.0081	2.40E-14
rs4939883	C	T	0.8193	0.0799	0.0045	1.80E-66
rs9951669	G	A	0.2177	0.0408	0.0042	3.01E-21
rs6567160	T	C	0.7691	0.0257	0.0041	2.92E-09
rs737337	T	C	0.9314	0.0565	0.0061	4.56E-17
rs12133576	A	G	0.3549	0.0243	0.0035	6.15E-11
rs731839	A	G	0.6583	0.022	0.0037	3.44E-09
rs2075650	A	G	0.8734	0.0554	0.0051	9.72E-26
rs77301115	G	A	0.97361	0.0972	0.0157	1.03E-08
rs7412	T	C	0.06596	0.0978	0.0097	4.44E-19
rs5167	G	T	0.3694	0.032	0.0037	4.88E-16
rs17695224	G	A	0.7612	0.029	0.0039	2.42E-13
rs103294	T	C	0.186	0.0523	0.0044	4.00E-30
rs2278236	A	G	0.5435	0.0331	0.0035	3.19E-18
rs3111576	T	C	0.1372	0.0448	0.0054	1.20E-14
rs1800961	C	T	0.9657	0.127	0.0099	1.64E-34
rs4465830	A	G	0.7982	0.0597	0.0044	5.18E-40
rs17380117	A	G	0.8087	0.0253	0.0042	3.85E-09
rs7607980	C	T	0.1491	0.0447	0.0052	1.81E-15
rs676210	A	G	0.2309	0.066	0.004	2.35E-54
rs1047891	C	A	0.6979	0.0269	0.0039	8.73E-10
rs181360	T	G	0.8008	0.0376	0.0042	9.24E-18
rs1515110	G	T	0.3813	0.0323	0.0035	8.04E-18
rs2606736	C	T	0.3945	0.0246	0.0043	4.80E-08
rs6805251	T	C	0.3813	0.02	0.0035	1.33E-08

rs13076253	A	C	0.8522	0.0283	0.0048	4.96E-09
rs687339	C	T	0.2335	0.0316	0.0042	7.11E-13
rs2290547	G	A	0.7889	0.0297	0.0046	3.69E-09
rs2013208	T	C	0.5053	0.0254	0.0036	8.92E-12
rs13326165	A	G	0.1873	0.0289	0.0043	9.04E-11
rs2602836	A	G	0.4274	0.0192	0.0034	4.96E-08
rs13107325	C	T	0.92216	0.0708	0.0078	1.07E-15
rs10019888	A	G	0.8364	0.027	0.0046	4.90E-08
rs442177	G	T	0.4472	0.0215	0.0034	2.19E-09
rs3822072	G	A	0.5119	0.0251	0.0034	4.06E-12
rs6450176	G	A	0.7216	0.0254	0.0039	6.88E-10
rs3936511	A	G	0.8311	0.0308	0.0046	2.96E-09
rs1936800	C	T	0.5277	0.02	0.0034	3.06E-10
rs3861397	A	G	0.6583	0.024	0.0036	8.40E-11
rs9457931	A	G	0.9314	0.0552	0.0073	7.30E-13
rs3823417	A	G	0.2322	0.0285	0.0042	2.07E-11
rs715299	T	G	0.7441	0.024	0.0039	6.47E-09
rs205262	A	G	0.7335	0.0283	0.0039	3.88E-13
rs998584	C	A	0.4855	0.026	0.0038	2.27E-11
rs11765979	C	A	0.4578	0.0412	0.0048	3.11E-17
rs13225097	A	G	0.7678	0.0227	0.0039	4.33E-08
rs17173637	T	C	0.90237	0.0363	0.0057	1.90E-08
rs4142995	G	T	0.6161	0.0263	0.0037	9.37E-12
rs4917014	G	T	0.3404	0.0222	0.0036	1.03E-08
rs702485	G	A	0.4499	0.0243	0.0034	6.45E-12
rs17145738	T	C	0.1174	0.0408	0.0053	4.95E-13
rs7014168	G	A	0.7586	0.0267	0.0041	9.20E-10
rs2293889	G	T	0.5871	0.0312	0.0035	4.27E-17
rs10808546	T	C	0.4459	0.0409	0.0034	4.11E-30
rs10087900	G	A	0.5607	0.0231	0.0036	2.17E-09
rs7016529	T	C	0.98681	0.2186	0.0141	9.27E-45
rs13702	C	T	0.3127	0.1058	0.0038	1.30E-160
rs13265868	A	G	0.4604	0.0478	0.0035	6.10E-40
rs16842	T	C	0.7467	0.03	0.0038	3.82E-14
rs4240624	A	G	0.9248	0.0818	0.0058	1.32E-45
rs2230808	C	T	0.7889	0.0385	0.004	1.59E-20
rs2853579	T	G	0.1108	0.0499	0.0053	1.32E-19
rs11789603	T	C	0.08971	0.06	0.006	3.70E-21
rs1883025	C	T	0.7573	0.0698	0.0041	1.50E-65
rs686030	A	C	0.8588	0.055	0.0049	4.29E-27
rs964184	C	G	0.838	0.1065	0.0071	6.09E-48
rs6589581	T	A	0.021	0.0845	0.0137	2.26E-09

Supplementary Table 3: 73 variants included in the genetic risk score for triglycerides

Variant ID	Effect allele	Other allele	Effect allele frequency	Beta	SE	P
rs2250802	A	G	0.6807	0.023	0.0037	1.21E-10
rs1832007	A	G	0.8681	0.0327	0.0047	1.72E-12
rs10761762	T	C	0.533	0.027	0.0033	1.06E-17
rs2068888	G	A	0.5092	0.0241	0.0034	1.68E-11
rs7350481	T	C	0.09763	0.2254	0.0066	1.00E-200
rs2187126	A	G	0.94591	0.0543	0.0069	2.90E-15
rs12294259	T	C	0.05937	0.219	0.0069	1.80E-200
rs9804646	C	T	0.91029	0.0524	0.0064	2.82E-17
rs5110	A	C	0.06464	0.156	0.0124	2.14E-34
rs7943309	G	A	0.96042	0.0605	0.0087	1.16E-11
rs10501321	T	C	0.686	0.0216	0.0035	1.41E-08
rs174535	C	T	0.3628	0.047	0.0034	1.73E-41
rs11057408	G	T	0.6372	0.0258	0.0035	2.05E-12
rs1321257	G	A	0.4063	0.0402	0.0034	5.99E-31
rs11613352	C	T	0.8087	0.028	0.0039	9.40E-14
rs12748152	T	C	0.07124	0.0372	0.0059	1.10E-09
rs17513135	T	C	0.2322	0.022	0.0039	1.63E-08
rs16948098	A	G	0.0409	0.08	0.0089	4.84E-17
rs10468017	T	C	0.2757	0.0379	0.0039	7.56E-21
rs588136	C	T	0.2058	0.0495	0.0041	3.37E-30
rs3198697	C	T	0.6174	0.0198	0.0034	2.21E-08
rs4587594	G	A	0.69	0.0694	0.0035	3.50E-82
rs749671	G	A	0.6055	0.0211	0.0034	6.11E-10
rs9930333	G	T	0.4485	0.0208	0.0037	3.25E-08
rs247616	C	T	0.7071	0.0393	0.0037	1.12E-25
rs5880	C	G	0.05937	0.0475	0.0085	4.71E-08
rs8077889	C	A	0.2441	0.0252	0.0042	9.88E-09
rs117877390	C	T	0.9657	0.1099	0.0141	1.53E-09
rs10401969	T	C	0.92876	0.121	0.0065	9.70E-70
rs731839	G	A	0.3417	0.0224	0.0036	2.65E-09
rs4803750	G	A	0.05541	0.0423	0.007	9.52E-09
rs7254892	A	G	0.03166	0.1235	0.0106	1.40E-24
rs439401	C	T	0.6201	0.0659	0.0038	1.42E-66
rs3760627	C	T	0.4683	0.0189	0.0034	5.29E-09
rs7248104	G	A	0.5831	0.0222	0.0034	5.05E-10
rs4804311	A	G	0.8905	0.0392	0.006	1.49E-09
rs6029143	C	T	0.94195	0.0388	0.0071	4.93E-08
rs4810479	C	T	0.2876	0.0474	0.0038	2.07E-34
rs6066141	T	C	0.7586	0.0297	0.0053	2.34E-08
rs13389219	C	T	0.591	0.0271	0.0034	2.60E-15
rs676210	G	A	0.7691	0.0733	0.0039	3.28E-71

rs2972146	T	G	0.6227	0.0281	0.0034	2.97E-15
rs3761445	A	G	0.6148	0.0232	0.0034	8.06E-12
rs2304684	T	C	0.02507	0.086	0.0127	5.00E-11
rs1260326	T	C	0.4129	0.1148	0.0034	1.00E-200
rs11674085	A	G	0.2005	0.0251	0.0044	2.86E-08
rs10440120	C	A	0.8325	0.0306	0.0044	5.34E-11
rs645040	T	G	0.7691	0.0293	0.004	1.83E-12
rs6831256	G	A	0.409	0.0258	0.0035	1.60E-12
rs442177	T	G	0.5528	0.0309	0.0033	1.32E-18
rs6882076	C	T	0.6662	0.0286	0.0035	1.51E-15
rs9686661	T	C	0.1768	0.0379	0.0044	2.54E-16
rs719726	T	C	0.529	0.0199	0.0035	2.49E-08
rs634869	T	C	0.438	0.0272	0.0033	1.78E-14
rs2665357	C	A	0.5092	0.0212	0.0033	8.33E-10
rs2508015	G	A	0.6715	0.0252	0.0038	1.33E-10
rs2247056	C	T	0.7823	0.0378	0.0039	3.86E-21
rs11752643	T	C	0.02639	0.0802	0.0088	3.96E-19
rs998584	A	C	0.5145	0.0293	0.0037	3.42E-15
rs38855	A	G	0.5264	0.0187	0.0033	2.11E-08
rs287621	T	C	0.2704	0.0222	0.0037	7.67E-09
rs4719841	G	A	0.3826	0.0232	0.0034	8.86E-11
rs11974409	A	G	0.8061	0.0899	0.0042	1.40E-100
rs72555385	G	A	0.06201	0.0749	0.0124	3.76E-09
rs6995541	G	A	0.3219	0.0265	0.0037	1.34E-12
rs1062219	T	C	0.4921	0.0223	0.0034	1.69E-09
rs2954022	C	A	0.5303	0.078	0.0033	2.20E-113
rs4871624	G	T	0.2652	0.0254	0.0037	1.07E-11
rs4921914	C	T	0.248	0.0353	0.004	4.87E-17
rs7016529	C	T	0.01319	0.1911	0.014	3.57E-35
rs12678919	A	G	0.8786	0.1702	0.0056	1.80E-199
rs4738684	A	G	0.3522	0.0205	0.0035	8.82E-09
rs7005265	T	A	0.297	0.0336	0.0053	1.26E-10

Supplementary Table 4. One-sample MR with a single instrument and additional adjustment for all three lipid instruments

Lipid parameter	Phenotype	Single instrument MR effect size	Single instrument MR 95% CI	Single instrument MR p-value	Multiple instrument MR effect size	Multiple instrument MR 95% CI	Multiple instrument MR p-value
LDL Cholesterol	LV EDV (ml)	1.85	0.59 to 3.14	0.004	2.12	0.08 to 3.46	0.001
	LV mass (g)	0.81	0.11 to 1.51	0.023	0.77	0.04 to 1.51	0.037
Triglycerides	LV EF (%)	-0.52	-0.92 to -0.13	0.011	-0.54	-0.99 to -0.10	0.019
	LV mass (g)	1.37	0.45 to 2.3	0.004	1.54	0.50 to 2.59	0.004

Supplementary Table 5. One-sample MR adjusted for all potential confounders

Lipid parameter	CMR parameter	MR effect size	MR 95% CI	MR p-value
LDL Cholesterol	LV EDV (ml)	1.68	0.38 to 3.0	0.010
	LV EF (%)	0.06	-0.25 to 0.37	0.710
	LV mass (g)	0.72	0.01 to 1.45	0.046
HDL Cholesterol	LV EDV (ml)	3.41	-0.35 to 7.16	0.071
	LV EF (%)	0.44	-0.47 to 1.35	0.338
	LV mass (g)	0.40	-1.68 to 2.49	0.703
Triglycerides	LV EDV (ml)	-0.93	-2.62 to 0.78	0.279
	LV EF (%)	-0.56	-0.98 to -0.15	0.008
	LV mass (g)	1.04	0.1 to 1.99	0.034

One-sample MR data following additional adjustment for age at recruitment, sex, BMI, BSA, systolic blood pressure adjusted for anti-hypertensive medication use, physical activity, smoking status, HbA1c and presence of cardiovascular disease; data is presented for change in LV parameter per 1 mmol/L increase in lifetime exposure to lipid parameter

Supplementary Table 6: Associations between LV parameters and lipid parameter with phenotypic and genetically-determined lipid level included as covariates

Phenotype	Lipid parameter	Effect size	95% CI	p-value
LV EDV	Measured LDL cholesterol	-3.91	-4.39 to -3.44	1.60E-58
LV EDV	Genetically-determined LDL cholesterol	5.91	4.54 to 7.29	3.63E-17
LV EF	Measured LDL cholesterol	0.24	0.12 to 0.35	4.18E-05
LV EF	Genetically-determined LDL cholesterol	-0.20	-0.53 to 0.12	2.24E-01
LV mass	Measured LDL cholesterol	-0.52	-0.79 to -0.26	1.11E-04
LV mass	Genetically-determined LDL cholesterol	1.36	0.60 to 2.13	5.00E-04
LV EDV	Measured HDL cholesterol	12.26	11.02 to 13.50	4.30E-83
LV EDV	Genetically-determined HDL cholesterol	-8.96	-12.82 to -5.10	5.44E-06
LV EF	Measured HDL cholesterol	0.05	-0.25 to 0.35	7.55E-01
LV EF	Genetically-determined HDL cholesterol	0.39	-0.54 to 1.32	4.12E-01
LV mass	Measured HDL cholesterol	2.05	1.35 to 2.74	8.25E-09
LV mass	Genetically-determined HDL cholesterol	-1.97	-4.14 to 0.20	7.48E-02
LV EDV	Measured triglycerides	-5.18	-5.59 to -4.77	1.78E-134
LV EDV	Genetically-determined triglycerides	4.47	2.86 to 6.08	5.61E-08
LV EF	Measured triglycerides	0.23	0.13 to 0.33	5.16E-06
LV EF	Genetically-determined triglycerides	-0.73	-1.12 to -0.34	2.37E-04
LV mass	Measured triglycerides	-0.46	-0.69 to -0.23	7.73E-05
LV mass	Genetically-determined triglycerides	1.79	0.88 to 2.70	1.19E-04

Models are adjusted for age, sex, body surface area and the first 5 genetic principal components. The effect sizes represent the change in LV parameter for every 1 mmol/L increment in lipid concentration.

Supplementary Table 7: One-sample MR results using restricted list of variants in GRS

Lipid parameter	Phenotype	MR effect size	MR 95% CI	MR p value
LDL Cholesterol	LV EDV (ml)	2.12	0.74 to 3.53	0.002
LDL Cholesterol	LV EF (%)	-0.06	-0.39 to 0.26	0.695
LDL Cholesterol	LV mass (g)	1.01	0.24 to 1.78	0.009
Triglycerides	LV EDV (ml)	-0.61	-2.26 to 1.08	0.469
Triglycerides	LV EF (%)	-0.40	-0.8 to 0.001	0.052
Triglycerides	LV mass (g)	1.13	0.21 to 2.08	0.018

One-sample MR data utilising a weighted genetic risk score built using a restricted list of variants following removal of variants which might potentially influence LV remodeling. The total number of included variants is 69, 81 and 50 for LDL, HDL and triglycerides genetic risk scores, respectively. Data is adjusted for age, sex, BSA and the first five principal components and data is presented as change in LV parameter per 39 mg/dL (1 mmol/L) for LDL and HDL cholesterol and 89 mg/dL for triglyceride increase in lifetime lipid parameter exposure.

Supplementary Table 8: Two-sample single instrument and multivariable Mendelian randomization analysis using summary level data

Lipid parameter	Phenotype	Single instrument IVW beta	IVW confidence interval	IVW p-value	Multivariable MR IVW beta	Multivariable MR IVW confidence interval	Multivariable MR IVW p-value
LDL Cholesterol	LV EDV (ml)	1.62	0.32 to 2.91	0.014	1.90	1.13 to 2.67	<0.0001
	LV EF (%)	0.04	-0.17 to 0.25	0.705	0.11	-0.06 to 0.28	0.207
	LV mass (g)	0.66	0.1 to 1.22	0.021	0.55	0.13 to 0.96	0.010
Triglycerides	LV EDV (ml)	-0.43	-1.73 to 0.86	0.512	-1.1	-2.21 to 0.01	0.052
	LV EF (%)	-0.30	-0.66 to 0.06	0.106	-0.23	-0.47 to 0.01	0.060
	LV mass (g)	0.61	0.04 to 1.18	0.036	0.61	0.01 to 1.20	0.047

For two-sample MR the change in LV parameter reflects an increase per 34 mg/dL (0.87 mmol/L) 15 mg/dL (0.38 mmol/L) and 90 mg/dL (1.02 mmol/L) increase in LDL cholesterol, HDL cholesterol and triglycerides, respectively.

Supplementary Table 9: Two-sample MR with MR-Egger, weighted median and weighted mode methods

Lipid parameter	CMR parameter	Egger effect size	Egger confidence interval	Egger p-value	Weighted median effect size	Weighted median confidence interval	Weighted median p-value	Weighted mode effect size	Weighted mode confidence interval	Weighted mode p-value
LDL Cholesterol	LV EDV (ml)	1.90	0.2 to 3.59	0.029	2.12	0.44 to 3.8	0.014	1.93	0.28 to 3.58	0.022
	LV EF (%)	0.12	-0.18 to 0.42	0.422	0.14	-0.19 to 0.48	0.407	0.40	-0.52 to 1.32	0.395
	LV mass (g)	0.32	-0.6 to 1.25	0.497	0.58	-0.27 to 1.43	0.182	0.14	-0.18 to 0.46	0.402
HDL Cholesterol	LV EDV (ml)	1.00	-1.15 to 3.15	0.363	1.26	-0.65 to 3.17	0.195	1.48	-0.38 to 3.34	0.119
	LV EF (%)	0.23	-0.26 to 0.73	0.359	0.26	-0.15 to 0.67	0.209	0.32	-0.12 to 0.76	0.158
	LV mass (g)	0.81	-0.12 to 1.73	0.087	0.36	-0.62 to 1.35	0.472	0.63	-0.39 to 1.65	0.227
Triglycerides	LV EDV (ml)	0.14	-1.82 to 2.1	0.886	-0.96	-3.04 to 1.12	0.365	-0.32	-2.41 to 1.76	0.762
	LV EF (%)	-0.27	-0.86 to 0.33	0.380	0.05	-0.44 to 0.53	0.851	0.11	-1.1 to 1.33	0.858
	LV mass (g)	0.09	-0.74 to 0.93	0.824	0.33	-0.75 to 1.4	0.549	-0.18	-0.67 to 0.32	0.487

For two-sample MR the change in LV parameter reflects an increase per 34 mg/dL (0.87 mmol/L) 15 mg/dL (0.38 mmol/L) and 90 mg/dL (1.02 mmol/L) increase in LDL cholesterol, HDL cholesterol and triglycerides, respectively.

Supplementary Table 10: MR pleiotropy residual sum and outlier (MR-PRESSO) analysis for horizontal pleiotropy

Lipid parameter	Phenotype	Global p-value	Original beta	Original CI	Original p-value	Corrected beta	Corrected CI	Corrected p-value	Distortion p-value
LDL Cholesterol	LV EDV	<0.0001	1.62	0.32 to 2.91	0.014	1.61	0.46 to 2.76	0.007	0.788
	LV EF	0.3824	0.04	-0.17 to 0.25	0.705	No outliers			
	LV mass	0.0314	0.66	0.1 to 1.22	0.021	No outliers			
HDL cholesterol	LV EDV	<0.0001	1.16	-0.07 to 2.39	0.065	0.98	-0.41 to 2.37	0.169	0.38
	LV EF	0.0042	0.18	-0.08 to 0.44	0.184	0.17	-0.11 to 0.44	0.233	0.764
	LV mass	0.0018	0.32	-0.26 to 0.89	0.279	0.32	-0.37 to 1.01	0.37	0.711
Triglycerides	LV EDV	0.0356	-0.43	-1.73 to 0.86	0.512	-0.48	-1.85 to 0.89	0.496	0.39
	LV EF	0.0417	-0.3	-0.66 to 0.06	0.106	No outliers			
	LV mass	0.1318	0.61	0.04 to 1.18	0.036	No outliers			

Supplementary Table 11: MR-Steiger analysis

Exposure	Outcome	SNP r^2 for exposure	SNP r^2 for outcome	Directionality test	MR-Steiger p-value
LDL Cholesterol	LV EDV (ml)	0.0879	0.0106	TRUE	1.30×10^{-138}
	LV EF (%)	0.0879	0.0061	TRUE	7.50×10^{-174}
	LV mass (g)	0.0879	0.0078	TRUE	1.03×10^{-158}
Triglycerides	LV EDV (ml)	0.0570	0.0057	TRUE	3.27×10^{-96}
	LV EF (%)	0.0570	0.0057	TRUE	7.03×10^{-96}
	LV mass (g)	0.0570	0.0053	TRUE	1.48×10^{-99}

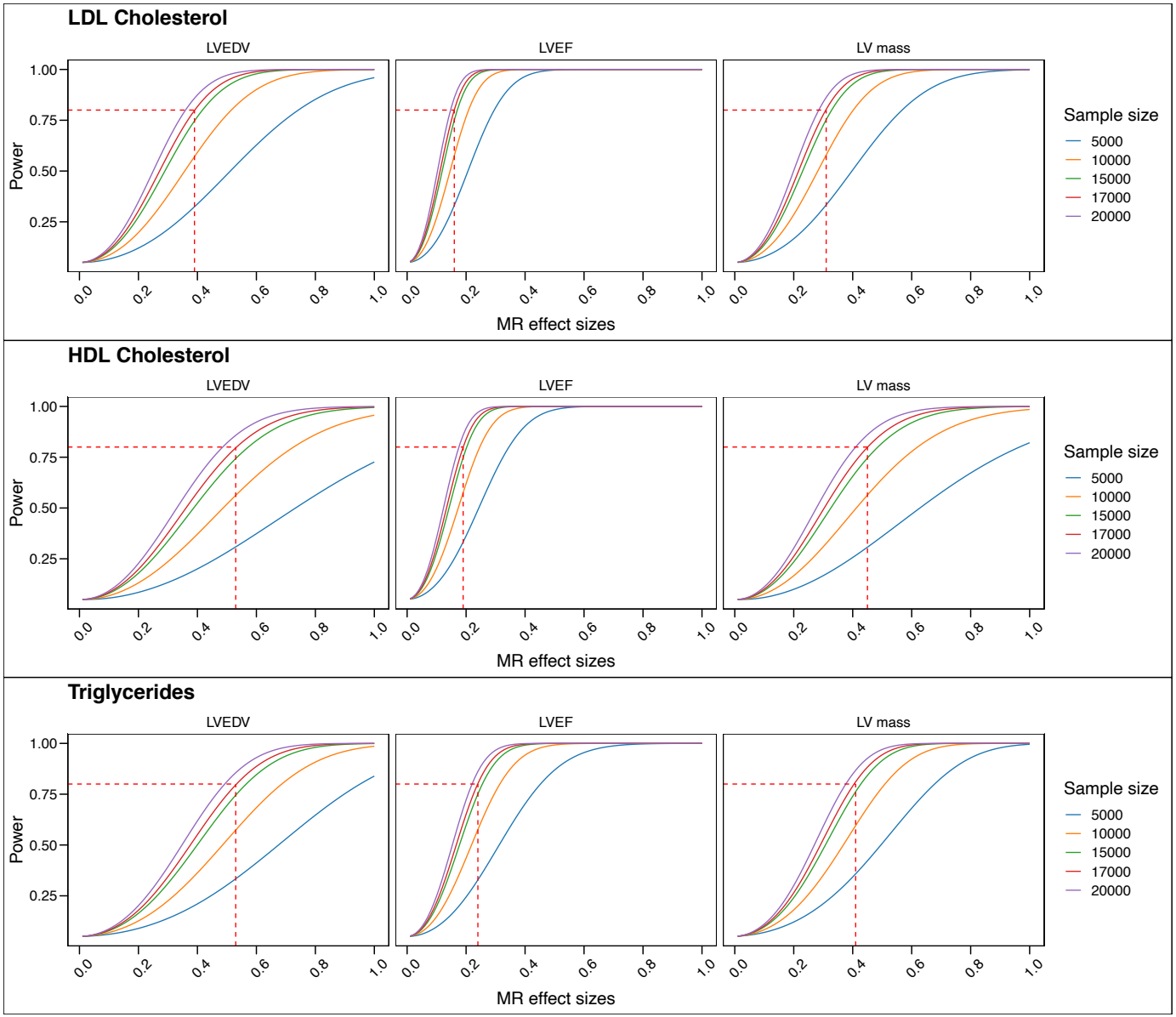
Supplementary Table 12. Interaction analysis of the statin therapy on the relationships between the genetic risk score for LDL cholesterol and LV parameters

Lipid parameter	CMR parameter	Interaction effect size	Interaction standard error	Interaction p-value
LDL Cholesterol	LV EDV (ml)	0.26	0.50	0.610
	LV EF (%)	-0.19	0.12	0.110
	LV mass (g)	-0.07	0.27	0.788

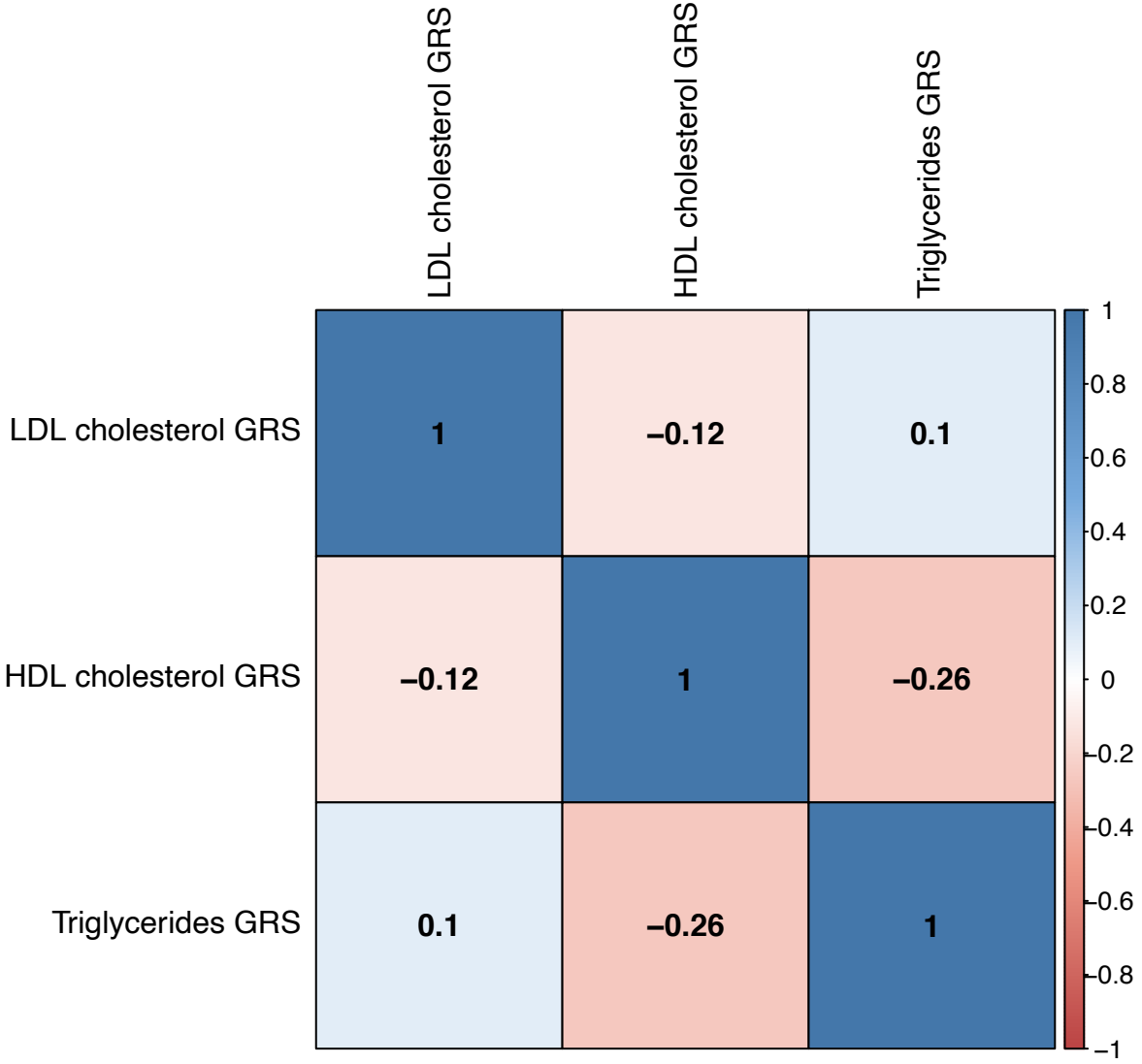
Supplementary Table 13: The variance of phenotypic LV parameters explained by observed lipid measurements and lipid genetic risk scores

Lipid parameter	Phenotype	R^2
Variance of LV phenotypes explained by measured lipids		
LDL Cholesterol	LV EDV	0.35%
	LV EF	0.06%
	LV mass	0.10%
HDL Cholesterol	LV EDV	6.46%
	LV EF	1.68%
	LV mass	14.48%
Triglycerides	LV EDV	0.60%
	LV EF	0.18%
	LV mass	5.42%
Variance of LV phenotypes explained by GRS		
LDL Cholesterol	LV EDV	0.01%
	LV EF	0.00%
	LV mass	0.00%
HDL Cholesterol	LV EDV	0.01%
	LV EF	0.01%
	LV mass	0.00%
Triglycerides	LV EDV	0.00%
	LV EF	0.04%
	LV mass	0.01%

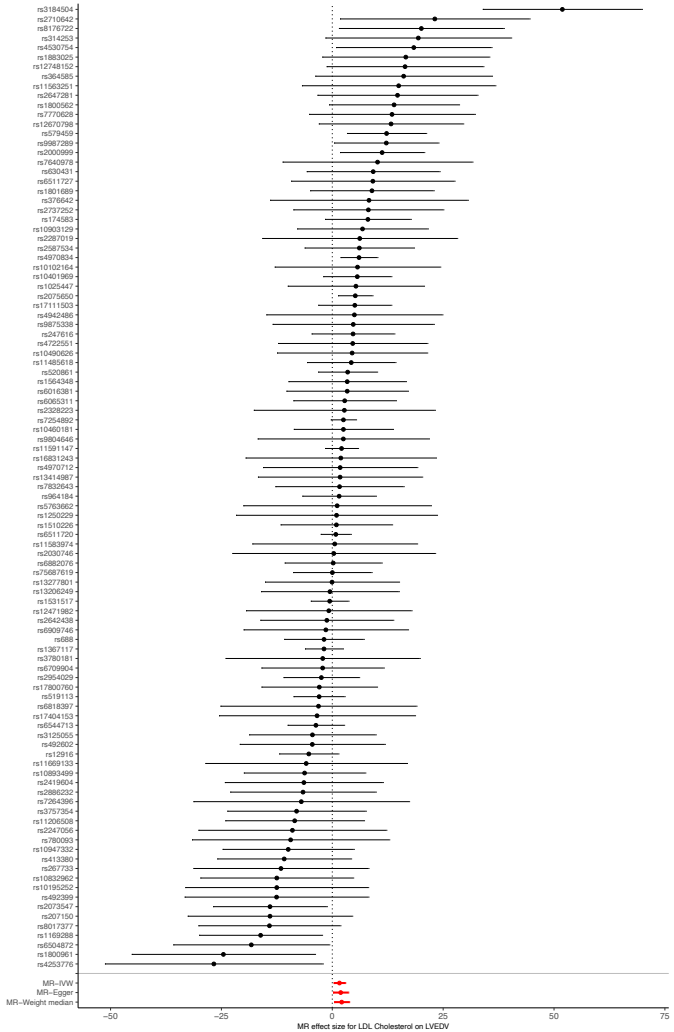
Supplementary Figure 1

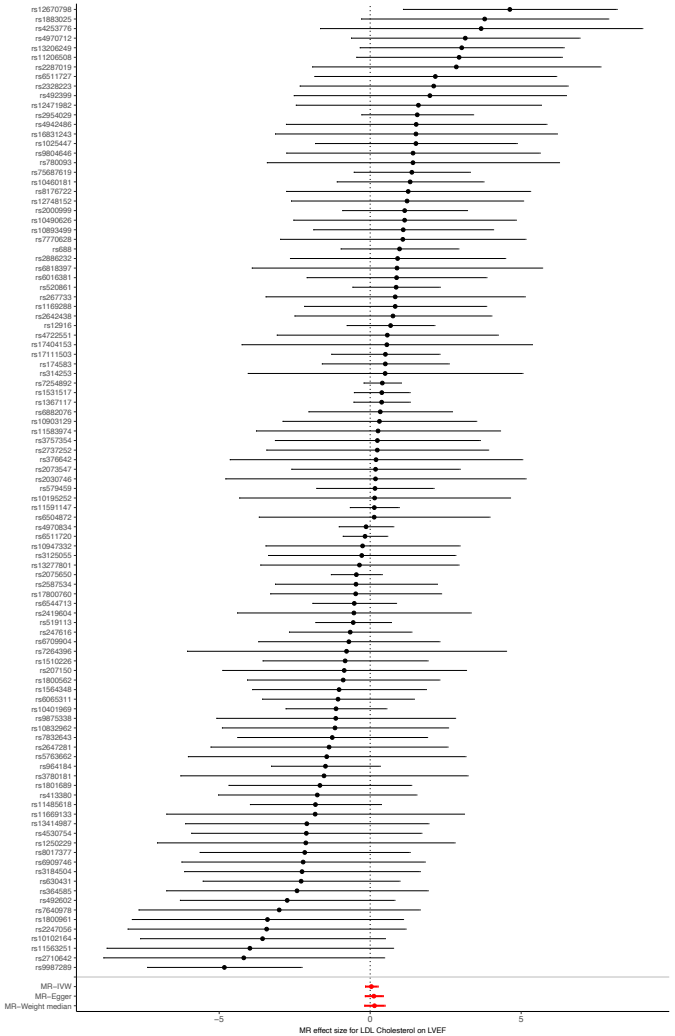


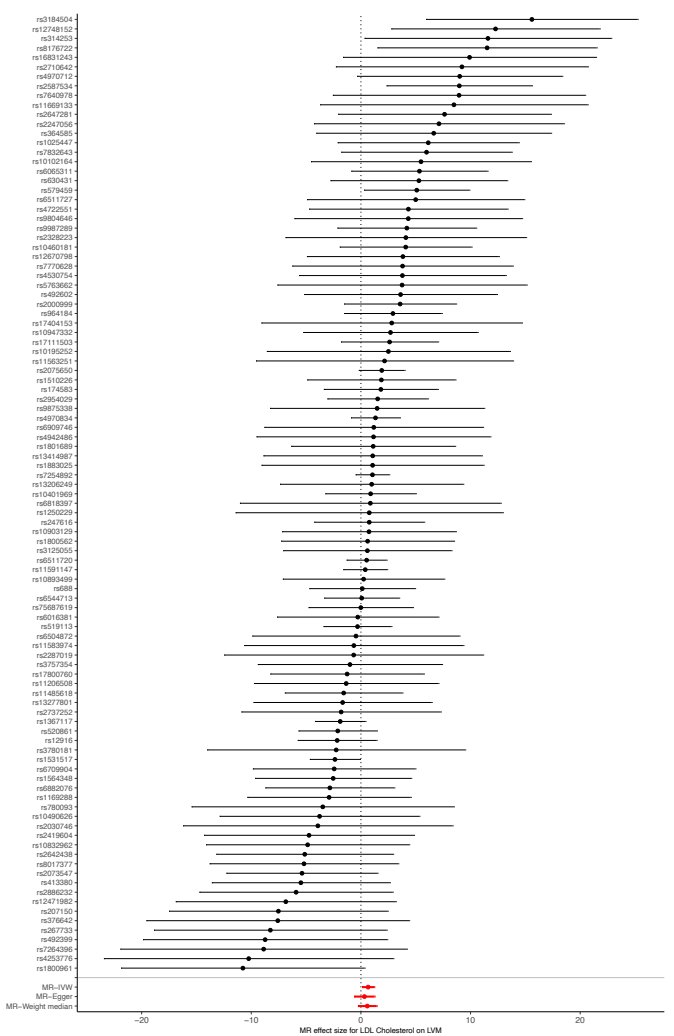
Supplementary Figure 2



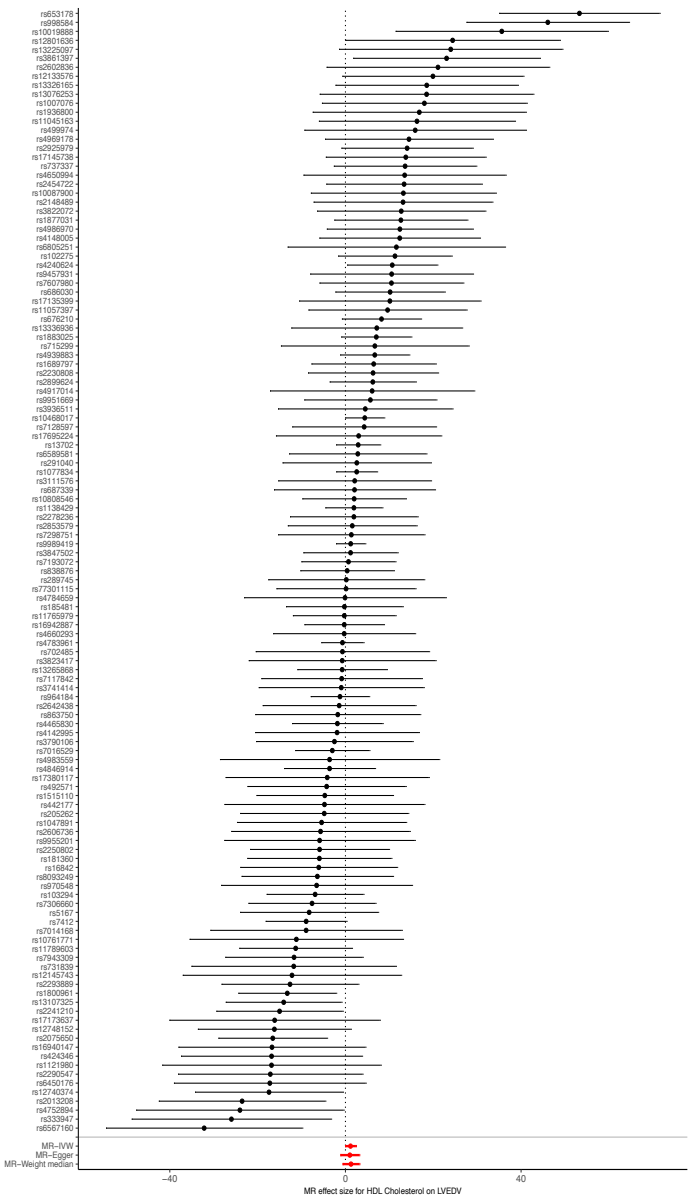
Supplementary Figure 3

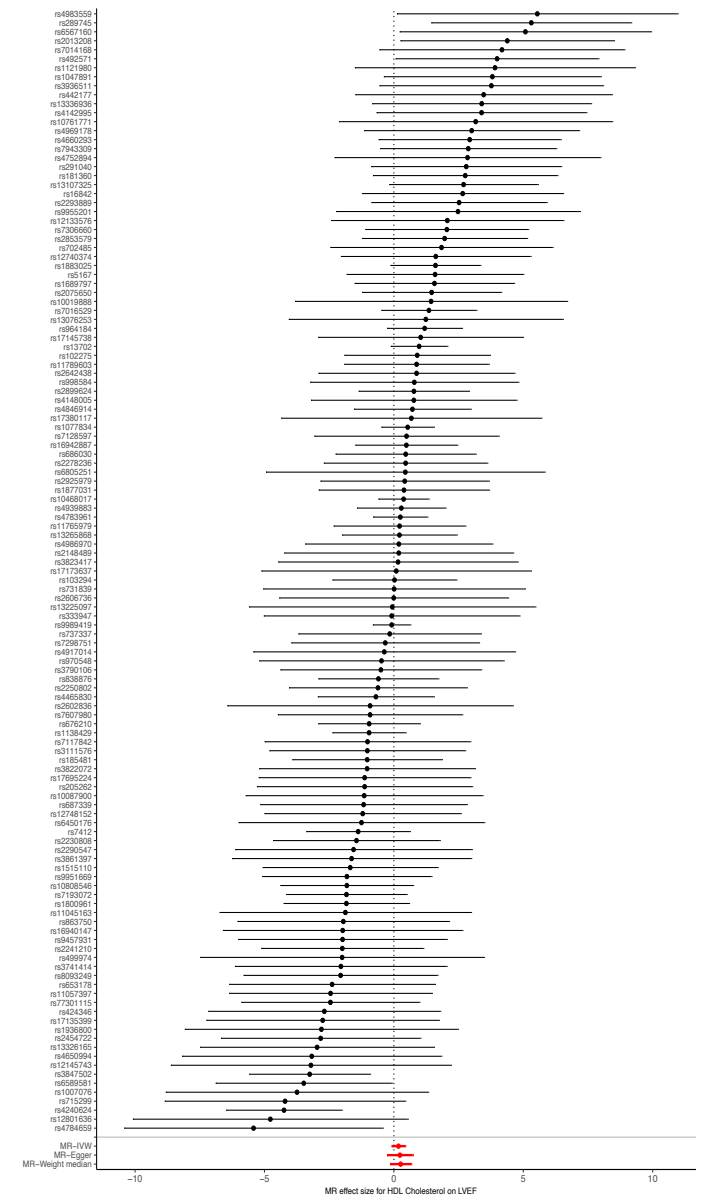


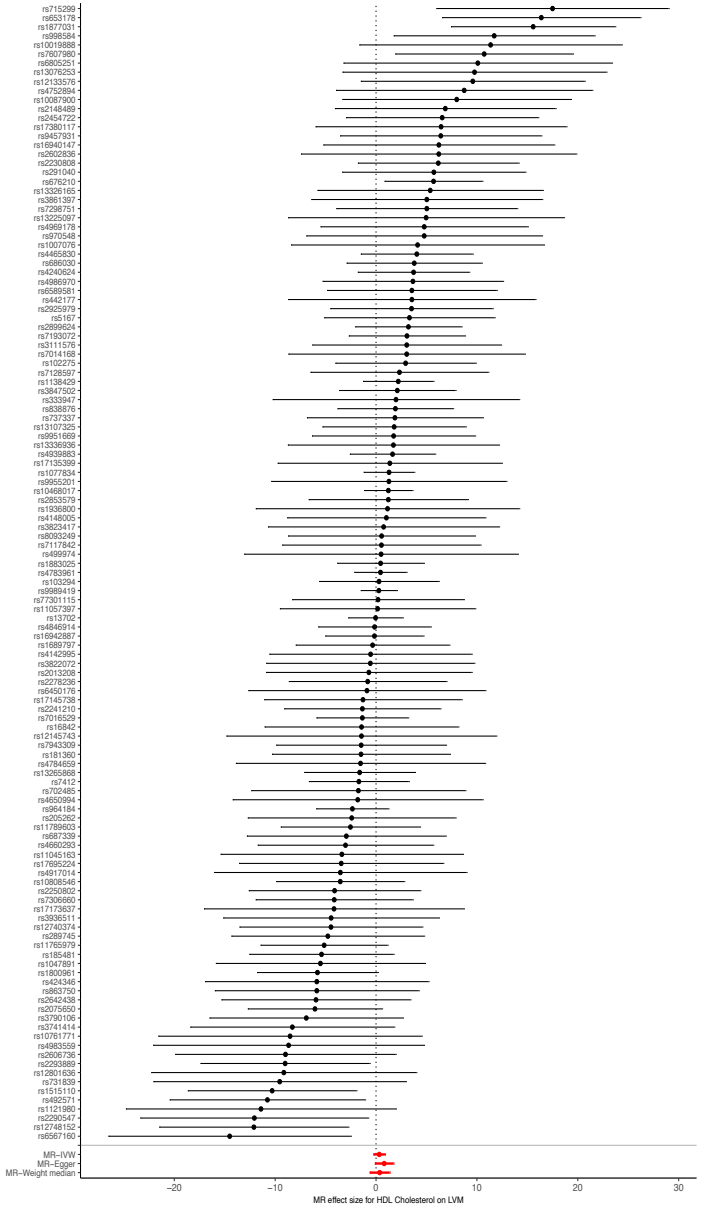




Supplementary Figure 4







›id paramet	SNP	Category	Trait	Excluded
LDL	rs6511720	CVD	abdominal	Yes
HDL	rs1274037	CVD	acute coro	Yes
HDL	rs7412	CVD	acute coro	Yes
LDL,Triglyc	rs1040196	CVD	atrial fibrill	Yes
LDL,HDL	rs964184	CVD	atrial fibrill	Yes
Triglyceride	rs4803750	CVD	atrial fibrill	Yes
LDL	rs780093	CVD	blood pres	Yes
LDL	rs3184504	CVD	cardiovasc	Yes
LDL	rs1159114	CVD	cardiovasc	Yes
LDL	rs1367117	CVD	cardiovasc	Yes
LDL	rs780093	CVD	cardiovasc	Yes
LDL	rs12916	CVD	cardiovasc	Yes
LDL,HDL	rs964184	CVD	cardiovasc	Yes
HDL	rs1274037	CVD	cardiovasc	Yes
HDL	rs7412	CVD	cardiovasc	Yes
LDL	rs6511720	CVD	coronary a	Yes
LDL,HDL	rs964184	CVD	coronary a	Yes
HDL	rs102275	CVD	coronary a	Yes
Triglyceride	rs4810479	CVD	coronary a	Yes
Triglyceride	rs1260326	CVD	coronary a	Yes
Triglyceride	rs1267891	CVD	coronary a	Yes
LDL	rs3184504	CVD	coronary a	Yes
LDL	rs1169288	CVD	coronary a	Yes
LDL	rs1159114	CVD	coronary a	Yes
LDL	rs6511720	CVD	coronary a	Yes
LDL	rs1250229	CVD	coronary a	Yes
LDL	rs6544713	CVD	coronary a	Yes
LDL	rs7770628	CVD	coronary a	Yes
LDL	rs2954029	CVD	coronary a	Yes
LDL,HDL	rs964184	CVD	coronary a	Yes
HDL	rs1274037	CVD	coronary a	Yes
HDL	rs1280163	CVD	coronary a	Yes
HDL	rs7412	CVD	coronary a	Yes
HDL	rs3936511	CVD	coronary a	Yes
Triglyceride	rs1161335	CVD	coronary a	Yes
Triglyceride	rs2972146	CVD	coronary a	Yes
LDL,Triglyc	rs1040196	CVD	coronary h	Yes
LDL	rs579459	CVD	coronary h	Yes
LDL,HDL	rs964184	CVD	coronary h	Yes
HDL	rs1274037	CVD	coronary h	Yes
HDL	rs7412	CVD	coronary h	Yes
Triglyceride	rs4803750	CVD	coronary h	Yes
LDL	rs3184504	CVD	diastolic bl	Yes
LDL,Triglyc	rs1040196	CVD	diastolic bl	Yes
LDL	rs1800562	CVD	diastolic bl	Yes
LDL,HDL	rs964184	CVD	diastolic bl	Yes
HDL	rs653178	CVD	diastolic bl	Yes
HDL	rs1310732	CVD	diastolic bl	Yes
Triglyceride	rs4803750	CVD	diastolic bl	Yes
Triglyceride	rs2972146	CVD	diastolic bl	Yes
LDL,Triglyc	rs1040196	CVD	heart failur	Yes

LDL,HDL	rs964184	CVD	heart failur	Yes
Triglyceride	rs4803750	CVD	heart failur	Yes
HDL	rs1310732	CVD	hypertensi	Yes
LDL	rs3184504	CVD	Ischemic st	Yes
LDL	rs579459	CVD	large artery	Yes
LDL,HDL	rs964184	CVD	large artery	Yes
HDL	rs653178	CVD	myocardial	Yes
LDL	rs174583	CVD	QT interval	Yes
LDL	rs3184504	CVD	stroke	Yes
LDL,Triglyc	rs1040196	CVD	stroke	Yes
LDL	rs579459	CVD	stroke	Yes
LDL,HDL	rs964184	CVD	stroke	Yes
Triglyceride	rs4803750	CVD	stroke	Yes
LDL	rs3184504	CVD	systolic blo	Yes
LDL,Triglyc	rs1040196	CVD	systolic blo	Yes
LDL,HDL	rs964184	CVD	systolic blo	Yes
HDL	rs6567160	CVD	systolic blo	Yes
HDL	rs7412	CVD	systolic blo	Yes
HDL	rs1047891	CVD	systolic blo	Yes
HDL	rs2606736	CVD	systolic blo	Yes
HDL	rs1310732	CVD	systolic blo	Yes
Triglyceride	rs4803750	CVD	systolic blo	Yes
Triglyceride	rs7248104	CVD	systolic blo	Yes
Triglyceride	rs1338921	CVD	systolic blo	Yes
LDL	rs579459	CVD	venous thr	Yes
LDL	rs1019525	CV risk	age at asses	Yes
HDL	rs2925979	CV risk	age at asses	Yes
HDL,Triglyc	rs998584	CV risk	age at asses	Yes
HDL,Triglyc	rs1046801	CV risk	age-related	Yes
LDL,HDL	rs2642438	CV risk	alcohol cor	Yes
LDL	rs1159114	CV risk	alcohol cor	Yes
LDL	rs1531517	CV risk	alcohol cor	Yes
LDL	rs2328223	CV risk	alcohol cor	Yes
LDL,HDL	rs1800961	CV risk	alcohol cor	Yes
LDL	rs4722551	CV risk	alcohol cor	Yes
HDL	rs9989419	CV risk	alcohol cor	Yes
HDL	rs2925979	CV risk	alcohol cor	Yes
HDL	rs1047891	CV risk	alcohol cor	Yes
HDL	rs2013208	CV risk	alcohol cor	Yes
HDL	rs1310732	CV risk	alcohol cor	Yes
Triglyceride	rs1260326	CV risk	alcohol cor	Yes
HDL	rs1310732	CV risk	alcohol dep	Yes
Triglyceride	rs1260326	CV risk	alcohol dep	Yes
LDL,HDL	rs2642438	CV risk	alcohol dri	Yes
LDL	rs1159114	CV risk	alcohol dri	Yes
LDL	rs1531517	CV risk	alcohol dri	Yes
LDL	rs2328223	CV risk	alcohol dri	Yes
LDL,HDL	rs1800961	CV risk	alcohol dri	Yes
LDL	rs1800562	CV risk	alcohol dri	Yes
LDL	rs4722551	CV risk	alcohol dri	Yes
HDL	rs9989419	CV risk	alcohol dri	Yes
HDL	rs2925979	CV risk	alcohol dri	Yes

HDL	rs1047891	CV risk	alcohol dri	Yes
HDL	rs2013208	CV risk	alcohol dri	Yes
HDL	rs1310732	CV risk	alcohol dri	Yes
Triglyceride	rs1260326	CV risk	alcohol dri	Yes
LDL	rs492602	CV risk	alcohol use	Yes
HDL	rs1310732	CV risk	alcohol use	Yes
Triglyceride	rs1260326	CV risk	alcohol use	Yes
HDL	rs1121980	CV risk	appendicul	Yes
HDL	rs1047891	CV risk	appendicul	Yes
Triglyceride	rs1260326	CV risk	appendicul	Yes
Triglyceride	rs1260326	CV risk	bitter alcol	Yes
Triglyceride	rs1260326	CV risk	bitter beve	Yes
LDL	rs1019525	CV risk	BMI-adjust	Yes
LDL	rs780093	CV risk	BMI-adjust	Yes
LDL	rs1019525	CV risk	BMI-adjust	Yes
HDL	rs1105739	CV risk	BMI-adjust	Yes
HDL	rs2925979	CV risk	BMI-adjust	Yes
HDL	rs1310732	CV risk	BMI-adjust	Yes
HDL,Triglyc	rs998584	CV risk	BMI-adjust	Yes
Triglyceride	rs4804311	CV risk	BMI-adjust	Yes
Triglyceride	rs634869	CV risk	BMI-adjust	Yes
LDL,Triglyc	rs1040196	CV risk	BMI-adjust	Yes
LDL	rs1019525	CV risk	BMI-adjust	Yes
HDL	rs863750	CV risk	BMI-adjust	Yes
HDL	rs2925979	CV risk	BMI-adjust	Yes
HDL	rs7607980	CV risk	BMI-adjust	Yes
HDL	rs1310732	CV risk	BMI-adjust	Yes
HDL	rs1001988	CV risk	BMI-adjust	Yes
HDL,Triglyc	rs998584	CV risk	BMI-adjust	Yes
HDL	rs7014168	CV risk	BMI-adjust	Yes
HDL	rs1080854	CV risk	BMI-adjust	Yes
Triglyceride	rs634869	CV risk	BMI-adjust	Yes
HDL	rs6567160	CV risk	body fat pe	Yes
HDL	rs1310732	CV risk	body fat pe	Yes
Triglyceride	rs3761445	CV risk	body fat pe	Yes
LDL	rs3184504	CV risk	body mass i	Yes
LDL,Triglyc	rs1040196	CV risk	body mass i	Yes
LDL,HDL	rs2075650	CV risk	body mass i	Yes
LDL	rs2287019	CV risk	body mass i	Yes
LDL,HDL	rs964184	CV risk	body mass i	Yes
HDL	rs1121980	CV risk	body mass i	Yes
HDL	rs6567160	CV risk	body mass i	Yes
HDL	rs7607980	CV risk	body mass i	Yes
HDL	rs1310732	CV risk	body mass i	Yes
HDL	rs205262	CV risk	body mass i	Yes
HDL,Triglyc	rs998584	CV risk	body mass i	Yes
Triglyceride	rs9930333	CV risk	body mass i	Yes
Triglyceride	rs4803750	CV risk	body mass i	Yes
Triglyceride	rs645040	CV risk	body mass i	Yes
HDL	rs1310732	CV risk	cardiovascu	Yes
HDL	rs7412	CV risk	clinical and	Yes
HDL	rs7412	CV risk	common ca	Yes

HDL	rs6567160	CV risk	fat body ma	Yes
HDL	rs6567160	CV risk	lean body n	Yes
HDL	rs1047891	CV risk	lean body n	Yes
Triglyceride	rs1260326	CV risk	lean body n	Yes
LDL	rs780093	CV risk	leptin meas	Yes
HDL	rs1310732	CV risk	longitudina	Yes
Triglyceride	rs1260326	CV risk	longitudina	Yes
HDL	rs1280163	CV risk	mean arteri	Yes
HDL	rs653178	CV risk	mean arteri	Yes
HDL	rs1310732	CV risk	mean arteri	Yes
LDL,HDL	rs1800961	CV risk	metabolic s	Yes
LDL	rs780093	CV risk	metabolic s	Yes
LDL	rs9987289	CV risk	metabolic s	Yes
LDL,HDL	rs1883025	CV risk	metabolic s	Yes
LDL,HDL	rs964184	CV risk	metabolic s	Yes
HDL	rs2925979	CV risk	metabolic s	Yes
HDL	rs1310732	CV risk	metabolic s	Yes
HDL,Triglyc	rs998584	CV risk	metabolic s	Yes
HDL	rs1178960	CV risk	metabolic s	Yes
Triglyceride	rs1260326	CV risk	metabolic s	Yes
Triglyceride	rs9930333	CV risk	obese body	Yes
LDL,Triglyc	rs247616	CV risk	obesity	Yes
LDL	rs2000999	CV risk	obesity	Yes
HDL	rs6567160	CV risk	obesity	Yes
LDL	rs1159114	CV risk	physical act	Yes
LDL,HDL	rs1800961	CV risk	physical act	Yes
LDL	rs12916	CV risk	physical act	Yes
LDL	rs4722551	CV risk	physical act	Yes
LDL,HDL	rs964184	CV risk	physical act	Yes
HDL	rs2925979	CV risk	physical act	Yes
HDL	rs2013208	CV risk	physical act	Yes
Triglyceride	rs4810479	CV risk	physical act	Yes
Triglyceride	rs1260326	CV risk	physical act	Yes
LDL	rs1019525	CV risk	physical act	Yes
HDL	rs1105739	CV risk	physical act	Yes
HDL	rs2925979	CV risk	physical act	Yes
HDL	rs1310732	CV risk	physical act	Yes
HDL,Triglyc	rs998584	CV risk	physical act	Yes
Triglyceride	rs9930333	CV risk	physical act	Yes
LDL	rs1019525	CV risk	pulse pressu	Yes
HDL	rs7412	CV risk	pulse pressu	Yes
Triglyceride	rs7248104	CV risk	pulse pressu	Yes
Triglyceride	rs1260326	CV risk	resting hea	Yes
LDL	rs2287019	CV risk	smoking be	Yes
LDL	rs1019525	CV risk	smoking be	Yes
HDL	rs863750	CV risk	smoking be	Yes
HDL	rs2925979	CV risk	smoking be	Yes
HDL	rs6567160	CV risk	smoking be	Yes
HDL	rs1310732	CV risk	smoking be	Yes
HDL	rs205262	CV risk	smoking be	Yes
HDL,Triglyc	rs998584	CV risk	smoking be	Yes
LDL	rs3184504	CV risk	smoking sta	Yes

LDL,Triglyc	rs1040196	CV risk	ventricular	Yes
LDL,HDL	rs964184	CV risk	ventricular	Yes
Triglyceride	rs4803750	CV risk	ventricular	Yes
LDL,HDL	rs2075650	CV risk	waist circu	Yes
LDL	rs2287019	CV risk	waist circu	Yes
HDL	rs6567160	CV risk	waist circu	Yes
LDL,HDL	rs2075650	CV risk	waist-hip ra	Yes
LDL	rs2287019	CV risk	waist-hip ra	Yes
LDL	rs1019525	CV risk	waist-hip ra	Yes
LDL,HDL	rs1883025	CV risk	waist-hip ra	Yes
HDL	rs863750	CV risk	waist-hip ra	Yes
HDL	rs1121980	CV risk	waist-hip ra	Yes
HDL	rs2925979	CV risk	waist-hip ra	Yes
HDL	rs6567160	CV risk	waist-hip ra	Yes
HDL	rs7607980	CV risk	waist-hip ra	Yes
HDL	rs1310732	CV risk	waist-hip ra	Yes
HDL	rs1001988	CV risk	waist-hip ra	Yes
HDL,Triglyc	rs998584	CV risk	waist-hip ra	Yes
Triglyceride	rs1338921	CV risk	waist-hip ra	Yes
Triglyceride	rs645040	CV risk	waist-hip ra	Yes
Triglyceride	rs634869	CV risk	waist-hip ra	Yes
LDL	rs4970834	CV pharma	Agents acti	Yes
LDL,HDL	rs964184	CV pharma	Agents acti	Yes
HDL	rs7412	CV pharma	Agents acti	Yes
HDL	rs1310732	CV pharma	Agents acti	Yes
LDL,HDL	rs964184	CV pharma	Antithroml	Yes
HDL	rs1274037	CV pharma	Antithroml	Yes
HDL	rs7412	CV pharma	Antithroml	Yes
HDL	rs7412	CV pharma	aspirin use	Yes
LDL	rs4970834	CV pharma	Beta blocki	Yes
LDL	rs3184504	CV pharma	Calcium ch	Yes
HDL	rs7412	CV pharma	Calcium ch	Yes
HDL,Triglyc	rs998584	CV pharma	Calcium ch	Yes
LDL	rs1800562	DM	a1c measur	Yes
LDL	rs579459	DM	a1c measur	Yes
LDL,Triglyc	rs1040196	DM	diabetes m	Yes
LDL	rs780093	DM	diabetes m	Yes
LDL,HDL	rs964184	DM	diabetes m	Yes
HDL	rs1047891	DM	diabetes m	Yes
Triglyceride	rs4803750	DM	diabetes m	Yes
LDL,HDL	rs1800961	DM	Drugs used	Yes
LDL	rs780093	DM	Drugs used	Yes
LDL	rs174583	DM	fasting bloc	Yes
Triglyceride	rs174535	DM	fasting bloc	Yes
Triglyceride	rs1260326	DM	fasting bloc	Yes
HDL	rs7607980	DM	fasting bloc	Yes
Triglyceride	rs174535	DM	fasting bloc	Yes
Triglyceride	rs4803750	DM	fasting bloc	Yes
Triglyceride	rs1260326	DM	fasting bloc	Yes
LDL,Triglyc	rs1040196	DM	glucose me	Yes
LDL,HDL	rs964184	DM	glucose me	Yes
Triglyceride	rs4803750	DM	glucose me	Yes

Triglyceride	rs1260326	DM	glucose me	Yes
Triglyceride	rs1260326	DM	glucose tol	Yes
LDL	rs3184504	DM	latent auto	Yes
LDL	rs3184504	DM	type i diabe	Yes
HDL	rs653178	DM	type i diabe	Yes
LDL	rs3184504	DM	type ii diab	Yes
LDL	rs1169288	DM	type ii diab	Yes
LDL,Triglyc	rs1040196	DM	type ii diab	Yes
LDL,HDL	rs1800961	DM	type ii diab	Yes
LDL	rs1019525	DM	type ii diab	Yes
HDL	rs2925979	DM	type ii diab	Yes
HDL	rs7607980	DM	type ii diab	Yes
Triglyceride	rs1751313	DM	type ii diab	Yes
Triglyceride	rs1338921	DM	type ii diab	Yes
Triglyceride	rs1260326	DM	type ii diab	Yes
Triglyceride	rs9686661	DM	type ii diab	Yes
Triglyceride	rs174535	DM	HOMA-B	Yes
Triglyceride	rs1260326	DM	HOMA-B	Yes
LDL	rs174583	Respiratory	adult onset	Yes
Triglyceride	rs174535	Respiratory	adult onset	Yes
HDL	rs653178	Respiratory	allergic rhi	Yes
LDL	rs174583	Respiratory	asthma	Yes
HDL	rs653178	Respiratory	asthma	Yes
Triglyceride	rs174535	Respiratory	asthma	Yes
LDL	rs492602	Respiratory	FEV/FEC rat	Yes
Triglyceride	rs1751313	Respiratory	FEV/FEC rat	Yes
Triglyceride	rs174535	Respiratory	respiratory	Yes
HDL	rs1310732	Respiratory	vital capaci	Yes
HDL,Triglyc	rs442177	Respiratory	vital capaci	Yes
LDL	rs3184504	Immune	ankylosing	Yes
Triglyceride	rs174535	Immune	ankylosing	Yes
Triglyceride	rs1260326	Immune	ankylosing	Yes
LDL	rs3184504	Immune	beta-2 micr	Yes
HDL	rs653178	Immune	Eczema	Yes
HDL	rs1310732	Immune	Eczema	Yes
HDL	rs653178	Immune	immune sy	Yes
LDL	rs3184504	Immune	multiple sc	Yes
LDL	rs3184504	Immune	psoriasis	Yes
LDL	rs492602	Immune	psoriasis	Yes
Triglyceride	rs174535	Immune	psoriasis	Yes
Triglyceride	rs1260326	Immune	psoriasis	Yes
HDL	rs653178	Immune	sarcoidosis	Yes
LDL	rs3184504	Immune	serum IgA r	Yes
HDL	rs653178	Immune	systemic lu	Yes
HDL	rs4917014	Immune	systemic lu	Yes
HDL	rs103294	Immune	Takayasu ar	Yes
HDL	rs653178	Immune	thyroid per	Yes
LDL,HDL	rs2075650	Dementia	Alzheimer's	Yes
LDL	rs519113	Dementia	Alzheimer's	Yes
HDL	rs7730111	Dementia	Alzheimer's	Yes
HDL	rs7412	Dementia	Alzheimer's	Yes
Triglyceride	rs4803750	Dementia	Alzheimer's	Yes

Triglyceride	rs439401	Dementia	Alzheimer's	Yes
LDL,HDL	rs2075650	Dementia	beta-amylo	Yes
LDL,HDL	rs2075650	Dementia	cerebral an	Yes
HDL	rs1310732	Dementia	cognitive fu	Yes
LDL,HDL	rs2075650	Dementia	cognitive ir	Yes
HDL	rs7412	Dementia	family histo	Yes
HDL	rs7412	Dementia	late-onset A	Yes
LDL,HDL	rs2075650	Dementia	Mental det	Yes
HDL	rs1310732	Dementia	nucleus acc	Yes
LDL,HDL	rs2075650	Dementia	p-tau:beta-	Yes
LDL,HDL	rs2075650	Dementia	posterior c	Yes
LDL,HDL	rs2075650	Dementia	t-tau measu	Yes
LDL,HDL	rs2075650	Dementia	t-tau:beta-a	Yes
HDL	rs2925979	Cholesterol	adiponecti	Yes
HDL,Triglyc	rs731839	Cholesterol	adiponecti	Yes
HDL,Triglyc	rs998584	Cholesterol	adiponecti	Yes
Triglyceride	rs1260326	Cholesterol	alpha-hydr	Yes
HDL	rs102275	Cholesterol	alpha-linol	Yes
LDL,HDL	rs964184	Cholesterol	alpha-toco	Yes
LDL	rs7770628	Cholesterol	apolipopro	Yes
HDL	rs7412	Cholesterol	apolipopro	Yes
LDL	rs1169288	Cholesterol	ceramide m	Yes
LDL	rs364585	Cholesterol	ceramide m	Yes
LDL,Triglyc	rs247616	Cholesterol	cholesterol	Yes
LDL,HDL	rs964184	Cholesterol	cholesterol	Yes
Triglyceride	rs174535	Cholesterol	cholesteryl	Yes
LDL,Triglyc	rs247616	Cholesterol	cholesteryl	Yes
LDL	rs174583	Cholesterol	cis/trans-18	Yes
HDL	rs102275	Cholesterol	cis/trans-18	Yes
Triglyceride	rs174535	Cholesterol	cis/trans-18	Yes
LDL,HDL	rs964184	Cholesterol	diacylglyce	Yes
LDL,HDL	rs964184	Cholesterol	diacylglyce	Yes
LDL,HDL	rs964184	Cholesterol	diacylglyce	Yes
HDL	rs102275	Cholesterol	docosapent	Yes
Triglyceride	rs174535	Cholesterol	docosapent	Yes
Triglyceride	rs174535	Cholesterol	eicosapenta	Yes
LDL	rs780093	Cholesterol	fatty acid m	Yes
HDL	rs102275	Cholesterol	fatty acid m	Yes
Triglyceride	rs174535	Cholesterol	fatty acid m	Yes
Triglyceride	rs1260326	Cholesterol	follistatin r	Yes
LDL	rs1169288	Cholesterol	HMG CoA r	Yes
LDL	rs1159114	Cholesterol	HMG CoA r	Yes
LDL	rs6511720	Cholesterol	HMG CoA r	Yes
LDL	rs1367117	Cholesterol	HMG CoA r	Yes
LDL	rs12916	Cholesterol	HMG CoA r	Yes
LDL,HDL	rs1883025	Cholesterol	HMG CoA r	Yes
LDL,HDL	rs964184	Cholesterol	HMG CoA r	Yes
HDL	rs1274037	Cholesterol	HMG CoA r	Yes
HDL,Triglyc	rs1046801	Cholesterol	HMG CoA r	Yes
HDL	rs7412	Cholesterol	HMG CoA r	Yes
HDL,Triglyc	rs998584	Cholesterol	HMG CoA r	Yes
Triglyceride	rs2068888	Cholesterol	HMG CoA r	Yes

Triglyceride	rs1260326	Cholesterol	HMG CoA r	Yes
Triglyceride	rs645040	Cholesterol	HMG CoA r	Yes
LDL	rs6511720	Cholesterol	lipid measu	Yes
LDL	rs1367117	Cholesterol	lipid measu	Yes
HDL	rs4939883	Cholesterol	lipid measu	Yes
HDL	rs7412	Cholesterol	lipid measu	Yes
HDL,Triglyc	rs676210	Cholesterol	lipid measu	Yes
Triglyceride	rs4803750	Cholesterol	lipid measu	Yes
Triglyceride	rs1260326	Cholesterol	lipid measu	Yes
LDL,HDL	rs964184	Cholesterol	lipid or lipc	Yes
HDL,Triglyc	rs676210	Cholesterol	lipid or lipc	Yes
LDL	rs7770628	Cholesterol	lipoprotein	Yes
HDL	rs7412	Cholesterol	lipoprotein	Yes
LDL	rs1159114	Cholesterol	lipoprotein	Yes
LDL	rs2954029	Cholesterol	lipoprotein	Yes
LDL,HDL	rs964184	Cholesterol	lipoprotein	Yes
HDL	rs7412	Cholesterol	lipoprotein	Yes
HDL	rs686030	Cholesterol	lipoprotein	Yes
HDL	rs7412	Cholesterol	lipoprotein	Yes
LDL,Triglyc	rs247616	Cholesterol	lipoprotein	Yes
LDL	rs6511720	Cholesterol	lipoprotein	Yes
LDL,HDL	rs964184	Cholesterol	lipoprotein	Yes
HDL	rs1274037	Cholesterol	lipoprotein	Yes
HDL	rs7412	Cholesterol	lipoprotein	Yes
HDL	rs102275	Cholesterol	oleic acid n	Yes
Triglyceride	rs174535	Cholesterol	oleic acid n	Yes
HDL	rs102275	Cholesterol	omega-6 pc	Yes
LDL	rs780093	Cholesterol	palmitoleic	Yes
HDL	rs102275	Cholesterol	palmitoleic	Yes
LDL	rs1159114	Cholesterol	PCSK9 prot	Yes
HDL	rs102275	Cholesterol	phosphatic	Yes
LDL,HDL	rs964184	Cholesterol	phospholip	Yes
HDL	rs102275	Cholesterol	phospholip	Yes
HDL,Triglyc	rs1046801	Cholesterol	phospholip	Yes
LDL	rs1159114	Cholesterol	response tc	Yes
LDL,Triglyc	rs247616	Cholesterol	response tc	Yes
HDL	rs7412	Cholesterol	response tc	Yes
LDL,Triglyc	rs9804646	Cholesterol	total chole	Yes
LDL	rs1089349	Cholesterol	total chole	Yes
LDL	rs1083296	Cholesterol	total chole	Yes
LDL	rs174583	Cholesterol	total chole	Yes
LDL	rs3184504	Cholesterol	total chole	Yes
LDL	rs1169288	Cholesterol	total chole	Yes
LDL,HDL	rs2642438	Cholesterol	total chole	Yes
LDL	rs1090312	Cholesterol	total chole	Yes
LDL	rs8017377	Cholesterol	total chole	Yes
LDL	rs1711150	Cholesterol	total chole	Yes
LDL	rs1159114	Cholesterol	total chole	Yes
LDL	rs2000999	Cholesterol	total chole	Yes
LDL	rs1801689	Cholesterol	total chole	Yes
LDL	rs314253	Cholesterol	total chole	Yes
LDL	rs6511720	Cholesterol	total chole	Yes

LDL	rs688	Cholesterol	total chole	Yes
LDL,Triglyc	rs1040196	Cholesterol	total chole	Yes
LDL	rs1046018	Cholesterol	total chole	Yes
LDL	rs1531517	Cholesterol	total chole	Yes
LDL,Triglyc	rs7254892	Cholesterol	total chole	Yes
LDL,HDL	rs2075650	Cholesterol	total chole	Yes
LDL	rs492602	Cholesterol	total chole	Yes
LDL	rs7264396	Cholesterol	total chole	Yes
LDL,HDL	rs1800961	Cholesterol	total chole	Yes
LDL	rs1049062	Cholesterol	total chole	Yes
LDL	rs1367117	Cholesterol	total chole	Yes
LDL	rs1250229	Cholesterol	total chole	Yes
LDL	rs1156325	Cholesterol	total chole	Yes
LDL	rs780093	Cholesterol	total chole	Yes
LDL	rs6544713	Cholesterol	total chole	Yes
LDL	rs2710642	Cholesterol	total chole	Yes
LDL	rs7640978	Cholesterol	total chole	Yes
LDL	rs6818397	Cholesterol	total chole	Yes
LDL	rs4530754	Cholesterol	total chole	Yes
LDL,Triglyc	rs6882076	Cholesterol	total chole	Yes
LDL	rs12916	Cholesterol	total chole	Yes
LDL	rs1564348	Cholesterol	total chole	Yes
LDL	rs3757354	Cholesterol	total chole	Yes
LDL	rs1800562	Cholesterol	total chole	Yes
LDL,Triglyc	rs2247056	Cholesterol	total chole	Yes
LDL	rs1267079	Cholesterol	total chole	Yes
LDL	rs4722551	Cholesterol	total chole	Yes
LDL	rs2737252	Cholesterol	total chole	Yes
LDL	rs2954029	Cholesterol	total chole	Yes
LDL	rs7832643	Cholesterol	total chole	Yes
LDL	rs1010216	Cholesterol	total chole	Yes
LDL	rs1327780	Cholesterol	total chole	Yes
LDL	rs9987289	Cholesterol	total chole	Yes
LDL,HDL	rs1883025	Cholesterol	total chole	Yes
LDL	rs579459	Cholesterol	total chole	Yes
LDL	rs3780181	Cholesterol	total chole	Yes
LDL,HDL	rs964184	Cholesterol	total chole	Yes
HDL	rs970548	Cholesterol	total chole	Yes
HDL	rs1274037	Cholesterol	total chole	Yes
HDL	rs7117842	Cholesterol	total chole	Yes
HDL	rs653178	Cholesterol	total chole	Yes
HDL,Triglyc	rs1046801	Cholesterol	total chole	Yes
HDL	rs1077834	Cholesterol	total chole	Yes
HDL	rs9989419	Cholesterol	total chole	Yes
HDL	rs4939883	Cholesterol	total chole	Yes
HDL	rs737337	Cholesterol	total chole	Yes
HDL	rs7412	Cholesterol	total chole	Yes
HDL,Triglyc	rs676210	Cholesterol	total chole	Yes
HDL	rs1310732	Cholesterol	total chole	Yes
HDL	rs1080854	Cholesterol	total chole	Yes
HDL	rs2853579	Cholesterol	total chole	Yes
HDL	rs1178960	Cholesterol	total chole	Yes

Triglyceride	rs2068888	Cholesterol	total chole	Yes
Triglyceride	rs7350481	Cholesterol	total chole	Yes
Triglyceride	rs5880	Cholesterol	total chole	Yes
Triglyceride	rs4803750	Cholesterol	total chole	Yes
Triglyceride	rs1260326	Cholesterol	total chole	Yes
Triglyceride	rs6831256	Cholesterol	total chole	Yes
Triglyceride	rs2954022	Cholesterol	total chole	Yes
Triglyceride	rs4738684	Cholesterol	total chole	Yes
LDL	rs174583	Cholesterol	trans fatty a	Yes
HDL	rs102275	Cholesterol	trans fatty a	Yes
Triglyceride	rs174535	Cholesterol	trans fatty a	Yes
LDL,HDL	rs964184	Cholesterol	very low de	Yes
Triglyceride	rs1260326	Biochemist	alanine me	No
LDL	rs3184504	Biochemist	blood meta	No
LDL	rs1159114	Biochemist	blood meta	No
LDL,Triglyc	rs247616	Biochemist	blood meta	No
LDL	rs2954029	Biochemist	blood meta	No
LDL	rs579459	Biochemist	blood meta	No
LDL,HDL	rs964184	Biochemist	blood meta	No
HDL	rs102275	Biochemist	blood meta	No
HDL,Triglyc	rs1046801	Biochemist	blood meta	No
HDL	rs7412	Biochemist	blood meta	No
HDL	rs1047891	Biochemist	blood meta	No
HDL	rs686030	Biochemist	blood meta	No
Triglyceride	rs174535	Biochemist	blood meta	No
Triglyceride	rs588136	Biochemist	blood meta	No
Triglyceride	rs1260326	Biochemist	blood meta	No
Triglyceride	rs4921914	Biochemist	blood meta	No
LDL	rs3184504	Biochemist	blood prot	No
LDL	rs1801689	Biochemist	blood prot	No
LDL	rs492602	Biochemist	blood prot	No
LDL	rs579459	Biochemist	blood prot	No
LDL,HDL	rs964184	Biochemist	blood prot	No
HDL	rs1274037	Biochemist	blood prot	No
HDL	rs333947	Biochemist	blood prot	No
HDL	rs7412	Biochemist	blood prot	No
HDL	rs5167	Biochemist	blood prot	No
Triglyceride	rs1260326	Biochemist	blood prot	No
HDL	rs1047891	Biochemist	blood urea	No
HDL	rs1936800	Biochemist	blood urea	No
Triglyceride	rs1260326	Biochemist	C-peptide n	No
LDL,Triglyc	rs1040196	Biochemist	c-reactive p	Yes
LDL,HDL	rs2075650	Biochemist	c-reactive p	Yes
LDL,HDL	rs1800961	Biochemist	c-reactive p	Yes
LDL	rs9987289	Biochemist	c-reactive p	Yes
HDL	rs4660293	Biochemist	c-reactive p	Yes
HDL	rs1077834	Biochemist	c-reactive p	Yes
HDL	rs4465830	Biochemist	c-reactive p	Yes
HDL	rs687339	Biochemist	c-reactive p	Yes
Triglyceride	rs2068888	Biochemist	c-reactive p	Yes
Triglyceride	rs1260326	Biochemist	c-reactive p	Yes
Triglyceride	rs645040	Biochemist	c-reactive p	Yes

LDL	rs1169288	Biochemist chloride m	No
HDL	rs333947	Biochemist creatine kir	No
LDL	rs1801689	Biochemist Dickkopf-re	No
HDL	rs102275	Biochemist glyceropho	No
LDL	rs9987289	Biochemist glycine mea	No
HDL	rs1047891	Biochemist glycine mea	No
LDL	rs2000999	Biochemist heparin cof	No
HDL	rs333947	Biochemist lactate deh	No
LDL	rs9987289	Biochemist lactate mea	No
Triglyceride	rs1260326	Biochemist lactate mea	No
Triglyceride	rs1260326	Biochemist mannose m	No
Triglyceride	rs1260326	Biochemist metabolite	No
Triglyceride	rs4921914	Biochemist metabolite	No
LDL	rs1801689	Biochemist NAD-depen	No
Triglyceride	rs1260326	Biochemist percent gly	No
Triglyceride	rs1260326	Biochemist phosphatic	No
Triglyceride	rs1260326	Biochemist phosphatic	No
HDL	rs102275	Biochemist phosphatic	No
Triglyceride	rs174535	Biochemist phosphatic	No
Triglyceride	rs174535	Biochemist phosphatic	No
Triglyceride	rs1260326	Biochemist protein c m	No
LDL	rs2000999	Biochemist protein me	No
HDL	rs1047891	Biochemist protein me	No
Triglyceride	rs1260326	Biochemist protein me	No
Triglyceride	rs1694809	Biochemist serum albu	No
Triglyceride	rs1260326	Biochemist serum albu	No
LDL	rs1800562	Biochemist serum hepc	No
LDL	rs174583	Biochemist serum meta	No
LDL	rs1159114	Biochemist serum meta	No
LDL	rs6511720	Biochemist serum meta	No
LDL	rs1367117	Biochemist serum meta	No
LDL	rs780093	Biochemist serum meta	No
HDL	rs102275	Biochemist serum meta	No
HDL,Triglyc	rs676210	Biochemist serum meta	No
HDL	rs1047891	Biochemist serum meta	No
HDL	rs13702	Biochemist serum meta	No
Triglyceride	rs174535	Biochemist serum meta	No
Triglyceride	rs588136	Biochemist serum meta	No
Triglyceride	rs439401	Biochemist serum meta	No
Triglyceride	rs4810479	Biochemist serum meta	No
Triglyceride	rs1260326	Biochemist serum meta	No
Triglyceride	rs2954022	Biochemist serum meta	No
LDL	rs780093	Biochemist sex hormor	No
Triglyceride	rs1260326	Biochemist sodium me	No
LDL,HDL	rs1800961	Biochemist urate measu	Yes
LDL	rs780093	Biochemist urate measu	Yes
HDL	rs653178	Biochemist urate measu	Yes
HDL	rs3741414	Biochemist urate measu	Yes
HDL	rs1047891	Biochemist urate measu	Yes
HDL	rs1714573	Biochemist urate measu	Yes
Triglyceride	rs1260326	Biochemist urate measu	Yes
HDL	rs3741414	Biochemist uric acid m	No

Triglyceride	rs1260326	Biochemist	uric acid m	No
LDL	rs579459	Biochemist	urinary me	No
HDL	rs1047891	Biochemist	urinary me	No
Triglyceride	rs4921914	Biochemist	urinary me	No
LDL	rs492602	Biochemist	vitamin B1	No
LDL,HDL	rs964184	Biochemist	vitamin D n	No
HDL	rs1047891	Biochemist	vitamin D n	No
LDL,HDL	rs964184	Biochemist	vitamin E n	No
HDL	rs653178	Biochemist	cystatin c n	Yes
LDL,Triglyc	rs1040196	Cancer	cancer	No
LDL,HDL	rs964184	Cancer	cancer	No
Triglyceride	rs4803750	Cancer	cancer	No
HDL	rs103294	Cancer	prostate ca	No
LDL	rs3184504	Early years	birth weigh	No
LDL	rs3184504	Endocrinol	hypothyroi	No
LDL	rs3184504	Endocrinol	Thyroid pre	No
LDL,Triglyc	rs1040196	Gastro	alcoholic li	No
LDL,HDL	rs2642438	Gastro	alkaline ph	No
LDL	rs314253	Gastro	alkaline ph	No
LDL	rs579459	Gastro	alkaline ph	No
Triglyceride	rs1260326	Gastro	alkaline ph	No
HDL	rs333947	Gastro	aspartate a	No
LDL	rs3184504	Gastro	celiac disea	No
HDL	rs653178	Gastro	celiac disea	No
LDL	rs3184504	Gastro	colorectal c	No
LDL	rs3184504	Gastro	crohn's dise	No
LDL	rs780093	Gastro	crohn's dise	No
HDL	rs102275	Gastro	crohn's dise	No
Triglyceride	rs174535	Gastro	crohn's dise	No
Triglyceride	rs1260326	Gastro	crohn's dise	No
LDL	rs1169288	Gastro	gallstones	No
LDL,HDL	rs1800961	Gastro	gallstones	No
HDL	rs686030	Gastro	gallstones	No
Triglyceride	rs1260326	Gastro	gallstones	No
LDL	rs3184504	Gastro	inflammatc	No
HDL	rs653178	Gastro	inflammatc	No
Triglyceride	rs1260326	Gastro	inflammatc	No
Triglyceride	rs1260326	Gastro	non-alcohc	No
LDL	rs3184504	Gastro	sclerosing c	No
Triglyceride	rs174535	Gastro	sclerosing c	No
Triglyceride	rs1260326	Gastro	sclerosing c	No
LDL,HDL,Tr	rs1274815	Gastro	serum alani	No
LDL	rs2954029	Gastro	serum alani	No
HDL	rs1047891	Gastro	serum alani	No
Triglyceride	rs645040	Gastro	serum alani	No
LDL	rs1169288	Gastro	serum alph	No
Triglyceride	rs1260326	Gastro	serum alph	No
LDL	rs1169288	Gastro	serum gam	No
Triglyceride	rs1260326	Gastro	serum gam	No
LDL	rs3184504	Gastro	ulcerative c	No
Triglyceride	rs174535	Gastro	ulcerative c	No
Triglyceride	rs1260326	Gastro	ulcerative c	No

LDL,HDL,Tr	rs1274815	Haem	acute lymp	No
HDL	rs4969178	Haem	acute myel	No
HDL	rs1213357	Haem	acute myel	No
LDL	rs579459	Haem	adhesion m	No
LDL	rs3184504	Haem	basophil cc	No
LDL,HDL	rs1800961	Haem	basophil cc	No
HDL	rs653178	Haem	basophil cc	No
Triglyceride	rs1260326	Haem	basophil cc	No
LDL	rs1090312	Haem	blood sedir	No
LDL	rs579459	Haem	e-selectin n	No
LDL	rs3184504	Haem	eosinophil	No
LDL,HDL	rs1800961	Haem	eosinophil	No
LDL,HDL	rs964184	Haem	eosinophil	No
HDL	rs653178	Haem	eosinophil	No
Triglyceride	rs1260326	Haem	eosinophil	No
HDL	rs653178	Haem	eosinophil	No
HDL	rs653178	Haem	eosinophil	No
LDL	rs3184504	Haem	erythrocyte	No
LDL,HDL	rs1800961	Haem	erythrocyte	No
LDL	rs1800562	Haem	erythrocyte	No
LDL	rs579459	Haem	erythrocyte	No
HDL	rs102275	Haem	erythrocyte	No
HDL	rs1213357	Haem	erythrocyte	No
HDL	rs7412	Haem	erythrocyte	No
HDL	rs1310732	Haem	erythrocyte	No
Triglyceride	rs1338921	Haem	erythrocyte	No
Triglyceride	rs1260326	Haem	factor VII m	No
LDL	rs1010216	Haem	factor VIII n	No
LDL	rs1800562	Haem	ferritin mea	No
LDL	rs3184504	Haem	fibrinogen l	No
LDL,HDL	rs1800961	Haem	fibrinogen l	No
HDL	rs5167	Haem	granulocyte	No
LDL	rs3184504	Haem	granulocyte	No
LDL,HDL	rs1800961	Haem	granulocyte	No
Triglyceride	rs1260326	Haem	granulocyte	No
LDL	rs2000999	Haem	haptoglobi	No
LDL	rs3184504	Haem	hematocrit	No
LDL,Triglyc	rs1040196	Haem	hematocrit	No
LDL,HDL	rs1800961	Haem	hematocrit	No
LDL	rs1800562	Haem	hematocrit	No
LDL,HDL	rs964184	Haem	hematocrit	No
Triglyceride	rs4803750	Haem	hematocrit	No
Triglyceride	rs1260326	Haem	hematocrit	No
LDL	rs3184504	Haem	hemoglobi	No
LDL	rs2000999	Haem	hemoglobi	No
LDL,HDL	rs1800961	Haem	hemoglobi	No
LDL	rs1800562	Haem	hemoglobi	No
HDL	rs1877031	Haem	hemoglobi	No
HDL	rs1310732	Haem	hemoglobi	No
HDL,Triglyc	rs442177	Haem	hemoglobi	No
Triglyceride	rs1338921	Haem	hemoglobi	No
LDL	rs1800562	Haem	hepcidin:fe	No

LDL	rs1800562	Haem	iron bioma	No
LDL	rs3184504	Haem	leukocyte c	No
LDL,HDL	rs1800961	Haem	leukocyte c	No
HDL	rs333947	Haem	leukocyte c	No
HDL	rs291040	Haem	leukocyte c	No
HDL	rs1047891	Haem	leukocyte c	No
HDL,Triglyc	rs998584	Haem	leukocyte c	No
Triglyceride	rs1260326	Haem	leukocyte c	No
HDL	rs103294	Haem	leukocyte i	No
LDL	rs3184504	Haem	lymphocyt	No
Triglyceride	rs1260326	Haem	lymphocyt	No
LDL	rs1800562	Haem	mean corpı	No
HDL	rs7412	Haem	mean corpı	No
HDL	rs1047891	Haem	mean corpı	No
LDL,HDL	rs964184	Haem	mean corpı	No
LDL	rs1800562	Haem	mean corpı	No
HDL	rs1047891	Haem	mean corpı	No
LDL,HDL	rs964184	Haem	mean plate	No
HDL	rs1047891	Haem	mean plate	No
HDL	rs333947	Haem	monocyte (	No
HDL	rs653178	Haem	monocyte (	No
LDL	rs3184504	Haem	myeloid wh	No
LDL,HDL	rs1800961	Haem	myeloid wh	No
Triglyceride	rs1260326	Haem	myeloid wh	No
LDL	rs3184504	Haem	neutrophil	No
LDL,HDL	rs1800961	Haem	neutrophil	No
Triglyceride	rs1260326	Haem	neutrophil	No
HDL	rs653178	Haem	neutrophil	No
LDL,HDL	rs1800961	Haem	neutrophil	No
LDL,HDL	rs964184	Haem	platelet coı	No
LDL	rs3184504	Haem	platelet coı	No
LDL	rs1801689	Haem	platelet coı	No
HDL	rs1047891	Haem	platelet coı	No
Triglyceride	rs2068888	Haem	platelet coı	No
Triglyceride	rs1260326	Haem	platelet coı	No
LDL	rs3184504	Haem	platelet crit	No
Triglyceride	rs2068888	Haem	platelet crit	No
Triglyceride	rs1260326	Haem	platelet crit	No
LDL	rs579459	Haem	platelet rea	No
LDL,HDL	rs964184	Haem	red blood c	No
HDL	rs1214574	Haem	red blood c	No
HDL	rs863750	Haem	red blood c	No
HDL	rs7412	Haem	red blood c	No
Triglyceride	rs1260326	Haem	red blood c	No
LDL	rs3184504	Haem	reticulocyt	No
LDL,HDL	rs964184	Haem	reticulocyt	No
HDL	rs7412	Haem	reticulocyt	No
HDL,Triglyc	rs998584	Haem	reticulocyt	No
Triglyceride	rs1338921	Haem	reticulocyt	No
Triglyceride	rs1260326	Haem	reticulocyt	No
LDL	rs1800562	Haem	serum iron	No
LDL	rs579459	Haem	soluble p-se	No

LDL	rs492602	Haem	stromelysir	No
LDL	rs1800562	Haem	total iron b	No
LDL	rs1800562	Haem	transferrin	No
LDL	rs1800562	Haem	transferrin	No
HDL	rs1310732	Ophth	Abnormalit	No
HDL	rs3936511	Ophth	Abnormalit	No
Triglyceride	rs1260326	Ophth	Abnormalit	No
LDL	rs3184504	Ophth	glaucoma	No
HDL	rs1047891	Other	amino acid	No
Triglyceride	rs1260326	Other	amino acid	No
HDL	rs1310732	Other	balding me	No
LDL	rs3184504	Other	body heigh	Yes
LDL	rs6818397	Other	body heigh	Yes
LDL,Triglyc	rs2247056	Other	body heigh	Yes
HDL	rs1274037	Other	body heigh	Yes
HDL	rs6567160	Other	body heigh	Yes
HDL	rs1047891	Other	body heigh	Yes
HDL	rs1310732	Other	body heigh	Yes
Triglyceride	rs1260326	Other	body heigh	Yes
HDL	rs1310732	Other	brain volur	No
LDL	rs267733	Other	chronotype	No
Triglyceride	rs1260326	Other	coffee cons	No
Triglyceride	rs1260326	Other	cups of coff	No
Triglyceride	rs1260326	Other	diet measu	No
Triglyceride	rs1260326	Other	gout	Yes
HDL	rs1310732	Other	grip strengt	No
LDL	rs2737252	Other	heel bone r	No
HDL,Triglyc	rs998584	Other	heel bone r	No
Triglyceride	rs4810479	Other	heel bone r	No
HDL	rs1047891	Other	homocyste	No
HDL	rs2013208	Other	intelligence	No
HDL	rs1310732	Other	intelligence	No
HDL	rs102275	Other	irritability	No
Triglyceride	rs4810479	Other	kit ligand r	No
HDL	rs1310732	Other	lifestyle me	No
Triglyceride	rs749671	Other	lifestyle me	No
LDL,HDL	rs2075650	Other	longevity	No
HDL	rs7412	Other	longevity	No
LDL	rs8176722	Other	malaria	No
HDL	rs1310732	Other	mathemati	No
LDL,Triglyc	rs1040196	Other	mortality	No
LDL,HDL	rs964184	Other	mortality	No
Triglyceride	rs4803750	Other	mortality	No
Triglyceride	rs174535	Other	Nasal cavity	No
HDL	rs1310732	Other	neuroimagi	No
HDL	rs1310732	Other	osteoarthri	No
LDL	rs1800562	Other	osteoarthri	No
Triglyceride	rs9930333	Other	osteoarthri	No
Triglyceride	rs9930333	Other	osteoarthri	No
LDL	rs3184504	Other	parental ge	No
LDL	rs3184504	Other	parental lo	No
LDL	rs6511720	Other	parental lo	No

Triglyceride	rs749671	Other	response tc	No
HDL	rs4917014	Other	response tc	No
LDL,HDL,Tr	rs1274815	Other	response tc	No
HDL	rs7412	Other	response tc	No
LDL,HDL	rs964184	Other	response tc	No
LDL,HDL	rs964184	Other	response tc	No
HDL	rs1310732	Other	risk-taking	No
HDL	rs1310732	Other	schizophre	No
HDL	rs1310732	Other	self reporte	No
LDL	rs1019525	Other	sex interact	No
HDL	rs2925979	Other	sex interact	No
HDL,Triglyc	rs998584	Other	sex interact	No
LDL	rs1711150	Other	sleep durat	No
LDL	rs1367117	Other	sleep durat	No
LDL	rs1564348	Other	sleep durat	No
LDL,HDL	rs964184	Other	sleep durat	No
HDL	rs1274037	Other	sleep durat	No
HDL	rs1138429	Other	sleep durat	No
HDL	rs4783961	Other	sleep durat	No
HDL	rs2925979	Other	sleep durat	No
HDL	rs103294	Other	sleep durat	No
HDL	rs7607980	Other	sleep durat	No
HDL,Triglyc	rs676210	Other	sleep durat	No
HDL	rs1310732	Other	sleep durat	No
HDL	rs13702	Other	sleep durat	No
HDL	rs686030	Other	sleep durat	No
Triglyceride	rs4810479	Other	sleep durat	No
Triglyceride	rs1260326	Other	sleep durat	No
HDL	rs4917014	Other	Stevens-Joh	No
LDL	rs3184504	Other	tonsillecto	No
HDL	rs653178	Other	tonsillecto	No
HDL	rs4917014	Other	toxic epide	No
LDL,HDL	rs964184	Other	vitamin me	No
HDL	rs1047891	Renal disea	albuminuri	No
LDL	rs174583	Renal disea	chronic kid	Yes
HDL	rs102275	Renal disea	chronic kid	Yes
HDL	rs653178	Renal disea	chronic kid	Yes
HDL	rs1047891	Renal disea	chronic kid	Yes
Triglyceride	rs1260326	Renal disea	chronic kid	Yes
Triglyceride	rs4921914	Renal disea	chronic kid	Yes
LDL	rs780093	Renal disea	creatinine r	Yes
HDL	rs1047891	Renal disea	creatinine r	Yes
Triglyceride	rs1260326	Renal disea	creatinine r	Yes
LDL	rs780093	Renal disea	glomerular	Yes
HDL	rs3741414	Renal disea	glomerular	Yes
HDL	rs1047891	Renal disea	glomerular	Yes
Triglyceride	rs2068888	Renal disea	glomerular	Yes
Triglyceride	rs1260326	Renal disea	glomerular	Yes
LDL	rs780093	Renal disea	kidney ston	No
HDL	rs1936800	Renal disea	renal syster	No
LDL	rs780093	Renal disea	urinary albu	Yes
HDL	rs1047891	Renal disea	urinary albu	Yes

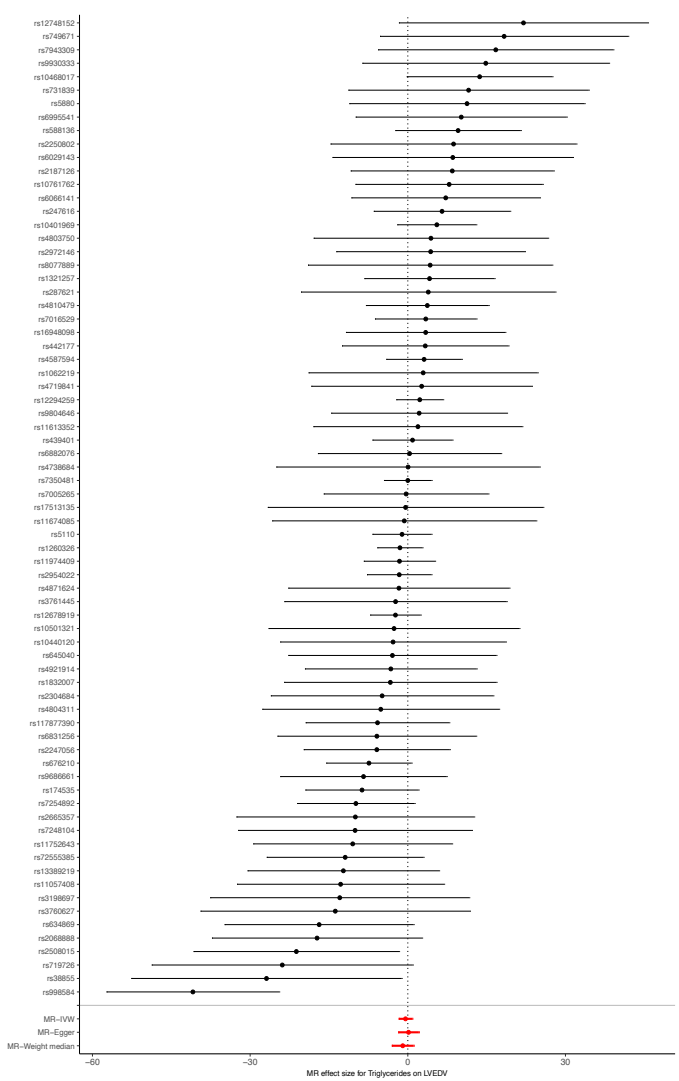
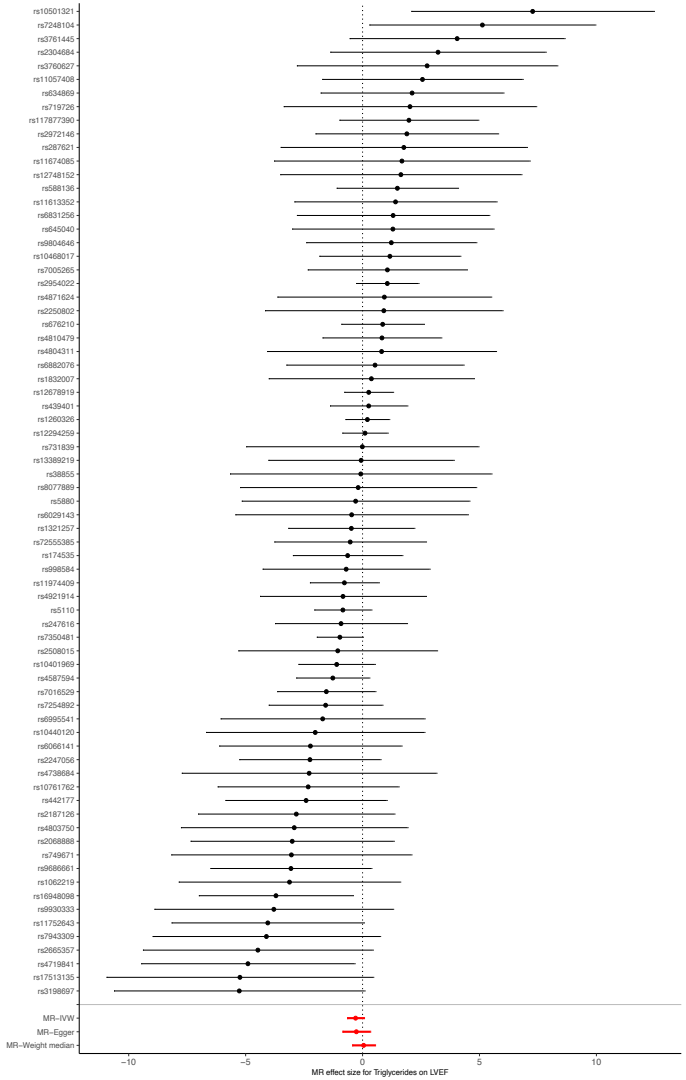
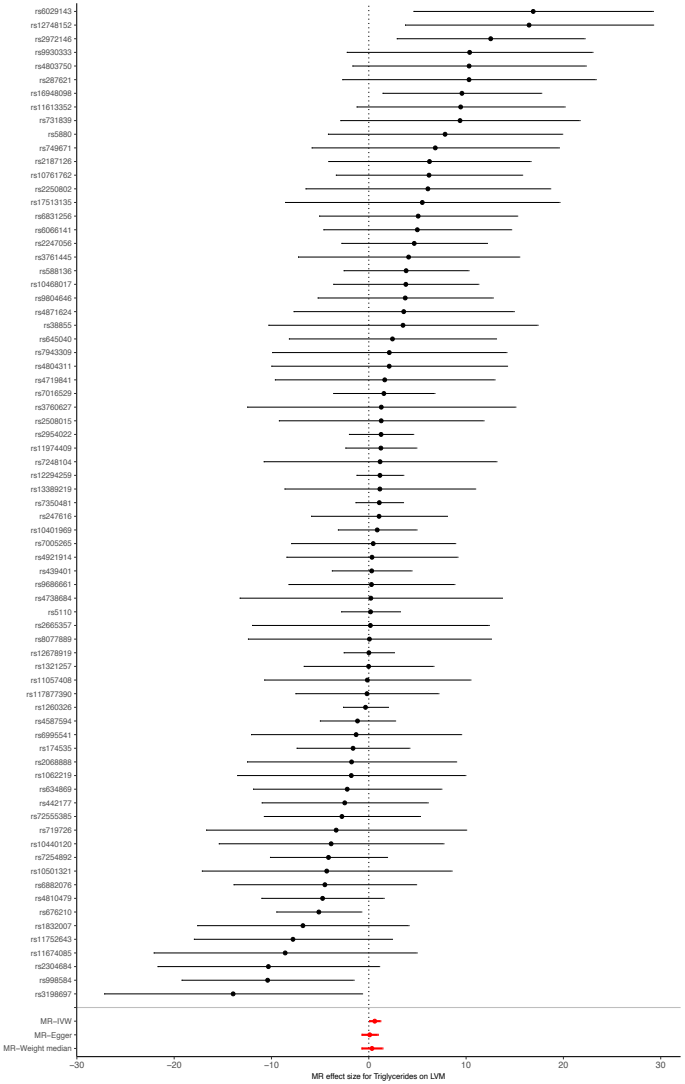
Triglyceride	rs2068888	Renal disea	urinary alb	Yes
HDL	rs1047891	Renal disea	urinary pot	No
HDL	rs1047891	Renal disea	urinary sod	No
Triglyceride	rs1260326	Renal disea	urinary sod	No
Triglyceride	rs1260326	Renal disea	urolithiasis	No
LDL	rs3184504	Women's h	endometria	No
LDL	rs3184504	Women's h	endometria	No
LDL	rs1159114	LDL	LDL cholest	No
HDL	rs7412	LDL	LDL cholest	No
LDL	rs1089349	LDL	low density	No
LDL	rs267733	LDL	low density	No
LDL	rs174583	LDL	low density	No
LDL	rs3184504	LDL	low density	No
LDL	rs1169288	LDL	low density	No
LDL,HDL	rs2642438	LDL	low density	No
LDL	rs2587534	LDL	low density	No
LDL	rs1090312	LDL	low density	No
LDL,HDL,Tr	rs1274815	LDL	low density	No
LDL	rs4942486	LDL	low density	No
LDL	rs8017377	LDL	low density	No
LDL	rs1711150	LDL	low density	No
LDL	rs1159114	LDL	low density	No
LDL	rs1148561	LDL	low density	No
LDL,Triglyc	rs247616	LDL	low density	No
LDL	rs2000999	LDL	low density	No
LDL	rs1801689	LDL	low density	No
LDL	rs314253	LDL	low density	No
LDL	rs1166913	LDL	low density	No
LDL	rs6511720	LDL	low density	No
LDL	rs688	LDL	low density	No
LDL,Triglyc	rs1040196	LDL	low density	No
LDL	rs1046018	LDL	low density	No
LDL	rs1531517	LDL	low density	No
LDL,Triglyc	rs7254892	LDL	low density	No
LDL,HDL	rs2075650	LDL	low density	No
LDL	rs492602	LDL	low density	No
LDL	rs364585	LDL	low density	No
LDL	rs2328223	LDL	low density	No
LDL	rs6016381	LDL	low density	No
LDL	rs6065311	LDL	low density	No
LDL,HDL	rs1800961	LDL	low density	No
LDL	rs1049062	LDL	low density	No
LDL	rs2030746	LDL	low density	No
LDL	rs1367117	LDL	low density	No
LDL	rs1250229	LDL	low density	No
LDL	rs5763662	LDL	low density	No
LDL	rs1156325	LDL	low density	No
LDL	rs6544713	LDL	low density	No
LDL	rs2710642	LDL	low density	No
LDL	rs1740415	LDL	low density	No
LDL	rs7640978	LDL	low density	No
LDL	rs6818397	LDL	low density	No

LDL	rs4530754	LDL	low density	No
LDL,Triglyc	rs6882076	LDL	low density	No
LDL	rs12916	LDL	low density	No
LDL	rs6909746	LDL	low density	No
LDL	rs1564348	LDL	low density	No
LDL	rs3757354	LDL	low density	No
LDL	rs1800562	LDL	low density	No
LDL,Triglyc	rs2247056	LDL	low density	No
LDL	rs1267079	LDL	low density	No
LDL	rs4722551	LDL	low density	No
LDL	rs2073547	LDL	low density	No
LDL	rs2737252	LDL	low density	No
LDL	rs2954029	LDL	low density	No
LDL	rs7832643	LDL	low density	No
LDL	rs1010216	LDL	low density	No
LDL	rs1327780	LDL	low density	No
LDL	rs9987289	LDL	low density	No
LDL,HDL	rs1883025	LDL	low density	No
LDL	rs579459	LDL	low density	No
LDL	rs3780181	LDL	low density	No
LDL,HDL	rs964184	LDL	low density	No
HDL	rs1274037	LDL	low density	No
HDL	rs1713539	LDL	low density	No
HDL	rs653178	LDL	low density	No
HDL	rs9989419	LDL	low density	No
HDL	rs737337	LDL	low density	No
HDL	rs7412	LDL	low density	No
HDL,Triglyc	rs676210	LDL	low density	No
HDL	rs1714573	LDL	low density	No
HDL	rs1080854	LDL	low density	No
HDL	rs4240624	LDL	low density	No
Triglyceride	rs4587594	LDL	low density	No
Triglyceride	rs4803750	LDL	low density	No
Triglyceride	rs1260326	LDL	low density	No
Triglyceride	rs6831256	LDL	low density	No
Triglyceride	rs2954022	LDL	low density	No
Triglyceride	rs4738684	LDL	low density	No
LDL,Triglyc	rs247616	HDL	HDL choles	No
LDL,HDL	rs1800961	HDL	HDL choles	No
LDL,HDL	rs1883025	HDL	HDL choles	No
HDL	rs2925979	HDL	HDL choles	No
HDL	rs2013208	HDL	HDL choles	No
Triglyceride	rs4810479	HDL	HDL choles	No
LDL,Triglyc	rs9804646	HDL	high densit	No
LDL	rs174583	HDL	high densit	No
LDL	rs3184504	HDL	high densit	No
LDL,HDL	rs2642438	HDL	high densit	No
LDL,HDL,Tr	rs1274815	HDL	high densit	No
LDL,Triglyc	rs247616	HDL	high densit	No
LDL,Triglyc	rs1040196	HDL	high densit	No
LDL	rs1531517	HDL	high densit	No
LDL,HDL	rs1800961	HDL	high densit	No

LDL	rs1740415	HDL	high densit	No
LDL	rs2954029	HDL	high densit	No
LDL	rs9987289	HDL	high densit	No
LDL,HDL	rs1883025	HDL	high densit	No
LDL	rs519113	HDL	high densit	No
LDL,HDL	rs964184	HDL	high densit	No
HDL	rs970548	HDL	high densit	No
HDL	rs1274037	HDL	high densit	No
HDL	rs333947	HDL	high densit	No
HDL	rs1214574	HDL	high densit	No
HDL	rs1280163	HDL	high densit	No
HDL	rs499974	HDL	high densit	No
HDL	rs4650994	HDL	high densit	No
HDL	rs1689797	HDL	high densit	No
HDL	rs2241210	HDL	high densit	No
HDL	rs863750	HDL	high densit	No
HDL	rs838876	HDL	high densit	No
HDL	rs7298751	HDL	high densit	No
HDL	rs1104516	HDL	high densit	No
HDL	rs4846914	HDL	high densit	No
HDL	rs3741414	HDL	high densit	No
HDL	rs4660293	HDL	high densit	No
HDL	rs4983559	HDL	high densit	No
HDL	rs492571	HDL	high densit	No
HDL,Triglyc	rs1046801	HDL	high densit	No
HDL	rs1077834	HDL	high densit	No
HDL	rs1121980	HDL	high densit	No
HDL	rs1138429	HDL	high densit	No
HDL	rs9989419	HDL	high densit	No
HDL	rs4783961	HDL	high densit	No
HDL	rs1694288	HDL	high densit	No
HDL	rs2925979	HDL	high densit	No
HDL	rs1877031	HDL	high densit	No
HDL	rs4969178	HDL	high densit	No
HDL	rs4939883	HDL	high densit	No
HDL	rs737337	HDL	high densit	No
HDL,Triglyc	rs731839	HDL	high densit	No
HDL	rs7730111	HDL	high densit	No
HDL	rs7412	HDL	high densit	No
HDL	rs5167	HDL	high densit	No
HDL	rs1769522	HDL	high densit	No
HDL	rs103294	HDL	high densit	No
HDL	rs2278236	HDL	high densit	No
HDL	rs4465830	HDL	high densit	No
HDL	rs7607980	HDL	high densit	No
HDL,Triglyc	rs676210	HDL	high densit	No
HDL	rs1047891	HDL	high densit	No
HDL	rs181360	HDL	high densit	No
HDL	rs6805251	HDL	high densit	No
HDL	rs1307625	HDL	high densit	No
HDL	rs2290547	HDL	high densit	No
HDL	rs2013208	HDL	high densit	No

HDL	rs1332616	HDL	high densit	No
HDL	rs1310732	HDL	high densit	No
HDL,Triglyc	rs442177	HDL	high densit	No
HDL	rs3822072	HDL	high densit	No
HDL	rs6450176	HDL	high densit	No
HDL	rs1936800	HDL	high densit	No
HDL,Triglyc	rs998584	HDL	high densit	No
HDL	rs1176597	HDL	high densit	No
HDL	rs1717363	HDL	high densit	No
HDL	rs4142995	HDL	high densit	No
HDL	rs4917014	HDL	high densit	No
HDL	rs702485	HDL	high densit	No
HDL	rs1714573	HDL	high densit	No
HDL	rs2293889	HDL	high densit	No
HDL	rs1080854	HDL	high densit	No
HDL	rs1008790	HDL	high densit	No
HDL,Triglyc	rs7016529	HDL	high densit	No
HDL	rs13702	HDL	high densit	No
HDL	rs4240624	HDL	high densit	No
HDL	rs2853579	HDL	high densit	No
HDL	rs1178960	HDL	high densit	No
HDL	rs686030	HDL	high densit	No
Triglyceride	rs2068888	HDL	high densit	No
Triglyceride	rs7350481	HDL	high densit	No
Triglyceride	rs1321257	HDL	high densit	No
Triglyceride	rs1161335	HDL	high densit	No
Triglyceride	rs1751313	HDL	high densit	No
Triglyceride	rs588136	HDL	high densit	No
Triglyceride	rs5880	HDL	high densit	No
Triglyceride	rs4803750	HDL	high densit	No
Triglyceride	rs439401	HDL	high densit	No
Triglyceride	rs4810479	HDL	high densit	No
Triglyceride	rs2972146	HDL	high densit	No
Triglyceride	rs9686661	HDL	high densit	No
Triglyceride	rs634869	HDL	high densit	No
Triglyceride	rs2954022	HDL	high densit	No
Triglyceride	rs1267891	HDL	high densit	No
Triglyceride	rs1260326	Triglyceride	triacylglyce	No
Triglyceride	rs1260326	Triglyceride	triacylglyce	No
Triglyceride	rs1260326	Triglyceride	triacylglyce	No
Triglyceride	rs1229425	Triglyceride	triacylglyce	No
LDL,HDL	rs964184	Triglyceride	triacylglyce	No
LDL,HDL	rs964184	Triglyceride	triacylglyce	No
LDL,HDL	rs964184	Triglyceride	triacylglyce	No
LDL,HDL	rs964184	Triglyceride	triacylglyce	No
LDL,HDL	rs964184	Triglyceride	triacylglyce	No
LDL,HDL	rs964184	Triglyceride	triacylglyce	No
LDL	rs780093	Triglyceride	hypertrigly	No
LDL,HDL	rs964184	Triglyceride	hypertrigly	No
HDL	rs1714573	Triglyceride	hypertrigly	No
Triglyceride	rs1260326	Triglyceride	hypertrigly	No
LDL,HDL	rs964184	Triglyceride	triglyceride	No

LDL,Triglyc	rs9804646	Triglyceride	triglyceride	No
LDL	rs174583	Triglyceride	triglyceride	No
LDL,HDL	rs2642438	Triglyceride	triglyceride	No
LDL,HDL,Tr	rs1274815	Triglyceride	triglyceride	No
LDL,Triglyc	rs247616	Triglyceride	triglyceride	No
LDL	rs1801689	Triglyceride	triglyceride	No
LDL,Triglyc	rs1040196	Triglyceride	triglyceride	No
LDL,Triglyc	rs7254892	Triglyceride	triglyceride	No
LDL	rs492602	Triglyceride	triglyceride	No
LDL	rs1019525	Triglyceride	triglyceride	No
LDL	rs1367117	Triglyceride	triglyceride	No
LDL	rs780093	Triglyceride	triglyceride	No
LDL,Triglyc	rs6882076	Triglyceride	triglyceride	No
LDL,Triglyc	rs2247056	Triglyceride	triglyceride	No
LDL	rs4722551	Triglyceride	triglyceride	No
LDL	rs2954029	Triglyceride	triglyceride	No
LDL	rs9987289	Triglyceride	triglyceride	No
LDL,HDL	rs1883025	Triglyceride	triglyceride	No
LDL,HDL	rs964184	Triglyceride	triglyceride	No
HDL	rs863750	Triglyceride	triglyceride	No
HDL	rs4846914	Triglyceride	triglyceride	No
HDL	rs3741414	Triglyceride	triglyceride	No
HDL,Triglyc	rs1046801	Triglyceride	triglyceride	No
HDL	rs1077834	Triglyceride	triglyceride	No
HDL	rs1121980	Triglyceride	triglyceride	No
HDL	rs9989419	Triglyceride	triglyceride	No
HDL	rs2925979	Triglyceride	triglyceride	No
HDL,Triglyc	rs731839	Triglyceride	triglyceride	No
HDL	rs7412	Triglyceride	triglyceride	No
HDL	rs5167	Triglyceride	triglyceride	No
HDL	rs4465830	Triglyceride	triglyceride	No
HDL	rs7607980	Triglyceride	triglyceride	No
HDL,Triglyc	rs676210	Triglyceride	triglyceride	No
HDL	rs687339	Triglyceride	triglyceride	No
HDL,Triglyc	rs442177	Triglyceride	triglyceride	No
HDL	rs3822072	Triglyceride	triglyceride	No
HDL	rs1936800	Triglyceride	triglyceride	No
HDL,Triglyc	rs998584	Triglyceride	triglyceride	No
HDL	rs1176597	Triglyceride	triglyceride	No
HDL	rs1714573	Triglyceride	triglyceride	No
HDL	rs1080854	Triglyceride	triglyceride	No
HDL,Triglyc	rs7016529	Triglyceride	triglyceride	No
HDL	rs13702	Triglyceride	triglyceride	No
Triglyceride	rs1832007	Triglyceride	triglyceride	No
Triglyceride	rs2068888	Triglyceride	triglyceride	No
Triglyceride	rs7350481	Triglyceride	triglyceride	No
Triglyceride	rs1105740	Triglyceride	triglyceride	No
Triglyceride	rs1321257	Triglyceride	triglyceride	No
Triglyceride	rs1161335	Triglyceride	triglyceride	No
Triglyceride	rs588136	Triglyceride	triglyceride	No
Triglyceride	rs3198697	Triglyceride	triglyceride	No
Triglyceride	rs4587594	Triglyceride	triglyceride	No

Triglyceride	rs5880	Triglyceride	triglyceride	No
Triglyceride	rs8077889	Triglyceride	triglyceride	No
Triglyceride	rs4803750	Triglyceride	triglyceride	No
Triglyceride	rs439401	Triglyceride	triglyceride	No
Triglyceride	rs7248104	Triglyceride	triglyceride	No
Triglyceride	rs4810479	Triglyceride	triglyceride	No
Triglyceride	rs6066141	Triglyceride	triglyceride	No
Triglyceride	rs2972146	Triglyceride	triglyceride	No
Triglyceride	rs3761445	Triglyceride	triglyceride	No
Triglyceride	rs1260326	Triglyceride	triglyceride	No
Triglyceride	rs645040	Triglyceride	triglyceride	No
Triglyceride	rs6831256	Triglyceride	triglyceride	No
Triglyceride	rs9686661	Triglyceride	triglyceride	No
Triglyceride	rs719726	Triglyceride	triglyceride	No
Triglyceride	rs38855	Triglyceride	triglyceride	No
Triglyceride	rs4719841	Triglyceride	triglyceride	No
Triglyceride	rs6995541	Triglyceride	triglyceride	No
Triglyceride	rs2954022	Triglyceride	triglyceride	No
Triglyceride	rs4921914	Triglyceride	triglyceride	No
Triglyceride	rs1267891	Triglyceride	triglyceride	No

Supplementary Figure 5