Genetics and life course epidemiology of cardiometabolic disease: towards personalized medicine

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Triglyceride-lowering *LPL* alleles combined with LDL-C-lowering alleles are associated with an additively improved lipoprotein profile

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ABSTRACT

Background and aims: Mendelian randomization studies have shown that triglyceride (TG) lowering *lipoprotein lipase (LPL)* alleles and low-density lipoprotein-cholesterol (LDL-C) lowering alleles have independent beneficial associations on cardiovascular disease (CVD) risk. We aimed to provide further insight in this observation by applying Mendelian randomization analyses of genetically influenced TG and LDL-C levels on plasma metabolomic profiles.

Methods: We quantified over 100 lipoprotein metabolomic measures in the Netherlands Epidemiology of Obesity (NEO) study (N=4,838) and Oxford Biobank (OBB) (N=6,999) by nuclear magnetic resonance (NMR) spectroscopy. Weighted genetic scores for TG via five *LPL* alleles and LDL-C via 19 alleles were calculated and dichotomized by the median, resulting in four genotype combinations of high/low TG and high/low LDL-C. We performed linear regression analyses using a two × two design with the group with genetically influenced high TG and LDL-C as a reference.

Results: Compared to the individual groups with genetically influenced lower TG or lower LDL-C only, the group with combined genetically influenced lower TG and LDL-C showed an overall independent and additive pattern of changes in metabolomic measures. Over 100 measures were different ($p<1.35x10^{-3}$) compared to the reference, with effect sizes and directionality being similar in NEO and OBB. Most notably, levels of all very-low density lipoprotein (VLDL) and LDL sub-particles were lower.

Conclusions: Our findings provide evidence that TG lowering on top of LDL-C lowering has additive beneficial effects on the lipoprotein profile compared to TG lowering or LDL-C lowering only, which is in accordance with reported additive genetic effects on CVD risk reduction.

Keywords: Metabolomics; Mendelian Randomization, Cardiovascular Disease; Lipoprotein lipase; LDL-cholesterol lowering; Triglyceride lowering

INTRODUCTION

Cardiovascular disease (CVD) is the number one cause of death worldwide (1). Dyslipidemia, characterized by abnormally elevated serum concentrations of low-density lipoprotein-cholesterol (LDL-C) and triglycerides (TG) and low levels of high-density lipoprotein-cholesterol (HDL-C), is recognized as one of the main risk factors associated with CVD (2,3). At present, statins are the first-line therapy for prevention of CVD risk by reducing LDL-C. Statin therapy results in an approximately 30% reduction in primary CVD events (4,5). To achieve additional reduction of CVD risk, novel lipid-lowering therapies on top of statins are currently being investigated.

In addition to LDL-C, TG-rich lipoproteins (TRLs) have recently been identified as an independent additional risk factor for CVD (6–8). Since the enzyme lipoprotein lipase (LPL) is a key player in TRL removal (9), it has gained attention as a druggable target. Several therapies that enhance LPL-mediated clearance of TRL-derived TG are in development for CVD prevention (10–14). A recent phase 3 trial in which patients with homozygous familial hypercholesterolemia were treated for 24 weeks with the Angiopoietin-like 3 protein inhibitor Evinacumab, to enhance LPL-mediated TRL clearance, on top of classical LDL-C lowering therapy showed a 47.1% reduction in LDL-C levels compared with a 1.9% increase in the group who received only lipid-lowering therapy (11). However, large randomized clinical trials in the general population are needed to show whether these drugs provide cardiovascular benefit in addition to statins.

In addition to randomized controlled clinical trials, Mendelian randomization studies have been exploited to assess whether enhanced LPL-mediated lipolysis has an additional benefit on top of decreased LDL-C in lowering CVD risk. For example, people with genetically influenced lower TG levels via *LPL* alleles genetically influenced lower LDL-C levels showed an additional 10% lower CVD risk compared to those with genetically influenced lower LDL-C levels only (15). This study suggested that drugs that enhance LPL-mediated lipolysis are likely to provide additional cardiovascular benefit on top of LDL-C lowering agents. However, the association of genotypes with cardiovascular outcomes does not provide insight in the mechanisms behind the beneficial effects of these potentially novel drugs. Since metabolites provide a functional read out of the biological processes in the human body (16,17), they can serve as intermediate phenotypes between genetic variation and CVD outcomes (18,19). Metabolomics analyses (20) may thus provide additional insight in the pathways that mediate the effects of genetically influenced lower TG levels via *LPL* alleles and genetically influenced lower LDL-C levels on CVD risk.

In the current study, we assessed the causal associations between lower TG levels via *LPL* alleles and mainly lipoprotein-related metabolomic measures determined with nuclear magnetic resonance (NMR) with and without a background of lower LDL-C levels, through Mendelian randomization in two large population-based cohorts.

METHODS

Study design and population

The Netherlands Epidemiology of Obesity (NEO) study is a population-based prospective cohort study of men and women aged between 45 and 65 years. From the greater area of Leiden, The Netherlands, all inhabitants with a self-reported body mass index (BMI) of 27 kg/m^2 or higher were eligible to participate. In addition, inhabitants from one nearby municipality (Leiderdorp, The Netherlands) in the same age group were invited to participate regardless of their BMI, forming a reference population for BMI distribution. In total, 6,671 participants were included from September 2008 until September 2012. Participants visited the NEO study center for extensive physical examination. After an overnight fast of at least 10 hours, fasting blood samples were taken at the study center. Research nurses recorded current medication use by means of a medication inventory. Prior to the study visit, participants completed questionnaires at home with respect to demographic, lifestyle, and clinical information. The NEO study design was approved by the medical ethics committee of the Leiden University Medical Center (LUMC), and all participants gave their written informed consent. Detailed information about the study design and data collection has been described elsewhere (21).

For our study, we excluded participants lacking genetic data (N = 927), as described in detail below and elsewhere (22). Additionally, we excluded participants using lipid-lowering medication (N=906).

Genotyping and imputation

DNA was isolated from venous blood samples. Genotyping was performed using the Illumina HumanCoreExome-24 BeadChip (Illumina Inc., San Diego, California, United States of America). Participants were excluded in the process of quality control when 1) the sample call rate was <98%, 2) there was a sex mismatch, 3) heterozygosity rate was not within ±3 SD of mean heterozygosity rate, 4) participants widely diverged based on the first two principal components (PCs) (±3.5 SD), 5) samples were duplicates, and 6) concordance with another DNA sample was >0.25 (related individuals). Genetic variants were excluded when 1) genotype call rate was <98%,

and 2) variants were not in Hardy-Weinberg equilibrium ($p < 1 \times 10^{-6}$). Detailed quality control steps have been described elsewhere (22). Subsequently, genotypes were imputed to the 1000 Genome Project reference panel (23) (v3 2011) using IMPUTE (v2.2) software (24).

NMR-based metabolomics

A high-throughput proton NMR metabolomics platform (25) (Nightingale Health Ltd., Helsinki, Finland) was used to measure 159 metabolomic markers (excluding ratios) in plasma at the Medical Research Council Integrative Epidemiology Unit (MRC IEU) at the University of Bristol, Bristol, United Kingdom, which were quantified by Nightingale library. This method provides lipoprotein subclass profiling with lipid concentrations within 14 lipoprotein subclasses, defined as a subclass of extremely large very-low density lipoproteins (VLDL) with particle diameters from 75 nm upwards and a possible contribution of chylomicrons, five VLDL subclasses (average particle diameters of 64.0 nm, 53.6 nm, 44.5 nm, 36.8 nm, and 31.3 nm), an intermediate density lipoprotein (IDL) subclass (28.6 nm), three LDL subclasses (25.5 nm, 23.0 nm, and 18.7 nm), and four HDL subclasses (14.3 nm, 12.1 nm, 10.9 nm, and 8.7 nm). Within the lipoprotein subclasses, the following components were quantified: total cholesterol, total lipids, phospholipids, free cholesterol, cholesteryl esters, and triglycerides. The mean size for VLDL, LDL and HDL particles was calculated by weighting the corresponding subclass diameters with their particle concentrations. Furthermore, 58 metabolomic measures were determined that belong to classes of apolipoproteins, cholesterol, fatty acids (FAs), glycerides, phospholipids, amino acids, fluid balance, glycolysis-related metabolites, inflammation, and ketone bodies. Details of the experimentation and applications of the NMR metabolomics platform (25) as well as representative coefficients of variations (CVs) for the metabolomic biomarkers (26) have been described previously. A full list of the NMR-based metabolomic measures and their full names are provided elsewhere (27).

In this study, we excluded all reported ratios between metabolites as well as the metabolites that were not measured in the replication cohort (see below), resulting in a final number of 145 NMR-based metabolomic measures. The analyses were performed on ranked-based inverse normally transformed (INT) NMR-metabolites.

Replication dataset

Oxford Biobank (OBB) Study design

The OBB is a population-based cohort of randomly selected healthy participants aged 30 to 50 years from Oxfordshire (UK). Individuals with a history of Omyocardial

infarction, diabetes mellitus, heart failure, untreated malignancy, other ongoing systemic diseases or ongoing pregnancy were not eligible for study inclusion. Participants were included between 1999 and May 2015. The OBB cohort comprises 7,185 individuals. A more detailed description of the study recruitment criteria and population characteristics is reported elsewhere (28).

Genotyping

For each OBB participant, 35 mL aliquots of whole blood were collected and frozen at -80°C for isolation of genomic DNA. Genotyping was performed using the Illumina Infinium Human Exome Beadchip 12v1 array platform for the first consecutive 5900 DNAs, and Affymetrix UK Biobank Axiom Array chip on the first consecutive 7500 participants (28). In total 6,999 genotyped participants were included in the current study.

Metabolomics

The Nightingale NMR-based metabolomics platform containing >200 metabolomic markers was performed on 7100 Oxford biobank fasting plasma samples. For the replication, we used 145 metabolites overlapping with the NEO cohort.

Stratified Genetic Analyses

In this study, we calculated two independent *LPL* and LDL-C genetic scores, similar as described by Lotta et al (15). The TG genetic score was constructed using variants associated with TG concentrations that were mapped to the *LPL* gene, which were weighted by their effect on TG levels in the analyses of the Global Lipids Genetics Consortium (29). One of the six variants used by Lotta et al was not measured in the NEO cohort and therefore we constructed the *LPL* genetic score using the other five *LPL* variants (rs268, rs301, rs326, rs328 and rs10096633). All variants were independently and strongly associated with TG. More details on the selection of these *LPL* variants are described by Lotta et al (15). For the LDL-C score, we added 19 LDL-C lowering alleles and weighted them by their effect on LDL-C lipid levels in the analyses of the Global Lipids Genetics Consortium (30). These alleles were genome-wide significantly associated with LDL-C levels without showing associations with the other lipid traits. In addition, all LDL-C variants were over 500 kb away from each other and had no or negligible linkage disequilibrium ($R^2 < 0.01$). The list of variants used for *LPL* and LDL-C genetic scores is given in Supplementary Table 1. The linkage disequilibrium scores between the *LPL* variants are shown in Supplementary Table 2.

Then, we dichotomized each score at their corresponding median value to "naturally randomize" the participants into 4 groups: (1) a reference group, with genetically influenced higher TG and LDL-C levels, (2) a group with genetically influenced lower TG levels, as proxy for LPL enhancing therapy and (3) a group with genetically influenced lower LDL-C levels, as proxy for LDL-C lowering therapy like statins (4) a group with both genetically influenced lower TG and genetically influenced lower LDL-C levels, as proxy for LPL enhancing therapy on top of LDL-C lowering therapy. This process of natural allocation is schematically depicted elsewhere (15).

Statistical Analyses

Using the four "naturally randomized" groups constructed as described above, we performed linear regression analyses to estimate the associations with NMR-based metabolomic measures between groups using a two × two factorial design. These association analyses were adjusted for age, sex and the first four genomic principal components to correct for possible population stratification. In addition, we performed interaction analyses between the *LPL* and LDL-C genetic scores in order to test whether they had had synergetic effects on the NMR-based metabolomics measures.

We corrected for multiple testing using the method described by Li and Ji (31). Using this method, we were able to correct for the number of independent metabolomic measures, as other correction factors are too stringent given the high intercorrelations between the metabolomic measures, which could give false-negative results. In this study, we corrected for 37 independent tests, and therefore, associations with a $p < 1.35 \times 10^{-3}$ were considered statistically significant.

In the NEO study, persons with a BMI of 27 kg/m^2 or higher are oversampled. Therefore, all results were based on analyses weighted towards a normal reference BMI distribution, and thus apply to populations without oversampling of individuals with overweight or obesity. A more detailed description of the weighting can be found elsewhere (22).

Analyses were performed using STATA Statistical Software version 12.0 (Statacorp, College Station, Texas, USA) and R version 3.6.1 (The R Project, https://www.r-project.org/). The circular plots were designed with Python version 2.7.6 (Python Software Foundation, https://www.python.org/). The other figures were designed using IBM SPSS Statistics version 25 (SPSS, Inc., Chicago, USA).

RESULTS

Population characteristics

Characteristics of the NEO study population (N=4,838) and OBB cohort (N=6,999) are summarized in Table 1. Compared to participants from the NEO cohort, OBB participants had a lower mean age (41.6 vs. 55.5 years, respectively) but a similar mean BMI (25.8 and 26.0 kg/m^2 for OBB and NEO, respectively). Levels of TG, total cholesterol, LDL-C and HDL-C were higher in the NEO cohort compared to the OBB cohort. The median *LPL* and LDL genetic scores (in SD units) were similar between the two cohorts. The characteristics of the NEO and OBB cohorts stratified by the dichotomized TG and LDL-C genetic scores are shown in Supplementary Tables 3 and 4.

Table 1 Characteristics of the discovery cohort (NEO) and replication cohort (OBB)

Characteristics	Discovery cohort[a] NEO (n=4,838)	Replication cohort OBB (n=6,999)
Age (years)	55.5 (6.0)	41.6 (5.9)
Men	42.0%	43.6%
BMI (kg/m^2)	26.0 (4.3)	25.8 (4.6)
Fasting serum concentrations (mmol/L)		
TG (median (IQR))	0.99 (0.71; 1.42)	0.93 (0.69; 1.34)
Total cholesterol	5.80 (1.01)	5.18 (1.01)
LDL-cholesterol	3.66 (0.94)	3.22 (1.26)
HDL-cholesterol	1.60 (0.47)	1.38 (0.42)
GRS LDL (median (IQR))	0.88 (0.80; 0.97)	0.90 (0.82; 0.99)
GRS *LPL* (median (IQR))	0.48 (0.39; 0.63)	0.48 (0.39; 0.63)

Values are mean (SD), unless otherwise specified. GRS unit is in SD. BMI, body mass index; TG, triglycerides; HD, high-density lipoprotein; LDL, low-density lipoprotein; IQR, interquartile range; GRS genetic risk score.
[a] In NEO, results are based on analyses weighted towards the reference BMI distribution of the general Dutch population.

Two by two factorial analyses of genetically influenced lower TG and genetically influenced lower LDL-C in the NEO cohort.

The results of the factorial analyses of groups with genetically influenced lower TG and/or LDL-C levels on the fasting NMR metabolomic measures are shown in Figures 1-3 and detailed results are provided in Supplementary Table 5. Compared with the reference group (combined genetically influenced higher TG and LDL-C levels), the group with genetically influenced lower TG levels only had lower levels of TG in VLDL and lower small and medium sized VLDL particle concentrations (SVLDLP: beta (SE)= -0.21 (0.06), p = 3.9x10^{-4}, MVLDLP: -0.19 (0.06), p = 7.6x10^{-4}) and higher levels of HDL-C (HDL-C: 0.17 (0.05), p = 4.9x10^{-4}) (Figure 1). The group with genetically influenced lower LDL-C levels had lower levels of ApoB and lower levels of medium

and large sized LDL sub-particles (strongest association on phospholipid content of medium LDL (MLDLPL): -0.19 (0.05), p = 6.4 x10-4 and LLDLPL: -0.18 (0.05), p = 8.1 x10-4) (Figure 2). The group with combined genetically influenced lower TG and LDL-C levels showed the largest number of measures being different in concentration from the reference group (both genetic exposures: n=102 vs. genetically influenced lower LDL-C only: n=13 vs. genetically influenced lower TG only: n=18) and the effect sizes were substantially larger compared to with the other groups (Figure 3). Overall, these effects showed an additive pattern between the LPL and LDL-C genetic scores, but no evidence for an interaction between these scores (p for interaction > 1.4x10-03). All components of all VLDL sub-particles and LDL sub-particles were significantly lower, with the exception of the TG component of medium LDL (MLDLTG). In this combination group, ApoB, remnant cholesterol, total serum cholesterol, VLDL-cholesterol (VLDL-C) and LDL-C were significantly lower whereas large HDL particle concentrations and HDL-C were higher. Furthermore, the combination group had a lower average VLDL particle size (VLDLD, -0.27 (0.05), p = 3.83 x 10-07) and higher average HDL particle size (HDLD, 0.22 (0.05), p = 3.26 x 10-05), but no differences in LDL particle size compared to the reference group. Total FAs (-0.29 (0.06), p = 2.46 x 10-07) and several free FAs including omega-3, omega-6, monounsaturated FAs, polyunsaturated FAs and linoleic acid were also lower in the combination group. TG content in almost all lipoprotein sub-particles was lower, as well as total TG (-0.35 (0.05), $p = 9.8 \times 10^{-11}$). Despite not being significantly different in either the genetically lower TG or LDL-C group only versus the reference group, the inflammation marker glycoprotein acetyls was significantly lower in the combination group (glycoprotein acetyls: -0.31 (0.06), $p = 1.9 \times 10^{-07}$).

Two by two factorial analyses of genetically influenced lower TG and genetically influenced lower LDL-C in the OBB cohort.

In OBB, the group with genetically influenced lower TG levels only, did not exhibit any differences in NMR-based total TG or lipoprotein sub-particle TG levels, contrasting the findings in NEO. However, genetically influenced lower TG levels were associated with higher levels of ApoA1 and HDL sub-particles (Supplementary figure 1A), similar to the findings in NEO. In the OBB, the group with genetically influenced lower LDL-C levels had lower levels of ApoB and lower numbers of medium and large sized LDL particles (strongest association on MLDLP: beta (SE)= -0.20 (0.03), $p = 1.8 \times 10^{-10}$). These observations were consistent with the findings in NEO (Supplementary figure 1B). Also similar to NEO, the group of combined genetically influenced lower TG and LDL-C levels had the largest number of significant differences with the largest effect sizes compared with the reference group (both genetic exposures: n=106 vs. genetically influenced lower LDL-C only: n=65 vs. genetically influenced lower TG

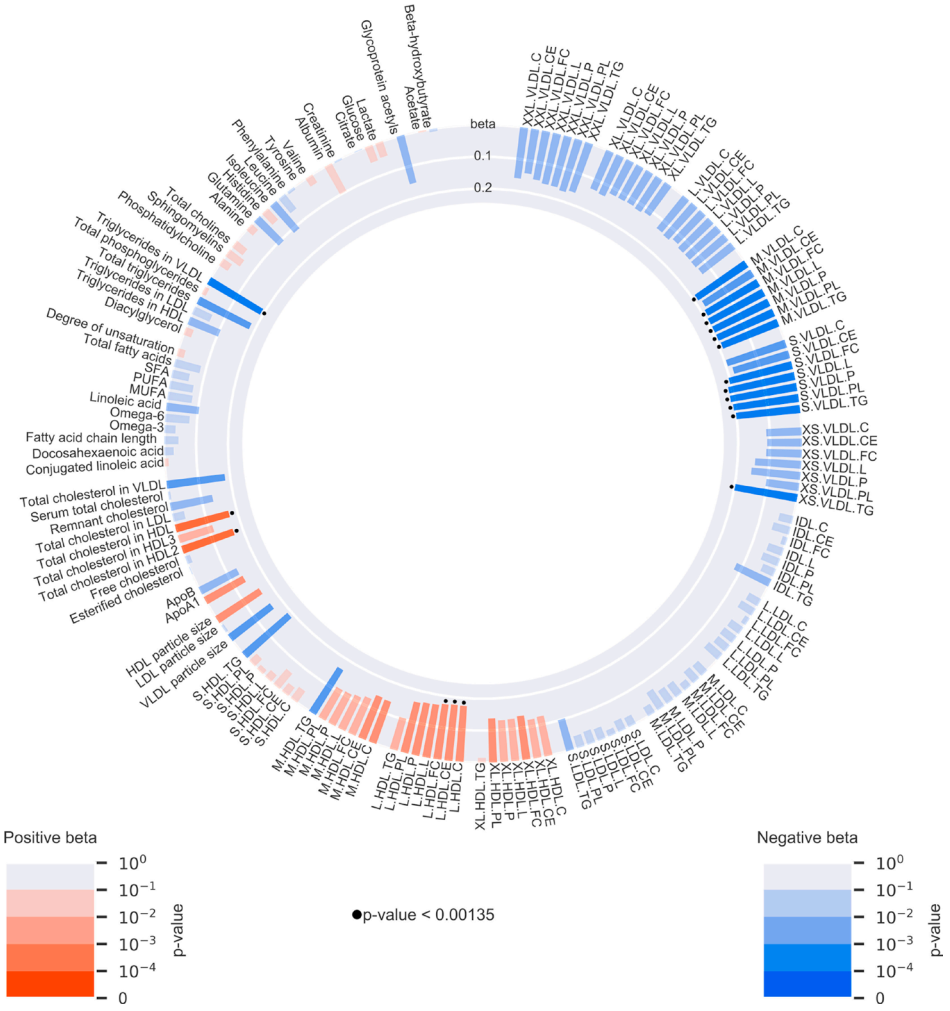

Figure 1: Associations of the group with genetically influenced lower TG levels with 145 NMR-based metabolomic measures in two x two factorial analyses. Group with genetically influenced lower TG levels compared with the reference group in the NEO cohort. Bar heights represent the magnitude of the beta coefficient from linear regression, which is expressed in standard deviation (SD) units. Red bars indicate positive betas and blue bars indicate negative betas. The transparency of the bars indicates the level of statistical significance. A p <1.35 x 10^{-3} is regarded statistical significant, as represented by the black dots.

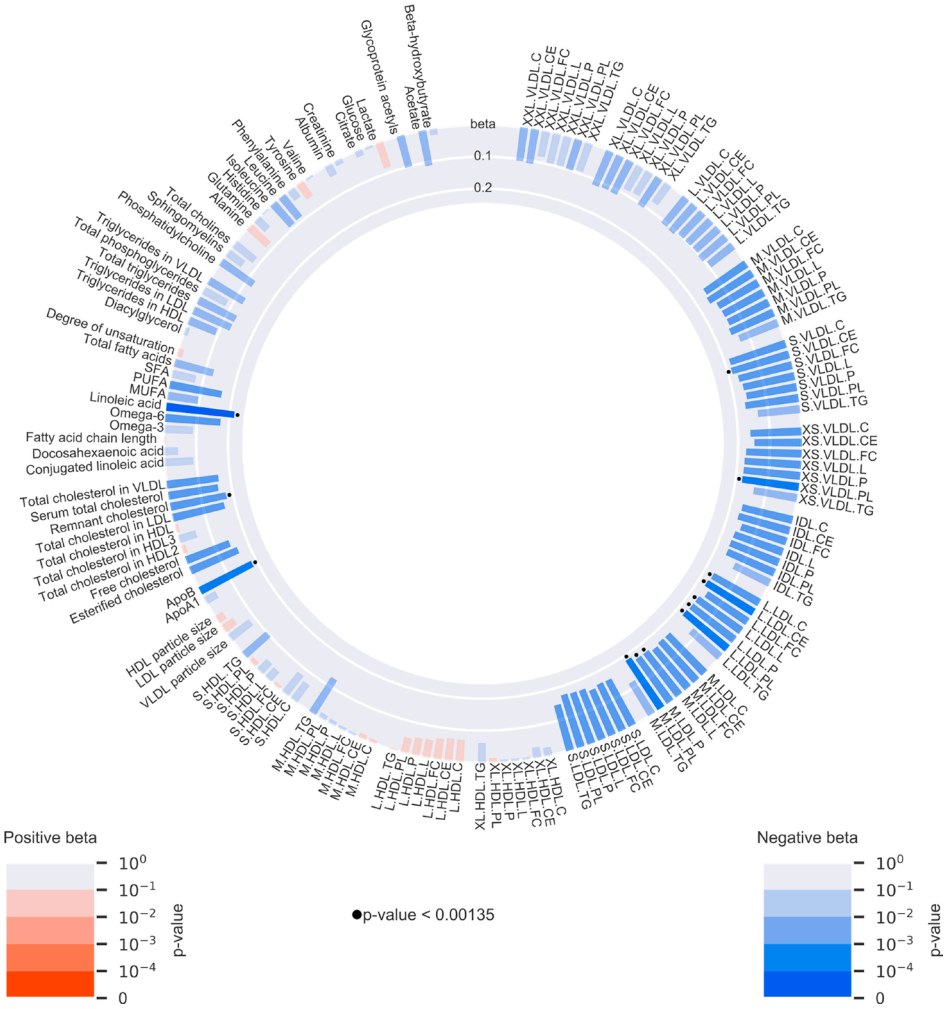

Figure 2: Associations of the group with genetically influenced lower LDL-C levels with 145 NMR-based metabolomic measures in two x two factorial analyses. Group with genetically influenced lower LDL-C levels compared with the reference group in the NEO cohort. Bar heights represent the magnitude of the beta coefficient from linear regression, which is expressed in standard deviation (SD) units. Red bars indicate positive betas and blue bars indicate negative betas. The transparency of the bars indicates the level of statistical significance. A p <1.35 x 10^{-3} is regarded statistical significant, as represented by the black dots.

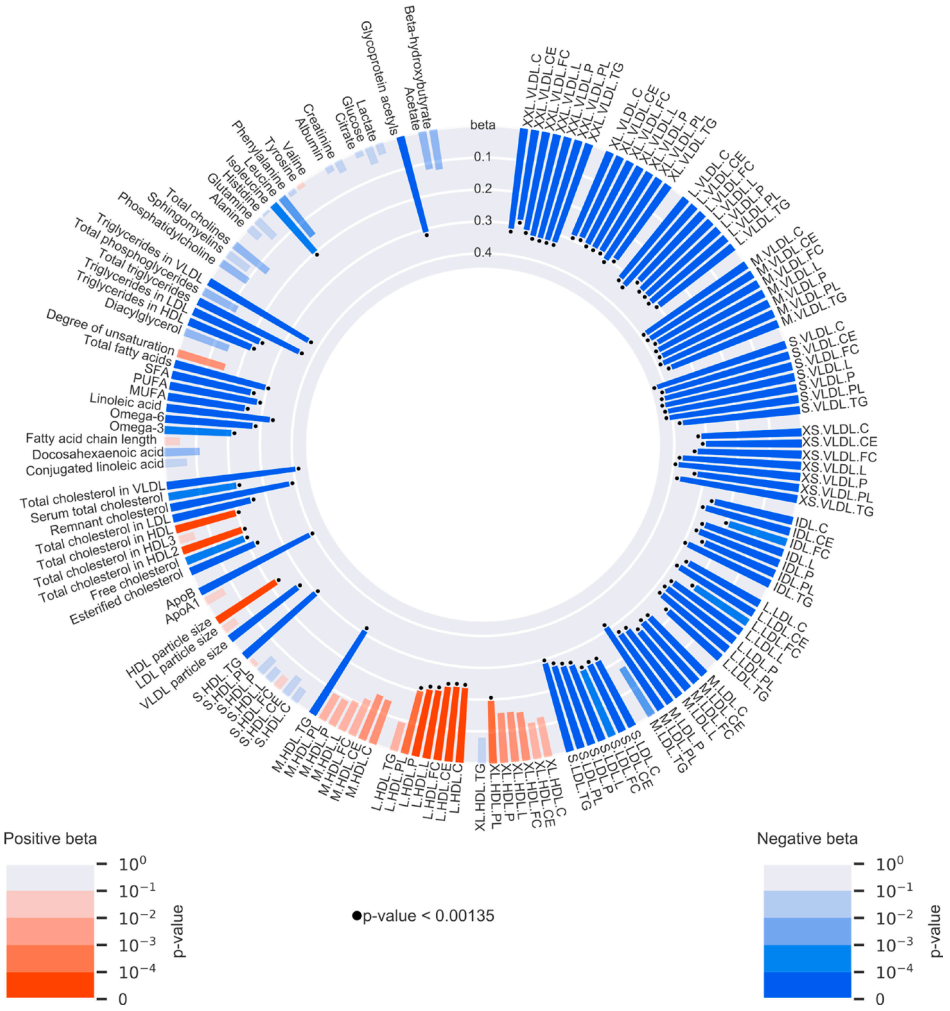

Figure 3: Associations of the group with combined genetically influenced lower TG and LDL-C levels with 145 NMR-based metabolomic measures in two x two factorial analyses. Group with combined genetically influenced lower TG and LDL-C levels compared with the reference group in the NEO cohort. Bar heights represent the magnitude of the beta coefficient from linear regression, which is expressed in standard deviation (SD) units. Red bars indicate positive betas and blue bars indicate negative betas. The transparency of the bars indicates the level of statistical significance. A p <1.35 x 10^{-3} is regarded statistical significant, as represented by the black dots.

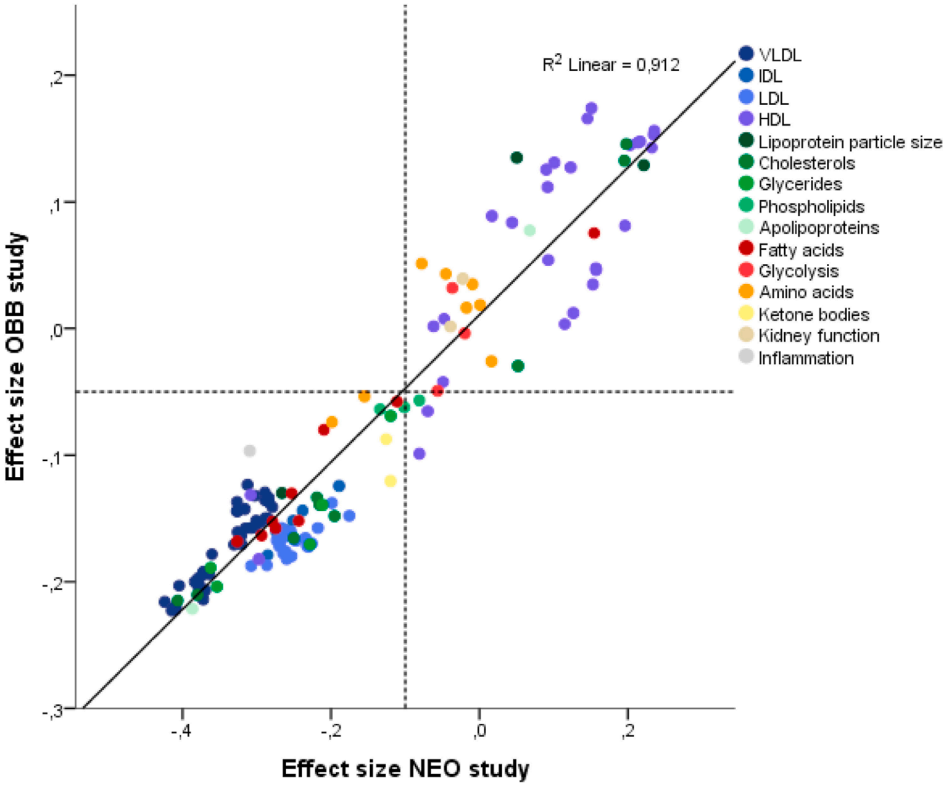

Figure 4: Correlation between beta coefficients of the discovery and replication cohorts. The effect sizes (i.e. beta coefficients) for the associations between genetically influenced lower TG and LDL-C levels and 145 NMR-based metabolomic measures in the Netherlands Epidemiology of Obesity (NEO) study are partially replicated in Oxford Biobank (OBB) cohort, as shown by the high correlation between the beta coefficients from both cohorts.

only: n=16) (Supplementary figure 1C). With the exception of glycoprotein acetyls, there was large consistency in the findings between NEO and OBB (Figure 4). Also, consistent with findings in NEO, formal interaction analysis of genetically lower TG and genetically lower LDL-C showed that there was no interaction between these genetic scores (*p* for interaction >0.00135) for any of the metabolomic measures.

DISCUSSION

In this study, we assessed the effects of genetically-influenced lower TG levels via five *LPL* alleles and genetically-influenced lower LDL-C levels via 19 LDL-C lowering genes separately and in combination, on NMR-based metabolomic measures, including detailed measures of lipoprotein levels and composition. Our results

showed that in the NEO study, genetically influenced lower TG levels are mainly associated with lower levels of small and medium sized VLDL particles. Although these effects were most apparent in the NEO study, direction and pattern of the effects were mostly overlapping in the OBB. The genetically influenced lower LDL-C levels were associated with lower levels of ApoB and lower levels of medium and large sized LDL particles in both NEO and OBB, and the effect sizes of these changes were similar between the two cohorts. In the group with both genetically influenced lower TG and genetically influenced lower LDL-C levels, the most interesting observations were that concomitant with a lower level of ApoB, the vast majority of the number and sub-particles of LDL, IDL and VLDL lipoproteins were lower. The effect sizes, direction and pattern of these changes were highly overlapping between NEO and OBB studies. Importantly, the effect sizes of the associations observed in the combination group were independent and additive, indicating that pharmacological TG lowering therapy on top of LDL-C lowering therapy will have additional beneficial effects on the lipoprotein profile.

Our results show that the combined genetic effects of lower TG and lower LDL-C levels on the metabolomic profile are independent and additive. These findings further support the previously reported independent and additive effects of genetically influenced lower TG and LDL-C levels on CVD risk (15,32). The study from Lotta et al (15), that also used a two by two factorial design, showed that people in the combined group with genetically influenced lower TG levels and lower LDL-C levels had the largest reduction in CVD, compared to the reference group. This was 7% more than expected based on the separate associations of the two genetic exposures individually *(p* for interaction = 0.02). However, Lotta et al. further reported that interaction analyses using a continuous score of *LPL* and stratifying above or below the median or by quintiles of distribution of LDL-C-lowering alleles were not consistent with an interaction between the two genetic scores. These results indicated that the effects of TG lowering via *LPL* and LDL-C lowering on CVD are independent. This finding is in line with the absence of an interaction between genetically influenced lower TG and LDL-C as observed in our study.

A recent study from Ference et al. (32), that used similar *LPL* variants to the ones we used for the TG genetic score and *LDLR* variants for the LDL-C genetic score, also showed that these scores were associated with lower CVD risk. They further concluded that the individual associations of the *LPL* and LDL-C genetic scores with CVD appeared to be independent, additive, and proportional to the absolute change in ApoB. In our study, the effect size of the combination of genetic exposures on ApoB was close to the sum of the effect sizes on ApoB for each of the *LPL* and LDL-C

genetic scores separately (beta combined (SE): -0.39(0.06); *LPL*: -0.13 (0.06); LDL-C: -0.18(0.06), respectively), which is thus in concordance with the paper of Ference et al. The independent and additive effects of genetically influenced lower TG levels via *LPL* and lower LDL-C levels on the lipoprotein profile is further evidence for an expected additional effect of pharmacologically enhanced LPL activity on top of LDL-C lowering therapy on reduction of CVD risk.

The effects of genetically influenced lower TG levels on the lipoprotein profile are fully in line with the current understanding of the role of LPL in lipid metabolism, and they confirm the previously reported associations of increased LPL activity with decreased TG and VLDL-C and increased HDL-C (33). Apart from changes in TRLs, we also observed that genetically influenced lower TG levels associated with increased HDL-C levels. This is in line with the previously reported inverse association between TG levels and HDL-C levels and particle size (34,35), and most likely explained by increased HDL formation from TRL surface remnants generated during LPL-mediated TG hydrolysis. Furthermore, our study showed that total FAs and several specific free FAs were significantly lower in the combination group both in the NEO and OBB cohort. High levels of circulating FFAs have been associated with increased oxidative stress and inflammation, which, in turn, lead to formation of atherosclerotic plaques (36,37). Therefore, the lower levels of FFAs observed in the group with both genetically influenced lower TG levels and lower LDL-C levels may play an additional role in reducing CVD risk beyond lowering of atherogenic lipoproteins.

When interpreting the results of our study, several assumptions and limitations of the Mendelian randomization approach should be taken into consideration. First, when translating genetic findings into pharmacological strategies, it should be realized that the consequences of lifelong exposure to genetically influenced lower TG and LDL-C determined by Mendelian randomization may differ from the relatively short-term pharmacological (combined) effects of TG and LDL-C lowering agents. Second, Mendelian randomization assumes that genetic variants are associated with the end point of interest only via the pathway of the exposure of interest and thus pleiotropic effects could invalidate the results. For this study, we attempted to minimize possible pleiotropic effects of the LDL-C genetic score by including variants associated with LDL-C only, hence without associations to the other lipid traits. The results of the group with genetically influenced lower LDL-C levels (Figure 1B), which were predominantly lower levels of LDL sub-particles and ApoB, confirm that the effects are most likely exerted via lowering LDL-C only. Furthermore, the *LPL* genetic score comprised variants that were in or within 10 kb of the *LPL* gene itself.

Two of the *LPL* variants were intronic variants (rs326 and rs301) that were significant eQTLs in adipose tissue, one intronic (rs10096633) located in a regulatory region and two coding variants (rs268 and rs328) associated with LPL function (38,39). This makes it likely that the effects of genetically influenced lower TG resulted through LPL. Another limitation of our study is that our data are pertinent only to European populations, given that both the NEO and the OBB are European cohorts.

In conclusion, our study showed that exposure to both genetically influenced lower TG levels via enhanced LPL-mediated lipolysis and genetically influenced lower LDL-C levels have an independent and additive effect on the lipoprotein profile, providing insight on how these genetic exposures might reduce CVD risk. Altogether, these findings provide further evidence for an additional clinical benefit of pharmacologically enhancing LPL activity on top of LDL-C lowering to further improve cardiovascular outcomes of patients at risk.

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Supplementary Table 1 List of five triglyceride-lowering *LPL* variants and LDL-C lowering variants via 19 genetic genetic regions investigated in this study

Genetic score	SNP	Gene	EA[a]/NEA	EAF	Phenotype	Effect size (SD units)	SE	Reference[b]
Lower TG via *LPL*	rs10096633	*LPL*	T/C	0.13	INT-triglycerides	-0.1471	0.0050	24097068
	rs301	*LPL*	C/T	0.24	INT-triglycerides	-0.1089	0.0039	24097068
	rs326	*LPL*	G/A	0.31	INT-triglycerides	- 0.0869	0.0050	24097068
	rs328	*LPL*	G/C	0.10	INT-triglycerides	-0.1670	0.0058	24097068
	rs268	*LPL*	A/G	0.98	INT-triglycerides	-0.1971	0.0364	30326043[c]
Lower LDL-C via 19 genetic regions								
	rs11136341	*PLEC1*	A/G	0.40	INT-LDL-C	-0.045	0.0066	24097068
	rs11563251	*UGT1A1*	C/T	0.12	INT-LDL-C	-0.034	0.0062	24097068
	rs12027135	*LDLRAP1*	A/T	0.46	INT-LDL-C	-0.03	0.0039	24097068
	rs12916	*HMGCR*	T/C	0.40	INT-LDL-C	-0.073	0.0039	24097068
	rs2030746	*LOC84931*	C/T	0.40	INT-LDL-C	-0.021	0.0037	24097068
	rs2072183	*NPC1L1*	G/C	0.29	INT-LDL-C	-0.039	0.0048	24097068
	rs2328223	*SNX5*	A/C	0.21	INT-LDL-C	-0.03	0.0052	24097068
	rs2642442	*MOSC1*	C/T	0.33	INT-LDL-C	-0.036	0.0055	24097068
	rs2710642	*EHBP1*	G/A	0.35	INT-LDL-C	-0.024	0.0041	24097068
	rs2902940	*MAFB*	G/A	0.30	INT-LDL-C	-0.027	0.0040	24097068
	rs2954029	*TRIB1*	T/A	0.47	INT-LDL-C	-0.056	0.0037	24097068
	rs4299376	*ABCG5*	T/G	0.31	INT-LDL-C	-0.081	0.0045	24097068
	rs4942486	*BRCA2*	C/T	0.48	INT-LDL-C	-0.024	0.0036	24097068
	rs514230	*IRF2BP2*	A/T	0.48	INT-LDL-C	-0.036	0.0053	24097068
	rs6029526	*TOP1*	T/A	0.47	INT-LDL-C	-0.044	0.0051	24097068
	rs7206971	*OSBPL7*	G/A	0.49	INT-LDL-C	-0.029	0.0057	24097068

Supplementary Table 1 List of five triglyceride-lowering *LPL* variants and LDL-C lowering variants via 19 genetic genetic regions investigated in this study (continued)

Genetic score	SNP	Gene	EA[a]/NEA	EAF	Phenotype	Effect size (SD units)	SE	Reference[b]
	rs9488822	*FRK*	A/T	0.36	INT-LDL-C	-0.031	0.0060	24097068
	rs964184	*APOA1*	C/G	0.84	INT-LDL-C	-0.086	0.0081	24097068
	rs9987289	*PPP1R3B*	A/G	0.10	INT-LDL-C	-0.071	0.0071	24097068

Abbreviations: EA, effect allele; NEA, non-effect allele; EAF, effect allele frequency; SNP, single nucleotide polymorphism; SE, standard error; *LPL, lipoprotein lipase;* LDL-C, low-density lipoprotein cholesterol; *PLEC1, Plectin; UGT1A, UDP Glucuronosyltransferase Family 1 Member A; LDLRAP, Low Density Lipoprotein Receptor Adaptor Protein 1 HMGCR, 3-Hydroxy-3-Methylglutaryl-CoA Reductase; NPC1L1, Niemann-Pick C1-Like 1; PCSK9, Proprotein convertase subtilisin/kexin type 9; SNX5, Sorting Nexin 5; MOSC1, Molybdenum Cofactor Sulfurase C-terminal Domain-Containing; EHBP1, EH Domain Binding Protein 1; MAFB, MAF BZIP Transcription Factor B; TRIB1, Tribbles Pseudokinase 1; ABCG5, ATP Binding Cassette Subfamily G Member 5; BRCA2, Breast Cancer Type 2 Susceptibility Protein; IRF2BP2, Interferon Regulatory Factor 2 Binding Protein 2; TOP1, DNA Topoisomerase I; OSBPL7, Oxysterol Binding Protein Like 7; FRK, Fyn Related Src Family Tyrosine Kinase; APOA1, Apolipoprotein A1; PPP1R3B, Protein Phosphatase 1 Regulatory Subunit 3B.*

a The effect allele is the triglyceride-lowering allele or the lipid-lowering allele.

b PubMed ID of the original manuscript from which beta coefficients and standard errors are derived.

c Estimated in EPIC-Norfolk.

Supplementary Table 2 Linkage disequilibrium between the five *LPL* genetic variants included in the analysis.

SNP	rs268	rs301	rs326	rs328	rs10096633
rs268	1	0.002	0.0008	0.002	0.003
rs301	0.002	1	0.243	0.171	0.098
rs326	0.0008	0.243	1	0.308	0.418
rs328	0.002	0.171	0.308	1	0.736
rs10096633	0.003	0.098	0.418	0.736	1

LDpair tool was used to derive the R^2 measures above using five European ancestry populations from the 1000 Genomes project.

Supplementary Table 3: Characteristics of the discovery study population (NEO) stratified by genotype

Characteristics	Reference	Genetically-influenced lower TG	Genetically-influenced lower LDL-C	Genetically-influenced lower TG and LDL-C
Number of participants	1,264	1,086	1,360	1,128
Age (years)	55.4 (6.1)	55.7 (6.0)	55.2 (5.9)	55.6 (6.0)
Men (%)	40.1%	41.8 %	43.4 %	42.4 %
BMI (kg/m^2)	25.9 (4.3)	26.0 (4.4)	26.1 (4.2)	26.0 (4.3)
Fasting serum concentrations (mmol/L) TG (median (IQR)) Total cholesterol LDL-cholesterol HDL-cholesterol	1.02 (0.75 ; 1.56) 5.95 (1.06) 3.81(0.97) 1.64 (0.47)	0.97 (0.69 ; 1.42) 5.91 (1.07) 3.74 (0.99) 1.61 (0.48)	1.02 (0.72 ; 1.46) 5.69 (0.93) 3.58 (0.86) 1.56 (0.45)	0.93 (0.69 ; 1.30) 5.63 (0.96) 3.50 (0.90) 1.65 (0.50)
GRS LDL (median (IQR))	0.80 (0.73 ; 0.84)	0.80 (0.73 ; 0.84)	0.97 (0.93 ; 1.03)	0.97 (0.92 ; 1.03)
GRS *LPL* (median (IQR))	0.39 (0.39 ; 0.39)	0.79 (0.59 ; 0.90)	0.39 (0.39 ; 0.39)	0.79 (0.59 ; 0.90)

Values are mean (SD), unless otherwise specified. GRS unit is in SD. N = 4,838. Results are based on analyses weighted towards the reference BMI distribution of the general Dutch population. Abbreviations: BMI, body mass index; TG, triglycerides; HDL high-density lipoprotein, LDL low-density lipoprotein,
IQR interquartile range, GRS genetic risk score.

Supplementary Table 4: Characteristics of the Oxford Biobank (OBB) study population stratified by genotype

Characteristics	Reference	Genetically-influenced lower TG	Genetically-influenced lower LDL-C	Genetically-influenced lower TG and LDL-C
Number of participants	1,935	1,557	1,896	1,611
Age (years)	41.5 (5.9)	41.5 (5.9)	41.8 (5.9)	41.4 (5.9)
Men (%)	44.8 %	42.1%	43.8 %	43.5 %
BMI (kg/m^2)	25.9 (4.6)	25.7 (4.5)	25.7 (4.5)	25.8 (4.6)
Fasting serum concentrations (mmol/L) TG (median (IQR)) Total cholesterol LDL-cholesterol HDL-cholesterol	0.97 (0.72 ; 1.41) 5.26 (0.99) 3.38 (0.88) 1.36 (0.38)	0.93 (0.70 ; 1.31) 5.24 (0.97) 3.33 (0.87) 1.41 (0.38)	0.95 (0.68 ; 1.35) 5.09 (0.95) 3.21 (0.83) 1.36 (0.38)	0.87 (0.67 ; 1.28) 5.11 (0.97) 3.21 (0.85) 1.41 (0.37)
GRS LDL (median (IQR)) GRS *LPL* (median (IQR))	0.82 (0.75 ; 0.86) 0.39 (0.39 ; 0.39)	0.82 (0.76 ; 0.86) 0.63 (0.59 ; 0.90)	0.99 (0.94 ; 1.05) 0.39 (0.39 ; 0.39)	0.98 (0.94 ; 1.04) 0.68 (0.59 ; 0.90)

Values are mean (SD), unless otherwise specified. GRS unit is in SD. N = 6,999. Abbreviations: BMI, body mass index; TG, triglycerides; HDL high-density lipoprotein, LDL low-density lipoprotein, IQR interquartile range, GRS genetic risk score.

Supplementary table 5 The associations between genetically-influenced lower triglyceride levels and genetically-influenced LDL-C levels, separately and in combination and 145 NMR-based metabolomic measures in the Netherlands Epidemiology of Obesity (NEO) study (n = 4,838)

	Lower TG via *LPL*			Lower LDL-C			Lower TG via *LPL* & lower LDL-C		
Metabolic measure	**BETA***	**SE**	***P* VALUE**	**BETA**	**SE**	***P* VALUE**	**BETA***	**SE**	***P* VALUE**
Very-low-density lipoproteins (VLDL)									
XXL.VLDL.C	-0.161	0.065	1.41E-02	-0.106	0.060	7.58E-02	-0.316	0.062	3.25E-07
XXL.VLDL.CE	-0.141	0.064	2.70E-02	-0.109	0.059	6.41E-02	-0.285	0.060	2.28E-06
XXL.VLDL.FC	-0.156	0.066	1.77E-02	-0.082	0.060	1.70E-01	-0.313	0.062	4.29E-07
XXL.VLDL.L	-0.163	0.066	1.40E-02	-0.096	0.060	1.06E-01	-0.326	0.062	1.55E-07
XXL.VLDL.P	-0.163	0.066	1.39E-02	-0.096	0.059	1.05E-01	-0.327	0.062	1.44E-07
XXL.VLDL.PL	-0.170	0.067	1.15E-02	-0.099	0.059	9.62E-02	-0.327	0.062	1.16E-07
XXL.VLDL.TG	-0.162	0.066	1.44E-02	-0.094	0.059	1.41E-01	-0.326	0.062	1.44E-07
XL.VLDL.C	-0.131	0.064	4.01E-02	-0.117	0.060	5.00E-02	-0.284	0.058	1.26E-06
XL.VLDL.CE	-0.136	0.063	3.20E-02	-0.114	0.059	5.64E-02	-0.279	0.058	1.52E-06
XL.VLDL.FC	-0.120	0.065	6.30E-02	-0.115	0.060	5.75E-02	-0.289	0.060	1.40E-06
XL.VLDL.L	-0.120	0.066	6.93E-02	-0.086	0.062	1.67E-01	-0.289	0.062	2.95E-06
XL.VLDL.P	-0.118	0.066	7.39E-02	-0.082	0.062	1.85E-01	-0.287	0.062	3.49E-06
XL.VLDL.PL	-0.122	0.066	6.47E-02	-0.106	0.062	8.73E-02	-0.303	0.062	9.45E-07
XL.VLDL.TG	-0.115	0.066	8.11E-02	-0.074	0.062	2.36E-01	-0.284	0.062	4.67E-06
L.VLDL.C	-0.132	0.057	2.04E-02	-0.109	0.055	4.57E-02	-0.321	0.056	1.20E-08
L.VLDL.CE	-0.135	0.056	1.61E-02	-0.112	0.054	3.91E-02	-0.331	0.056	4.31E-09
L.VLDL.FC	-0.125	0.058	3.22E-02	-0.102	0.056	6.89E-02	-0.288	0.056	2.43E-07
L.VLDL.L	-0.133	0.059	2.36E-02	-0.102	0.056	7.10E-02	-0.304	0.057	8.01E-08
L.VLDL.P	-0.133	0.059	2.45E-02	-0.100	0.056	7.63E-02	-0.303	0.057	9.43E-08
L.VLDL.PL	-0.134	0.059	2.41E-02	-0.105	0.056	6.19E-02	-0.308	0.057	6.18E-08
L.VLDL.TG	-0.130	0.059	2.79E-02	-0.095	0.057	9.44E-02	-0.295	0.057	2.08E-07

Supplementary table 5 The associations between genetically-influenced lower triglyceride levels and genetically-influenced LDL-C levels, separately and in combination and 145 NMR-based metabolomic measures in the Netherlands Epidemiology of Obesity (NEO) study (n = 4,838) (continued)

	Lower TG via *LPL*			Lower LDL-C			Lower TG via *LPL* & lower LDL-C		
Metabolic measure	**BETA***	**SE**	***P* VALUE**	**BETA**	**SE**	***P* VALUE**	**BETA***	**SE**	***P* VALUE**
M.VLDL.C	-0.189	0.057	9.32E-04	-0.157	0.054	3.73E-03	-0.380	0.054	3.55E-12
M.VLDL.CE	-0.181	0.057	1.56E-03	-0.163	0.054	2.50E-03	-0.378	0.055	5.34E-12
M.VLDL.FC	-0.189	0.057	9.11E-04	-0.146	0.054	7.54E-03	-0.364	0.054	2.22E-11
M.VLDL.L	-0.194	0.057	7.10E-04	-0.143	0.054	8.29E-03	-0.374	0.055	1.11E-11
M.VLDL.P	-0.194	0.057	7.06E-04	-0.142	0.054	8.97E-03	-0.372	0.055	1.36E-11
M.VLDL.PL	-0.193	0.057	7.56E-04	-0.149	0.054	6.27E-03	-0.379	0.055	6.85E-12
M.VLDL.TG	-0.190	0.057	8.42E-04	-0.131	0.054	1.61E-02	-0.361	0.055	5.75E-11
S.VLDL.C	-0.195	0.061	1.55E-03	-0.184	0.058	1.38E-03	-0.424	0.061	4.41E-12
S.VLDL.CE	-0.182	0.062	3.12E-03	-0.188	0.058	1.33E-03	-0.405	0.062	6.95E-11
S.VLDL.FC	-0.203	0.060	7.91E-04	-0.173	0.057	2.24E-03	-0.412	0.058	1.90E-12
S.VLDL.L	-0.212	0.060	4.17E-04	-0.165	0.056	3.36E-03	-0.415	0.058	1.25E-12
S.VLDL.P	-0.212	0.060	3.88E-04	-0.161	0.056	4.22E-03	-0.410	0.058	1.72E-12
S.VLDL.PL	-0.206	0.061	7.88E-04	-0.169	0.057	3.15E-03	-0.409	0.059	4.27E-12
S.VLDL.TG	-0.201	0.058	5.11E-04	-0.133	0.055	1.60E-02	-0.370	0.056	4.64E-11
XS.VLDL.C	-0.111	0.059	6.11E-02	-0.161	0.057	4.46E-03	-0.315	0.061	2.26E-07
XS.VLDL.CE	-0.108	0.060	6.89E-02	-0.149	0.057	8.87E-03	-0.301	0.061	7.84E-07
XS.VLDL.FC	-0.112	0.059	5.80E-02	-0.175	0.056	1.66E-03	-0.326	0.060	6.24E-08
XS.VLDL.L	-0.145	0.060	1.56E-02	-0.178	0.057	1.68E-03	-0.372	0.060	6.92E-10
XS.VLDL.P	-0.154	0.060	1.06E-02	-0.179	0.057	1.69E-03	-0.384	0.060	1.77E-10
XS.VLDL.PL	-0.104	0.058	7.00E-02	-0.180	0.054	9.20E-04	-0.321	0.058	3.25E-08
XS.VLDL.TG	-0.199	0.060	9.14E-04	-0.139	0.057	1.52E-02	-0.373	0.058	1.21E-10
Intermediate-density lipoproteins (IDL)									3.4E-04

Supplementary table 5 The associations between genetically-influenced lower triglyceride levels and genetically-influenced LDL-C levels, separately and in combination and 145 NMR-based metabolomic measures in the Netherlands Epidemiology of Obesity (NEO) study (n = 4,838) (continued)

	Lower TG via *LPL*			Lower LDL-C			Lower TG via *LPL* & lower LDL-C		
Metabolic measure	**BETA***	**SE**	***P* VALUE**	**BETA**	**SE**	***P* VALUE**	**BETA***	**SE**	***P* VALUE**
IDL.C	-0.044	0.056	4.33E-01	-0.163	0.053	2.07E-03	-0.251	0.058	1.38E-05
IDL.CE	-0.056	0.057	3.28E-01	-0.168	0.054	1.85E-03	-0.274	0.059	3.17E-06
IDL.FC	-0.016	0.054	7.61E-01	-0.150	0.051	3.26E-03	-0.189	0.055	5.55E-04
IDL.L	-0.051	0.056	3.60E-01	-0.163	0.053	1.98E-03	-0.259	0.057	5.52E-06
IDL.P	-0.057	0.056	3.10E-01	-0.164	0.053	1.88E-03	-0.269	0.057	2.56E-06
IDL.PL	-0.043	0.055	4.28E-01	-0.163	0.052	1.70E-03	-0.238	0.056	2.02E-05
IDL.TG	-0.120	0.058	3.97E-02	-0.125	0.057	2.80E-02	-0.285	0.057	6.20E-07
Low-density lipoproteins (LDL)									
L.LDL.C	-0.043	0.056	4.44E-01	-0.170	0.052	1.21E-03	-0.255	0.057	9.07E-06
L.LDL.CE	-0.052	0.057	3.60E-01	-0.174	0.053	9.93E-04	-0.273	0.058	2.61E-06
L.LDL.FC	-0.017	0.054	7.56E-01	-0.156	0.051	2.20E-03	-0.199	0.055	2.94E-04
L.LDL.L	-0.045	0.056	4.18E-01	-0.170	0.052	1.15E-03	-0.261	0.057	4.94E-06
L.LDL.P	-0.049	0.056	3.86E-01	-0.172	0.053	1.10E-03	-0.267	0.057	3.03E-06
L.LDL.PL	-0.047	0.056	4.01E-01	-0.175	0.052	8.08E-04	-0.267	0.057	2.80E-06
L.LDL.TG	-0.057	0.056	3.05E-01	-0.122	0.054	2.44E-02	-0.218	0.055	7.75E-05
M.LDL.C	-0.042	0.057	4.63E-01	-0.167	0.053	1.65E-03	-0.247	0.057	1.83E-05
M.LDL.CE	-0.046	0.057	4.20E-01	-0.168	0.053	1.56E-03	-0.250	0.058	1.47E-05
M.LDL.FC	-0.026	0.057	6.46E-01	-0.162	0.053	2.21E-03	-0.235	0.057	4.52E-05
M.LDL.L	-0.047	0.057	4.12E-01	-0.171	0.053	1.34E-03	-0.261	0.057	5.58E-06
M.LDL.P	-0.049	0.057	3.91E-01	-0.171	0.053	1.30E-03	-0.264	0.057	4.21E-06
M.LDL.PL	-0.065	0.059	2.65E-01	-0.185	0.054	6.37E-04	-0.308	0.058	1.15E-07
M.LDL.TG	-0.031	0.055	5.70E-01	-0.119	0.054	2.71E-02	-0.176	0.055	1.37E-03

Supplementary table 5 The associations between genetically-influenced lower triglyceride levels and genetically-influenced LDL-C levels, separately and in combination and 145 NMR-based metabolomic measures in the Netherlands Epidemiology of Obesity (NEO) study (n = 4,838) (continued)

	Lower TG via *LPL*			Lower LDL-C			Lower TG via *LPL* & lower LDL-C		
Metabolic measure	**BETA***	**SE**	***P* VALUE**	**BETA**	**SE**	***P* VALUE**	**BETA***	**SE**	***P* VALUE**
S.LDL.C	-0.032	0.057	5.76E-01	-0.162	0.053	2.22E-03	-0.231	0.057	5.63E-05
S.LDL.CE	-0.037	0.057	5.20E-01	-0.163	0.053	1.95E-03	-0.232	0.057	4.73E-05
S.LDL.FC	-0.021	0.057	7.18E-01	-0.156	0.054	3.66E-03	-0.226	0.058	1.10E-04
S.LDL.L	-0.039	0.058	4.96E-01	-0.168	0.053	1.63E-03	-0.253	0.058	1.17E-05
S.LDL.P	-0.043	0.058	4.59E-01	-0.170	0.053	1.48E-03	-0.260	0.058	6.94E-06
S.LDL.PL	-0.039	0.058	5.01E-01	-0.173	0.054	1.36E-03	-0.270	0.058	3.32E-06
S.LDL.TG	-0.101	0.057	7.75E-02	-0.149	0.055	6.91E-03	-0.287	0.055	1.99E-07
High-density lipoproteins (HDL)									3.7E-04
XL.HDL.C	0.127	0.054	1.88E-02	-0.027	0.052	6.06E-01	0.126	0.054	1.98E-02
XL.HDL.CE	0.123	0.054	2.40E-02	-0.034	0.052	5.15E-01	0.115	0.055	1.58E-02
XL.HDL.FC	0.138	0.053	9.45E-03	-0.007	0.051	8.93E-01	0.153	0.054	4.57E-03
XL.HDL.L	0.132	0.052	1.09E-02	-0.008	0.050	8.80E-01	0.157	0.053	2.91E-03
XL.HDL.P	0.131	0.052	1.14E-02	-0.007	0.050	8.81E-01	0.157	0.053	2.93E-03
XL.HDL.PL	0.138	0.052	7.74E-03	-0.014	0.050	7.84E-01	0.196	0.052	1.88E-04
XL.HDL.TG	0.015	0.059	8.01E-01	-0.061	0.054	2.55E-01	-0.081	0.056	1.49E-01
L.HDL.C	0.176	0.054	1.13E-03	0.069	0.051	1.82E-01	0.235	0.054	1.63E-05
L.HDL.CE	0.176	0.054	1.08E-03	0.070	0.052	1.74E-01	0.236	0.054	1.54E-05
L.HDL.FC	0.175	0.054	1.20E-03	0.066	0.051	2.02E-01	0.232	0.054	2.00E-05
L.HDL.L	0.169	0.053	1.39E-03	0.057	0.051	2.61E-01	0.216	0.054	5.54E-05
L.HDL.P	0.168	0.053	1.47E-03	0.055	0.051	2.76E-01	0.213	0.054	6.83E-05
L.HDL.PL	0.163	0.053	1.88E-03	0.048	0.051	3.41E-01	0.203	0.053	1.47E-04
L.HDL.TG	0.104	0.055	5.69E-02	0.005	0.051	9.18E-01	0.093	0.055	9.16E-02

Supplementary table 5 The associations between genetically-influenced lower triglyceride levels and genetically-influenced LDL-C levels, separately and in combination and 145 NMR-based metabolomic measures in the Netherlands Epidemiology of Obesity (NEO) study (n = 4,838) (continued)

	Lower TG via *LPL*			Lower LDL-C			Lower TG via *LPL* & lower LDL-C		
Metabolic measure	**BETA***	**SE**	***P* VALUE**	**BETA**	**SE**	***P* VALUE**	**BETA***	**SE**	***P* VALUE**
M.HDL.C	0.140	0.053	7.58E-03	0.011	0.050	8.27E-01	0.145	0.051	4.32E-03
M.HDL.CE	0.144	0.053	6.68E-03	0.016	0.050	7.54E-01	0.151	0.051	3.23E-03
M.HDL.FC	0.126	0.052	1.44E-02	-0.007	0.049	8.81E-01	0.123	0.050	1.44E-02
M.HDL.L	0.117	0.052	2.50E-02	-0.010	0.050	8.38E-01	0.101	0.051	4.78E-02
M.HDL.P	0.112	0.052	3.25E-02	-0.014	0.050	7.77E-01	0.090	0.051	7.76E-02
M.HDL.PL	0.110	0.052	3.34E-02	-0.017	0.050	7.30E-01	0.092	0.051	7.19E-02
M.HDL.TG	-0.165	0.061	6.71E-03	-0.128	0.057	2.43E-02	-0.309	0.058	1.05E-07
S.HDL.C	0.044	0.059	4.54E-01	-0.067	0.053	2.06E-01	-0.049	0.056	3.81E-01
S.HDL.CE	0.033	0.058	5.68E-01	-0.079	0.053	1.34E-01	-0.070	0.055	2.09E-01
S.HDL.FC	0.063	0.060	2.93E-01	0.011	0.056	8.42E-01	0.044	0.057	4.44E-01
S.HDL.L	0.027	0.063	6.64E-01	-0.040	0.057	4.89E-01	-0.048	0.061	4.32E-01
S.HDL.P	0.017	0.063	7.86E-01	-0.044	0.058	4.50E-01	-0.062	0.061	3.13E-01
S.HDL.PL	0.032	0.061	5.98E-01	0.018	0.056	7.55E-01	0.017	0.059	7.75E-01
S.HDL.TG	-0.189	0.059	1.48E-03	-0.100	0.057	8.00E-02	-0.298	0.057	2.15E-07
Lipoprotein particle size									
VLDL particle size	-0.165	0.054	2.12E-03	-0.082	0.052	1.15E-01	-0.266	0.052	3.83E-07
LDL particle size	-0.009	0.061	8.78E-01	0.043	0.053	4.12E-01	0.050	0.058	3.84E-01
HDL particle size	0.164	0.061	1.95E-03	0.027	0.051	5.90E-01	0.221	0.053	3.26E-05
Apolipoproteins									
ApoA1	0.139	0.054	5.54E-03	-0.041	0.049	3.97E-01	0.068	0.051	1.85E-01
ApoB	-0.133	0.068	2.37E-02	-0.185	0.055	8.07E-01	-0.387	0.058	3.64E-11
Cholesterols									

Supplementary table 5 The associations between genetically-influenced lower triglyceride levels and genetically-influenced LDL-C levels, separately and in combination and 145 NMR-based metabolomic measures in the Netherlands Epidemiology of Obesity (NEO) study (n = 4,838) (continued)

	Lower TG via *LPL*			Lower LDL-C			Lower TG via *LPL* & lower LDL-C		
Metabolic measure	**BETA***	**SE**	***P* VALUE**	**BETA**	**SE**	***P* VALUE**	**BETA***	**SE**	***P* VALUE**
Esterified cholesterol	-0.003	0.055	9.58E-01	-0.162	0.052	1.77E-03	-0.219	0.056	9.02E-05
Free cholesterol	-0.017	0.054	7.61E-01	-0.146	0.052	5.00E-03	-0.195	0.056	4.91E-04
Total cholesterol in HDL2	0.170	0.050	6.13E-04	0.014	0.049	7.71E-01	0.198	0.050	6.70E-05
Total cholesterol in HDL3	0.113	0.051	2.67E-02	-0.058	0.050	2.48E-01	0.052	0.051	3.09E-01
Total cholesterol in HDL	0.174	0.050	4.89E-04	0.010	0.049	8.30E-01	0.195	0.050	8.66E-05
Total cholesterol in LDL	-0.038	0.056	4.99E-01	-0.166	0.053	1.57E-03	-0.250	0.057	1.34E-05
Remnant cholesterol	-0.135	0.059	2.18E-02	-0.178	0.055	1.26E-03	-0.380	0.059	9.15E-11
Serum total cholesterol	-0.007	0.055	8.94E-01	-0.158	0.052	2.23E-03	-0.216	0.056	1.07E-04
Total cholesterol in VLDL	-0.184	0.059	1.80E-03	-0.163	0.055	3.11E-03	-0.407	0.058	2.43E-12
Fatty acids									
Conjugated linoleic acid	0.012	0.069	8.61E-01	-0.090	0.064	1.61E-01	-0.070	0.066	2.86E-01
Docosahexaenoic acid	-0.030	0.062	6.30E-01	-0.044	0.060	4.65E-01	-0.111	0.062	7.40E-02
Fatty acid chain length	-0.045	0.066	4.99E-01	0.005	0.062	9.34E-01	0.049	0.064	4.41E-01
Omega-3	-0.035	0.058	5.53E-01	-0.089	0.057	1.15E-01	-0.210	0.060	4.51E-04
Omega-6	-0.077	0.058	1.84E-01	-0.174	0.055	1.60E-03	-0.275	0.059	2.97E-06
Linoleic acid	-0.103	0.055	6.27E-02	-0.215	0.054	7.79E-05	-0.327	0.057	8.71E-09
MUFA	-0.077	0.059	1.90E-01	-0.096	0.055	7.88E-02	-0.244	0.056	1.27E-05
PUFA	-0.074	0.058	1.99E-01	-0.166	0.055	2.60E-03	-0.279	0.059	2.56E-06
SFA	-0.055	0.059	3.50E-01	-0.076	0.055	1.69E-01	-0.253	0.059	1.56E-05
Total fatty acids	-0.083	0.058	1.52E-01	-0.126	0.054	2.03E-02	-0.294	0.057	2.46E-07

Supplementary table 5 The associations between genetically-influenced lower triglyceride levels and genetically-influenced LDL-C levels, separately and in combination and 145 NMR-based metabolomic measures in the Netherlands Epidemiology of Obesity (NEO) study (n = 4,838) (continued)

	Lower TG via *LPL*			Lower LDL-C			Lower TG via *LPL* & lower LDL-C		
Metabolic measure	**BETA***	**SE**	***P* VALUE**	**BETA**	**SE**	***P* VALUE**	**BETA***	**SE**	***P* VALUE**
Degree of unsaturation	0.023	0.056	6.79E-01	0.018	0.055	7.44E-01	0.154	0.055	4.94E-03
Glycerides									
Diacylglycerol	0.026	0.074	7.29E-01	-0.013	0.069	8.48E-01	-0.147	0.070	3.49E-02
Triglycerides in HDL	-0.104	0.056	6.42E-02	-0.093	0.053	8.02E-02	-0.211	0.053	7.27E-05
Triglycerides in LDL	-0.060	0.056	2.81E-01	-0.129	0.054	1.75E-02	-0.228	0.055	3.64E-05
Total triglycerides	-0.182	0.057	1.39E-03	-0.131	0.055	1.64E-02	-0.354	0.055	9.77E-11
Total phosphoglycerides	0.014	0.060	8.12E-01	-0.083	0.053	1.19E-01	-0.120	0.058	3.93E-02
Triglycerides in VLDL	-0.192	0.057	7.97E-04	-0.128	0.054	1.89E-02	-0.362	0.055	4.79E-11
Phospholipids									
Phosphatidylcholine	0.033	0.058	5.73E-01	-0.123	0.054	2.32E-02	-0.102	0.058	8.23E-02
Sphingomyelins	0.056	0.055	3.12E-01	-0.060	0.052	2.48E-01	-0.081	0.056	1.47E-01
Total cholines	0.042	0.063	5.05E-01	-0.082	0.058	1.56E-01	-0.134	0.064	3.68E-02
Amino acids									
Alanine	0.027	0.058	6.41E-01	0.083	0.058	1.52E-01	-0.045	0.057	4.25E-01
Glutamine	-0.108	0.057	6.10E-02	-0.047	0.055	3.94E-01	-0.078	0.058	1.81E-01
Histidine	0.048	0.058	4.10E-01	-0.005	0.056	9.25E-01	0.009	0.060	8.74E-01
Isoleucine	-0.112	0.054	3.73E-02	-0.090	0.050	7.23E-02	-0.199	0.051	1.13E-04
Leucine	-0.058	0.050	2.46E-01	-0.088	0.047	6.45E-02	-0.155	0.050	2.13E-03
Phenylalanine	-0.009	0.055	8.67E-01	-0.037	0.053	4.90E-01	-0.018	0.057	7.56E-01
Tyrosine	0.001	0.052	9.85E-01	0.056	0.052	2.80E-01	0.016	0.056	7.76E-01
Valine	0.030	0.050	5.57E-01	-0.007	0.047	8.77E-01	0.001	0.052	9.85E-01
Kidney function									

Supplementary table 5 The associations between genetically-influenced lower triglyceride levels and genetically-influenced LDL-C levels, separately and in combination and 145 NMR-based metabolomic measures in the Netherlands Epidemiology of Obesity (NEO) study (n = 4,838) (continued)

	Lower TG via *LPL*			Lower LDL-C			Lower TG via *LPL* & lower LDL-C		
Metabolic measure	**BETA***	**SE**	***P* VALUE**	**BETA**	**SE**	***P* VALUE**	**BETA***	**SE**	***P* VALUE**
Albumin	0.099	0.062	1.11E-01	-0.038	0.060	5.32E-01	-0.022	0.058	6.98E-01
Creatinine	-0.006	0.048	9.07E-01	-0.017	0.044	7.00E-01	-0.039	0.048	4.11E-01
Glycolysis									
Citrate	-0.003	0.064	9.65E-01	-0.020	0.061	7.40E-01	-0.020	0.061	7.45E-01
Glucose	0.052	0.053	3.22E-01	-0.008	0.050	8.67E-01	-0.057	0.054	2.99E-01
Lactate	0.048	0.056	3.94E-01	0.084	0.056	1.38E-01	-0.037	0.057	5.25E-01
Inflammation									
Glycoprotein acetyls	-0.154	0.063	1.40E-02	-0.102	0.059	8.43E-02	-0.310	0.059	1.89E-07
Ketone bodies									
Acetate	0.004	0.061	9.42E-01	-0.112	0.057	4.98E-02	-0.120	0.060	4.66E-02
Beta-hydroxybutyrate	-0.009	0.068	8.94E-01	-0.020	0.064	7.57E-01	-0.126	0.066	5.51E-02

BETA, beta coefficient; SE, standard error. A $p < 1.35 \times 10^{-3}$ is considered statistically significant. Results are based on analyses weighted towards the BMI distribution of the general Dutch population. *The beta coefficient is rank transformed SD difference in metabolic measure for genetically-influenced lower TG levels by *LPL*, genetically-influenced lower LDL-C levels or both compared to genetically-influenced higher TG and LDL-C levels (reference).

Supplementary table 6 The associations between genetically-influenced lower triglyceride levels and genetically-influenced LDL-C levels, separately and in combination and 145 NMR-based metabolomic measures in the Oxford Biobank (OBB) cohort (n = 6,999)

	Lower TG via *LPL*			Lower LDL-C			Lower TG via *LPL* & lower LDL-C		
	BETA*	SE	*P* VALUE	BETA	SE	*P* VALUE	BETA	SE	*P* VALUE
Very-low-density lipoproteins (VLDL)									
XXL.VLDL.C	-0.031	0.031	3.14E-01	-0.087	0.029	2.81E-03	-0.143	0.030	2.69E-06
XXL.VLDL.CE	-0.033	0.031	2.81E-01	-0.098	0.029	8.20E-04	-0.150	0.030	8.71E-07
XXL.VLDL.FC	-0.024	0.031	4.41E-01	-0.061	0.029	3.58E-02	-0.123	0.030	4.78E-05
XXL.VLDL.L	-0.035	0.030	2.44E-01	-0.089	0.029	1.97E-03	-0.144	0.030	1.63E-06
XXL.VLDL.P	-0.036	0.030	2.34E-01	-0.090	0.029	1.78E-03	-0.144	0.030	1.50E-06
XXL.VLDL.PL	-0.025	0.030	4.07E-01	-0.078	0.029	7.15E-03	-0.137	0.030	5.12E-06
XXL.VLDL.TG	-0.038	0.030	2.09E-01	-0.090	0.029	1.63E-03	-0.144	0.030	1.49E-06
XL.VLDL.C	-0.036	0.030	2.29E-01	-0.077	0.028	6.55E-03	-0.137	0.029	3.19E-06
XL.VLDL.CE	-0.041	0.030	1.67E-01	-0.076	0.028	6.76E-03	-0.141	0.029	1.69E-06
XL.VLDL.FC	-0.025	0.030	3.97E-01	-0.076	0.028	7.25E-03	-0.129	0.030	1.23E-05
XL.VLDL.L	-0.034	0.030	2.55E-01	-0.071	0.028	1.20E-02	-0.135	0.030	4.52E-06
XL.VLDL.P	-0.034	0.030	2.56E-01	-0.071	0.028	1.28E-02	-0.135	0.030	4.68E-06
XL.VLDL.PL	-0.026	0.030	3.86E-01	-0.076	0.028	7.29E-03	-0.132	0.030	8.27E-06
XL.VLDL.TG	-0.034	0.030	2.52E-01	-0.068	0.028	1.58E-02	-0.134	0.030	6.25E-06
L.VLDL.C	-0.054	0.030	7.29E-02	-0.090	0.029	1.89E-03	-0.164	0.030	5.44E-08
L.VLDL.CE	-0.065	0.030	3.33E-02	-0.096	0.029	8.97E-04	-0.171	0.030	1.44E-08
L.VLDL.FC	-0.040	0.030	1.90E-01	-0.081	0.029	5.14E-03	-0.150	0.030	7.38E-07
L.VLDL.L	-0.049	0.030	1.05E-01	-0.088	0.029	2.33E-03	-0.157	0.030	1.95E-07
L.VLDL.P	-0.049	0.030	1.06E-01	-0.088	0.029	2.36E-03	-0.156	0.030	2.16E-07
L.VLDL.PL	-0.047	0.030	1.27E-01	-0.092	0.029	1.55E-03	-0.158	0.030	1.85E-07
L.VLDL.TG	-0.048	0.030	1.18E-01	-0.086	0.029	2.96E-03	-0.153	0.030	4.00E-07

Supplementary table 6 The associations between genetically-influenced lower triglyceride levels and genetically-influenced LDL-C levels, separately and in combination and 145 NMR-based metabolomic measures in the Oxford Biobank (OBB) cohort (n = 6,999) (*continued*)

	Lower TG via *LPL*			Lower LDL-C			Lower TG via *LPL* & lower LDL-C		
	BETA*	SE	*P* VALUE	BETA	SE	*P* VALUE	BETA	SE	*P* VALUE
M.VLDL.C	-0.057	0.032	7.53E-02	-0.128	0.030	2.46E-05	-0.203	0.032	1.34E-10
M.VLDL.CE	-0.050	0.032	1.23E-01	-0.137	0.031	7.10E-06	-0.202	0.032	2.54E-10
M.VLDL.FC	-0.066	0.032	3.67E-02	-0.104	0.030	5.40E-04	-0.194	0.031	6.61E-10
M.VLDL.L	-0.067	0.031	3.35E-02	-0.106	0.030	3.58E-04	-0.194	0.031	4.08E-10
M.VLDL.P	-0.067	0.031	3.22E-02	-0.103	0.030	5.21E-04	-0.192	0.031	6.26E-10
M.VLDL.PL	-0.066	0.031	3.52E-02	-0.111	0.030	1.92E-04	-0.197	0.031	2.10E-10
M.VLDL.TG	-0.069	0.031	2.69E-02	-0.086	0.030	3.88E-03	-0.17	0.031	9.30E-09
S.VLDL.C	-0.070	0.032	2.74E-02	-0.148	0.030	7.87E-07	-0.216	0.031	5.94E-12
S.VLDL.CE	-0.061	0.032	5.46E-02	-0.155	0.030	2.75E-07	-0.203	0.031	1.18E-10
S.VLDL.FC	-0.081	0.032	1.08E-02	-0.124	0.030	3.95E-05	-0.220	0.031	2.69E-12
S.VLDL.L	-0.084	0.031	7.71E-03	-0.125	0.030	2.75E-05	-0.223	0.031	8.08E-13
S.VLDL.P	-0.085	0.031	6.64E-03	-0.121	0.030	4.99E-05	-0.222	0.031	9.82E-13
S.VLDL.PL	-0.084	0.032	7.82E-03	-0.120	0.030	6.87E-05	-0.220	0.031	2.55E-12
S.VLDL.TG	-0.092	0.031	3.52E-03	-0.092	0.030	2.07E-03	-0.207	0.031	3.63E-11
XS.VLDL.C	-0.045	0.033	1.83E-01	-0.159	0.032	6.01E-07	-0.158	0.033	2.01E-06
XS.VLDL.CE	-0.041	0.034	2.21E-01	-0.158	0.032	8.18E-07	-0.152	0.033	5.13E-06
XS.VLDL.FC	-0.051	0.033	1.26E-01	-0.153	0.032	1.43E-06	-0.161	0.033	1.26E-06
XS.VLDL.L	-0.059	0.033	7.72E-02	-0.168	0.031	9.25E-08	-0.193	0.033	4.37E-09
XS.VLDL.P	-0.062	0.033	5.97E-02	-0.168	0.031	8.85E-08	-0.200	0.033	1.06E-09
XS.VLDL.PL	-0.042	0.034	2.16E-01	-0.179	0.032	2.41E-08	-0.170	0.033	3.27E-07
XS.VLDL.TG	-0.095	0.033	3.64E-03	-0.114	0.031	2.72E-04	-0.214	0.032	5.01E-11

Intermediate-density lipoproteins (IDL)

Supplementary table 6 The associations between genetically-influenced lower triglyceride levels and genetically-influenced LDL-C levels, separately and in combination and 145 NMR-based metabolomic measures in the Oxford Biobank (OBB) cohort (n = 6,999) (*continued*)

	Lower TG via *LPL*			Lower LDL-C			Lower TG via *LPL* & lower LDL-C		
	BETA*	SE	*P* VALUE	BETA	SE	*P* VALUE	BETA	SE	*P* VALUE
IDL.C	-0.025	0.034	4.66E-01	-0.193	0.032	2.13E-09	-0.152	0.034	6.05E-06
IDL.CE	-0.026	0.034	4.43E-01	-0.194	0.032	1.47E-09	-0.161	0.033	1.47E-06
IDL.FC	-0.020	0.034	5.50E-01	-0.185	0.032	1.31E-08	-0.124	0.034	2.46E-04
IDL.L	-0.031	0.034	3.52E-01	-0.194	0.032	1.79E-09	-0.159	0.034	2.05E-06
IDL.P	-0.034	0.034	3.13E-01	-0.194	0.032	1.59E-09	-0.165	0.034	9.36E-07
IDL.PL	-0.026	0.034	4.41E-01	-0.190	0.032	4.52E-09	-0.144	0.034	2.06E-05
IDL.TG	-0.069	0.034	4.27E-02	-0.135	0.033	3.57E-05	-0.179	0.034	1.42E-07
Low-density lipoproteins (LDL)									
L.LDL.C	-0.039	0.034	2.47E-01	-0.200	0.032	4.34E-10	-0.160	0.033	1.63E-06
L.LDL.CE	-0.041	0.034	2.21E-01	-0.201	0.032	2.95E-10	-0.167	0.033	4.95E-07
L.LDL.FC	-0.032	0.034	3.47E-01	-0.195	0.032	1.87E-09	-0.138	0.034	4.60E-05
L.LDL.L	-0.039	0.034	2.51E-01	-0.200	0.032	4.87E-10	-0.164	0.033	9.96E-07
L.LDL.P	-0.040	0.034	2.38E-01	-0.200	0.032	4.57E-10	-0.167	0.033	6.15E-07
L.LDL.PL	-0.030	0.034	3.73E-01	-0.195	0.032	1.28E-09	-0.157	0.033	2.63E-06
L.LDL.TG	-0.051	0.034	1.36E-01	-0.147	0.032	5.95E-06	-0.158	0.034	3.28E-06
M.LDL.C	-0.054	0.034	1.08E-01	-0.201	0.032	3.10E-10	-0.167	0.033	4.86E-07
M.LDL.CE	-0.055	0.034	9.79E-02	-0.202	0.032	2.43E-10	-0.167	0.033	4.93E-07
M.LDL.FC	-0.050	0.034	1.40E-01	-0.194	0.032	1.50E-09	-0.165	0.033	7.14E-07
M.LDL.L	-0.054	0.033	1.05E-01	-0.203	0.032	2.02E-10	-0.176	0.033	1.20E-07
M.LDL.P	-0.055	0.033	1.03E-01	-0.203	0.032	1.81E-10	-0.178	0.033	9.16E-08
M.LDL.PL	-0.047	0.033	1.55E-01	-0.197	0.032	5.60E-10	-0.187	0.033	1.42E-08
M.LDL.TG	-0.049	0.034	1.50E-01	-0.146	0.032	7.13E-06	-0.148	0.034	1.24E-05
S.LDL.C	-0.058	0.034	8.46E-02	-0.201	0.032	2.86E-10	-0.172	0.033	2.19E-07
S.LDL.CE	-0.058	0.034	8.59E-02	-0.204	0.032	1.78E-10	-0.171	0.033	2.69E-07
S.LDL.FC	-0.055	0.033	1.02E-01	-0.186	0.032	5.55E-09	-0.170	0.033	3.21E-07
S.LDL.L	-0.055	0.033	9.85E-02	-0.201	0.032	2.89E-10	-0.180	0.033	5.80E-08
S.LDL.P	-0.055	0.033	9.84E-02	-0.201	0.032	2.59E-10	-0.182	0.033	3.90E-08
S.LDL.PL	-0.039	0.033	2.39E-01	-0.182	0.032	9.90E-09	-0.172	0.033	2.17E-07
S.LDL.TG	-0.060	0.034	7.61E-02	-0.142	0.032	9.66E-06	-0.187	0.033	2.37E-08
High-density lipoproteins (HDL)									

Supplementary table 6 The associations between genetically-influenced lower triglyceride levels and genetically-influenced LDL-C levels, separately and in combination and 145 NMR-based metabolomic measures in the Oxford Biobank (OBB) cohort (n = 6,999) (*continued*)

	Lower TG via *LPL*			Lower LDL-C			Lower TG via *LPL* & lower LDL-C		
	BETA*	SE	*P* VALUE	BETA	SE	*P* VALUE	BETA	SE	*P* VALUE
XL.HDL.C	0.042	0.032	1.94E-01	-0.045	0.031	1.40E-01	0.012	0.032	7.01E-01
XL.HDL.CE	0.034	0.033	2.97E-01	-0.051	0.031	1.04E-01	0.003	0.032	9.16E-01
XL.HDL.FC	0.062	0.031	4.69E-02	-0.029	0.030	3.25E-01	0.035	0.031	2.61E-01
XL.HDL.L	0.065	0.031	3.58E-02	-0.024	0.029	4.09E-01	0.046	0.031	1.33E-01
XL.HDL.P	0.067	0.031	3.07E-02	-0.023	0.029	4.24E-01	0.048	0.031	1.20E-01
XL.HDL.PL	0.081	0.030	6.79E-03	0.002	0.028	9.51E-01	0.081	0.030	6.28E-03
XL.HDL.TG	0.019	0.035	5.78E-01	-0.108	0.033	1.03E-03	-0.099	0.034	3.85E-03
L.HDL.C	0.118	0.030	7.37E-05	0.063	0.028	2.64E-02	0.153	0.029	2.14E-07
L.HDL.CE	0.120	0.030	5.48E-05	0.065	0.028	2.15E-02	0.156	0.029	1.25E-07
L.HDL.FC	0.111	0.030	2.10E-04	0.055	0.028	5.03E-02	0.143	0.030	1.37E-06
L.HDL.L	0.123	0.030	3.52E-05	0.056	0.028	4.94E-02	0.148	0.030	5.59E-07
L.HDL.P	0.124	0.030	3.12E-05	0.054	0.028	5.58E-02	0.147	0.030	6.78E-07
L.HDL.PL	0.128	0.030	1.75E-05	0.049	0.028	8.37E-02	0.145	0.030	1.06E-06
L.HDL.TG	0.071	0.032	2.69E-02	-0.009	0.031	7.78E-01	0.054	0.032	8.93E-02
M.HDL.C	0.168	0.034	7.05E-07	0.069	0.032	3.14E-02	0.166	0.033	7.43E-07
M.HDL.CE	0.173	0.034	3.09E-07	0.077	0.032	1.68E-02	0.174	0.034	2.17E-07
M.HDL.FC	0.143	0.034	2.16E-05	0.038	0.032	2.38E-01	0.127	0.033	1.31E-04
M.HDL.L	0.157	0.034	3.72E-06	0.045	0.032	1.61E-01	0.131	0.034	9.61E-05
M.HDL.P	0.156	0.034	4.52E-06	0.042	0.032	1.91E-01	0.126	0.034	1.90E-04
M.HDL.PL	0.146	0.034	1.46E-05	0.029	0.032	3.70E-01	0.112	0.033	8.00E-04
M.HDL.TG	-0.022	0.034	5.32E-01	-0.083	0.033	1.12E-02	-0.132	0.034	1.20E-04

Supplementary table 6 The associations between genetically-influenced lower triglyceride levels and genetically-influenced LDL-C levels, separately and in combination and 145 NMR-based metabolomic measures in the Oxford Biobank (OBB) cohort (n = 6,999) (*continued*)

	Lower TG via *LPL*			Lower LDL-C			Lower TG via *LPL* & lower LDL-C		
	BETA*	SE	*P* VALUE	BETA	SE	*P* VALUE	BETA	SE	*P* VALUE
S.HDL.C	0.003	0.035	9.32E-01	-0.079	0.033	1.67E-02	-0.042	0.034	2.20E-01
S.HDL.CE	-0.016	0.035	6.38E-01	-0.108	0.033	1.09E-03	-0.065	0.034	5.70E-02
S.HDL.FC	0.085	0.035	1.51E-02	0.078	0.033	1.96E-02	0.084	0.035	1.61E-02
S.HDL.L	0.046	0.035	1.90E-01	-0.006	0.033	8.48E-01	0.008	0.035	8.26E-01
S.HDL.P	0.043	0.035	2.23E-01	-0.008	0.033	8.20E-01	0.002	0.035	9.62E-01
S.HDL.PL	0.097	0.035	5.76E-03	0.079	0.033	1.80E-02	0.089	0.035	1.06E-02
S.HDL.TG	-0.105	0.033	1.62E-03	-0.079	0.032	1.21E-02	-0.182	0.033	3.54E-08
Lipoprotein particle size									
VLDL particle size	-0.053	0.032	9.60E-02	-0.044	0.030	1.48E-01	-0.130	0.032	4.00E-05
LDL particle size	0.081	0.034	1.77E-02	0.086	0.032	7.94E-03	0.135	0.034	6.46E-05
HDL particle size	0.111	0.030	2.50E-04	0.034	0.029	2.34E-01	0.129	0.030	1.65E-05
Apolipoproteins									
ApoA1	0.141	0.033	2.00E-05	-0.012	0.032	7.13E-01	0.077	0.033	1.84E-02
ApoB	-0.054	0.032	9.15E-02	-0.189	0.031	6.18E-10	-0.221	0.032	4.00E-12
Cholesterols									
Esterified cholesterol	-0.022	0.034	5.19E-01	-0.171	0.032	1.23E-07	-0.133	0.034	7.67E-05
Free cholesterol	-0.023	0.034	4.96E-01	-0.190	0.032	4.06E-09	-0.148	0.034	1.14E-05
Total cholesterol in HDL2	0.130	0.031	3.31E-05	0.035	0.030	2.35E-01	0.133	0.031	1.99E-05
Total cholesterol in HDL3	0.135	0.031	1.35E-05	0.045	0.030	1.30E-01	0.146	0.031	2.34E-06
Total cholesterol in HDL	0.044	0.034	2.00E-01	-0.076	0.032	1.91E-02	-0.030	0.034	3.81E-01
Total cholesterol in LDL	-0.048	0.034	1.53E-01	-0.202	0.032	2.97E-10	-0.166	0.033	6.87E-04
Remnant cholesterol	-0.046	0.032	1.56E-01	-0.179	0.031	6.19E-09	-0.210	0.032	5.98E-08
Serum total cholesterol	0.001	0.034	9.81E-01	-0.180	0.032	2.47E-08	-0.139	0.034	3.61E-05
Total cholesterol in VLDL	-0.056	0.032	7.78E-02	-0.144	0.030	1.78E-06	-0.215	0.031	7.82E-09

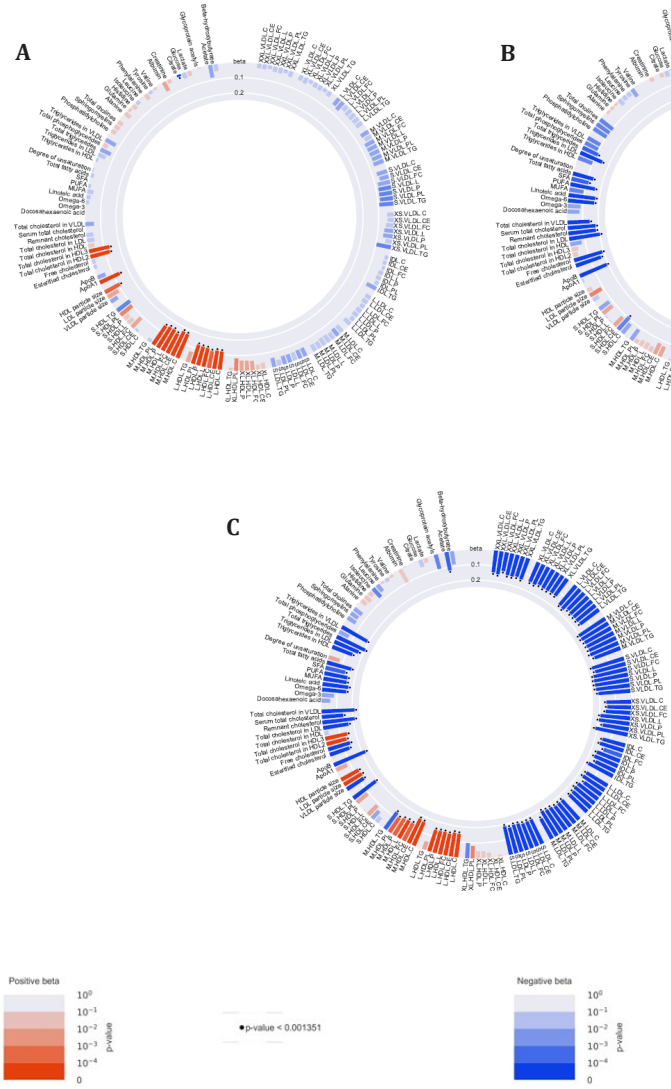
Supplementary table 6 The associations between genetically-influenced lower triglyceride levels and genetically-influenced LDL-C levels, separately and in combination and 145 NMR-based metabolomic measures in the Oxford Biobank (OBB) cohort (n = 6,999) (*continued*)

	Lower TG via *LPL*			Lower LDL-C			Lower TG via *LPL* & lower LDL-C		
	BETA*	SE	*P* VALUE	BETA	SE	*P* VALUE	BETA	SE	*P* VALUE
Fatty acids									
Docosahexaenoic acid	0.003	0.035	9.32E-01	-0.079	0.033	1.65E-02	-0.058	0.034	9.35E-02
Omega-3	-0.002	0.034	9.54E-01	-0.084	0.033	1.01E-02	-0.080	0.034	1.92E-02
Omega-6	-0.021	0.034	5.43E-01	-0.170	0.033	2.11E-04	-0.158	0.034	3.91E-06
Linoleic acid	-0.027	0.035	4.28E-01	-0.175	0.033	1.04E-04	-0.168	0.034	9.15E-07
MUFA	-0.041	0.034	2.30E-01	-0.092	0.032	3.97E-03	-0.152	0.033	5.66E-06
PUFA	-0.017	0.034	6.18E-01	-0.163	0.033	6.65E-04	-0.153	0.034	7.65E-06
SFA	0.001	0.034	9.76E-01	-0.113	0.033	5.01E-04	-0.130	0.034	1.22E-04
Total fatty acids	-0.021	0.034	5.43E-01	-0.137	0.032	2.30E-05	-0.163	0.034	1.31E-06
Degree of unsaturation	-0.009	0.034	8.04E-01	0.003	0.033	9.33E-01	0.075	0.034	2.72E-02
Glycerides									
Triglycerides in HDL	-0.015	0.035	6.74E-01	-0.139	0.035	5.49E-05	-0.139	0.035	5,49E-05
Triglycerides in LDL	-0.052	0.034	1.26E-01	-0.171	0.034	4.72E-04	-0.171	0.034	4,72E-04
Total triglycerides	-0.073	0.032	2.30E-02	-0.204	0.032	1.71E-07	-0.204	0.032	1,71E-07
Total phosphoglycerides	0.035	0.035	3.14E-01	-0.069	0.034	4.40E-02	-0.069	0.034	4,40E-02
Triglycerides in VLDL	-0.074	0.031	1.86E-02	-0.189	0.031	1.42E-06	-0.189	0.031	1,42E-06
Phospholipids									
Phosphatidylcholine	0.036	0.034	2.98E-01	-0.100	0.033	2.19E-03	-0.062	0.034	6.73E-02
Sphingomyelins	0.038	0.034	2.62E-01	-0.100	0.032	2.00E-03	-0.057	0.034	9.38E-02
Total cholines	0.038	0.034	2.68E-01	-0.104	0.033	1.46E-03	-0.064	0.034	6.10E-02
Kidney function									
Albumin	0.065	0.035	6.10E-02	0.002	0.033	9.62E-01	0.099	0.062	1.11E-01
Creatinine	0.026	0.028	3.47E-01	0.029	0.027	2.84E-01	-0.006	0.048	9.07E-01

Supplementary table 6 The associations between genetically-influenced lower triglyceride levels and genetically-influenced LDL-C levels, separately and in combination and 145 NMR-based metabolomic measures in the Oxford Biobank (OBB) cohort (n = 6,999) (*continued*)

	Lower TG via *LPL*			Lower LDL-C			Lower TG via *LPL* & lower LDL-C		
	BETA*	**SE**	***P* VALUE**	**BETA**	**SE**	***P* VALUE**	**BETA**	**SE**	***P* VALUE**
Amino acids									
Alanine	0.046	0.035	1.86E-01	0.017	0.033	6.00E-01	0.043	0.035	2.14E-01
Glutamine	0.020	0.033	5.43E-01	0.019	0.032	5.38E-01	0.051	0.033	1.20E-01
Histidine	0.035	0.035	3.13E-01	0.017	0.033	5.96E-01	0.035	0.034	3.07E-01
Isoleucine	-0.025	0.029	3.93E-01	-0.045	0.027	1.04E-01	-0.074	0.029	9.80E-03
Leucine	0.005	0.029	8.55E-01	-0.033	0.028	2.26E-01	-0.054	0.029	6.17E-02
Phenylalanine	0.042	0.035	2.29E-01	-0.033	0.033	3.23E-01	0.016	0.034	6.34E-01
Tyrosine	-0.022	0.033	5.13E-01	-0.058	0.032	6.74E-02	-0.026	0.033	4.32E-01
Valine	0.016	0.030	6.03E-01	0.004	0.029	8.78E-01	0.019	0.030	5.37E-01
Glycolysis									
Citrate	-0.014	0.035		0.029	0.033	3.75E-01	-0.004	0.035	9.13E-01
Glucose	-0.039	0.033	2.32E-01	-0.040	0.031	2.07E-01	-0.049	0.033	1.32E-01
Lactate	0.036	0.035	3.07E-01	-0.008	0.033	8.12E-01	0.032	0.034	3.53E-01
Inflammation									
Glycoprotein acetyls	0.006	0.034	8.61E-01	-0.067	0.032	3.73E-02	-0.097	0.034	4.24E-03
Ketone bodies									
Acetate	-0.083	0.035	1.63E-02	-0.056	0.033	9.10E-02	-0.120	0.034	4.71E-04
Beta-hydroxybutyrate	-0.046	0.035	1.91E-01	-0.040	0.033	2.33E-01	-0.087	0.035	1.20E-02

BETA, beta coefficient; SE, standard error. A $p < 1.35 \times 10^{-3}$ is considered statistically significant. *The beta coefficient is rank transformed SD difference in metabolic measure for genetically-influenced lower TG levels by *LPL*, genetically-influenced lower LDL-C levels or both compared to genetically-influenced higher TG and LDL-C levels (reference).



Supplementary Figure 1: Associations of genotype group with 145 NMR-based metabolomic measures in the OBB replication cohort. (A) Group with genetically-influenced lower TG levels compared with the group with combined genetically-influenced higher TG and LDL-C levels (reference). (B) Group with genetically-influenced lower LDL-C levels compared with the reference group. (C) Group with both genetically-influenced lower TG and LDL-C levels compared with the reference group. Bar heights represent the magnitude of the beta coefficient from linear regression, which is expressed in standard deviation (SD) units. Red bars indicate positive betas and blue bars indicate negative betas. The transparency of the bars indicates the level of statistical significance. A $p < 1.35 \times 10^{-3}$ is regarded statistical significant, as represented by the black dots.