

Coronary Artery Disease Risk and Lipidomic Profiles Are Similar in Hyperlipidemias With Family History and Population-Ascertained Hyperlipidemias

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Background—We asked whether, after excluding familial hypercholesterolemia, individuals with high low-density lipoprotein cholesterol (LDL-C) or triacylglyceride levels and a family history of the same hyperlipidemia have greater coronary artery disease risk or different lipidomic profiles compared with population-based hyperlipidemias.

Methods and Results—We determined incident coronary artery disease risk for 755 members of 66 hyperlipidemic families (≥ 2 first-degree relatives with similar hyperlipidemia) and 19 644 Finnish FINRISK population study participants. We quantified 151 circulating lipid species from 550 members of 73 hyperlipidemic families and 897 FINRISK participants using mass spectrometric shotgun lipidomics. Familial hypercholesterolemia was excluded using functional LDL receptor testing and genotyping. Hyperlipidemias (LDL-C or triacylglycerides >90 th population percentile) associated with increased coronary artery disease risk in meta-analysis of the hyperlipidemic families and the population cohort (high LDL-C: hazard ratio, 1.74 [95% CI, 1.48–2.04]; high triacylglycerides: hazard ratio, 1.38 [95% CI, 1.09–1.74]). Risk estimates were similar in the family and population cohorts also after adjusting for lipid-lowering medication. In lipidomic profiling, high LDL-C associated with 108 lipid species, and high triacylglycerides associated with 131 lipid species in either cohort (at 5% false discovery rate; P -value range 0.038– 2.3×10^{-56}). Lipidomic profiles were highly similar for hyperlipidemic individuals in the families and the population (LDL-C: $r=0.80$; triacylglycerides: $r=0.96$; no lipid species deviated between the cohorts).

Conclusions—Hyperlipidemias with family history conferred similar coronary artery disease risk as population-based hyperlipidemias. We identified distinct lipidomic profiles associated with high LDL-C and triacylglycerides. Lipidomic profiles were similar between hyperlipidemias with family history and population-ascertained hyperlipidemias, providing evidence of similar and overlapping underlying mechanisms. (*J Am Heart Assoc.* 2019;00:e012415. DOI: 10.1161/JAHA.119.012415.)

Key Words: coronary artery disease • family study • high-risk populations • hypercholesterolemia • hypertriglyceridemia • lipids and lipoproteins

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Accompanying Data S1, Tables S1 through S7 and Figures S1 through S5 are available at <https://www.ahajournals.org/doi/suppl/10.1161/JAHA.119.012415>

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Clinical Perspective

What Is New?

- Beyond familial hypercholesterolemia, the impact of hyperlipidemic family history on coronary artery disease risk is debated.
- Coronary artery disease risk was comparable in our hyperlipidemic subjects (low-density lipoprotein cholesterol or triacylglycerides >90th population percentile) with family history and subjects with population-ascertained hyperlipidemias.
- The lipidomic profiles of such hyperlipidemias were independent of family history, providing evidence for similar and/or overlapping metabolic pathways.

What Are the Clinical Implications?

- Our results do not support different screening for those with a family history of hyperlipidemia and sporadically discovered hyperlipidemic cases.

High levels of low-density lipoprotein cholesterol (LDL-C) and triacylglycerides have been identified as causal risk factors for atherosclerotic cardiovascular disease (ASCVD).^{1,2} These hyperlipidemias may arise through lifestyle factors, but they are also highly heritable.^{3–6} An estimated half of patients with premature coronary artery disease (CAD) have dyslipidemia with a family history of dyslipidemia, most of which are characterized by increases in LDL-C and/or triacylglycerides.⁷

Whether dyslipidemias with family history should be diagnosed and managed differently from hyperlipidemias observed in randomly ascertained individuals in the general population is uncertain. Clinical guidelines emphasize their identification but, with the exception of familial hypercholesterolemia (FH), refrain from strong management recommendations.^{8,9} The monogenic FH patients with rare high-impact LDL-C-elevating variants have a higher risk of developing CAD than noncarriers with similar lipid levels.¹⁰ This is potentially related to lifelong exposure to high LDL-C levels and suggests that these individuals may benefit from earlier or more aggressive LDL-C-lowering therapy. In contrast with FH, many other hyperlipidemias with family history appear genetically similar to population-ascertained hyperlipidemias.^{11–13} Whether such hyperlipidemias with family history also confer additional elevation in ASCVD risk is not known.

Herein, we assess incident ASCVD risk associated with familial aggregation of high LDL-C and triacylglycerides, excluding individuals with FH. We also ask whether their circulating lipid phenotypes are similar compared with population-ascertained hyperlipidemias. Recent technological advancements have allowed replicable and simultaneous quantification of hundreds of lipid species, the main

constituents of LDL and triacylglyceride-rich lipoproteins, through lipidomic profiling.^{14,15} We test whether detailed phenotypic differences in lipidomic profiles, which might reflect different pathophysiological features and ASCVD susceptibility, exist between hyperlipidemias with family history and population-ascertained hyperlipidemias. Using a direct infusion platform that combines absolute quantification with high throughput, we were able to overcome problems that have hampered many previous studies.¹⁶

In this study, we first estimated the CAD risk associated with high LDL-C or triacylglyceride levels with family history and population-ascertained hyperlipidemias with similarly high LDL-C or triacylglycerides. Second, we characterized the lipidomic profiles associated with elevated plasma levels of LDL-C and triacylglycerides. Finally, we compared the lipidomic profiles of hyperlipidemias with family history and population-ascertained hyperlipidemias to assess their potential differences.

Materials and Methods

Subjects and Clinical Ascertainment

The Finnish hyperlipidemia families included in this cohort study (74 families, n=1445 individuals with LDL-C and triacylglyceride measures) were identified as part of the EUFAM (European Multicenter Study on Familial Dyslipidemias in Patients With Premature Coronary Heart Disease) project. Initial recruitment aimed to identify families with familial combined hyperlipidemia (at least 2 family members with total cholesterol and/or triacylglycerides \geq 90th population percentile) or families with aggregation of low high-density lipoprotein cholesterol. Classic FH was excluded on the basis of an in-house functional LDL receptor test for the probands and later genotyping of selected Finnish FH mutations in other family members with high LDL-C; further recruitment was not pursued in putative FH pedigrees.¹⁷ For the present study, designation of “high LDL-C with family history” or “high triacylglycerides with family history” was made if at least 2 first-degree relatives had LDL-C or triacylglyceride levels, respectively, that were >90th age- and sex-specific Finnish 1997 population percentiles (Table S1) without being affected by diabetes mellitus or other relevant comorbidities (Figure S1). More detailed information is given in Data S1.

Individuals from the Finnish National FINRISK study were used as a Finnish population-based comparison group. A total of 19 644 individuals from the FINRISK study 1992 to 2002 cohorts and 755 individuals from EUFAM families were linked with the national hospital discharge and causes-of-death registries. Clinical incident CAD event end points were defined as either myocardial infarction or coronary revascularization (coronary angioplasty or coronary artery bypass grafting).

CVD was defined as CAD or stroke, excluding subarachnoid hemorrhage. Mean (range) follow-up time from baseline to CAD end point, death, or end of registry follow-up was 16.1 (0.1–20.1) years in EUFAM and 12.6 (0.02–19.0) years in the FINRISK study. More detailed information is given in Data S1.

Written informed consent was obtained from all participants, except the 1992 FINRISK study survey, for which verbal informed consent was obtained, as required by legislation and ethics committees at the time. All samples were collected in accordance with the Declaration of Helsinki, and study protocols were approved by the ethics committees of the participating centers (The Hospital District of Helsinki and Uusimaa Coordinating Ethics committees, approval No. 184/13/03/00/12). Because of the consent given by the study participants, the data cannot be made publicly available. The data are available through the Institute for Molecular Medicine Finland Data Access Committee for authorized researchers who have an institutional review board/ethics approval and an institutionally approved study plan. For more details, please contact the Institute for Molecular Medicine Finland Data Access Committee (fimm-dac@helsinki.fi).

Lipidomics Measurements

Lipidomic profiling of circulating lipid species was performed for 550 EUFAM family members (all members with available plasma samples) and for 897 individuals from the FINRISK 2012 study cohort, after excluding individuals with predefined comorbidities (Data S1) and individuals known to use lipid-lowering medication or sex hormones at the time of the measurements. Mass spectrometry–based lipid analysis was performed at Lipotype GmbH (Dresden, Germany), as described.¹⁴ Plasma and serum lipids were extracted with methyl tert-butyl ether/methanol (7:2, v/v).¹⁸ Samples were analyzed by direct infusion in a QExactive mass spectrometer (Thermo Scientific) equipped with a TriVersa NanoMate ion source (Advion Biosciences). Samples were analyzed in both positive and negative ion modes in a single acquisition.

Data were analyzed with in-house–developed lipid identification software based on LipidXplorer.^{19,20} Reproducibility was assessed by the inclusion of reference plasma samples. The median coefficient of variation was <10% across all batches. A total of 151 species were detected in ≥80% of both EUFAM and FINRISK study samples and were included in subsequent analyses. Right-skewed lipidomics measures were natural logarithm transformed before normalization. More detailed information is given in Data S1.

Statistical Analyses

To assess the risk of incident CAD associated with the hyperlipidemias, we used Cox proportional hazards models

using age as the time scale, stratified by sex and clustered by family, to estimate hazard ratios (HRs) for incident CAD (or CVD) events, excluding individuals with prevalent CAD (or CVD). Additional models were also adjusted by lipid-lowering medication and smoking. The statistical significance of intercohort differences in HRs was estimated on the basis of an interaction term between hyperlipidemia status and cohort designation.

We used linear mixed models to estimate the association between lipidomic measurements and predictors of interest (hyperlipidemia status or continuous lipid measurement), as implemented in MMM (version 1.01).²¹ Age, age², and sex were used as additional fixed-effect covariates.

To account for relatedness among individuals, an empirical genetic relationship matrix was included as the covariance structure of a random effect. Statistical significance was evaluated using the Benjamini-Hochberg method at the 5% level to account for multiple comparisons similarly to recent lipidomics studies of CVDs.^{22,23} R (version 3.4.3) was used for data transformations and other analyses.²⁴ Detailed information is given in Data S1.

Results

Clinical Characteristics and CAD Risk of Individuals With High Levels of LDL-C or Triacylglycerides

We first assessed the risk of developing CAD associated with high levels of LDL-C or triacylglycerides in individuals from the Finnish FINRISK study population survey and in hyperlipidemic families ascertained as part of the EUFAM (Figure 1; Table S2; Figure S1A). Individuals with LDL-C >90th percentile had an increased risk of incident CAD in the FINRISK study population surveys (n=19 644 individuals) compared with other individuals (HR, 1.74; 95% CI, 1.48–2.05) (Figure 1). The members of hyperlipidemic families with high LDL-C had a similar HR for CAD compared with their relatives without high LDL-C in 47 “high LDL-C” families (n=625 individuals) (HR, 1.71; 95% CI, 0.94–3.10). The HRs did not differ between the cohorts ($P=0.84$). The mean age at incident CAD diagnosis was similar among individuals with high LDL-C in the hyperlipidemic families (62.8 years) and in the population cohort (63.5 years). We also observed increased CAD risk in individuals with high triacylglycerides in the population (HR, 1.38; 95% CI, 1.09–1.75) and a similar HR in 35 “high triacylglyceride” families (n=371 individuals) (HR, 1.35; 95% CI, 0.52–3.51). The HRs did not differ between the cohorts ($P=0.82$). The results remained similar after adjusting for lipid-lowering medication use and smoking (Figure S2 and Table S3) and body mass index (Table S3). Furthermore, we found no differences between the cohorts in the risk of

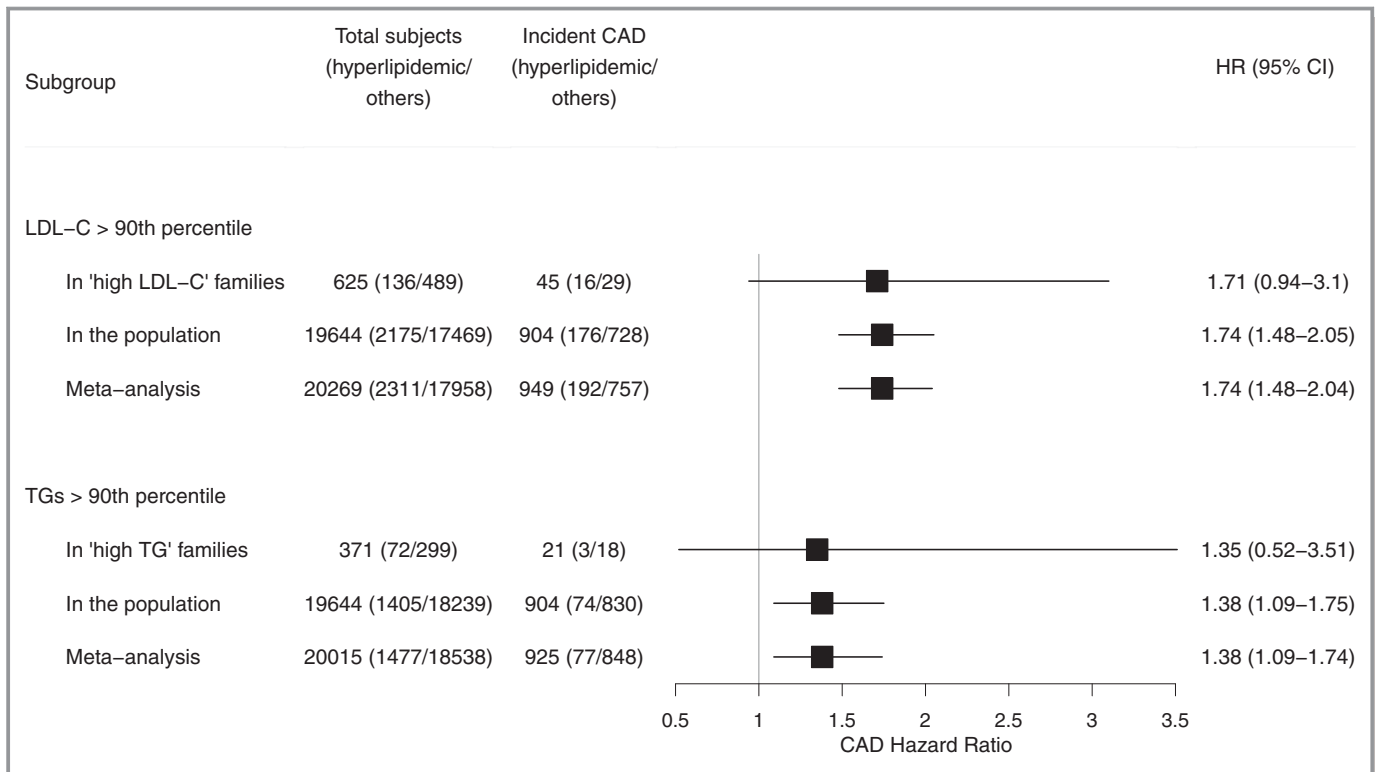


Figure 1. Risk of incident coronary artery disease (CAD) in hyperlipidemias with family history and population-ascertained hyperlipidemias. To assess the risk of incident CAD associated with the hyperlipidemia types, we used Cox proportional hazards models using age as the time scale, stratified by sex and clustered by family, to estimate hazard ratios (HRs) for incident CAD events, excluding individuals with prevalent CAD. Further details on the participants are presented in Table S2. LDL-C indicates low-density lipoprotein cholesterol; TG, triacylglycerides.

incident CVD ($P=0.42-0.98$; Figure S3A and S3B; Table S3). Meta-analyses of HRs closely approximated estimates derived from the population cohort.

We then characterized the detailed lipidomic profiles of 550 individuals from 73 hyperlipidemic families and 897 individuals from the FINRISK population study (Methods; Tables S4, S5 and S6). These included 105 individuals (23%) of 463 family members in 53 high LDL-C families who had LDL-C levels >90th percentile (mean \pm SD, 5.2 \pm 0.8 mmol/L) and 64 individuals (22%) of 287 family members in 39 high triacylglyceride families who had triacylglycerides >90th percentile (mean \pm interquartile range, 3.6 \pm 1.8 mmol/L). Using similar cutoffs in the population, 56 individuals (6%) and 65 individuals (7%) of 897 were affected by high LDL-C levels (mean \pm SD, 5.3 \pm 1.1 mmol/L) and high triacylglycerides (mean \pm interquartile range, 3.5 \pm 1.9 mmol/L), respectively. Both high LDL-C and triacylglyceride levels were observed in 31 individuals (6%) in the family cohort and 9 individuals (1%) in the population cohort.

High LDL-C and Lipidomic Profiles

To characterize the lipidomic profiles associated with elevated values of LDL-C, we compared individuals with high LDL-C

levels with those without. In the hyperlipidemic families, individuals with a high LDL-C had significantly elevated levels of 99 lipid species spread out across most of the studied lipid classes. Reduced levels among the high LDL-C individuals were observed for 3 lysophosphatidylcholine, 2 lysophosphatidylethanolamine, and 1 phosphatidylcholine-ether (PCO) species (Figure 2A; Table S7). Similar trends were seen in the population cohort, in which the levels of 51 lipid species were elevated among high LDL-C individuals (Figure 2B; Table S7). The effect estimates correlated strongly across all lipid species between the hyperlipidemic families and the population cohorts (Pearson's $r=0.80$; Figure 3). Furthermore, we observed no significant differences in the effect estimates between the cohorts at the 5% false discovery rate (FDR).

We also studied the association of high LDL-C levels with the degree of saturation of fatty acids in each lipid class. In the hyperlipidemic families, high LDL-C levels were associated with increased saturation of lysophosphatidylcholines and ceramides, as well as reduced saturation of lysophosphatidylethanolamines, phosphatidylcholines, PCOs, and phosphatidylinositols (P -value range=0.019–0.0014) (Figure S4). In the population cohort, the trends were similar, although there was an association for increased lysophosphatidylcholine

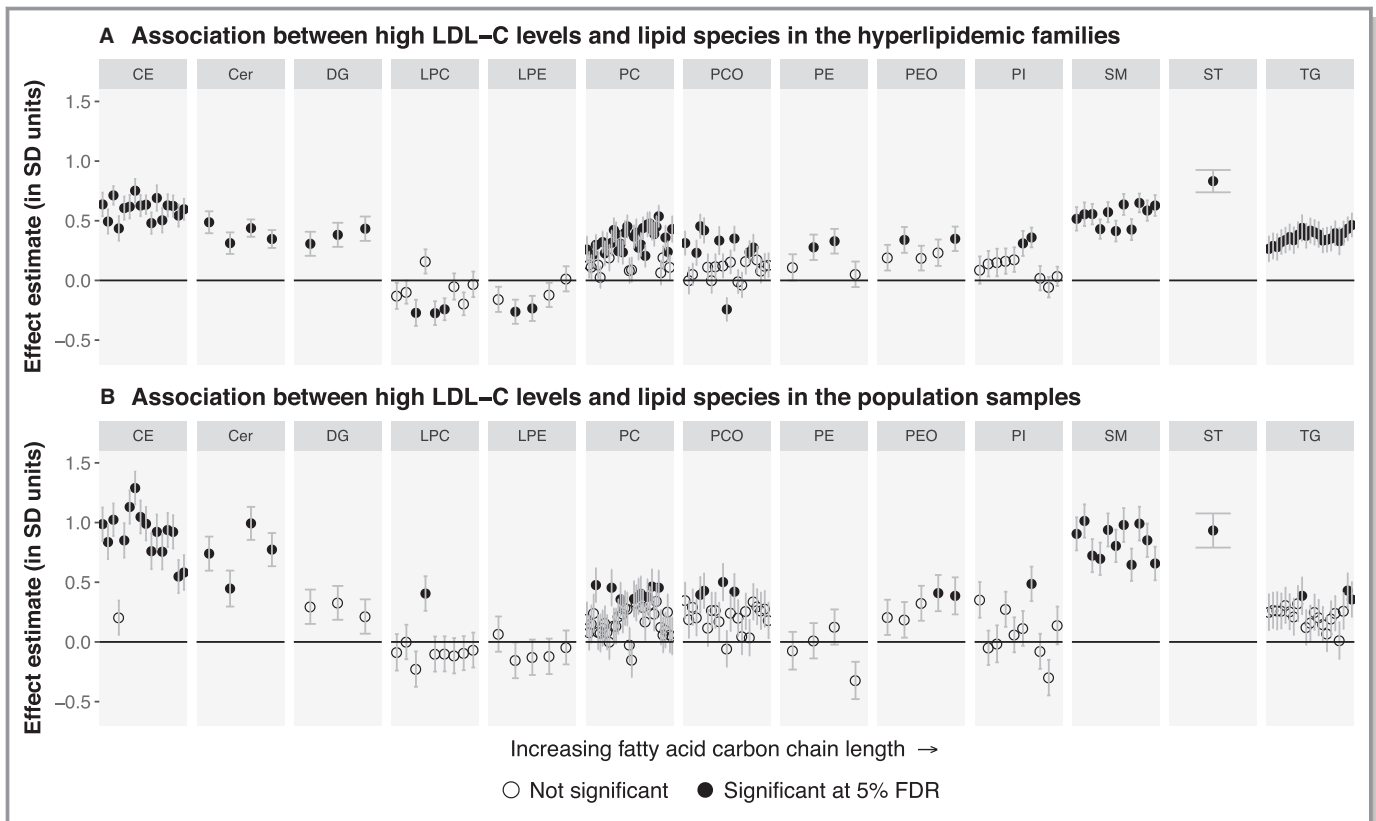


Figure 2. Associations between high low-density lipoprotein cholesterol (LDL-C) status and the levels of 151 lipid species. **A**, Individuals affected by high LDL-C levels ($n=105$) were compared with their unaffected relatives ($n=358$) in the 53 “high LDL-C” families. **B**, Individuals affected by high LDL-C ($n=56$) were compared with other individuals ($n=841$) in the FINRISK study population cohort. The association of high LDL-C status with the lipid species was estimated using linear mixed models with age, age², and sex as the other fixed-effect covariates. Statistical significance was evaluated using the Benjamini-Hochberg method at a 5% false discovery rate (FDR). The ordering of the lipid species within each class is the same as in Table S7. Cer indicates ceramide; DG, diacylglyceride; FDR, false discovery rate; LDL-C, low-density lipoprotein cholesterol; LPA, lysophosphatic acid; LPC, lysophosphatidylcholine; LPE, lysophosphatidylethanolamine; PC, phosphatidylcholine; PCO, phosphatidylcholine-ether; PE, phosphatidylethanolamine; PEO, phosphatidylethanolamine-ether; PI, phosphatidylinositol; CE, cholesteryl ester; SM, sphingomyelin; ST, sterol; TG, triacylglyceride.

saturation only ($P=7.2 \times 10^{-4}$). The effect estimates did not differ significantly between the hyperlipidemic families and the population sample at the 5% FDR. Overall, the lipidomic profiles associated with high LDL-C levels appeared similar in the hyperlipidemic families and the general population.

High Triacylglycerides and Lipidomic Profiles

In the hyperlipidemic families, individuals with high triacylglycerides had elevated levels of 107 lipid species covering all studied lipid classes with the exception of lysophosphatidylethanolamines. In addition, we observed reduced levels of 7 PCO, 2 lysophosphatidylcholine, and 1 phosphatidylinositol species (Figure 4A; Table S7). Similar profiles were seen in the population when comparing individuals with high triacylglycerides with those without, including elevated levels of 108 species and reduced levels of 10 PCO and 1

lysophosphatidylcholine species (Figure 4B; Table S7). The effect estimates correlated highly across all species between the families and the population cohort (Pearson’s $r=0.96$; Figure 3). Furthermore, we observed no significant differences in the effect estimates between the cohorts at the 5% FDR.

When contrasting the profiles observed for the 2 types of hyperlipidemias, we saw that high triacylglyceride levels were more uniquely reflected in a range of circulating lipid classes, including triacylglycerides, diacylglycerides, phosphatidylethanolamines, phosphatidylcholines, PCOs, and phosphatidylinositols. However, associations with sphingomyelin species appeared more unique to high LDL-C levels.

Next, we studied the association of high triacylglyceride levels with the degree of saturation of fatty acids in each lipid class. In both the hyperlipidemic families and the population, having high triacylglycerides was associated with increased saturation of triacylglycerides, diacylglycerides,

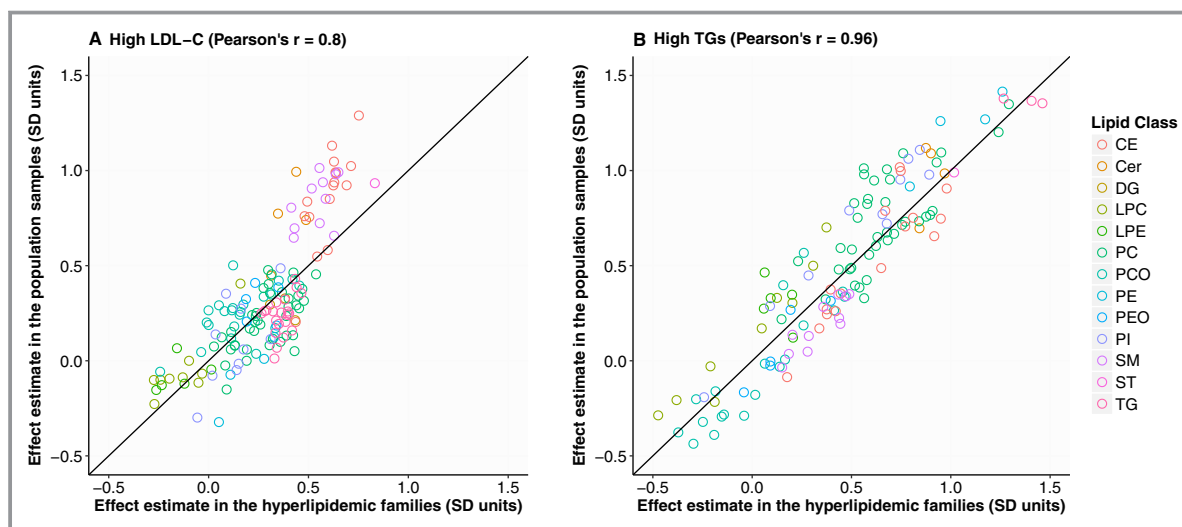


Figure 3. Correlation of effect estimates for hyperlipidemia status between the hyperlipidemic families and the population samples. The correlation between the effect estimates observed in the family and population cohorts is presented for high low-density lipoprotein cholesterol (LDL-C) (effect estimates presented in Figure 2; **A**) and for high triacylglycerides (effect estimates presented in Figure 4; **B**). Cer indicates ceramide; DG, diacylglyceride; LDL-C, low-density lipoprotein cholesterol; LPA, lysophosphatic acid; LPC, lysophosphatidylcholine; LPE, lysophosphatidylethanolamine; PC, phosphatidylcholine; PCO, phosphatidylcholine-ether; PE, phosphatidylethanolamine; PEO, phosphatidylethanolamine-ether; PI, phosphatidylinositol; CE, cholesteryl ester; SM, sphingomyelin; ST, sterol; TG, triacylglyceride.

lysophosphatidylcholines, and cholesteryl esters (CEs) (P -value range=0.0012– 5.9×10^{-11}) (Figure S5). The effect estimates did not differ significantly between the hyperlipidemic families and the population sample at the 5% FDR. Overall, we observed great similarity in the lipidomic profiles associated with high triacylglycerides in the hyperlipidemic families and in the general population.

Independent Associations of LDL-C and Triacylglyceride Values With the Lipid Species

We then tested if the variation in the lipid species was driven by both LDL-C and triacylglyceride levels or if either was dominating the profiles. For this, we estimated the independent associations of LDL-C and triacylglyceride levels with each lipid species in coadjusted models (Figure 5; Table S7). In these analyses, many of the observed associations with LDL-C were greatly diluted in magnitude, most notably for triacylglyceride, diacylglyceride, and phosphatidylcholine species. LDL-C levels remained most strongly associated with CE, sphingomyelin, ceramide, phosphatidylcholine, and PCO species in both cohorts. A total of 83 species in the hyperlipidemic families and 91 species in the population were independently associated with LDL-C at the 5% FDR. In contrast, triacylglycerides remained strongly associated with a wide range of lipid species, including all individual triacylglyceride species, diacylglycerides, phosphatidylcholines, phosphatidylethanolamines, phosphatidylinositols, ceramides,

and a subset of CEs in both cohorts. A total of 125 species in the hyperlipidemic families and 124 species in the population were independently associated with triacylglycerides at the 5% FDR. Overall, only 13 species were uniquely associated with LDL-C in either cohort, whereas 42 species were uniquely associated with triacylglycerides (Figure 6).

Discussion

Recent lipidomic approaches have identified several hundreds of different lipid species in the human circulation, some of which could be better prognostic biomarkers for ASCVD than the traditional clinical chemistry measurements. In this study, we used a mass spectrometric lipidomics platform to assess the lipidomic profiles in individuals with high LDL-C and/or triacylglyceride levels. We found that individuals affected by high levels of LDL-C or triacylglycerides had CAD HRs between 1.35 and 1.74 in the family and population cohorts and exhibited distinct lipidomic profiles with clear variation between lipid classes. In total, of 151 lipidomic species, 108 were significantly associated with high LDL-C and 131 with high triacylglyceride levels in at least one cohort. Of these species, 96 were associated with both high LDL-C and triacylglycerides. In addition, we observed highly similar lipidomic profiles between the hyperlipidemias with family history and population-ascertained hyperlipidemias. The present study is the most comprehensive lipidomic profiling of common hyperlipidemias to date.

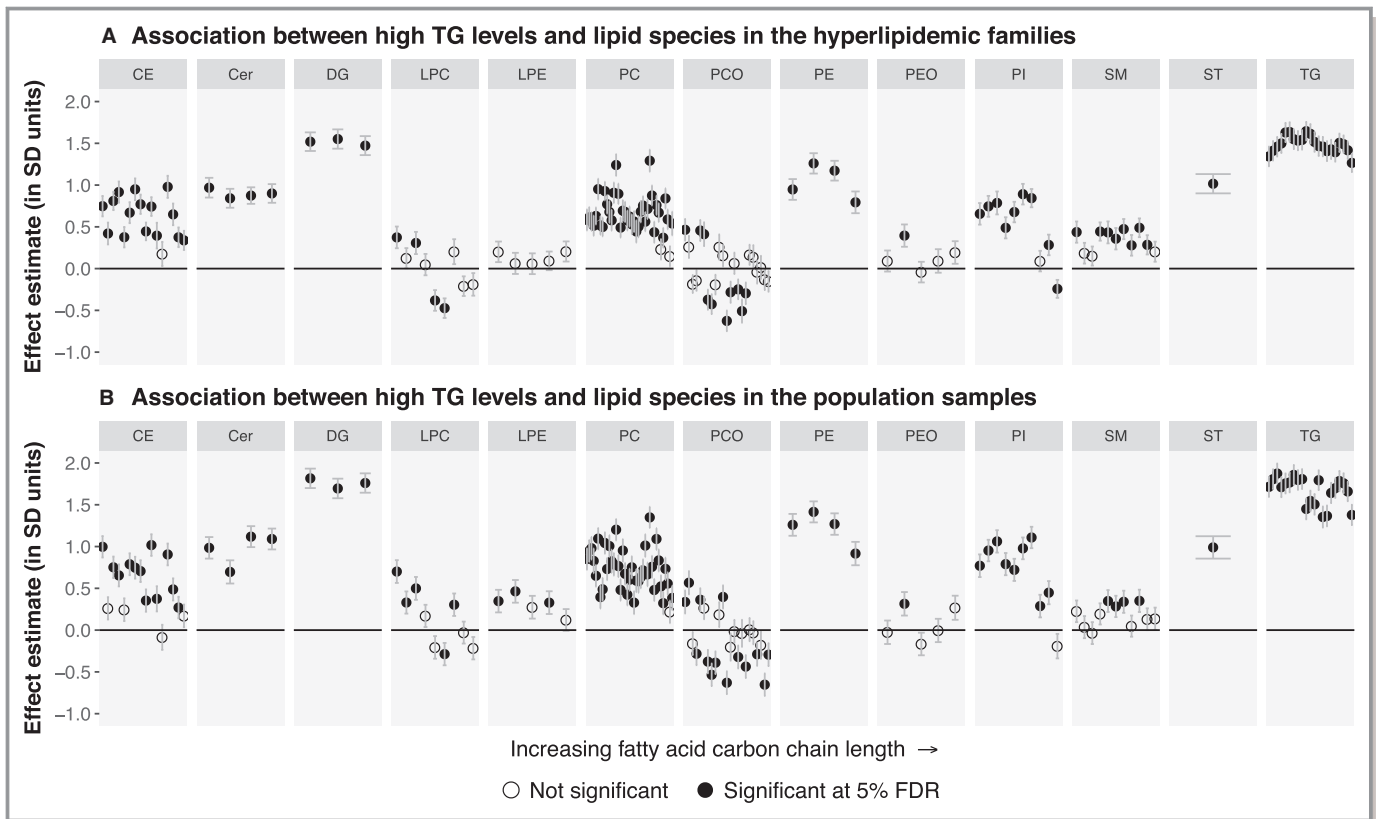


Figure 4. Associations between high triacylglyceride status and the levels of 151 lipid species. **A**, Individuals affected by high triacylglycerides ($n=64$) were compared with their unaffected relatives ($n=223$) in 39 “high TG” families. **B**, Individuals affected by high triacylglycerides ($n=65$) were compared with other individuals ($n=832$) in the FINRISK study population cohort. The association analyses were performed similarly to Figure 2. Cer indicates ceramide; DG, diacylglyceride; FDR, false discovery rate; LDL-C, low-density lipoprotein cholesterol; LPA, lysophosphatic acid; LPC, lysophosphatidylcholine; LPE, lysophosphatidylethanolamine; PC, phosphatidylcholine; PCO, phosphatidylcholine-ether; PE, phosphatidylethanolamine; PEO, phosphatidylethanolamine-ether; PI, phosphatidylinositol; CE, cholesteryl ester; SM, sphingomyelin; ST, sterol; TG, triacylglyceride.

These findings allow us to draw several conclusions. First, the CAD risks are highly similar regardless of whether hyperlipidemic individuals were identified from families with a high prevalence of similar hyperlipidemia or from the general population. Earlier studies have found higher CAD risk in relatives of familial combined hyperlipidemia probands compared with spouses.^{25–27} Our study, however, compares the estimates between family members and individuals with similar lipid levels from the population to quantify the effect of familiarity. We also studied the risk associated with elevated LDL-C and triacylglycerides separately. Our estimates for CAD risk caused by high LDL-C with family history are lower than typically reported for monogenic FH, despite comparable differences in LDL-C levels.^{10,28,29} In the present study, we excluded probands with monogenic FH based on a functional LDL receptor test and genetic testing in the families. Excepting monogenic FH, hyperlipidemias with family history of high LDL-C and/or triacylglyceride levels have been reported to be highly polygenic.^{11–13,30} The pleiotropic effects of diverse genes and pathways, in contrast with the single affected pathway in monogenic FH, may partly explain why we

did not observe increased CAD risk caused by familiarity in our study.

Second, to more deeply characterize potential differences between hyperlipidemias with family history and population-ascertained hyperlipidemias, we performed precise phenotyping of circulating lipid species known to be associated with ASCVD risk.^{22,23,31} Individual lipid species, including sphingolipids, glycerophospholipids, glycerolipids, and CEs, have previously been associated with ASCVD incidence or event risk over traditional risk factors.^{22,23,31,32} Major differences in the metabolic pathways underlying different types of hyperlipidemias would thus be expected to be reflected in different lipidomic profiles. As an example, individuals with low high-density lipoprotein cholesterol levels have previously been shown to have low phosphatidylethanolamine-plasmalogen levels in high-density lipoprotein particles, a putative marker of high-density lipoprotein antioxidative capacity.³³ Herein, in contrast, we observed similar profiles in hyperlipidemias with family history and population-ascertained hyperlipidemias, highlighting the biochemical similarity of the conditions.

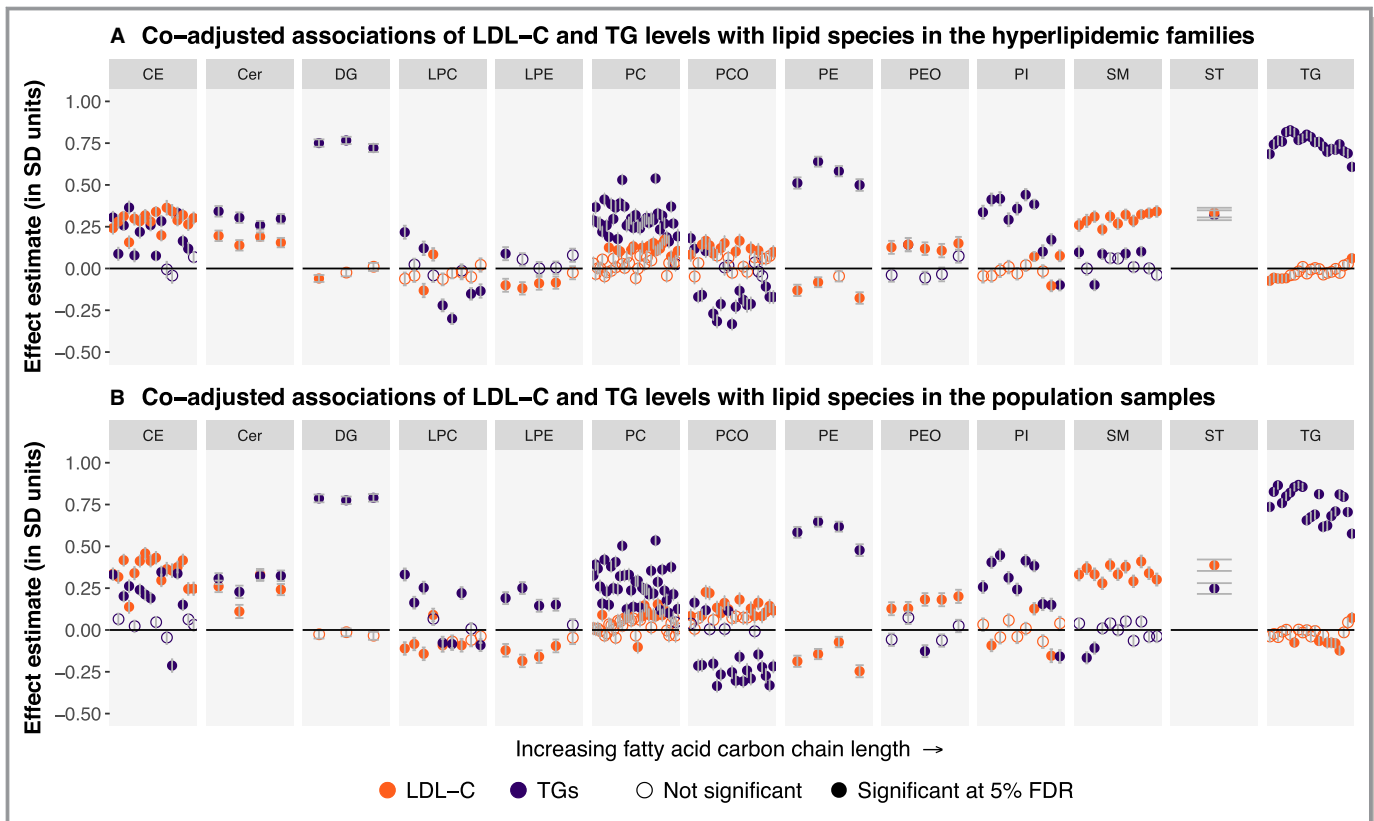


Figure 5. Independent (coadjusted) associations of low-density lipoprotein cholesterol (LDL-C) and triacylglycerides with 151 lipid species. Effect estimates for LDL-C and triacylglycerides were derived from linear mixed models with the lipid species as outcomes and LDL-C, log (triacylglycerides), age, age², and sex as fixed-effect covariates. The effect estimates were derived separately in the hyperlipidemic families (n=550 individuals; **A**) and the FINRISK study population cohort (n=897 individuals; **B**). Effect estimates are presented for LDL-C in orange and triacylglycerides in purple. Statistical significance was evaluated using the Benjamini-Hochberg method at a 5% false discovery rate (FDR). The ordering of the lipid species within each class is the same as in Table S7. Cer indicates ceramide; DG, diacylglyceride; FDR, false discovery rate; LDL-C, low-density lipoprotein cholesterol; LPA, lysophosphatic acid; LPC, lysophosphatidylcholine; LPE, lysophosphatidylethanolamine; PC, phosphatidylcholine; PCO, phosphatidylcholine-ether; PE, phosphatidylethanolamine; PEO, phosphatidylethanolamine-ether; PI, phosphatidylinositol; CE, cholesteryl ester; SM, sphingomyelin; ST, sterol; TG, triacylglyceride.

We started by characterizing the lipid profiles associated with high LDL-C and triacylglyceride levels. Many of the associations were not specific to LDL-C but were rather caused by combined dyslipidemia. LDL particles are generated in circulation as downstream metabolic products from the triacylglyceride-rich lipoproteins and their postlipolytic remnants by the action of 2 lipases, lipoprotein lipase and hepatic lipase.^{34,35} A proportion of the core lipids, especially cholesterol esters, and the particle surface phospholipids thus remains in the generated LDL particles. The actions of the CE transfer protein and phospholipid transfer protein, however, further modulate the constituents of triacylglyceride-rich and LDL particles.³⁶ Percentual lipid compositions have been reported for different lipoprotein classes, but they do not directly reflect variation in plasma LDL-C or triacylglyceride concentrations. For example, phosphatidylcholines have been estimated to constitute 12% of all lipids in LDL particles versus 3% to 9% in triacylglyceride-rich lipoproteins.³⁷

However, in our study, phosphatidylcholines were overall more strongly associated with triacylglyceride levels than with LDL-C levels. Nevertheless, LDL-C remained positively associated with a range of species, including CEs, ceramides, sphingomyelins, phosphatidylcholines, and PCOs. Among the strongly increased species, CE(14:0), CE(16:0), CE(16:1), CE(18:0), sphingomyelin(34:1;2), sphingomyelin(34:2;2), sphingomyelin(42:2;2), ceramide(42:1;2), and ceramide(42:2;2) have previously been associated with the risk of ASCVD.^{22,23}

Elevated triacylglyceride levels were associated with differences in the levels of lipid species across most of the studied classes. More important, most of these associations appeared to be independent of LDL-C levels. Among the lipid species that were strongly correlated with high triacylglycerides after correction for LDL-C levels were several species that have previously been associated with risk of ASCVD.^{22,23,31} These include the species CE(14:0), CE(16:0), CE(16:1), CE(18:0), triacylglyceride(50:1), triacylglyceride

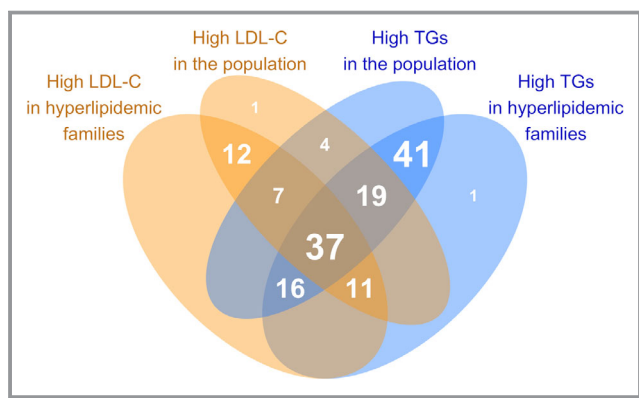


Figure 6. Overlap of the statistically significant independent (coadjusted) associations of low-density lipoprotein cholesterol (LDL-C) and triacylglycerides with 151 lipid species. Each shaded area shows the number of lipid species associated with the corresponding types of hyperlipidemias. More detailed methods are presented in Figure 5 legend. TG indicates triacylglyceride; LDL, low-density lipoprotein cholesterol.

(50:2), triacylglyceride(50:3), triacylglyceride(52:2), triacylglyceride(52:3), triacylglyceride(52:5), triacylglyceride(56:5), triacylglyceride(56:6), ceramide(42:1;2), and ceramide(42:2;2). Furthermore, high triacylglycerides were associated with increased saturation of fatty acids in the triacylglyceride, diacylglyceride, CE, and lysophosphatidylcholine classes. Such differences in the relative fatty acid concentrations can be partly related to dietary intake and reflected in liver-derived very low-density lipoprotein particles, but they are also influenced by endogenous metabolism.³⁸ Overall, a larger proportion of the lipid species previously linked with increased ASCVD risk was more strongly associated with elevated triacylglycerides rather than with elevated LDL-C. This suggests that the levels of these lipid biomarkers are more closely linked with circulating triacylglyceride-rich lipoprotein metabolism than with LDLs.

Third, several lipid species, such as specific CEs, ceramides, and PCOs, remained independently associated with both elevated LDL-C and triacylglycerides. Among these species, the ceramides ceramide(42:1;2) (presumably ceramide[d18:1/24:0]) and ceramide(42:2;2) (presumably ceramide[d18:1/24:1]), the sterol esters CE(16:1) and CE(18:0), and the sphingomyelin(34:1;2) may have added value in ASCVD prediction over traditional lipid measurements.^{22,23,31} Plasma ceramides have been reported to be independent predictors of cardiovascular events in addition to LDL-C in the population and in patients with CAD.^{31,39,40} Both LDL-C and triacylglycerides remained independently associated with all 4 ceramides quantified in our study, and LDL-C was additionally associated with increased saturation of ceramides. Unlike most CE species, CE(16:1) was more strongly associated with the concentration of triacylglycerides than with LDL-C in our

study. Sphingomyelin(34:1;2) was the only sphingomyelin species that was negatively associated with triacylglycerides; and this association became evident only after adjusting for LDL-C levels. In addition, some species, such as ceramide(42:1;2) and triacylglyceride(56:6), which were positively associated with hyperlipidemias in our sample, have previously been reported to be associated with decreased risk of ASCVD events.^{23,31} These coassociations and discordances between reported associations might explain why some lipid species can improve risk prediction. Consequently, there is an urgent need for a better understanding of the potential underlying signaling and metabolic pathways.

Finally, the lipidomic profiles associated with high LDL-C or triacylglyceride levels were comparable between hyperlipidemias with family history and population-ascertained hyperlipidemias. We observed no differences in either the levels of individual lipid species or the saturation of fatty acids within lipid classes. Our findings are in line with a pediatric study of hypercholesterolemia, in which similar nuclear magnetic resonance metabolite profiles (including lipoprotein parameters and circulating fatty acids) were seen for FH and for continuous LDL-C measures in healthy children.⁴¹ These results support the hypothesis that hyperlipidemias with family history and population-ascertained hyperlipidemias have similar, overlapping, and heterogeneous pathophysiological features. Our results are also reassuring for studies that combine familial and population-based hyperlipidemic samples to increase statistical power.

Although we present the most comprehensive characterization of CAD risk and circulating lipid species in common hyperlipidemias with family history to date, our study has limitations. Although we were unable to observe significant differences in CAD risk caused by hyperlipidemic family history, the large CIs in the family samples do not preclude their possibility. Careful exclusion of individuals with comorbidities or using lipid-lowering medication reduced our sample size but enabled more robust analyses. We could not perform detailed analyses on individuals with FH as the original study protocol led to their exclusion from further ascertainment. Clinical ascertainment was based on 90th population lipid percentiles; different cutoffs have also been used in other family studies. Some of the individuals surveyed in population cohorts might, in fact, have a family history of hyperlipidemia, including FH, as we could not fully rule out such cases. It is also unclear how well our results can be generalized to other populations than Finns. The field of lipidomics is still relatively young, and concerns have been raised about the replicability of individual lipidomics platforms. The platform used herein overcomes these problems by using direct infusion mass spectrometry for high-throughput screening studies. The similarity of lipidomic profiles between the 2 independent cohorts also supports the replicability of the platform.

Furthermore, the lipid species included in our analyses are heritable and associated with both known and novel genetic lipid loci with similar effect sizes in the 2 cohorts.⁴² We excluded poorly captured lipid species from the analyses; future advances in lipidomics technology might enable their detection. The blood samples from the hyperlipidemic families were obtained after overnight fasting, whereas participants in the FINRISK population study were advised to fast for 4 hours before the examination and avoid heavy meals earlier during the day. In this light, the similarity of lipidomic profiles between the cohorts becomes even more striking. Moreover, recent recommendations support routine use of nonfasting blood samples for the assessment of plasma lipid profiles.⁴³

In conclusion, our results highlight the similarity between hyperlipidemias with family history and population-based hyperlipidemias in terms of both CAD risk and detailed lipidomic profiles. Except for FH, our results do not support different screening for sporadically discovered cases and those with a family history of hyperlipidemia. Additional work is needed to confirm the validity of this hypothesis in clinical settings.

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Disclosures

Dr Gerl is an employee of Lipotype GmbH. Dr Klose is a shareholder and employee of Lipotype GmbH. Dr Simons is a shareholder and chief executive officer of Lipotype GmbH. Dr Surma is a shareholder of Lipotype GmbH and an employee of Polish Center for Technology Development (PORT). This does not alter the authors' adherence to all policies on sharing data and materials. The remaining authors have no disclosures to report.

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SUPPLEMENTAL MATERIAL

1

2 **Data S1. Supplemental Methods**

3 **Subjects and clinical measurements**

4 The Finnish hyperlipidemia families included in this study (74 families, $n = 1,445$ individuals with
5 LDL-C and TG measurements) were identified as part of The European Multicenter Study on Familial
6 Dyslipidemias in Patients with Premature Coronary Heart Disease (EUFAM) as reported previously.^{1,2}
7 The probands had premature CAD and high levels of total cholesterol, TGs, or both ($\geq 90^{\text{th}}$ Finnish age-
8 and sex-specific population percentile), or low HDL-C levels ($\leq 10^{\text{th}}$ percentile). Initial recruitment
9 aimed to identify families with Familial Combined Hyperlipidemia (elevation of TC and/or TGs in at
10 least two family members including the proband) or families with aggregation of low HDL-C. To
11 exclude families with classic familial hypercholesterolemia (FH), probands were screened with an in-
12 house functional low-density lipoprotein receptor (LDLR) test similar to a test developed by Cuthbert
13 and colleagues; further ascertainment of these families not pursued.³ Founder mutations in LDLR have
14 been estimated to explain most (approximately 80%) of FH cases in Finland.⁴ Genotyping and
15 imputation did not identify such FH mutations in the members of the remaining families.⁵

16 For the present study, designation of “high LDL-C with family history” or “high TGs with
17 family history” was made if at least two first-degree relatives of each other had LDL-C or TG levels,
18 respectively, that were $> 90^{\text{th}}$ age- and sex-specific Finnish 1997 population percentiles (Supplemental
19 Table 1). All other relatives meeting the same lipid criteria within the pedigrees were also classified as
20 affected by the same type of hyperlipidemia with family history. A pedigree was designated as being
21 characterized by both types of hyperlipidemias if the criteria for both designations were simultaneously
22 fulfilled (Supplemental Figure 1). Individuals with known diabetes, hepatic or renal disease, hypo- or
23 hyperthyroidism, pregnancy, or malignancies did not contribute to establishing family history of
24 hyperlipidemia and were excluded from all analyses.

1 Samples from the Finnish National FINRISK study were used as a Finnish population-based
2 comparison group. The National FINRISK Study is a population survey conducted every 5 years since
3 1972.² Collections from the 1992, 1997, 2002, 2007, and 2012 surveys are stored in the National Institute
4 for Health and Welfare (THL) biobank. All available individuals from the 1992-2002 surveys ($n =$
5 19,644 individuals) without CAD at baseline and who passed exclusion criteria were used to study the
6 incidence of coronary artery disease associated with hyperlipidemias, and samples from the FINRISK
7 2012 cohort underwent lipidomic profiling ($n = 1,141$ individuals, 897 of whom passed exclusion
8 criteria). Individuals with known diabetes, pregnancy or cancer were excluded from the analyses.
9 Individuals in all FINRISK cohorts were classified as being affected or unaffected by high LDL-C and
10 high TGs based on the same lipid thresholds as in the EUFAM study.

11 For the EUFAM families, venous serum samples were obtained after an overnight fast and
12 measurements were obtained as described.⁵ Participants in the FINRISK population study were advised
13 to fast for four hours before the examination and avoid heavy meals earlier during the day, and
14 measurements were obtained from plasma samples as described.² In addition to those with chronic
15 diseases and pregnancy, individuals known to use lipid-lowering or estrogen medication were excluded
16 from the lipidomic analyses.

17 **Registry data**

18 Tracking of incident CAD and CVD diagnoses was based on the National Finnish Hospital Discharge
19 Register and the National Causes-of-Death Register, whose diagnoses have been previously validated.⁶

20 ⁷ The endpoint of incident CHD was defined as the first occurrence of fatal or nonfatal myocardial
21 infarction (International Classification of Diseases [ICD]-10 codes I20.0 or I21-22, ICD-9 codes 410 or
22 411.0, or ICD-8 codes 410 or 411.0 for hospital discharge; or ICD-10 I21-25, I46, R96, or R98, ICD-9
23 410-414 or 798 [excluding 7980A], or ICD-8 410-414 or 798 for main cause-of-death) or cardiac
24 revascularization (percutaneous transluminal angioplasty or coronary artery bypass graft surgery).
25 Similar to a previous study, the endpoint of incident CVD additionally included stroke (ICD-10 codes
26 I61 or I63-64 [excluding code I63.6 corresponding to subarachnoid hemorrhage]; ICD-9 codes 431,

1 433.0, 433.1, 433.9, 434.0, 434.1, 434.9, or 436; or ICD-8 codes 431 [excluding codes 431.01 and
2 431.91 of the Finnish adaptation of ICD-8], 433, 434, or 436 for hospital discharge or main cause-of-
3 death).⁸

4 **Lipidomics measurements**

5 Lipidomics measurements were performed for the EUFAM family samples in two batches (228 and 322
6 individuals), and for the FINRISK population samples in a single batch. Plasma and serum lipids were
7 extracted with methyl tert-butyl ether/methanol (7:2, V:V) as in Matyash et al.⁹ Plasma was diluted 50-
8 fold with 150 mM ammonium bicarbonate (in water). For lipid extraction, an equivalent of 1 μ L of
9 undiluted plasma was used. Internal standards were pre-mixed with the organic solvents mixture. The
10 internal standard mixture contained: cholesterol D6, cholesteryl ester 20:0, ceramide 18:1;2/17:0,
11 diacylglyceride 17:0/17:0, phosphatidylcholine 17:0/17:0, phosphatidylethanolamine 17:0/17:0,
12 lysophosphatidylcholine 12:0, lysophosphatidylethanolamine 17:1, triacylglyceride 17:0/17:0/17:0 and
13 sphingomyelin 18:1;2/12:0. After extraction, the organic phase was transferred to an infusion plate and
14 dried in a speed vacuum concentrator. Dried extract was re-suspended in 7.5 mM ammonium acetate in
15 chloroform/methanol/propanol (1:2:4, vol/vol/vol). All liquid handling steps were performed using
16 Hamilton Robotics STARlet robotic platform with the Anti Droplet Control feature for organic solvents
17 pipetting.

18 Samples were analyzed by direct infusion in a QExactive mass spectrometer (Thermo
19 Scientific) equipped with a TriVersa NanoMate ion source (Advion Biosciences). Samples were
20 analyzed in both positive and negative ion modes with a resolution of $R_{m/z=200}=280000$ for MS and
21 $R_{m/z=200}=17500$ for MSMS experiments, in a single acquisition. MSMS was triggered by an inclusion
22 list encompassing corresponding MS mass ranges scanned in 1 Da increments. Both MS and MSMS
23 data were combined to monitor CE, DAG and TAG ions as ammonium adducts; PC, PC O-, as acetate
24 adducts; and PE, PE O- and PI as deprotonated anions. MS only was used to monitor LPE as
25 deprotonated anion; Cer, SM and LPC as acetate adducts and cholesterol as ammonium adduct.

1 Data were analyzed with in-house developed lipid identification software based on
2 LipidXplorer.^{10,11} Data post-processing and normalization were performed using an in-house developed
3 data management system. Only lipid identifications with a signal-to-noise ratio >5, and a signal intensity
4 5-fold higher than in corresponding blank samples were considered for further data analysis.
5 Reproducibility was assessed by the inclusion of reference plasma samples (8 reference samples for
6 EUFAM and 3 reference samples for FINRISK) per 96 well plate. Data were corrected for batch and
7 drift effects. Median coefficient of variation was <10% across all batches.

8 A total of 230 lipid species were successfully detected in both the EUFAM and FINRISK 2012
9 cohorts, with detection rates (proportion of samples with successful quantification) between 9.7-100%.
10 Among these, 151 species were detected in at least 80% of both EUFAM and FINRISK samples and
11 were included in the subsequent analyses. The median absolute concentrations of the analyzed lipid
12 species are presented separately for the family and population cohorts in Supplemental Table 5.
13 SwissLipids names and ID codes are presented for each of the 151 lipid species in Supplemental Table
14 6.¹² Right-skewed lipidomics measures (skewness > 1 in the FINRISK population cohort) were natural
15 logarithm transformed prior to analyses. Values were then normalized using mean and standard
16 deviation values derived from the FINRISK population cohort. Additionally, we calculated weighted
17 class-specific saturation averages for each subject using the following formula: $1*p_1 + 2*p_2 + \dots + n*p_n$
18 (where p_n = the concentration of lipid species with n double bonds divided by the total concentration of
19 all species belonging to the class).

20 **Genotyping and imputation**

21 To assess the association of known genetic lipid loci with the circulating lipid species, we genotyped
22 and imputed the EUFAM and FINRISK samples using several arrays: the HumanCoreExome BeadChip,
23 the Human610-Quad BeadChip, the Affymetrix6.0, and the Infinium HumanOmniExpress (Illumina
24 Inc., San Diego, CA, USA). Genotype calls were generated together with other available data sets using
25 zCall at the Institute for Molecular Medicine Finland (FIMM). After quality control, the samples were
26 phased using SHAPEIT (version 2)¹³ and imputed with IMPUTE (version 2.3.1)¹⁴. We used a combined

1 reference panel based on 1000 Genomes Phase I integrated haplotypes produced using SHAPEIT
2 (version 2) release on June 2014 and an in-house reference panel from 1941 whole genome sequenced
3 Finnish individuals from the FINRISK and Health 2000 population cohorts.¹⁵ We successfully
4 genotyped or imputed 87 lead variants associated with LDL-C and 74 lead variants associated with TGs
5 in published genome-wide association studies.¹⁶⁻¹⁸

6 **Statistical analyses**

7 To assess the risk of incident coronary artery disease associated with the hyperlipidemias, we used Cox
8 proportional hazards models stratified by sex and excluding individuals with prevalent CAD to estimate
9 hazard ratios (HR) for incident CAD events. We confirmed the validity of Cox proportional hazards
10 assumptions using the *cox.zph* function in R.

11 We used linear mixed models to estimate the association between lipidomic parameters
12 (concentrations of lipid species or weighted saturation averages) and the other parameter of interest
13 (hyperlipidemia status, continuous lipid measurement, or genotype) as implemented in MMM (version
14 1.01).¹⁹ Transformed lipid species values (or weighted saturation averages) were used as the outcomes,
15 and hyperlipidemia status, age, age², and sex were used as fixed effect covariates. We first assessed both
16 cohorts (the EUFAM family cohort and the FINRISK population cohort) separately, and then together
17 by including an interaction term between cohort and hyperlipidemia status. We examined the
18 independent effects of LDL-C and TG levels by using transformed lipid species as the outcomes and
19 LDL-C, log(*TGs*), age, age², and sex as fixed effect covariates. Because the lipid species had been
20 quantified in two batches for the EUFAM cohort, we performed all EUFAM analyses separately for
21 both batches, and combined the results using fixed effects inverse-variance weighted meta-analysis as
22 implemented in the R package ‘metafor’. P-values were calculated using Wald test.

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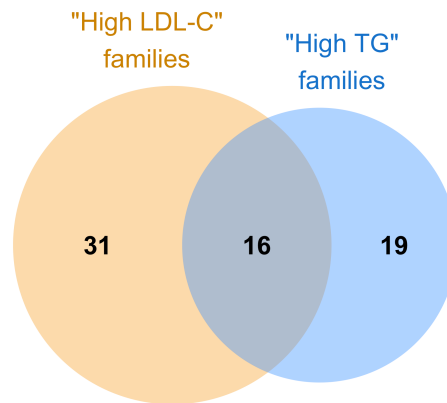
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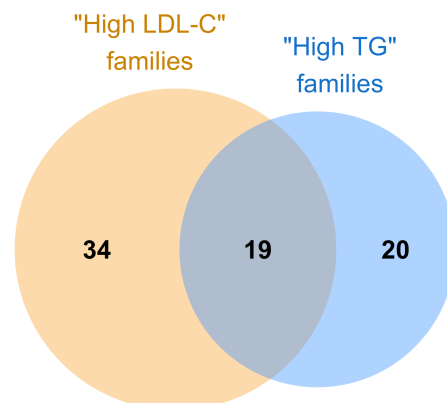
1 Supplemental Figures

2 Figure S1. Overlap of families with family histories of high LDL-C and high TGs.

A. Families included in the analysis of incident CAD risk



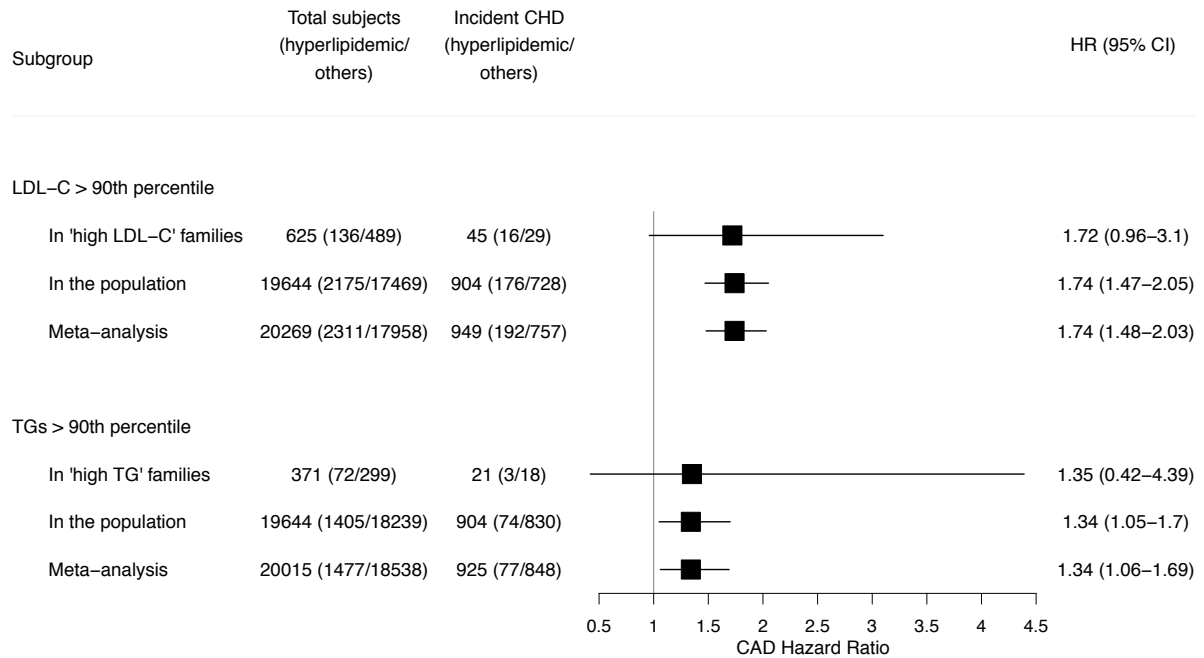
B. Families included in the analysis of detailed lipidomic profiles



3

4 Designation of high LDL-C with family history or high TGs with family history was made if at least
5 two first-degree relatives of each other had LDL-C or TG levels, respectively, that were $\geq 90^{\text{th}}$ age- and
6 sex-specific Finnish 1997 population percentiles. A pedigree was designated as being affected by both
7 high LDL-C with family history and high TGs with family history if the criteria for both designations
8 were simultaneously fulfilled. The diagrams are presented separately for the set of families included in
9 the analysis of incident CAD risk and B) the families included in the analysis of detailed lipidomic
10 profiles. *LDL-C = low-density lipoprotein cholesterol, TG = triglyceride.*

Figure S 2. Risk of incident CAD in hyperlipidemias with family history and population-ascertained hyperlipidemias, adjusted by lipid lowering medication usage and smoking.

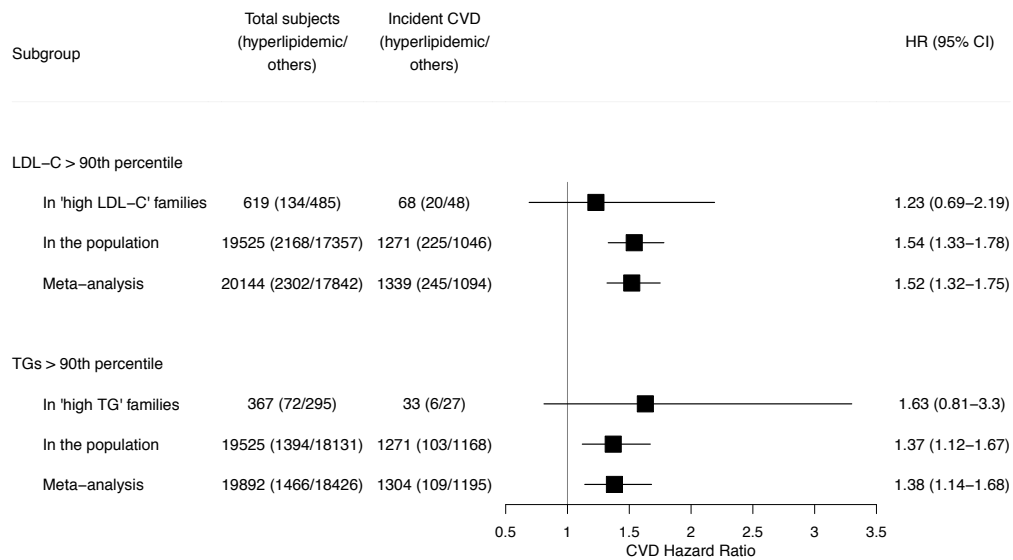


4

5 The risk of incident coronary artery disease (CAD) was estimated with Cox proportional hazards models
 6 similarly to Figure 1. Smoking and use of lipid lowering medication at baseline were included as
 7 additional covariates.

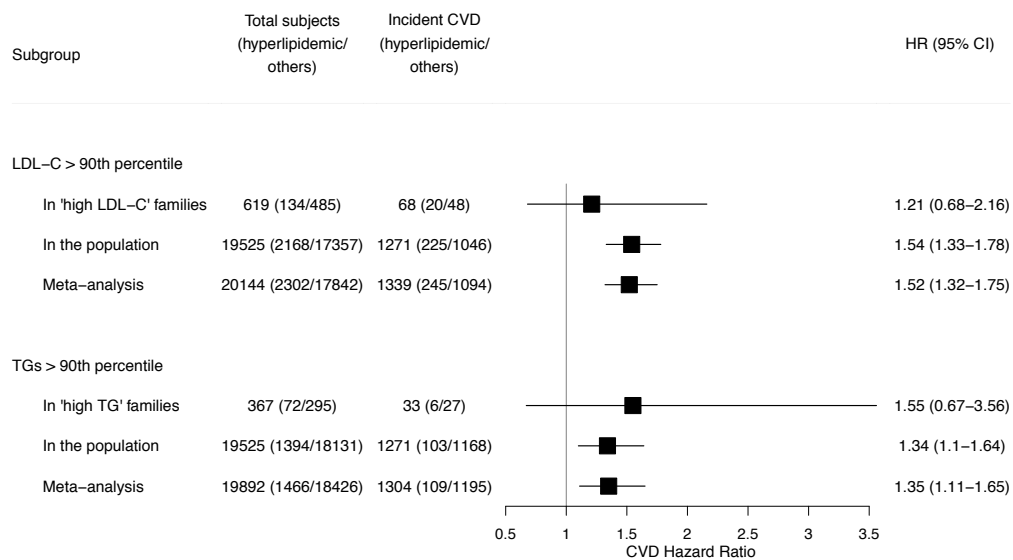
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1 **Figure S3. A. Risk of incident CVD in hyperlipidemias with family history and**
 2 **population-ascertained hyperlipidemias**



3

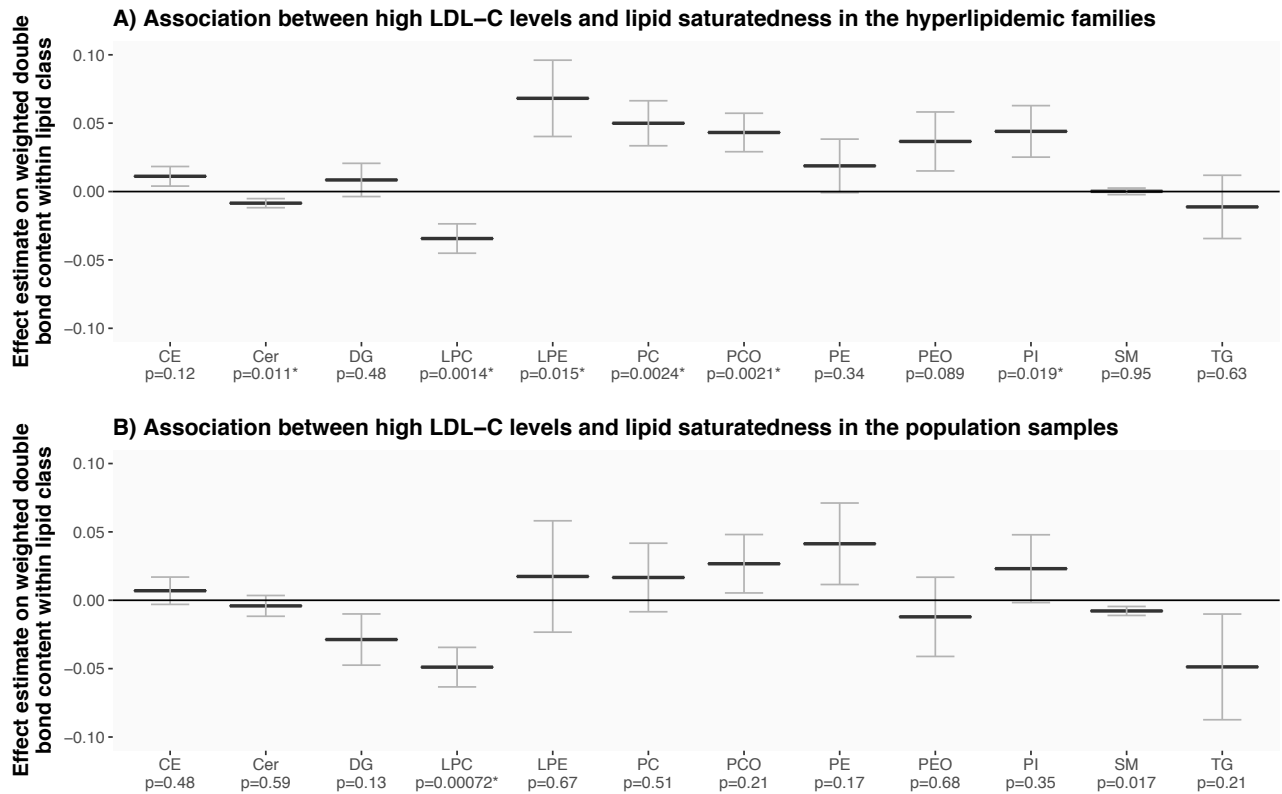
4 **B. Risk of incident CVD in hyperlipidemias with family history and population-ascertained**
 5 **hyperlipidemias, adjusted for lipid lowering medication usage and smoking.**



6

7 Panel A: The risk of incident cardiovascular disease (CVD) was estimated with Cox proportional
 8 hazards models similarly to Figure 1. Panel B: Smoking and use of lipid lowering medication at baseline
 9 were included as additional covariates.

1 **Figure S4. Association of high LDL-C status and weighted saturation averages**
 2 **within each class.**

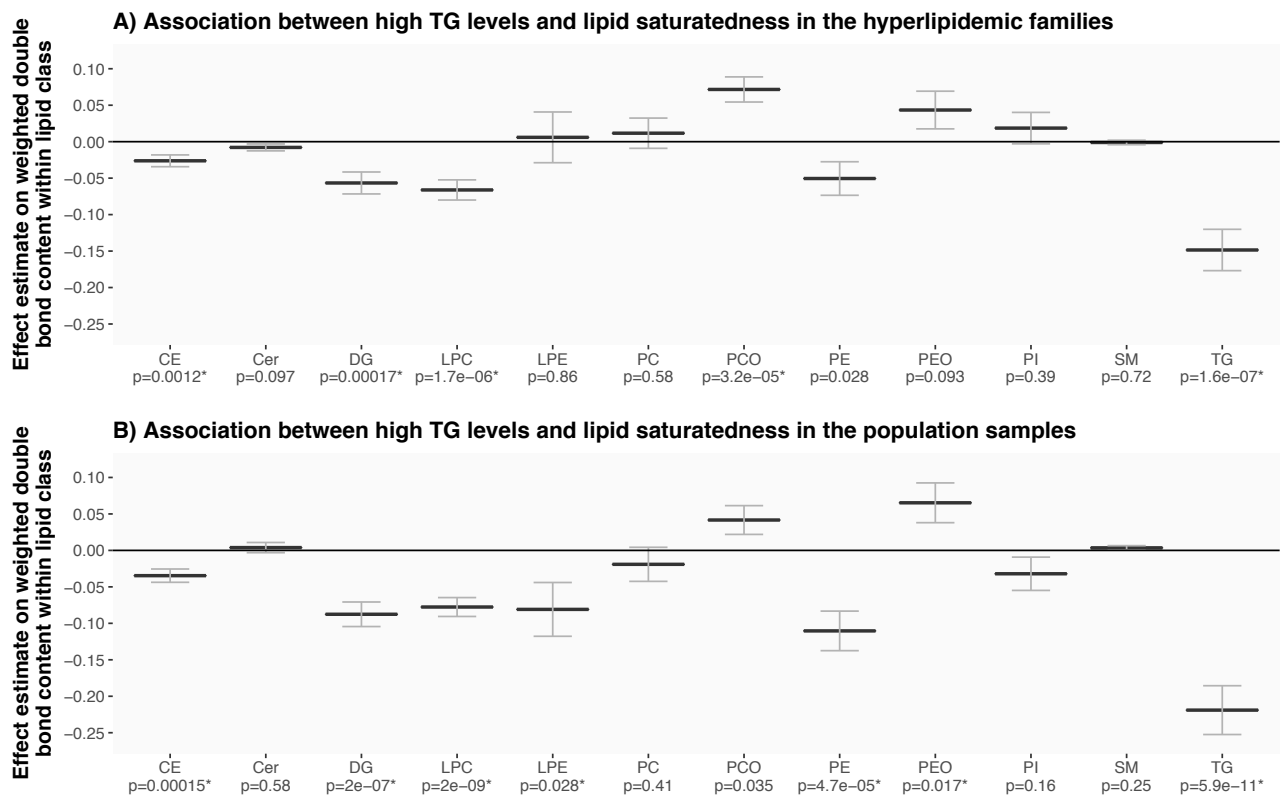


3
 4 The associations were estimated separately A) in “high LDL-C” families (total $n = 463$ individuals) and
 5 B) in the population samples (total $n = 897$ individuals). Negative effect estimates correspond to
 6 increased average saturation, and positive effect estimates correspond to decreased average saturation
 7 (increased unsaturation). Statistically significant effects at 5% FDR are marked with an asterisk (*). *Cer*
 8 = *ceramide*, *DG* = *diacylglyceride*, *FDR* = *false detection rate*, *LDL-C* = *low-density lipoprotein*
 9 *cholesterol*, *LPC* = *lysophosphatidylcholine*, *LPE* = *lysophosphatidylethanolamine*, *PC* =
 10 *phosphatidylcholine*, *PCO* = *phosphatidylcholine-ether*, *PE* = *phosphatidylethanolamine*, *PEO* =
 11 *phosphatidylethanolamine-ether*, *PI* = *phosphatidylinositol*, *CE* = *cholesteryl ester*; *SM* =
 12 *sphingomyelin*, *ST* = *sterol*, *TG* = *triacylglyceride*.

13

1 **Figure S5. Association of high TG status and weighted saturation averages within each class.**

2



3

4 The associations were estimated separately A) in “high TG” families (total $n = 287$ individuals) and B)
 5 in the population (total $n = 897$ individuals). Negative effect estimates correspond to increased average
 6 saturation, and positive effect estimates correspond to decreased average saturation (increased
 7 unsaturation). Statistically significant effects at 5% FDR are marked with an asterisk (*). *Cer* =
 8 *ceramide*, *DG* = *diacylglyceride*, *FDR* = *false detection rate*, *LDL-C* = *low-density lipoprotein*
 9 *cholesterol*, *LPC* = *lysophosphatidylcholine*, *LPE* = *lysophosphatidylethanolamine*, *PC* =
 10 *phosphatidylcholine*, *PCO* = *phosphatidylcholine-ether*, *PE* = *phosphatidylethanolamine*, *PEO* =
 11 *phosphatidylethanolamine-ether*, *PI* = *phosphatidylinositol*, *CE* = *cholesteryl ester*; *SM* =
 12 *sphingomyelin*, *ST* = *sterol*, *TG* = *triacylglyceride*.

13

Supplemental Tables

Table S1. Sex- and age-specific 90th population percentiles for LDL-C and TGs based on the FINRISK 1997 cohort.

Sex	Age	90 th percentile for LDL-C (mmol/l)	90 th percentile for TGs (mmol/l)
Male	25	4,25	2,27
	30	4,27	2,79
	35	4,51	2,98
	40	4,76	3,36
	45	4,79	3,40
	50	4,86	2,90
	55	4,79	3,09
	60	4,76	3,01
Female	25	3,93	1,56
	30	3,86	1,75
	35	4,03	1,68
	40	4,18	1,88
	45	4,59	1,93
	50	4,65	2,33
	55	5,09	2,49
	60	5,12	2,70

Individuals with known diabetes, pregnancy or cancer were excluded prior to estimation of 90th percentile values. *LDL-C* = low-density lipoprotein cholesterol, *TGs* = triglycerides.

Table S2. Clinical and metabolic characteristics of the study individuals included in the analyses of incident CAD risk.

	EUFAM (n = 755)								FINRISK (n = 19,644)								Effect of "high LDL-C" status in EUFAM vs. FINRISK	Effect of "high TG" status in EUFAM vs. FINRISK
	High LDL-C families (n = 47)				High TG families (n = 35)													
	All	Affected by High LDL-C	Unaffected by High LDL-C	p-value	Affected by High TGs	Unaffected by High TGs	p-value	All	Affected by High LDL-C	Unaffected by High LDL-C	p-value	Affected by High TGs	Unaffected by High TGs	p-value	p-value	p-value		
n (male/female)	755 (347/408)	136 (67/69)	489 (228/261)		72 (23/49)	299 (137/162)		19,644 (9,026/10,618)	2,175 (1,102/1,073)	17,469 (7,924/9,545)		1,405 (581/824)	18,239 (8,445/9,794)					
Age (years)	40.0 ± 13.9	43.7 ± 12.4	39.2 ± 14.0	0.0014	37.1 ± 14.1	40.6 ± 14.1	0.07	46.1 ± 12.8	46.7 ± 12.3	46.0 ± 12.9	0.017	44.4 ± 12.6	46.2 ± 12.8	7.6e-07	0.0047	0.37		
BMI (kg/m ²)	25.5 ± 5.0	26.5 ± 4.7	25.2 ± 4.9	0.03	27.3 ± 4.5	25.4 ± 4.8	7e-07	26.1 ± 5.3	27.0 ± 5.1	25.9 ± 5.3	1.2e-26	28.5 ± 5.9	25.9 ± 5.2	5.5e-144	0.63	0.56		
LDL-C (mmol/l)	3.6 ± 1.0	5.1 ± 0.7	3.2 ± 0.8	3.9e-135	3.7 ± 1.0	3.4 ± 1.0	1.2e-05	3.5 ± 1.0	5.1 ± 0.7	3.3 ± 0.8	<5e-324	3.6 ± 1.0	3.5 ± 0.9	1.8e-11	0.026	0.033		
TGs (mmol/l)	1.4 ± 0.9	1.7 ± 1.0	1.3 ± 0.7	2.2e-10	2.8 ± 1.4	1.2 ± 0.6	6.1e-87	1.3 ± 0.8	1.6 ± 0.9	1.3 ± 0.7	1.8e-86	3.0 ± 1.2	1.2 ± 0.7	<5e-324	0.15	0.32		
TC (mmol/l)	5.6 ± 1.2	7.1 ± 0.9	5.2 ± 0.9	6.6e-106	6.1 ± 1.1	5.3 ± 1.1	7.3e-15	5.5 ± 1.1	7.2 ± 0.8	5.3 ± 0.9	<5e-324	6.1 ± 1.1	5.5 ± 1.0	3.2e-155	0.079	0.21		
HDL-C (mmol/l)	1.4 ± 0.4	1.3 ± 0.4	1.4 ± 0.4	0.0013	1.2 ± 0.4	1.4 ± 0.4	3.8e-08	1.5 ± 0.4	1.4 ± 0.4	1.5 ± 0.4	2.3e-10	1.2 ± 0.4	1.5 ± 0.4	9.3e-178	0.22	0.99		

Values are presented as mean ± interquartile range for TGs, BMI, and waist circumference, and mean ± standard deviation for all other variables. A subset of the families fulfilled criteria for both “high LDL-C with family history” and “high TGs with family history” and were thus included in both analysis groups (Supplemental Figure 1.A.). P-values for between-group comparisons were calculated using Wald test by a linear mixed model correcting for genetic sample relatedness. Sex and age were used as other fixed effect covariates in addition to the group variable except when age was used as the outcome. *BMI* = *Body Mass Index*, *HDL-C* = *high-density lipoprotein cholesterol*, *LDL-C* = *low-density lipoprotein cholesterol*, *TGs* = *triglycerides*, *TC* = *total cholesterol*.

Table S3. Risk of incident CAD or CVD in hyperlipidemias with family history and population-ascertained hyperlipidemias.

Outcome	Hyperlipidemia type	Covariates	HR in hyperlipidemic families	HR in the population	<i>p</i> -value for between-cohort difference	Meta-analysis HR
CAD	High LDL-C	None	1.71 (0.94-3.10)	1.74 (1.48-2.05)	0.84	1.74 (1.48-2.04)
		Lipid-lowering therapy + Smoking	1.72 (0.96-3.10)	1.74 (1.47-2.05)	0.73	1.74 (1.48-2.03)
		Lipid-lowering therapy + Smoking + BMI	1.83 (1.02-3.30)	1.76 (1.49-2.07)	0.92	1.76 (1.50-2.07)
	High TGs	None	1.35 (0.52-3.51)	1.38 (1.09-1.75)	0.82	1.38 (1.09-1.74)
		Lipid-lowering therapy + Smoking	1.35 (0.42-4.39)	1.34 (1.05-1.70)	0.59	1.34 (1.06-1.69)
		Lipid-lowering therapy + Smoking + BMI	1.67 (0.60-4.65)	1.16 (0.91-1.48)	0.75	1.18 (0.93-1.50)
CVD	High LDL-C	None	1.23 (0.69-2.19)	1.54 (1.33-1.78)	0.45	1.52 (1.32-1.75)
		Lipid-lowering therapy + Smoking	1.21 (0.68-2.16)	1.54 (1.33-1.78)	0.42	1.52 (1.32-1.75)
		Lipid-lowering therapy + Smoking + BMI	1.33 (0.74-2.38)	1.54 (1.33-1.79)	0.59	1.53 (1.33-1.76)
	High TGs	None	1.63 (0.81-3.30)	1.37 (1.12-1.67)	0.74	1.38 (1.14-1.68)
		Lipid-lowering therapy + Smoking	1.55 (0.67-3.56)	1.34 (1.10-1.64)	0.98	1.35 (1.11-1.65)
		Lipid-lowering therapy + Smoking + BMI	1.98 (0.98-3.98)	1.17 (0.95-1.45)	0.81	1.23 (1.00-1.50)

The risk of incident CAD or CVD was estimated with Cox proportional hazards models similarly to Figure 1. Additional models included adjustment for selected covariates.

Table S4. Clinical and metabolic characteristics of the study individuals included in the analyses of circulating lipidomics profiles.

	EUFAM (n = 550)							FINRISK (n = 897)							Effect of "high LDL-C" status in EUFAM vs. FINRISK	Effect of "high TG" status in EUFAM vs. FINRISK
	High LDL-C families (n = 53)			p-value	High TG families (n = 39)			All	Affected by High LDL-C	Unaffected by High LDL-C	p-value	Affected by High TGs	Unaffected by High TGs	p-value		
	All	Affected by High LDL-C	Unaffected by High LDL-C		Affected by High TGs	Unaffected by High TGs										
n (male/female)	550 (276/274)	105 (54/51)	358 (178/180)		64 (30/34)	223 (108/115)		897 (399/498)	56 (27/29)	841 (372/469)		65 (34/31)	832 (365/467)			
Age (years)	39.5 ± 14.0	41.8 ± 13.7	39.2 ± 14.0	0.11	40.3 ± 13.3	39.0 ± 14.5	0.63	48.3 ± 13.7	49.0 ± 15.4	48.2 ± 13.6	0.61	44.6 ± 12.2	48.6 ± 13.8	0.0054	0.36	0.039
BMI (kg/m ²)	25.6 ± 4.3	26.1 ± 4.2	25.3 ± 4.0	0.00054	28.1 ± 7.7	25.5 ± 3.4	0.051	26.0 ± 5.4	27.9 ± 6.2	25.9 ± 5.3	0.0051	29.1 ± 6.1	25.7 ± 5.3	1.6e-10	0.41	0.46
Waist circumference (cm)	86.9 ± 12.8	88.4 ± 11.0	85.7 ± 11.0	0.0034	92.5 ± 19.0	88.0 ± 15.0	0.011	89.3 ± 19.0	95.1 ± 16.1	88.9 ± 19.0	0.0014	99.1 ± 16.0	88.6 ± 18.4	2.5e-13	0.38	0.23
LDL-C (mmol/l)	3.6 ± 1.1	5.2 ± 0.8	3.2 ± 0.8	3.7e-120	3.9 ± 1.3	3.5 ± 1.1	4.2e-05	3.3 ± 0.9	5.3 ± 1.1	3.2 ± 0.7	8.8e-113	3.5 ± 1.4	3.3 ± 0.9	0.081	0.0019	0.38
TGs (mmol/l)	1.5 ± 0.9	1.8 ± 1.1	1.4 ± 0.7	2e-06	3.6 ± 1.8	1.2 ± 0.6	3.4e-94	1.3 ± 0.7	1.6 ± 1.0	1.3 ± 0.7	0.00074	3.5 ± 1.9	1.1 ± 0.6	8.9e-117	0.52	0.11
TC (mmol/l)	5.6 ± 1.2	7.0 ± 1.0	5.2 ± 1.0	1.3e-75	6.6 ± 1.4	5.3 ± 1.1	1.9e-21	5.4 ± 1.1	7.5 ± 1.2	5.3 ± 0.9	2e-85	6.3 ± 1.5	5.3 ± 1.0	1.9e-15	0.00044	0.48
HDL-C (mmol/l)	1.3 ± 0.4	1.2 ± 0.3	1.4 ± 0.4	0.00095	1.0 ± 0.3	1.3 ± 0.4	5.4e-12	1.5 ± 0.4	1.5 ± 0.4	1.5 ± 0.4	0.5	1.2 ± 0.3	1.5 ± 0.4	3.6e-09	0.2	0.97

Values are presented as mean ± interquartile range for TGs and BMI, and mean ± standard deviation for all other variables. A subset of the families fulfilled criteria for both “high LDL-C with family history” and “high TGs with family history” and were thus included in both analysis groups (Supplemental Figure 1.B.). P-values for between-group comparisons were calculated using Wald test by a linear mixed model correcting for genetic sample relatedness. Sex and age were used as other fixed effect covariates in addition to the group variable except when age was used as the outcome. *BMI = Body Mass Index, HDL-C = high-density lipoprotein cholesterol, LDL-C = low-density lipoprotein cholesterol, TGs = triglycerides, TC = total cholesterol, WC = waist circumference.*

Table S5. Median concentrations of the 151 lipid species in the family and population cohorts.

Species	Median concentration (pmols/mcL) in the hyperlipidemic families	Median concentration (pmols/mcL) in the population	Species	Median concentration (pmols/mcL) in the hyperlipidemic families	Median concentration (pmols/mcL) in the population	Species	Median concentration (pmols/mcL) in the hyperlipidemic families	Median concentration (pmols/mcL) in the population
Cholesterol	1900 ± 580	1600 ± 530	PC(16:0;0_18:3;0)	10 ± 5.6	8.8 ± 5.4	PCO(18:2;0/18:1;0)	0.44 ± 0.29	0.46 ± 0.28
CE(14:0;0)	35 ± 21	28 ± 16	PC(16:0;0_20:1;0)	1.1 ± 0.61	1.1 ± 0.57	PCO(18:2;0/18:2;0)	2.4 ± 1.1	2.4 ± 1.2
CE(15:0;0)	8.8 ± 5.1	8 ± 3.7	PC(16:0;0_20:2;0)	9 ± 4.3	7.9 ± 3.4	SM(32:1;2)	7.9 ± 3	7.7 ± 2.9
CE(16:0;0)	430 ± 170	370 ± 120	PC(16:0;0_20:3;0)	63 ± 34	53 ± 33	SM(34:0;2)	1.7 ± 0.84	1.8 ± 0.72
CE(16:1;0)	190 ± 120	150 ± 100	PC(16:0;0_20:4;0)	140 ± 63	130 ± 68	SM(34:1;2)	75 ± 25	69 ± 20
CE(17:0;0)	7.6 ± 3.8	6.2 ± 2.7	PC(16:0;0_20:5;0)	30 ± 25	33 ± 29	SM(34:2;2)	9.6 ± 3.2	9.2 ± 2.9
CE(17:1;0)	16 ± 8.2	12 ± 5.7	PC(16:0;0_22:4;0)	5.5 ± 2.3	4.6 ± 2.2	SM(36:1;2)	14 ± 4.9	12 ± 4.2
CE(18:0;0)	21 ± 11	16 ± 8.1	PC(16:0;0_22:5;0)	21 ± 9.4	21 ± 11	SM(36:2;2)	6.5 ± 2.5	5.9 ± 2.1
CE(18:1;0)	910 ± 350	770 ± 290	PC(16:0;0_22:6;0)	88 ± 56	82 ± 49	SM(38:1;2)	9.7 ± 3.4	9.5 ± 3.2
CE(18:2;0)	2700 ± 1000	2200 ± 710	PC(16:1;0_18:1;0)	8.1 ± 4.4	7.1 ± 3.5	SM(38:2;2)	3.8 ± 1.4	3.7 ± 1.3
CE(18:3;0)	110 ± 55	88 ± 48	PC(16:1;0_18:2;0)	6.5 ± 3.5	5.7 ± 2.9	SM(40:1;2)	16.6 ± 3	16 ± 5.1
CE(19:1;0)	1.9 ± 0.87	1.8 ± 0.84	PC(17:0;0_18:2;0)	33 ± 15	30 ± 13	SM(40:2;2)	15 ± 5	15 ± 5
CE(20:2;0)	2.6 ± 1.2	2.3 ± 1.2	PC(17:0;0_20:3;0)	7.2 ± 4.3	5.6 ± 3.1	SM(42:2;2)	38 ± 14	36 ± 12
CE(20:3;0)	39 ± 19	30 ± 14	PC(17:0;0_20:4;0)	13 ± 5.9	11 ± 5	Cer(40:1;2)	0.75 ± 0.34	0.66 ± 0.3
CE(20:4;0)	320 ± 140	270 ± 120	PC(18:0;0_18:1;0)	31 ± 16	27 ± 14	Cer(40:2;2)	0.21 ± 0.1	0.17 ± 0.09
CE(20:5;0)	82 ± 74	82 ± 73	PC(18:0;0_18:2;0)	200 ± 81	190 ± 71	Cer(42:1;2)	2 ± 0.93	1.8 ± 0.79
CE(22:6;0)	38 ± 25	34 ± 22	PC(18:0;0_18:3;0)	3.2 ± 2.2	3.3 ± 2.1	Cer(42:2;2)	1.4 ± 0.62	1.2 ± 0.55
DG(16:0;0_18:1;0)	5 ± 4.4	3.1 ± 2.8	PC(18:0;0_20:2;0)	4.1 ± 2.1	3.5 ± 1.6	PI(16:0;0_18:1;0)	1.8 ± 1.3	1.6 ± 1
DG(18:1;0_18:1;0)	7.9 ± 6.6	5.2 ± 4.2	PC(18:0;0_20:3;0)	29 ± 16	25 ± 14	PI(16:0;0_18:2;0)	1.2 ± 0.7	1.2 ± 0.69
DG(18:1;0_18:2;0)	6.6 ± 5	4.6 ± 3	PC(18:0;0_20:4;0)	61 ± 31	58 ± 25	PI(16:0;0_20:4;0)	1.8 ± 0.99	1.7 ± 1
TG(48:0;0)	5.2 ± 8.2	4.6 ± 7.7	PC(18:0;0_20:5;0)	9.9 ± 8.4	12 ± 13	PI(18:0;0_18:1;0)	2.3 ± 1.3	2.1 ± 1.1
TG(48:1;0)	29 ± 38	20 ± 27	PC(18:0;0_22:5;0)	7.1 ± 3.9	6.3 ± 2.9	PI(18:0;0_18:2;0)	4 ± 2	4.1 ± 2.1
TG(48:2;0)	24 ± 28	17 ± 20	PC(18:0;0_22:6;0)	27 ± 18	24 ± 13	PI(18:0;0_20:3;0)	2.6 ± 1.4	2.5 ± 1.3
TG(50:1;0)	66 ± 71	43 ± 53	PC(18:1;0_18:1;0)	23 ± 11	21 ± 8.7	PI(18:0;0_20:4;0)	18 ± 7.8	18 ± 6.6
TG(50:2;0)	110 ± 100	74 ± 75	PC(18:1;0_18:2;0)	62 ± 29	53 ± 23	PI(18:1;0_18:1;0)	0.82 ± 0.51	0.78 ± 0.51
TG(50:3;0)	51 ± 50	36 ± 32	PC(18:1;0_20:3;0)	9.7 ± 5.4	8.5 ± 4.1	PI(18:1;0_18:2;0)	0.66 ± 0.42	0.6 ± 0.27
TG(50:4;0)	15 ± 14	11 ± 9.8	PC(18:1;0_20:4;0)	17 ± 7.1	16 ± 6.9	PI(18:2;0_18:2;0)	0.95 ± 0.49	0.83 ± 0.52
TG(51:2;0)	10 ± 9	7 ± 5.9	PC(18:2;0_18:2;0)	26 ± 14	23 ± 12	PE(16:0;0_18:2;0)	1.6 ± 1.6	1.5 ± 1.3
TG(51:3;0)	6.4 ± 5.3	4.7 ± 3.5	PC(18:2;0_20:4;0)	11 ± 4.3	9.9 ± 4.4	PE(18:0;0_18:2;0)	4.1 ± 3.2	3.5 ± 2.6
TG(52:2;0)	240 ± 210	160 ± 140	PCO(16:0;0/16:0;0)	0.83 ± 0.45	0.64 ± 0.37	PE(18:0;0_20:4;0)	5.4 ± 3.8	4.8 ± 3.1
TG(52:3;0)	240 ± 200	160 ± 130	PCO(16:0;0/16:1;0)	0.7 ± 0.43	0.67 ± 0.57	PE(18:1;0_18:1;0)	0.48 ± 0.43	0.62 ± 0.76
TG(52:4;0)	99 ± 86	75 ± 58	PCO(16:0;0/18:1;0)	1.7 ± 0.7	1.6 ± 0.56	PEO(16:1;0/18:2;0)	1.3 ± 0.75	1.1 ± 0.61
TG(52:5;0)	26 ± 24	21 ± 16	PCO(16:0;0/18:2;0)	3.5 ± 1.6	3.4 ± 1.5	PEO(16:1;0/20:4;0)	3.7 ± 2.3	3.4 ± 2
TG(54:3;0)	64 ± 52	46 ± 37	PCO(16:0;0/20:3;0)	0.83 ± 0.57	0.95 ± 0.47	PEO(18:1;0/18:2;0)	2.3 ± 1.4	1.8 ± 1.1
TG(54:4;0)	60 ± 48	46 ± 35	PCO(16:0;0/20:4;0)	5.5 ± 2.9	5.1 ± 2.4	PEO(18:2;0/18:2;0)	1.6 ± 0.86	1.6 ± 0.82
TG(54:5;0)	43 ± 37	34 ± 27	PCO(16:1;0/16:0;0)	1.9 ± 0.77	1.8 ± 0.79	PEO(18:2;0/20:4;0)	5.7 ± 3.2	5.8 ± 2.9
TG(54:6;0)	25 ± 23	22 ± 17	PCO(16:1;0/18:1;0)	0.32 ± 0.18	0.35 ± 0.22	LPE(16:0;0)	0.56 ± 0.25	0.51 ± 0.22
TG(56:4;0)	3.8 ± 2.8	3 ± 2.1	PCO(16:1;0/18:2;0)	5.3 ± 2.6	5.2 ± 2.3	LPE(18:1;0)	0.52 ± 0.29	0.56 ± 0.37
TG(56:5;0)	10 ± 7	7.7 ± 5.1	PCO(16:1;0/20:3;0)	0.6 ± 0.29	0.57 ± 0.46	LPE(18:2;0)	1 ± 0.56	1.2 ± 0.72
TG(56:6;0)	18 ± 13	15 ± 10	PCO(17:0;0/17:1;0)	0.087 ± 0.047	0.076 ± 0.044	LPE(20:4;0)	0.71 ± 0.33	0.76 ± 0.31
TG(56:7;0)	25 ± 23	22 ± 19	PCO(18:0;0/14:0;0)	2.1 ± 0.74	1.9 ± 0.48	LPE(22:6;0)	0.7 ± 0.35	0.78 ± 0.35
PC(14:0;0_16:0;0)	2.8 ± 2	2.4 ± 1.6	PCO(18:0;0/18:2;0)	0.77 ± 0.44	0.71 ± 0.33	LPC(14:0;0)	1.1 ± 0.58	0.88 ± 0.4
PC(14:0;0_18:1;0)	3.5 ± 2.6	2.9 ± 1.9	PCO(18:0;0/20:4;0)	3.4 ± 1.6	3 ± 1.2	LPC(16:0;0)	72 ± 25	56 ± 17
PC(14:0;0_18:2;0)	3.8 ± 2.3	3.4 ± 1.7	PCO(18:1;0/16:0;0)	0.93 ± 0.37	0.87 ± 0.31	LPC(16:1;0)	1.8 ± 0.83	1.4 ± 0.66
PC(15:0;0_18:2;0)	47 ± 20	44 ± 16	PCO(18:1;0/18:1;0)	0.18 ± 0.099	0.14 ± 0.079	LPC(18:0;0)	18 ± 8.3	14 ± 5.6
PC(16:0;0_16:0;0)	9.5 ± 3.7	9.1 ± 3.4	PCO(18:1;0/18:2;0)	2.2 ± 1.1	2 ± 0.92	LPC(18:1;0)	14 ± 7.4	12 ± 5.2
PC(16:0;0_16:1;0)	12 ± 8.7	9.6 ± 7.6	PCO(18:1;0/20:3;0)	1.2 ± 0.62	0.9 ± 0.48	LPC(18:2;0)	17 ± 11	18 ± 11
PC(16:0;0_17:1;0)	20 ± 12	18 ± 11	PCO(18:1;0/20:4;0)	8.5 ± 2.8	7.6 ± 2.9	LPC(20:3;0)	1 ± 0.53	1 ± 0.5
PC(16:0;0_18:0;0)	30 ± 10	25 ± 10	PCO(18:2;0/16:0;0)	1.2 ± 0.48	1.1 ± 0.44	LPC(20:4;0)	3 ± 1.6	2.8 ± 1.4
PC(16:0;0_18:1;0)	240 ± 110	210 ± 96	PCO(18:2;0/18:0;0)	0.17 ± 0.099	0.16 ± 0.072	LPC(22:6;0)	1.1 ± 0.66	1.2 ± 0.63
PC(16:0;0_18:2;0)	480 ± 180	440 ± 150						

Table S6. SwissLipids names and ID codes for the 151 lipid species included in the analyses of circulating lipidomic profiles.

Species	SwissLipids Name	SwissLipids ID	Species	SwissLipids Name	SwissLipids ID
Cholesterol	cholesterol	SLM:000000287	PC(18:1;0_20:3;0)	Phosphatidylcholine (18:1_20:3)	SLM:000063992
CE(14:0;0)	Sterol ester (27:1/14:0)	SLM:000500342	PC(18:1;0_20:4;0)	Phosphatidylcholine (18:1_20:4)	SLM:000063993
CE(15:0;0)	Sterol ester (27:1/15:0)	SLM:000500343	PC(18:2;0_18:2;0)	Phosphatidylcholine (18:2_18:2)	SLM:000064033
CE(16:0;0)	Sterol ester (27:1/16:0)	SLM:000500346	PC(18:2;0_20:4;0)	Phosphatidylcholine (18:2_20:4)	SLM:000064041
CE(16:1;0)	Sterol ester (27:1/16:1)	SLM:000500345	PCO(16:0;0/16:0;0)	Phosphatidylcholine (O-16:0_16:0)	SLM:000065919
CE(17:0;0)	Sterol ester (27:1/17:0)	SLM:000500347	PCO(16:0;0/16:1;0)	Phosphatidylcholine (O-16:0_16:1)	SLM:000065920
CE(17:1;0)	Sterol ester (27:1/17:1)	n/a	PCO(16:0;0/18:1;0)	Phosphatidylcholine (O-16:0_18:1)	SLM:000065924
CE(18:0;0)	Sterol ester (27:1/18:0)	SLM:000500352	PCO(16:0;0/18:2;0)	Phosphatidylcholine (O-16:0_18:2)	SLM:000065925
CE(18:1;0)	Sterol ester (27:1/18:1)	SLM:000500351	PCO(16:0;0/20:3;0)	Phosphatidylcholine (O-16:0_20:3)	SLM:000065932
CE(18:2;0)	Sterol ester (27:1/18:2)	SLM:000500350	PCO(16:0;0/20:4;0)	Phosphatidylcholine (O-16:0_20:4)	SLM:000065933
CE(18:3;0)	Sterol ester (27:1/18:3)	SLM:000500349	PCO(16:1;0/16:0;0)	Phosphatidylcholine (O-16:1_16:0)	SLM:000065984
CE(19:1;0)	Sterol ester (27:1/19:1)	n/a	PCO(16:1;0/18:1;0)	Phosphatidylcholine (O-16:1_18:1)	SLM:000065989
CE(20:2;0)	Sterol ester (27:1/20:2)	SLM:000500357	PCO(16:1;0/18:2;0)	Phosphatidylcholine (O-16:1_18:2)	SLM:000065990
CE(20:3;0)	Sterol ester (27:1/20:3)	SLM:000500356	PCO(16:1;0/20:3;0)	Phosphatidylcholine (O-16:1_20:3)	SLM:000065997
CE(20:4;0)	Sterol ester (27:1/20:4)	SLM:000500355	PCO(17:0;0/17:1;0)	Phosphatidylcholine (O-17:0_17:1)	n/a
CE(20:5;0)	Sterol ester (27:1/20:5)	SLM:000500354	PCO(18:0;0/14:0;0)	Phosphatidylcholine (O-18:0_14:0)	SLM:000066176
CE(22:6;0)	Sterol ester (27:1/22:6)	SLM:000500361	PCO(18:0;0/18:2;0)	Phosphatidylcholine (O-18:0_18:2)	SLM:000066185
DG(16:0;0_18:1;0)	Diacylglycerol (16:0_18:1)	SLM:000308862	PCO(18:0;0/20:4;0)	Phosphatidylcholine (O-18:0_20:4)	SLM:000066193
DG(18:1;0_18:1;0)	Diacylglycerol (18:1_18:1)	SLM:000309012	PCO(18:1;0/16:0;0)	Phosphatidylcholine (O-18:1_16:0)	SLM:000066244
DG(18:1;0_18:2;0)	Diacylglycerol (18:1_18:2)	SLM:000309013	PCO(18:1;0/18:1;0)	Phosphatidylcholine (O-18:1_18:1)	SLM:000066249
TG(48:0;0)	Triacylglycerol (48:0)	SLM:000308257	PCO(18:1;0/18:2;0)	Phosphatidylcholine (O-18:1_18:2)	SLM:000066250
TG(48:1;0)	Triacylglycerol (48:1)	SLM:000308258	PCO(18:1;0/20:3;0)	Phosphatidylcholine (O-18:1_20:3)	SLM:000066257
TG(48:2;0)	Triacylglycerol (48:2)	SLM:000308259	PCO(18:1;0/20:4;0)	Phosphatidylcholine (O-18:1_20:4)	SLM:000066258
TG(50:1;0)	Triacylglycerol (50:1)	SLM:000308276	PCO(18:2;0/16:0;0)	Phosphatidylcholine (O-18:2_16:0)	SLM:000066309
TG(50:2;0)	Triacylglycerol (50:2)	SLM:000308277	PCO(18:2;0/18:0;0)	Phosphatidylcholine (O-18:2_18:0)	SLM:000066313
TG(50:3;0)	Triacylglycerol (50:3)	SLM:000308278	PCO(18:2;0/18:1;0)	Phosphatidylcholine (O-18:2_18:1)	SLM:000066314
TG(50:4;0)	Triacylglycerol (50:4)	SLM:000308279	PCO(18:2;0/18:2;0)	Phosphatidylcholine (O-18:2_18:2)	SLM:000066315
TG(51:2;0)	Triacylglycerol (51:2)	SLM:000308287	SM(32:1;2)	Sphingomyelin (d32:1)	SLM:000390695
TG(51:3;0)	Triacylglycerol (51:3)	SLM:000308288	SM(34:0;2)	Sphingomyelin (d34:0)	SLM:000390716
TG(52:2;0)	Triacylglycerol (52:2)	SLM:000308298	SM(34:1;2)	Sphingomyelin (d34:1)	SLM:000390714
TG(52:3;0)	Triacylglycerol (52:3)	SLM:000308299	SM(34:2;2)	Sphingomyelin (d34:2)	SLM:000390712
TG(52:4;0)	Triacylglycerol (52:4)	SLM:000308300	SM(36:1;2)	Sphingomyelin (d36:1)	SLM:000390739
TG(52:5;0)	Triacylglycerol (52:5)	SLM:000308301	SM(36:2;2)	Sphingomyelin (d36:2)	SLM:000390737
TG(54:3;0)	Triacylglycerol (54:3)	SLM:000308323	SM(38:1;2)	Sphingomyelin (d38:1)	SLM:000390767
TG(54:4;0)	Triacylglycerol (54:4)	SLM:000308324	SM(38:2;2)	Sphingomyelin (d38:2)	SLM:000390765
TG(54:5;0)	Triacylglycerol (54:5)	SLM:000308325	SM(40:1;2)	Sphingomyelin (d40:1)	SLM:000390797
TG(54:6;0)	Triacylglycerol (54:6)	SLM:000308326	SM(40:2;2)	Sphingomyelin (d40:2)	SLM:000390795
TG(56:4;0)	Triacylglycerol (56:4)	SLM:000308350	SM(42:2;2)	Sphingomyelin (d42:2)	SLM:000390823

TG(56:5;0)	Triacylglycerol (56:5)	SLM:000308351	Cer(40:1;2)	Ceramide (d40:1)	SLM:000391319
TG(56:6;0)	Triacylglycerol (56:6)	SLM:000308352	Cer(40:2;2)	Ceramide (d40:2)	SLM:000391317
TG(56:7;0)	Triacylglycerol (56:7)	SLM:000308353	Cer(42:1;2)	Ceramide (d42:1)	SLM:000391346
PC(14:0;0_16:0;0)	Phosphatidylcholine (14:0_16:0)	SLM:000063559	Cer(42:2;2)	Ceramide (d42:2)	SLM:000391345
PC(14:0;0_18:1;0)	Phosphatidylcholine (14:0_18:1)	SLM:000063564	PI(16:0;0_18:1;0)	Phosphatidylinositol (16:0_18:1)	SLM:000073801
PC(14:0;0_18:2;0)	Phosphatidylcholine (14:0_18:2)	SLM:000063565	PI(16:0;0_18:2;0)	Phosphatidylinositol (16:0_18:2)	SLM:000073802
PC(15:0;0_18:2;0)	Phosphatidylcholine (15:0_18:2)	SLM:000063676	PI(16:0;0_20:4;0)	Phosphatidylinositol (16:0_20:4)	SLM:000073810
PC(16:0;0_16:0;0)	Phosphatidylcholine (16:0_16:0)	SLM:000063724	PI(18:0;0_18:1;0)	Phosphatidylinositol (18:0_18:1)	SLM:000074007
PC(16:0;0_16:1;0)	Phosphatidylcholine (16:0_16:1)	SLM:000063725	PI(18:0;0_18:2;0)	Phosphatidylinositol (18:0_18:2)	SLM:000074008
PC(16:0;0_17:1;0)	Phosphatidylcholine (16:0_17:1)	n/a	PI(18:0;0_20:3;0)	Phosphatidylinositol (18:0_20:3)	SLM:000074015
PC(16:0;0_18:0;0)	Phosphatidylcholine (16:0_18:0)	SLM:000063728	PI(18:0;0_20:4;0)	Phosphatidylinositol (18:0_20:4)	SLM:000074016
PC(16:0;0_18:1;0)	Phosphatidylcholine (16:0_18:1)	SLM:000063729	PI(18:1;0_18:1;0)	Phosphatidylinositol (18:1_18:1)	SLM:000074056
PC(16:0;0_18:2;0)	Phosphatidylcholine (16:0_18:2)	SLM:000063730	PI(18:1;0_18:2;0)	Phosphatidylinositol (18:1_18:2)	SLM:000074057
PC(16:0;0_18:3;0)	Phosphatidylcholine (16:0_18:3)	SLM:000063731	PI(18:2;0_18:2;0)	Phosphatidylinositol (18:2_18:2)	SLM:000074105
PC(16:0;0_20:1;0)	Phosphatidylcholine (16:0_20:1)	SLM:000063735	PE(16:0;0_18:2;0)	Phosphatidylethanolamine (16:0_18:2)	SLM:000067694
PC(16:0;0_20:2;0)	Phosphatidylcholine (16:0_20:2)	SLM:000063736	PE(18:0;0_18:2;0)	Phosphatidylethanolamine (18:0_18:2)	SLM:000067900
PC(16:0;0_20:3;0)	Phosphatidylcholine (16:0_20:3)	SLM:000063737	PE(18:0;0_20:4;0)	Phosphatidylethanolamine (18:0_20:4)	SLM:000067908
PC(16:0;0_20:4;0)	Phosphatidylcholine (16:0_20:4)	SLM:000063738	PE(18:1;0_18:1;0)	Phosphatidylethanolamine (18:1_18:1)	SLM:000067948
PC(16:0;0_20:5;0)	Phosphatidylcholine (16:0_20:5)	SLM:000063739	PEO(16:1;0/18:2;0)	Phosphatidylethanolamine (O-16:1_18:2)	SLM:000069954
PC(16:0;0_22:4;0)	Phosphatidylcholine (16:0_22:4)	SLM:000063745	PEO(16:1;0/20:4;0)	Phosphatidylethanolamine (O-16:1_20:4)	SLM:000069962
PC(16:0;0_22:5;0)	Phosphatidylcholine (16:0_22:5)	SLM:000063746	PEO(18:1;0/18:2;0)	Phosphatidylethanolamine (O-18:1_18:2)	SLM:000070214
PC(16:0;0_22:6;0)	Phosphatidylcholine (16:0_22:6)	SLM:000063747	PEO(18:2;0/18:2;0)	Phosphatidylethanolamine (O-18:2_18:2)	SLM:000070279
PC(16:1;0_18:1;0)	Phosphatidylcholine (16:1_18:1)	SLM:000063782	PEO(18:2;0/20:4;0)	Phosphatidylethanolamine (O-18:2_20:4)	SLM:000070287
PC(16:1;0_18:2;0)	Phosphatidylcholine (16:1_18:2)	SLM:000063783	LPE(16:0;0)	Phosphatidylethanolamine (16:0_0:0)	SLM:000067687
PC(17:0;0_18:2;0)	Phosphatidylcholine (17:0_18:2)	SLM:000063886	LPE(18:1;0)	Phosphatidylethanolamine (18:1_0:0)	SLM:000067947
PC(17:0;0_20:3;0)	Phosphatidylcholine (17:0_20:3)	SLM:000063893	LPE(18:2;0)	Phosphatidylethanolamine (18:2_0:0)	SLM:000067996
PC(17:0;0_20:4;0)	Phosphatidylcholine (17:0_20:4)	SLM:000063894	LPE(20:4;0)	Phosphatidylethanolamine (20:4_0:0)	SLM:000068352
PC(18:0;0_18:1;0)	Phosphatidylcholine (18:0_18:1)	SLM:000063935	LPE(22:6;0)	Phosphatidylethanolamine (22:6_0:0)	SLM:000068676
PC(18:0;0_18:2;0)	Phosphatidylcholine (18:0_18:2)	SLM:000063936	LPC(14:0;0)	Phosphatidylcholine (14:0_0:0)	SLM:000063555
PC(18:0;0_18:3;0)	Phosphatidylcholine (18:0_18:3)	SLM:000063937	LPC(16:0;0)	Phosphatidylcholine (16:0_0:0)	SLM:000063723
PC(18:0;0_20:2;0)	Phosphatidylcholine (18:0_20:2)	SLM:000063942	LPC(16:1;0)	Phosphatidylcholine (16:1_0:0)	SLM:000063777
PC(18:0;0_20:3;0)	Phosphatidylcholine (18:0_20:3)	SLM:000063943	LPC(18:0;0)	Phosphatidylcholine (18:0_0:0)	SLM:000063933
PC(18:0;0_20:4;0)	Phosphatidylcholine (18:0_20:4)	SLM:000063944	LPC(18:1;0)	Phosphatidylcholine (18:1_0:0)	SLM:000063983
PC(18:0;0_20:5;0)	Phosphatidylcholine (18:0_20:5)	SLM:000063945	LPC(18:2;0)	Phosphatidylcholine (18:2_0:0)	SLM:000064032
PC(18:0;0_22:5;0)	Phosphatidylcholine (18:0_22:5)	SLM:000063952	LPC(20:3;0)	Phosphatidylcholine (20:3_0:0)	SLM:000064347
PC(18:0;0_22:6;0)	Phosphatidylcholine (18:0_22:6)	SLM:000063953	LPC(20:4;0)	Phosphatidylcholine (20:4_0:0)	SLM:000064388
PC(18:1;0_18:1;0)	Phosphatidylcholine (18:1_18:1)	SLM:000063984	LPC(22:6;0)	Phosphatidylcholine (22:6_0:0)	SLM:000064712
PC(18:1;0_18:2;0)	Phosphatidylcholine (18:1_18:2)	SLM:000063985			

Table S7. Effect estimates in SD units (\pm SE) and p-values from linear mixed models for each lipid species.

Class	Species	Effect of high LDL-C affection in "high LDL-C" families		Effect of high LDL-C affection in FINRISK		Effect of high TG affection in "high TG" families		Effect of high TG affection in FINRISK		Independent association with LDL-C in EUFAM		Independent association with LDL-C in FINRISK		Independent association with TG in EUFAM		Independent association with TG in FINRISK	
		Effect estimate	p-value	Effect estimate	p-value	Effect estimate	p-value	Effect estimate	p-value	Effect estimate	p-value	Effect estimate	p-value	Effect estimate	p-value	Effect estimate	p-value
ST	Cholesterol	0.83 \pm 0.093	5.4e-19*	0.93 \pm 0.14	7.1e-11*	1 \pm 0.12	1.3e-18*	0.99 \pm 0.13	1.4e-13*	0.33 \pm 0.029	4.2e-31*	0.39 \pm 0.034	7.7e-30*	0.32 \pm 0.029	3.3e-27*	0.25 \pm 0.032	1.3e-14*
CE	CE(14:0;0)	0.64 \pm 0.099	1.3e-10*	0.99 \pm 0.14	2.1e-12*	0.75 \pm 0.12	9.5e-10*	1 \pm 0.13	7.5e-15*	0.24 \pm 0.033	2.7e-13*	0.34 \pm 0.033	1.4e-24*	0.31 \pm 0.034	1e-19*	0.33 \pm 0.031	1.9e-26*
	CE(15:0;0)	0.49 \pm 0.1	1.1e-06*	0.84 \pm 0.14	4.1e-09*	0.42 \pm 0.13	0.0013*	0.26 \pm 0.13	0.051	0.28 \pm 0.036	8.7e-15*	0.32 \pm 0.036	1.3e-18*	0.088 \pm 0.037	0.017*	0.064 \pm 0.034	0.061
	CE(16:0;0)	0.71 \pm 0.078	7.3e-20*	1 \pm 0.14	6.5e-14*	0.81 \pm 0.11	1.4e-13*	0.75 \pm 0.13	5e-09*	0.31 \pm 0.027	7.1e-32*	0.42 \pm 0.033	1.6e-37*	0.26 \pm 0.027	1e-21*	0.2 \pm 0.031	7.9e-11*
	CE(16:1;0)	0.44 \pm 0.1	2.3e-05*	0.2 \pm 0.14	0.15	0.92 \pm 0.13	4.4e-13*	0.65 \pm 0.13	6.3e-07*	0.16 \pm 0.035	8.5e-06*	0.14 \pm 0.036	0.00011*	0.37 \pm 0.036	9.1e-25*	0.26 \pm 0.034	1.6e-14*
	CE(17:0;0)	0.61 \pm 0.097	4.6e-10*	0.85 \pm 0.14	4.2e-09*	0.38 \pm 0.12	0.0021*	0.24 \pm 0.14	0.073	0.3 \pm 0.035	3.4e-17*	0.34 \pm 0.037	2.2e-20*	0.079 \pm 0.036	0.03*	0.022 \pm 0.035	0.53
	CE(17:1;0)	0.62 \pm 0.098	2.9e-10*	1.1 \pm 0.14	6.2e-16*	0.67 \pm 0.13	1e-07*	0.79 \pm 0.13	1.7e-09*	0.28 \pm 0.034	1.2e-16*	0.41 \pm 0.033	1.1e-35*	0.22 \pm 0.035	2.1e-10*	0.24 \pm 0.031	1.8e-14*
	CE(18:0;0)	0.75 \pm 0.099	2.3e-14*	1.3 \pm 0.14	6.8e-21*	0.95 \pm 0.13	3.1e-13*	0.75 \pm 0.13	1.1e-08*	0.32 \pm 0.032	1.8e-23*	0.46 \pm 0.033	4.4e-45*	0.31 \pm 0.032	7.4e-22*	0.21 \pm 0.031	5.2e-12*
	CE(18:1;0)	0.63 \pm 0.089	1.6e-12*	1 \pm 0.14	3.2e-14*	0.77 \pm 0.12	3e-11*	0.71 \pm 0.13	6.1e-08*	0.28 \pm 0.031	1.2e-19*	0.41 \pm 0.033	2.3e-35*	0.26 \pm 0.031	1.7e-16*	0.19 \pm 0.032	2.1e-09*
	CE(18:2;0)	0.63 \pm 0.078	3.6e-16*	0.99 \pm 0.14	1.4e-12*	0.45 \pm 0.11	2.6e-05*	0.35 \pm 0.13	0.008*	0.34 \pm 0.027	3.7e-35*	0.43 \pm 0.034	5.3e-36*	0.076 \pm 0.028	0.0068*	0.046 \pm 0.033	0.17
	CE(18:3;0)	0.48 \pm 0.09	9.6e-08*	0.76 \pm 0.15	4.5e-07*	0.74 \pm 0.11	4.6e-11*	1 \pm 0.13	3.8e-15*	0.2 \pm 0.031	8.1e-11*	0.3 \pm 0.035	3.1e-17*	0.28 \pm 0.031	1.6e-19*	0.35 \pm 0.032	1.2e-26*
	CE(19:1;0)	0.69 \pm 0.11	9e-11*	0.92 \pm 0.15	2.4e-10*	0.39 \pm 0.15	0.01*	0.37 \pm 0.15	0.013*	0.36 \pm 0.041	1.1e-18*	0.36 \pm 0.038	1.7e-21*	-0.0066 \pm 0.047	0.89	-0.046 \pm 0.038	0.22
	CE(20:2;0)	0.5 \pm 0.1	8.2e-07*	0.76 \pm 0.15	3.1e-07*	0.18 \pm 0.14	0.22	-0.086 \pm 0.15	0.57	0.34 \pm 0.038	4.3e-19*	0.36 \pm 0.038	6.5e-21*	-0.044 \pm 0.042	0.3	-0.21 \pm 0.038	1.6e-08*
	CE(20:3;0)	0.63 \pm 0.093	1.2e-11*	0.94 \pm 0.14	5.7e-11*	0.98 \pm 0.13	1.4e-13*	0.91 \pm 0.13	3.9e-12*	0.29 \pm 0.031	5.3e-21*	0.38 \pm 0.033	7.4e-31*	0.33 \pm 0.031	7.2e-27*	0.34 \pm 0.031	7.7e-28*
	CE(20:4;0)	0.62 \pm 0.088	1.7e-12*	0.92 \pm 0.14	3.9e-11*	0.65 \pm 0.13	5.4e-07*	0.49 \pm 0.13	0.00022*	0.32 \pm 0.032	2.1e-23*	0.42 \pm 0.034	6.9e-35*	0.16 \pm 0.032	3.3e-07*	0.15 \pm 0.032	2.8e-06*
CE(20:5;0)	0.54 \pm 0.092	3.8e-09*	0.55 \pm 0.14	8.2e-05*	0.37 \pm 0.12	0.0015*	0.27 \pm 0.13	0.037*	0.26 \pm 0.034	5.6e-15*	0.25 \pm 0.036	5.2e-12*	0.12 \pm 0.034	0.00044*	0.062 \pm 0.034	0.066	
CE(22:6;0)	0.6 \pm 0.088	1.2e-11*	0.58 \pm 0.14	6e-05*	0.34 \pm 0.11	0.0032*	0.17 \pm 0.13	0.21	0.3 \pm 0.033	1.7e-20*	0.25 \pm 0.037	2.9e-11*	0.068 \pm 0.033	0.038	0.03 \pm 0.035	0.39	
DG	DG(16:0;0_18:1;0)	0.31 \pm 0.1	0.0023*	0.29 \pm 0.14	0.041	1.5 \pm 0.11	2.5e-42*	1.8 \pm 0.12	6e-55*	-0.06 \pm 0.021	0.0043*	-0.027 \pm 0.024	0.27	0.75 \pm 0.022	6e-255*	0.79 \pm 0.023	6.8e-246*
	DG(18:1;0_18:1;0)	0.38 \pm 0.1	0.00015*	0.33 \pm 0.14	0.021	1.6 \pm 0.12	3.7e-41*	1.7 \pm 0.12	1.8e-47*	-0.026 \pm 0.021	0.23	-0.014 \pm 0.024	0.54	0.77 \pm 0.022	1.8e-267*	0.78 \pm 0.022	1.9e-260*
	DG(18:1;0_18:2;0)	0.43 \pm 0.1	2.2e-05*	0.21 \pm 0.14	0.14	1.5 \pm 0.11	2.4e-38*	1.8 \pm 0.12	3.9e-52*	0.0094 \pm 0.024	0.7	-0.035 \pm 0.024	0.14	0.72 \pm 0.024	9e-194*	0.79 \pm 0.023	7e-269*
TG	TG(48:0;0)	0.26 \pm 0.1	0.01*	0.25 \pm 0.15	0.096	1.3 \pm 0.12	1.4e-30*	1.7 \pm 0.12	7.8e-47*	-0.074 \pm 0.026	0.0047*	-0.04 \pm 0.027	0.15	0.68 \pm 0.027	7.8e-144*	0.74 \pm 0.026	3.7e-175*
	TG(48:1;0)	0.29 \pm 0.1	0.0057*	0.26 \pm 0.15	0.072	1.4 \pm 0.12	3.2e-34*	1.8 \pm 0.12	1.4e-53*	-0.055 \pm 0.024	0.024*	-0.025 \pm 0.022	0.27	0.74 \pm 0.025	1.1e-190*	0.83 \pm 0.021	<5e-324*
	TG(48:2;0)	0.28 \pm 0.11	0.0088*	0.26 \pm 0.16	0.094	1.5 \pm 0.12	3.5e-36*	1.9 \pm 0.12	4.4e-56*	-0.06 \pm 0.025	0.014*	-0.044 \pm 0.022	0.043	0.77 \pm 0.025	2.1e-200*	0.86 \pm 0.02	<5e-324*
	TG(50:1;0)	0.32 \pm 0.1	0.0013*	0.26 \pm 0.15	0.076	1.5 \pm 0.11	1.4e-39*	1.7 \pm 0.12	2.5e-46*	-0.06 \pm 0.021	0.0043*	-0.011 \pm 0.026	0.67	0.76 \pm 0.022	1.4e-266*	0.76 \pm 0.024	1.3e-218*

	TG(50;2;0)	0.34 ± 0.1	0.0011*	0.31 ± 0.15	0.039	1.6 ± 0.12	1.5e-45*	1.8 ± 0.12	6.3e-49*	-0.058 ± 0.02	0.0033*	0.00052 ± 0.024	0.98	0.82 ± 0.02	<5e-324*	0.8 ± 0.022	2.5e-277*
	TG(50;3;0)	0.36 ± 0.11	0.00054*	0.25 ± 0.15	0.084	1.6 ± 0.12	4e-45*	1.8 ± 0.12	3e-51*	-0.042 ± 0.02	0.04	-0.03 ± 0.022	0.17	0.83 ± 0.021	<5e-324*	0.82 ± 0.021	<5e-324*
	TG(50;4;0)	0.34 ± 0.11	0.0016*	0.21 ± 0.15	0.16	1.5 ± 0.12	1.4e-39*	1.9 ± 0.12	2.3e-56*	-0.038 ± 0.022	0.083	-0.075 ± 0.022	0.00048*	0.81 ± 0.023	1.1e-283*	0.85 ± 0.02	<5e-324*
	TG(51;2;0)	0.38 ± 0.1	0.00026*	0.32 ± 0.15	0.028	1.5 ± 0.11	5.4e-41*	1.8 ± 0.12	4.5e-53*	-0.018 ± 0.023	0.42	0.0012 ± 0.019	0.95	0.77 ± 0.023	4.3e-244*	0.87 ± 0.019	<5e-324*
	TG(51;3;0)	0.44 ± 0.11	3.5e-05*	0.39 ± 0.15	0.012*	1.5 ± 0.12	1.4e-40*	1.8 ± 0.12	6.2e-53*	0.0087 ± 0.022	0.7	-0.016 ± 0.021	0.44	0.78 ± 0.022	9.7e-264*	0.86 ± 0.019	<5e-324*
	TG(52;2;0)	0.37 ± 0.1	2e-04*	0.12 ± 0.14	0.4	1.6 ± 0.11	1.8e-49*	1.4 ± 0.12	8.7e-32*	-0.031 ± 0.018	0.086	-0.0023 ± 0.029	0.94	0.8 ± 0.019	<5e-324*	0.66 ± 0.028	1.9e-124*
	TG(52;3;0)	0.42 ± 0.1	4.1e-05*	0.16 ± 0.15	0.28	1.6 ± 0.12	8.2e-44*	1.5 ± 0.12	2.4e-36*	-0.0075 ± 0.021	0.72	-0.04 ± 0.029	0.16	0.79 ± 0.022	2.1e-289*	0.67 ± 0.027	2.9e-137*
	TG(52;4;0)	0.4 ± 0.1	8.5e-05*	0.25 ± 0.15	0.093	1.5 ± 0.12	5.8e-38*	1.5 ± 0.12	2.2e-34*	0.0019 ± 0.024	0.94	-0.0072 ± 0.028	0.8	0.76 ± 0.024	3.4e-217*	0.69 ± 0.027	9.5e-147*
	TG(52;5;0)	0.39 ± 0.1	2e-04*	0.2 ± 0.15	0.17	1.5 ± 0.12	2.6e-36*	1.8 ± 0.12	1.4e-52*	-0.0045 ± 0.024	0.85	-0.066 ± 0.023	0.0047*	0.76 ± 0.024	5.5e-215*	0.81 ± 0.022	5.8e-298*
	TG(54;3;0)	0.33 ± 0.099	0.00072*	0.15 ± 0.15	0.32	1.5 ± 0.12	1.4e-36*	1.4 ± 0.13	2.8e-27*	-0.037 ± 0.023	0.11	-0.032 ± 0.031	0.29	0.73 ± 0.024	6e-207*	0.62 ± 0.029	5.8e-102*
	TG(54;4;0)	0.34 ± 0.1	0.00067*	0.068 ± 0.15	0.64	1.4 ± 0.12	2.4e-32*	1.4 ± 0.12	2.3e-28*	-0.027 ± 0.026	0.3	-0.076 ± 0.03	0.012*	0.7 ± 0.027	8.5e-153*	0.62 ± 0.028	7.6e-108*
	TG(54;5;0)	0.35 ± 0.1	0.00046*	0.19 ± 0.15	0.19	1.4 ± 0.11	1.2e-35*	1.6 ± 0.12	4.7e-42*	-0.021 ± 0.025	0.41	-0.076 ± 0.029	0.0082*	0.72 ± 0.025	1.2e-175*	0.68 ± 0.027	1.4e-141*
	TG(54;6;0)	0.4 ± 0.099	6.6e-05*	0.24 ± 0.14	0.094	1.4 ± 0.11	2.3e-35*	1.7 ± 0.12	2.2e-48*	-0.0034 ± 0.024	0.89	-0.08 ± 0.026	0.0025*	0.71 ± 0.024	1.8e-185*	0.71 ± 0.025	5e-181*
	TG(56;4;0)	0.33 ± 0.11	0.0029*	0.012 ± 0.15	0.94	1.5 ± 0.11	6.3e-43*	1.8 ± 0.12	2.1e-49*	-0.028 ± 0.024	0.26	-0.12 ± 0.025	7.3e-07*	0.74 ± 0.024	1.5e-216*	0.81 ± 0.024	1.5e-245*
	TG(56;5;0)	0.4 ± 0.098	5.2e-05*	0.26 ± 0.15	0.082	1.5 ± 0.1	3.9e-46*	1.8 ± 0.12	2.2e-49*	0.017 ± 0.023	0.45	-0.015 ± 0.024	0.52	0.7 ± 0.023	2.7e-212*	0.8 ± 0.023	2.1e-269*
	TG(56;6;0)	0.43 ± 0.096	6.2e-06*	0.43 ± 0.14	0.0027*	1.4 ± 0.1	3.3e-42*	1.7 ± 0.12	1.7e-46*	0.027 ± 0.022	0.23	0.045 ± 0.026	0.079	0.69 ± 0.022	1.6e-208*	0.71 ± 0.024	8.7e-191*
	TG(56;7;0)	0.46 ± 0.096	1.3e-06*	0.36 ± 0.14	0.014*	1.3 ± 0.11	3.8e-31*	1.4 ± 0.12	4.8e-30*	0.061 ± 0.025	0.016*	0.072 ± 0.03	0.016*	0.61 ± 0.026	9.6e-122*	0.58 ± 0.028	8.6e-91*
PC	PC(14;0;0_16;0;0)	0.26 ± 0.11	0.019*	0.19 ± 0.14	0.18	0.58 ± 0.13	4.2e-06*	0.85 ± 0.13	4.7e-11*	0.029 ± 0.039	0.46	0.0087 ± 0.036	0.81	0.29 ± 0.039	7.2e-14*	0.32 ± 0.034	1.3e-21*
	PC(14;0;0_18;1;0)	0.13 ± 0.11	0.23	0.079 ± 0.15	0.59	0.61 ± 0.12	6e-07*	0.95 ± 0.13	5e-13*	-0.034 ± 0.037	0.35	0.0035 ± 0.035	0.92	0.37 ± 0.036	6.8e-24*	0.39 ± 0.034	6.4e-31*
	PC(14;0;0_18;2;0)	0.11 ± 0.1	0.26	0.15 ± 0.16	0.33	0.56 ± 0.11	3e-07*	0.98 ± 0.14	5.3e-13*	0.00082 ± 0.034	0.98	0.0067 ± 0.039	0.86	0.28 ± 0.034	7.6e-16*	0.37 ± 0.035	3.9e-25*
	PC(15;0;0_18;2;0)	0.22 ± 0.1	0.033*	0.24 ± 0.16	0.13	0.51 ± 0.12	2.1e-05*	0.83 ± 0.15	2.2e-08*	0.0014 ± 0.038	0.97	-0.0068 ± 0.04	0.86	0.27 ± 0.04	1.8e-11*	0.26 ± 0.038	8.2e-12*
	PC(16;0;0_16;0;0)	0.3 ± 0.086	0.00052*	0.48 ± 0.14	0.00089*	0.63 ± 0.1	8.2e-10*	0.65 ± 0.13	6.9e-07*	0.053 ± 0.031	0.092	0.09 ± 0.037	0.015*	0.22 ± 0.033	1.6e-11*	0.16 ± 0.035	6.7e-06*
	PC(16;0;0_16;1;0)	0.13 ± 0.11	0.25	0.082 ± 0.15	0.57	0.95 ± 0.12	2.2e-14*	1.1 ± 0.13	1.3e-17*	-0.048 ± 0.037	0.19	-0.035 ± 0.035	0.31	0.41 ± 0.037	1.1e-29*	0.42 ± 0.033	2.7e-37*
	PC(16;0;0_17;1;0)	0.027 ± 0.09	0.77	0.075 ± 0.16	0.63	0.52 ± 0.11	3e-06*	0.4 ± 0.14	0.0039*	-0.023 ± 0.033	0.48	-0.022 ± 0.039	0.58	0.26 ± 0.033	1.2e-14*	0.23 ± 0.037	5.9e-10*
	PC(16;0;0_18;0;0)	0.32 ± 0.089	3e-04*	0.12 ± 0.15	0.44	0.5 ± 0.11	8.7e-06*	0.49 ± 0.14	0.00036*	0.13 ± 0.032	1e-04*	0.033 ± 0.039	0.4	0.19 ± 0.033	1.1e-08*	0.15 ± 0.037	4.4e-05*
	PC(16;0;0_18;1;0)	0.23 ± 0.1	0.026*	0.16 ± 0.14	0.28	0.93 ± 0.11	1.2e-16*	1 ± 0.13	1.1e-15*	-0.015 ± 0.035	0.67	0.028 ± 0.035	0.43	0.39 ± 0.035	9.2e-28*	0.38 ± 0.034	2.3e-29*
	PC(16;0;0_18;2;0)	0.3 ± 0.095	0.0013*	0.082 ± 0.15	0.58	0.77 ± 0.11	5e-12*	0.73 ± 0.13	4.2e-08*	0.058 ± 0.034	0.082	0.00071 ± 0.037	0.98	0.3 ± 0.034	5.1e-18*	0.25 ± 0.035	1.8e-12*
	PC(16;0;0_18;3;0)	0.19 ± 0.11	0.083	-3e-04 ± 0.15	1	0.68 ± 0.13	1.8e-07*	1 ± 0.13	8.5e-15*	0.006 ± 0.038	0.87	-0.048 ± 0.035	0.17	0.36 ± 0.038	1.4e-21*	0.41 ± 0.033	4.3e-34*
	PC(16;0;0_20;1;0)	0.32 ± 0.1	0.0025*	0.45 ± 0.15	0.0028*	0.58 ± 0.12	3.4e-06*	0.82 ± 0.14	2.7e-09*	0.11 ± 0.038	0.0035*	0.054 ± 0.038	0.16	0.18 ± 0.038	4e-06*	0.24 ± 0.036	2.3e-11*
	PC(16;0;0_20;2;0)	0.42 ± 0.1	2.7e-05*	0.13 ± 0.15	0.37	0.91 ± 0.12	1.5e-13*	0.79 ± 0.14	6.1e-09*	0.1 ± 0.033	0.002*	0.051 ± 0.037	0.17	0.39 ± 0.034	2.4e-30*	0.32 ± 0.035	6.8e-20*

	PC(16:0;0_20:3;0)	0.39 ± 0.1	9.5e-05*	0.13 ± 0.15	0.37	1.2 ± 0.13	3.2e-21*	1.2 ± 0.13	8e-21*	0.027 ± 0.031	0.39	0.023 ± 0.033	0.49	0.53 ± 0.032	7.3e-61*	0.5 ± 0.032	1.3e-56*
	PC(16:0;0_20:4;0)	0.25 ± 0.092	0.0079*	0.21 ± 0.15	0.15	0.9 ± 0.12	2.1e-13*	0.77 ± 0.13	7.1e-09*	0.0024 ± 0.033	0.94	0.068 ± 0.036	0.059	0.37 ± 0.033	2.3e-29*	0.33 ± 0.034	2.2e-21*
	PC(16:0;0_20:5;0)	0.31 ± 0.1	0.0024*	0.36 ± 0.14	0.011*	0.49 ± 0.12	4e-05*	0.48 ± 0.13	0.00019*	0.067 ± 0.036	0.061	0.08 ± 0.037	0.029*	0.26 ± 0.036	6.5e-13*	0.12 ± 0.035	0.00034*
	PC(16:0;0_22:4;0)	0.24 ± 0.098	0.016*	0.24 ± 0.16	0.14	0.69 ± 0.13	5e-08*	0.95 ± 0.14	3.1e-12*	0.031 ± 0.035	0.37	0.083 ± 0.039	0.031*	0.27 ± 0.036	2.5e-14*	0.33 ± 0.036	1.3e-19*
	PC(16:0;0_22:5;0)	0.4 ± 0.1	6.1e-05*	0.28 ± 0.14	0.049	0.68 ± 0.12	2.5e-08*	0.67 ± 0.13	2.6e-07*	0.11 ± 0.035	0.0015*	0.055 ± 0.037	0.14	0.3 ± 0.035	1.3e-17*	0.24 ± 0.035	1.3e-11*
	PC(16:0;0_22:6;0)	0.45 ± 0.095	1.8e-06*	0.28 ± 0.14	0.05	0.58 ± 0.12	1.2e-06*	0.42 ± 0.13	0.00099*	0.13 ± 0.034	8.5e-05*	0.067 ± 0.036	0.066	0.24 ± 0.034	1.8e-12*	0.14 ± 0.035	6.3e-05*
	PC(16:1;0_18:1;0)	0.083 ± 0.11	0.43	-0.025 ± 0.15	0.86	0.62 ± 0.12	2.4e-07*	0.6 ± 0.13	4.4e-06*	-0.059 ± 0.037	0.11	-0.035 ± 0.037	0.34	0.32 ± 0.037	5.3e-18*	0.29 ± 0.035	5.2e-17*
	PC(16:1;0_18:2;0)	0.09 ± 0.1	0.38	-0.15 ± 0.15	0.3	0.53 ± 0.12	7.5e-06*	0.75 ± 0.13	1.6e-08*	-0.0016 ± 0.037	0.96	-0.1 ± 0.036	0.0047*	0.25 ± 0.037	7.8e-12*	0.29 ± 0.034	8.7e-18*
	PC(17:0;0_18:2;0)	0.37 ± 0.096	0.00014*	0.36 ± 0.15	0.017*	0.56 ± 0.13	8.4e-06*	0.33 ± 0.14	0.017*	0.075 ± 0.036	0.037	0.059 ± 0.039	0.13	0.24 ± 0.037	7.4e-11*	0.13 ± 0.037	0.00027*
	PC(17:0;0_20:3;0)	0.4 ± 0.11	0.00046*	0.33 ± 0.15	0.029	0.44 ± 0.13	0.00086*	0.59 ± 0.14	1.9e-05*	0.12 ± 0.04	0.0017*	0.082 ± 0.038	0.032*	0.27 ± 0.039	3.3e-12*	0.25 ± 0.036	2.8e-12*
	PC(17:0;0_20:4;0)	0.27 ± 0.1	0.0066*	0.38 ± 0.15	0.011*	0.5 ± 0.13	7.7e-05*	0.58 ± 0.14	2.1e-05*	0.026 ± 0.037	0.48	0.15 ± 0.038	0.00011*	0.28 ± 0.037	9.8e-15*	0.24 ± 0.036	2.2e-11*
	PC(18:0;0_18:1;0)	0.3 ± 0.099	0.0025*	0.4 ± 0.15	0.0058*	0.68 ± 0.13	1.2e-07*	0.63 ± 0.13	1.7e-06*	0.066 ± 0.038	0.081	0.12 ± 0.037	0.0015*	0.3 ± 0.038	2.5e-15*	0.24 ± 0.035	2.3e-12*
	PC(18:0;0_18:2;0)	0.44 ± 0.092	2e-06*	0.29 ± 0.15	0.045	0.75 ± 0.11	2.1e-11*	0.71 ± 0.13	8.7e-08*	0.14 ± 0.033	4e-05*	0.09 ± 0.037	0.016*	0.27 ± 0.033	2.6e-16*	0.21 ± 0.036	2.2e-09*
	PC(18:0;0_18:3;0)	0.21 ± 0.094	0.028*	0.17 ± 0.16	0.28	0.56 ± 0.12	1e-06*	1 ± 0.14	7.5e-14*	0.047 ± 0.033	0.15	0.014 ± 0.038	0.71	0.3 ± 0.034	5.5e-19*	0.35 ± 0.035	7.6e-24*
	PC(18:0;0_20:2;0)	0.47 ± 0.1	3.2e-06*	0.38 ± 0.15	0.011*	0.71 ± 0.12	2.5e-09*	0.67 ± 0.14	2.5e-06*	0.15 ± 0.034	8.8e-06*	0.088 ± 0.039	0.022*	0.29 ± 0.034	3.1e-17*	0.22 ± 0.038	6.4e-09*
	PC(18:0;0_20:3;0)	0.48 ± 0.098	1.1e-06*	0.31 ± 0.15	0.033	1.3 ± 0.13	1.3e-22*	1.3 ± 0.13	2.4e-26*	0.1 ± 0.03	0.00056*	0.081 ± 0.033	0.013*	0.54 ± 0.03	6.7e-70*	0.53 ± 0.031	1.5e-66*
	PC(18:0;0_20:4;0)	0.42 ± 0.085	5.6e-07*	0.46 ± 0.15	0.0016*	0.88 ± 0.12	3.6e-13*	0.76 ± 0.13	1e-08*	0.11 ± 0.03	0.00019*	0.15 ± 0.036	2.4e-05*	0.33 ± 0.031	5e-27*	0.29 ± 0.034	6.5e-17*
	PC(18:0;0_20:5;0)	0.39 ± 0.1	0.00011*	0.24 ± 0.14	0.098	0.44 ± 0.13	0.00058*	0.48 ± 0.13	0.00028*	0.12 ± 0.036	0.00097*	0.11 ± 0.037	0.002*	0.23 ± 0.036	1.5e-10*	0.12 ± 0.035	0.00074*
	PC(18:0;0_22:5;0)	0.45 ± 0.09	6.9e-07*	0.34 ± 0.15	0.019	0.76 ± 0.12	5.4e-11*	1.1 ± 0.13	4.3e-17*	0.15 ± 0.03	1e-06*	0.088 ± 0.036	0.013*	0.32 ± 0.031	1.3e-24*	0.36 ± 0.034	1.2e-26*
	PC(18:0;0_22:6;0)	0.54 ± 0.091	3.5e-09*	0.45 ± 0.14	0.0017*	0.67 ± 0.11	2.3e-09*	0.83 ± 0.13	2.7e-10*	0.17 ± 0.032	7.4e-08*	0.12 ± 0.036	0.001*	0.27 ± 0.032	3.9e-17*	0.23 ± 0.035	1e-11*
	PC(18:1;0_18:1;0)	0.065 ± 0.1	0.52	0.12 ± 0.15	0.4	0.23 ± 0.12	0.064	0.52 ± 0.13	9.7e-05*	-0.045 ± 0.036	0.22	-0.0037 ± 0.038	0.92	0.19 ± 0.037	4.6e-07*	0.18 ± 0.036	8.7e-07*
	PC(18:1;0_18:2;0)	0.19 ± 0.099	0.052	0.059 ± 0.15	0.69	0.37 ± 0.12	0.0018*	0.32 ± 0.13	0.017*	0.031 ± 0.036	0.39	-0.033 ± 0.038	0.39	0.16 ± 0.037	1.2e-05*	0.1 ± 0.036	0.0051*
	PC(18:1;0_20:3;0)	0.36 ± 0.1	0.00032*	0.099 ± 0.15	0.5	0.84 ± 0.12	4.1e-12*	0.73 ± 0.13	4.5e-08*	0.072 ± 0.033	0.029*	0.041 ± 0.036	0.26	0.37 ± 0.034	5.3e-28*	0.38 ± 0.034	4.7e-28*
	PC(18:1;0_20:4;0)	0.24 ± 0.089	0.0069*	0.25 ± 0.15	0.089	0.59 ± 0.12	6.7e-07*	0.56 ± 0.13	3.7e-05*	0.029 ± 0.032	0.37	0.072 ± 0.038	0.058	0.27 ± 0.033	1.9e-16*	0.21 ± 0.036	2.5e-09*
	PC(18:2;0_18:2;0)	0.11 ± 0.1	0.28	0.059 ± 0.15	0.69	0.15 ± 0.12	0.23	0.22 ± 0.14	0.11	0.038 ± 0.038	0.32	-0.034 ± 0.038	0.38	0.025 ± 0.039	0.53	0.045 ± 0.036	0.22
	PC(18:2;0_20:4;0)	0.43 ± 0.11	7.6e-05*	0.05 ± 0.16	0.75	0.54 ± 0.14	0.00014*	0.38 ± 0.15	0.0084*	0.11 ± 0.039	0.0073*	0.0077 ± 0.04	0.85	0.19 ± 0.041	2.4e-06*	0.13 ± 0.038	0.00099*
PCO	PCO(16:0;0/16:0;0)	0.31 ± 0.097	0.0012*	0.35 ± 0.15	0.019	0.46 ± 0.13	0.00031*	0.34 ± 0.14	0.014*	0.083 ± 0.037	0.026*	0.083 ± 0.039	0.032*	0.18 ± 0.037	1e-06*	0.038 ± 0.037	0.31
	PCO(16:0;0/16:1;0)	-0.00036 ± 0.11	1	0.19 ± 0.15	0.22	0.26 ± 0.13	0.05	0.57 ± 0.14	4.3e-05*	-0.049 ± 0.04	0.23	0.0052 ± 0.039	0.9	0.12 ± 0.041	0.0043*	0.16 ± 0.037	1.1e-05*
	PCO(16:0;0/18:1;0)	0.051 ± 0.089	0.56	0.29 ± 0.15	0.049	-0.18 ± 0.11	0.082	-0.16 ± 0.14	0.24	0.031 ± 0.032	0.32	0.07 ± 0.038	0.065	-0.17 ± 0.033	2.9e-07*	-0.21 ± 0.036	2.6e-09*
	PCO(16:0;0/18:2;0)	0.23 ± 0.1	0.024*	0.2 ± 0.15	0.17	-0.14 ± 0.12	0.25	-0.28 ± 0.14	0.038*	0.14 ± 0.038	0.00014*	0.086 ± 0.038	0.024*	-0.16 ± 0.038	3.3e-05*	-0.21 ± 0.036	6.7e-09*

	PCO(16:0;0/20:3;0)	0.45 ± 0.097	3e-06*	0.4 ± 0.15	0.008*	0.46 ± 0.13	0.00027*	0.36 ± 0.14	0.0081*	0.17 ± 0.036	3.3e-06*	0.23 ± 0.038	2.4e-09*	0.1 ± 0.036	0.0041*	0.12 ± 0.036	0.00096*
	PCO(16:0;0/20:4;0)	0.42 ± 0.1	4.6e-05*	0.43 ± 0.15	0.0032*	0.41 ± 0.14	0.0038*	0.26 ± 0.13	0.048	0.14 ± 0.038	0.00029*	0.22 ± 0.037	3.5e-09*	0.11 ± 0.039	0.0029*	0.0033 ± 0.035	0.93
	PCO(16:1;0/16:0;0)	0.11 ± 0.11	0.29	0.12 ± 0.15	0.44	-0.37 ± 0.12	0.0019*	-0.38 ± 0.14	0.007*	0.089 ± 0.038	0.018*	0.058 ± 0.039	0.13	-0.27 ± 0.038	1.3e-12*	-0.2 ± 0.037	5.5e-08*
	PCO(16:1;0/18:1;0)	-8e-04 ± 0.1	0.99	0.26 ± 0.15	0.072	-0.43 ± 0.12	0.00031*	-0.53 ± 0.13	7e-05*	0.076 ± 0.036	0.035	0.13 ± 0.036	0.00026*	-0.32 ± 0.037	1.1e-17*	-0.33 ± 0.034	2.5e-22*
	PCO(16:1;0/18:2;0)	0.12 ± 0.1	0.26	0.27 ± 0.15	0.071	-0.19 ± 0.12	0.1	-0.39 ± 0.14	0.0039*	0.12 ± 0.037	0.0011*	0.1 ± 0.037	0.0072*	-0.21 ± 0.038	2.4e-08*	-0.27 ± 0.035	5.3e-14*
	PCO(16:1;0/20:3;0)	0.33 ± 0.11	0.0034*	0.17 ± 0.16	0.27	0.26 ± 0.15	0.085	0.19 ± 0.15	0.21	0.15 ± 0.042	3e-04*	0.16 ± 0.041	7.4e-05*	0.0052 ± 0.043	0.9	0.0044 ± 0.039	0.91
	PCO(17:0;0/17:1;0)	0.12 ± 0.097	0.21	0.5 ± 0.15	0.0011*	0.16 ± 0.13	0.23	0.4 ± 0.14	0.004*	0.062 ± 0.038	0.097	0.12 ± 0.039	0.0013*	0.017 ± 0.038	0.66	0.11 ± 0.037	0.0019*
	PCO(18:0;0/14:0;0)	-0.24 ± 0.096	0.012*	-0.058 ± 0.15	0.7	-0.63 ± 0.12	3.7e-07*	-0.63 ± 0.14	3.8e-06*	-0.027 ± 0.033	0.41	0.07 ± 0.038	0.066	-0.33 ± 0.033	1.8e-23*	-0.25 ± 0.036	3e-12*
	PCO(18:0;0/18:2;0)	0.16 ± 0.096	0.11	0.24 ± 0.15	0.11	-0.28 ± 0.13	0.025*	-0.2 ± 0.16	0.21	0.1 ± 0.034	0.0026*	0.08 ± 0.039	0.039	-0.23 ± 0.038	1.3e-09*	-0.3 ± 0.039	1.6e-14*
	PCO(18:0;0/20:4;0)	0.35 ± 0.1	0.00047*	0.42 ± 0.15	0.0047*	0.063 ± 0.13	0.62	-0.015 ± 0.14	0.91	0.17 ± 0.037	6.7e-06*	0.18 ± 0.038	2.2e-06*	-0.13 ± 0.038	0.00041*	-0.16 ± 0.036	9.1e-06*
	PCO(18:1;0/16:0;0)	-0.0099 ± 0.097	0.92	0.2 ± 0.15	0.18	-0.25 ± 0.12	0.035*	-0.32 ± 0.14	0.018*	0.0093 ± 0.035	0.79	0.073 ± 0.037	0.051	-0.19 ± 0.035	1.1e-07*	-0.31 ± 0.035	2.5e-18*
	PCO(18:1;0/18:1;0)	-0.038 ± 0.1	0.71	0.046 ± 0.15	0.76	-0.51 ± 0.14	0.00022*	-0.038 ± 0.16	0.81	-0.021 ± 0.038	0.58	0.073 ± 0.039	0.061	-0.22 ± 0.041	1.2e-07*	-0.24 ± 0.04	1e-09*
	PCO(18:1;0/18:2;0)	0.16 ± 0.1	0.12	0.26 ± 0.15	0.085	-0.3 ± 0.13	0.022*	-0.44 ± 0.14	0.0014*	0.12 ± 0.038	0.0015*	0.13 ± 0.037	0.00062*	-0.21 ± 0.039	4e-08*	-0.29 ± 0.035	2e-16*
	PCO(18:1;0/20:3;0)	0.24 ± 0.092	0.0098*	0.036 ± 0.15	0.81	0.17 ± 0.12	0.17	0.0061 ± 0.14	0.97	0.065 ± 0.035	0.059	0.083 ± 0.039	0.034*	0.035 ± 0.036	0.33	-0.0088 ± 0.037	0.81
	PCO(18:1;0/20:4;0)	0.28 ± 0.11	0.011*	0.34 ± 0.15	0.024	0.14 ± 0.14	0.33	-0.032 ± 0.14	0.82	0.11 ± 0.04	0.0065*	0.16 ± 0.038	2.1e-05*	-0.019 ± 0.041	0.64	-0.15 ± 0.036	5.8e-05*
	PCO(18:2;0/16:0;0)	0.17 ± 0.11	0.12	0.3 ± 0.15	0.045	-0.041 ± 0.14	0.77	-0.29 ± 0.14	0.035*	0.058 ± 0.04	0.15	0.083 ± 0.038	0.028*	-0.046 ± 0.041	0.26	-0.22 ± 0.036	7.2e-10*
	PCO(18:2;0/18:0;0)	0.079 ± 0.097	0.41	0.26 ± 0.15	0.087	0.015 ± 0.14	0.91	-0.18 ± 0.16	0.28	0.059 ± 0.036	0.098	0.11 ± 0.04	0.0078*	-0.11 ± 0.04	0.0062*	-0.27 ± 0.04	1.2e-11*
	PCO(18:2;0/18:1;0)	0.12 ± 0.1	0.24	0.28 ± 0.15	0.065	-0.13 ± 0.13	0.3	-0.65 ± 0.13	1e-06*	0.074 ± 0.037	0.043	0.14 ± 0.037	1e-04*	-0.17 ± 0.037	4e-06*	-0.33 ± 0.035	8.5e-22*
	PCO(18:2;0/18:2;0)	0.13 ± 0.098	0.19	0.18 ± 0.15	0.23	-0.15 ± 0.12	0.21	-0.29 ± 0.14	0.032*	0.099 ± 0.035	0.0049*	0.12 ± 0.038	0.0024*	-0.17 ± 0.037	3.1e-06*	-0.22 ± 0.036	1.8e-09*
SM	SM(32:1;2)	0.52 ± 0.099	1.7e-07*	0.91 ± 0.14	5.6e-11*	0.44 ± 0.13	0.00058*	0.22 ± 0.13	0.082	0.26 ± 0.035	1.2e-13*	0.33 ± 0.035	1.8e-21*	0.097 ± 0.035	0.006*	0.038 ± 0.033	0.25
	SM(34:0;2)	0.55 ± 0.099	2.2e-08*	1 ± 0.14	3.6e-13*	0.18 ± 0.12	0.14	0.036 ± 0.13	0.79	0.28 ± 0.037	7.8e-15*	0.37 ± 0.035	1.3e-25*	-0.0017 ± 0.037	0.96	-0.17 ± 0.034	7.3e-07*
	SM(34:1;2)	0.56 ± 0.086	8.7e-11*	0.72 ± 0.14	1.8e-07*	0.15 ± 0.11	0.19	-0.036 ± 0.13	0.79	0.31 ± 0.031	2.7e-23*	0.33 ± 0.035	3.4e-21*	-0.098 ± 0.032	0.0023*	-0.11 ± 0.034	0.0013*
	SM(34:2;2)	0.43 ± 0.081	1.1e-07*	0.7 ± 0.14	2.8e-07*	0.44 ± 0.11	5e-05*	0.19 ± 0.13	0.13	0.23 ± 0.03	7.3e-15*	0.28 ± 0.035	6e-16*	0.087 ± 0.03	0.004*	0.0088 ± 0.033	0.79
	SM(36:1;2)	0.57 ± 0.084	1.2e-11*	0.94 ± 0.14	1.3e-11*	0.43 ± 0.13	0.00098*	0.35 ± 0.13	0.0079*	0.31 ± 0.031	4.2e-23*	0.39 ± 0.035	2.9e-29*	0.062 ± 0.032	0.053	0.039 ± 0.033	0.24
	SM(36:2;2)	0.41 ± 0.087	2.1e-06*	0.8 ± 0.14	3.2e-09*	0.36 ± 0.13	0.0053*	0.28 ± 0.13	0.026*	0.27 ± 0.032	6.8e-17*	0.33 ± 0.034	2.7e-22*	0.059 ± 0.032	0.068	-0.0013 ± 0.033	0.97
	SM(38:1;2)	0.64 ± 0.088	4.9e-13*	0.98 ± 0.14	4.5e-12*	0.47 ± 0.12	8.7e-05*	0.34 ± 0.13	0.011*	0.32 ± 0.031	1.8e-25*	0.38 ± 0.035	6.2e-27*	0.089 ± 0.032	0.0047*	0.051 ± 0.033	0.13
	SM(38:2;2)	0.43 ± 0.088	1.3e-06*	0.65 ± 0.14	1.8e-06*	0.28 ± 0.12	0.024*	0.048 ± 0.13	0.71	0.28 ± 0.032	4.7e-19*	0.29 ± 0.035	3.4e-17*	0.0082 ± 0.032	0.8	-0.066 ± 0.033	0.045
	SM(40:1;2)	0.65 ± 0.078	1.1e-16*	0.99 ± 0.14	2.6e-12*	0.49 ± 0.11	1.3e-05*	0.35 ± 0.13	0.0088*	0.32 ± 0.028	3e-31*	0.41 ± 0.035	2.7e-31*	0.1 ± 0.028	0.00035*	0.049 ± 0.033	0.14
	SM(40:2;2)	0.59 ± 0.086	8e-12*	0.85 ± 0.14	1.1e-09*	0.28 ± 0.12	0.014*	0.13 ± 0.13	0.32	0.33 ± 0.029	9.4e-30*	0.34 ± 0.035	4.8e-22*	0.00011 ± 0.03	1	-0.041 ± 0.033	0.22
SM(42:2;2)	0.63 ± 0.087	6.9e-13*	0.66 ± 0.14	3e-06*	0.2 ± 0.12	0.092	0.14 ± 0.13	0.3	0.34 ± 0.032	5.5e-27*	0.3 ± 0.036	5.9e-17*	-0.04 ± 0.032	0.22	-0.039 ± 0.034	0.26	

Cer	Cer(40:1;2)	0.49 ± 0.092	1.1e-07*	0.74 ± 0.14	2.2e-07*	0.97 ± 0.12	2.5e-16*	0.98 ± 0.13	2.2e-14*	0.2 ± 0.032	5.5e-10*	0.26 ± 0.035	4.5e-14*	0.34 ± 0.032	3.4e-27*	0.31 ± 0.033	6.8e-21*
	Cer(40:2;2)	0.31 ± 0.09	0.00054*	0.45 ± 0.15	0.003*	0.84 ± 0.11	1.1e-13*	0.7 ± 0.14	5.1e-07*	0.14 ± 0.031	1e-05*	0.11 ± 0.039	0.005*	0.3 ± 0.032	5.5e-22*	0.23 ± 0.037	7.5e-10*
	Cer(42:1;2)	0.44 ± 0.072	1.5e-09*	0.99 ± 0.14	6.8e-13*	0.87 ± 0.099	1e-18*	1.1 ± 0.13	4.8e-19*	0.19 ± 0.025	3e-14*	0.33 ± 0.033	1.5e-24*	0.26 ± 0.025	3e-24*	0.32 ± 0.031	7e-26*
	Cer(42:2;2)	0.35 ± 0.075	3.5e-06*	0.77 ± 0.14	2.7e-08*	0.9 ± 0.11	8.5e-16*	1.1 ± 0.12	2.4e-18*	0.15 ± 0.028	3.9e-08*	0.24 ± 0.033	5.5e-13*	0.3 ± 0.028	1.5e-25*	0.32 ± 0.032	1.8e-24*
PI	PI(16:0;0_18:1;0)	0.087 ± 0.11	0.45	0.35 ± 0.15	0.019	0.66 ± 0.13	3.8e-07*	0.77 ± 0.14	1.4e-08*	-0.046 ± 0.039	0.24	0.031 ± 0.038	0.41	0.34 ± 0.039	6.7e-18*	0.26 ± 0.036	8.9e-13*
	PI(16:0;0_18:2;0)	0.14 ± 0.11	0.19	-0.049 ± 0.14	0.73	0.75 ± 0.13	2.6e-09*	0.95 ± 0.13	1.2e-13*	-0.045 ± 0.035	0.2	-0.092 ± 0.035	0.0083*	0.41 ± 0.036	2e-30*	0.4 ± 0.033	3.1e-34*
	PI(16:0;0_20:4;0)	0.15 ± 0.12	0.19	-0.016 ± 0.16	0.92	0.79 ± 0.14	1e-08*	1.1 ± 0.13	2.2e-15*	-0.012 ± 0.039	0.75	-0.044 ± 0.036	0.22	0.42 ± 0.04	5.1e-26*	0.45 ± 0.035	4.9e-37*
	PI(18:0;0_18:1;0)	0.16 ± 0.11	0.13	0.27 ± 0.15	0.062	0.49 ± 0.13	0.00011*	0.79 ± 0.13	2.7e-09*	0.0087 ± 0.038	0.82	0.057 ± 0.037	0.12	0.29 ± 0.039	4.2e-14*	0.31 ± 0.035	3.1e-19*
	PI(18:0;0_18:2;0)	0.17 ± 0.1	0.09	0.059 ± 0.15	0.69	0.68 ± 0.12	3.4e-08*	0.72 ± 0.13	5.3e-08*	-0.031 ± 0.035	0.37	-0.042 ± 0.037	0.26	0.36 ± 0.036	9.5e-24*	0.24 ± 0.035	8.5e-12*
	PI(18:0;0_20:3;0)	0.31 ± 0.11	0.0031*	0.11 ± 0.15	0.44	0.89 ± 0.12	5e-13*	0.98 ± 0.13	5.7e-14*	0.019 ± 0.034	0.58	0.0082 ± 0.035	0.82	0.44 ± 0.034	2.6e-38*	0.41 ± 0.034	9e-35*
	PI(18:0;0_20:4;0)	0.36 ± 0.083	1.4e-05*	0.49 ± 0.14	0.00075*	0.84 ± 0.11	1.3e-14*	1.1 ± 0.13	5e-18*	0.071 ± 0.027	0.0086*	0.13 ± 0.035	0.00024*	0.38 ± 0.028	7.7e-44*	0.38 ± 0.033	1e-31*
	PI(18:1;0_18:1;0)	0.019 ± 0.1	0.85	-0.079 ± 0.15	0.59	0.09 ± 0.12	0.47	0.29 ± 0.14	0.034*	-0.017 ± 0.037	0.64	-0.069 ± 0.038	0.069	0.1 ± 0.038	0.0084*	0.16 ± 0.036	2.1e-05*
	PI(18:1;0_18:2;0)	-0.057 ± 0.086	0.51	-0.3 ± 0.15	0.045	0.28 ± 0.12	0.022*	0.45 ± 0.14	0.0012*	-0.1 ± 0.032	0.0014*	-0.15 ± 0.039	7.8e-05*	0.17 ± 0.034	3e-07*	0.15 ± 0.037	4.4e-05*
	PI(18:2;0_18:2;0)	0.035 ± 0.081	0.67	0.14 ± 0.16	0.38	-0.24 ± 0.11	0.024*	-0.19 ± 0.15	0.19	0.076 ± 0.032	0.019*	0.039 ± 0.04	0.33	-0.099 ± 0.033	0.0024*	-0.16 ± 0.039	4.1e-05*
	PE	PE(16:0;0_18:2;0)	0.11 ± 0.11	0.32	-0.074 ± 0.16	0.64	0.95 ± 0.12	2.3e-14*	1.3 ± 0.13	5.7e-22*	-0.13 ± 0.034	0.00012*	-0.19 ± 0.034	3.1e-08*	0.51 ± 0.034	2.9e-51*	0.58 ± 0.032
PE(18:0;0_18:2;0)		0.28 ± 0.11	0.0091*	0.0098 ± 0.15	0.95	1.3 ± 0.12	4.4e-25*	1.4 ± 0.13	2.5e-29*	-0.082 ± 0.03	0.0059*	-0.14 ± 0.031	2.9e-06*	0.64 ± 0.03	1.6e-101*	0.65 ± 0.029	2.8e-107*
PE(18:0;0_20:4;0)		0.33 ± 0.1	0.0015*	0.12 ± 0.15	0.4	1.2 ± 0.12	4.3e-23*	1.3 ± 0.13	4.5e-23*	-0.047 ± 0.031	0.12	-0.072 ± 0.031	0.022*	0.58 ± 0.031	3.1e-79*	0.62 ± 0.03	3.1e-95*
PE(18:1;0_18:1;0)		0.051 ± 0.11	0.63	-0.32 ± 0.16	0.039	0.79 ± 0.13	1.1e-09*	0.92 ± 0.14	5.8e-11*	-0.18 ± 0.035	3.3e-07*	-0.25 ± 0.036	1.1e-11*	0.5 ± 0.035	5.9e-46*	0.48 ± 0.035	8e-42*
PEO	PEO(16:1;0/18:2;0)	0.19 ± 0.11	0.077	0.21 ± 0.15	0.16	0.091 ± 0.13	0.47	-0.026 ± 0.14	0.85	0.13 ± 0.039	0.0012*	0.13 ± 0.039	0.0011*	-0.04 ± 0.039	0.31	-0.058 ± 0.037	0.12
	PEO(16:1;0/20:4;0)	0.34 ± 0.11	0.0017*	0.19 ± 0.15	0.22	0.4 ± 0.13	0.0031*	0.31 ± 0.14	0.025*	0.14 ± 0.04	0.00029*	0.13 ± 0.039	0.001*	0.14 ± 0.04	0.00036*	0.073 ± 0.037	0.05
	PEO(18:1;0/18:2;0)	0.19 ± 0.1	0.071	0.32 ± 0.15	0.027	-0.042 ± 0.12	0.73	-0.17 ± 0.14	0.22	0.12 ± 0.038	0.0018*	0.18 ± 0.038	1.5e-06*	-0.057 ± 0.038	0.14	-0.13 ± 0.036	0.00043*
	PEO(18:2;0/18:2;0)	0.23 ± 0.11	0.036	0.41 ± 0.15	0.007*	0.092 ± 0.14	0.52	-0.0042 ± 0.14	0.98	0.11 ± 0.04	0.0077*	0.18 ± 0.039	3.9e-06*	-0.035 ± 0.041	0.39	-0.063 ± 0.037	0.089
	PEO(18:2;0/20:4;0)	0.35 ± 0.1	0.00066*	0.39 ± 0.16	0.013*	0.19 ± 0.14	0.15	0.27 ± 0.14	0.064	0.15 ± 0.038	8.8e-05*	0.2 ± 0.04	4e-07*	0.073 ± 0.039	0.059	0.024 ± 0.037	0.52
LPE	LPE(16:0;0)	-0.16 ± 0.11	0.13	0.066 ± 0.15	0.66	0.2 ± 0.12	0.1	0.35 ± 0.14	0.01*	-0.1 ± 0.039	0.01*	-0.12 ± 0.038	0.0014*	0.089 ± 0.039	0.024*	0.19 ± 0.036	1e-07*
	LPE(18:1;0)	-0.26 ± 0.1	0.0094*	-0.15 ± 0.15	0.31	0.063 ± 0.13	0.62	0.46 ± 0.14	0.00063*	-0.12 ± 0.037	0.0014*	-0.18 ± 0.038	9.4e-07*	0.054 ± 0.038	0.15	0.25 ± 0.036	1.6e-12*
	LPE(18:2;0)	-0.23 ± 0.11	0.026*	-0.13 ± 0.15	0.39	0.058 ± 0.12	0.64	0.27 ± 0.14	0.044	-0.089 ± 0.039	0.022*	-0.16 ± 0.038	2.9e-05*	5.3e-06 ± 0.039	1	0.14 ± 0.036	5.9e-05*
	LPE(20:4;0)	-0.12 ± 0.1	0.23	-0.12 ± 0.15	0.42	0.093 ± 0.11	0.41	0.33 ± 0.14	0.016*	-0.085 ± 0.037	0.022*	-0.095 ± 0.038	0.013*	0.0044 ± 0.037	0.91	0.15 ± 0.036	2.9e-05*
	LPE(22:6;0)	0.013 ± 0.11	0.9	-0.046 ± 0.14	0.74	0.21 ± 0.12	0.089	0.12 ± 0.13	0.35	-0.026 ± 0.039	0.51	-0.047 ± 0.037	0.2	0.079 ± 0.04	0.045	0.03 ± 0.035	0.4
LPC	LPC(14:0;0)	-0.13 ± 0.11	0.23	-0.087 ± 0.15	0.57	0.37 ± 0.13	0.004*	0.7 ± 0.14	2.7e-07*	-0.062 ± 0.038	0.11	-0.11 ± 0.038	0.0033*	0.22 ± 0.039	2.6e-08*	0.33 ± 0.036	3.2e-20*
	LPC(16:0;0)	-0.098 ± 0.097	0.31	-0.00033 ± 0.14	1	0.12 ± 0.12	0.3	0.33 ± 0.13	0.013*	-0.044 ± 0.036	0.22	-0.084 ± 0.037	0.025*	0.022 ± 0.036	0.54	0.16 ± 0.035	4.2e-06*

LPC(16:1;0)	-0.27 ± 0.11	0.013*	-0.23 ± 0.15	0.13	0.31 ± 0.13	0.021*	0.5 ± 0.14	0.00026*	-0.13 ± 0.04	0.0011*	-0.14 ± 0.038	0.00017*	0.12 ± 0.041	0.0029*	0.25 ± 0.036	2.3e-12*
LPC(18:0;0)	0.16 ± 0.1	0.12	0.41 ± 0.15	0.0052*	0.048 ± 0.13	0.71	0.17 ± 0.13	0.2	0.085 ± 0.038	0.024*	0.09 ± 0.038	0.017*	-0.042 ± 0.038	0.26	0.066 ± 0.036	0.067
LPC(18:1;0)	-0.27 ± 0.1	0.0059*	-0.1 ± 0.15	0.49	-0.38 ± 0.12	0.0021*	-0.21 ± 0.14	0.13	-0.065 ± 0.036	0.069	-0.092 ± 0.038	0.016*	-0.22 ± 0.036	1.1e-09*	-0.077 ± 0.036	0.035*
LPC(18:2;0)	-0.24 ± 0.092	0.0086*	-0.1 ± 0.15	0.49	-0.47 ± 0.12	5.4e-05*	-0.29 ± 0.13	0.032*	-0.028 ± 0.031	0.38	-0.07 ± 0.038	0.064	-0.3 ± 0.032	5.8e-21*	-0.084 ± 0.036	0.02*
LPC(20:3;0)	-0.051 ± 0.11	0.64	-0.12 ± 0.15	0.43	0.2 ± 0.15	0.18	0.3 ± 0.13	0.024*	-0.025 ± 0.04	0.52	-0.091 ± 0.038	0.016*	-0.015 ± 0.04	0.71	0.22 ± 0.036	7.4e-10*
LPC(20:4;0)	-0.2 ± 0.096	0.04	-0.094 ± 0.14	0.51	-0.21 ± 0.12	0.074	-0.03 ± 0.13	0.82	-0.051 ± 0.034	0.14	-0.061 ± 0.037	0.11	-0.15 ± 0.035	1.4e-05*	0.0063 ± 0.035	0.86
LPC(22:6;0)	-0.033 ± 0.11	0.76	-0.068 ± 0.15	0.64	-0.19 ± 0.14	0.16	-0.22 ± 0.13	0.11	0.021 ± 0.04	0.6	-0.039 ± 0.038	0.3	-0.13 ± 0.04	0.00083*	-0.09 ± 0.036	0.012*

Effect estimates for having high LDL-C or TG values were derived from linear mixed models with the lipid species as outcomes, and hyperlipidemia status, age, age², and sex as fixed effect covariates. The effect estimates were estimated separately in “high LDL-C” families for high LDL-C status (total $n = 463$ individuals), in “high TG” families for high TG status (total $n = 287$ individuals) and in the population for both high LDL-C and high TG status (total $n = 897$ individuals). To estimate independent associations between the lipid species and LDL-C or TG levels, LDL-C, $\log(TGs)$, age, age², and sex were used simultaneously as fixed effect covariates. This analysis was performed separately in the hyperlipidemic families (a); $n = 550$ individuals) and the FINRISK population cohort (b); $n = 897$ individuals). An empirical genetic correlation matrix between individuals was used as the covariance structure of a random effect in all models. Lipid species and continuous values of LDL-C and $\log(TGs)$ were normalized based on mean and standard deviation values observed in the FINRISK population cohort. P-values were calculated using Wald test and statistical significance was evaluated using the Benjamini-Hochberg method at a 5% false discovery rate. Statistically significant effects are marked with an asterisk (*). *Cer* = ceramide, *DG* = diacylglyceride, *LDL-C* = low-density lipoprotein cholesterol, *LPC* = lysophosphatidylcholine, *LPE* = lysophosphatidylethanolamine, *PC* = phosphatidylcholine, *PCO* = phosphatidylcholine-ether, *PE* = phosphatidylethanolamine, *PEO* = phosphatidylethanolamine-ether, *PI* = phosphatidylinositol, *CE* = cholesteryl ester; *SM* = sphingomyelin, *ST* = sterol, *TG* = triacylglyceride.