ORIGINAL RESEARCH

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

Joel T. Rämö, MD; Pietari Ripatti, MD; Rubina Tabassum, PhD; Sanni Söderlund, MD, PhD; Niina Matikainen, MD, PhD; Mathias J. Gerl, PhD; Christian Klose, PhD; Michal A. Surma, PhD; Nathan O. Stitziel, MD, PhD; Aki S. Havulinna, DSc; Matti Pirinen, PhD; Veikko Salomaa, MD, PhD; Nelson B. Freimer, MD; Matti Jauhiainen, PhD; Aarno Palotie, MD, PhD; Marja-Riitta Taskinen, MD, PhD; Kai Simons, MD, PhD; Samuli Ripatti, PhD

***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 >90th 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 $0.038–2.3\times10^{-56}$). 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

From the Institute for Molecular Medicine Finland, HiLIFE (J.T.R., P.R., R.T., A.S.H., M.P., A.P., S.R.), Research Programs Unit, Clinical and Molecular Metabolism (S.S., N.M., M.-R.T.), Department of Mathematics and Statistics, Faculty of Science (M.P.), and Department of Public Health, Clinicum, Faculty of Medicine (M.P., S.R.), University of Helsinki, Finland; Endocrinology, Abdominal Center, Helsinki University Hospital, Helsinki, Finland (S.S., N.M.); Lipotype GmbH, Dresden, Germany (M.J.G., C.K., M.A.S., K.S.); Łukasiewicz Research Network–PORT Polish Center for Technology Development, Wroclaw, Poland (M.A.S.); Cardiovascular Division, Department of Medicine (N.O.S.), Department of Genetics (N.O.S.), and McDonnell Genome Institute (N.O.S.), Washington University School of Medicine, St. Louis, MO; National Institute for Health and Welfare, Helsinki, Finland (A.S.H., V.S., M.J.); Center for Neurobehavioral Genetics, Semel Institute for Neuroscience and Human Behavior, University of California, Los Angeles, CA (N.B.F.); Minerva Foundation Institute for Medical Research, Biomedicum, Helsinki, Finland (M.J.); Program in Medical and Population Genetics and The Stanley Center for Psychiatric Research, The Broad Institute of MIT and Harvard, Cambridge, MA (A.P., S.R.); Psychiatric and Neurodevelopmental Genetics Unit, Department of Psychiatry, Analytic and Translational Genetics Unit, Department of Medicine, and the Department of Neurology, Massachusetts General Hospital, Boston, MA (A.P.); and Max Planck Institute of Cell Biology and Genetics, Dresden, Germany (K.S.).

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

Correspondence to: Samuli Ripatti, PhD, Institute for Molecular Medicine Finland, PO Box 20, FI-00014 University of Helsinki, Helsinki, Finland. E-mail: samuli.ripatti@helsinki

Received March 15, 2019; accepted June 7, 2019.

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 ≥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, age^2, 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

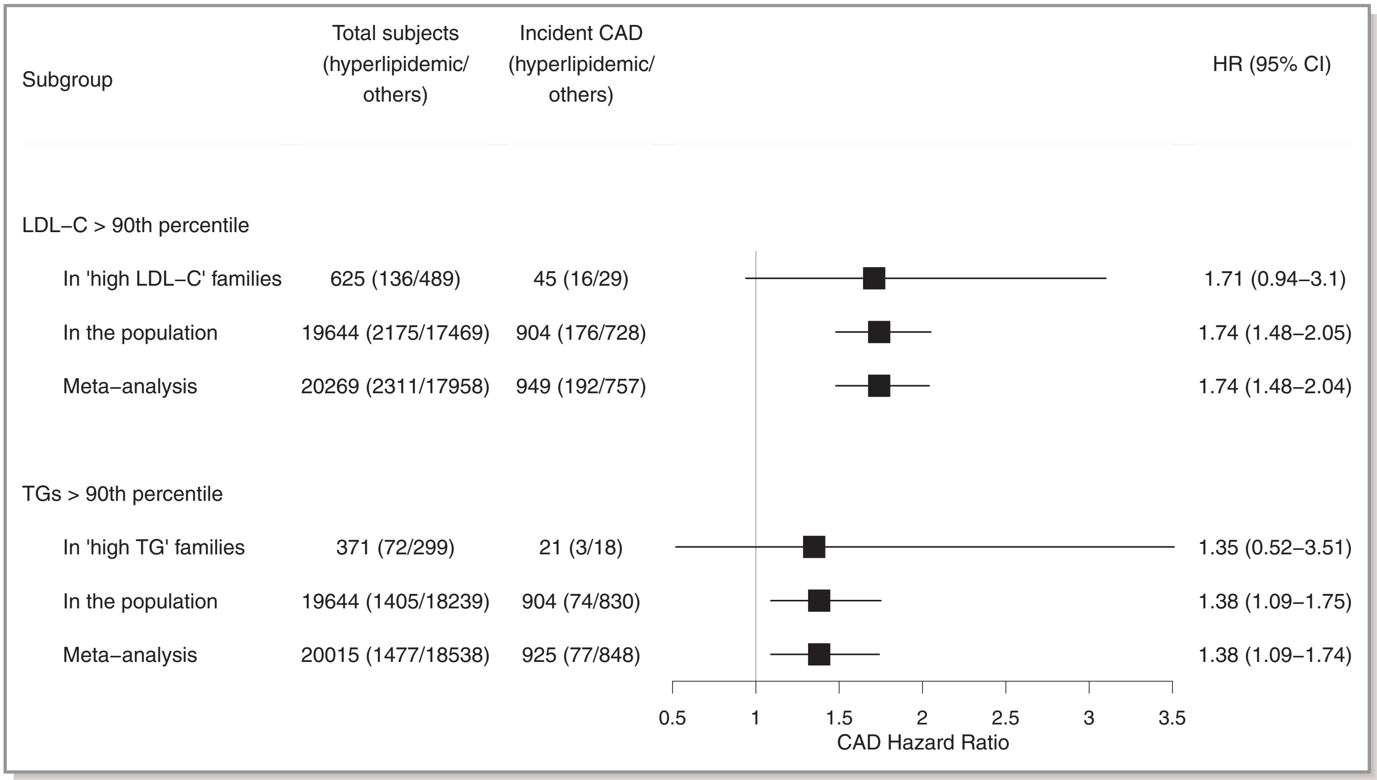


Figure 1. Risk of incident coronary artery disease (CAD) in hyperlipidemias with family history and population-ascertained hyperlipidemias. To assess the risk of incident CAD associated with the hyperlipidemia types, we used Cox proportional hazards models using age as the time scale, stratified by sex 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±SD, 5.2±0.8 mmol/L) and 64 individuals (22%) of 287 family members in 39 high triacylglyceride families who had triacylglycerides >90th percentile (mean±interquartile range, 3.6±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±SD, 5.3±1.1 mmol/L) and high triacylglycerides (mean±interquartile range, 3.5±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 lysophospatidylcholine, 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 lysophospatidylcholines 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 lysophospatidylcholine

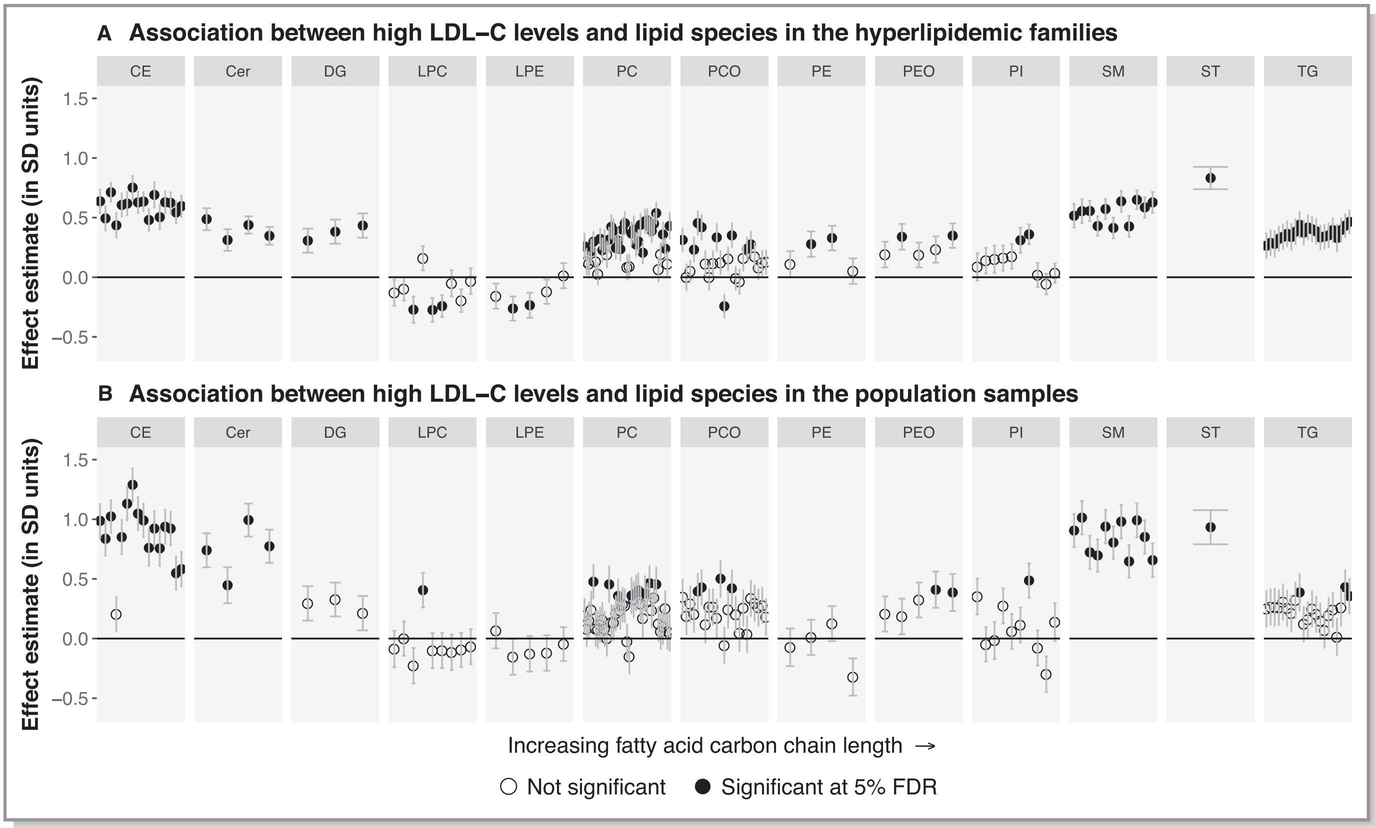


Figure 2. Associations between high low-density lipoprotein cholesterol (LDL-C) status and the levels of 151 lipid species. **A**, Individuals affected by high LDL-C levels (n=105) were compared with their unaffected relatives (n=358) in the 53 "high LDL-C" families. **B**, Individuals affected by high 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, age^2, 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=7.2×10^{-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 lysophospatidylcholine, 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 lysophospatidylcholine 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,

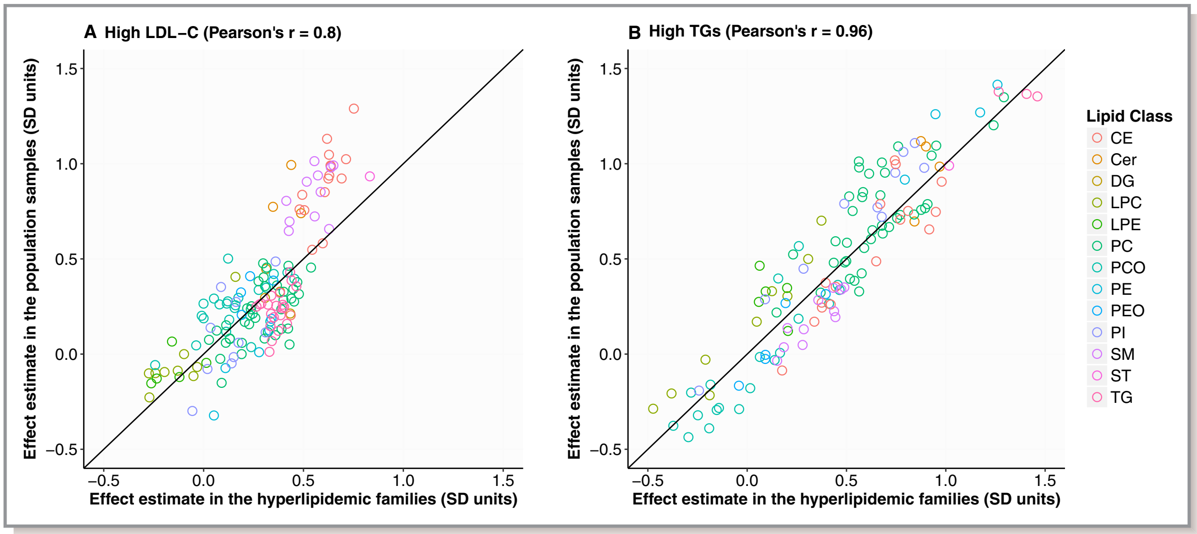


Figure 3. Correlation of effect estimates for hyperlipidemia status between the hyperlipidemic families and the population samples. The correlation between the effect estimates observed in the family and population cohorts is presented for high low-density lipoprotein cholesterol (LDL-C) (effect estimates 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.

lysophospatidylcholines, 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.

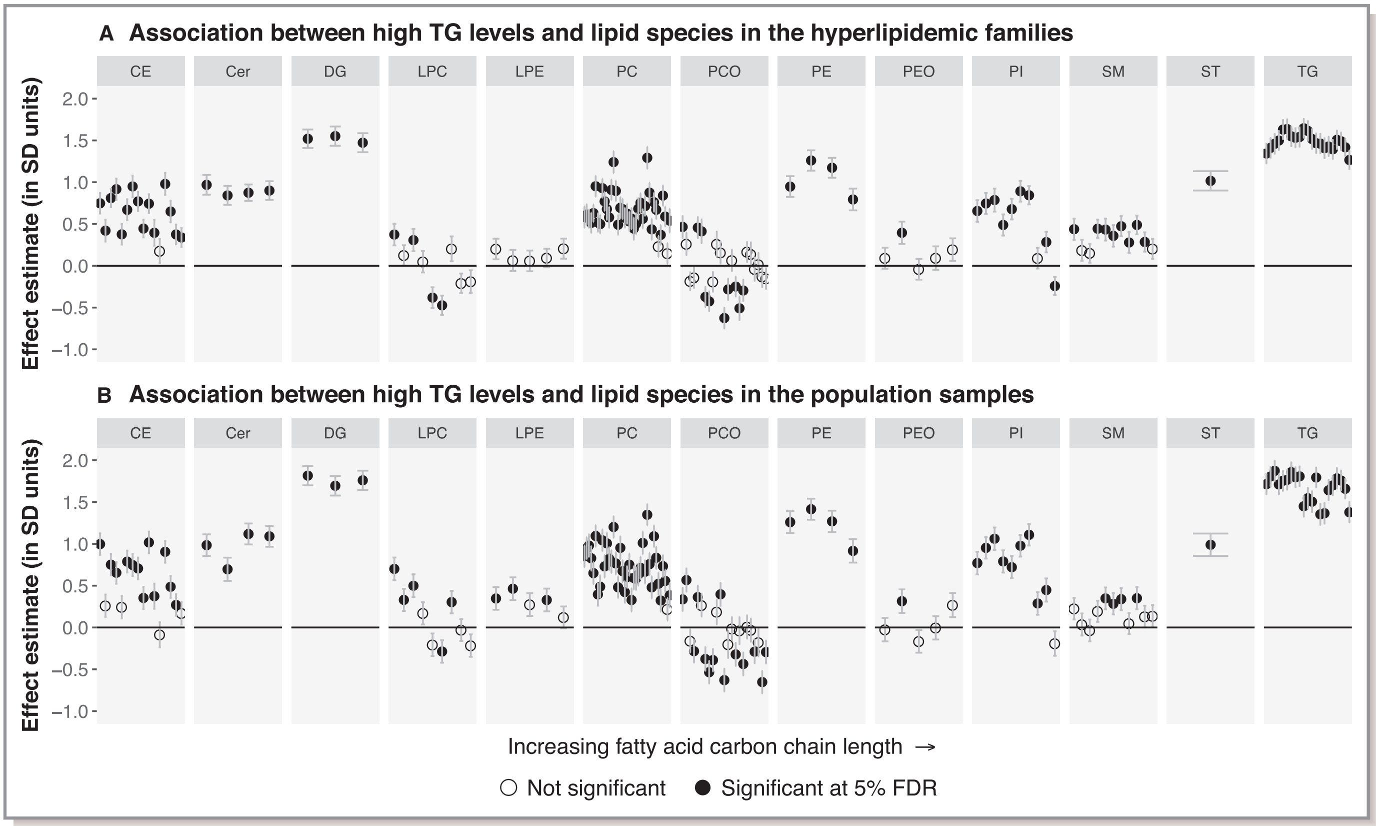


Figure 4. Associations between high triacylglyceride status and the levels of 151 lipid species. **A**, Individuals affected by high triacylglycerides (n=64) were compared with their unaffected relatives (n=223) in 39 "high TG" families. **B**, Individuals affected by high triacylglycerides (n=65) were 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 familiality. 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 familiality 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.

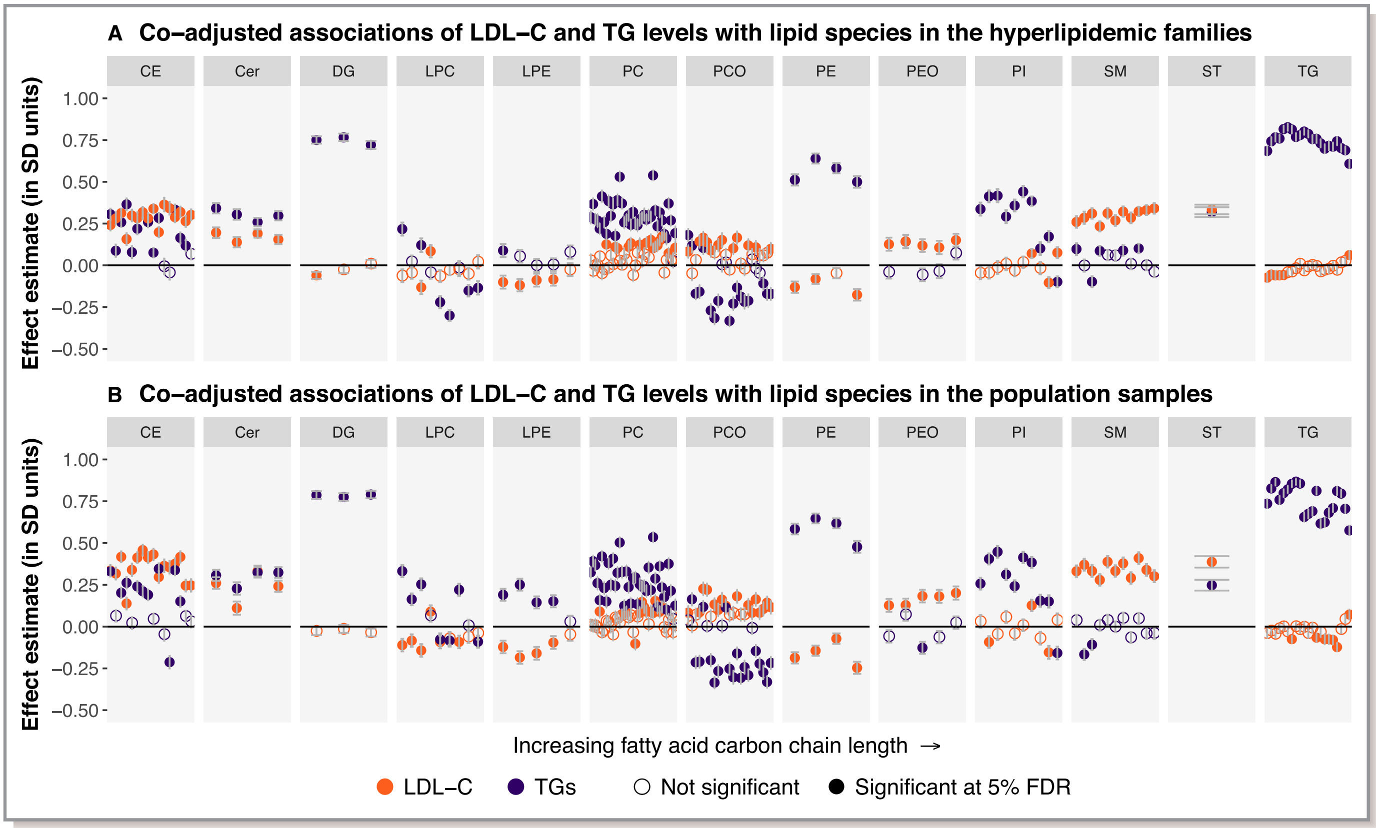


Figure 5. Independent (coadjusted) associations of low-density lipoprotein cholesterol (LDL-C) and triacylglycerides with 151 lipid species. Effect estimates for LDL-C and triacylglycerides were derived from linear mixed models with the lipid species as outcomes and LDL-C, log (triacylglycerides), age, age^2, 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

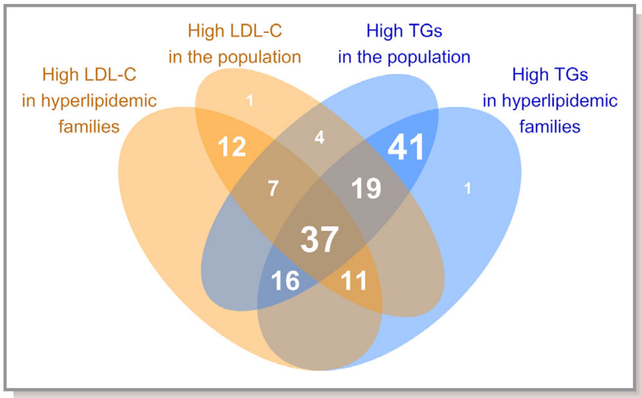


Figure 6. Overlap of the statistically significant independent (coadjusted) associations of low-density lipoprotein cholesterol (LDL-C) and triacylglycerides with 151 lipid species. Each shaded area shows the number of lipid species associated with the corresponding types of hyperlipidemias. More detailed 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 lysophospatidylcholine 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.

Acknowledgments

We would like to thank Sari Kivikko, Huei-Yi Shen, and Ulla Tuomainen for management assistance. The FINRISK study data used for the research were obtained from THL Biobank. We thank all study participants for their generous participation in the FINRISK study and the EUFAM (European Multicenter Study on Familial Dyslipidemias in Patients With Premature Coronary Heart Disease). Drs Ripatti and Rämö acknowledge support from the Doctoral Programme in Population Health, University of Helsinki.

Sources of Funding

This work was supported by National Institutes of Health (grant HL113315 to Drs Ripatti, Taskinen, Freimer, and Palotie); Finnish Foundation for Cardiovascular Research (to Drs Ripatti, Salomaa, Taskinen, Jauhiainen, and Palotie); Academy of Finland Center of Excellence in Complex Disease Genetics (grants 213506 and 129680 to Drs Ripatti, Pirinen and Palotie); Academy of Finland (grants 251217 and 285380 to Dr Ripatti and grant 286500 to Dr Palotie); Jane and Aatos Erkko Foundation (to Dr Jauhiainen); Sigrid Jusélius Foundation (to Drs Ripatti, Palotie, and Taskinen); Biocentrum Helsinki (to Dr Ripatti); Horizon 2020 Research and Innovation Programme (grant 692145 to Dr Ripatti); EU (European Union)-project RESOLVE (EU 7th Framework Program) (grant 305707 to Dr Taskinen); HiLIFE Fellowship (to Dr Ripatti); Helsinki University Central Hospital Research Funds (to Dr Taskinen); Magnus Ehrnrooth Foundation (to Dr Jauhiainen); Leducq Foundation (to Dr Taskinen); Ida Montin Foundation (to Dr Ripatti); MD-PhD Programme of the Faculty of Medicine, University of Helsinki (to Dr Rämö); Doctoral Programme in Population Health, University of Helsinki (to Drs Rämö and Ripatti); Finnish Medical Foundation (to Dr Rämö); Emil Aaltonen Foundation (to Drs Rämö and Ripatti); Biomedicum Helsinki Foundation (to Dr Rämö); Paulo Foundation (to Dr Rämö); Idman Foundation (to Dr Rämö); and Veritas Foundation (to Dr Rämö). The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

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.

References

1. Ference BA, Ginsberg HN, Graham I, Ray KK, Packard CJ, Bruckert E, Hegele RA, Krauss RM, Raal FJ, Schunkert H, Watts GF, Boren J, Fazio S, Horton JD, Masana L, Nicholls SJ, Nordestgaard BG, van de Sluis B, Taskinen MR, Tokgozoglu L, Landmesser U, Laufs U, Wiklund O, Stock JK, Chapman MJ, Catapano AL. Low-density lipoproteins cause atherosclerotic cardiovascular disease, 1: evidence from genetic, epidemiologic, and clinical studies: a consensus statement from the European Atherosclerosis Society Consensus Panel. *Eur Heart J*. 2017;38:2459–2472.
2. Nordestgaard BG. Triglyceride-rich lipoproteins and atherosclerotic cardiovascular disease: new insights from epidemiology, genetics, and biology. *Circ Res*. 2016;118:547–563.
3. Yuan G, Al-Shali KZ, Hegele RA. Hypertriglyceridemia: its etiology, effects and treatment. *CMAJ*. 2007;176:1113–1120.
4. Berglund L, Brunzell JD, Goldberg AC, Goldberg IJ, Sacks F, Murad MH, Stalenhoef AF; Endocrine Society. Evaluation and treatment of hypertriglyceridemia: an Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab*. 2012;97:2969–2989.
5. Kathiresan S, Manning AK, Demissie S, D'Agostino RB, Surti A, Guiducci C, Gianniny L, Burtt NP, Melander O, Orho-Melander M, Arnett DK, Peloso GM, Ordovas JM, Cupples LA. A genome-wide association study for blood lipid phenotypes in the Framingham Heart Study. *BMC Med Genet*. 2007;8(suppl 1):S17.
6. Weiss LA, Pan L, Abney M, Ober C. The sex-specific genetic architecture of quantitative traits in humans. *Nat Genet*. 2006;38:218–222.
7. Genest JJ Jr, Martin-Munley SS, McNamara JR, Ordovas JM, Jenner J, Myers RH, Silberman SR, Wilson PW, Salem DN, Schaefer EJ. Familial lipoprotein disorders in patients with premature coronary artery disease. *Circulation*. 1992;85:2025–2033.
8. Grundy SM, Stone NJ, Bailey AL, Beam C, Birtcher KK, Blumenthal RS, Braun LT, Ferranti SD, Faiella-Tommasino J, Forman DE, Goldberg R, Heidenreich PA, Hlatky MA, Jones DW, Lloyd-Jones D, Lopez-Pajares N, Ndumele CE, Orringer CE, Peralta CA, Saseen JJ, Smith SC, Sperling L, Virani SS, Yeboah J. 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA guideline on the management of blood cholesterol. *Circulation*. 2019;139:e1082–e1143.
9. Catapano AL, Graham I, De Backer G, Wiklund O, Chapman MJ, Drexel H, Hoes AW, Jennings CS, Landmesser U, Pedersen TR, Reiner Ž, Riccardi G, Taskinen M-R, Tokgozoglu L, Verschuren WMM, Vlachopoulos C, Wood DA, Zamorano JL, Cooney M-T; ESC Scientific Document Group. 2016 ESC/EAS guidelines for the management of dyslipidaemias. *Eur Heart J*. 2016;37:2999–3058.
10. Khera AV, Won HH, Peloso GM, Lawson KS, Bartz TM, Deng X, van Leeuwen EM, Natarajan P, Emdin CA, Bick AG, Morrison AC, Brody JA, Gupta N, Nomura A, Kessler T, Duga S, Bis JC, van Duijn CM, Cupples LA, Psaty B, Rader DJ, Danesh J, Schunkert H, McPherson R, Farrall M, Watkins H, Lander E, Wilson JG, Correa A, Boerwinkle E, Merlini PA, Ardissino D, Saleheen D, Gabriel S, Kathiresan S. Diagnostic yield and clinical utility of sequencing familial hypercholesterolemia genes in patients with severe hypercholesterolemia. *J Am Coll Cardiol*. 2016;67:2578–2589.
11. Ripatti P, Ramo JT, Soderlund S, Surakka I, Matikainen N, Pirinen M, Pajukanta P, Sarin AP, Service SK, Laurila PP, Ehnholm C, Salomaa V, Wilson RK, Palotie

A, Freimer NB, Taskinen MR, Ripatti S. The contribution of GWAS loci in familial dyslipidemias. *PLoS Genet*. 2016;12:e1006078.
12. Stitziel NO, Peloso GM, Abifadel M, Cefalu AB, Fouchier S, Motazacker MM, Tada H, Larach DB, Awan Z, Haller JF, Pullinger CR, Varret M, Rabes JP, Noto D, Tarugi P, Kawashiri MA, Nohara A, Yamagishi M, Risman M, Deo R, Ruel I, Shendure J, Nickerson DA, Wilson JG, Rich SS, Gupta N, Farlow DN, Neale BM, Daly MJ, Kane JP, Freeman MW, Genest J, Rader DJ, Mabuchi H, Kastelein JJ, Hovingh GK, Averna MR, Gabriel S, Boileau C, Kathiresan S. Exome sequencing in suspected monogenic dyslipidemias. *Circ Cardiovasc Genet*. 2015;8:343–350.
13. Talmud PJ, Shah S, Whittall R, Futema M, Howard P, Cooper JA, Harrison SC, Li K, Drenos F, Karpe F, Neil HA, Descamps OS, Langenberg C, Lench N, Kivimaki M, Whittaker J, Hingorani AD, Kumari M, Humphries SE. Use of low-density lipoprotein cholesterol gene score to distinguish patients with polygenic and monogenic familial hypercholesterolaemia: a case-control study. *Lancet*. 2013;381:1293–1301.
14. Surma MA, Herzog R, Vasilj A, Klose C, Christinat N, Morin-Rivron D, Simons K, Masoodi M, Sampaio JL. An automated shotgun lipidomics platform for high throughput, comprehensive, and quantitative analysis of blood plasma intact lipids. *Eur J Lipid Sci Technol*. 2015;117:1540–1549.
15. Han X. Lipidomics for studying metabolism. *Nat Rev Endocrinol*. 2016;12:668–679.
16. Simons K. How can omic science be improved? *Proteomics*. 2018;18: e1800039.
17. Cuthbert JA, East CA, Bilheimer DW, Lipsky PE. Detection of familial hypercholesterolemia by assaying functional low-density-lipoprotein receptors on lymphocytes. *N Engl J Med*. 1986;314:879–883.
18. Matyash V, Liebisch G, Kurzchalia TV, Shevchenko A, Schwudke D. Lipid extraction by methyl-tert-butyl ether for high-throughput lipidomics. *J Lipid Res*. 2008;49:1137–1146.
19. Herzog R, Schuhmann K, Schwudke D, Sampaio JL, Bornstein SR, Schroeder M, Shevchenko A. LipidXplorer: a software for consensual cross-platform lipidomics. *PLoS One*. 2012;7:e29851.
20. Herzog R, Schwudke D, Schuhmann K, Sampaio JL, Bornstein SR, Schroeder M, Shevchenko A. A novel informatics concept for high-throughput shotgun lipidomics based on the molecular fragmentation query language. *Genome Biol*. 2011;12:R8.
21. Pirinen M, Donnelly P, Spencer CCA. Efficient computation with a linear mixed model on large-scale data sets with applications to genetic studies. *Ann Appl Stat*. 2013;7:369–390.
22. Stegemann C, Pechlaner R, Willeit P, Langley SR, Mangino M, Mayr U, Menni C, Moayyeri A, Santer P, Rungger G, Spector TD, Willeit J, Kiechl S, Mayr M. Lipidomics profiling and risk of cardiovascular disease in the prospective population-based Bruneck study. *Circulation*. 2014;129:1821–1831.
23. Alshehry ZH, Mundra PA, Barlow CK, Mellett NA, Wong G, McConville MJ, Simes J, Tonkin AM, Sullivan DR, Barnes EH, Nestel PJ, Kingwell BA, Marre M, Neal B, Poulter NR, Rodgers A, Williams B, Zoungas S, Hillis GS, Chalmers J, Woodward M, Meikle PJ. Plasma lipidomic profiles improve on traditional risk factors for the prediction of cardiovascular events in type 2 diabetes mellitus. *Circulation*. 2016;134:1637–1650.
24. R Core Team. *R: A language and environment for statistical computing*. Vienna, Austria: R Foundation for Statistical Computing; 2018. Available at: https://www.R-project.org/.
25. Voors-Pette C, de Bruin TW. Excess coronary heart disease in familial combined hyperlipidemia, in relation to genetic factors and central obesity. *Atherosclerosis*. 2001;157:481–489.
26. Luijten J, van Greevenbroek MMJ, Schaper NC, Meex SJR, van der Steen C, Meijer LJ, de Boer D, de Graaf J, Stehouwer CDA, Brouwers MCGJ. Incidence of cardiovascular disease in familial combined hyperlipidemia: a 15-year follow-up study. *Atherosclerosis*. 2019;280:1–6.
27. Austin MA, McKnight B, Edwards KL, Bradley CM, McNeely MJ, Psaty BM, Brunzell JD, Motulsky AG. Cardiovascular disease mortality in familial forms of hypertriglyceridemia: a 20-year prospective study. *Circulation*. 2000;101:2777–2782.
28. Lahtinen AM, Havulinna AS, Jula A, Salomaa V, Kontula K. Prevalence and clinical correlates of familial hypercholesterolemia founder mutations in the general population. *Atherosclerosis*. 2015;238:64–69.
29. Abul-Husn NS, Manickam K, Jones LK, Wright EA, Hartzel DN, Gonzaga-Jauregui C, O'Dushlaine C, Leader JB, Lester Kirchner H, Lindbuchler DAM, Barr ML, Giovanni MA, Ritchie MD, Overton JD, Reid JG, Metpally RPR, Wardeh AH, Borecki IB, Yancopoulos GD, Baras A, Shuldiner AR, Gottesman O, Ledbetter DH, Carey DJ, Dewey FE, Murray MF. Genetic identification of familial hypercholesterolemia within a single U.S. health care system. *Science*. 2016;354:aaf7000.
30. Hegele RA, Ginsberg HN, Chapman MJ, Nordestgaard BG, Kuivenhoven JA, Averna M, Boren J, Bruckert E, Catapano AL, Descamps OS, Hovingh GK, Humphries SE, Kovanen PT, Masana L, Pajukanta P, Parhofer KG, Raal FJ, Ray KK, Santos RD, Stalenhoef AF, Stroes E, Taskinen MR, Tybjaerg-Hansen A, Watts GF, Wiklund O; European Atherosclerosis Society Consensus Panel. The polygenic nature of hypertriglyceridaemia: implications for definition, diagnosis, and management. *Lancet Diabetes Endocrinol*. 2014;2:655–666.
31. Laaksonen R, Ekroos K, Sysi-Aho M, Hilvo M, Vihervaara T, Kauhanen D, Suoniemi M, Hurme R, Marz W, Scharnagl H, Stojakovic T, Vlachopoulou E, Lokki ML, Nieminen MS, Klingenberg R, Matter CM, Hornemann T, Juni P, Rodondi N, Raber L, Windecker S, Gencer B, Pedersen ER, Tell GS, Nygard O, Mach F, Sinisalo J, Luscher TF. Plasma ceramides predict cardiovascular death in patients with stable coronary artery disease and acute coronary syndromes beyond LDL-cholesterol. *Eur Heart J*. 2016;37:1967–1976.
32. Demirkan A, van Duijn CM, Ugocsai P, Isaacs A, Pramstaller PP, Liebisch G, Wilson JF, Johansson A, Rudan I, Aulchenko YS, Kirichenko AV, Janssens AC, Jansen RC, Gnewuch C, Domingues FS, Pattaro C, Wild SH, Jonasson I, Polasek O, Zorkoltseva IV, Hofman A, Karssen LC, Struchalin M, Floyd J, Igl W, Biloglav Z, Broer L, Pfeufer A, Pichler I, Campbell S, Zaboli G, Kolcic I, Rivadeneira F, Huffman J, Hastie ND, Uitterlinden A, Franke L, Franklin CS, Vitart V; DIAGRAM Consortium, Nelson CP, Preuss M; CARDIoGRAM Consortium, Bis JC, O'Donnell CJ, Franceschini N; CHARGE Consortium, Witteman JC, Axenovich T, Oostra BA, Meitinger T, Hicks AA, Hayward C, Wright AF, Gyllensten U, Campbell H, Schmitz G; EUROSPAN Consortium. Genome-wide association study identifies novel loci associated with circulating phospho- and sphingolipid concentrations. *PLoS Genet*. 2012;8:e1002490.
33. Laurila PP, Surakka I, Sarin AP, Yetukuri L, Hyotylainen T, Soderlund S, Naukkarinen J, Tang J, Kettunen J, Mirel DB, Soronen J, Lehtimaki T, Ruokonen A, Ehnholm C, Eriksson JG, Salomaa V, Jula A, Raitakari OT, Jarvelin MR, Palotie A, Peltonen L, Oresic M, Jauhiainen M, Taskinen MR, Ripatti S. Genomic, transcriptomic, and lipidomic profiling highlights the role of inflammation in individuals with low high-density lipoprotein cholesterol. *Arterioscler Thromb Vasc Biol*. 2013;33:847–857.
34. Olivecrona G. Role of lipoprotein lipase in lipid metabolism. *Curr Opin Lipidol*. 2016;27:233–241.
35. Kobayashi J, Miyashita K, Nakajima K, Mabuchi H. Hepatic lipase: a comprehensive view of its role on plasma lipid and lipoprotein metabolism. *J Atheroscler Thromb*. 2015;22:1001–1011.
36. Masson D, Jiang X-C, Lagrost L, Tall AR. The role of plasma lipid transfer proteins in lipoprotein metabolism and atherogenesis. *J Lipid Res*. 2009;50: S201–S206.
37. Christinat N, Masoodi M. Comprehensive lipoprotein characterization using lipidomics analysis of human plasma. *J Proteome Res*. 2017;16:2947–2953.
38. Raatz SK, Bibus D, Thomas W, Kris-Etherton P. Total fat intake modifies plasma fatty acid composition in humans. *J Nutr*. 2001;131:231–234.
39. Tarasov K, Ekroos K, Suoniemi M, Kauhanen D, Sylvanne T, Hurme R, Gouni-Berthold I, Berthold HK, Kleber ME, Laaksonen R, Marz W. Molecular lipids identify cardiovascular risk and are efficiently lowered by simvastatin and PCSK9 deficiency. *J Clin Endocrinol Metab*. 2014;99:E45–E52.
40. Havulinna AS, Sysi-Aho M, Hilvo M, Kauhanen D, Hurme R, Ekroos K, Salomaa V, Laaksonen R. Circulating ceramides predict cardiovascular outcomes in the population-based FINRISK 2002 cohort. *Arterioscler Thromb Vasc Biol*. 2016;36:2424–2430.
41. Christensen JJ, Ulven SM, Retterstøl K, Narverud I, Bogsrud MP, Henriksen T, Bollerslev J, Halvorsen B, Aukrust P, Holven KB. Comprehensive lipid and metabolite profiling of children with and without familial hypercholesterolemia: a cross-sectional study. *Atherosclerosis*. 2017;266:48–57.
42. Tabassum R, Rämö JT, Ripatti P, Koskela JT, Kurki M, Karjalainen J, Hassan S, Nunez-Fontarnau J, Kiiskinen TTJ, Söderlund S, Matikainen N, Gerl MJ, Surma MA, Klose C, Stitziel NO, Laivuori H, Havulinna AS, Service SK, Salomaa V, Pirinen M, Jauhiainen M, Daly MJ, Freimer NB, Palotie A, Taskinen M-R, Simons K, Ripatti S. Genetics of human plasma lipidome: understanding lipid metabolism and its link to diseases beyond traditional lipids. *bioRxiv*. 2018;457960.
43. Nordestgaard BG, Langsted A, Mora S, Kolovou G, Baum H, Bruckert E, Watts GF, Sypniewska G, Wiklund O, Boren J, Chapman MJ, Cobbaert C, Descamps OS, von Eckardstein A, Kamstrup PR, Pulkki K, Kronenberg F, Remaley AT, Rifai N, Ros E, Langlois M; European Atherosclerosis Society (EAS) and the European Federation of Clinical Chemistry and Laboratory Medicine (EFLM) Joint Consensus Initiative. Fasting is not routinely required for determination of a lipid profile: clinical and laboratory implications including flagging at desirable concentration cutpoints—a joint consensus statement from the European Atherosclerosis Society and European Federation of Clinical Chemistry and Laboratory Medicine. *Clin Chem*. 2016;62:930–946.

SUPPLEMENTAL MATERIAL

Data S1. Supplemental Methods

Subjects and clinical measurements

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

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

Samples from the Finnish National FINRISK study were used as a Finnish population-based comparison group. The National FINRISK Study is a population survey conducted every 5 years since 1972.[2] Collections from the 1992, 1997, 2002, 2007, and 2012 surveys are stored in the National Institute for Health and Welfare (THL) biobank. All available individuals from the 1992-2002 surveys (*n* = 19,644 individuals) without CAD at baseline and who passed exclusion criteria were used to study the incidence of coronary artery disease associated with hyperlipidemias, and samples from the FINRISK 2012 cohort underwent lipidomic profiling (*n* = 1,141 individuals, 897 of whom passed exclusion criteria). Individuals with known diabetes, pregnancy or cancer were excluded from the analyses. Individuals in all FINRISK cohorts were classified as being affected or unaffected by high LDL-C and high TGs based on the same lipid thresholds as in the EUFAM study.

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

Registry data

Tracking of incident CAD and CVD diagnoses was based on the National Finnish Hospital Discharge Register and the National Causes-of-Death Register, whose diagnoses have been previously validated.[6, 7] The endpoint of incident CHD was defined as the first occurrence of fatal or nonfatal myocardial infarction (International Classification of Diseases [ICD]-10 codes I20.0 or I21-22, ICD-9 codes 410 or 411.0, or ICD-8 codes 410 or 411.0 for hospital discharge; or ICD-10 I21-25, I46, R96, or R98, ICD-9 410-414 or 798 [excluding 7980A], or ICD-8 410-414 or 798 for main cause-of-death) or cardiac revascularization (percutaneous transluminal angioplasty or coronary artery bypass graft surgery). Similar to a previous study, the endpoint of incident CVD additionally included stroke (ICD-10 codes I61 or I63-64 [excluding code I63.6 corresponding to subarachnoid hemorrhage]; ICD-9 codes 431, 433.0, 433.1, 433.9, 434.0, 434.1, 434.9, or 436; or ICD-8 codes 431 [excluding codes 431.01 and 431.91 of the Finnish adaptation of ICD-8], 433, 434, or 436 for hospital discharge or main cause-of-death).[8]

Lipidomics measurements

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

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 with a resolution of $R_{m/z=200}$=280000 for MS and $R_{m/z=200}$=17500 for MSMS experiments, in a single acquisition. MSMS was triggered by an inclusion list encompassing corresponding MS mass ranges scanned in 1 Da increments. Both MS and MSMS data were combined to monitor CE, DAG and TAG ions as ammonium adducts; PC, PC O-, as acetate adducts; and PE, PE O- and PI as deprotonated anions. MS only was used to monitor LPE as deprotonated anion; Cer, SM and LPC as acetate adducts and cholesterol as ammonium adduct.

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

A total of 230 lipid species were successfully detected in both the EUFAM and FINRISK 2012 cohorts, with detection rates (proportion of samples with successful quantification) between 9.7-100%. Among these, 151 species were detected in at least 80% of both EUFAM and FINRISK samples and were included in the subsequent analyses. The median absolute concentrations of the analyzed lipid species are presented separately for the family and population cohorts in Supplemental Table 5. SwissLipids names and ID codes are presented for each of the 151 lipid species in Supplemental Table 6.[12] Right-skewed lipidomics measures (skewness > 1 in the FINRISK population cohort) were natural logarithm transformed prior to analyses. Values were then normalized using mean and standard deviation values derived from the FINRISK population cohort. Additionally, we calculated weighted class-specific saturation averages for each subject using the following formula: $1*p_1 + 2*p_2 + \ldots + n*p_n$ (where p_n = the concentration of lipid species with n double bonds divided by the total concentration of all species belonging to the class).

Genotyping and imputation

To assess the association of known genetic lipid loci with the circulating lipid species, we genotyped and imputed the EUFAM and FINRISK samples using several arrays: the HumanCoreExome BeadChip, the Human610-Quad BeadChip, the Affymetrix6.0, and the Infinium HumanOmniExpress (Illumina Inc., San Diego, CA, USA). Genotype calls were generated together with other available data sets using zCall at the Institute for Molecular Medicine Finland (FIMM). After quality control, the samples were phased using SHAPEIT (version 2)[13] and imputed with IMPUTE (version 2.3.1)[14]. We used a combined reference panel based on 1000 Genomes Phase I integrated haplotypes produced using SHAPEIT (version 2) release on June 2014 and an in-house reference panel from 1941 whole genome sequenced Finnish individuals from the FINRISK and Health 2000 population cohorts.[15] We successfully genotyped or imputed 87 lead variants associated with LDL-C and 74 lead variants associated with TGs in published genome-wide association studies.[16-18]

Statistical analyses

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

We used linear mixed models to estimate the association between lipidomic parameters (concentrations of lipid species or weighted saturation averages) and the other parameter of interest (hyperlipidemia status, continuous lipid measurement, or genotype) as implemented in MMM (version 1.01).[19] Transformed lipid species values (or weighted saturation averages) were used as the outcomes, and hyperlipidemia status, age, age^2, and sex were used as fixed effect covariates. We first assessed both cohorts (the EUFAM family cohort and the FINRISK population cohort) separately, and then together by including an interaction term between cohort and hyperlipidemia status. We examined the independent effects of LDL-C and TG levels by using transformed lipid species as the outcomes and LDL-C, $\log(TGs)$, age, age^2, and sex as fixed effect covariates. Because the lipid species had been quantified in two batches for the EUFAM cohort, we performed all EUFAM analyses separately for both batches, and combined the results using fixed effects inverse-variance weighted meta-analysis as implemented in the R package 'metafor'. P-values were calculated using Wald test.

Supplemental References

1. Porkka KV, Nuotio I, Pajukanta P, Ehnholm C, Suurinkeroinen L, Syvanne M, Lehtimaki T, Lahdenkari AT, Lahdenpera S, Ylitalo K, Antikainen M, Perola M, Raitakari OT, Kovanen P, Viikari JS, Peltonen L and Taskinen MR. Phenotype expression in familial combined hyperlipidemia. *Atherosclerosis*. 1997;133:245-53.
2. Borodulin K, Vartiainen E, Peltonen M, Jousilahti P, Juolevi A, Laatikainen T, Mannisto S, Salomaa V, Sundvall J and Puska P. Forty-year trends in cardiovascular risk factors in Finland. *Eur J Public Health*. 2015;25:539-46.
3. Cuthbert JA, East CA, Bilheimer DW and Lipsky PE. Detection of familial hypercholesterolemia by assaying functional low-density-lipoprotein receptors on lymphocytes. *N Engl J Med*. 1986;314:879-83.
4. Lahtinen AM, Havulinna AS, Jula A, Salomaa V and Kontula K. Prevalence and clinical correlates of familial hypercholesterolemia founder mutations in the general population. *Atherosclerosis*. 2015;238:64-69.
5. Ripatti P, Ramo JT, Soderlund S, Surakka I, Matikainen N, Pirinen M, Pajukanta P, Sarin AP, Service SK, Laurila PP, Ehnholm C, Salomaa V, Wilson RK, Palotie A, Freimer NB, Taskinen MR and Ripatti S. The Contribution of GWAS Loci in Familial Dyslipidemias. *PLoS Genet*. 2016;12:e1006078.
6. Tolonen H, Salomaa V, Torppa J, Sivenius J, Immonen-Raiha P, Lehtonen A and register F. The validation of the Finnish Hospital Discharge Register and Causes of Death Register data on stroke diagnoses. *Eur J Cardiovasc Prev Rehabil*. 2007;14:380-5.
7. Pajunen P, Koukkunen H, Ketonen M, Jerkkola T, Immonen-Raiha P, Karja-Koskenkari P, Mahonen M, Niemela M, Kuulasmaa K, Palomaki P, Mustonen J, Lehtonen A, Arstila M, Vuorenmaa T, Lehto S, Miettinen H, Torppa J, Tuomilehto J, Kesaniemi YA, Pyorala K and Salomaa V. The validity of the Finnish Hospital Discharge Register and Causes of Death Register data on coronary heart disease. *Eur J Cardiovasc Prev Rehabil*. 2005;12:132-7.
8. Würtz P, Havulinna AS, Soininen P, Tynkkynen T, Prieto-Merino D, Tillin T, Ghorbani A, Artati A, Wang Q, Tiainen M, Kangas AJ, Kettunen J, Kaikkonen J, Mikkila V, Jula A, Kahonen M, Lehtimaki T, Lawlor DA, Gaunt TR, Hughes AD, Sattar N, Illig T, Adamski J, Wang TJ, Perola M, Ripatti S, Vasan RS, Raitakari OT, Gerszten RE, Casas JP, Chaturvedi N, Ala-Korpela M and Salomaa V. Metabolite Profiling and Cardiovascular Event Risk: A Prospective Study of Three Population-Based Cohorts. *Circulation*. 2015.
9. Matyash V, Liebisch G, Kurzchalia TV, Shevchenko A and Schwudke D. Lipid extraction by methyl-tert-butyl ether for high-throughput lipidomics. *J Lipid Res*. 2008;49:1137-46.
10. Herzog R, Schuhmann K, Schwudke D, Sampaio JL, Bornstein SR, Schroeder M and Shevchenko A. LipidXplorer: a software for consensual cross-platform lipidomics. *PLoS One*. 2012;7:e29851.
11. Herzog R, Schwudke D, Schuhmann K, Sampaio JL, Bornstein SR, Schroeder M and Shevchenko A. A novel informatics concept for high-throughput shotgun lipidomics based on the molecular fragmentation query language. *Genome Biol*. 2011;12:R8.
12. Aimo L, Liechti R, Hyka-Nouspikel N, Niknejad A, Gleizes A, Götz L, Kuznetsov D, David FPA, van der Goot FG, Riezman H, Bougueleret L, Xenarios I and Bridge A. The SwissLipids knowledgebase for lipid biology. *Bioinformatics*. 2015;31:2860-2866.
13. Delaneau O, Marchini J and Zagury JF. A linear complexity phasing method for thousands of genomes. *Nature methods*. 2012;9:179-81.
14. Howie B, Marchini J and Stephens M. Genotype imputation with thousands of genomes. *G3*. 2011;1:457-70.
15. Genomes Project C, Abecasis GR, Auton A, Brooks LD, DePristo MA, Durbin RM, Handsaker RE, Kang HM, Marth GT and McVean GA. An integrated map of genetic variation from 1,092 human genomes. *Nature*. 2012;491:56-65.

16. Teslovich TM, Musunuru K, Smith AV, Edmondson AC, Stylianou IM, Koseki M, Pirruccello JP, Ripatti S, Chasman DI, Willer CJ, Johansen CT, Fouchier SW, Isaacs A, Peloso GM, Barbalic M, Ricketts SL, Bis JC, Aulchenko YS, Thorleifsson G, Feitosa MF, Chambers J, Orho-Melander M, Melander O, Johnson T, Li X, Guo X, Li M, Shin Cho Y, Jin Go M, Jin Kim Y, Lee JY, Park T, Kim K, Sim X, Twee-Hee Ong R, Croteau-Chonka DC, Lange LA, Smith JD, Song K, Hua Zhao J, Yuan X, Luan J, Lamina C, Ziegler A, Zhang W, Zee RY, Wright AF, Witteman JC, Wilson JF, Willemsen G, Wichmann HE, Whitfield JB, Waterworth DM, Wareham NJ, Waeber G, Vollenweider P, Voight BF, Vitart V, Uitterlinden AG, Uda M, Tuomilehto J, Thompson JR, Tanaka T, Surakka I, Stringham HM, Spector TD, Soranzo N, Smit JH, Sinisalo J, Silander K, Sijbrands EJ, Scuteri A, Scott J, Schlessinger D, Sanna S, Salomaa V, Saharinen J, Sabatti C, Ruokonen A, Rudan I, Rose LM, Roberts R, Rieder M, Psaty BM, Pramstaller PP, Pichler I, Perola M, Penninx BW, Pedersen NL, Pattaro C, Parker AN, Pare G, Oostra BA, O'Donnell CJ, Nieminen MS, Nickerson DA, Montgomery GW, Meitinger T, McPherson R, McCarthy MI, McArdle W, Masson D, Martin NG, Marroni F, Mangino M, Magnusson PK, Lucas G, Luben R, Loos RJ, Lokki ML, Lettre G, Langenberg C, Launer LJ, Lakatta EG, Laaksonen R, Kyvik KO, Kronenberg F, Konig IR, Khaw KT, Kaprio J, Kaplan LM, Johansson A, Jarvelin MR, Janssens AC, Ingelsson E, Igl W, Kees Hovingh G, Hottenga JJ, Hofman A, Hicks AA, Hengstenberg C, Heid IM, Hayward C, Havulinna AS, Hastie ND, Harris TB, Haritunians T, Hall AS, Gyllensten U, Guiducci C, Groop LC, Gonzalez E, Gieger C, Freimer NB, Ferrucci L, Erdmann J, Elliott P, Ejebe KG, Doring A, Dominiczak AF, Demissie S, Deloukas P, de Geus EJ, de Faire U, Crawford G, Collins FS, Chen YD, Caulfield MJ, Campbell H, Burtt NP, Bonnycastle LL, Boomsma DI, Boekholdt SM, Bergman RN, Barroso I, Bandinelli S, Ballantyne CM, Assimes TL, Quertermous T, Altshuler D, Seielstad M, Wong TY, Tai ES, Feranil AB, Kuzawa CW, Adair LS, Taylor HA, Jr., Borecki IB, Gabriel SB, Wilson JG, Holm H, Thorsteinsdottir U, Gudnason V, Krauss RM, Mohlke KL, Ordovas JM, Munroe PB, Kooner JS, Tall AR, Hegele RA, Kastelein JJ, Schadt EE, Rotter JI, Boerwinkle E, Strachan DP, Mooser V, Stefansson K, Reilly MP, Samani NJ, Schunkert H, Cupples LA, Sandhu MS, Ridker PM, Rader DJ, van Duijn CM, Peltonen L, Abecasis GR, Boehnke M and Kathiresan S. Biological, clinical and population relevance of 95 loci for blood lipids. *Nature*. 2010;466:707-13.

17. Surakka I, Horikoshi M, Magi R, Sarin AP, Mahajan A, Lagou V, Marullo L, Ferreira T, Miraglio B, Timonen S, Kettunen J, Pirinen M, Karjalainen J, Thorleifsson G, Hagg S, Hottenga JJ, Isaacs A, Ladenvall C, Beekman M, Esko T, Ried JS, Nelson CP, Willenborg C, Gustafsson S, Westra HJ, Blades M, de Craen AJ, de Geus EJ, Deelen J, Grallert H, Hamsten A, Havulinna AS, Hengstenberg C, Houwing-Duistermaat JJ, Hypponen E, Karssen LC, Lehtimaki T, Lyssenko V, Magnusson PK, Mihailov E, Muller-Nurasyid M, Mpindi JP, Pedersen NL, Penninx BW, Perola M, Pers TH, Peters A, Rung J, Smit JH, Steinthorsdottir V, Tobin MD, Tsernikova N, van Leeuwen EM, Viikari JS, Willems SM, Willemsen G, Schunkert H, Erdmann J, Samani NJ, Kaprio J, Lind L, Gieger C, Metspalu A, Slagboom PE, Groop L, van Duijn CM, Eriksson JG, Jula A, Salomaa V, Boomsma DI, Power C, Raitakari OT, Ingelsson E, Jarvelin MR, Thorsteinsdottir U, Franke L, Ikonen E, Kallioniemi O, Pietiainen V, Lindgren CM, Stefansson K, Palotie A, McCarthy MI, Morris AP, Prokopenko I, Ripatti S and Consortium E. The impact of low-frequency and rare variants on lipid levels. *Nat Genet*. 2015;47:589-97.

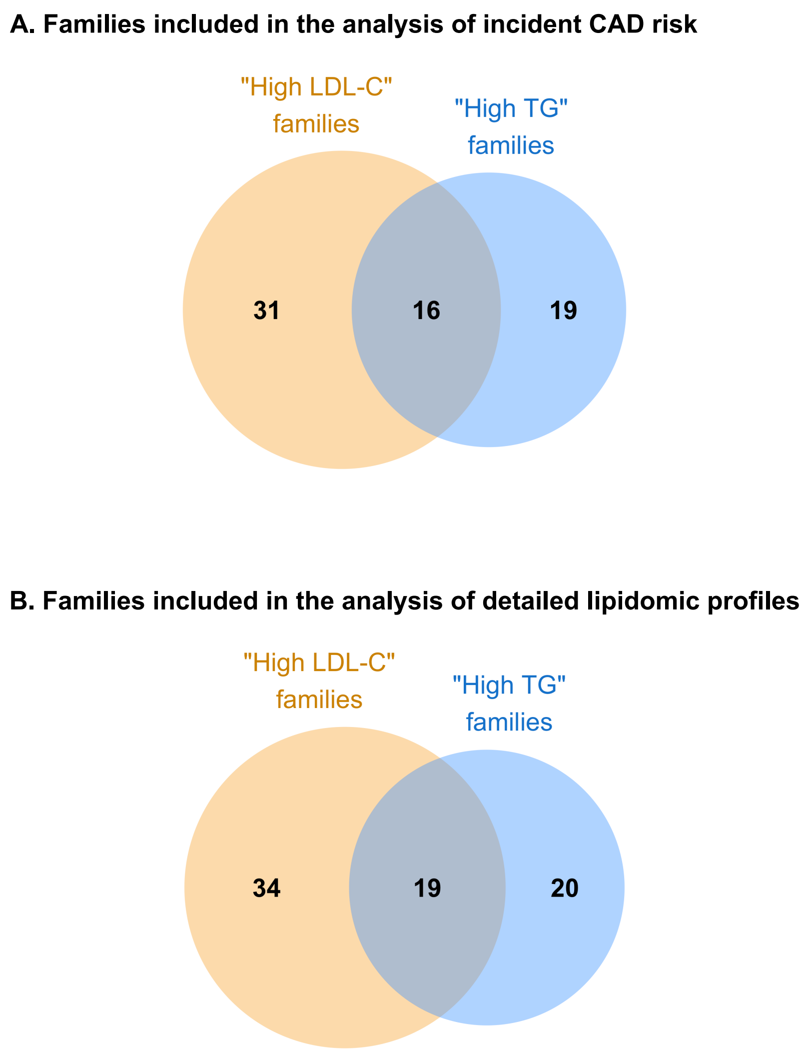
18. Global Lipids Genetics Consortium, Willer CJ, Schmidt EM, Sengupta S, Peloso GM, Gustafsson S, Kanoni S, Ganna A, Chen J, Buchkovich ML, Mora S, Beckmann JS, Bragg-Gresham JL, Chang HY, Demirkan A, Den Hertog HM, Do R, Donnelly LA, Ehret GB, Esko T, Feitosa MF, Ferreira T, Fischer K, Fontanillas P, Fraser RM, Freitag DF, Gurdasani D, Heikkila K, Hypponen E, Isaacs A, Jackson AU, Johansson A, Johnson T, Kaakinen M, Kettunen J, Kleber ME, Li X, Luan J, Lyytikainen LP, Magnusson PK, Mangino M, Mihailov E, Montasser ME, Muller-Nurasyid M, Nolte IM, O'Connell JR, Palmer CD, Perola M, Petersen AK, Sanna S, Saxena R, Service SK, Shah S, Shungin D, Sidore C, Song C, Strawbridge RJ, Surakka I, Tanaka T, Teslovich TM, Thorleifsson G, Van den Herik EG, Voight BF, Volcik KA, Waite LL, Wong A, Wu Y, Zhang W, Absher D, Asiki G, Barroso I, Been LF, Bolton JL, Bonnycastle LL, Brambilla P, Burnett MS, Cesana G, Dimitriou M, Doney AS, Doring A, Elliott P, Epstein SE, Eyjolfsson GI, Gigante B, Goodarzi MO, Grallert H, Gravito ML, Groves CJ, Hallmans G,

Hartikainen AL, Hayward C, Hernandez D, Hicks AA, Holm H, Hung YJ, Illig T, Jones MR, Kaleebu P, Kastelein JJ, Khaw KT, Kim E, Klopp N, Komulainen P, Kumari M, Langenberg C, Lehtimaki T, Lin SY, Lindstrom J, Loos RJ, Mach F, McArdle WL, Meisinger C, Mitchell BD, Muller G, Nagaraja R, Narisu N, Nieminen TV, Nsubuga RN, Olafsson I, Ong KK, Palotie A, Papamarkou T, Pomilla C, Pouta A, Rader DJ, Reilly MP, Ridker PM, Rivadeneira F, Rudan I, Ruokonen A, Samani N, Scharnagl H, Seeley J, Silander K, Stancakova A, Stirrups K, Swift AJ, Tiret L, Uitterlinden AG, van Pelt LJ, Vedantam S, Wainwright N, Wijmenga C, Wild SH, Willemsen G, Wilsgaard T, Wilson JF, Young EH, Zhao JH, Adair LS, Arveiler D, Assimes TL, Bandinelli S, Bennett F, Bochud M, Boehm BO, Boomsma DI, Borecki IB, Bornstein SR, Bovet P, Burnier M, Campbell H, Chakravarti A, Chambers JC, Chen YD, Collins FS, Cooper RS, Danesh J, Dedoussis G, de Faire U, Feranil AB, Ferrieres J, Ferrucci L, Freimer NB, Gieger C, Groop LC, Gudnason V, Gyllensten U, Hamsten A, Harris TB, Hingorani A, Hirschhorn JN, Hofman A, Hovingh GK, Hsiung CA, Humphries SE, Hunt SC, Hveem K, Iribarren C, Jarvelin MR, Jula A, Kahonen M, Kaprio J, Kesaniemi A, Kivimaki M, Kooner JS, Koudstaal PJ, Krauss RM, Kuh D, Kuusisto J, Kyvik KO, Laakso M, Lakka TA, Lind L, Lindgren CM, Martin NG, Marz W, McCarthy MI, McKenzie CA, Meneton P, Metspalu A, Moilanen L, Morris AD, Munroe PB, Njolstad I, Pedersen NL, Power C, Pramstaller PP, Price JF, Psaty BM, Quertermous T, Rauramaa R, Saleheen D, Salomaa V, Sanghera DK, Saramies J, Schwarz PE, Sheu WH, Shuldiner AR, Siegbahn A, Spector TD, Stefansson K, Strachan DP, Tayo BO, Tremoli E, Tuomilehto J, Uusitupa M, van Duijn CM, Vollenweider P, Wallentin L, Wareham NJ, Whitfield JB, Wolffenbuttel BH, Ordovas JM, Boerwinkle E, Palmer CN, Thorsteinsdottir U, Chasman DI, Rotter JI, Franks PW, Ripatti S, Cupples LA, Sandhu MS, Rich SS, Boehnke M, Deloukas P, Kathiresan S, Mohlke KL, Ingelsson E and Abecasis GR. Discovery and refinement of loci associated with lipid levels. *Nat Genet*. 2013;45:1274-1283.

19. Pirinen M, Donnelly P and Spencer CCA. Efficient computation with a linear mixed model on large-scale data sets with applications to genetic studies. *Ann Appl Stat*. 2013;7:369-390.

Supplemental Figures

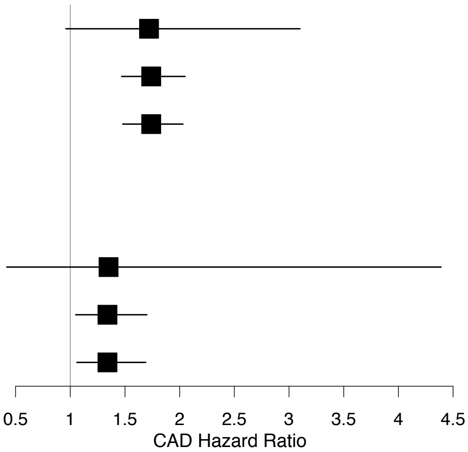
Figure S1. Overlap of families with family histories of high LDL-C and high TGs.



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

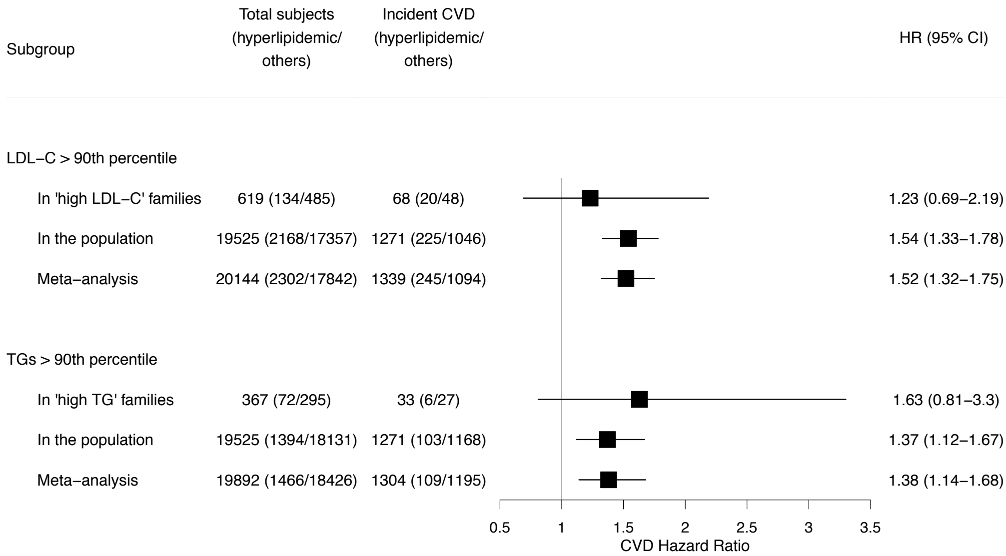
Figure S 2. Risk of incident CAD in hyperlipidemias with family history and population-ascertained hyperlipidemias, adjusted by lipid lowering medication usage and smoking.

Subgroup	Total subjects (hyperlipidemic/ others)	Incident CHD (hyperlipidemic/ others)	HR (95% CI)
LDL−C > 90th percentile			
In 'high LDL−C' families	625 (136/489)	45 (16/29)	1.72 (0.96–3.1)
In the population	19644 (2175/17469)	904 (176/728)	1.74 (1.47–2.05)
Meta−analysis	20269 (2311/17958)	949 (192/757)	1.74 (1.48–2.03)
TGs > 90th percentile			
In 'high TG' families	371 (72/299)	21 (3/18)	1.35 (0.42–4.39)
In the population	19644 (1405/18239)	904 (74/830)	1.34 (1.05–1.7)
Meta−analysis	20015 (1477/18538)	925 (77/848)	1.34 (1.06–1.69)

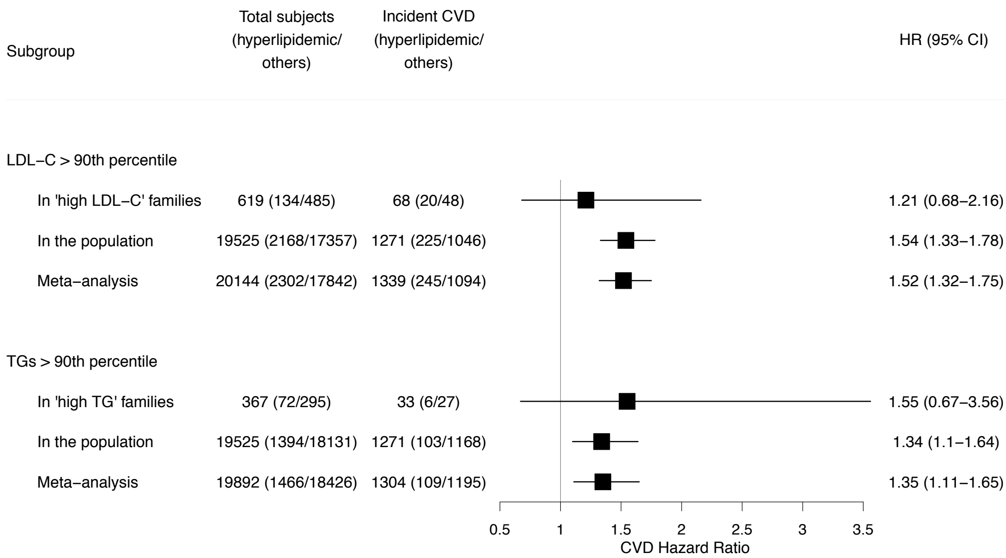


The risk of incident coronary artery disease (CAD) was estimated with Cox proportional hazards models similarly to Figure 1. Smoking and use of lipid lowering medication at baseline were included as additional covariates.

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

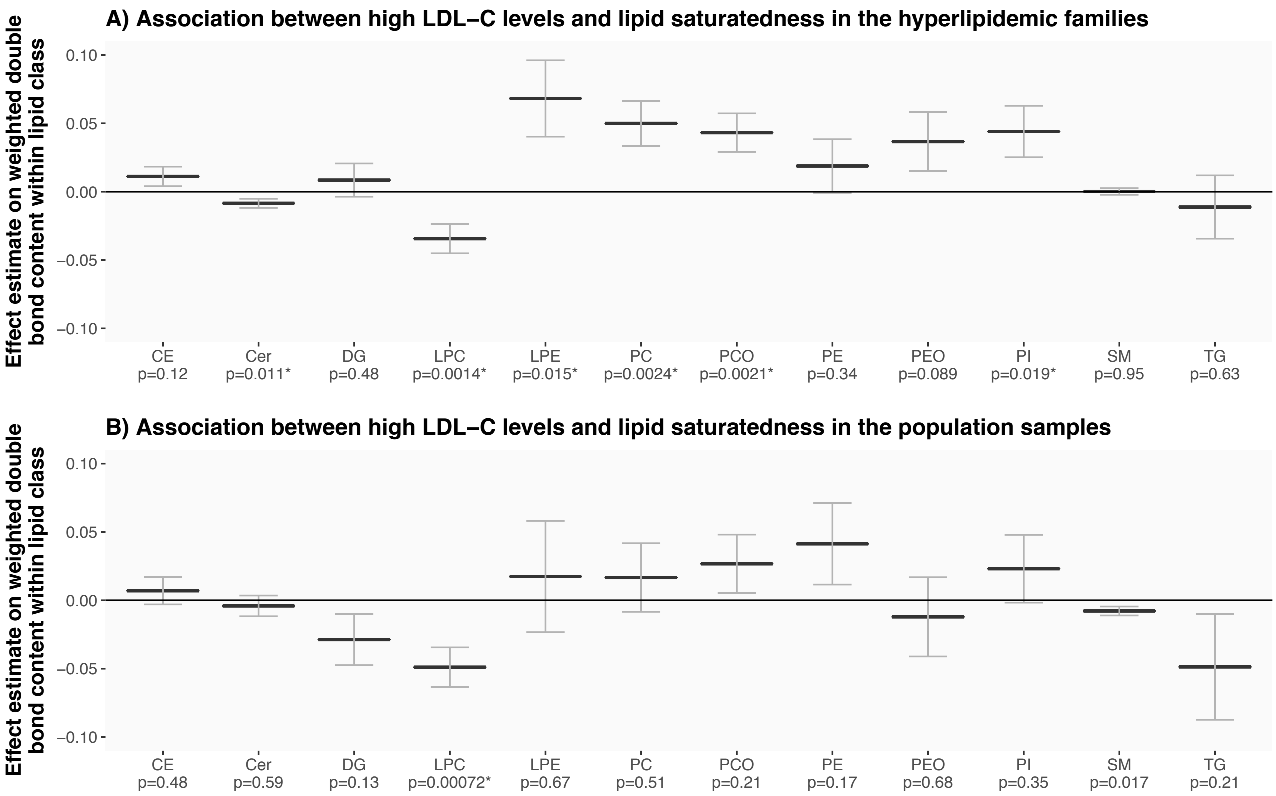


B. Risk of incident CVD in hyperlipidemias with family history and population-ascertained hyperlipidemias, adjusted for lipid lowering medication usage and smoking.



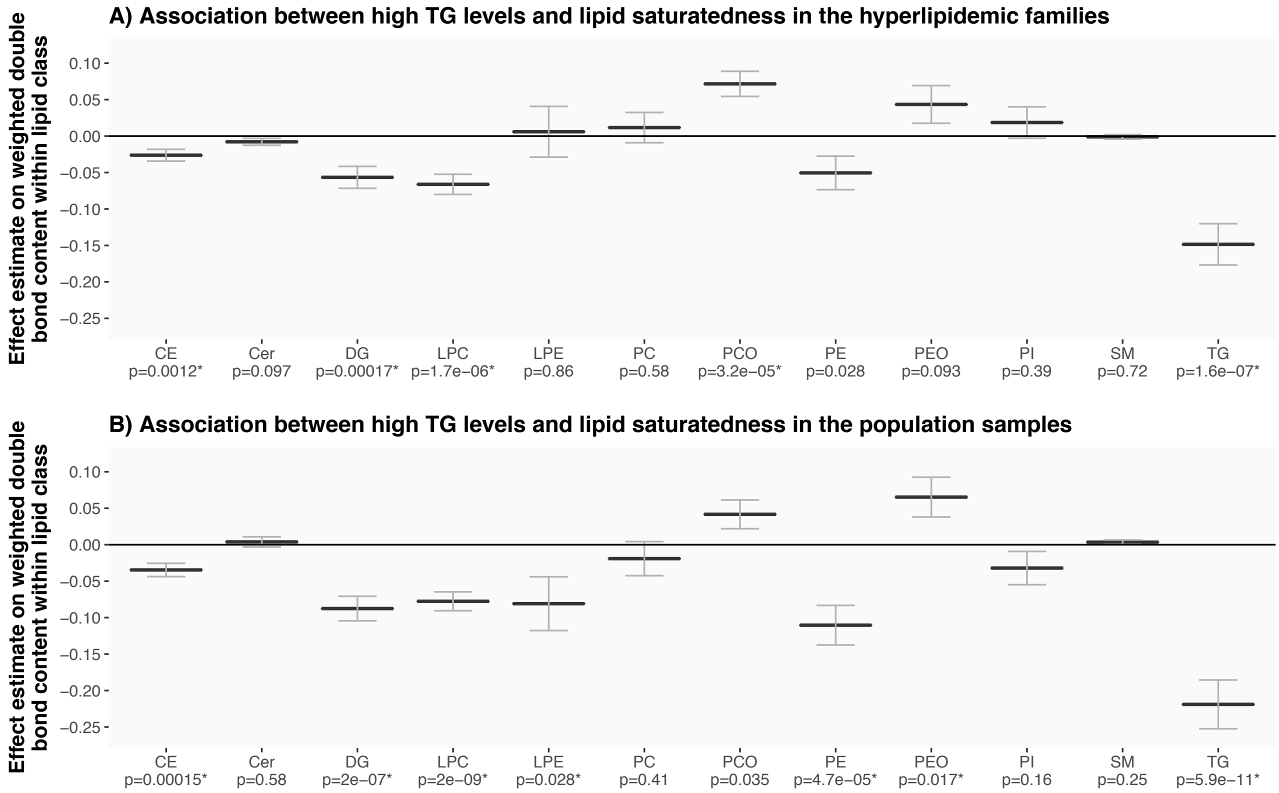
Panel A: The risk of incident cardiovascular disease (CVD) was estimated with Cox proportional hazards models similarly to Figure 1. Panel B: Smoking and use of lipid lowering medication at baseline were included as additional covariates.

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



The associations were estimated separately A) in "high LDL-C" families (total *n* = 463 individuals) and B) in the population samples (total *n* = 897 individuals). Negative effect estimates correspond to increased average saturation, and positive effect estimates correspond to decreased average saturation (increased unsaturation). Statistically significant effects at 5% FDR are marked with an asterisk (*). *Cer = ceramide, DG = diacylglyceride, FDR = false detection rate, 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.*

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



The associations were estimated separately A) in "high TG" families (total *n* = 287 individuals) and B) in the population (total *n* = 897 individuals). Negative effect estimates correspond to increased average saturation, and positive effect estimates correspond to decreased average saturation (increased unsaturation). Statistically significant effects at 5% FDR are marked with an asterisk (*). *Cer = ceramide, DG = diacylglyceride, FDR = false detection rate, 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.*

Supplemental Tables

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

Sex	Age	90th percentile for LDL-C (mmol/l)	90th 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/m2)	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 ± interquantile 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	*p*-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)			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	*p-value*	Affected by High TGs	Unaffected by High TGs	*p-value*	*p-value*	*p-value*
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/m2)	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 ± interquantile 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
Cholesterol	1900 ± 580	1600 ± 530
CE(14:0;0)	35 ± 21	28 ± 16
CE(15:0;0)	8.8 ± 5.1	8 ± 3.7
CE(16:0;0)	430 ± 170	370 ± 120
CE(16:1;0)	190 ± 120	150 ± 100
CE(17:0;0)	7.6 ± 3.8	6.2 ± 2.7
CE(17:1;0)	16 ± 8.2	12 ± 5.7
CE(18:0;0)	21 ± 11	16 ± 8.1
CE(18:1;0)	910 ± 350	770 ± 290
CE(18:2;0)	2700 ± 1000	2200 ± 710
CE(18:3;0)	110 ± 55	88 ± 48
CE(19:1;0)	1.9 ± 0.87	1.8 ± 0.84
CE(20:2;0)	2.6 ± 1.2	2.3 ± 1.2
CE(20:3;0)	39 ± 19	30 ± 14
CE(20:4;0)	320 ± 140	270 ± 120
CE(20:5;0)	82 ± 74	82 ± 73
CE(22:6;0)	38 ± 25	34 ± 22
DG(16:0;0_18:1;0)	5 ± 4.4	3.1 ± 2.8
DG(18:1;0_18:1;0)	7.9 ± 6.6	5.2 ± 4.2
DG(18:1;0_18:2;0)	6.6 ± 5	4.6 ± 3
TG(48:0;0)	5.2 ± 8.2	4.6 ± 7.7
TG(48:1;0)	29 ± 38	20 ± 27
TG(48:2;0)	24 ± 28	17 ± 20
TG(50:1;0)	66 ± 71	43 ± 53
TG(50:2;0)	110 ± 100	74 ± 75
TG(50:3;0)	51 ± 50	36 ± 32
TG(50:4;0)	15 ± 14	11 ± 9.8
TG(51:2;0)	10 ± 9	7 ± 5.9
TG(51:3;0)	6.4 ± 5.3	4.7 ± 3.5
TG(52:2;0)	240 ± 210	160 ± 140
TG(52:3;0)	240 ± 200	160 ± 130
TG(52:4;0)	99 ± 86	75 ± 58
TG(52:5;0)	26 ± 24	21 ± 16
TG(54:3;0)	64 ± 52	46 ± 37
TG(54:4;0)	60 ± 48	46 ± 35
TG(54:5;0)	43 ± 37	34 ± 27
TG(54:6;0)	25 ± 23	22 ± 17
TG(56:4;0)	3.8 ± 2.8	3 ± 2.1
TG(56:5;0)	10 ± 7	7.7 ± 5.1
TG(56:6;0)	18 ± 13	15 ± 10
TG(56:7;0)	25 ± 23	22 ± 19
PC(14:0;0_16:0;0)	2.8 ± 2	2.4 ± 1.6
PC(14:0;0_18:1;0)	3.5 ± 2.6	2.9 ± 1.9
PC(14:0;0_18:2;0)	3.8 ± 2.3	3.4 ± 1.7
PC(15:0;0_18:2;0)	47 ± 20	44 ± 16
PC(16:0;0_16:0;0)	9.6 ± 3.7	9.1 ± 3.4
PC(16:0;0_16:1;0)	12 ± 8.7	9.6 ± 7.6
PC(16:0;0_17:1;0)	20 ± 12	18 ± 11
PC(16:0;0_18:0;0)	30 ± 10	25 ± 10
PC(16:0;0_18:1;0)	240 ± 110	210 ± 96
PC(16:0;0_18:2;0)	480 ± 180	440 ± 150
PC(16:0;0_18:3;0)	10 ± 5.6	8.8 ± 5.4
PC(16:0;0_20:1;0)	1.1 ± 0.61	1.1 ± 0.57
PC(16:0;0_20:2;0)	9 ± 4.3	7.9 ± 3.4
PC(16:0;0_20:3;0)	63 ± 34	53 ± 33
PC(16:0;0_20:4;0)	140 ± 63	130 ± 68
PC(16:0;0_20:5;0)	30 ± 25	33 ± 29
PC(16:0;0_22:4;0)	5.5 ± 2.3	4.6 ± 2.2
PC(16:0;0_22:5;0)	21 ± 9.4	21 ± 11
PC(16:0;0_22:6;0)	88 ± 56	82 ± 49
PC(16:1;0_18:1;0)	8.1 ± 4.4	7.1 ± 3.5
PC(16:1;0_18:2;0)	6.5 ± 3.5	5.7 ± 2.9
PC(17:0;0_18:2;0)	33 ± 15	30 ± 13
PC(17:0;0_20:3;0)	7.2 ± 4.3	5.6 ± 3.1
PC(17:0;0_20:4;0)	13 ± 5.9	11 ± 5
PC(18:0;0_18:1;0)	31 ± 16	27 ± 14
PC(18:0;0_18:2;0)	200 ± 81	190 ± 71
PC(18:0;0_18:3;0)	3.2 ± 2.2	3.3 ± 2.1
PC(18:0;0_20:2;0)	4.1 ± 2.1	3.5 ± 1.6
PC(18:0;0_20:3;0)	29 ± 16	25 ± 14
PC(18:0;0_20:4;0)	61 ± 31	58 ± 25
PC(18:0;0_20:5;0)	9.9 ± 8.4	12 ± 13
PC(18:0;0_22:5;0)	7.1 ± 3.9	6.3 ± 2.9
PC(18:0;0_22:6;0)	27 ± 18	24 ± 13
PC(18:1;0_18:1;0)	23 ± 11	21 ± 8.7
PC(18:1;0_18:2;0)	62 ± 29	53 ± 23
PC(18:1;0_20:3;0)	9.7 ± 5.4	8.5 ± 4.1
PC(18:1;0_20:4;0)	17 ± 7.1	16 ± 6.9
PC(18:2;0_18:2;0)	26 ± 14	23 ± 12
PC(18:2;0_20:4;0)	11 ± 4.3	9.9 ± 4.4
PCO(16:0;0/16:0;0)	0.83 ± 0.45	0.64 ± 0.37
PCO(16:0;0/16:1;0)	0.7 ± 0.43	0.67 ± 0.57
PCO(16:0;0/18:1;0)	1.7 ± 0.7	1.6 ± 0.56
PCO(16:0;0/18:2;0)	3.5 ± 1.6	3.4 ± 1.5
PCO(16:0;0/20:3;0)	0.83 ± 0.57	0.95 ± 0.47
PCO(16:0;0/20:4;0)	5.5 ± 2.9	5.1 ± 2.4
PCO(16:1;0/16:0;0)	1.9 ± 0.77	1.8 ± 0.79
PCO(16:1;0/18:1;0)	0.32 ± 0.18	0.35 ± 0.22
PCO(16:1;0/18:2;0)	5.3 ± 2.6	5.2 ± 2.3
PCO(16:1;0/20:3;0)	0.6 ± 0.29	0.57 ± 0.46
PCO(17:0;0/17:1;0)	0.087 ± 0.047	0.076 ± 0.044
PCO(18:0;0/14:0;0)	2.1 ± 0.74	1.9 ± 0.48
PCO(18:0;0/18:2;0)	0.77 ± 0.44	0.71 ± 0.33
PCO(18:0;0/20:4;0)	3.4 ± 1.6	3 ± 1.2
PCO(18:1;0/16:0;0)	0.93 ± 0.37	0.87 ± 0.31
PCO(18:1;0/18:1;0)	0.18 ± 0.099	0.14 ± 0.079
PCO(18:1;0/18:2;0)	2.2 ± 1.1	2 ± 0.92
PCO(18:1;0/20:3;0)	1.2 ± 0.62	0.9 ± 0.48
PCO(18:1;0/20:4;0)	8.5 ± 2.8	7.6 ± 2.9
PCO(18:2;0/16:0;0)	1.2 ± 0.48	1.1 ± 0.44
PCO(18:2;0/18:0;0)	0.17 ± 0.099	0.16 ± 0.072
PCO(18:2;0/18:1;0)	0.44 ± 0.29	0.46 ± 0.28
PCO(18:2;0/18:2;0)	2.4 ± 1.1	2.4 ± 1.2
SM(32:1;2)	7.9 ± 3	7.7 ± 2.9
SM(34:0;2)	1.7 ± 0.84	1.8 ± 0.72
SM(34:1;2)	75 ± 25	69 ± 20
SM(34:2;2)	9.6 ± 3.2	9.2 ± 2.9
SM(36:1;2)	14 ± 4.9	12 ± 4.2
SM(36:2;2)	6.5 ± 2.5	5.9 ± 2.1
SM(38:1;2)	9.7 ± 3.4	9.5 ± 3.2
SM(38:2;2)	3.8 ± 1.4	3.7 ± 1.3
SM(40:1;2)	16 ± 6.3	16 ± 5.1
SM(40:2;2)	15 ± 5	15 ± 5
SM(42:2;2)	38 ± 14	36 ± 12
Cer(40:1;2)	0.75 ± 0.34	0.66 ± 0.3
Cer(40:2;2)	0.21 ± 0.1	0.17 ± 0.09
Cer(42:1;2)	2 ± 0.93	1.8 ± 0.79
Cer(42:2;2)	1.4 ± 0.62	1.2 ± 0.55
PI(16:0;0_18:1;0)	1.8 ± 1.3	1.6 ± 1
PI(16:0;0_18:2;0)	1.2 ± 0.7	1.2 ± 0.69
PI(16:0;0_20:4;0)	1.8 ± 0.99	1.7 ± 1
PI(18:0;0_18:1;0)	2.3 ± 1.3	2.1 ± 1.1
PI(18:0;0_18:2;0)	4 ± 2	4.1 ± 2.1
PI(18:0;0_20:3;0)	2.6 ± 1.4	2.5 ± 1.3
PI(18:0;0_20:4;0)	18 ± 7.8	18 ± 6.6
PI(18:1;0_18:1;0)	0.82 ± 0.51	0.78 ± 0.51
PI(18:1;0_18:2;0)	0.66 ± 0.42	0.6 ± 0.27
PI(18:2;0_18:2;0)	0.95 ± 0.49	0.83 ± 0.52
PE(16:0;0_18:2;0)	1.6 ± 1.6	1.5 ± 1.3
PE(18:0;0_18:2;0)	4.1 ± 3.2	3.5 ± 2.6
PE(18:0;0_20:4;0)	5.4 ± 3.8	4.8 ± 3.1
PE(18:1;0_18:1;0)	0.48 ± 0.43	0.62 ± 0.76
PEO(16:1;0/18:2;0)	1.3 ± 0.75	1.1 ± 0.61
PEO(16:1;0/20:4;0)	3.7 ± 2.3	3.4 ± 2
PEO(18:1;0/18:2;0)	2.3 ± 1.4	1.8 ± 1.1
PEO(18:2;0/18:2;0)	1.6 ± 0.86	1.6 ± 0.82
PEO(18:2;0/20:4;0)	5.7 ± 3.2	5.8 ± 2.9
LPE(16:0;0)	0.56 ± 0.25	0.51 ± 0.22
LPE(18:1;0)	0.52 ± 0.29	0.56 ± 0.37
LPE(18:2;0)	1 ± 0.56	1.2 ± 0.72
LPE(20:4;0)	0.71 ± 0.33	0.76 ± 0.31
LPE(22:6;0)	0.7 ± 0.35	0.78 ± 0.35
LPC(14:0;0)	1.1 ± 0.58	0.88 ± 0.4
LPC(16:0;0)	72 ± 25	56 ± 17
LPC(16:1;0)	1.8 ± 0.83	1.4 ± 0.66
LPC(18:0;0)	18 ± 8.3	14 ± 5.6
LPC(18:1;0)	14 ± 7.4	12 ± 5.2
LPC(18:2;0)	17 ± 11	18 ± 11
LPC(20:3;0)	1 ± 0.53	1 ± 0.5
LPC(20:4;0)	3 ± 1.6	2.8 ± 1.4
LPC(22:6;0)	1.1 ± 0.66	1.2 ± 0.63

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
Cholesterol	cholesterol	SLM:000000287
CE(14:0;0)	Sterol ester (27:1/14:0)	SLM:000500342
CE(15:0;0)	Sterol ester (27:1/15:0)	SLM:000500343
CE(16:0;0)	Sterol ester (27:1/16:0)	SLM:000500346
CE(16:1;0)	Sterol ester (27:1/16:1)	SLM:000500345
CE(17:0;0)	Sterol ester (27:1/17:0)	SLM:000500347
CE(17:1;0)	Sterol ester (27:1/17:1)	n/a
CE(18:0;0)	Sterol ester (27:1/18:0)	SLM:000500352
CE(18:1;0)	Sterol ester (27:1/18:1)	SLM:000500351
CE(18:2;0)	Sterol ester (27:1/18:2)	SLM:000500350
CE(18:3;0)	Sterol ester (27:1/18:3)	SLM:000500349
CE(19:1;0)	Sterol ester (27:1/19:1)	n/a
CE(20:2;0)	Sterol ester (27:1/20:2)	SLM:000500357
CE(20:3;0)	Sterol ester (27:1/20:3)	SLM:000500356
CE(20:4;0)	Sterol ester (27:1/20:4)	SLM:000500355
CE(20:5;0)	Sterol ester (27:1/20:5)	SLM:000500354
CE(22:6;0)	Sterol ester (27:1/22:6)	SLM:000500361
DG(16:0;0_18:1;0)	Diacylglycerol (16:0_18:1)	SLM:000308862
DG(18:1;0_18:1;0)	Diacylglycerol (18:1_18:1)	SLM:000309012
DG(18:1;0_18:2;0)	Diacylglycerol (18:1_18:2)	SLM:000309013
TG(48:0;0)	Triacylglycerol (48:0)	SLM:000308257
TG(48:1;0)	Triacylglycerol (48:1)	SLM:000308258
TG(48:2;0)	Triacylglycerol (48:2)	SLM:000308259
TG(50:1;0)	Triacylglycerol (50:1)	SLM:000308276
TG(50:2;0)	Triacylglycerol (50:2)	SLM:000308277
TG(50:3;0)	Triacylglycerol (50:3)	SLM:000308278
TG(50:4;0)	Triacylglycerol (50:4)	SLM:000308279
TG(51:2;0)	Triacylglycerol (51:2)	SLM:000308287
TG(51:3;0)	Triacylglycerol (51:3)	SLM:000308288
TG(52:2;0)	Triacylglycerol (52:2)	SLM:000308298
TG(52:3;0)	Triacylglycerol (52:3)	SLM:000308299
TG(52:4;0)	Triacylglycerol (52:4)	SLM:000308300
TG(52:5;0)	Triacylglycerol (52:5)	SLM:000308301
TG(54:3;0)	Triacylglycerol (54:3)	SLM:000308323
TG(54:4;0)	Triacylglycerol (54:4)	SLM:000308324
TG(54:5;0)	Triacylglycerol (54:5)	SLM:000308325
TG(54:6;0)	Triacylglycerol (54:6)	SLM:000308326
TG(56:4;0)	Triacylglycerol (56:4)	SLM:000308350

Species	SwissLipids Name	SwissLipids ID
PC(18:1;0_20:3;0)	Phosphatidylcholine (18:1_20:3)	SLM:000063992
PC(18:1;0_20:4;0)	Phosphatidylcholine (18:1_20:4)	SLM:000063993
PC(18:2;0_18:2;0)	Phosphatidylcholine (18:2_18:2)	SLM:000064033
PC(18:2;0_20:4;0)	Phosphatidylcholine (18:2_20:4)	SLM:000064041
PCO(16:0;0/16:0;0)	Phosphatidylcholine (O-16:0_16:0)	SLM:000065919
PCO(16:0;0/16:1;0)	Phosphatidylcholine (O-16:0_16:1)	SLM:000065920
PCO(16:0;0/18:1;0)	Phosphatidylcholine (O-16:0_18:1)	SLM:000065924
PCO(16:0;0/18:2;0)	Phosphatidylcholine (O-16:0_18:2)	SLM:000065925
PCO(16:0;0/20:3;0)	Phosphatidylcholine (O-16:0_20:3)	SLM:000065932
PCO(16:0;0/20:4;0)	Phosphatidylcholine (O-16:0_20:4)	SLM:000065933
PCO(16:1;0/16:0;0)	Phosphatidylcholine (O-16:1_16:0)	SLM:000065984
PCO(16:1;0/18:1;0)	Phosphatidylcholine (O-16:1_18:1)	SLM:000065989
PCO(16:1;0/18:2;0)	Phosphatidylcholine (O-16:1_18:2)	SLM:000065990
PCO(16:1;0/20:3;0)	Phosphatidylcholine (O-16:1_20:3)	SLM:000065997
PCO(17:0;0/17:1;0)	Phosphatidylcholine (O-17:0_17:1)	n/a
PCO(18:0;0/14:0;0)	Phosphatidylcholine (O-18:0_14:0)	SLM:000066176
PCO(18:0;0/18:2;0)	Phosphatidylcholine (O-18:0_18:2)	SLM:000066185
PCO(18:0;0/20:4;0)	Phosphatidylcholine (O-18:0_20:4)	SLM:000066193
PCO(18:1;0/16:0;0)	Phosphatidylcholine (O-18:1_16:0)	SLM:000066244
PCO(18:1;0/18:1;0)	Phosphatidylcholine (O-18:1_18:1)	SLM:000066249
PCO(18:1;0/18:2;0)	Phosphatidylcholine (O-18:1_18:2)	SLM:000066250
PCO(18:1;0/20:3;0)	Phosphatidylcholine (O-18:1_20:3)	SLM:000066257
PCO(18:1;0/20:4;0)	Phosphatidylcholine (O-18:1_20:4)	SLM:000066258
PCO(18:2;0/16:0;0)	Phosphatidylcholine (O-18:2_16:0)	SLM:000066309
PCO(18:2;0/18:0;0)	Phosphatidylcholine (O-18:2_18:0)	SLM:000066313
PCO(18:2;0/18:1;0)	Phosphatidylcholine (O-18:2_18:1)	SLM:000066314
PCO(18:2;0/18:2;0)	Phosphatidylcholine (O-18:2_18:2)	SLM:000066315
SM(32:1;2)	Sphingomyelin (d32:1)	SLM:000390695
SM(34:0;2)	Sphingomyelin (d34:0)	SLM:000390716
SM(34:1;2)	Sphingomyelin (d34:1)	SLM:000390714
SM(34:2;2)	Sphingomyelin (d34:2)	SLM:000390712
SM(36:1;2)	Sphingomyelin (d36:1)	SLM:000390739
SM(36:2;2)	Sphingomyelin (d36:2)	SLM:000390737
SM(38:1;2)	Sphingomyelin (d38:1)	SLM:000390767
SM(38:2;2)	Sphingomyelin (d38:2)	SLM:000390765
SM(40:1;2)	Sphingomyelin (d40:1)	SLM:000390797
SM(40:2;2)	Sphingomyelin (d40:2)	SLM:000390795
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 (± 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	*p-value*	Effect of high LDL-C affection in FINRISK	*p-value*	Effect of high TG affection in "high TG" families	*p-value*	Effect of high TG affection in FINRISK	*p-value*	Independent association with LDL-C in EUFAM	*p-value*	Independent association with LDL-C in FINRISK	*p-value*	Independent association with TG in EUFAM	*p-value*	Independent association with TG in FINRISK	*p-value*
ST	Cholesterol	0.83 ± 0.093	5.4e-19*	0.93 ± 0.14	7.1e-11*	1 ± 0.12	1.3e-18*	0.99 ± 0.13	1.4e-13*	0.33 ± 0.029	4.2e-31*	0.39 ± 0.034	7.7e-30*	0.32 ± 0.029	3.3e-27*	0.25 ± 0.032	1.3e-14*
CE	CE(14:0;0)	0.64 ± 0.099	1.3e-10*	0.99 ± 0.14	2.1e-12*	0.75 ± 0.12	9.5e-10*	1 ± 0.13	7.5e-15*	0.24 ± 0.033	2.7e-13*	0.34 ± 0.033	1.4e-24*	0.31 ± 0.034	1e-19*	0.33 ± 0.031	1.9e-26*
	CE(15:0;0)	0.49 ± 0.1	1.1e-06*	0.84 ± 0.14	4.1e-09*	0.42 ± 0.13	0.0013*	0.26 ± 0.13	0.051	0.28 ± 0.036	8.7e-15*	0.32 ± 0.036	1.3e-18*	0.088 ± 0.037	0.017*	0.064 ± 0.034	0.061
	CE(16:0;0)	0.71 ± 0.078	7.3e-20*	1 ± 0.14	6.5e-14*	0.81 ± 0.11	1.4e-13*	0.75 ± 0.13	5e-09*	0.31 ± 0.027	7.1e-32*	0.42 ± 0.033	1.6e-37*	0.26 ± 0.027	1e-21*	0.2 ± 0.031	7.9e-11*
	CE(16:1;0)	0.44 ± 0.1	2.3e-05*	0.2 ± 0.14	0.15	0.92 ± 0.13	4.4e-13*	0.65 ± 0.13	6.3e-07*	0.16 ± 0.035	8.5e-06*	0.14 ± 0.036	0.00011*	0.37 ± 0.036	9.1e-25*	0.26 ± 0.034	1.6e-14*
	CE(17:0;0)	0.61 ± 0.097	4.6e-10*	0.85 ± 0.14	4.2e-09*	0.38 ± 0.12	0.0021*	0.24 ± 0.14	0.073	0.3 ± 0.035	3.4e-17*	0.34 ± 0.037	2.2e-20*	0.079 ± 0.036	0.03*	0.022 ± 0.035	0.53
	CE(17:1;0)	0.62 ± 0.098	2.9e-10*	1.1 ± 0.14	6.2e-16*	0.67 ± 0.13	1e-07*	0.79 ± 0.13	1.7e-09*	0.28 ± 0.034	1.2e-16*	0.41 ± 0.033	1.1e-35*	0.22 ± 0.035	2.1e-10*	0.24 ± 0.031	1.8e-14*
	CE(18:0;0)	0.75 ± 0.099	2.3e-14*	1.3 ± 0.14	6.8e-21*	0.95 ± 0.13	3.1e-13*	0.75 ± 0.13	1.1e-08*	0.32 ± 0.032	1.8e-23*	0.46 ± 0.033	4.4e-45*	0.31 ± 0.032	7.4e-22*	0.21 ± 0.031	5.2e-12*
	CE(18:1;0)	0.63 ± 0.089	1.6e-12*	1 ± 0.14	3.2e-14*	0.77 ± 0.12	3e-11*	0.71 ± 0.13	6.1e-08*	0.28 ± 0.031	1.2e-19*	0.41 ± 0.033	2.3e-35*	0.26 ± 0.031	1.7e-16*	0.19 ± 0.032	2.1e-09*
	CE(18:2;0)	0.63 ± 0.078	3.6e-16*	0.99 ± 0.14	1.4e-12*	0.45 ± 0.11	2.6e-05*	0.35 ± 0.13	0.008*	0.34 ± 0.027	3.7e-35*	0.43 ± 0.034	5.3e-36*	0.076 ± 0.028	0.0068*	0.046 ± 0.033	0.17
	CE(18:3;0)	0.48 ± 0.09	9.6e-08*	0.76 ± 0.15	4.5e-07*	0.74 ± 0.11	4.6e-11*	1 ± 0.13	3.8e-15*	0.2 ± 0.031	8.1e-11*	0.3 ± 0.035	3.1e-17*	0.28 ± 0.031	1.6e-19*	0.35 ± 0.032	1.2e-26*
	CE(19:1;0)	0.69 ± 0.11	9e-11*	0.92 ± 0.15	2.4e-10*	0.39 ± 0.15	0.01*	0.37 ± 0.15	0.013*	0.36 ± 0.041	1.1e-18*	0.36 ± 0.038	1.7e-21*	-0.0066 ± 0.047	0.89	-0.046 ± 0.038	0.22
	CE(20:2;0)	0.5 ± 0.1	8.2e-07*	0.76 ± 0.15	3.1e-07*	0.18 ± 0.14	0.22	-0.086 ± 0.15	0.57	0.34 ± 0.038	4.3e-19*	0.36 ± 0.038	6.5e-21*	-0.044 ± 0.042	0.3	-0.21 ± 0.038	1.6e-08*
	CE(20:3;0)	0.63 ± 0.093	1.2e-11*	0.94 ± 0.14	5.7e-11*	0.98 ± 0.13	1.4e-13*	0.91 ± 0.13	3.9e-12*	0.29 ± 0.031	5.3e-21*	0.38 ± 0.033	7.4e-31*	0.33 ± 0.031	7.2e-27*	0.34 ± 0.031	7.7e-28*
	CE(20:4;0)	0.62 ± 0.088	1.7e-12*	0.92 ± 0.14	3.9e-11*	0.65 ± 0.13	5.4e-07*	0.49 ± 0.13	0.00022*	0.32 ± 0.032	2.1e-23*	0.42 ± 0.034	6.9e-35*	0.16 ± 0.032	3.3e-07*	0.15 ± 0.032	2.8e-06*
	CE(20:5;0)	0.54 ± 0.092	3.8e-09*	0.55 ± 0.14	8.2e-05*	0.37 ± 0.12	0.0015*	0.27 ± 0.13	0.037*	0.26 ± 0.034	5.6e-15*	0.25 ± 0.036	5.2e-12*	0.12 ± 0.034	0.00044*	0.062 ± 0.034	0.066
	CE(22:6;0)	0.6 ± 0.088	1.2e-11*	0.58 ± 0.14	6e-05*	0.34 ± 0.11	0.0032*	0.17 ± 0.13	0.21	0.3 ± 0.033	1.7e-20*	0.25 ± 0.037	2.9e-11*	0.068 ± 0.033	0.038	0.03 ± 0.035	0.39
DG	DG(16:0;0_18:1;0)	0.31 ± 0.1	0.0023*	0.29 ± 0.14	0.041	1.5 ± 0.11	2.5e-42*	1.8 ± 0.12	6e-55*	-0.06 ± 0.021	0.0043*	-0.027 ± 0.024	0.27	0.75 ± 0.022	6e-255*	0.79 ± 0.023	6.8e-246*
	DG(18:1;0_18:1;0)	0.38 ± 0.1	0.00015*	0.33 ± 0.14	0.021	1.6 ± 0.12	3.7e-41*	1.7 ± 0.12	1.8e-47*	-0.026 ± 0.021	0.23	-0.014 ± 0.024	0.54	0.77 ± 0.022	1.8e-267*	0.78 ± 0.022	1.9e-260*
	DG(18:1;0_18:2;0)	0.43 ± 0.1	2.2e-05*	0.21 ± 0.14	0.14	1.5 ± 0.11	2.4e-38*	1.8 ± 0.12	3.9e-52*	0.0094 ± 0.024	0.7	-0.035 ± 0.024	0.14	0.72 ± 0.024	9e-194*	0.79 ± 0.023	7e-269*
TG	TG(48:0;0)	0.26 ± 0.1	0.01*	0.25 ± 0.15	0.096	1.3 ± 0.12	1.4e-30*	1.7 ± 0.12	7.8e-47*	-0.074 ± 0.026	0.0047*	-0.04 ± 0.027	0.15	0.68 ± 0.027	7.8e-144*	0.74 ± 0.026	3.7e-175*
	TG(48:1;0)	0.29 ± 0.1	0.0057*	0.26 ± 0.15	0.072	1.4 ± 0.12	3.2e-34*	1.8 ± 0.12	1.4e-53*	-0.055 ± 0.024	0.024*	-0.025 ± 0.022	0.27	0.74 ± 0.025	1.1e-190*	0.83 ± 0.021	<5e-324*
	TG(48:2;0)	0.28 ± 0.11	0.0088*	0.26 ± 0.16	0.094	1.5 ± 0.12	3.5e-36*	1.9 ± 0.12	4.4e-56*	-0.06 ± 0.025	0.014*	-0.044 ± 0.022	0.043	0.77 ± 0.025	2.1e-200*	0.86 ± 0.02	<5e-324*
	TG(50:1;0)	0.32 ± 0.1	0.0013*	0.26 ± 0.15	0.076	1.5 ± 0.11	1.4e-39*	1.7 ± 0.12	2.5e-46*	-0.06 ± 0.021	0.0043*	-0.011 ± 0.026	0.67	0.76 ± 0.022	1.4e-266*	0.76 ± 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	2e-72*
	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, age^2, 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, age^2, 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.*