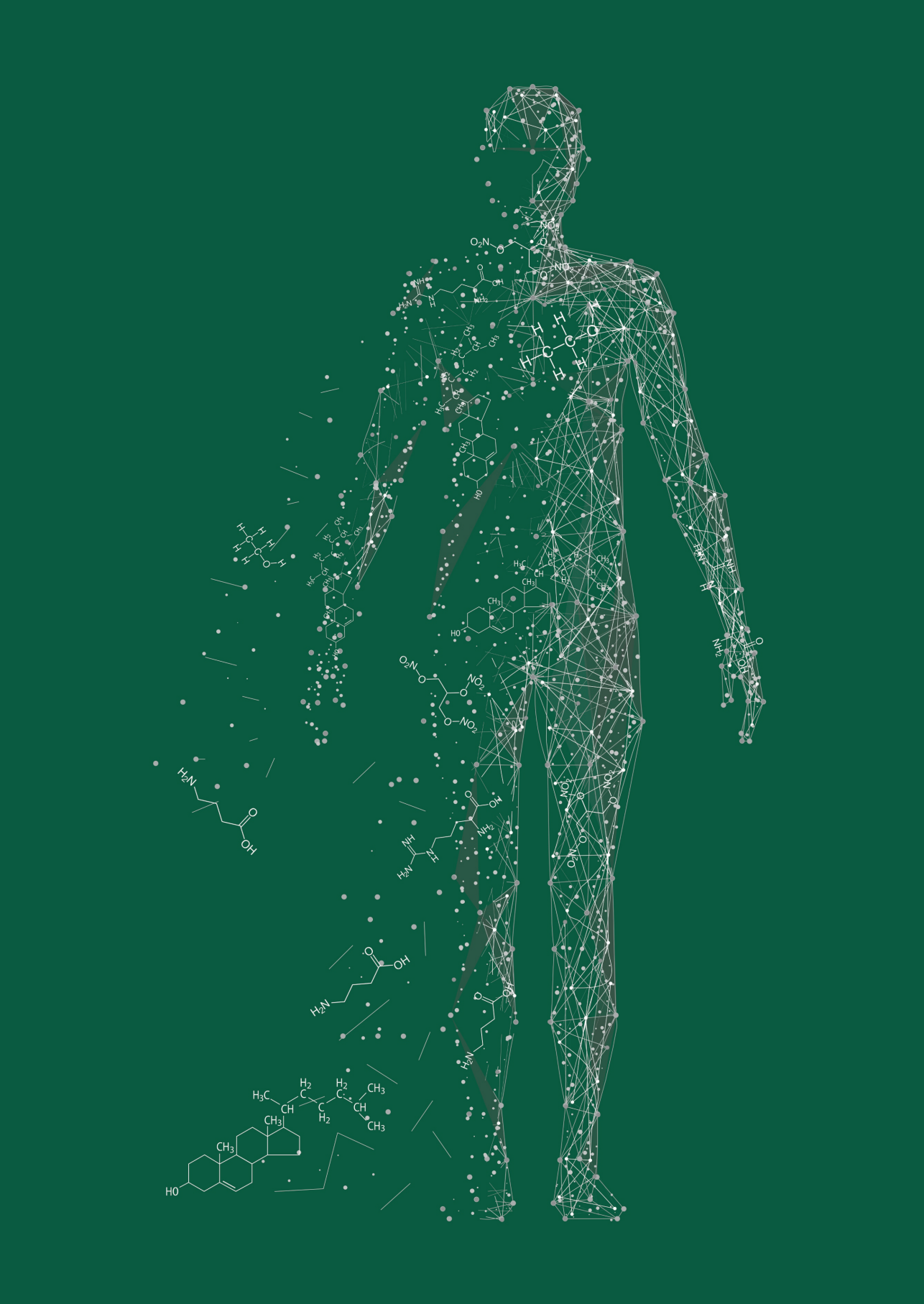
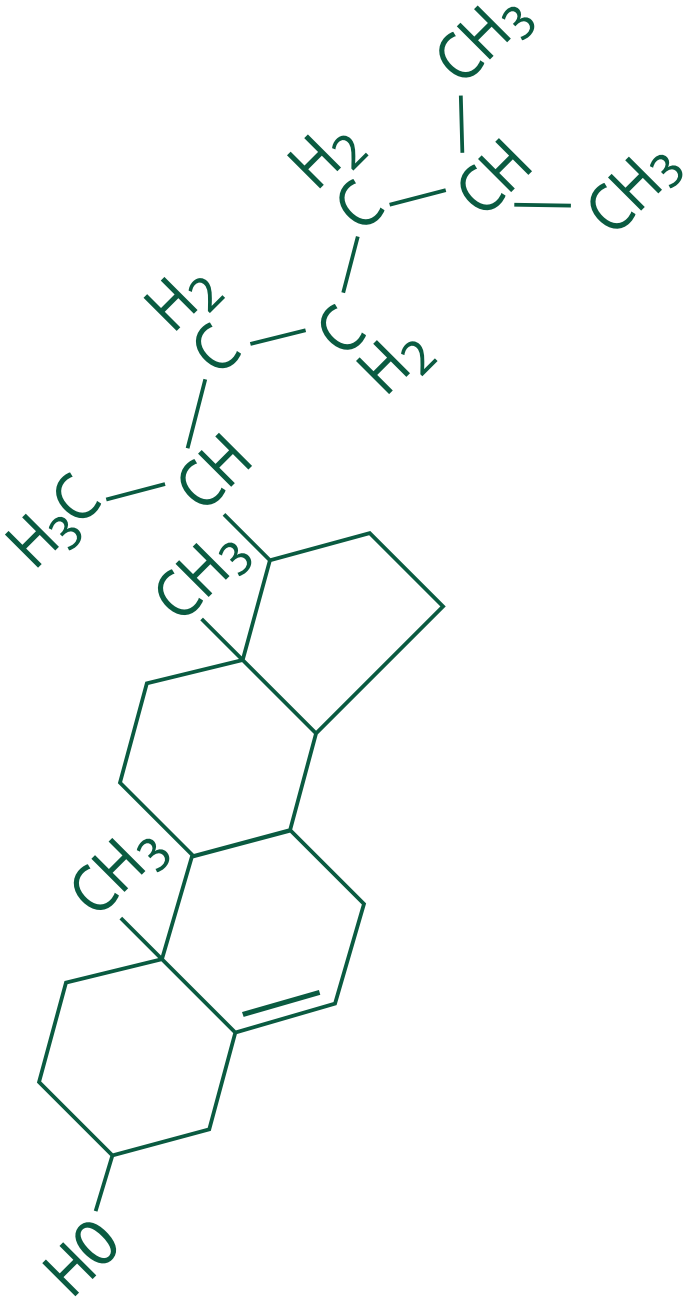
Biochemistry in different phases of the migraine attack

Onderwater, G.L.J.



PART I

MIGRAINE BIOCHEMICAL PROFILING IN BIOFLUIDS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Chapter 2

Large-scale plasma metabolome analysis reveals alterations in HDL metabolism in migraine

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Abstract

Objective

To identify a plasma metabolomic biomarker signature for migraine.

Methods

Plasma samples from 8 Dutch cohorts (n = 10,153: 2,800 migraine patients and 7,353 controls) were profiled on a ^{1}H-NMR-based metabolomics platform, to quantify 146 individual metabolites (e.g., lipids, fatty acids, and lipoproteins) and 79 metabolite ratios. Metabolite measures associated with migraine were obtained after single-metabolite logistic regression combined with a random-effects meta-analysis performed in a nonstratified and sex-stratified manner. Next, a global test analysis was performed to identify sets of related metabolites associated with migraine. The Holm procedure was applied to control the family-wise error rate at 5% in single-metabolite and global test analyses.

Results

Decreases in the level of apolipoprotein A1 (β −0.10; 95% confidence interval [CI] −0.16, −0.05; adjusted p= 0.029) and free cholesterol to total lipid ratio present in small high-density lipoprotein subspecies (HDL) (β −0.10; 95% CI −0.15, −0.05; adjusted p= 0.029) were associated with migraine status. In addition, only in male participants, a decreased level of omega-3 fatty acids (β −0.24; 95% CI −0.36, −0.12; adjusted p= 0.033) was associated with migraine. Global test analysis further supported that HDL traits (but not other lipoproteins) were associated with migraine status.

Conclusions

Metabolic profiling of plasma yielded alterations in HDL metabolism in migraine patients and decreased omega-3 fatty acids only in male migraineurs.

Introduction

Migraine is an episodic brain disorder affecting about 15% of the general population, occurs 3 times more frequently in women than men, and is ranked as the second most disabling disease worldwide.[1–4] In one-third of patients, transient focal neurologic symptoms precede the headache (migraine with aura).[1] Migraine, especially in women, has been linked to an increased risk for cerebrovascular and cardiovascular diseases.[5–8] Systemic (micro)vascular dysfunction, but not atherosclerosis,[9,10] has been suggested to be the underlying cause for this association.[11,12]

Previous studies showed elevations of total cholesterol, low-density lipoprotein cholesterol (LDL-C), and triglyceride levels, and decreases of high-density lipoprotein cholesterol (HDL-C) levels, to be associated with migraine.[13] However, results were not consistently replicated due to methodologic variability,[13] emphasizing the need for a systematic approach. High-throughput proton nuclear magnetic resonance (^{1}H-NMR) allows for the rapid simultaneous identification and quantification of hundreds of metabolite measures in body fluids, providing metabolic profiles in large patient cohorts[14] that hopefully provide more detailed pathophysiologic insight, beyond the traditional blood-based measurements. Identifying circulating biomarkers might provide insights into molecular signature of migraine, and perhaps its relation with cerebrovascular and cardiovascular disease.[12]

We performed large-scale metabolic profiling of plasma on a ^{1}H-NMR platform measuring >220 metabolite measures in 8 large Dutch cohorts.[14] The platform was designed for a detailed assessment of cholesterol measures, triglycerides, creatine, lipids, fatty acids, apolipoproteins, amino acids, glycolysis-related metabolites, and ketone bodies.[14] We aimed to find circulating biomarkers and functionally related metabolite sets in plasma associated with migraine. Furthermore, we investigated these separately for female or male participants.

Methods

Study population

Eight Dutch cohorts, which collaborate in the Dutch Biobanking and BioMolecular resources Research Infrastructure (BBMRI; bbmri.nl/), provided samples: The Leiden University Migraine Neuro-Analysis (LUMINA),[15] The Netherlands Study of Depression and Anxiety (NESDA-1, NESDA-2),[16] The Netherlands Twin Registry (NTR),[17] The Erasmus Rucphen Family study (ERF),[18,19] The Rotterdam Study (RS),[20] The Maastricht Study (TMS),[21] and LifeLines.[22,23] These cohorts include population-based cohorts

(NTR, ERF, RS, and LifeLines), web-based (clinic-based) (LUMINA) cohorts, and mixed clinic- and population-based cohorts (NESDA-1, NESDA-2, and TMS). Participants were unrelated, except for NTR and ERF participants. NTR participants included twins, their parents, siblings, and spouses. ERF participants originated from a genetically isolated population in the southwest of the Netherlands. Cases were patients diagnosed with migraine. Probable migraine cases were not included. The control group consisted of participants negative for (probable) migraine. Apart from probable migraine patients, no participants were excluded. Information on migraine symptomatology, used for migraine assessment, was collected by means of surveys based on the International Classification of Headache Disorders (ICHD) criteria (NESDA, NTR, and TMS),[24] self-reported only (LifeLines), or a combination of questionnaires based on the ICHD criteria and a follow-up (telephone) interview (LUMINA, ERF, and RS). [24,25] For details regarding the cohorts, migraine assessments, other relevant disorders, and sampling procedures, see supplementary Methods. All blood samples were measured essentially in one batch in 2014, with the exception of part of the samples from NESDA (the NESDA-2 samples), which were analyzed a few months later.

Standard protocol approvals, registrations, and patient consents

All participants of the respective cohorts provided written informed consent. The study was approved by the local ethics committees of each study.

Metabolite quantification

Metabolites were quantified from EDTA plasma samples of 10,174 individuals (after quality control, 10,153 samples remained), analyzed using the same high-throughput ^{1}H-NMR metabolomics platform (Nightingale Health Ltd., Helsinki, Finland; nightingalehealth.com/).[14] This platform provides simultaneous quantification of 147 individual metabolites and 79 metabolite ratios; for example, routine lipids, lipoprotein subclass profiling with lipid concentrations within 14 subclasses, esterified fatty acid composition, and various low-molecular metabolites including amino acids, ketone bodies, and gluconeogenesis-related metabolites in molar concentration units. Details of the experimentation and applications of the NMR metabolomics platform have been described previously.[14]

Data preprocessing

The study flowchart is presented in figure 1. Metabolite measures that failed quality control (in particular glutamine, pyruvate, glycerol,β-hydroxybutyrate, and acetate) were excluded from the analysis. Metabolite measures with >10% missing values were excluded entirely. The final set of metabolite measures comprised 146 metabolites and 79 ratios, totaling 225 metabolite measures. Second, outliers (>5 SD) were removed in concordance with previous research in this field.[26] Third, metabolite measurements

were raised by 1 to allow log-transformation. Thereafter all metabolite values were log-transformed and scaled to approximate normality using a z-transformation prior to the analyses of each cohort. This process was conducted using R 3.3.2 (R Foundation for Statistical Computing, Vienna, Austria).

Single-metabolite logistic regression

For each metabolite measure separately, logistic regression was performed with the metabolite measure, age at blood draw, and sex as independent variables, and migraine status as dependent variable. The obtained estimates and standard errors for the metabolite measures were used in the subsequent random-effects meta-analysis. A random-effects model was chosen to account for possible heterogeneity due to differences in migraine assessment, sample processing, and sample collection between cohorts. Heterogeneity was assessed using the I^2 statistic and by visual inspection of forest plots. The family-wise error rate (the probability of making at least one type I error [false-positive] in a set of measures) was controlled at 5% with the Holm procedure (Holm-Bonferroni).[27] This multiple testing correction procedure was used because it is appropriate in case of strongly correlated measures, as is the case for our 225 metabolite measures. We investigated the influence of familial relatedness on metabolite levels in NTR and ERF using Pearson correlation analysis, but the effect of heritability on metabolite measure estimates (NTR r = 0.984 and ERF r = 0.838) and p values (NTR r =0.972 and ERF r = 0.702) was negligible (figure S1). Therefore, we did not include relatedness in the model. Meta-analyses were conducted with the meta-software package for R 3.3.2.

Influence of other covariates

First, we independently assessed, within LUMINA and NESDA, the influence of depression, smoking, fasting status, body mass index (BMI), and lipid-lowering medication usage on the metabolite levels of the candidate biomarkers identified in the single-metabolite logistic regression, using stratification plots. LUMINA and NESDA cohorts were selected, because the catalogue of covariates was most complete for these cohorts and because the current migraine assessment (LUMINA) and depression assessment (NESDA) were most accurate and detailed. Furthermore, NESDA was the only cohort that was measured in 2 separate batches. BMI and lipid-lowering medication usage showed to be of influence on the candidate biomarkers and were added to the single-metabolite logistic regression model in all 8 cohorts. Subsequently, meta-analyses were repeated.

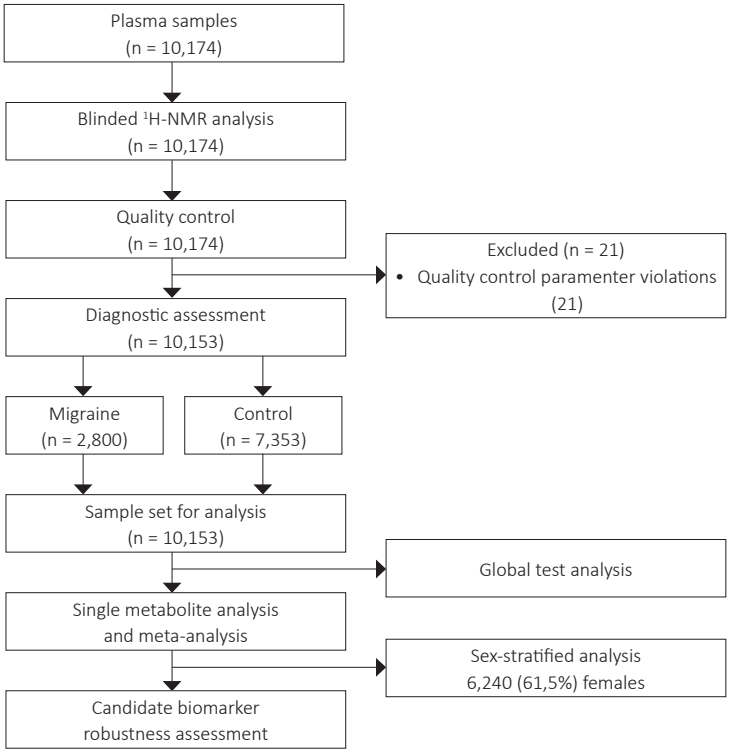

Figure 1. Study flowchart. Determination of the sample set used for data analysis and the different data analysis approaches performed in the current study. ^{1}H-NMR=proton nuclear magnetic resonance.

Stability measure

We studied the stability of metabolite measures in LUMINA participants (n = 41) that were sampled twice and measured in the same batch on the ^{1}H-NMR platform.[14] For these participants, time between blood draws ranged from 15 days to almost 4 years (average 833 ± 434 days). To investigate correlation between measurements and assess the effect of time on metabolite levels, the absolute values on the first and second measurement and the value difference between the paired measurements vs the days between the measurements was computed and analyzed with Pearson correlation analysis. p Values <0.05 were regarded as statistically significant. Analyses were performed using SPSS 23.0 (SPSS Inc., IBM, Armonk, NY) and GraphPad Prism version 7.02 for Windows (GraphPad Software, La Jolla, CA).

Sex-stratified analysis

In order to ascertain if the association of metabolites with migraine status may be different between male and female participants, we performed analyses stratified for sex in accordance with the aforementioned single-metabolite logistic regression and

random-effects meta-analysis model with family-wise error rate at 5% controlled using the Holm procedure (Holm-Bonferroni).[27]

Global test analysis

Associations of predefined sets of related metabolites with migraine status were tested with the global test framework,[28,29] adjusted for sex, age at blood draw, BMI, and lipid-lowering medication usage. The global test is aimed at associations between particular sets of (functionally) related metabolites and migraine status and does not test the direction of the association, that is, whether sets of metabolites are upregulated or downregulated. Metabolites were assigned to 23 different groups (tables S1 and S2) in agreement with the Kyoto Encyclopedia of Genes and Genomes pathways and in accordance with a previous pathway analysis conducted with the same NMR platform.[30] The test statistics for the separate cohorts (p values) from the global test were meta-analyzed using the Fisher combination method.[31] p Values < 0.05 after Holm-Bonferroni correction were considered statistically significant. Statistical analyses were conducted using the global test 5.30.0 software package for R 3.3.2.

Data availability

The data that support the findings of this study will be available in the BBMRI-omics atlas (bbmri.researchlumc.nl/atlas) and in the depository (doi:10.5061/dryad.p698mn7).

Results

Study population

Reliable quantification of 146 blood plasma metabolites and 79 metabolite ratios were available for 10,153 participants from 8 different cohorts: 2,800 migraine patients (80.6% female) and 7,353 controls (54.1% female) (see study flowchart [figure 1]). Clinical characteristics from all cohorts are shown in table 1.

Single-metabolite logistic regression

To identify potential metabolite biomarkers associated with migraine status, we performed a separate logistic regression for each metabolite measure in each cohort (table S3). Corresponding results were used in a random-effects meta-analysis. Migraine was associated with decreased apolipoprotein A1 levels (apoA1, an apoprotein with specific association with high-density lipoprotein [HDL]) (β −0.10, 95% confidence interval [CI] −0.16, −0.05, adjusted p = 0.029) and decreased free cholesterol to total lipid ratio in small HDL (S-HDL-FC ratio; β −0.10, 95% CI −0.15, −0.05, adjusted p =0.029)(figure 2). Heterogeneity between cohorts was minimal with I^2 = 0% for both metabolite measures. A β of −0.10 translates to an odds ratio for having migraine of 1.22 when comparing an individual with a typical

low metabolite score (z = −1 or 1 SD below average) and an individual with a typical high metabolite score (z = 1 or 1 SD above average). Other HDL particle measures (XL-HDL–[C, CE, FC, L, P, and PL], L-HDL–[C, CE, FC, L, P, PL, and TG], total cholesterol in HDL and HDL2, the mean diameter for HDL particles, and the total cholesterol to total lipids ratio in very large HDL) were also reduced in migraine, but failed to reach significance after correction for multiple comparisons (table S4). Despite the high negative correlation between HDL and very low-density lipoprotein (VLDL) or low-density lipoprotein (LDL) measures, only a few associations with LDL or VLDL measures were found nominally significant and none remained significant after correction for multiple comparisons.

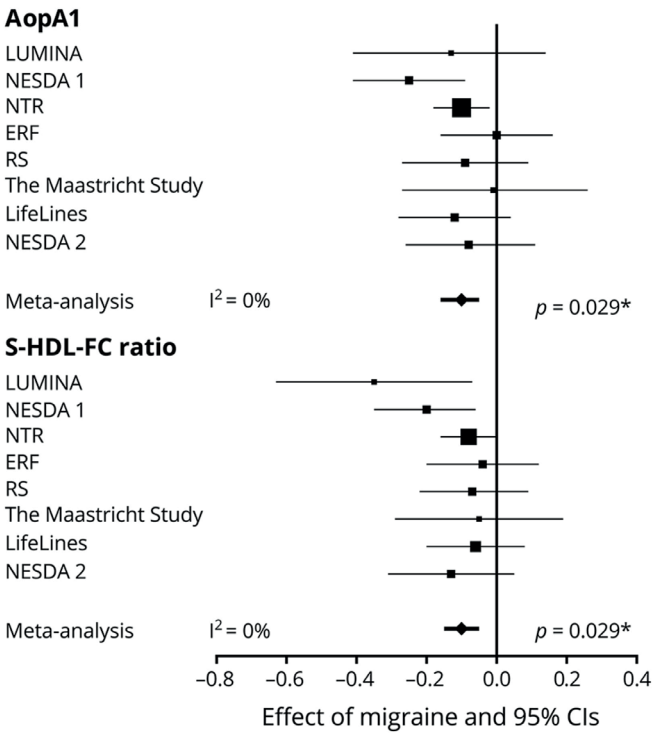

Figure 2. Forest plots of candidate migraine biomarkers apolipoprotein A1 (apoA1) and the free cholesterol to total lipid ratio in small high-density lipoprotein ratio (S-HDL-FC). Associations with migraine in random-effects meta-analyses. The effect sizes and 95% confidence intervals (CIs) for apoA1 and S-HDL-FC are presented per cohort and in a random-effects meta-analysis. Values from logistic regression with metabolite levels, sex, and age as independent variables and migraine status as dependent variable. Error bars denote 95% CIs. To facilitate the interpretation of the effect sizes (β coefficients), we calculated the odds ratio (OR) for having migraine for a typical low metabolite score (z score = −1, 1 SD below average) and a typical high metabolite score: β −0.10, OR 1.22; β −0.20, OR 1.49; β −0.30, OR 1.82; β −0.40, OR 2.22; β −0.50, OR 2.72. *p Values after Holm-Bonferroni (p<0.0002) multiple testing correction. ERF=Erasmus Rucphen Family study; I2=measure of heterogeneity; LUMINA=Leiden University Migraine Neuro-Analysis; NESDA=Netherlands Study of Depression and Anxiety 1 and 2; NTR=Netherlands Twin Registry; RS=Rotterdam Study.

Table 1. Baseline characteristics of the study populations

	LUMINA (n=408)				**NESDA-1** (n=1,082)				**NTR** (n=2,873)				**ERF** (n=1,413)			
	Cases (n=317)		Controls (n=91)		Cases (n=276)		Controls (n=806)		Cases (n=1,360)		Controls (n=1,513)		Cases (n=178)		Controls (n=1,235)	
	M	F	M	F	M	F	M	F	M	F	M	F	M	F	M	F
Total, n	105	212	47	44	48	228	353	453	217	1143	571	942	39	139	598	637
Age in years, mean (SD)	44.6 ± 13.0	42.4 ± 12.1	42.1 ± 13.9	36.2 ± 14.0	41.7 ± 11.6	39.7 ± 11.3	44.1 ± 12.8	41.9 ± 13.8	44.5 ± 14.0	41.4 ± 12.7	40.4 ± 14.4	39.3 ± 13.6	46.6 ± 11.9	45.8 ± 12.3	48.8 ± 14.0	48.3 ± 14.5
BMI in kg/m^2, mean (SD)	24.5 ± 2.6	23.9 ± 3.8	24.2 ± 2.7	23.4 ± 3.4	26.5 ± 5.1	25.5 ± 5.2	26.1 ± 4.5	25.1 ± 5.0	25.2 ± 3.9	24.8 ± 4.5	24.9 ± 3.4	23.9 ± 3.9	28.0 ± 5.5	27.2 ± 5.6	27.3 ± 4.3	26.4 ± 4.9
LLMU, n	1	5	2	0	8	12	40	20	22	37	37	41	3	16	73	64
	RS (n=1,425)				**TMS** (n=687)				**LifeLines** (n=1,319)				**NESDA-2** (n=946)			
	Cases (n=173)		Controls (n=1,252)		Cases (n=79)		Controls (n=608)		Cases (n=249)		Controls (n=1,070)		Cases (n=168)		Controls (n=778)	
	M	F	M	F	M	F	M	F	M	F	M	F	M	F	M	F
Total, n	29	144	556	696	27	52	458	150	49	200	504	566	27	141	285	493
Age in years, mean (SD)	77.4 ± 4.2	79.3 ± 5.1	79.3 ± 4.6	79.5 ± 4.9	59.2 ± 8.5	61.5 ± 7.1	63.2 ± 7.3	61.8 ± 8.1	44.1 ± 11.1	43.3 ± 12.3	44.8 ± 14.1	43.9 ± 13.8	39.8 ± 9.8	41.8 ± 12.4	44.7 ± 13.5	42.7 ± 13.6
BMI in kg/m^2, mean (SD)	26.9 ± 3.0	27.6 ± 4.6	27.0 ± 3.3	27.8 ± 4.3	28.0 ± 3.4	30.0 ± 5.8	29.6 ± 4.7	30.3 ± 5.5	26.1 ± 3.3	25.6 ± 5.2	25.3 ± 3.4	24.8 ± 4.2	26.7 ± 5.2	24.8 ± 4.7	25.9 ± 4.2	24.9 ± 4.7
LLMU, n	8	31	142	153	21	31	335	113	0	8	29	20	0	4	32	36

BMI=body mass index; ERF=Erasmus Rucphen Family study; LLMU=lipid-lowering medication usage; LUMINA=Leiden University Migraine Neuro-Analysis; NESDA=Netherlands Study of Depression and Anxiety; NTR=Netherlands Twin Registry; RS=Rotterdam Study; TMS=The Maastricht Study.

Candidate biomarker robustness assessment

Next, we assessed the influence of smoking, fasting status, depression, lipid-lowering medication usage, and BMI (figures S2–S6) on apoA1 levels and the S-HDL-FC ratio in the LUMINA and NESDA cohorts. Small effects of lipid-lowering medication usage and BMI on apoA1 and S-HDL-FC ratio plasma levels were identified. Other covariates did not influence these levels. For all cohorts, BMI and lipid-lowering medication usage were subsequently added to our model. The expanded model revealed that a decreased apoA1 level (β −0.092, 95% CI −0.15, −0.04) and S-HDL-FC ratio (β −0.068, 95% CI −0.12, −0.02) were still associated (uncorrected p values 0.0010 and 0.0095) with migraine. To further support the robustness of the candidate biomarkers, correlation analyses using 82 samples from 41 participants, acquired on 2 occasions (833 ± 434 days apart), revealed particularly stable results between measurements in the same individual patient for apoA1 (r = 0.859) and to a lesser extent for S-HDL-FC ratio (r = 0.497) (figure S7).

Sex-stratified analysis

Given the preponderance of females among migraine patients, we searched for possible differences in the metabolite profile associated with migraine between male and female participants (figure 3). ApoA1 levels were significantly associated with migraine in male participants, with smaller effects, but in similar direction, in female participants. Furthermore, the apoB/apoA1 ratio was significantly higher in female migraineurs compared to female controls. The S-HDL-FC ratio (table S5) was negatively associated with migraine in female participants, but failed to reach significance after correction for multiple testing. In male participants, no apparent relation was identified for the S-HDL-FC ratio. Associations with lower medium and large HDL measures (L-HDL–[C, CE, FC, L, P, and PL]) were significant in female participants, with a similar finding in male participants, although not significant. Interestingly, in male participants, lower omega-3 fatty acids (p = 0.033) were associated with migraine, an association not seen in female participants. Clinical characteristics from all cohorts stratified for sex and the sex-stratified meta-analysis are shown in table 1.

Global test analysis

To detect if migraine status was associated with particular sets of (functionally) related metabolites, we tested the association of 23 different predefined sets of metabolites with migraine status using the global test. The global test does not evaluate each metabolite measure individually, but tests whether the levels of a group of metabolites are associated with an outcome (in this case, migraine status). We controlled for the same covariates as in the logistic regression per metabolite. The global test was first applied per cohort, after which the p values were combined in a meta-analysis using the Fisher method (figure 4 and table 2). The global test analysis confirmed the association of HDL-associated metabolites with migraine, already apparent from the single metabolite

analysis, with large clusters of medium (M–) to very large (XL–) HDL subclasses generally associated with migraine status across the majority of cohorts (figure S8). Interestingly, no other lipoprotein classes were associated with migraine. Somewhat surprisingly, the metabolism of valine, leucine, and isoleucine was significantly associated with migraine, and not in line with the findings from the single-metabolite analyses. This is a false-positive result, obtained because this meta-analysis method is based on nondirectional p values, and may provide a significant p value even when the direction of change is not consistent between cohorts, as is the case for these branched chain amino acids.

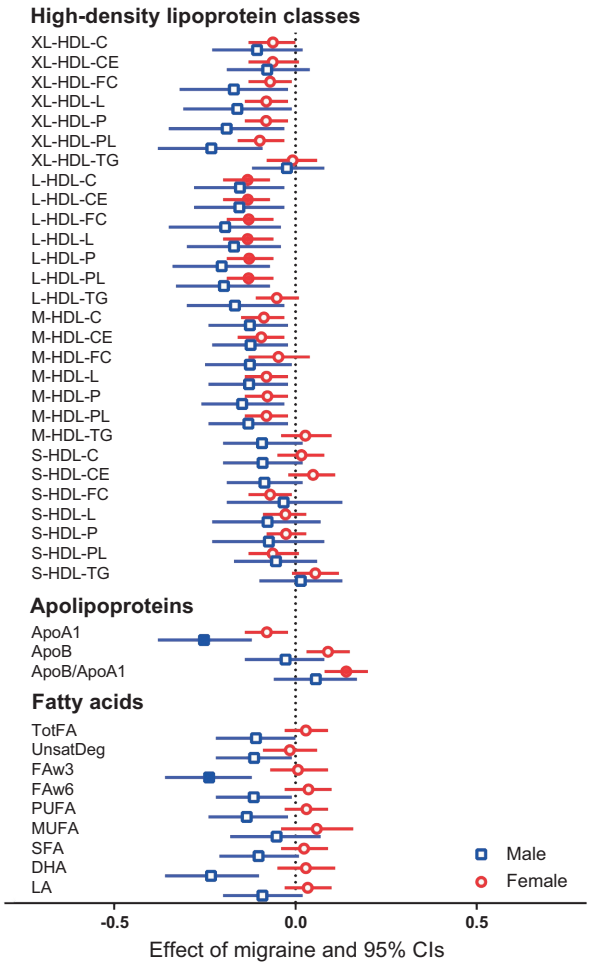

Figure 3. Sex-stratified metabolite associations with migraine. Metabolite associations with migraine in male (blue squares) and female (red circles) participants in a random-effects meta-analysis comprised of 8 cohorts. The effect sizes and 95% confidence intervals (CIs) are shown. Values are from logistic regression with metabolite levels, sex, age, body mass index, and lipid-lowering medication usage as

independent variables and migraine status as dependent variable. Error bars denote 95% CIs, filled squares (male participants) or circles (female participants) indicate significance after Holm-Bonferroni ($p<0.0002$) multiple testing correction. All other metabolite classes without significant metabolites after Holm-Bonferroni correction as well as I^2 values can be found in table S5. To facilitate the interpretation of the effect sizes (β coefficients), we calculated the odds ratio (OR) for having migraine fora typical low metabolite score (z score=−1, 1 SD below average) and a typical high metabolite score: β −0.10, OR 1.22; β −0.20, OR 1.49; β −0.30, OR 1.82; β −0.40, OR 2.22; β −0.50, OR 2.72. All metabolite abbreviations can be found in tables S1 and S2.

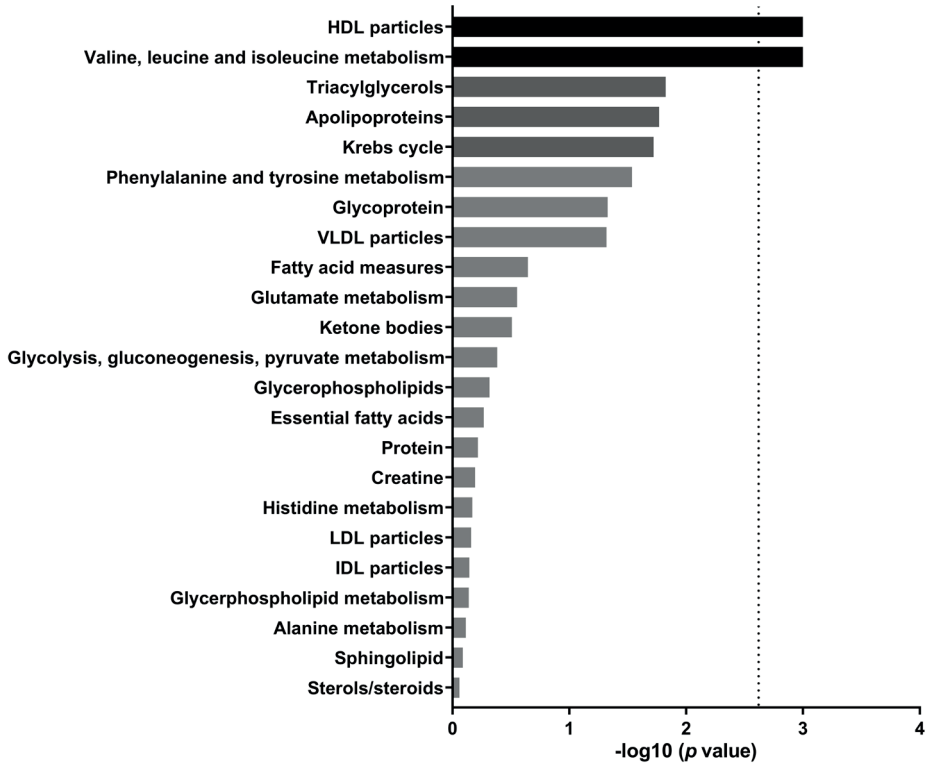

Figure 4. Global test analysis. Meta-analysis of the results of the 23 sets of (functionally) related metabolites tested in 8 cohorts for their association with migraine. The analysis using the global test framework has been adjusted for a sex, age, body mass index, and lipid-lowering medication usage. Glutamate metabolism does not include results from the Netherlands Twin Registry as glutamine levels could not be determined in this cohort. Bars denote $-\log^{10}$ of the p value (Fisher combination of global test p values for the individual cohorts) per pathway, where only the black bars remain significant after multiple testing correction using Holm-Bonferroni. The threshold for withstanding multiple testing correction is indicated by a dotted line. IDL= intermediate-density lipoprotein; LDL=low-density lipoprotein; VLDL=very low-density lipoprotein.

Table 2. Cohort results of global test analysis and Fisher combination method

	LUMINA p-value	NESDA-1 p-value	NTR p-value	ERF p-value	RS p-value	TMS p-value	LifeLines p-value	NESDA-2 p-value	Fisher method	H-B corrected p-value
HDL particles	0.059	0.0091	0.047	0.052	0.228	0.372	0.059	0.448	0.00098	**0.022**
Valine, Leucine, Isoleucine metabolism	0.018	0.068	0.246	0.108	0.964	0.00014	0.743	0.766	0.00088	**0.020**
Triacylglycerols	0.099	0.507	0.567	0.225	0.236	0.473	0.00088	0.374	0.015	0.325
Apolipoproteins	0.059	0.023	0.133	0.056	0.570	0.609	0.123	0.631	0.017	0.336
Krebs cycle	0.118	0.254	0.066	0.0041	0.399	0.445	0.382	0.591	0.019	0.356
Phenylalanine and tyrosine metabolism	0.0036	0.795	0.429	0.039	0.315	0.271	0.400	0.436	0.029	0.524
Glycoprotein	0.015	0.115	0.415	0.484	0.849	0.104	0.966	0.059	0.047	0.804
VLDL particles	0.062	0.406	0.396	0.481	0.461	0.538	0.0050	0.295	0.048	0.804
Fatty acid measures	0.283	0.271	0.153	0.294	0.607	0.735	0.057	0.544	0.226	1.000
Glutamate metabolism[a]	0.190	0.069	NA	0.369	0.478	0.706	0.259	0.601	0.280	1.000
Ketone bodies	0.279	0.035	0.806	0.568	0.213	0.768	0.290	0.523	0.310	1.000
Glycolysis, gluconeogenesis, pyruvate metabolism	0.826	0.820	0.182	0.045	0.899	0.093	0.586	0.927	0.413	1.000
Glycerophospholipids	0.660	0.166	0.068	0.645	0.827	0.521	0.404	0.490	0.482	1.000
Essential fatty acids	0.608	0.045	0.663	0.416	0.483	0.775	0.645	0.334	0.539	1.000
Protein	0.639	0.777	0.086	0.591	0.179	0.451	0.588	0.800	0.606	1.000
Creatine	0.617	0.994	0.352	0.068	0.194	0.528	0.966	0.822	0.639	1.000
Histidine metabolism	0.957	0.873	0.549	0.520	0.987	0.330	0.605	0.033	0.676	1.000
LDL particles	0.205	0.378	0.775	0.122	0.972	0.866	0.443	0.626	0.691	1.000
IDL particles	0.163	0.376	0.673	0.292	0.900	0.925	0.352	0.576	0.716	1.000
Glycerolipid metabolism	0.536	0.244	0.237	0.426	0.658	0.622	0.705	0.563	0.724	1.000
Alanine metabolism	0.408	0.588	0.812	0.353	0.906	0.130	0.590	0.633	0.770	1.000
Sphingolipids	0.164	0.383	0.306	0.909	0.550	0.776	0.781	0.736	0.816	1.000
Sterols/steroids	0.232	0.428	0.965	0.268	0.922	0.880	0.343	0.981	0.871	1.000

ERF=Erasmus Rucphen Family study; H-B=Holm-Bonferroni; HDL=high-density lipoprotein; IDL=intermediate-density lipoprotein; LDL=low-density lipoprotein; LUMINA=Leiden University Migraine Neuro-Analysis; NA=not applicable; NESDA=Netherlands Study of Depression and Anxiety; NTR=Netherlands Twin Registry; RS=Rotterdam Study; TMS=The Maastricht Study; VLDL=very low-density lipoprotein. Corrected for age, sex, body mass index, and use of lipid-lowering medication. [a] Determined without NTR due to nonquantified glutamine measurements.

Discussion

We performed high-throughput ^{1}H-NMR metabolite profiling of 225 metabolite measures in plasma samples from 8 Dutch cohorts and identified a consistent association between migraine and decreased HDL levels. We identified 2 circulating candidate migraine biomarkers, which are both related to HDL status: a decreased level of apoA1 (an apoprotein with a specific association with HDL) and a decreased S-HDL-FC ratio (the free cholesterol to total lipid ratio in small HDL). In addition, fatty acids of the omega-3 class were shown to be associated with migraine, but only in male participants.

Dyslipidemia and migraine have been extensively studied because of the comorbidity of cerebrovascular and cardiovascular disease and migraine, with the strongest associations in young women without elevated conventional cardiovascular risk profiles.[5–8,13] Large population-based studies suggested elevated total cholesterol, LDL-C, or triglycerides, and decreased levels of HDL-C, in migraine. [5–8,13] However, earlier results were conflicting[13] due to cohort variability and measurement of crude lipoprotein levels,[5–8,13] or failed to detect differences in apoA1 levels, possibly due to lack of power.[32,33] Notably, the sufficiently powered Women's Health Study observed a nonsignificant effect with decreased apoA1 levels in 5,087 female participants with a history of migraine (total population 27,626, mean age 54.7 years).[34] A more prominent association between migraine and apoA1 in men compared to women, and lower mean age in the current study, might explain the difference between the studies. To the best of our knowledge, lower omega-3 fatty acid levels have not been reported in migraine. Of note, omega-3 fatty acid supplements, due to their anti-inflammatory action, have been investigated in migraine attack prevention.[35] A recent meta-analysis found no apparent reduction in headache frequency after omega-3 fatty acid supplementation; however, a significant reduction in headache duration was found across studies.[35]

HDL subclasses are composed of proteins and lipids, each roughly representing 50% of the total mass of HDL. Major proteins are apoA1 (70%) and apoA2 (20%) together with proteins such as apoA4, apoE, apoJ, haptoglobin, paraoxanase, α2-macroglobulin, and lecithin cholesterol acyltransferase.[36] These proteins contribute to various functions of HDL, including mediating the reverse cholesterol transport pathway and antioxidative, anti-inflammatory, and antithrombotic effects.[37] Combining the different analyses conducted, we identified an association between deceased apoA1 level and S-HDL-FC ratio and migraine together with decreased levels of medium to very large HDL measures, in the absence of clear LDL, intermediate-density lipoprotein, or VLDL involvement. Thus, the observed profiles suggest that migraine is associated with alterations in specific HDL functions but not with a general dyslipidemia profile characteristic for cardiovascular conditions.

Although this biomarker discovery study was not aimed to unravel pathophysiologic mechanisms, several hypotheses regarding pathophysiological mechanisms emerge from the study. First, our findings provide some biochemical evidence for a link with endothelium dysfunction in migraine as HDL with its antioxidative, anti-inflammatory, and antithrombotic effects plays a role in endothelial function.[36–38] Interestingly, omega-3 fatty acids, which showed decreased levels associated with migraine in male participants, have also been shown to be vasoprotective and have been deemed to generate anti-inflammatory resolvins.[39] It is at this point, however, only speculation whether reduced protective actions of HDL and omega-3 through endothelial dysfunction may explain the association with migraine. Second, it has been suggested that omega-3 fatty acids and certain HDL subclasses can travel across the blood–brain barrier, which may have effects on a neuronal level.[40–42] Third, that omega-3 fatty acids are associated with migraine exclusively in male participants may suggest distinct sex-specific mechanisms. However, this might also be due to differences in omega-3-rich food consumption[43] and requires further specific investigation.

The strengths of this study are the large sample size (>10,000 participants) and extensive metabolic profiling (225 metabolite measures) to identify candidate biochemical biomarkers for migraine. Furthermore, similar methods (EDTA samples, ^{1}H-NMR platform, and facility) were used across cohorts. A possible limitation of the study is that migraine status was assessed with varying degrees of detail in the various cohorts, which also made us unable to look into possible differences between migraine with and without aura. Still, many cohorts used validated questionnaires based on ICHD criteria and have shown their effectiveness and precision in diagnosing migraine,[1,15,18] which is why metabolite measure associations with migraine were chosen as main study outcome. To make a clear distinction between definite migraineurs and non-migraine participants, we excluded probable migraine cases whenever possible. Additional variability due to sampling protocols used, foremost time-to-freezer and centrifuge settings, we aimed to control for by using meta-analysis approaches with a random-effects model. The low heterogeneity seen in the random-effects meta-analysis, in particular for the candidate biomarkers, seems to indicate that the aforementioned variability only had a limited influence on the study outcome. Our top metabolites related to HDL concentrations are known to be affected by BMI. Although we corrected for BMI in our analysis, we cannot exclude a residual confounding effect of this variable nor of any other variable that we have not tested. However, the robustness of our finding across different cohorts that differed in BMI distributions makes it likely that the HDL-related traits are truly associated with migraine. Genetic variability was limited because all cohorts were comprised predominantly of participants from the Netherlands, with Western European ancestry, but as a direct consequence the generalizability of our findings to other populations may be limited. The current study design does not allow the study of causality. Intervention

or animal studies are needed to further explore the interplay between BMI, HDL-related traits, and migraine. Another limitation of our multicohort design using distributed data analysis algorithms is that we cannot make definitive estimates of the sensitivity and specificity of the candidate biomarkers.

The current study illustrates the power of detailed metabolite profiling for biomarker discovery in a large meta-analytic design, pointing towards consistent associations of mainly medium to very large HDL measures with migraine. Furthermore, we identified a male-specific association between migraine status and omega-3 fatty acids. Our study suggests that alterations in HDL metabolism may be involved in the association between migraine and cerebrovascular and cardiovascular disease.

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Supplementary data

Supplementary Methods

Cohort background, migraine assessment method, and sampling procedure.

LUMINA

Participants of the Leiden University Migraine Neuro-Analysis (LUMINA) were recruited through a dedicated, nationwide website inviting migraine patients and non-migraine controls to participate in migraine research. In addition, patients attending the Leiden University Medical Centre (LUMC) dedicated headache clinic were invited to participate. We therefore consider this a web-based "clinic-based" cohort.

Participants recruited through the website were considered eligible after a two-step inclusion process using validated questionnaires via the dedicated LUMINA website[1]. A migraine diagnosis or non-migraine control status was validated by a semi-structured telephone interview, in accordance with the International Classification of Headache Disorders (ICDH-3β)[2]. Finally, the diagnosis was checked by the study-physician at the day of blood draw. Migraine patients recruited through the headache clinic were diagnosed with migraine by a neurologist specialized in headache. Patients with a diagnosis of probable migraine in accordance with the ICHD-3β were excluded[2]. Non-migraine controls were free of any primary disorder, apart from tension-type headache[2]. Migraine assessment was conducted on the day of sampling blood.

EDTA plasma samples were available for 317 migraine cases and 91 non-migraine controls. Samples from 279 participants were collected after overnight fasting. Blood samples were drawn by venipuncture from the median cubital vein, after centrifugation on room temperature; plasma was aliquoted and stored at -80°C. Samples were freeze-thawed no more than once prior to shipment to Nightingale Health for analysis, where samples were measured in April 2014.

NESDA

The Netherlands Study of Depression and Anxiety (NESDA) is an observational longitudinal naturistic cohort study on the long term course and consequences of depressive and anxiety disorders[3]. We consider this a mixed clinic- and population-based cohort. In total 2,981 participants were recruited between 2004 and 2007 through different settings: community, primary care and specialized mental health clinics in order to obtain a representative sample of persons with and without depressive and anxiety disorders. Using this approach NESDA created a range in psychopathology: participants ('controls') without symptoms or disorders, those at risk due to subthreshold symptoms or with a personal or family history, and participants with a current or remitted depressive or

anxiety disorders. A more extensive description of the composition of NESDA can be found elsewhere[3].

Migraine was assessed at the baseline assessment using a headache questionnaire based on the criteria for migraine listed in the ICHD-2[4]. The migraine part of the questionnaire was preceded by one screening question ("Do you ever experience headache attacks, for instance migraine?"), participants had to answer positive in order to be required to answer the remaining detailed questions about their headaches. This provided information on the presence of symptoms and criteria present in the ICHD-2: number of experienced headache attack (≥5), pain intensity (moderate/severe), pain duration (4-72 hours), and pulsating pain (yes/no). During a headache attack: visual aura (yes/no), aggravation by physical activity (yes/no), presence of nausea and/or vomiting (yes/no), and phonophobia or photophobia (yes/no). Based on the criteria in the ICHD-2 participants were classified as: migraine patients, probable migraine patients, mild non-migrainous headache patients, and participants without headache (participants answering negative to the first screening question). In the current study only participants characterized as migraine patients using the questionnaire were included as migraine patients. Probable migraine patients were excluded. Participants characterized as mild non-migrainous headache patients, and participants without headache were included in the analysis as controls. Questionnaires were completed in close temporal relation to sample collection (on average within seventeen days).

Baseline EDTA plasma samples were available for 444 migraine cases and 1,584 non-migraine controls. Samples from 1,944 participants were collected after overnight fasting. Samples were drawn by venipuncture from the median cubital vein, after centrifugation on room temperature; plasma was aliquoted and stored at -85°C. Samples were freeze-thawed no more than once prior to shipment to Nightingale Health for analysis. Samples were measured at Nightingale Health at two separate occasions (April and December 2014). Based on this two separate NESDA cohorts were defined, NESDA-1 (n=1,082) and NESDA-2 (n=946), respectively.

NTR

The Netherlands Twin Registry (NTR) is composed of and collects data from Dutch twins, other siblings, their parents and partners. We consider this a population-based cohort. Participants were recruited either at birth through 'birth felicitation' services or when already older at the start of NTR, through city councils in 1990-1991 and through additional efforts in later years. A detailed description of NTR can be found elsewhere[5]. Migraine was diagnosed using a headache questionnaire based on the criteria for migraine listed in the ICHD-2[4]. The migraine part of the questionnaire was preceded by one screening question ("Do you ever experience headache attacks, for instance

migraine?"), participants had to answer positive in order to be required the answer to remaining detailed questions about their headaches. This provided information on the presence of symptoms and criteria present in the ICHD-2: number of experienced headache attacks (≥5), pain intensity (moderate/severe), pain duration (4-72 hours), and pulsating pain (yes/no). During a headache attack: visual aura (yes/no), aggravation by physical activity (yes/no), presence of nausea and/or vomiting (yes/no), and phonophobia or photophobia (yes/no). Based on the criteria in the ICHD-2 participants were classified as: migraine patients, probable migraine patients, mild non-migrainous headache patients, and participants without headache (participants answering negative to the first screening question). In a small number of cases (<60 cases), detailed symptom information was not available and self-reported migraine was used. In the current study only participants characterized as migraine patients using the questionnaire were included as cases. Probable migraine patients were excluded. Participants characterized as mild non-migrainous headache patients, and participants without headache are were included in the analysis as controls. If diagnosed with migraine after blood sampling, the participant was included as a migraine patient (case). If diagnosed prior to blood sampling as healthy control this was no more than 6 months prior to the sampling, otherwise the sample was excluded because of the risk of developing migraine.

EDTA plasma samples were available for 1,360 migraine cases and 1,513 non-migraine controls. Samples from 2,673 participants were collected after overnight fasting. Samples were drawn by venipuncture from the medial cubital vein during a home-visit, after centrifugation back at the laboratory at 4°C, plasma was aliquoted and stored at -20°C[5]. Samples were collected in two biobanking initiatives (the first between June 2004 and July 2008 and the latter between January 2011 and December 2011) and freeze-thawed once prior to shipment to Nightingale Health for analysis. Samples were measured in 2014 at Nightingale Health.

ERF

The Erasmus Rucphen Family (ERF) study is a large family-based cohort study, in a young genetically isolated population in the Southwest of The Netherlands. We consider this a population-based cohort. Possible participants were selected based on genealogical background. Eligible participants included three generations of living descendants, of twenty couples with at least six children living in the community in the 19th century. Participants were therefore not selected based on phenotypes of interest, and traced back through church and municipality records[6].

Migraine was diagnosed using a headache questionnaire based on the criteria for migraine listed in the ICHD-2[4]. A previously validated three-stage screening procedure was used to assess lifetime occurrence of migraine[7,8]. In short, stage one consisted of 5

screening questions on aura and headache symptoms. In stage two only screen-positive participants received an extensive questionnaire on headache and aura symptoms. The extensive questionnaire was based on ICHD-2 criteria for migraine headache and aura[4]. In stage three, screen-positive participants, or participants which did not fill in or complete the extensive questionnaire, were interviewed by telephone using a semi-structured to clarify their reported signs and symptoms of migraine headache and aura by a physician with experience in diagnosing migraine patients, and well trained supervised medical students. The final migraine diagnosis was made after this telephone interview and in consultation with a neurologist (GMT) specialized in headache. Probable migraine patients were excluded. ERF participants who were negative for migraine or probable migraine based on the aforementioned three-stage screening procedure were included as controls[7,8]. If diagnosed with migraine after blood sampling, the participant was included as a migraine patient (case). If diagnosed prior to blood sampling as healthy control this should not be more than 6 months prior to the sampling, otherwise the sample was excluded because of the risk participants developing migraine.

EDTA plasma samples were available for 178 migraine cases and 1,235 non-migraine controls. Samples from 1,413 participants were collected after overnight fasting. Samples were drawn by venipuncture from the median cubital vein, after centrifugation at 4°C, plasma was aliquoted in cryovials and stored at -80°C. Samples were not freeze-thawed prior to shipment to Nightingale Health for analysis. Samples were measured in the spring of 2014 at Nightingale Health.

RS

The Rotterdam study (RS) is a large prospective population-based cohort study, among people 55 years of age or older living in the well-defined Ommoord district in Rotterdam (NL) in 1990. Later the RS was expanded in 2000 and 2006 to include people 45 years of age or older living in the Ommoord district[9].

Migraine was assessed using a modified questionnaire of the questionnaire used in the Leiden Genetic Epidemiology of Migraine (GEM) study[7,8], based on the ICHD-2 criteria[4] as part of a face-to-face structured interview or telephone interview[10]. Participants were first asked if they had ever experienced a headache with severe pain that affected their daily activities. If the answer to this question was negative or if the participant clearly indicated that severe headache was due to other causes, such as a tumor, sinusitis, stroke, trauma or meningitis, no further headache related questions were asked. Participants who replied positive to the first question received further questions on headache duration and attack frequency. Participants who experienced headaches of which (1) the duration was between four and seventy-two hours (untreated) or if the participant did not know the answer to this question, because they always treated their

headaches and (2) the attack frequency was two or more attacks in a lifetime, further details on the characteristics and symptoms of the headaches were asked. Participants whose duration of headache was unknown, because they always used medication to prevent or treat the attack, were considered migraine patients if they fulfilled the remaining ICHD-2 criteria[10]. Probable migraine patients were excluded. Participants not classified as (probable) migraine patients were included as controls[10]. If diagnosed with migraine after blood sampling, the participant was included as a migraine patient (case). If diagnosed prior to blood sampling as healthy control this should not be more than 6 months prior to the sampling, otherwise the sample was excluded because of the risk participants developing migraine.

EDTA plasma samples were available for 173 migraine cases and 1,252 non-migraine controls. Samples from 1,425 participants were collected after overnight fasting. Samples were drawn by venipuncture from the median cubital vein, after centrifugation at 4°C, plasma was aliquoted in cryovials and stored at -80°C. Samples were not freeze-thawed prior to shipment to Nightingale Health for analysis. Samples were measured in the spring of 2014 at Nightingale Health.

LifeLines-DEEP

The LifeLines-DEEP cohort is a sub-cohort of the LifeLines cohort (167,729 participants), which is a large three-generation observational follow-up study set up to investigate universal risk factors and their modifiers for multifactorial diseases[11,12]. Participants include a large representative sample of the Northern part of the Netherlands. We consider this a population-based cohort. At the start of the study a random sample of inhabitants aged between 25 and 50 years were invited to participate through their general practitioner. After inclusion initial participants were asked if family members (partners, parents, partners-in-law and children) might be interested to participate. Interested family members were included in the study. Additional participants, again living in the Northern part of the Netherlands, were included via the LifeLines website[11,12]. A subset of 1,539 participants (636 males and 903 females, age range 18–84 years) also took part in the more detailed phenotyping and omics profiling, called the LifeLines-DEEP study. For these participants, additional biological materials were collected, including additional blood (n=1,387), exhaled air (n=1,425) and fecal samples (n=1,248), and elicited responses to gastrointestinal health questionnaires (n=1,176) for analysis of the genome, epigenome, transcriptome, microbiome, metabolome and other biological levels. The overview of the different data layers in LifeLines DEEP and the baseline characteristics of the study population has been described previously[13].

This study included the baseline information and plasma samples of LifeLines-DEEP participants. The migraine status was assessed using a single question, which was

part of a general health questionnaire. The question "could you indicate which of the following disorders you have (had): migraine", was used to classify migraine patients and non-migraine controls. The participants who answered "yes" were included as a migraine patient (case) and those who answered "no" were included as healthy control. If diagnosed with migraine after blood sampling, the participant was included as a migraine patient (case). If diagnosed prior to blood sampling as healthy control this should not be more than 6 months prior to the sampling, otherwise the sample was excluded because of the risk of participants developing migraine.

EDTA plasma samples from participants were collected after overnight fasting. Samples were drawn by venipuncture from the median cubital vein, placed at 4°C and transported from the research site to the LifeLines laboratory in Groningen, under tightly controlled and continuously monitored conditions. After preparation plasma was aliquoted and stored at-80°C[11]. Samples were freeze-thawed two times prior to shipment to Nightingale Health for metabolome analysis. With some sample drop-off, this study finally included 1,319 LifeLines-DEEP participants, including 249 migraine cases and 1,070 migraine controls.

TMS

The Maastricht Study (TMS) is a prospective observational population-based cohort study enriched with individuals suffering from type 2 diabetes mellitus. We therefore consider this a mixed clinic- and population-based cohort. Eligible participants were selected based on age (between 40 and 75 years) and place of residence (the Southern part of the Netherlands). Recruitment proceeded through mass media campaigns, municipal registries and the regional Diabetes Patient Registry via mailings[14]. In the current study only subjects suffering from diabetes were included.

Migraine status was assessed via web-based questionnaires. First, a screening questionnaire based on the screening questionnaire used in the GEM study was offered to all participants[7]. Second, only screen-positive participants received an extensive questionnaire on headache and aura symptoms based on the ICHD-2 criteria[4]. Based on the results from the extensive questionnaire participants were classified as definite, probable or possible migraine patients. Participants classified as probable migraine patients were excluded from the current study. TMS participants who were negative for definite or probable migraine based on the screening or extensive questionnaire were included as controls[7,8]. Migraine questionnaires were taken within 3 months after plasma samples were collected.

EDTA plasma samples were available for 79 migraine cases and 608 non-migraine controls. Samples from all participants were collected after overnight fasting. Plasma

was collected via venipuncture in EDTA tubes on ice, separated after centrifugation, and stored at −80°C until the assays were performed. The time between collection and storage was less than 2 hours. Samples were collected from April 2010 until April 2013 and not freeze-thawed prior to shipment to Nightingale Health for analysis. Samples were measured in April 2014 at Nightingale Health.

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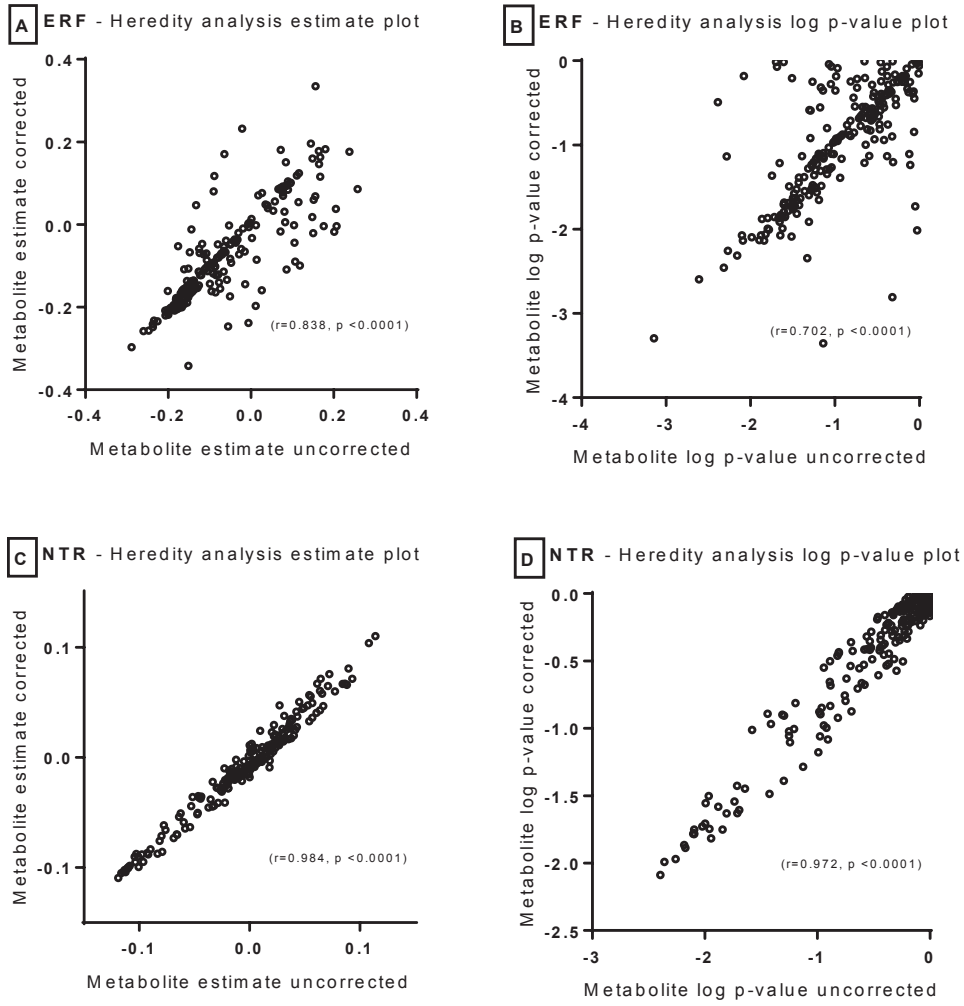


Figure S1. Influence of heritability on metabolite measure estimates and log p-values in ERF and NTR. To investigate for possible effects of heritability on metabolite measures in ERF (A and B) and NTR (C and D) we compared the estimates (A and C) and log p-values (B and D) between single metabolite logistic regression with metabolite concentrations, sex, and age as independent variables and migraine status as dependent variable, corrected for heritability with the same model uncorrected for heritability. Pearson correlation (r) and corresponding p-values of correlations between the estimates and log p-values are given in the respected plots. ERF=Erasmus Rucphen Family study, NTR=Netherlands Twin Registry.

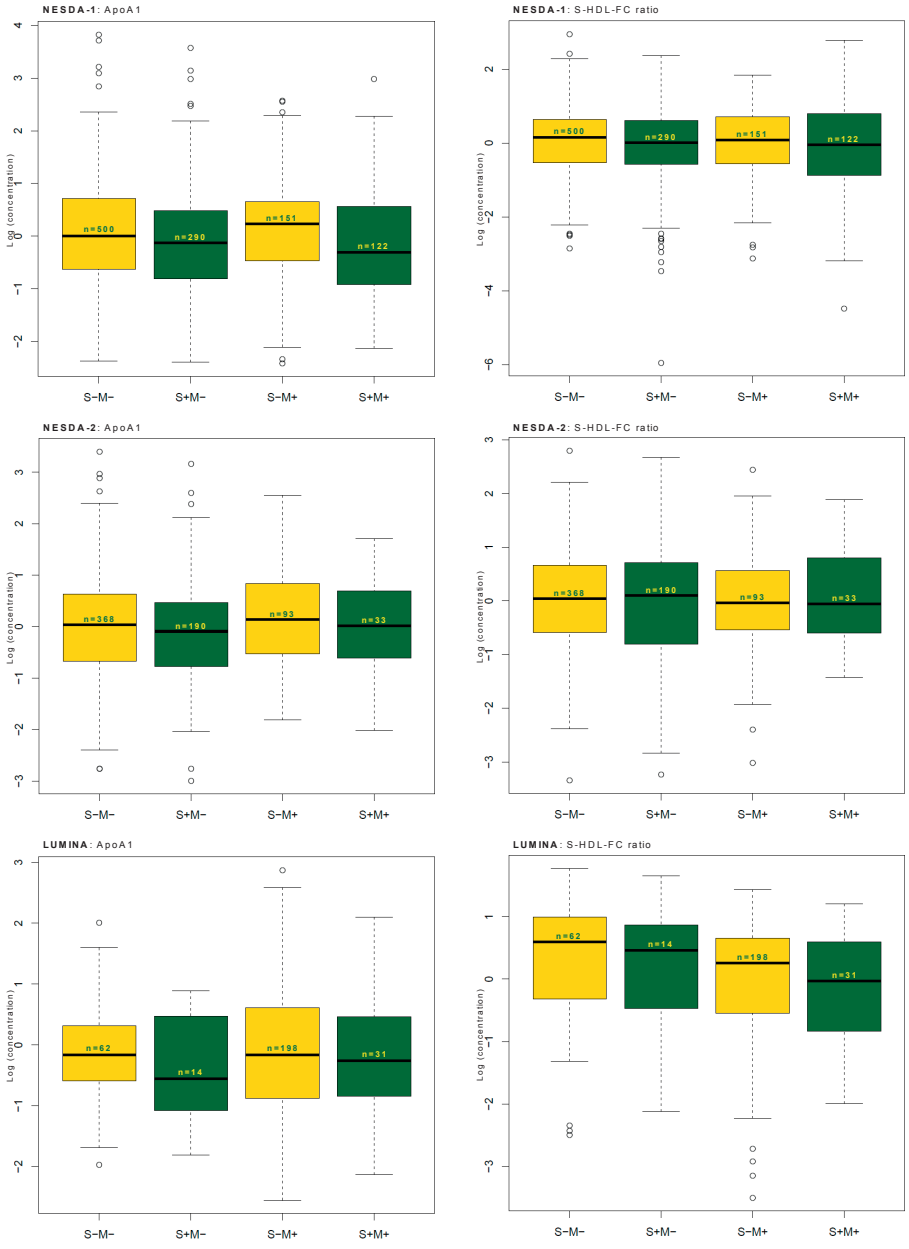


Figure S2. ApoA1 and S-HDL-FC ratio stratification plots for migraine and smoking in NESDA and LUMINA. Stratification plots for smoking (yes=S+/no=S-) and migraine (yes=M+/no=M-) in both cohorts of The Netherlands Study of Depression and Anxiety (NESDA) and Leiden University Migraine Neuro-Analysis (LUMINA). Participant numbers are provided in the boxplots. ApoA1=Apolipoprotein A1, S-HDL-FC=Free cholesterol to total lipids ratio in small high-density lipoprotein.

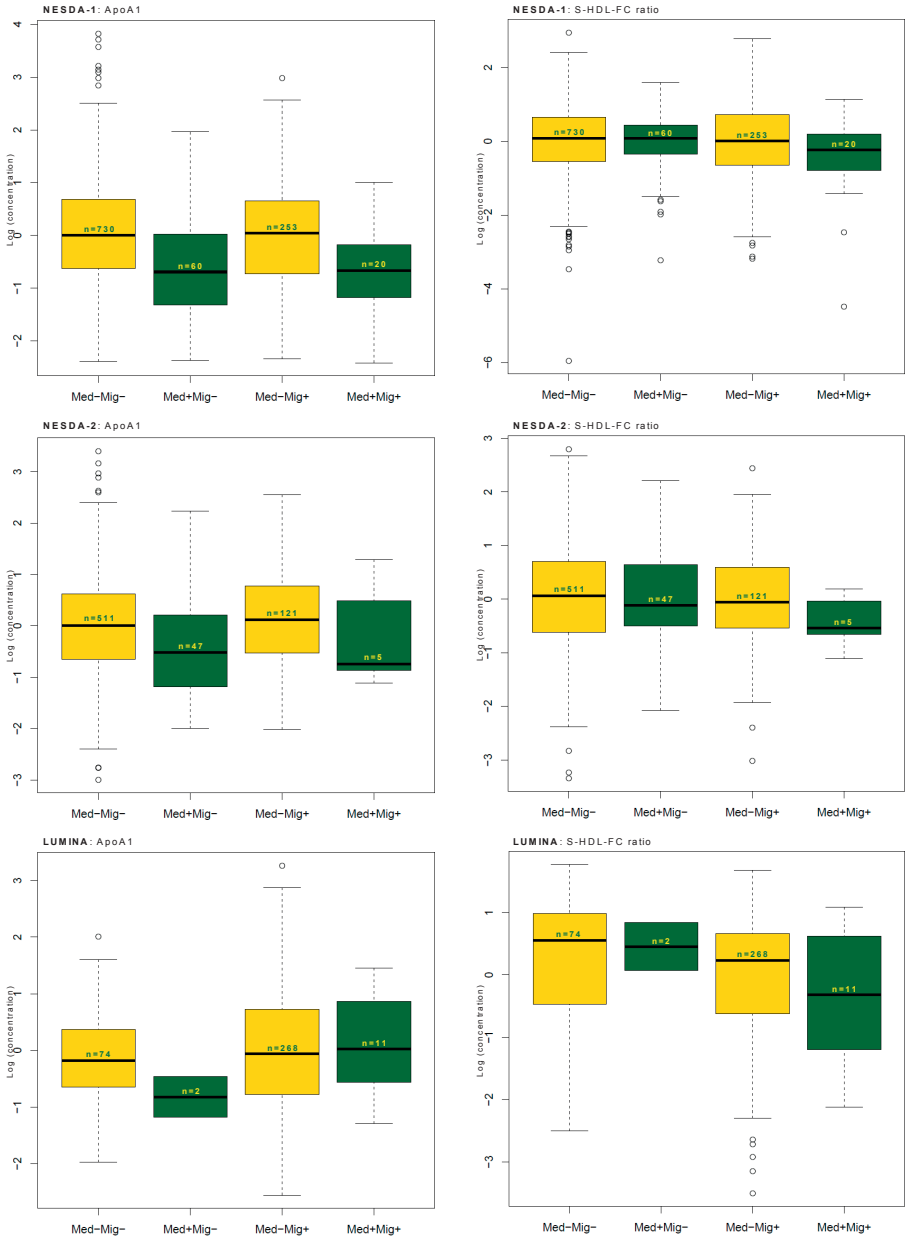


Figure S3. ApoA1 and S-HDL-FC ratio stratification plots for migraine and lipid lowering medication usage in NESDA and LUMINA. Stratification plots for lipid lowering medication usage (yes=Med+/no=Med-) and migraine (yes=Mig+/no=Mig-) in both cohorts of The Netherlands Study of Depression and Anxiety (NESDA) and Leiden University Migraine Neuro-Analysis (LUMINA). Participant numbers are provided in the boxplots. ApoA1=Apolipoprotein A1, S-HDL-FC=Free cholesterol to total lipids ratio in small high-density lipoprotein.

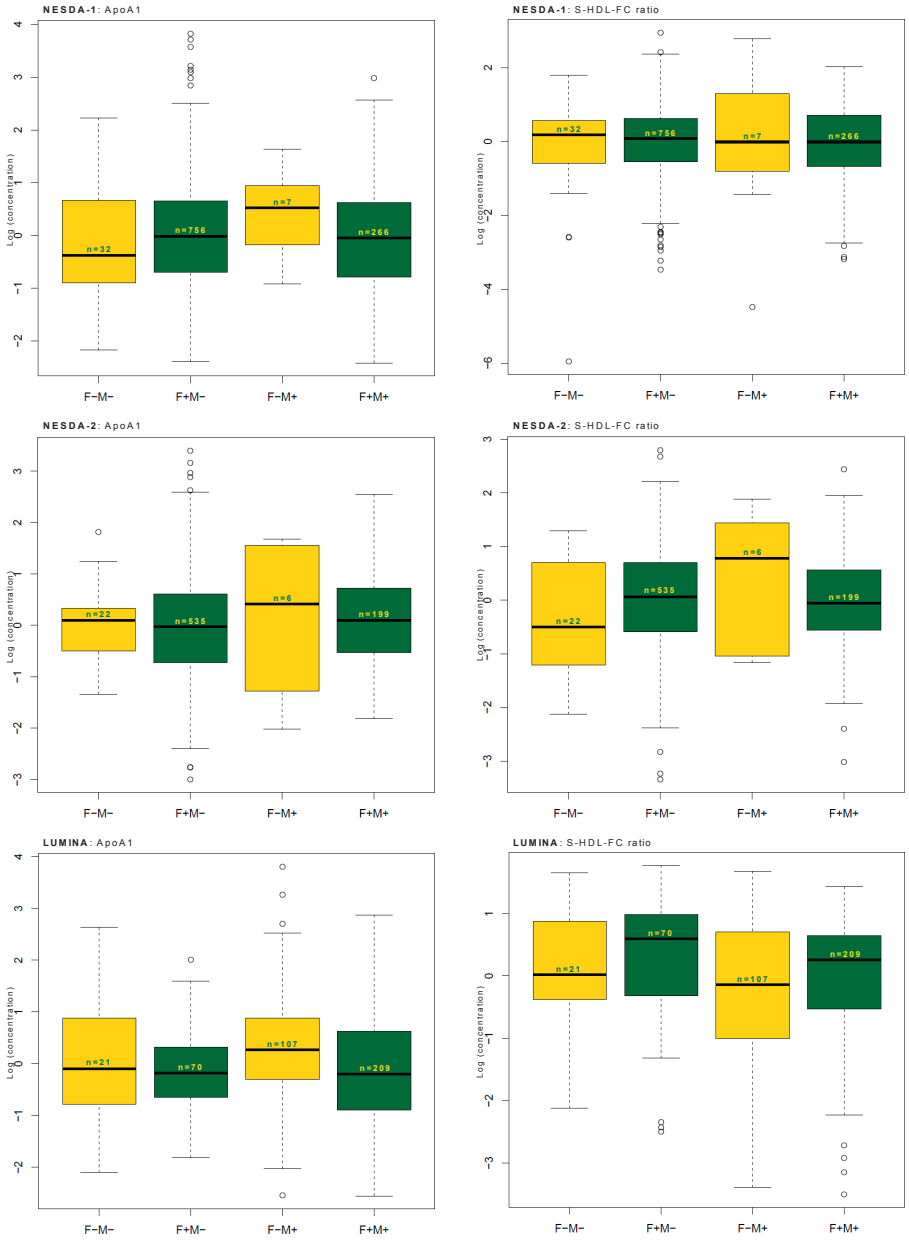


Figure S4. ApoA1 and S-HDL-FC ratio stratification plots for migraine and fasting in NESDA and LUMINA. Stratification plots for fasting (yes=F+/no=F-) and migraine (yes=M+/no=M-) in both cohorts of The Netherlands Study of Depression and Anxiety (NESDA) and Leiden University Migraine Neuro-Analysis (LUMINA). Participant numbers are provided in the boxplots. ApoA1=Apolipoprotein A1, S-HDL-FC=Free cholesterol to total lipids ratio in small high-density lipoprotein.

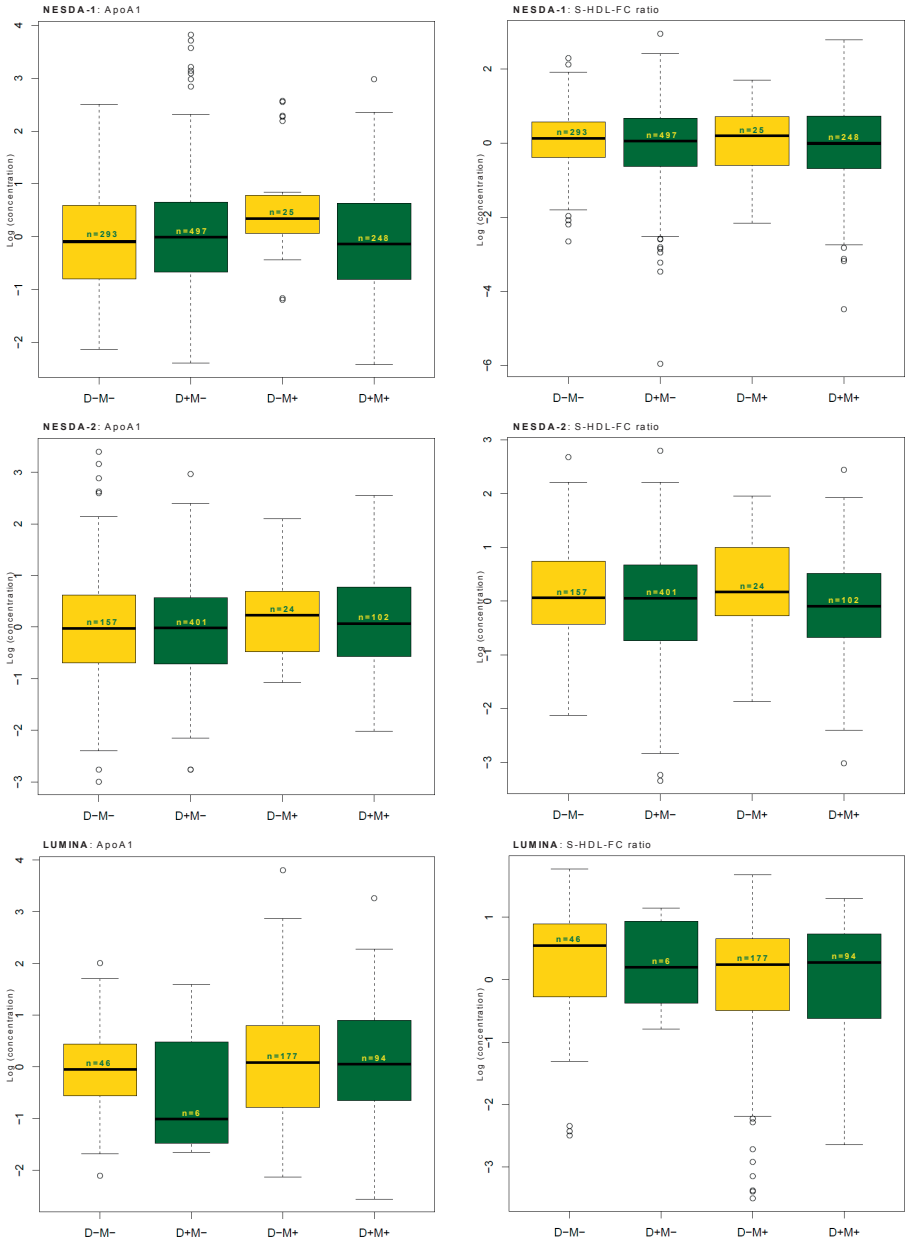


Figure S5. ApoA1 and S-HDL-FC ratio stratification plots for migraine and depression in NESDA and LUMINA. Stratification plots for depression (yes=D+/no=D-) and migraine (yes=M+/no=M-) in both cohorts of The Netherlands Study of Depression and Anxiety (NESDA) and Leiden University Migraine Neuro-Analysis (LUMINA). Participant numbers are provided in the boxplots. ApoA1=Apolipoprotein A1, S-HDL-FC=Free cholesterol to total lipids ratio in small high-density lipoprotein.

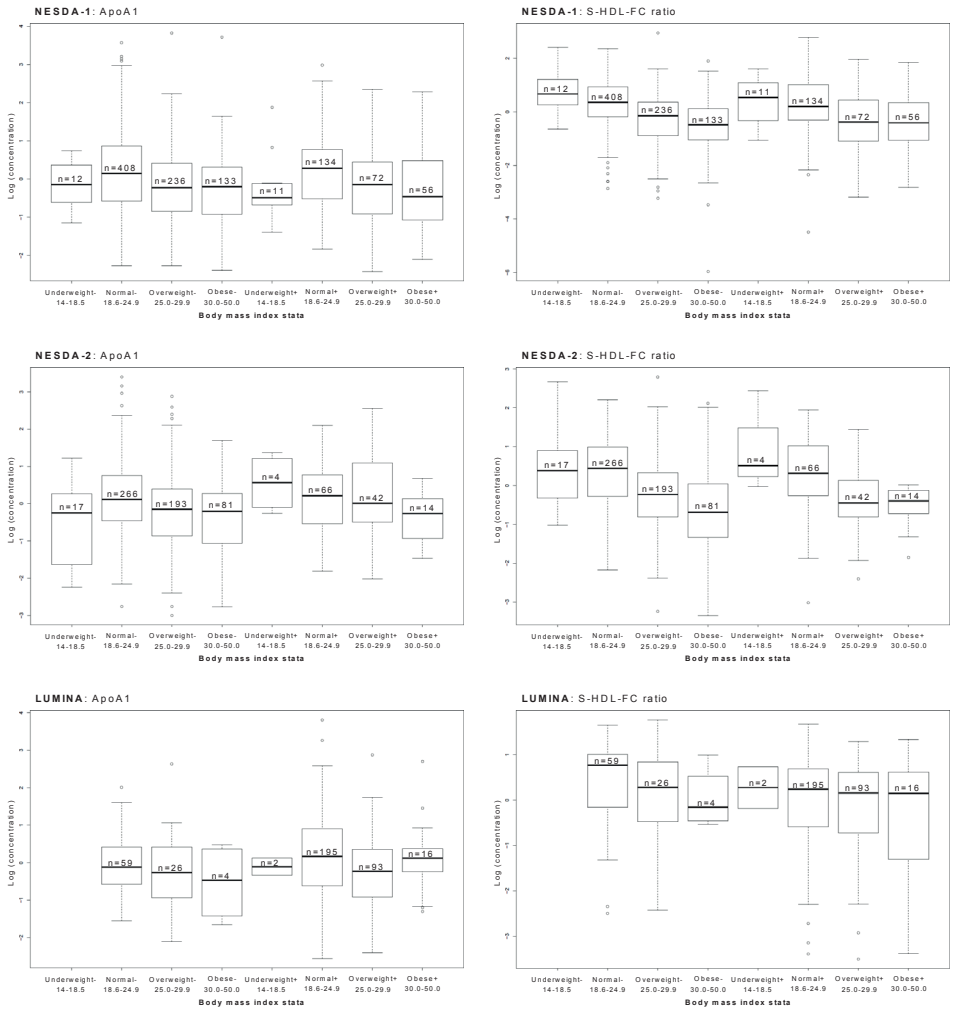


Figure S6. ApoA1 and S-HDL-FC ratio stratification plots for migraine and body mass index in NESDA and LUMINA. Stratification plots for body mass index strata (underweight, normal, overweight, and obese) and migraine (yes=+/no=-) in both cohorts of The Netherlands Study of Depression and Anxiety (NESDA) and Leiden University Migraine Neuro-Analysis (LUMINA). Participant numbers are provided in the boxplots. ApoA1=Apolipoprotein A1, S-HDL-FC=Free cholesterol to total lipids ratio in small high-density lipoprotein.

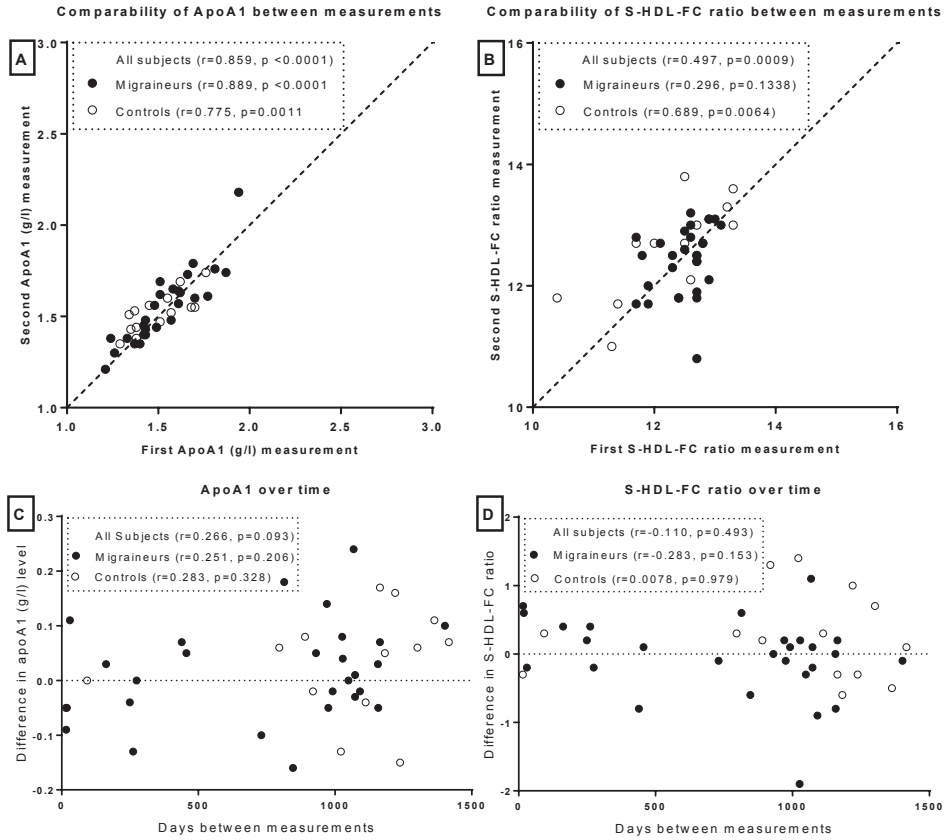
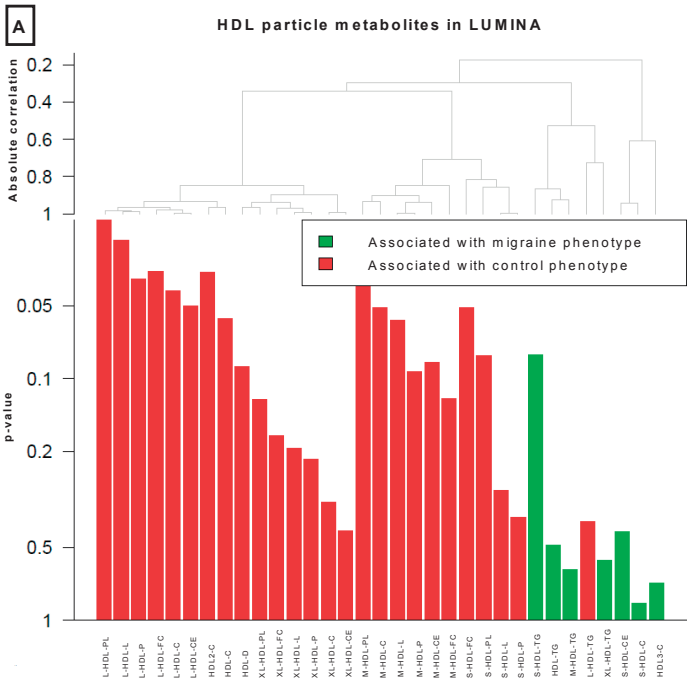
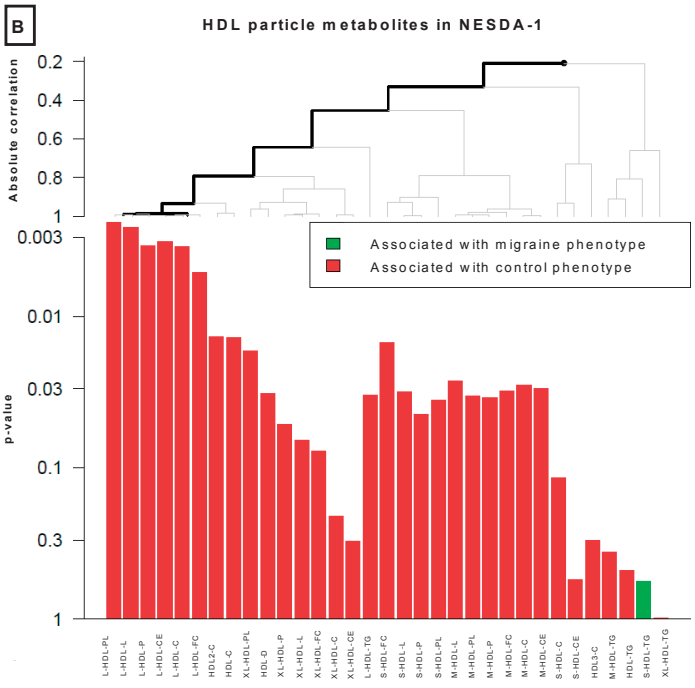


Figure S7. Metabolite correlations between measurements and over time for apoA1 and the S-HDL-FC ratio. To investigate for stability of apoA1 and S-HDL-FC ratio measurements between 82 samples temporally separate from 41 participants (27 migraine patients and 14 controls). ApoA1 (A) levels between the two temporally separate plasma samples were highly correlated in all subjects (r=0.859, p< 0.0001), the S-HDL-FC ratio (B) correlated to a lesser degree in all subjects (r=0.497, p=0.0009) and did not correlate in migraine patients (r=0.296, p=0.134). The difference of ApoA1 (C) levels and S-HDL-FC ratio (D) over time (measurement 1- measurement 2) did not reveal a strong temporal correlation for both measures. The dotted line represents r=1 in A and B, and r=0 in C and D. ApoA1=Apolipoprotein A1, S-HDL-FC=Free cholesterol to total lipids ratio in small high-density lipoprotein.


A
HDL particle metabolites in LUMINA
Absolute correlation
0.2
0.4
0.6
0.8
1
p-value
0.05
0.1
0.2
0.5
1
Associated with migraine phenotype
Associated with control phenotype
L-HDL-PL
L-HDL-L
L-HDL-P
L-HDL-FC
L-HDL-C
L-HDL-CE
HDL2-C
HDL-C
HDL-D
XL-HDL-PL
XL-HDL-FC
XL-HDL-L
XL-HDL-P
XL-HDL-C
XL-HDL-CE
M-HDL-PL
M-HDL-C
M-HDL-L
M-HDL-P
M-HDL-CE
M-HDL-FC
S-HDL-FC
S-HDL-PL
S-HDL-L
S-HDL-P
S-HDL-TG
HDL-TG
M-HDL-TG
L-HDL-TG
XL-HDL-TG
S-HDL-CE
S-HDL-C
HDL3-C


B
HDL particle metabolites in NESDA-1
Absolute correlation
0.2
0.4
0.6
0.8
1
p-value
0.003
0.01
0.03
0.1
0.3
1
Associated with migraine phenotype
Associated with control phenotype
L-HDL-PL
L-HDL-L
L-HDL-P
L-HDL-CE
L-HDL-C
L-HDL-FC
HDL2-C
HDL-C
XL-HDL-PL
HDL-D
XL-HDL-P
XL-HDL-L
XL-HDL-FC
XL-HDL-C
XL-HDL-CE
L-HDL-TG
S-HDL-FC
S-HDL-L
S-HDL-P
S-HDL-PL
M-HDL-L
M-HDL-PL
M-HDL-P
M-HDL-FC
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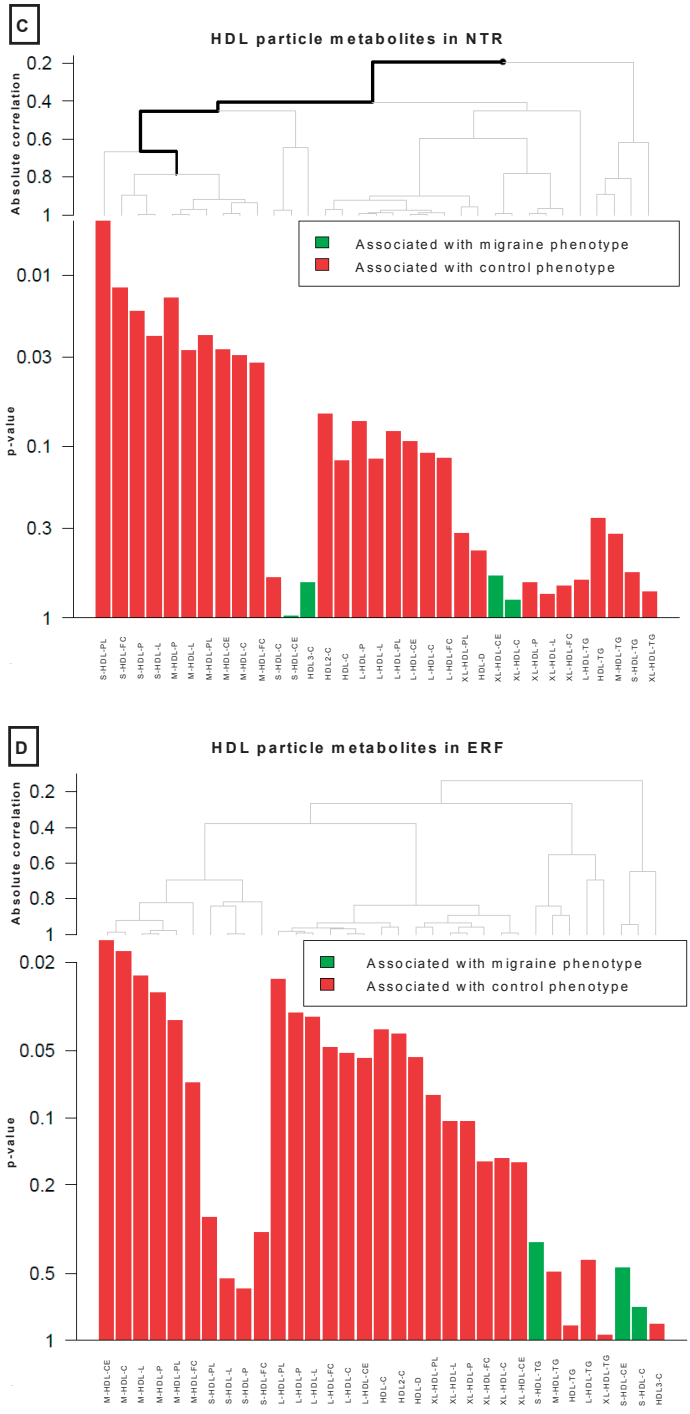
HDL-TG
S-HDL-TG
XL-HDL-TG


C
HDL particle metabolites in NTR
Absolute correlation
0.2
0.4
0.6
0.8
1
p-value
0.01
0.03
0.1
0.3
1
Associated with migraine phenotype
Associated with control phenotype
S-HDL-PL
S-HDL-FC
S-HDL-P
S-HDL-L
M-HDL-P
M-HDL-L
M-HDL-PL
M-HDL-CE
M-HDL-C
M-HDL-FC
S-HDL-C
S-HDL-CE
HDL3-C
HDL2-C
HDL-C
L-HDL-P
L-HDL-L
L-HDL-PL
L-HDL-CE
L-HDL-C
L-HDL-FC
XL-HDL-PL
HDL-D
XL-HDL-CE
XL-HDL-C
XL-HDL-P
XL-HDL-L
XL-HDL-FC
L-HDL-TG
HDL-TG
M-HDL-TG
S-HDL-TG
XL-HDL-TG
D
HDL particle metabolites in ERF
Absolute correlation
0.2
0.4
0.6
0.8
1
p-value
0.02
0.05
0.1
0.2
0.5
1
Associated with migraine phenotype
Associated with control phenotype
M-HDL-CE
M-HDL-C
M-HDL-L
M-HDL-P
M-HDL-PL
M-HDL-FC
S-HDL-PL
S-HDL-L
S-HDL-P
S-HDL-FC
L-HDL-PL
L-HDL-P
L-HDL-L
L-HDL-FG
L-HDL-C
L-HDL-CE
HDL-C
HDL2-C
HDL-D
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XL-HDL-L
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XL-HDL-FC
XL-HDL-C
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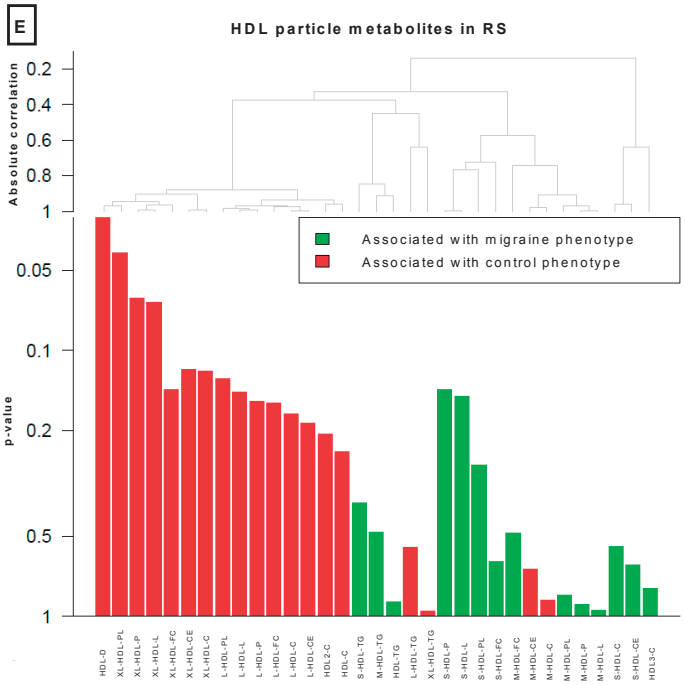
S-HDL-CE
S-HDL-C
HDL3-C


E
HDL particle metabolites in RS
Absolute correlation
0.2
0.4
0.6
0.8
1
Associated with migraine phenotype
Associated with control phenotype
p-value
0.05
0.1
0.2
0.5
1
HDL-D
XL-HDL-PL
XL-HDL-P
XL-HDL-L
XL-HDL-FC
XL-HDL-CE
XL-HDL-C
L-HDL-PL
L-HDL-L
L-HDL-P
L-HDL-FC
L-HDL-C
L-HDL-CE
HDL2-C
HDL-C
S-HDL-TG
M-HDL-TG
HDL-TG
L-HDL-TG
XL-HDL-TG
S-HDL-P
S-HDL-L
S-HDL-PL
S-HDL-FC
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M-HDL-L
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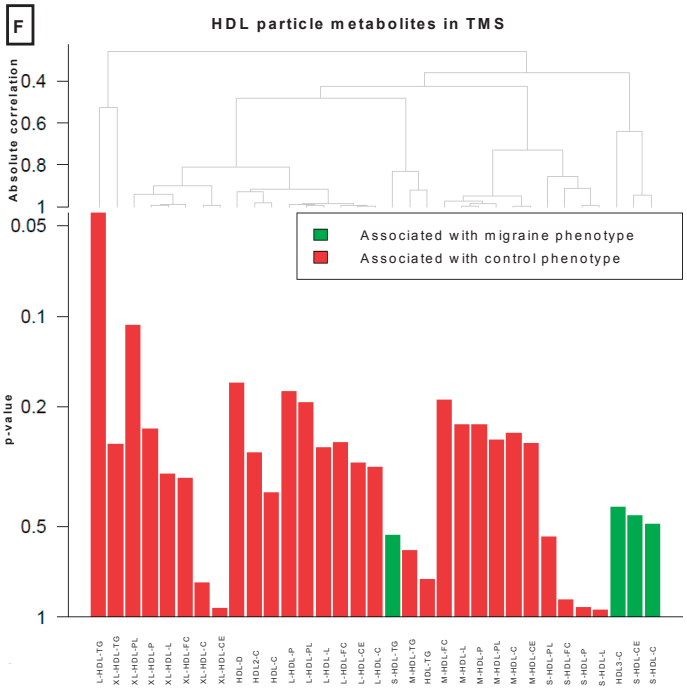
S-HDL-CE
HDL3-C


F
HDL particle metabolites in TMS
Absolute correlation
0.4
0.6
0.8
1
Associated with migraine phenotype
Associated with control phenotype
p-value
0.05
0.1
0.2
0.5
1
L-HDL-TG
XL-HDL-TG
XL-HDL-PL
XL-HDL-P
XL-HDL-L
XL-HDL-FC
XL-HDL-C
XL-HDL-CE
HDL-D
HDL2-C
HDL-C
L-HDL-P
L-HDL-PL
L-HDL-L
L-HDL-FC
L-HDL-CE
L-HDL-C
S-HDL-TG
M-HDL-TG
HDL-TG
M-HDL-FC
M-HDL-L
M-HDLP
M-HDL-PL
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S-HDL-C

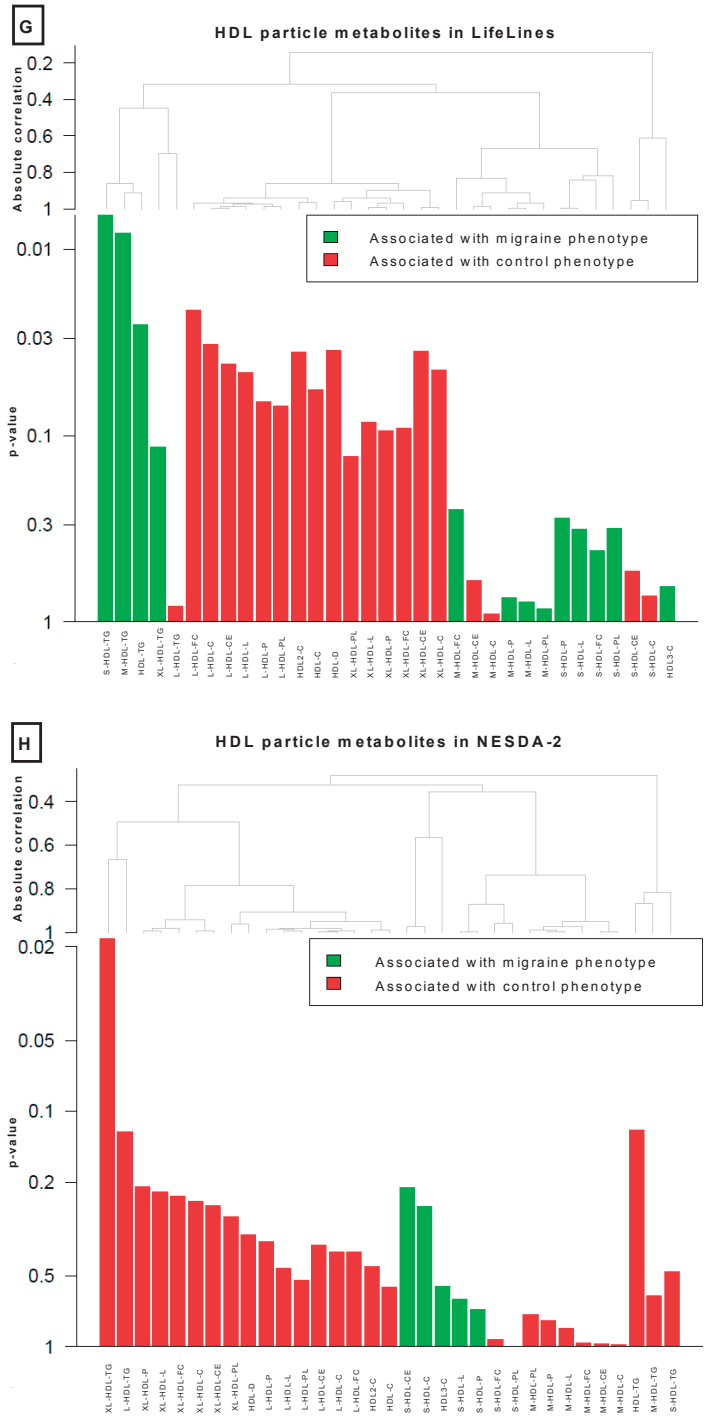

Figure S8. HDL feature plots for all individual cohorts. The global test framework in a single set of (functionally) related metabolites (HDL) tests the correlation between the various metabolites of this specific set by subsequently identifying metabolite(s) best predicting migraine status (1=yes/0=no).

Significant metabolite clusters and ultimately individual metabolites after multiplicity correction are indicated by a bold black line in de correlation dendrogram (non-significant in gray). P-values for the individual metabolites are presented in the bar plot below. Plots are presented per cohort; LUMINA (A), NESDA-1 (B), NTR (C), ERF (D), RS (E), TMS (F), LifeLines (G), and NESDA-2 (H). C=Cholesterol, CE=Cholesterol esters, TMS=The Maastricht Study, ERF=Erasmus Rucphen Family study, FC=Free cholesterol, HDL=High-density lipoprotein, L=Total lipids, L=Large, LUMINA=Leiden University Migraine Neuro-Analysis, M=Medium, NESDA=Netherlands Study of Depression and Anxiety, NTR=Netherlands Twin Registry, P=Particle concentration, PL=Phospholipids, RS=Rotterdam Study, S=Small, TG=Triglycerides, XL=Very large.

Table S1. Included metabolites in (sub-)pathways

Metabolite pathway	Metabolite subpathway	Metabolite abbreviation	Metabolite name
Lipids	VLDL	XXL-VLDL-P	Concentration of chylomicrons and extremely large VLDL particles
		XXL-VLDL-L	Total lipids in chylomicrons and extremely large VLDL
		XXL-VLDL-PL	Phospholipids in chylomicrons and extremely large VLDL
		XXL-VLDL-C	Total cholesterol in chylomicrons and extremely large VLDL
		XXL-VLDL-CE	Cholesterol esters in chylomicrons and extremely large VLDL
		XXL-VLDL-FC	Free cholesterol in chylomicrons and extremely large VLDL
		XXL-VLDL-TG	Triglycerides in chylomicrons and extremely large VLDL
		XL-VLDL-P	Concentration of very large VLDL particles
		XL-VLDL-L	Total lipids in very large VLDL
		XL-VLDL-PL	Phospholipids in very large VLDL
		XL-VLDL-C	Total cholesterol in very large VLDL
		XL-VLDL-CE	Cholesterol esters in very large VLDL
		XL-VLDL-FC	Free cholesterol in very large VLDL
		XL-VLDL-TG	Triglycerides in very large VLDL
		L-VLDL-P	Concentration of large VLDL particles
		L-VLDL-L	Total lipids in large VLDL
		L-VLDL-PL	Phospholipids in large VLDL
		L-VLDL-C	Total cholesterol in large VLDL
		L-VLDL-CE	Cholesterol esters in large VLDL
		L-VLDL-FC	Free cholesterol in large VLDL
		L-VLDL-TG	Triglycerides in large VLDL
		M-VLDL-P	Concentration of medium VLDL particles
		M-VLDL-L	Total lipids in medium VLDL
		M-VLDL-PL	Phospholipids in medium VLDL
		M-VLDL-C	Total cholesterol in medium VLDL
		M-VLDL-CE	Cholesterol esters in medium VLDL
		M-VLDL-FC	Free cholesterol in medium VLDL
		M-VLDL-TG	Triglycerides in medium VLDL
		S-VLDL-P	Concentration of small VLDL particles
		S-VLDL-L	Total lipids in small VLDL
		S-VLDL-PL	Phospholipids in small VLDL
		S-VLDL-C	Total cholesterol in small VLDL
		S-VLDL-CE	Cholesterol esters in small VLDL
		S-VLDL-FC	Free cholesterol in small VLDL
		S-VLDL-TG	Triglycerides in small VLDL
		XS-VLDL-P	Concentration of very small VLDL particles
		XS-VLDL-L	Total lipids in very small VLDL
		XS-VLDL-PL	Phospholipids in very small VLDL
		XS-VLDL-C	Total cholesterol in very small VLDL
		XS-VLDL-CE	Cholesterol esters in very small VLDL
		XS-VLDL-FC	Free cholesterol in very small VLDL
		XS-VLDL-TG	Triglycerides in very small VLDL
		VLDL-D	Mean diameter for VLDL particles
		VLDL-C	Total cholesterol in VLDL
		VLDL-TG	Triglycerides in VLDL

Table S1. Continued

Metabolite pathway	Metabolite subpathway	Metabolite abbreviation	Metabolite name
	IDL	IDL-P	Concentration of IDL particles
		IDL-L	Total lipids in IDL
		IDL-PL	Phospholipids in IDL
		IDL-C	Total cholesterol in IDL
		IDL-CE	Cholesterol esters in IDL
		IDL-FC	Free cholesterol in IDL
		IDL-TG	Triglycerides in IDL
	LDL	L-LDL-P	Concentration of large LDL particles
		L-LDL-L	Total lipids in large LDL
		L-LDL-PL	Phospholipids in large LDL
		L-LDL-C	Total cholesterol in large LDL
		L-LDL-CE	Cholesterol esters in large LDL
		L-LDL-FC	Free cholesterol in large LDL
		L-LDL-TG	Triglycerides in large LDL
		M-LDL-P	Concentration of medium LDL particles
		M-LDL-L	Total lipids in medium LDL
		M-LDL-PL	Phospholipids in medium LDL
		M-LDL-C	Total cholesterol in medium LDL
		M-LDL-CE	Cholesterol esters in medium LDL
		M-LDL-FC	Free cholesterol in medium LDL
		M-LDL-TG	Triglycerides in medium LDL
		S-LDL-P	Concentration of small LDL particles
		S-LDL-L	Total lipids in small LDL
		S-LDL-PL	Phospholipids in small LDL
		S-LDL-C	Total cholesterol in small LDL
		S-LDL-CE	Cholesterol esters in small LDL
		S-LDL-FC	Free cholesterol in small LDL
		S-LDL-TG	Triglycerides in small LDL
		LDL-D	Mean diameter for LDL particles
		LDL-C	Total cholesterol in LDL
		LDL-TG	Triglycerides in LDL
	HDL	XL-HDL-P	Concentration of very large HDL particles
		XL-HDL-L	Total lipids in very large HDL
		XL-HDL-PL	Phospholipids in very large HDL
		XL-HDL-C	Total cholesterol in very large HDL
		XL-HDL-CE	Cholesterol esters in very large HDL
		XL-HDL-FC	Free cholesterol in very large HDL
		XL-HDL-TG	Triglycerides in very large HDL
		L-HDL-P	Concentration of large HDL particles
		L-HDL-L	Total lipids in large HDL
		L-HDL-PL	Phospholipids in large HDL
		L-HDL-C	Total cholesterol in large HDL
		L-HDL-CE	Cholesterol esters in large HDL
		L-HDL-FC	Free cholesterol in large HDL
		L-HDL-TG	Triglycerides in large HDL
		M-HDL-P	Concentration of medium HDL particles

Table S1. Continued

Metabolite pathway	Metabolite subpathway	Metabolite abbreviation	Metabolite name
		M-HDL-L	Total lipids in medium HDL
		M-HDL-PL	Phospholipids in medium HDL
		M-HDL-C	Total cholesterol in medium HDL
		M-HDL-CE	Cholesterol esters in medium HDL
		M-HDL-FC	Free cholesterol in medium HDL
		M-HDL-TG	Triglycerides in medium HDL
		S-HDL-P	Concentration of small HDL particles
		S-HDL-L	Total lipids in small HDL
		S-HDL-PL	Phospholipids in small HDL
		S-HDL-C	Total cholesterol in small HDL
		S-HDL-CE	Cholesterol esters in small HDL
		S-HDL-FC	Free cholesterol in small HDL
		S-HDL-TG	Triglycerides in small HDL
		HDL-D	Mean diameter for HDL particles
		HDL-C	Total cholesterol in HDL
		HDL2-C	Total cholesterol in HDL2
		HDL3-C	Total cholesterol in HDL3
		HDL-TG	Triglycerides in HDL
	Sterol/Steroid	Serum-C	Serum total cholesterol
		Remnant-C	Remnant cholesterol (non-HDL, non-LDL-cholesterol)
		EstC	Esterified cholesterol
		FreeC	Free cholesterol
	Triacylglycerol	Serum-TG	Serum total triglycerides
	Glycerophospholipids	TotPG	Total phosphoglycerides
		PC	Phosphatidylcholine and other cholines
	Sphingolipid	SM	Sphingomyelins
	Glycerolipid metabolism	TotCho	Total cholines
	Fatty acid, summary measure	TotFA	Total fatty acids
		UnsatDeg	Estimated degree of unsaturation
		FAw3	Omega-3 fatty acids
		FAw6	Omega-6 fatty acids
		PUFA	Polyunsaturated fatty acids
		MUFA	Monounsaturated fatty acids; 16:1, 18:1
		SFA	Saturated fatty acids
	Essential fatty acid	DHA	22:6, docosahexaenoic acid
		LA	18:2, linoleic acid
	Ketone bodies	AcAce	Acetoacetate
		bOHBut	3-hydroxybutyrate
Carbohydrates	Glycolysis, gluconeogenesis, pyruvate metabolism	Glc	Glucose
		Lac	Lactate
		Pyr	Pyruvate
Energy	Krebs cycle	Cit	Citrate

Table S1. Continued

Metabolite pathway	Metabolite subpathway	Metabolite abbreviation	Metabolite name
Amino acids	Alanine and aspartate metabolism	Ala	Alanine
	Glutamate metabolism	Gln	Glutamine
	Histidine metabolism	His	Histidine
	Valine, leucine and isoleucine metabolism	Ile	Isoleucine
		Leu	Leucine
		Val	Valine
	Phenylalanine & tyrosine metabolism	Phe	Phenylalanine
		Tyr	Tyrosine
	Creatine metabolism	Crea	Creatinine
Peptides	Apolipoprotein	ApoA1	Apolipoprotein A-I
		ApoB	Apolipoprotein B
	Protein	Alb	Albumin
	Glycoprotein	Gp	Glycoprotein acetyls, mainly a1-acid glycoprotein

HDL=High-density lipoprotein, IDL=Intermediate-density lipoprotein, LDL=Low-density lipoprotein, VLDL=Very-low-density lipoprotein.

Table S2. Included metabolite ratio's

Metabolite group	Metabolite abbreviation	Ratio description
Ratio	XXL-VLDL-PL_%	Phospholipids to total lipids ratio in chylomicrons and extremely large VLDL
	XXL-VLDL-C_%	Total cholesterol to total lipids ratio in chylomicrons and extremely large VLDL
	XXL-VLDL-CE_%	Cholesterol esters to total lipids ratio in chylomicrons and extremely large VLDL
	XXL-VLDL-FC_%	Free cholesterol to total lipids ratio in chylomicrons and extremely large VLDL
	XXL-VLDL-TG_%	Triglycerides to total lipids ratio in chylomicrons and extremely large VLDL
	XL-VLDL-PL_%	Phospholipids to total lipids ratio in very large VLDL
	XL-VLDL-C_%	Total cholesterol to total lipids ratio in very large VLDL
	XL-VLDL-CE_%	Cholesterol esters to total lipids ratio in very large VLDL
	XL-VLDL-FC_%	Free cholesterol to total lipids ratio in very large VLDL
	XL-VLDL-TG_%	Triglycerides to total lipids ratio in very large VLDL
	L-VLDL-PL_%	Phospholipids to total lipids ratio in large VLDL
	L-VLDL-C_%	Total cholesterol to total lipids ratio in large VLDL
	L-VLDL-CE_%	Cholesterol esters to total lipids ratio in large VLDL
	L-VLDL-FC_%	Free cholesterol to total lipids ratio in large VLDL
	L-VLDL-TG_%	Triglycerides to total lipids ratio in large VLDL
	M-VLDL-PL_%	Phospholipids to total lipids ratio in medium VLDL
	M-VLDL-C_%	Total cholesterol to total lipids ratio in medium VLDL
	M-VLDL-CE_%	Cholesterol esters to total lipids ratio in medium VLDL
	M-VLDL-FC_%	Free cholesterol to total lipids ratio in medium VLDL
	M-VLDL-TG_%	Triglycerides to total lipids ratio in medium VLDL
	S-VLDL-PL_%	Phospholipids to total lipids ratio in small VLDL
	S-VLDL-C_%	Total cholesterol to total lipids ratio in small VLDL
	S-VLDL-CE_%	Cholesterol esters to total lipids ratio in small VLDL
	S-VLDL-FC_%	Free cholesterol to total lipids ratio in small VLDL
	S-VLDL-TG_%	Triglycerides to total lipids ratio in small VLDL
	XS-VLDL-PL_%	Phospholipids to total lipids ratio in very small VLDL
	XS-VLDL-C_%	Total cholesterol to total lipids ratio in very small VLDL
	XS-VLDL-CE_%	Cholesterol esters to total lipids ratio in very small VLDL
	XS-VLDL-FC_%	Free cholesterol to total lipids ratio in very small VLDL
	XS-VLDL-TG_%	Triglycerides to total lipids ratio in very small VLDL
	IDL-PL_%	Phospholipids to total lipids ratio in IDL
	IDL-C_%	Total cholesterol to total lipids ratio in IDL
	IDL-CE_%	Cholesterol esters to total lipids ratio in IDL
	IDL-FC_%	Free cholesterol to total lipids ratio in IDL
	IDL-TG_%	Triglycerides to total lipids ratio in IDL
	L-LDL-PL_%	Phospholipids to total lipids ratio in large LDL
	L-LDL-C_%	Total cholesterol to total lipids ratio in large LDL
	L-LDL-CE_%	Cholesterol esters to total lipids ratio in large LDL
	L-LDL-FC_%	Free cholesterol to total lipids ratio in large LDL
	L-LDL-TG_%	Triglycerides to total lipids ratio in large LDL
	M-LDL-PL_%	Phospholipids to total lipids ratio in medium LDL
	M-LDL-C_%	Total cholesterol to total lipids ratio in medium LDL
	M-LDL-CE_%	Cholesterol esters to total lipids ratio in medium LDL
	M-LDL-FC_%	Free cholesterol to total lipids ratio in medium LDL
	M-LDL-TG_%	Triglycerides to total lipids ratio in medium LDL
	S-LDL-PL_%	Phospholipids to total lipids ratio in small LDL

Table S2. Continued

Metabolite group	Metabolite abbreviation	Ratio description
	S-LDL-C_%	Total cholesterol to total lipids ratio in small LDL
	S-LDL-CE_%	Cholesterol esters to total lipids ratio in small LDL
	S-LDL-FC_%	Free cholesterol to total lipids ratio in small LDL
	S-LDL-TG_%	Triglycerides to total lipids ratio in small LDL
	XL-HDL-PL_%	Phospholipids to total lipids ratio in very large HDL
	XL-HDL-C_%	Total cholesterol to total lipids ratio in very large HDL
	XL-HDL-CE_%	Cholesterol esters to total lipids ratio in very large HDL
	XL-HDL-FC_%	Free cholesterol to total lipids ratio in very large HDL
	XL-HDL-TG_%	Triglycerides to total lipids ratio in very large HDL
	L-HDL-PL_%	Phospholipids to total lipids ratio in large HDL
	L-HDL-C_%	Total cholesterol to total lipids ratio in large HDL
	L-HDL-CE_%	Cholesterol esters to total lipids ratio in large HDL
	L-HDL-FC_%	Free cholesterol to total lipids ratio in large HDL
	L-HDL-TG_%	Triglycerides to total lipids ratio in large HDL
	M-HDL-PL_%	Phospholipids to total lipids ratio in medium HDL
	M-HDL-C_%	Total cholesterol to total lipids ratio in medium HDL
	M-HDL-CE_%	Cholesterol esters to total lipids ratio in medium HDL
	M-HDL-FC_%	Free cholesterol to total lipids ratio in medium HDL
	M-HDL-TG_%	Triglycerides to total lipids ratio in medium HDL
	S-HDL-PL_%	Phospholipids to total lipids ratio in small HDL
	S-HDL-C_%	Total cholesterol to total lipids ratio in small HDL
	S-HDL-CE_%	Cholesterol esters to total lipids ratio in small HDL
	S-HDL-FC_%	Free cholesterol to total lipids ratio in small HDL
	S-HDL-TG_%	Triglycerides to total lipids ratio in small HDL
	TG/PG	Ratio of triglycerides to phosphoglycerides
	DHA/FA	Ratio of 22:6 docosahexaenoic acid to total fatty acids
	LA/FA	Ratio of 18:2 linoleic acid to total fatty acids
	FAw3/FA	Ratio of omega-3 fatty acids to total fatty acids
	FAw6/FA	Ratio of omega-6 fatty acids to total fatty acids
	PUFA/FA	Ratio of polyunsaturated fatty acids to total fatty acids
	MUFA/FA	Ratio of monounsaturated fatty acids to total fatty acids
	SFA/FA	Ratio of saturated fatty acids to total fatty acids
	ApoB/ApoA1	Ratio of apolipoprotein B to apolipoprotein A-I

HDL=High-density lipoprotein, IDL=Intermediate-density lipoprotein, LDL=Low-density lipoprotein, VLDL=Very-low-density lipoprotein.

Table S3. Results from logistic regressions with metabolite concentrations, sex, and age as independent variables and migraine status as dependent variable.

	LUMINA		NESDA-1		NTR		ERF		RS		TMS		LifeLines		NESDA-2	
	B	CI	B	CI	B	CI	B	CI	B	CI	B	CI	B	CI	B	CI
XXL-VLDL-P	0.18	-0.10:0.46	0.11	-0.05:0.26	0.00	-0.08:0.08	-0,14	-0,31:0,04	0.07	-0.08:0.23	0.11	-0.13:0.36	0.24	0.09:0.39	-0.09	-0.30:0.11
XXL-VLDL-L	0.19	-0.09:0.47	0.11	-0.05:0.26	0.00	-0.08:0.09	-0,14	-0,31:0,03	0.07	-0.08:0.23	0.11	-0.13:0.36	0.24	0.09:0.39	-0.09	-0.29:0.11
XXL-VLDL-PL	0.18	-0.10:0.46	0.06	-0.09:0.22	-0.01	-0.09:0.07	-0,16	-0,33:0,02	0.07	-0.09:0.23	0.10	-0.14:0.35	0.23	0.08:0.38	-0.10	-0.31:0.11
XXL-VLDL-C	0.20	-0.09:0.48	0.11	-0.05:0.26	0.00	-0.08:0.08	-0,11	-0,28:0,06	0.07	-0.08:0.23	0.11	-0.13:0.36	0.25	0.10:0.40	-0.09	-0.29:0.12
XXL-VLDL-CE	0.22	-0.07:0.50	0.12	-0.03:0.27	0.00	-0.08:0.09	-0,1	-0,26:0,07	0.09	-0.07:0.24	0.13	-0.11:0.37	0.25	0.10:0.40	-0.06	-0.26:0.13
XXL-VLDL-FC	0.16	-0.11:0.44	0.09	-0.07:0.24	0.00	-0.08:0.09	-0,17	-0,34:0,01	0.06	-0.10:0.21	0.10	-0.14:0.35	0.26	0.11:0.41	-0.11	-0.32:0.09
XXL-VLDL-TG	0.18	-0.09:0.46	0.11	-0.05:0.27	0.00	-0.09:0.08	-0,14	-0,31:0,04	0.07	-0.08:0.23	0.11	-0.13:0.36	0.24	0.09:0.39	-0.10	-0.31:0.11
XL-VLDL-P	0.19	-0.09:0.48	0.06	-0.09:0.22	-0.01	-0.09:0.07	-0,15	-0,32:0,03	0.08	-0.08:0.23	0.08	-0.17:0.33	0.24	0.09:0.39	-0.11	-0.32:0.10
XL-VLDL-L	0.21	-0.07:0.49	0.07	-0.09:0.23	0.00	-0.09:0.08	-0,15	-0,32:0,03	0.08	-0.07:0.24	0.07	-0.18:0.32	0.25	0.10:0.40	-0.11	-0.31:0.10
XL-VLDL-PL	0.21	-0.08:0.49	0.05	-0.10:0.21	0.00	-0.08:0.08	-0,16	-0,34:0,01	0.08	-0.08:0.23	0.08	-0.16:0.33	0.23	0.08:0.38	-0.11	-0.31:0.10
XL-VLDL-C	0.22	-0.07:0.50	0.11	-0.04:0.27	0.00	-0.08:0.09	-0,15	-0,32:0,03	0.07	-0.08:0.23	0.09	-0.15:0.33	0.24	0.09:0.39	-0.10	-0.30:0.10
XL-VLDL-CE	0.20	-0.08:0.48	0.13	-0.03:0.28	0.01	-0.07:0.10	-0,11	-0,28:0,06	0.06	-0.09:0.22	0.09	-0.15:0.33	0.24	0.09:0.40	-0.10	-0.30:0.10
XL-VLDL-FC	0.23	-0.06:0.52	0.10	-0.06:0.25	0.00	-0.08:0.09	-0,14	-0,32:0,03	0.09	-0.07:0.24	0.09	-0.15:0.34	0.23	0.08:0.38	-0.10	-0.31:0.10
XL-VLDL-TG	0.20	-0.08:0.47	0.07	-0.09:0.22	-0.01	-0.09:0.07	-0,14	-0,32:0,03	0.08	-0.07:0.23	0.07	-0.18:0.32	0.25	0.10:0.40	-0.11	-0.32:0.10
L-VLDL-P	0.23	-0.06:0.51	0.06	-0.10:0.22	-0.01	-0.09:0.07	-0,17	-0,34:0,01	0.08	-0.07:0.24	0.08	-0.17:0.33	0.25	0.10:0.40	-0.09	-0.29:0.12
L-VLDL-L	0.25	-0.03:0.53	0.09	-0.06:0.25	-0.01	-0.09:0.08	-0,17	-0,34:0,00	0.09	-0.06:0.25	0.07	-0.18:0.32	0.27	0.12:0.42	-0.07	-0.27:0.12
L-VLDL-PL	0.24	-0.05:0.53	0.06	-0.10:0.22	-0.01	-0.09:0.07	-0,16	-0,33:0,01	0.06	-0.10:0.21	0.08	-0.17:0.32	0.25	0.10:0.40	-0.08	-0.28:0.12
L-VLDL-C	0.27	-0.02:0.56	0.10	-0.06:0.25	-0.01	-0.09:0.07	-0,17	-0,34:0,00	0.08	-0.07:0.24	0.08	-0.16:0.33	0.26	0.11:0.41	-0.08	-0.28:0.12
L-VLDL-CE	0.30	0.00:0.59	0.13	-0.02:0.28	0.00	-0.08:0.08	-0,14	-0,31:0,03	0.08	-0.07:0.24	0.09	-0.16:0.33	0.29	0.14:0.44	-0.08	-0.27:0.12
L-VLDL-FC	0.24	-0.05:0.53	0.06	-0.10:0.21	-0.01	-0.10:0.07	-0,17	-0,34:0,01	0.08	-0.08:0.23	0.08	-0.17:0.33	0.25	0.10:0.40	-0.09	-0.29:0.11
L-VLDL-TG	0.22	-0.06:0.51	0.06	-0.09:0.22	-0.01	-0.09:0.08	-0,17	-0,34:0,01	0.10	-0.06:0.26	0.07	-0.18:0.32	0.26	0.11:0.41	-0.08	-0.28:0.12
M-VLDL-P	0.31	0.01:0.61	0.13	-0.03:0.28	0.01	-0.08:0.09	-0,16	-0,33:0,01	0.08	-0.07:0.24	0.08	-0.17:0.33	0.29	0.14:0.43	-0.08	-0.28:0.12
M-VLDL-L	0.32	0.03:0.61	0.13	-0.03:0.29	0.01	-0.07:0.09	-0,16	-0,33:0,00	0.10	-0.06:0.26	0.07	-0.17:0.32	0.30	0.15:0.45	-0.06	-0.25:0.13
M-VLDL-PL	0.33	0.03:0.63	0.13	-0.03:0.28	0.01	-0.08:0.09	-0,17	-0,34:0,00	0.09	-0.06:0.25	0.08	-0.17:0.33	0.28	0.14:0.43	-0.07	-0.26:0.13
M-VLDL-C	0.34	0.04:0.64	0.11	-0.04:0.27	0.01	-0.07:0.09	-0,15	-0,32:0,01	0.08	-0.07:0.24	0.09	-0.16:0.33	0.29	0.14:0.44	-0.04	-0.24:0.15
M-VLDL-CE	0.35	0.05:0.65	0.12	-0.04:0.27	0.02	-0.06:0.10	-0,15	-0,31:0,01	0.06	-0.10:0.22	0.09	-0.15:0.34	0.28	0.13:0.43	-0.03	-0.22:0.16
M-VLDL-FC	0.29	0.00:0.59	0.12	-0.04:0.27	0.00	-0.08:0.08	-0,18	-0,35:-0,01	0.09	-0.07:0.25	0.08	-0.17:0.32	0.28	0.13:0.43	-0.08	-0.27:0.12
M-VLDL-TG	0.30	0.01:0.60	0.11	-0.05:0.26	0.00	-0.08:0.08	-0,15	-0,32:0,02	0.09	-0.06:0.25	0.07	-0.18:0.32	0.30	0.15:0.45	-0.08	-0.27:0.12
S-VLDL-P	0.41	0.09:0.72	0.12	-0.04:0.27	0.03	-0.06:0.11	-0,16	-0,32:0,01	0.09	-0.07:0.24	0.10	-0.15:0.34	0.27	0.13:0.42	-0.01	-0.21:0.18

Table S3. Continued.

	LUMINA		NESDA-1		NTR		ERF		RS		TMS		LifeLines		NESDA-2	
	B	CI	B	CI	B	CI	B	CI	B	CI	B	CI	B	CI	B	CI
S-VLDL-L	0.41	0.11:0.72	0.13	-0.02:0.29	0.03	-0.05:0.11	-0,17	-0,34:-0,01	0.10	-0.06:0.25	0.10	-0.15:0.34	0.28	0.13:0.43	0.00	-0.19:0.19
S-VLDL-PL	0.39	0.08:0.69	0.11	-0.04:0.27	0.02	-0.06:0.10	-0,14	-0,31:0,02	0.10	-0.06:0.25	0.10	-0.14:0.34	0.26	0.11:0.40	0.01	-0.18:0.20
S-VLDL-C	0.40	0.09:0.70	0.15	-0.01:0.31	0.05	-0.03:0.14	-0,19	-0,35:-0,03	0.07	-0.09:0.22	0.13	-0.11:0.37	0.20	0.05:0.36	0.04	-0.15:0.23
S-VLDL-CE	0.38	0.08:0.67	0.16	0.00:0.32	0.06	-0.02:0.15	-0,18	-0,34:-0,01	0.05	-0.11:0.21	0.15	-0.09:0.38	0.15	0.00:0.31	0.05	-0.14:0.24
S-VLDL-FC	0.37	0.07:0.68	0.12	-0.04:0.27	0.01	-0.07:0.10	-0,2	-0,37:-0,04	0.08	-0.07:0.24	0.11	-0.13:0.35	0.26	0.11:0.41	0.01	-0.18:0.19
S-VLDL-TG	0.36	0.06:0.66	0.11	-0.05:0.26	0.01	-0.07:0.09	-0,17	-0,34:0,00	0.10	-0.06:0.25	0.07	-0.18:0.32	0.30	0.15:0.45	-0.04	-0.23:0.15
XS-VLDL-P	0.40	0.09:0.70	0.10	-0.06:0.25	0.06	-0.02:0.14	-0,19	-0,36:-0,03	0.05	-0.10:0.21	0.10	-0.14:0.34	0.17	0.02:0.32	0.08	-0.11:0.27
XS-VLDL-L	0.37	0.08:0.66	0.11	-0.05:0.27	0.06	-0.02:0.14	-0,19	-0,35:-0,03	0.04	-0.12:0.20	0.11	-0.14:0.35	0.16	0.01:0.31	0.09	-0.10:0.28
XS-VLDL-PL	0.34	0.05:0.63	0.07	-0.09:0.22	0.03	-0.05:0.12	-0,19	-0,35:-0,02	0.02	-0.14:0.18	0.09	-0.15:0.34	0.12	-0.03:0.27	0.11	-0.07:0.30
XS-VLDL-C	0.25	-0.02:0.53	0.12	-0.04:0.28	0.09	0.00:0.17	-0,14	-0,30:0,02	0.02	-0.14:0.18	0.11	-0.13:0.36	0.09	-0.06:0.25	0.11	-0.08:0.29
XS-VLDL-CE	0.26	-0.02:0.53	0.11	-0.04:0.27	0.09	0.01:0.18	-0,13	-0,28:0,03	0.02	-0.14:0.18	0.10	-0.14:0.34	0.08	-0.07:0.23	0.11	-0.07:0.29
XS-VLDL-FC	0.23	-0.05:0.51	0.13	-0.03:0.28	0.07	-0.02:0.15	-0,16	-0,32:0,00	0.02	-0.13:0.18	0.13	-0.12:0.38	0.11	-0.04:0.26	0.10	-0.09:0.28
XS-VLDL-TG	0.35	0.05:0.64	0.08	-0.07:0.23	0.01	-0.07:0.09	-0,18	-0,35:-0,01	0.08	-0.07:0.24	0.07	-0.17:0.32	0.26	0.12:0.40	-0.01	-0.20:0.18
VLDL-D	0.22	-0.05:0.48	0.09	-0.06:0.24	-0.01	-0.09:0.07	-0.09	-0.25:0.08	0.12	-0.04:0.28	0.02	-0.23:0.27	0.28	0.13:0.44	-0.11	-0.30:0.07
VLDL-C	0.38	0.08:0.68	0.15	-0.01:0.31	0.03	-0.05:0.12	-0.18	-0.34:-0.02	0.07	-0.09:0.23	0.12	-0.12:0.36	0.25	0.09:0.40	0.01	-0.19:0.20
VLDL-TG	0.29	0.01:0.57	0.11	-0.05:0.26	0.00	-0.08:0.09	-0.16	-0.33:0.00	0.11	-0.05:0.27	0.07	-0.18:0.32	0.31	0.16:0.46	-0.07	-0.26:0.13
IDL-P	0.31	0.02:0.60	0.07	-0.09:0.22	0.03	-0.06:0.11	-0.18	-0.34:-0.01	0.00	-0.16:0.16	0.08	-0.17:0.32	0.08	-0.07:0.24	0.10	-0.09:0.28
IDL-L	0.29	0.01:0.57	0.07	-0.08:0.23	0.03	-0.05:0.12	-0.17	-0.33:-0.01	-0.01	-0.18:0.15	0.08	-0.17:0.32	0.08	-0.08:0.24	0.10	-0.09:0.29
IDL-PL	0.25	-0.02:0.53	0.03	-0.13:0.18	0.02	-0.06:0.11	-0.16	-0.32:0.00	-0.01	-0.17:0.15	0.06	-0.19:0.31	0.05	-0.10:0.21	0.12	-0.07:0.31
IDL-C	0.27	-0.01:0.54	0.06	-0.09:0.22	0.03	-0.06:0.11	-0.15	-0.31:0.01	-0.01	-0.17:0.15	0.09	-0.16:0.34	0.05	-0.11:0.20	0.10	-0.09:0.29
IDL-CE	0.29	0.01:0.57	0.07	-0.08:0.23	0.03	-0.06:0.11	-0.16	-0.32:0.00	-0.01	-0.17:0.15	0.10	-0.15:0.34	0.06	-0.09:0.22	0.09	-0.10:0.28
IDL-FC	0.21	-0.06:0.48	0.04	-0.11:0.20	0.03	-0.06:0.11	-0.14	-0.30:0.02	-0.02	-0.18:0.14	0.07	-0.18:0.32	0.01	-0.15:0.16	0.12	-0.07:0.31
IDL-TG	0.30	0.01:0.59	-0.02	-0.17:0.14	0.01	-0.07:0.10	-0.25	-0.42:-0.08	0.05	-0.11:0.21	0.07	-0.17:0.31	0.20	0.06:0.34	0.02	-0.16:0.21
L-LDL-P	0.30	0.01:0.59	0.05	-0.11:0.20	0.02	-0.06:0.11	-0.19	-0.35:-0.03	0.00	-0.16:0.17	0.08	-0.16:0.33	0.08	-0.07:0.24	0.10	-0.09:0.29
L-LDL-L	0.29	0.01:0.56	0.05	-0.10:0.21	0.02	-0.06:0.11	-0.18	-0.34:-0.03	-0.01	-0.17:0.16	0.08	-0.17:0.34	0.08	-0.08:0.24	0.10	-0.09:0.29
L-LDL-PL	0.29	0.01:0.57	0.04	-0.11:0.20	0.02	-0.07:0.10	-0.17	-0.33:-0.01	0.00	-0.16:0.17	0.08	-0.17:0.33	0.07	-0.08:0.23	0.11	-0.08:0.30
L-LDL-C	0.27	-0.01:0.55	0.05	-0.10:0.21	0.02	-0.06:0.10	-0.17	-0.33:-0.01	-0.01	-0.17:0.16	0.08	-0.17:0.34	0.07	-0.09:0.22	0.11	-0.08:0.30
L-LDL-CE	0.29	0.01:0.57	0.06	-0.10:0.22	0.02	-0.07:0.10	-0.18	-0.34:-0.02	0.00	-0.17:0.16	0.09	-0.16:0.34	0.08	-0.08:0.24	0.10	-0.09:0.29
L-LDL-FC	0.22	-0.06:0.49	0.03	-0.12:0.19	0.02	-0.06:0.11	-0.14	-0.30:0.02	-0.02	-0.18:0.14	0.12	-0.12:0.36	0.02	-0.14:0.17	0.12	-0.07:0.31

Table S3. Continued.

	LUMINA		NESDA-1		NTR		ERF		RS		TMS		LifeLines		NESDA-2	
	B	CI	B	CI	B	CI	B	CI	B	CI	B	CI	B	CI	B	CI
L-LDL-TG	0.24	-0.05:0.52	-0.04	-0.18:0.11	0.00	-0.08:0.09	-0.24	-0.41:-0.07	0.00	-0.17:0.17	0.05	-0.19:0.30	0.14	0.00:0.29	0.03	-0.16:0.21
M-LDL-P	0.32	0.03:0.61	0.06	-0.10:0.22	0.02	-0.06:0.11	-0.20	-0.36:-0.04	0.01	-0.15:0.17	0.09	-0.15:0.34	0.09	-0.07:0.24	0.10	-0.09:0.28
M-LDL-L	0.31	0.03:0.60	0.07	-0.08:0.23	0.02	-0.06:0.11	-0.20	-0.36:-0.04	0.01	-0.16:0.17	0.10	-0.15:0.35	0.09	-0.07:0.25	0.09	-0.10:0.29
M-LDL-PL	0.37	0.07:0.66	0.07	-0.09:0.23	0.01	-0.08:0.09	-0.18	-0.34:-0.02	0.03	-0.14:0.19	0.12	-0.14:0.37	0.11	-0.05:0.27	0.07	-0.12:0.27
M-LDL-C	0.29	0.01:0.57	0.08	-0.08:0.23	0.02	-0.06:0.11	-0.18	-0.34:-0.02	0.00	-0.16:0.17	0.10	-0.15:0.35	0.08	-0.08:0.24	0.10	-0.09:0.29
M-LDL-CE	0.29	0.01:0.57	0.07	-0.08:0.23	0.02	-0.06:0.11	-0.17	-0.34:-0.01	0.00	-0.16:0.17	0.09	-0.16:0.34	0.08	-0.08:0.23	0.11	-0.08:0.30
M-LDL-FC	0.25	-0.03:0.53	0.07	-0.09:0.23	0.01	-0.07:0.10	-0.19	-0.35:-0.02	0.00	-0.17:0.16	0.13	-0.12:0.38	0.07	-0.09:0.23	0.09	-0.10:0.28
M-LDL-TG	0.20	-0.08:0.48	-0.06	-0.21:0.09	0.00	-0.09:0.08	-0.23	-0.40:-0.05	-0.02	-0.19:0.15	0.03	-0.22:0.28	0.13	-0.02:0.28	0.02	-0.17:0.20
S-LDL-P	0.31	0.02:0.60	0.06	-0.10:0.21	0.01	-0.08:0.09	-0.21	-0.37:-0.04	0.02	-0.15:0.18	0.11	-0.14:0.36	0.08	-0.07:0.24	0.10	-0.09:0.29
S-LDL-L	0.30	0.01:0.58	0.07	-0.09:0.23	0.01	-0.08:0.09	-0.20	-0.36:-0.04	0.01	-0.15:0.18	0.12	-0.14:0.38	0.08	-0.07:0.24	0.11	-0.09:0.30
S-LDL-PL	0.28	-0.01:0.57	0.05	-0.11:0.22	-0.02	-0.1:0.06	-0.19	-0.35:-0.02	0.03	-0.13:0.20	0.20	-0.06:0.47	0.10	-0.05:0.26	0.08	-0.11:0.28
S-LDL-C	0.26	-0.02:0.54	0.07	-0.09:0.23	0.02	-0.07:0.10	-0.18	-0.34:-0.02	0.01	-0.16:0.17	0.10	-0.14:0.35	0.06	-0.10:0.21	0.12	-0.07:0.31
S-LDL-CE	0.26	-0.02:0.53	0.06	-0.10:0.22	0.02	-0.07:0.10	-0.17	-0.33:-0.01	0.01	-0.16:0.17	0.09	-0.16:0.33	0.07	-0.09:0.22	0.12	-0.07:0.31
S-LDL-FC	0.21	-0.07:0.49	0.09	-0.07:0.25	0.01	-0.07:0.09	-0.19	-0.35:-0.03	0.01	-0.16:0.17	0.18	-0.09:0.44	0.04	-0.11:0.20	0.11	-0.09:0.30
S-LDL-TG	0.27	-0.02:0.55	-0.02	-0.17:0.13	-0.03	-0.11:0.06	-0.24	-0.41:-0.06	0.04	-0.13:0.20	0.06	-0.19:0.30	0.19	0.04:0.33	-0.01	-0.20:0.18
LDL-D	-0.08	-0.33:0.17	-0.01	-0.16:0.14	0.04	-0.04:0.13	0.16	0.01:0.32	-0.11	-0.27:0.06	-0.12	-0.39:0.16	-0.11	-0.27:0.05	0.01	-0.18:0.20
LDL-C	0.27	-0.01:0.54	0.07	-0.09:0.23	0.02	-0.06:0.11	-0.17	-0.33:-0.02	0.00	-0.17:0.16	0.09	-0.17:0.34	0.07	-0.08:0.23	0.11	-0.08:0.30
LDL-TG	0.22	-0.06:0.50	-0.04	-0.19:0.11	-0.01	-0.09:0.08	-0.19	-0.36:-0.02	-0.01	-0.18:0.16	0.04	-0.21:0.28	0.16	0.02:0.31	0.01	-0.17:0.20
XL-HDL-P	-0.30	-0.57:-0.02	-0.20	-0.35:-0.04	-0.05	-0.13:0.03	0.00	-0.16:0.16	-0.15	-0.32:0.01	-0.04	-0.29:0.20	-0.19	-0.35:-0.03	-0.10	-0.28:0.08
XL-HDL-L	-0.31	-0.59:-0.03	-0.21	-0.36:-0.05	-0.05	-0.13:0.04	0.00	-0.16:0.16	-0.15	-0.31:0.02	-0.02	-0.27:0.22	-0.20	-0.35:-0.04	-0.10	-0.28:0.08
XL-HDL-PL	-0.34	-0.63:-0.05	-0.20	-0.35:-0.04	-0.08	-0.17:0.01	0.04	-0.12:0.20	-0.18	-0.35:-0.01	-0.10	-0.35:0.15	-0.19	-0.35:-0.02	-0.09	-0.27:0.10
XL-HDL-C	-0.27	-0.54:0.01	-0.21	-0.37:-0.06	-0.01	-0.09:0.07	-0.04	-0.20:0.12	-0.11	-0.27:0.05	0.05	-0.20:0.30	-0.21	-0.36:-0.06	-0.09	-0.27:0.08
XL-HDL-CE	-0.24	-0.51:0.03	-0.21	-0.37:-0.06	0.00	-0.08:0.08	-0.05	-0.21:0.11	-0.11	-0.27:0.05	0.07	-0.18:0.33	-0.21	-0.37:-0.06	-0.09	-0.27:0.08
XL-HDL-FC	-0.32	-0.59:-0.04	-0.21	-0.37:-0.05	-0.04	-0.12:0.04	-0.02	-0.18:0.14	-0.12	-0.28:0.05	-0.02	-0.26:0.23	-0.19	-0.34:-0.04	-0.10	-0.27:0.08
XL-HDL-TG	0.04	-0.22:0.30	-0.03	-0.18:0.11	-0.01	-0.09:0.07	-0.16	-0.33:0.01	0.00	-0.17:0.16	-0.06	-0.31:0.19	0.11	-0.03:0.26	-0.18	-0.37:0.00
L-HDL-P	-0.32	-0.60:-0.03	-0.14	-0.29:0.00	-0.12	-0.20:-0.03	0.08	-0.08:0.23	-0.13	-0.30:0.04	-0.10	-0.35:0.16	-0.21	-0.38:-0.05	-0.08	-0.27:0.10
L-HDL-L	-0.35	-0.65:-0.05	-0.16	-0.31:-0.01	-0.11	-0.20:-0.02	0.09	-0.07:0.24	-0.13	-0.30:0.04	-0.07	-0.33:0.19	-0.23	-0.39:-0.07	-0.07	-0.26:0.12
L-HDL-PL	-0.34	-0.64:-0.05	-0.15	-0.29:0.00	-0.11	-0.20:-0.03	0.09	-0.07:0.24	-0.14	-0.31:0.03	-0.10	-0.36:0.16	-0.21	-0.37:-0.05	-0.06	-0.25:0.13
L-HDL-C	-0.34	-0.63:-0.04	-0.16	-0.32:-0.01	-0.11	-0.20:-0.03	0.09	-0.07:0.25	-0.12	-0.29:0.05	-0.06	-0.32:0.19	-0.24	-0.40:-0.08	-0.08	-0.27:0.11

Table S3. Continued.

	LUMINA		NESDA-1		NTR		ERF		RS		TMS		LifeLines		NESDA-2	
	B	CI	B	CI	B	CI	B	CI	B	CI	B	CI	B	CI	B	CI
L-HDL-CE	-0.32	-0.61:-0.03	-0.08	-0.24:0.08	-0.12	-0.20:-0.03	0.09	-0.07:0.24	-0.11	-0.28:0.05	-0.07	-0.32:0.19	-0.23	-0.39:-0.07	-0.09	-0.27:0.10
L-HDL-FC	-0.37	-0.66:-0.07	-0.20	-0.35:-0.06	-0.11	-0.19:-0.02	0.08	-0.08:0.24	-0.13	-0.29:0.04	-0.07	-0.32:0.18	-0.25	-0.42:-0.09	-0.08	-0.27:0.11
L-HDL-TG	-0.08	-0.34:0.18	0.10	-0.04:0.25	-0.05	-0.14:0.03	-0.03	-0.19:0.13	-0.05	-0.22:0.11	-0.12	-0.38:0.14	-0.04	-0.19:0.11	-0.13	-0.31:0.06
M-HDL-P	-0.06	-0.32:0.20	-0.20	-0.35:-0.04	-0.11	-0.19:-0.03	0.11	-0.05:0.27	0.02	-0.16:0.20	-0.13	-0.39:0.13	0.02	-0.13:0.16	-0.02	-0.20:0.15
M-HDL-L	-0.10	-0.36:0.17	-0.21	-0.36:-0.05	-0.10	-0.18:-0.02	0.12	-0.04:0.27	0.02	-0.17:0.20	-0.13	-0.39:0.13	0.01	-0.14:0.16	-0.02	-0.19:0.16
M-HDL-PL	-0.15	-0.42:0.12	-0.20	-0.35:-0.04	-0.10	-0.19:-0.02	0.10	-0.06:0.25	0.02	-0.16:0.20	-0.12	-0.38:0.14	0.00	-0.14:0.15	-0.03	-0.20:0.15
M-HDL-C	-0.12	-0.39:0.15	-0.21	-0.37:-0.06	-0.10	-0.18:-0.02	0.15	-0.01:0.31	0.00	-0.18:0.18	-0.13	-0.39:0.13	-0.03	-0.19:0.12	-0.01	-0.18:0.17
M-HDL-CE	-0.10	-0.37:0.16	-0.21	-0.37:-0.06	-0.10	-0.18:-0.02	0.16	0.00:0.32	-0.03	-0.20:0.15	-0.13	-0.39:0.13	-0.06	-0.22:0.09	-0.01	-0.19:0.17
M-HDL-FC	-0.07	-0.33:0.19	-0.21	-0.37:-0.05	-0.11	-0.19:-0.03	0.08	-0.08:0.23	0.08	-0.10:0.26	-0.13	-0.40:0.13	0.07	-0.08:0.22	0.00	-0.18:0.18
M-HDL-TG	0.22	-0.04:0.49	-0.03	-0.18:0.11	-0.02	-0.10:0.06	-0.07	-0.23:0.10	0.05	-0.10:0.21	-0.05	-0.30:0.19	0.25	0.10:0.39	-0.02	-0.20:0.16
S-HDL-P	0.07	-0.18:0.32	-0.14	-0.29:0.00	-0.09	-0.17:-0.01	0.00	-0.17:0.16	0.14	-0.02:0.30	-0.04	-0.28:0.20	0.11	-0.03:0.24	0.04	-0.13:0.20
S-HDL-L	0.05	-0.20:0.30	-0.16	-0.31:-0.01	-0.09	-0.17:-0.01	-0.01	-0.17:0.15	0.14	-0.03:0.31	-0.04	-0.28:0.21	0.10	-0.04:0.24	0.04	-0.13:0.21
S-HDL-PL	-0.07	-0.32:0.18	-0.15	-0.29:0.00	-0.11	-0.19:-0.03	0.08	-0.08:0.24	0.10	-0.06:0.26	-0.12	-0.36:0.12	0.08	-0.06:0.22	-0.01	-0.18:0.16
S-HDL-C	0.12	-0.14:0.38	-0.16	-0.32:-0.01	-0.02	-0.11:0.06	-0.09	-0.25:0.07	0.07	-0.10:0.23	0.14	-0.14:0.42	0.01	-0.15:0.16	0.12	-0.06:0.30
S-HDL-CE	0.17	-0.09:0.42	-0.08	-0.24:0.08	0.00	-0.08:0.09	-0.09	-0.26:0.07	0.05	-0.11:0.21	0.17	-0.11:0.45	-0.01	-0.18:0.15	0.14	-0.05:0.32
S-HDL-FC	-0.12	-0.36:0.13	-0.20	-0.35:-0.06	-0.11	-0.19:-0.04	-0.03	-0.19:0.13	0.05	-0.11:0.22	-0.04	-0.29:0.20	0.06	-0.08:0.19	-0.02	-0.19:0.15
S-HDL-TG	0.32	0.04:0.61	0.10	-0.04:0.25	-0.01	-0.09:0.07	-0.17	-0.34:0.00	0.07	-0.09:0.22	0.04	-0.21:0.28	0.25	0.11:0.39	-0.04	-0.23:0.14
HDL-D	-0.36	-0.65:-0.07	-0.24	-0.40:-0.08	-0.08	-0.16:0.01	0.07	-0.09:0.23	-0.18	-0.35:-0.01	-0.09	-0.34:0.17	-0.23	-0.39:-0.07	-0.08	-0.27:0.10
HDL-C	-0.26	-0.55:0.03	-0.26	-0.43:-0.10	-0.10	-0.18:-0.01	0.07	-0.09:0.23	-0.10	-0.27:0.07	-0.05	-0.31:0.21	-0.21	-0.37:-0.05	-0.05	-0.24:0.14
HDL2-C	-0.32	-0.61:-0.03	-0.26	-0.42:-0.10	-0.11	-0.19:-0.03	0.09	-0.07:0.25	-0.11	-0.29:0.06	-0.09	-0.35:0.17	-0.23	-0.39:-0.07	-0.07	-0.25:0.12
HDL3-C	0.14	-0.12:0.40	-0.12	-0.28:0.04	0.01	-0.07:0.09	-0.06	-0.23:0.10	0.04	-0.12:0.20	0.18	-0.09:0.44	0.05	-0.10:0.21	0.07	-0.12:0.27
HDL-TG	0.19	-0.07:0.46	-0.03	-0.18:0.12	-0.04	-0.12:0.04	-0.12	-0.29:0.04	0.01	-0.15:0.17	-0.03	-0.28:0.22	0.20	0.05:0.34	-0.11	-0.30:0.07
Serum-C	0.22	-0.06:0.50	0.00	-0.16:0.16	-0.01	-0.09:0.08	-0.15	-0.31:0.01	-0.02	-0.19:0.15	0.07	-0.19:0.33	0.07	-0.10:0.23	0.06	-0.14:0.25
Remnant-C	0.38	0.08:0.67	0.14	-0.02:0.30	0.04	-0.04:0.12	-0.18	-0.34:-0.02	0.03	-0.13:0.19	0.09	-0.15:0.34	0.19	0.03:0.34	0.04	-0.15:0.23
EstC	0.21	-0.07:0.49	-0.02	-0.18:0.14	-0.01	-0.09:0.08	-0.13	-0.29:0.03	-0.01	-0.18:0.16	0.06	-0.20:0.31	0.05	-0.11:0.21	0.07	-0.13:0.26
FreeC	0.23	-0.05:0.52	0.03	-0.13:0.18	-0.01	-0.09:0.08	-0.20	-0.36:-0.04	-0.02	-0.19:0.14	0.15	-0.10:0.40	0.10	-0.07:0.26	0.03	-0.16:0.22
Serum-TG	0.30	0.02:0.58	0.11	-0.04:0.26	0.00	-0.08:0.08	-0.18	-0.35:-0.01	0.10	-0.06:0.26	0.06	-0.18:0.31	0.31	0.16:0.46	-0.06	-0.25:0.13
TotPG	0.13	-0.14:0.41	-0.14	-0.29:0.02	-0.10	-0.18:-0.01	-0.12	-0.28:0.04	0.01	-0.17:0.19	-0.02	-0.27:0.24	0.09	-0.06:0.25	-0.04	-0.22:0.15

Table S3. Continued.

	LUMINA		NESDA-1		NTR		ERF		RS		TMS		LifeLines		NESDA-2	
	B	CI	B	CI	B	CI	B	CI	B	CI	B	CI	B	CI	B	CI
PC	0.01	-0.26:0.28	-0.11	-0.27:0.04	-0.07	-0.15:0.02	-0.08	-0.25:0.08	-0.02	-0.20:0.16	-0.02	-0.28:0.23	0.04	-0.12:0.19	-0.04	-0.23:0.14
SM	0.31	0.01:0.61	0.06	-0.10:0.21	0.03	-0.06:0.11	-0.18	-0.35:-0.02	-0.06	-0.23:0.12	0.12	-0.15:0.38	0.04	-0.12:0.21	-0.01	-0.19:0.18
TotCho	0.05	-0.23:0.32	-0.12	-0.28:0.04	-0.07	-0.15:0.02	-0.11	-0.27:0.06	-0.03	-0.21:0.15	0.01	-0.25:0.28	0.04	-0.12:0.19	-0.03	-0.22:0.16
ApoA1	-0.13	-0.41:0.14	-0.25	-0.41:-0.09	-0.10	-0.18:-0.02	0.00	-0.16:0.16	-0.09	-0.27:0.09	-0.01	-0.27:0.26	-0.12	-0.28:0.04	-0.08	-0.26:0.11
ApoB	0.41	0.11:0.71	0.12	-0.04:0.28	0.03	-0.06:0.11	-0.20	-0.36:-0.04	0.04	-0.12:0.20	0.12	-0.12:0.37	0.20	0.04:0.35	0.05	-0.14:0.24
TotFA	0.24	-0.04:0.51	0.00	-0.16:0.15	-0.06	-0.14:0.02	-0.16	-0.32:0.00	0.03	-0.14:0.21	0.05	-0.21:0.30	0.20	0.05:0.36	-0.04	-0.23:0.16
UnsatDeg	0.02	-0.23:0.26	-0.08	-0.22:0.06	0.01	-0.07:0.08	0.08	-0.09:0.24	-0.02	-0.18:0.14	-0.13	-0.38:0.12	-0.17	-0.32:-0.02	0.07	-0.11:0.24
FAw3	-0.08	-0.35:0.19	-0.25	-0.42:-0.08	-0.03	-0.12:0.05	-0.07	-0.24:0.09	0.03	-0.14:0.19	-0.01	-0.26:0.24	-0.01	-0.18:0.15	-0.10	-0.30:0.11
FAw6	0.26	-0.01:0.54	-0.02	-0.17:0.14	-0.03	-0.11:0.05	-0.11	-0.28:0.05	-0.06	-0.23:0.11	0.12	-0.14:0.37	0.12	-0.03:0.28	0.07	-0.12:0.25
PUFA	0.23	-0.05:0.51	-0.05	-0.21:0.10	-0.03	-0.12:0.05	-0.12	-0.28:0.04	-0.05	-0.22:0.12	0.10	-0.15:0.35	0.11	-0.05:0.27	0.05	-0.14:0.24
MUFA	0.27	0.00:0.54	0.01	-0.15:0.16	-0.08	-0.16:0.00	-0.20	-0.37:-0.03	0.13	-0.04:0.29	-0.03	-0.28:0.23	0.24	0.09:0.39	-0.05	-0.24:0.14
SFA	0.22	-0.05:0.49	0.01	-0.14:0.16	-0.05	-0.13:0.03	-0.15	-0.32:0.01	0.02	-0.15:0.19	0.08	-0.17:0.33	0.18	0.03:0.34	-0.06	-0.25:0.13
DHA	0.08	-0.19:0.36	-0.20	-0.36:-0.04	-0.02	-0.1:0.06	-0.07	-0.24:0.10	0.01	-0.16:0.17	0.02	-0.22:0.27	0.02	-0.13:0.17	-0.11	-0.30:0.09
LA	0.23	-0.04:0.50	-0.02	-0.17:0.13	-0.03	-0.11:0.05	-0.07	-0.23:0.09	-0.08	-0.25:0.08	0.15	-0.09:0.40	0.09	-0.07:0.24	0.12	-0.06:0.30
Glc	-0.06	-0.33:0.21	-0.01	-0.17:0.15	0.02	-0.07:0.10	-0.11	-0.27:0.06	-0.05	-0.22:0.11	0.23	-0.01:0.47	0.13	-0.02:0.28	-0.07	-0.28:0.13
Lac	0.05	-0.20:0.29	0.06	-0.08:0.21	-0.05	-0.12:0.03	-0.05	-0.21:0.11	0.01	-0.16:0.17	0.16	-0.06:0.39	0.06	-0.08:0.20	0.00	-0.17:0.17
Pyr	-0.03	-0.28:0.21	0.04	-0.10:0.19	-	-	-0.18	-0.35:-0.01	0.01	-0.15:0.17	0.03	-0.20:0.27	0.07	-0.08:0.21	0.02	-0.16:0.19
Cit	-0.20	-0.46:0.05	-0.10	-0.25:0.04	-0.08	-0.16:0.00	0.05	-0.11:0.21	0.04	-0.12:0.21	0.08	-0.17:0.33	0.02	-0.12:0.16	0.04	-0.13:0.22
Ala	0.20	-0.06:0.46	-0.01	-0.15:0.14	0.00	-0.08:0.08	0.00	-0.17:0.16	-0.01	-0.17:0.15	0.14	-0.10:0.39	0.06	-0.09:0.20	-0.05	-0.23:0.13
Gln	0.04	-0.21:0.30	-0.16	-0.31:-0.01	-	-	-0.09	-0.25:0.07	-0.06	-0.22:0.11	-0.03	-0.27:0.20	0.05	-0.10:0.20	0.04	-0.14:0.22
His	-0.08	-0.33:0.17	0.00	-0.14:0.15	0.02	-0.06:0.10	0.09	-0.07:0.26	0.02	-0.15:0.18	0.17	-0.08:0.42	0.02	-0.13:0.16	-0.18	-0.35:0.00
Ile	0.00	-0.25:0.25	0.01	-0.16:0.18	0.07	-0.02:0.16	-0.11	-0.28:0.06	-0.01	-0.18:0.16	0.45	0.17:0.72	0.08	-0.09:0.26	-0.04	-0.24:0.17
Leu	-0.19	-0.43:0.05	-0.11	-0.29:0.07	0.09	0.00:0.18	-0.16	-0.34:0.01	0.01	-0.17:0.19	0.46	0.18:0.74	-0.01	-0.20:0.17	-0.06	-0.26:0.14
Val	-0.19	-0.44:0.05	-0.09	-0.25:0.07	0.08	0.00:0.17	-0.26	-0.43:-0.09	-0.03	-0.20:0.14	0.44	0.18:0.70	0.00	-0.16:0.16	-0.04	-0.23:0.14
Phe	-0.14	-0.38:0.10	-0.01	-0.15:0.14	0.06	-0.02:0.14	-0.21	-0.37:-0.04	-0.10	-0.27:0.07	0.03	-0.24:0.30	0.06	-0.09:0.21	-0.10	-0.29:0.08
Tyr	-0.07	-0.32:0.18	0.03	-0.12:0.18	0.00	-0.08:0.09	-0.29	-0.46:-0.12	-0.07	-0.23:0.10	0.14	-0.11:0.39	-0.06	-0.22:0.10	-0.02	-0.20:0.17
AcAce	-0.15	-0.37:0.08	-0.16	-0.32:0.00	-0.01	-0.09:0.07	-0.08	-0.25:0.09	0.13	-0.03:0.29	-0.02	-0.29:0.25	0.12	-0.02:0.26	0.07	-0.10:0.24
bOHBut	-0.16	-0.38:0.07	-0.15	-0.3:0.00	0.02	-0.06:0.10	-0.07	-0.24:0.11	0.06	-0.10:0.21	0.05	-0.20:0.30	0.00	-0.13:0.14	-0.04	-0.22:0.13
Crea	-0.02	-0.32:0.29	0.03	-0.15:0.21	0.04	-0.06:0.13	-0.08	-0.24:0.09	-0.15	-0.36:0.06	0.08	-0.22:0.37	0.04	-0.15:0.22	0.03	-0.18:0.24

Table S3. Continued.

	LUMINA		NESDA-1		NTR		ERF		RS		TMS		LifeLines		NESDA-2	
	B	CI	B	CI	B	CI	B	CI	B	CI	B	CI	B	CI	B	CI
Alb	0.24	-0.02:0.49	0.01	-0.14:0.15	-0.08	-0.16:0.00	0.01	-0.15:0.17	0.10	-0.06:0.25	0.10	-0.14:0.34	-0.06	-0.20:0.09	-0.03	-0.21:0.14
Gp	0.41	0.13:0.69	0.17	0.03:0.31	0.01	-0.07:0.08	-0.10	-0.27:0.06	0.00	-0.17:0.16	0.15	-0.10:0.40	0.21	0.07:0.36	-0.15	-0.33:0.03
XXL-VLDL-PL_%	-0.20	-0.47:0.07	-0.04	-0.17:0.09	-0.02	-0.09:0.06	-0.08	-0.22:0.06	-0.01	-0.17:0.15	-0.16	-0.42:0.10	0.07	-0.07:0.21	-0.03	-0.20:0.14
XXL-VLDL-C_%	-0.19	-0.46:0.09	-0.03	-0.16:0.10	0.06	-0.03:0.14	-0.05	-0.20:0.09	-0.05	-0.21:0.11	-0.02	-0.24:0.19	0.06	-0.08:0.21	0.06	-0.12:0.24
XXL-VLDL-CE_%	-0.20	-0.47:0.07	-0.02	-0.15:0.12	0.03	-0.05:0.11	-0.05	-0.20:0.09	-0.01	-0.17:0.16	0.03	-0.21:0.26	0.06	-0.09:0.20	0.09	-0.09:0.27
XXL-VLDL-FC_%	-0.14	-0.40:0.12	-0.13	-0.26:0.01	0.04	-0.04:0.12	-0.06	-0.21:0.09	-0.03	-0.18:0.13	-0.15	-0.35:0.05	0.11	-0.04:0.26	-0.11	-0.27:0.05
XXL-VLDL-TG_%	-0.16	-0.43:0.11	0.07	-0.08:0.21	0.00	-0.08:0.08	0.07	-0.10:0.24	0.09	-0.09:0.26	0.23	-0.18:0.65	0.05	-0.09:0.19	0.01	-0.16:0.19
XL-VLDL-PL_%	0.06	-0.18:0.30	-0.02	-0.15:0.11	0.06	-0.02:0.14	0.01	-0.15:0.17	0.08	-0.12:0.27	-0.04	-0.25:0.18	0.20	0.05:0.35	0.14	-0.08:0.37
XL-VLDL-C_%	0.05	-0.19:0.29	-0.02	-0.15:0.11	0.07	-0.01:0.15	0.08	-0.09:0.25	-0.01	-0.18:0.16	0.03	-0.21:0.28	0.18	0.03:0.33	0.05	-0.13:0.23
XL-VLDL-CE_%	0.04	-0.20:0.28	-0.01	-0.14:0.13	0.06	-0.02:0.14	0.08	-0.09:0.26	-0.05	-0.21:0.11	0.06	-0.19:0.31	0.17	0.03:0.32	0.02	-0.16:0.20
XL-VLDL-FC_%	0.03	-0.21:0.27	-0.04	-0.17:0.09	0.07	-0.01:0.15	0.07	-0.10:0.23	0.01	-0.17:0.18	-0.02	-0.24:0.20	0.19	0.04:0.34	0.11	-0.07:0.29
XL-VLDL-TG_%	0.10	-0.13:0.34	0.02	-0.12:0.16	0.03	-0.04:0.11	0.08	-0.09:0.25	0.13	-0.10:0.36	0.15	-0.17:0.47	0.18	0.03:0.34	-0.01	-0.19:0.16
L-VLDL-PL_%	0.19	-0.03:0.41	0.12	-0.04:0.28	0.02	-0.06:0.10	-0.05	-0.20:0.10	-0.04	-0.20:0.11	-0.03	-0.25:0.18	0.11	-0.04:0.25	0.05	-0.14:0.23
L-VLDL-C_%	0.12	-0.10:0.35	0.00	-0.14:0.13	0.00	-0.08:0.08	-0.07	-0.21:0.06	-0.10	-0.26:0.06	-0.05	-0.30:0.20	0.05	-0.09:0.19	0.06	-0.12:0.23
L-VLDL-CE_%	0.10	-0.13:0.33	-0.01	-0.14:0.12	0.04	-0.04:0.12	-0.06	-0.21:0.08	-0.05	-0.20:0.10	0.13	-0.14:0.40	0.03	-0.11:0.17	0.05	-0.13:0.22
L-VLDL-FC_%	0.17	-0.06:0.40	0.05	-0.10:0.20	0.04	-0.04:0.12	-0.08	-0.23:0.06	0.00	-0.17:0.17	-0.12	-0.34:0.10	0.07	-0.07:0.21	0.06	-0.13:0.25
L-VLDL-TG_%	0.07	-0.16:0.29	-0.01	-0.15:0.12	0.03	-0.05:0.11	0.07	-0.10:0.24	0.20	0.01:0.39	0.04	-0.21:0.30	0.03	-0.10:0.17	-0.07	-0.24:0.11
M-VLDL-PL_%	0.30	0.04:0.56	0.03	-0.11:0.17	-0.02	-0.10:0.06	-0.07	-0.23:0.10	-0.03	-0.18:0.13	0.07	-0.17:0.31	0.06	-0.07:0.20	0.02	-0.16:0.20
M-VLDL-C_%	-0.08	-0.35:0.19	-0.02	-0.17:0.13	0.00	-0.08:0.08	-0.08	-0.24:0.08	-0.12	-0.29:0.04	-0.05	-0.29:0.20	-0.08	-0.22:0.07	0.07	-0.11:0.25
M-VLDL-CE_%	-0.12	-0.40:0.16	-0.05	-0.19:0.08	0.02	-0.06:0.11	-0.03	-0.19:0.13	-0.14	-0.30:0.02	-0.04	-0.28:0.21	-0.11	-0.25:0.03	0.08	-0.10:0.26
M-VLDL-FC_%	-0.04	-0.30:0.22	0.02	-0.12:0.16	-0.02	-0.10:0.06	-0.15	-0.31:0.00	0.03	-0.13:0.19	-0.02	-0.26:0.23	0.08	-0.07:0.22	-0.05	-0.22:0.12
M-VLDL-TG_%	0.01	-0.26:0.27	0.02	-0.13:0.16	0.01	-0.07:0.09	0.09	-0.08:0.25	0.10	-0.07:0.26	0.04	-0.20:0.28	0.07	-0.07:0.22	-0.07	-0.24:0.10
S-VLDL-PL_%	-0.19	-0.45:0.08	-0.17	-0.32:-0.02	-0.05	-0.13:0.03	0.18	0.03:0.33	0.00	-0.15:0.16	-0.06	-0.30:0.19	-0.13	-0.27:0.02	0.07	-0.11:0.25
S-VLDL-C_%	-0.14	-0.40:0.11	-0.01	-0.15:0.14	0.04	-0.04:0.12	-0.02	-0.18:0.14	-0.12	-0.28:0.04	0.03	-0.22:0.28	-0.21	-0.35:-0.06	0.10	-0.08:0.28
S-VLDL-CE_%	-0.11	-0.36:0.14	-0.01	-0.15:0.13	0.05	-0.03:0.13	-0.01	-0.17:0.15	-0.11	-0.27:0.05	0.03	-0.21:0.28	-0.21	-0.35:-0.06	0.10	-0.08:0.28
S-VLDL-FC_%	-0.33	-0.61:-0.06	-0.10	-0.25:0.05	-0.07	-0.15:0.02	-0.10	-0.26:0.06	-0.09	-0.25:0.07	0.00	-0.26:0.26	-0.07	-0.22:0.07	0.09	-0.10:0.27
S-VLDL-TG_%	0.20	-0.05:0.46	0.03	-0.12:0.17	-0.01	-0.10:0.07	-0.01	-0.18:0.15	0.14	-0.02:0.31	0.01	-0.23:0.25	0.27	0.11:0.42	-0.10	-0.28:0.07
XS-VLDL-PL_%	0.12	-0.13:0.38	-0.07	-0.22:0.08	-0.02	-0.10:0.07	-0.06	-0.22:0.10	-0.08	-0.24:0.09	0.00	-0.27:0.28	-0.03	-0.19:0.13	0.12	-0.08:0.31

Table S3. Continued.

	LUMINA		NESDA-1		NTR		ERF		RS		TMS		LifeLines		NESDA-2	
	B	CI	B	CI	B	CI	B	CI	B	CI	B	CI	B	CI	B	CI
XS-VLDL-C_%	-0.27	-0.54:0.00	0.05	-0.09:0.20	0.05	-0.03:0.13	0.21	0.03:0.38	-0.06	-0.22:0.10	0.02	-0.24:0.27	-0.24	-0.38:-0.10	0.04	-0.14:0.22
XS-VLDL-CE_%	-0.24	-0.51:0.03	0.01	-0.13:0.15	0.04	-0.04:0.13	0.20	0.03:0.37	-0.05	-0.22:0.11	-0.01	-0.25:0.23	-0.21	-0.35:-0.07	0.04	-0.14:0.22
XS-VLDL-FC_%	-0.18	-0.45:0.09	0.08	-0.07:0.24	0.02	-0.06:0.10	0.10	-0.06:0.27	-0.04	-0.20:0.11	0.06	-0.20:0.33	-0.16	-0.31:-0.01	0.00	-0.18:0.19
XS-VLDL-TG_%	0.16	-0.09:0.41	-0.01	-0.16:0.13	-0.03	-0.11:0.05	-0.15	-0.32:0.01	0.12	-0.04:0.28	-0.01	-0.26:0.23	0.25	0.11:0.39	-0.05	-0.23:0.12
IDL-PL_%	-0.24	-0.52:0.05	-0.20	-0.36:-0.05	-0.01	-0.09:0.07	0.26	0.08:0.43	-0.02	-0.18:0.14	-0.17	-0.40:0.07	-0.19	-0.35:-0.03	0.11	-0.09:0.31
IDL-C_%	-0.02	-0.27:0.23	0.07	-0.07:0.22	0.02	-0.06:0.1	0.10	-0.06:0.27	-0.04	-0.20:0.12	0.07	-0.18:0.31	-0.09	-0.23:0.05	0.01	-0.16:0.18
IDL-CE_%	0.02	-0.24:0.27	0.10	-0.05:0.25	0.01	-0.07:0.09	0.06	-0.11:0.22	0.01	-0.16:0.17	0.12	-0.13:0.38	-0.02	-0.17:0.12	-0.04	-0.22:0.14
IDL-FC_%	-0.05	-0.29:0.19	-0.02	-0.16:0.13	0.04	-0.04:0.13	0.11	-0.07:0.28	-0.06	-0.21:0.10	0.09	-0.19:0.37	-0.17	-0.31:-0.02	0.08	-0.12:0.28
IDL-TG_%	0.05	-0.19:0.29	-0.08	-0.23:0.06	-0.02	-0.09:0.06	-0.18	-0.34:-0.02	0.06	-0.11:0.22	-0.01	-0.27:0.25	0.18	0.04:0.32	-0.02	-0.20:0.15
L-LDL-PL_%	-0.22	-0.48:0.04	-0.11	-0.26:0.05	-0.02	-0.1:0.07	0.20	0.05:0.36	0.02	-0.15:0.19	-0.09	-0.36:0.18	-0.11	-0.27:0.05	-0.05	-0.24:0.14
L-LDL-C_%	0.12	-0.12:0.37	0.08	-0.07:0.23	0.02	-0.06:0.1	-0.05	-0.20:0.10	-0.03	-0.19:0.13	0.05	-0.20:0.31	0.00	-0.15:0.15	0.08	-0.10:0.26
L-LDL-CE_%	0.24	-0.01:0.50	0.09	-0.07:0.24	0.02	-0.07:0.1	-0.12	-0.27:0.02	-0.01	-0.17:0.16	0.10	-0.17:0.36	0.11	-0.05:0.28	0.05	-0.13:0.24
L-LDL-FC_%	-0.33	-0.61:-0.06	-0.07	-0.22:0.07	0.02	-0.06:0.1	0.24	0.07:0.40	-0.04	-0.20:0.13	0.04	-0.23:0.30	-0.25	-0.41:-0.10	0.02	-0.17:0.21
L-LDL-TG_%	-0.03	-0.27:0.21	-0.05	-0.19:0.09	-0.02	-0.10:0.06	-0.14	-0.30:0.02	0.00	-0.17:0.16	-0.01	-0.26:0.25	0.08	-0.07:0.22	-0.02	-0.19:0.15
M-LDL-PL_%	-0.16	-0.41:0.09	-0.12	-0.28:0.03	-0.03	-0.12:0.06	0.18	0.02:0.33	0.00	-0.16:0.17	-0.06	-0.33:0.21	-0.04	-0.20:0.11	-0.08	-0.27:0.11
M-LDL-C_%	0.08	-0.16:0.32	0.10	-0.04:0.25	0.04	-0.04:0.12	-0.08	-0.24:0.08	-0.04	-0.20:0.12	0.06	-0.20:0.33	0.01	-0.14:0.16	0.08	-0.10:0.26
M-LDL-CE_%	0.15	-0.09:0.38	0.15	-0.01:0.30	0.04	-0.05:0.13	-0.13	-0.27:0.02	-0.04	-0.20:0.12	0.09	-0.24:0.42	0.10	-0.06:0.27	0.07	-0.12:0.26
M-LDL-FC_%	-0.35	-0.61:-0.08	-0.10	-0.25:0.06	-0.02	-0.11:0.07	0.16	0.00:0.31	0.00	-0.18:0.17	-0.03	-0.30:0.23	-0.15	-0.32:0.01	-0.07	-0.26:0.12
M-LDL-TG_%	-0.02	-0.26:0.23	-0.06	-0.21:0.08	-0.02	-0.10:0.07	-0.09	-0.25:0.07	-0.05	-0.22:0.12	-0.04	-0.30:0.22	0.10	-0.05:0.26	0.00	-0.19:0.18
S-LDL-PL_%	-0.17	-0.43:0.08	-0.12	-0.27:0.03	-0.05	-0.13:0.04	0.15	0.00:0.31	0.01	-0.15:0.17	-0.04	-0.30:0.22	-0.08	-0.24:0.08	-0.09	-0.28:0.10
S-LDL-C_%	0.05	-0.18:0.29	0.09	-0.05:0.24	0.05	-0.03:0.13	-0.04	-0.19:0.12	0.00	-0.17:0.16	0.02	-0.23:0.27	0.00	-0.15:0.15	0.10	-0.09:0.29
S-LDL-CE_%	0.10	-0.13:0.34	0.08	-0.07:0.23	0.04	-0.05:0.12	-0.09	-0.23:0.06	-0.03	-0.19:0.13	0.06	-0.25:0.38	0.11	-0.08:0.29	0.09	-0.11:0.28
S-LDL-FC_%	-0.29	-0.56:-0.02	-0.02	-0.17:0.13	0.00	-0.09:0.09	0.14	-0.01:0.30	-0.01	-0.18:0.16	0.03	-0.24:0.30	-0.17	-0.33:-0.01	-0.06	-0.26:0.13
S-LDL-TG_%	0.09	-0.15:0.32	-0.01	-0.15:0.14	-0.02	-0.10:0.06	-0.15	-0.31:0.01	0.02	-0.14:0.19	-0.05	-0.31:0.21	0.20	0.05:0.35	-0.05	-0.24:0.13
XL-HDL-PL_%	-0.52	-0.94:-0.10	-0.10	-0.25:0.05	-0.05	-0.13:0.04	-0.02	-0.17:0.13	-0.03	-0.19:0.14	0.00	-0.27:0.27	-0.05	-0.23:0.12	-0.01	-0.22:0.20
XL-HDL-C_%	0.30	0.01:0.60	0.20	0.03:0.36	0.11	0.02:0.20	-0.09	-0.25:0.07	0.23	0.06:0.41	0.07	-0.22:0.36	0.02	-0.17:0.20	0.02	-0.18:0.22
XL-HDL-CE_%	0.33	0.03:0.62	0.10	-0.1:0.29	0.11	0.02:0.20	-0.09	-0.25:0.07	0.29	-0.07:0.66	0.08	-0.21:0.37	0.03	-0.16:0.21	0.01	-0.18:0.19
XL-HDL-FC_%	-0.02	-0.27:0.23	0.02	-0.12:0.17	0.01	-0.08:0.09	0.00	-0.16:0.16	0.12	-0.06:0.29	0.04	-0.24:0.33	-0.10	-0.24:0.04	0.09	-0.09:0.28
XL-HDL-TG_%	0.17	-0.08:0.43	0.17	0.01:0.32	0.03	-0.05:0.11	-0.18	-0.34:-0.02	0.15	-0.02:0.32	-0.01	-0.27:0.25	0.31	0.15:0.47	-0.04	-0.23:0.14

Table S3. Continued.

	LUMINA		NESDA-1		NTR		ERF		RS		TMS		LifeLines		NESDA-2	
	B	CI	B	CI	B	CI	B	CI	B	CI	B	CI	B	CI	B	CI
L-HDL-PL_%	-0.08	-0.32:0.16	0.00	-0.15:0.15	-0.03	-0.11:0.05	0.03	-0.14:0.19	0.01	-0.15:0.18	-0.14	-0.34:0.06	0.09	-0.07:0.24	0.14	-0.04:0.32
L-HDL-C_%	-0.03	-0.28:0.21	-0.08	-0.23:0.08	0.00	-0.08:0.08	0.09	-0.09:0.26	-0.06	-0.21:0.10	0.28	-0.33:0.90	-0.12	-0.27:0.02	-0.06	-0.25:0.12
L-HDL-CE_%	0.06	-0.18:0.30	-0.07	-0.23:0.09	-0.01	-0.09:0.08	0.01	-0.15:0.18	-0.01	-0.17:0.15	0.22	-0.30:0.74	-0.07	-0.21:0.08	-0.08	-0.26:0.11
L-HDL-FC_%	-0.17	-0.45:0.11	-0.11	-0.26:0.03	0.00	-0.08:0.08	0.15	-0.03:0.33	-0.10	-0.25:0.05	0.27	-0.24:0.79	-0.16	-0.31:-0.02	-0.01	-0.19:0.17
L-HDL-TG_%	0.06	-0.18:0.30	0.13	-0.02:0.29	0.02	-0.06:0.10	-0.13	-0.29:0.03	0.11	-0.06:0.27	-0.03	-0.31:0.24	0.13	-0.03:0.29	-0.06	-0.24:0.13
M-HDL-PL_%	-0.32	-0.62:-0.03	0.08	-0.06:0.22	0.03	-0.05:0.11	-0.06	-0.21:0.10	-0.01	-0.17:0.15	0.08	-0.19:0.34	-0.02	-0.17:0.12	-0.03	-0.21:0.14
M-HDL-C_%	-0.03	-0.29:0.22	-0.13	-0.28:0.02	-0.02	-0.10:0.06	0.16	-0.01:0.32	-0.05	-0.21:0.11	-0.06	-0.32:0.20	-0.16	-0.31:-0.02	0.04	-0.15:0.22
M-HDL-CE_%	-0.02	-0.27:0.23	-0.11	-0.26:0.04	0.00	-0.08:0.08	0.17	0.00:0.33	-0.09	-0.25:0.07	-0.04	-0.30:0.22	-0.21	-0.36:-0.07	0.02	-0.16:0.21
M-HDL-FC_%	-0.03	-0.28:0.21	-0.20	-0.35:-0.04	-0.06	-0.14:0.02	-0.02	-0.17:0.14	0.09	-0.07:0.25	-0.11	-0.38:0.17	0.12	-0.03:0.27	0.05	-0.16:0.25
M-HDL-TG_%	0.20	-0.05:0.45	0.16	0.01:0.32	0.03	-0.05:0.11	-0.13	-0.29:0.02	0.07	-0.10:0.23	-0.01	-0.26:0.25	0.29	0.14:0.45	0.02	-0.16:0.20
S-HDL-PL_%	-0.22	-0.50:0.05	-0.07	-0.22:0.08	-0.06	-0.15:0.02	0.17	0.00:0.33	0.02	-0.14:0.18	-0.24	-0.49:0.02	0.01	-0.15:0.17	-0.09	-0.28:0.09
S-HDL-C_%	0.09	-0.15:0.34	-0.02	-0.18:0.13	0.05	-0.04:0.13	-0.11	-0.27:0.05	-0.03	-0.19:0.13	0.16	-0.12:0.45	-0.10	-0.26:0.06	0.13	-0.06:0.32
S-HDL-CE_%	0.14	-0.11:0.38	0.00	-0.16:0.15	0.06	-0.03:0.14	-0.10	-0.25:0.06	-0.01	-0.18:0.15	0.14	-0.15:0.44	-0.07	-0.23:0.08	0.15	-0.05:0.34
S-HDL-FC_%	-0.35	-0.63:-0.07	-0.20	-0.35:-0.06	-0.08	-0.16:0.00	-0.04	-0.20:0.12	-0.07	-0.22:0.09	-0.05	-0.29:0.19	-0.06	-0.20:0.08	-0.13	-0.31:0.05
S-HDL-TG_%	0.33	0.06:0.60	0.20	0.05:0.35	0.04	-0.04:0.12	-0.15	-0.31:0.01	0.06	-0.10:0.22	0.06	-0.19:0.30	0.27	0.12:0.41	-0.04	-0.22:0.14
TG/PG	0.23	-0.05:0.50	0.18	0.02:0.34	0.08	-0.01:0.16	-0.13	-0.29:0.04	0.08	-0.08:0.24	0.05	-0.20:0.30	0.28	0.12:0.43	-0.08	-0.28:0.11
DHA/FA	-0.04	-0.30:0.21	-0.24	-0.4:-0.09	-0.01	-0.09:0.07	-0.04	-0.20:0.13	-0.01	-0.17:0.16	-0.06	-0.32:0.19	-0.11	-0.26:0.04	-0.06	-0.24:0.12
LA/FA	-0.03	-0.28:0.21	-0.01	-0.15:0.14	0.03	-0.05:0.11	0.15	-0.02:0.32	-0.15	-0.31:0.01	0.18	-0.07:0.43	-0.19	-0.33:-0.04	0.23	0.04:0.42
FAw3/FA	-0.32	-0.57:-0.08	-0.28	-0.44:-0.13	-0.02	-0.10:0.06	0.02	-0.14:0.18	0.01	-0.16:0.17	-0.16	-0.42:0.10	-0.20	-0.36:-0.04	-0.05	-0.23:0.13
FAw6/FA	-0.03	-0.27:0.22	-0.01	-0.15:0.14	0.03	-0.05:0.11	0.11	-0.05:0.28	-0.14	-0.30:0.02	0.11	-0.14:0.37	-0.18	-0.33:-0.04	0.18	-0.01:0.37
PUFA/FA	-0.10	-0.34:0.15	-0.06	-0.21:0.08	0.03	-0.05:0.11	0.12	-0.05:0.29	-0.13	-0.29:0.02	0.08	-0.17:0.34	-0.23	-0.37:-0.08	0.14	-0.04:0.33
MUFA/FA	0.22	-0.03:0.47	0.03	-0.11:0.18	-0.06	-0.14:0.02	-0.14	-0.31:0.02	0.19	0.03:0.35	-0.14	-0.39:0.11	0.25	0.10:0.39	-0.06	-0.24:0.12
SFA/FA	-0.26	-0.51:0.00	0.05	-0.1:0.19	0.06	-0.01:0.14	0.03	-0.13:0.19	-0.08	-0.24:0.08	0.13	-0.14:0.39	-0.08	-0.22:0.06	-0.11	-0.28:0.07
ApoB/ApoA1	0.47	0.17:0.77	0.24	0.08:0.4	0.09	0.00:0.17	-0.19	-0.35:-0.03	0.08	-0.08:0.24	0.12	-0.13:0.37	0.24	0.09:0.40	0.07	-0.11:0.26

B=Beta coefficient, CI=Confidence interval, ERF=Erasmus Rucphen Family study, LUMINA=Leiden University Migraine Neuro-Analysis, NESDA=Netherlands Study of Depression and Anxiety, NTR=Netherlands Twin Registry, RS=Rotterdam Study, TMS=The Maastricht Study. All metabolite abbreviations can be found in tables S1 and S2.

Table S4. Meta-analysis results of the logistic regressions with sex, age, and metabolite concentrations as independent variables and migraine status as dependent variable.

Metabolite abbreviation	B	CI	Unadjusted P-value	P-value	I^2 (%)
XXL-VLDL-P	0.05	-0.03:0.14	0.222	1.000	55
XXL-VLDL-L	0.05	-0.03:0.14	0.219	1.000	56
XXL-VLDL-PL	0.04	-0.05:0.13	0.356	1.000	54
XXL-VLDL-C	0.06	-0.03:0.14	0.172	1.000	54
XXL-VLDL-CE	0.07	-0.01:0.15	0.105	1.000	52
XXL-VLDL-FC	0.05	-0.05:0.14	0.330	1.000	61
XXL-VLDL-TG	0.05	-0.03:0.14	0.236	1.000	56
XL-VLDL-P	0.04	-0.05:0.13	0.352	1.000	56
XL-VLDL-L	0.05	-0.04:0.14	0.307	1.000	58
XL-VLDL-PL	0.04	-0.05:0.13	0.358	1.000	56
XL-VLDL-C	0.05	-0.03:0.14	0.235	1.000	57
XL-VLDL-CE	0.06	-0.03:0.14	0.170	1.000	53
XL-VLDL-FC	0.05	-0.03:0.14	0.232	1.000	56
XL-VLDL-TG	0.04	-0.05:0.13	0.336	1.000	58
L-VLDL-P	0.05	-0.05:0.14	0.340	1.000	61
L-VLDL-L	0.06	-0.04:0.15	0.254	1.000	65
L-VLDL-PL	0.04	-0.05:0.14	0.354	1.000	61
L-VLDL-C	0.06	-0.04:0.16	0.258	1.000	65
L-VLDL-CE	0.07	-0.03:0.17	0.156	1.000	68
L-VLDL-FC	0.04	-0.05:0.14	0.358	1.000	62
L-VLDL-TG	0.05	-0.05:0.15	0.301	1.000	63
M-VLDL-P	0.07	-0.03:0.18	0.177	1.000	69
M-VLDL-L	0.08	-0.03:0.18	0.149	1.000	70
M-VLDL-PL	0.07	-0.03:0.18	0.167	1.000	70
M-VLDL-C	0.08	-0.02:0.18	0.138	1.000	68
M-VLDL-CE	0.08	-0.02:0.17	0.127	1.000	66
M-VLDL-FC	0.06	-0.04:0.17	0.226	1.000	69
M-VLDL-TG	0.07	-0.03:0.17	0.183	1.000	69
S-VLDL-P	0.09	-0.01:0.19	0.095	1.000	67
S-VLDL-L	0.09	-0.01:0.20	0.085	1.000	70
S-VLDL-PL	0.09	-0.01:0.18	0.075	1.000	63
S-VLDL-C	0.09	-0.01:0.18	0.081	1.000	63
S-VLDL-CE	0.08	-0.01:0.17	0.068	1.000	56
S-VLDL-FC	0.08	-0.03:0.18	0.144	1.000	69
S-VLDL-TG	0.08	-0.03:0.19	0.148	1.000	71
XS-VLDL-P	0.07	-0.01:0.16	0.102	1.000	57
XS-VLDL-L	0.07	-0.01:0.16	0.100	1.000	56
XS-VLDL-PL	0.05	-0.03:0.13	0.206	1.000	49
XS-VLDL-C	0.07	0.00:0.13	0.046	1.000	29
XS-VLDL-CE	0.07	0.01:0.13	0.033	1.000	21
XS-VLDL-FC	0.06	-0.01:0.13	0.071	1.000	32
XS-VLDL-TG	0.07	-0.03:0.17	0.169	1.000	66
VLDL-D	0.06	-0.04:0.15	0.222	1.000	64
VLDL-C	0.09	-0.01:0.19	0.094	1.000	66
VLDL-TG	0.07	-0.03:0.18	0.173	1.000	71
IDL-P	0.04	-0.04:0.11	0.314	1.000	38

Table S4. Continued.

Metabolite abbreviation	B	CI	Unadjusted P-value	P-value	I^2 (%)
IDL-L	0.04	-0.04:0.11	0.331	1.000	36
IDL-PL	0.02	-0.04:0.09	0.476	1.000	22
IDL-C	0.03	-0.03:0.09	0.367	1.000	23
IDL-CE	0.03	-0.03:0.10	0.321	1.000	30
IDL-FC	0.02	-0.03:0.07	0.473	1.000	4
IDL-TG	0.04	-0.06:0.13	0.452	1.000	65
L-LDL-P	0.03	-0.04:0.11	0.407	1.000	39
L-LDL-L	0.03	-0.04:0.11	0.417	1.000	40
L-LDL-PL	0.03	-0.04:0.10	0.409	1.000	34
L-LDL-C	0.03	-0.04:0.10	0.407	1.000	31
L-LDL-CE	0.03	-0.04:0.11	0.373	1.000	37
L-LDL-FC	0.02	-0.04:0.08	0.464	1.000	12
L-LDL-TG	0.01	-0.07:0.09	0.820	1.000	51
M-LDL-P	0.04	-0.04:0.12	0.366	1.000	46
M-LDL-L	0.04	-0.04:0.12	0.349	1.000	48
M-LDL-PL	0.04	-0.04:0.13	0.282	1.000	48
M-LDL-C	0.04	-0.04:0.11	0.331	1.000	40
M-LDL-CE	0.04	-0.03:0.11	0.307	1.000	38
M-LDL-FC	0.03	-0.04:0.10	0.424	1.000	35
M-LDL-TG	0.00	-0.08:0.07	0.899	1.000	43
S-LDL-P	0.03	-0.05:0.12	0.399	1.000	47
S-LDL-L	0.04	-0.05:0.12	0.383	1.000	48
S-LDL-PL	0.04	-0.04:0.12	0.365	1.000	49
S-LDL-C	0.03	-0.04:0.10	0.374	1.000	35
S-LDL-CE	0.03	-0.04:0.10	0.355	1.000	30
S-LDL-FC	0.03	-0.04:0.10	0.404	1.000	38
S-LDL-TG	0.02	-0.07:0.11	0.714	1.000	60
LDL-D	0.00	-0.07:0.06	0.900	1.000	28
LDL-C	0.03	-0.04:0.11	0.366	1.000	36
LDL-TG	0.01	-0.07:0.09	0.815	1.000	44
XL-HDL-P	-0.11	-0.17:-0.05	0.000	0.093	18
XL-HDL-L	-0.11	-0.17:-0.04	0.001	0.201	24
XL-HDL-PL	-0.13	-0.20:-0.06	0.000	0.104	35
XL-HDL-C	-0.09	-0.16:-0.03	0.007	1.000	29
XL-HDL-CE	-0.08	-0.15:-0.02	0.015	1.000	34
XL-HDL-FC	-0.10	-0.16:-0.04	0.001	0.187	19
XL-HDL-TG	-0.03	-0.09:0.04	0.436	1.000	26
L-HDL-P	-0.14	-0.22:-0.05	0.001	0.274	49
L-HDL-L	-0.14	-0.23:-0.05	0.003	0.629	56
L-HDL-PL	-0.14	-0.22:-0.05	0.003	0.577	55
L-HDL-C	-0.14	-0.22:-0.05	0.003	0.571	56
L-HDL-CE	-0.13	-0.22:-0.05	0.002	0.508	54
L-HDL-FC	-0.14	-0.23:-0.05	0.002	0.424	56
L-HDL-TG	-0.08	-0.13:-0.02	0.004	0.791	0
M-HDL-P	-0.05	-0.12:0.02	0.186	1.000	38
M-HDL-L	-0.05	-0.12:0.02	0.169	1.000	38

Table S4. Continued.

Metabolite abbreviation	B	CI	Unadjusted P-value	P-value	I^2 (%)
M-HDL-PL	-0.06	-0.13:0.01	0.099	1.000	31
M-HDL-C	-0.06	-0.13:0.02	0.164	1.000	46
M-HDL-CE	-0.06	-0.14:0.02	0.141	1.000	47
M-HDL-FC	-0.04	-0.12:0.04	0.374	1.000	49
M-HDL-TG	0.03	-0.05:0.12	0.404	1.000	54
S-HDL-P	0.00	-0.08:0.08	0.981	1.000	51
S-HDL-L	0.00	-0.08:0.07	0.903	1.000	50
S-HDL-PL	-0.03	-0.10:0.05	0.504	1.000	50
S-HDL-C	0.00	-0.07:0.06	0.894	1.000	26
S-HDL-CE	0.01	-0.04:0.07	0.686	1.000	7
S-HDL-FC	-0.06	-0.12:0.01	0.094	1.000	35
S-HDL-TG	0.06	-0.04:0.15	0.241	1.000	66
HDL-D	-0.13	-0.22:-0.05	0.002	0.390	50
HDL-C	-0.11	-0.19:-0.04	0.004	0.760	40
HDL2-C	-0.13	-0.21:-0.04	0.003	0.581	50
HDL3-C	0.01	-0.04:0.07	0.576	1.000	0
HDL-TG	0.00	-0.08:0.08	0.986	1.000	50
Serum-C	0.00	-0.05:0.06	0.954	1.000	1
Remnant-C	0.07	-0.02:0.16	0.135	1.000	59
EstC	0.00	-0.05:0.05	0.973	1.000	0
FreeC	0.01	-0.06:0.09	0.752	1.000	39
Serum-TG	0.07	-0.04:0.18	0.195	1.000	72
TotPG	-0.05	-0.11:0.02	0.145	1.000	20
PC	-0.05	-0.10:0.00	0.061	1.000	0
SM	0.01	-0.06:0.09	0.727	1.000	36
TotCho	-0.05	-0.10:0.00	0.061	1.000	0
ApoA1	-0.10	-0.16:-0.05	0.000	**0.029**	0
ApoB	0.07	-0.03:0.17	0.147	1.000	64
TotFA	0.01	-0.07:0.10	0.739	1.000	55
UnsatDeg	-0.02	-0.08:0.03	0.414	1.000	16
FAw3	-0.06	-0.11:0.00	0.039	1.000	0
FAw6	0.01	-0.06:0.08	0.716	1.000	32
PUFA	0.00	-0.07:0.06	0.921	1.000	19
MUFA	0.03	-0.09:0.14	0.653	1.000	74
SFA	0.01	-0.07:0.09	0.768	1.000	48
DHA	-0.04	-0.09:0.01	0.154	1.000	0
LA	0.02	-0.05:0.08	0.650	1.000	26
Glc	0.01	-0.06:0.07	0.797	1.000	23
Lac	0.00	-0.05:0.05	0.967	1.000	0
Pyr	0.00	-0.06:0.07	0.964	1.000	0
Cit	-0.03	-0.08:0.03	0.323	1.000	13
Ala	0.01	-0.04:0.06	0.599	1.000	0
Gln	-0.04	-0.11:0.03	0.234	1.000	0
His	0.01	-0.04:0.06	0.692	1.000	5
Ile	0.04	-0.05:0.12	0.359	1.000	47
Leu	-0.01	-0.12:0.10	0.898	1.000	68

Table S4. Continued.

Metabolite abbreviation	B	CI	Unadjusted P-value	P-value	I^2 (%)
Val	-0.02	-0.14:0.10	0.748	1.000	75
Phe	-0.04	-0.11:0.04	0.363	1.000	46
Tyr	-0.04	-0.12:0.03	0.262	1.000	46
AcAce	0.00	-0.08:0.07	0.899	1.000	43
bOHBut	-0.02	-0.06:0.03	0.534	1.000	0
Crea	0.01	-0.05:0.07	0.843	1.000	0
Alb	0.00	-0.06:0.06	0.986	1.000	29
Gp	0.07	-0.03:0.17	0.191	1.000	71
XXL-VLDL-PL_%	-0.03	-0.08:0.02	0.249	1.000	0
XXL-VLDL-C_%	0.01	-0.04:0.06	0.673	1.000	0
XXL-VLDL-CE_%	0.01	-0.04:0.06	0.629	1.000	0
XXL-VLDL-FC_%	-0.04	-0.11:0.03	0.258	1.000	42
XXL-VLDL-TG_%	0.03	-0.02:0.08	0.304	1.000	0
XL-VLDL-PL_%	0.06	0.01:0.11	0.025	1.000	0
XL-VLDL-C_%	0.06	0.01:0.11	0.020	1.000	0
XL-VLDL-CE_%	0.05	0.00:0.10	0.045	1.000	0
XL-VLDL-FC_%	0.06	0.01:0.11	0.026	1.000	0
XL-VLDL-TG_%	0.06	0.01:0.11	0.021	1.000	0
L-VLDL-PL_%	0.03	-0.02:0.08	0.192	1.000	0
L-VLDL-C_%	0.00	-0.05:0.04	0.856	1.000	0
L-VLDL-CE_%	0.02	-0.03:0.07	0.491	1.000	0
L-VLDL-FC_%	0.02	-0.03:0.07	0.342	1.000	0
L-VLDL-TG_%	0.03	-0.02:0.08	0.203	1.000	0
M-VLDL-PL_%	0.01	-0.04:0.06	0.630	1.000	4
M-VLDL-C_%	-0.03	-0.08:0.02	0.230	1.000	0
M-VLDL-CE_%	-0.03	-0.08:0.02	0.280	1.000	0
M-VLDL-FC_%	-0.02	-0.07:0.03	0.488	1.000	0
M-VLDL-TG_%	0.03	-0.02:0.08	0.284	1.000	0
S-VLDL-PL_%	-0.04	-0.12:0.05	0.386	1.000	53
S-VLDL-C_%	-0.04	-0.11:0.04	0.344	1.000	43
S-VLDL-CE_%	-0.03	-0.10:0.05	0.484	1.000	47
S-VLDL-FC_%	-0.07	-0.12:-0.02	0.007	1.000	0
S-VLDL-TG_%	0.06	-0.03:0.14	0.189	1.000	57
XS-VLDL-PL_%	-0.02	-0.07:0.03	0.482	1.000	0
XS-VLDL-C_%	-0.01	-0.12:0.09	0.777	1.000	71
XS-VLDL-CE_%	-0.02	-0.11:0.07	0.710	1.000	64
XS-VLDL-FC_%	0.00	-0.07:0.06	0.885	1.000	28
XS-VLDL-TG_%	0.03	-0.06:0.12	0.529	1.000	63
IDL-PL_%	-0.05	-0.16:0.06	0.384	1.000	71
IDL-C_%	0.01	-0.04:0.06	0.611	1.000	0
IDL-CE_%	0.02	-0.03:0.07	0.402	1.000	0
IDL-FC_%	0.00	-0.07:0.06	0.951	1.000	24
IDL-TG_%	0.00	-0.08:0.07	0.895	1.000	46
L-LDL-PL_%	-0.03	-0.11:0.05	0.494	1.000	48
L-LDL-C_%	0.02	-0.03:0.07	0.362	1.000	0
L-LDL-CE_%	0.04	-0.03:0.10	0.271	1.000	22

Table S4. Continued.

Metabolite abbreviation	B	CI	Unadjusted P-value	P-value	I^2 (%)
L-LDL-FC_%	-0.04	-0.15:0.07	0.497	1.000	71
L-LDL-TG_%	-0.02	-0.07:0.03	0.367	1.000	0
M-LDL-PL_%	-0.03	-0.10:0.04	0.415	1.000	29
M-LDL-C_%	0.03	-0.02:0.08	0.270	1.000	0
M-LDL-CE_%	0.04	-0.03:0.10	0.245	1.000	25
M-LDL-FC_%	-0.05	-0.14:0.03	0.225	1.000	51
M-LDL-TG_%	-0.02	-0.07:0.03	0.454	1.000	0
S-LDL-PL_%	-0.04	-0.10:0.02	0.230	1.000	22
S-LDL-C_%	0.04	-0.01:0.09	0.148	1.000	0
S-LDL-CE_%	0.03	-0.02:0.09	0.226	1.000	0
S-LDL-FC_%	-0.03	-0.11:0.05	0.437	1.000	41
S-LDL-TG_%	0.00	-0.07:0.08	0.920	1.000	40
XL-HDL-PL_%	-0.05	-0.11:0.00	0.061	1.000	0
XL-HDL-C_%	0.10	0.02:0.18	0.018	1.000	43
XL-HDL-CE_%	0.07	-0.01:0.15	0.073	1.000	26
XL-HDL-FC_%	0.01	-0.04:0.06	0.728	1.000	0
XL-HDL-TG_%	0.07	-0.03:0.18	0.170	1.000	70
L-HDL-PL_%	0.00	-0.05:0.05	0.926	1.000	0
L-HDL-C_%	-0.03	-0.08:0.02	0.307	1.000	0
L-HDL-CE_%	-0.02	-0.07:0.03	0.472	1.000	0
L-HDL-FC_%	-0.04	-0.12:0.03	0.249	1.000	41
L-HDL-TG_%	0.03	-0.03:0.09	0.347	1.000	23
M-HDL-PL_%	0.00	-0.05:0.05	0.946	1.000	4
M-HDL-C_%	-0.04	-0.10:0.03	0.285	1.000	33
M-HDL-CE_%	-0.04	-0.12:0.04	0.349	1.000	51
M-HDL-FC_%	-0.02	-0.09:0.06	0.631	1.000	41
M-HDL-TG_%	0.08	-0.02:0.17	0.105	1.000	62
S-HDL-PL_%	-0.04	-0.11:0.03	0.291	1.000	40
S-HDL-C_%	0.01	-0.05:0.07	0.814	1.000	16
S-HDL-CE_%	0.02	-0.04:0.08	0.454	1.000	9
S-HDL-FC_%	-0.10	-0.15:-0.05	0.000	**0.029**	0
S-HDL-TG_%	0.09	-0.01:0.19	0.090	1.000	68
TG/PG	0.08	-0.01:0.18	0.077	1.000	60
DHA/FA	-0.06	-0.12:0.00	0.037	1.000	13
LA/FA	0.02	-0.08:0.11	0.749	1.000	66
FAw3/FA	-0.11	-0.2:-0.02	0.017	1.000	60
FAw6/FA	0.00	-0.08:0.09	0.965	1.000	56
PUFA/FA	-0.02	-0.11:0.07	0.606	1.000	62
MUFA/FA	0.03	-0.07:0.14	0.531	1.000	73
SFA/FA	-0.02	-0.09:0.05	0.659	1.000	40
ApoB/ApoA1	0.12	0.01:0.23	0.029	1.000	72

B=Beta coefficient, CI=Confidence interval, I^2=measure of heterogeneity, P-value=Bonferroni-Holm corrected p-value. All metabolite abbreviations can be found in tables S1 and S2.

Table S5. Results logistic regressions with metabolite concentrations, lipid lowering medication usage, body mass index, sex, and age as independent variables and migraine status as dependent variable for males and females.

Metabolite abbreviation	Males					Females				
	B	CI	Unadjusted P-value	P-value	I^2 (%)	B	CI	Unadjusted P-value	P-value	I^2 (%)
XXL-VLDL-P	0.00	-0.10:0.09	0.981	1.000	0	0.05	-0.02:0.13	0.128	1.000	1
XXL-VLDL-L	0.00	-0.10:0.09	0.978	1.000	0	0.06	-0.02:0.13	0.123	1.000	3
XXL-VLDL-PL	-0.02	-0.11:0.08	0.710	1.000	0	0.05	-0.03:0.12	0.203	1.000	4
XXL-VLDL-C	-0.01	-0.11:0.09	0.814	1.000	0	0.05	-0.02:0.12	0.141	1.000	1
XXL-VLDL-CE	-0.02	-0.11:0.08	0.734	1.000	0	0.06	-0.01:0.13	0.093	1.000	3
XXL-VLDL-FC	0.00	-0.09:0.10	0.987	1.000	0	0.05	-0.03:0.13	0.204	1.000	14
XXL-VLDL-TG	0.00	-0.10:0.09	0.979	1.000	0	0.06	-0.02:0.13	0.142	1.000	7
XL-VLDL-P	-0.03	-0.12:0.07	0.603	1.000	0	0.06	-0.02:0.15	0.129	1.000	16
XL-VLDL-L	-0.02	-0.12:0.08	0.663	1.000	0	0.07	-0.02:0.15	0.110	1.000	18
XL-VLDL-PL	-0.02	-0.12:0.07	0.651	1.000	0	0.06	-0.02:0.13	0.145	1.000	8
XL-VLDL-C	-0.01	-0.11:0.09	0.871	1.000	0	0.06	-0.02:0.13	0.126	1.000	10
XL-VLDL-CE	0.00	-0.10:0.09	0.922	1.000	0	0.07	-0.01:0.14	0.096	1.000	12
XL-VLDL-FC	-0.01	-0.11:0.08	0.778	1.000	0	0.06	-0.01:0.12	0.113	1.000	0
XL-VLDL-TG	-0.02	-0.12:0.07	0.626	1.000	0	0.07	-0.02:0.15	0.118	1.000	20
L-VLDL-P	-0.02	-0.12:0.08	0.645	1.000	0	0.07	-0.01:0.15	0.086	1.000	18
L-VLDL-L	-0.01	-0.11:0.09	0.904	1.000	0	0.08	-0.01:0.16	0.071	1.000	22
L-VLDL-PL	-0.03	-0.13:0.07	0.517	1.000	0	0.08	-0.01:0.16	0.081	1.000	25
L-VLDL-C	-0.01	-0.11:0.09	0.842	1.000	0	0.07	-0.01:0.15	0.099	1.000	22
L-VLDL-CE	0.01	-0.09:0.11	0.890	1.000	4	0.08	0.00:0.17	0.063	1.000	29
L-VLDL-FC	-0.02	-0.12:0.08	0.656	1.000	0	0.06	-0.02:0.14	0.134	1.000	18
L-VLDL-TG	-0.01	-0.11:0.09	0.788	1.000	0	0.07	-0.01:0.15	0.077	1.000	18
M-VLDL-P	0.01	-0.09:0.11	0.836	1.000	2	0.09	0.01:0.17	0.038	1.000	21
M-VLDL-L	0.01	-0.09:0.12	0.776	1.000	0	0.09	0.01:0.17	0.029	1.000	22
M-VLDL-PL	0.01	-0.09:0.11	0.827	1.000	0	0.09	0.01:0.17	0.031	1.000	20
M-VLDL-C	-0.01	-0.12:0.09	0.779	1.000	0	0.09	0.01:0.17	0.026	1.000	20
M-VLDL-CE	-0.03	-0.13:0.08	0.628	1.000	0	0.09	0.01:0.16	0.019	1.000	9
M-VLDL-FC	-0.01	-0.11:0.10	0.922	1.000	0	0.08	0.00:0.16	0.043	1.000	20
M-VLDL-TG	0.02	-0.09:0.13	0.749	1.000	8	0.09	0.00:0.17	0.049	1.000	27
S-VLDL-P	-0.01	-0.11:0.10	0.920	1.000	0	0.09	0.03:0.16	0.005	0.975	0
S-VLDL-L	0.00	-0.10:0.11	0.933	1.000	0	0.10	0.03:0.16	0.003	0.659	0
S-VLDL-PL	-0.01	-0.12:0.10	0.847	1.000	0	0.09	0.02:0.15	0.007	1.000	0
S-VLDL-C	-0.01	-0.12:0.10	0.825	1.000	0	0.09	0.03:0.16	0.004	0.725	0
S-VLDL-CE	-0.02	-0.13:0.10	0.783	1.000	0	0.09	0.03:0.16	0.004	0.799	0
S-VLDL-FC	-0.01	-0.12:0.10	0.853	1.000	0	0.08	0.02:0.15	0.009	1.000	0
S-VLDL-TG	0.02	-0.09:0.12	0.780	1.000	2	0.10	0.02:0.18	0.014	1.000	22
XS-VLDL-P	-0.03	-0.14:0.09	0.676	1.000	0	0.10	0.03:0.16	0.002	0.506	0
XS-VLDL-L	-0.01	-0.13:0.10	0.810	1.000	0	0.09	0.03:0.16	0.003	0.639	0
XS-VLDL-PL	-0.04	-0.15:0.08	0.518	1.000	0	0.08	0.01:0.14	0.016	1.000	0
XS-VLDL-C	0.00	-0.12:0.11	0.948	1.000	0	0.09	0.03:0.16	0.003	0.654	0
XS-VLDL-CE	-0.01	-0.12:0.11	0.879	1.000	0	0.09	0.03:0.15	0.005	0.978	0
XS-VLDL-FC	0.00	-0.11:0.11	0.991	1.000	0	0.09	0.03:0.16	0.003	0.614	0
XS-VLDL-TG	-0.01	-0.12:0.10	0.866	1.000	0	0.08	0.02:0.14	0.012	1.000	0
VLDL-D	0.05	-0.08:0.17	0.484	1.000	20	0.06	-0.03:0.14	0.191	1.000	29
VLDL-C	-0.01	-0.12:0.10	0.826	1.000	0	0.09	0.03:0.16	0.006	1.000	0

Table S5. Continued.

Metabolite abbreviation	Males					Females				
	B	CI	Unadjusted P-value	P-value	I^2 (%)	B	CI	Unadjusted P-value	P-value	I^2 (%)
VLDL-TG	0.02	-0.09:0.13	0.710	1.000	7	0.09	0.01:0.18	0.032	1.000	27
IDL-P	-0.05	-0.16:0.07	0.438	1.000	0	0.07	0.01:0.13	0.023	1.000	0
IDL-L	-0.04	-0.15:0.07	0.492	1.000	0	0.07	0.01:0.14	0.026	1.000	0
IDL-PL	-0.05	-0.16:0.06	0.392	1.000	0	0.06	0.00:0.13	0.046	1.000	0
IDL-C	-0.04	-0.15:0.07	0.473	1.000	0	0.07	0.00:0.13	0.037	1.000	0
IDL-CE	-0.04	-0.16:0.07	0.468	1.000	0	0.07	0.00:0.13	0.036	1.000	0
IDL-FC	-0.04	-0.15:0.07	0.518	1.000	0	0.07	0.00:0.13	0.045	1.000	0
IDL-TG	-0.05	-0.17:0.07	0.408	1.000	0	0.06	0.01:0.12	0.030	1.000	0
L-LDL-P	-0.06	-0.17:0.06	0.348	1.000	0	0.07	0.01:0.13	0.030	1.000	0
L-LDL-L	-0.05	-0.16:0.07	0.412	1.000	0	0.07	0.01:0.14	0.030	1.000	0
L-LDL-PL	-0.05	-0.17:0.06	0.365	1.000	0	0.07	0.00:0.13	0.037	1.000	0
L-LDL-C	-0.04	-0.15:0.07	0.461	1.000	0	0.07	0.01:0.13	0.033	1.000	0
L-LDL-CE	-0.04	-0.16:0.07	0.461	1.000	0	0.07	0.01:0.13	0.031	1.000	0
L-LDL-FC	-0.05	-0.16:0.07	0.422	1.000	0	0.07	0.00:0.13	0.035	1.000	0
L-LDL-TG	-0.08	-0.02:0.05	0.226	1.000	0	0.04	-0.02:0.1	0.145	1.000	0
M-LDL-P	-0.04	-0.16:0.07	0.468	1.000	0	0.07	0.01:0.14	0.025	1.000	0
M-LDL-L	-0.03	-0.14:0.08	0.585	1.000	0	0.08	0.01:0.14	0.022	1.000	0
M-LDL-PL	-0.03	-0.14:0.07	0.556	1.000	0	0.07	0.01:0.14	0.034	1.000	0
M-LDL-C	-0.03	-0.14:0.08	0.612	1.000	0	0.08	0.01:0.14	0.020	1.000	0
M-LDL-CE	-0.03	-0.15:0.08	0.568	1.000	0	0.08	0.01:0.14	0.018	1.000	0
M-LDL-FC	-0.05	-0.16:0.06	0.375	1.000	0	0.07	0.01:0.14	0.024	1.000	0
M-LDL-TG	-0.09	-0.22:0.04	0.167	1.000	0	0.03	-0.03:0.09	0.280	1.000	0
S-LDL-P	-0.04	-0.16:0.07	0.467	1.000	0	0.07	0.01:0.13	0.034	1.000	0
S-LDL-L	-0.03	-0.14:0.08	0.581	1.000	0	0.07	0.01:0.14	0.030	1.000	0
S-LDL-PL	-0.04	-0.16:0.07	0.453	1.000	0	0.06	-0.01:0.12	0.089	1.000	0
S-LDL-C	-0.03	-0.14:0.08	0.607	1.000	0	0.07	0.01:0.14	0.025	1.000	0
S-LDL-CE	-0.04	-0.15:0.07	0.487	1.000	0	0.08	0.01:0.14	0.020	1.000	0
S-LDL-FC	-0.01	-0.12:0.10	0.867	1.000	0	0.06	0.00:0.13	0.051	1.000	0
S-LDL-TG	-0.06	-0.18:0.05	0.296	1.000	0	0.04	-0.02:0.10	0.250	1.000	0
LDL-D	0.03	-0.07:0.13	0.603	1.000	0	-0.04	-0.10:0.02	0.233	1.000	0
LDL-C	-0.03	-0.14:0.08	0.544	1.000	0	0.07	0.01:0.14	0.026	1.000	0
LDL-TG	-0.08	-0.21:0.04	0.195	1.000	0	0.04	-0.02:0.10	0.200	1.000	0
XL-HDL-P	-0.19	-0.35:-0.03	0.019	1.000	16	-0.08	-0.14:-0.02	0.011	1.000	0
XL-HDL-L	-0.16	-0.31:-0.01	0.034	1.000	19	-0.08	-0.14:-0.02	0.013	1.000	0
XL-HDL-PL	-0.23	-0.38:-0.09	0.002	0.350	0	-0.10	-0.16:-0.03	0.003	0.577	0
XL-HDL-C	-0.11	-0.23:0.02	0.098	1.000	6	-0.06	-0.13:0.00	0.065	1.000	8
XL-HDL-CE	-0.08	-0.19:0.04	0.188	1.000	1	-0.06	-0.13:0.01	0.080	1.000	14
XL-HDL-FC	-0.17	-0.32:-0.02	0.030	1.000	18	-0.07	-0.13:-0.01	0.026	1.000	0
XL-HDL-TG	-0.02	-0.12:0.08	0.643	1.000	0	-0.01	-0.08:0.06	0.828	1.000	13
L-HDL-P	-0.20	-0.34:-0.07	0.004	0.841	0	-0.13	-0.19:-0.06	0.000	**0.023**	0
L-HDL-L	-0.17	-0.30:-0.04	0.010	1.000	2	-0.13	-0.20:-0.06	0.000	**0.025**	0
L-HDL-PL	-0.20	-0.33:-0.07	0.003	0.645	1	-0.13	-0.19:-0.06	0.000	**0.025**	0
L-HDL-C	-0.15	-0.28:-0.03	0.019	1.000	0	-0.13	-0.20:-0.07	0.000	**0.020**	0
L-HDL-CE	-0.15	-0.28:-0.03	0.018	1.000	0	-0.13	-0.20:-0.07	0.000	**0.020**	0
L-HDL-FC	-0.19	-0.35:-0.04	0.017	1.000	17	-0.13	-0.19:-0.06	0.000	**0.021**	0

Table S5. Continued.

Metabolite abbreviation	Males					Females				
	B	CI	Unadjusted P-value	P-value	I^2 (%)	B	CI	Unadjusted P-value	P-value	I^2 (%)
L-HDL-TG	-0.17	-0.30:-0.03	0.016	1.000	0	-0.05	-0.11:0.01	0.090	1.000	0
M-HDL-P	-0.15	-0.26:-0.03	0.012	1.000	0	-0.08	-0.14:-0.02	0.011	1.000	0
M-HDL-L	-0.13	-0.24:-0.02	0.021	1.000	0	-0.08	-0.14:-0.02	0.011	1.000	0
M-HDL-PL	-0.13	-0.24:-0.02	0.024	1.000	0	-0.08	-0.14:-0.02	0.009	1.000	0
M-HDL-C	-0.13	-0.24:-0.02	0.025	1.000	0	-0.09	-0.15:-0.03	0.006	1.000	0
M-HDL-CE	-0.12	-0.23:-0.02	0.025	1.000	0	-0.09	-0.16:-0.03	0.003	0.536	0
M-HDL-FC	-0.13	-0.25:-0.01	0.040	1.000	0	-0.05	-0.13:0.04	0.285	1.000	38
M-HDL-TG	-0.09	-0.20:0.02	0.093	1.000	0	0.03	-0.04:0.10	0.431	1.000	13
S-HDL-P	-0.07	-0.23:0.08	0.347	1.000	26	-0.03	-0.08:0.03	0.377	1.000	5
S-HDL-L	-0.08	-0.23:0.07	0.315	1.000	27	-0.03	-0.09:0.03	0.366	1.000	7
S-HDL-PL	-0.05	-0.17:0.06	0.366	1.000	2	-0.06	-0.13:0.01	0.073	1.000	21
S-HDL-C	-0.09	-0.20:0.02	0.096	1.000	0	0.02	-0.05:0.08	0.605	1.000	0
S-HDL-CE	-0.09	-0.19:0.02	0.112	1.000	0	0.05	-0.02:0.11	0.137	1.000	0
S-HDL-FC	-0.03	-0.19:0.13	0.694	1.000	39	-0.07	-0.13:-0.01	0.029	1.000	12
S-HDL-TG	0.01	-0.10:0.13	0.803	1.000	5	0.05	-0.01:0.12	0.079	1.000	0
HDL-D	-0.18	-0.32:-0.05	0.006	1.000	4	-0.11	-0.18:-0.04	0.001	0.295	0
HDL-C	-0.18	-0.31:-0.06	0.003	0.733	0	-0.10	-0.17:-0.04	0.002	0.390	0
HDL2-C	-0.19	-0.31:-0.06	0.003	0.723	0	-0.12	-0.18:-0.05	0.000	0.068	0
HDL3-C	-0.04	-0.15:0.06	0.428	1.000	0	0.04	-0.03:0.10	0.277	1.000	0
HDL-TG	-0.09	-0.20:0.02	0.123	1.000	0	0.01	-0.05:0.07	0.793	1.000	0
Serum-C	-0.08	-0.20:0.03	0.141	1.000	0	0.04	-0.02:0.11	0.201	1.000	0
Remnant-C	-0.02	-0.14:0.09	0.661	1.000	0	0.09	0.02:0.15	0.009	1.000	0
EstC	-0.08	-0.20:0.03	0.140	1.000	0	0.03	-0.03:0.10	0.328	1.000	0
FreeC	-0.07	-0.19:0.04	0.215	1.000	0	0.06	0.00:0.13	0.065	1.000	0
Serum-TG	0.01	-0.10:0.11	0.903	1.000	1	0.09	0.01:0.17	0.025	1.000	22
TotPG	-0.19	-0.30:-0.07	0.002	0.532	0	-0.02	-0.08:0.04	0.463	1.000	0
PC	-0.20	-0.33:-0.08	0.002	0.367	0	-0.01	-0.07:0.05	0.724	1.000	0
SM	-0.07	-0.19:0.06	0.280	1.000	0	0.05	-0.01:0.12	0.125	1.000	3
TotCho	-0.19	-0.31:-0.07	0.002	0.521	0	-0.01	-0.08:0.05	0.660	1.000	0
ApoA1	-0.25	-0.38:-0.12	0.000	**0.035**	0	-0.08	-0.14:-0.02	0.011	1.000	0
ApoB	-0.03	-0.14:0.08	0.633	1.000	0	0.09	0.03:0.15	0.006	1.000	0
TotFA	-0.11	-0.22:0.00	0.048	1.000	0	0.03	-0.03:0.09	0.365	1.000	0
UnsatDeg	-0.11	-0.22:-0.01	0.030	1.000	0	-0.02	-0.09:0.06	0.697	1.000	27
FAw3	-0.24	-0.36:-0.12	0.000	**0.033**	0	0.01	-0.07:0.09	0.866	1.000	28
FAw6	-0.12	-0.22:-0.01	0.039	1.000	0	0.04	-0.03:0.10	0.259	1.000	0
PUFA	-0.13	-0.24:-0.02	0.017	1.000	0	0.03	-0.03:0.09	0.342	1.000	0
MUFA	-0.05	-0.18:0.07	0.411	1.000	19	0.06	-0.04:0.16	0.244	1.000	47
SFA	-0.10	-0.21:0.01	0.069	1.000	0	0.02	-0.04:0.09	0.456	1.000	0
DHA	-0.23	-0.36:-0.1	0.000	0.109	0	0.03	-0.05:0.11	0.472	1.000	32
LA	-0.09	-0.20:0.02	0.098	1.000	0	0.03	-0.03:0.10	0.282	1.000	0
Glc	0.02	-0.15:0.18	0.843	1.000	43	0.01	-0.06:0.08	0.802	1.000	0
Lac	-0.01	-0.14:0.11	0.847	1.000	23	0.01	-0.05:0.07	0.783	1.000	0
Pyr	-0.04	-0.18:0.11	0.624	1.000	0	0.08	-0.01:0.17	0.073	1.000	19
Cit	-0.06	-0.20:0.07	0.357	1.000	26	0.03	-0.05:0.11	0.479	1.000	38
Ala	0.04	-0.11:0.18	0.630	1.000	37	-0.02	-0.08:0.04	0.527	1.000	1
Gln	0.05	-0.12:0.21	0.578	1.000	9	-0.06	-0.14:0.03	0.178	1.000	2

Table S5. Continued.

Metabolite abbreviation	Males					Females				
	B	CI	Unadjusted P-value	P-value	I^2 (%)	B	CI	Unadjusted P-value	P-value	I^2 (%)
His	-0.03	-0.15:0.10	0.648	1.000	18	0.01	-0.05:0.07	0.804	1.000	4
Ile	-0.02	-0.20:0.16	0.809	1.000	46	0.02	-0.13:0.17	0.777	1.000	66
Leu	-0.01	-0.25:0.23	0.936	1.000	67	-0.04	-0.21:0.13	0.633	1.000	75
Val	-0.04	-0.25:0.17	0.714	1.000	62	-0.01	-0.12:0.11	0.916	1.000	60
Phe	-0.03	-0.13:0.08	0.636	1.000	0	-0.03	-0.14:0.08	0.591	1.000	55
Tyr	-0.13	-0.25:0.00	0.043	1.000	0	-0.04	-0.14:0.05	0.370	1.000	43
AcAce	-0.11	-0.22:-0.01	0.030	1.000	0	0.07	-0.02:0.15	0.137	1.000	42
bOHBut	-0.14	-0.26:-0.02	0.018	1.000	0	0.03	-0.02:0.09	0.267	1.000	0
Crea	0.05	-0.07:0.17	0.415	1.000	0	-0.01	-0.09:0.06	0.754	1.000	0
Alb	0.05	-0.06:0.16	0.375	1.000	0	-0.04	-0.10:0.02	0.210	1.000	0
Gp	-0.03	-0.17:0.12	0.707	1.000	31	0.07	-0.04:0.18	0.194	1.000	55
XXL-VLDL-PL_%	0.03	-0.11:0.18	0.643	1.000	0	-0.02	-0.08:0.03	0.394	1.000	0
XXL-VLDL-C_%	-0.02	-0.15:0.11	0.766	1.000	0	0.03	-0.03:0.08	0.379	1.000	0
XXL-VLDL-CE_%	-0.01	-0.13:0.11	0.865	1.000	0	0.03	-0.03:0.09	0.309	1.000	0
XXL-VLDL-FC_%	-0.04	-0.15:0.08	0.531	1.000	0	-0.02	-0.08:0.04	0.565	1.000	12
XXL-VLDL-TG_%	0.00	-0.13:0.14	0.957	1.000	0	0.04	-0.03:0.11	0.300	1.000	26
XL-VLDL-PL_%	-0.02	-0.15:0.11	0.787	1.000	13	0.03	-0.03:0.09	0.279	1.000	0
XL-VLDL-C_%	0.03	-0.12:0.18	0.654	1.000	18	0.02	-0.05:0.08	0.592	1.000	19
XL-VLDL-CE_%	0.05	-0.09:0.20	0.479	1.000	20	0.01	-0.06:0.08	0.744	1.000	20
XL-VLDL-FC_%	-0.03	-0.14:0.08	0.617	1.000	0	0.03	-0.05:0.10	0.458	1.000	33
XL-VLDL-TG_%	0.05	-0.11:0.21	0.524	1.000	0	0.02	-0.03:0.07	0.487	1.000	0
L-VLDL-PL_%	0.01	-0.11:0.12	0.923	1.000	0	0.03	-0.03:0.09	0.328	1.000	0
L-VLDL-C_%	-0.03	-0.14:0.08	0.582	1.000	0	-0.01	-0.06:0.05	0.836	1.000	0
L-VLDL-CE_%	0.03	-0.09:0.15	0.598	1.000	0	0.02	-0.04:0.07	0.586	1.000	0
L-VLDL-FC_%	0.02	-0.10:0.15	0.691	1.000	5	0.02	-0.04:0.08	0.544	1.000	0
L-VLDL-TG_%	0.03	-0.09:0.15	0.641	1.000	0	0.00	-0.05:0.06	0.863	1.000	0
M-VLDL-PL_%	0.12	0.00:0.24	0.060	1.000	0	0.00	-0.05:0.06	0.927	1.000	0
M-VLDL-C_%	-0.10	-0.21:0.02	0.113	1.000	0	-0.01	-0.07:0.05	0.779	1.000	0
M-VLDL-CE_%	-0.08	-0.20:0.03	0.168	1.000	0	-0.02	-0.08:0.04	0.526	1.000	0
M-VLDL-FC_%	-0.05	-0.17:0.07	0.394	1.000	0	0.01	-0.05:0.06	0.764	1.000	0
M-VLDL-TG_%	0.08	-0.06:0.21	0.265	1.000	0	0.01	-0.05:0.07	0.744	1.000	0
S-VLDL-PL_%	-0.03	-0.15:0.08	0.598	1.000	0	-0.06	-0.11:0.00	0.065	1.000	0
S-VLDL-C_%	-0.03	-0.14:0.08	0.582	1.000	0	-0.03	-0.11:0.04	0.403	1.000	23
S-VLDL-CE_%	-0.03	-0.14:0.08	0.579	1.000	0	-0.03	-0.11:0.05	0.453	1.000	32
S-VLDL-FC_%	-0.04	-0.16:0.09	0.553	1.000	7	-0.05	-0.11:0.01	0.113	1.000	0
S-VLDL-TG_%	0.06	-0.06:0.19	0.327	1.000	12	0.06	-0.02:0.15	0.161	1.000	37
XS-VLDL-PL_%	-0.05	-0.15:0.05	0.351	1.000	0	0.01	-0.06:0.08	0.833	1.000	6
XS-VLDL-C_%	0.00	-0.14:0.13	0.962	1.000	27	-0.05	-0.14:0.04	0.254	1.000	41
XS-VLDL-CE_%	0.02	-0.10:0.13	0.772	1.000	0	-0.06	-0.14:0.02	0.161	1.000	34
XS-VLDL-FC_%	-0.02	-0.15:0.11	0.757	1.000	33	-0.01	-0.07:0.06	0.804	1.000	0
XS-VLDL-TG_%	0.04	-0.08:0.16	0.562	1.000	12	0.05	-0.03:0.13	0.235	1.000	33
IDL-PL_%	-0.05	-0.14:0.05	0.336	1.000	0	-0.08	-0.17:0.02	0.121	1.000	40
IDL-C_%	-0.01	-0.13:0.10	0.820	1.000	0	-0.01	-0.06:0.05	0.854	1.000	0
IDL-CE_%	0.02	-0.11:0.15	0.757	1.000	12	-0.01	-0.07:0.05	0.752	1.000	0
IDL-FC_%	0.01	-0.09:0.10	0.910	1.000	0	0.01	-0.06:0.08	0.734	1.000	0
IDL-TG_%	0.00	-0.13:0.13	0.958	1.000	24	0.02	-0.05:0.08	0.617	1.000	3

Table S5. Continued.

Metabolite abbreviation	Males					Females				
	B	CI	Unadjusted P-value	P-value	I^2 (%)	B	CI	Unadjusted P-value	P-value	I^2 (%)
L-LDL-PL_%	0.02	-0.09:0.12	0.752	1.000	0	-0.07	-0.14:-0.01	0.030	1.000	0
L-LDL-C_%	0.00	-0.10:0.10	0.950	1.000	0	0.04	-0.03:0.10	0.253	1.000	0
L-LDL-CE_%	-0.01	-0.11:0.09	0.867	1.000	0	0.06	-0.01:0.12	0.092	1.000	0
L-LDL-FC_%	0.01	-0.11:0.13	0.863	1.000	13	-0.04	-0.11:0.02	0.182	1.000	0
L-LDL-TG_%	-0.02	-0.12:0.09	0.767	1.000	0	0.00	-0.06:0.06	0.950	1.000	0
M-LDL-PL_%	0.01	-0.09:0.12	0.835	1.000	0	-0.08	-0.15:-0.01	0.017	1.000	1
M-LDL-C_%	0.01	-0.09:0.11	0.814	1.000	0	0.05	-0.01:0.11	0.133	1.000	0
M-LDL-CE_%	0.04	-0.06:0.13	0.445	1.000	0	0.06	-0.01:0.13	0.094	1.000	1
M-LDL-FC_%	0.04	-0.07:0.14	0.520	1.000	0	-0.09	-0.15:-0.02	0.016	1.000	6
M-LDL-TG_%	-0.01	-0.10:0.09	0.878	1.000	0	0.00	-0.07:0.06	0.881	1.000	0
S-LDL-PL_%	0.01	-0.09:0.12	0.810	1.000	0	-0.09	-0.15:-0.02	0.008	1.000	0
S-LDL-C_%	0.01	-0.08:0.11	0.778	1.000	0	0.06	-0.01:0.12	0.083	1.000	0
S-LDL-CE_%	0.03	-0.07:0.12	0.557	1.000	0	0.06	-0.01:0.13	0.107	1.000	0
S-LDL-FC_%	0.08	-0.03:0.19	0.149	1.000	0	-0.07	-0.14:-0.01	0.034	1.000	0
S-LDL-TG_%	-0.01	-0.11:0.09	0.851	1.000	0	0.02	-0.04:0.08	0.571	1.000	0
XL-HDL-PL_%	-0.05	-0.14:0.04	0.298	1.000	11	-0.05	-0.13:0.04	0.280	1.000	0
XL-HDL-C_%	0.15	0.02:0.28	0.026	1.000	31	0.10	0.02:0.17	0.010	1.000	0
XL-HDL-CE_%	0.17	0.00:0.34	0.044	1.000	45	0.06	-0.01:0.14	0.095	1.000	0
XL-HDL-FC_%	-0.02	-0.11:0.07	0.700	1.000	0	0.02	-0.04:0.09	0.515	1.000	0
XL-HDL-TG_%	0.05	-0.04:0.14	0.247	1.000	0	0.10	0.00:0.20	0.049	1.000	39
L-HDL-PL_%	-0.06	-0.15:0.02	0.128	1.000	0	0.00	-0.07:0.07	0.997	1.000	0
L-HDL-C_%	0.05	-0.05:0.14	0.330	1.000	0	-0.04	-0.11:0.03	0.242	1.000	0
L-HDL-CE_%	0.05	-0.04:0.14	0.235	1.000	0	-0.03	-0.10:0.04	0.413	1.000	0
L-HDL-FC_%	-0.01	-0.10:0.08	0.764	1.000	0	-0.06	-0.13:0.02	0.134	1.000	0
L-HDL-TG_%	-0.01	-0.09:0.08	0.834	1.000	0	0.06	-0.01:0.13	0.070	1.000	0
M-HDL-PL_%	0.00	-0.11:0.11	0.948	1.000	8	0.01	-0.06:0.08	0.866	1.000	17
M-HDL-C_%	-0.02	-0.12:0.08	0.701	1.000	0	-0.04	-0.11:0.02	0.175	1.000	0
M-HDL-CE_%	-0.01	-0.11:0.10	0.923	1.000	0	-0.05	-0.11:0.01	0.105	1.000	0
M-HDL-FC_%	-0.02	-0.11:0.08	0.708	1.000	0	0.01	-0.12:0.13	0.900	1.000	61
M-HDL-TG_%	0.01	-0.09:0.11	0.841	1.000	0	0.08	0.01:0.14	0.020	1.000	0
S-HDL-PL_%	0.03	-0.08:0.14	0.595	1.000	0	-0.09	-0.15:-0.03	0.006	1.000	1
S-HDL-C_%	-0.04	-0.14:0.06	0.452	1.000	0	0.06	-0.01:0.12	0.080	1.000	0
S-HDL-CE_%	-0.04	-0.13:0.06	0.460	1.000	0	0.07	0.00:0.15	0.045	1.000	9
S-HDL-FC_%	0.03	-0.08:0.14	0.629	1.000	0	-0.11	-0.16:-0.05	0.000	0.093	0
S-HDL-TG_%	0.07	-0.04:0.17	0.215	1.000	0	0.09	0.03:0.15	0.006	1.000	0
TG/PG	0.09	-0.01:0.19	0.093	1.000	0	0.10	0.03:0.17	0.005	0.940	1
DHA/FA	-0.17	-0.30:-0.03	0.019	1.000	23	0.00	-0.07:0.07	0.985	1.000	23
LA/FA	0.02	-0.08:0.13	0.673	1.000	0	0.00	-0.10:0.10	0.971	1.000	51
FAw3/FA	-0.22	-0.38:-0.07	0.005	0.971	35	-0.05	-0.13:0.03	0.254	1.000	32
FAw6/FA	-0.01	-0.11:0.09	0.901	1.000	0	-0.01	-0.10:0.09	0.889	1.000	44
PUFA/FA	-0.04	-0.14:0.06	0.419	1.000	0	-0.02	-0.11:0.07	0.613	1.000	38
MUFA/FA	0.02	-0.11:0.14	0.769	1.000	22	0.06	-0.04:0.16	0.250	1.000	53
SFA/FA	0.02	-0.10:0.14	0.734	1.000	20	-0.05	-0.14:0.05	0.352	1.000	53
ApoB/ApoA1	0.06	-0.06:0.17	0.324	1.000	0	0.14	0.08:0.20	0.000	**0.005**	0

B=Beta coefficient, CI=Confidence interval, I^2=measure of heterogeneity, P-value=Bonferroni-Holm corrected p-value. All metabolite abbreviations can be found in tables S1 and S2.