Identification of Shared and Unique Serum Lipid Profiles in Diabetes Mellitus and Myocardial Infarction

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Background—Diabetes mellitus (DM) and cardiovascular disease are associated with dyslipidemia, but the detailed lipid molecular pattern in both diseases remains unknown.

Methods and Results—We used shotgun mass spectrometry to determine serum levels of 255 molecular lipids in 316 controls, 171 DM, and 99 myocardial infarction (MI) events from a cohort derived from the Malmö Diet and Cancer study. Orthogonal projections to latent structures analyses were conducted between the lipids and clinical parameters describing DM or MI. Fatty acid desaturases (FADS) and elongation of very long chain fatty acid protein 5 (ELOVL5) activities were estimated by calculating product to precursor ratios of polyunsaturated fatty acids in complex lipids. FADS genotypes encoding these desaturases were then tested for association with lipid levels and ratios. Differences in the levels of lipids belonging to the phosphatidylcholine and triacylglyceride (TAG) classes contributed the most to separating DM from controls. TAGs also played a dominating role in discriminating MI from controls. Levels of C18:2 fatty acids in complex lipids were lower both in DM and MI versus controls (DM, P<0.004; MI, P=6.0E-06) at least due to an acceleration in the metabolic flux from C18:2 to C20:4 (eg, increased estimated ELOVL5: DM, P=0.02; MI, P=0.04, and combined elongase-desaturase activities: DM, P=3.0E-06; MI, P=2.0E-06). Minor allele carriers of FADS genotypes were associated with increased levels of C18:2 (P≤0.007) and lower desaturase activity (P≤0.002).

Conclusions—We demonstrate a possible relationship between decreased levels of C18:2 in complex lipids and DM or MI. We thereby highlight the importance of molecular lipids in the pathogenesis of both diseases. (J Am Heart Assoc. 2016;5:e004503 doi: 10.1161/JAHA.116.004503)

Key Words: diabetes mellitus • fatty acid desaturase • genotype • lipid metabolites • myocardial infarction

It is well known that both diabetes mellitus (DM) and cardiovascular disease (CVD) are associated with dyslipidemia. Typically, DM is characterized by high total triacylglyceride (TAG) levels and low high-density lipoprotein (HDL) cholesterol1 while CVD is associated with elevated low-density lipoprotein (LDL) and low HDL cholesterol levels.2 There are also strong emerging evidences of a causal role of TAG levels in CVD.3-6 In addition, DM is one of the major risk factors for CVD7 and thus both may have similar determinants. The reason DM is a strong risk factor for CVD is still unknown; however, shared etiological disturbances of lipid metabolism are a possibility, and, if proven true, would open up novel treatment targets for both diseases.

Although used in clinical assessments for decades, total plasma TAGs as well as LDL and HDL cholesterol levels are sum measurements of numerous lipid molecular species and are only part of the different lipid classes present in the circulation.8 Lipidomics-based studies have now identified specific molecular lipids associated with DM9,10 and CVD,11 but the overall detailed high coverage lipid molecular pattern in both diseases is still largely unknown. We thus aimed to define fingerprints of lipid molecular species in DM and CVD in fasted serum. A mass spectrometry (MS)-based shotgun lipidomics approach was used. In contrast to our previous study,12 we have extended the lipid coverage down to the

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Accompanying Tables S1 through S8 and Figures S1, S2 are available at http://jaha.ahajournals.org/content/5/12/e004503/DC1/inline-supplementary-material-1.pdf

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molecular lipid species level with identification of individual fatty acids (i.e., chain length and degree of saturation) for the majority of the lipid classes analyzed.

Methods

Study Participants and Data Collection

The MDC-CC (Malmö Diet and Cancer Cardiovascular Cohort) is a Swedish cohort designed to study the epidemiology of carotid artery disease with baseline data recorded from 1991 through 1996. All individuals who were alive and still living in Sweden were invited to participate in a reexamination between 2007 and 2012, of whom 3734 attended. Participants in the reinvestigation cohort underwent a medical history assessment, a physical examination, and a laboratory assessment of DM and cardiovascular risk factors, including measurement of the common carotid artery intima-media thickness by ultrasound. The MDC-CC was approved by the ethics committee at Lund University, and all participants provided written informed consent.

DM was defined as the following: fasting plasma glucose level of ≥7.0 mmol/L, or a 120-minute value post-oral glucose tolerance test plasma glucose level of >11.0 mmol/L, or a history of physician diagnosis of DM, or taking anti diabetic medication, or having been registered in local or national diabetes mellitus registries. Myocardial infarction (MI) was defined as fatal or nonfatal MI on the basis of the International Classification of Disease–9th Revision (ICD-9) code 410 (i.e., acute MI) and ICD-10 code I21 (i.e., ST-segment elevation and non–ST-segment elevation MI), or death due to ischemic heart disease according to ICD-9 codes 412 (i.e., old MI) and 414 (i.e., other forms of chronic ischemic heart disease), or ICD-10 codes I22 (i.e., subsequent ST-segment elevation and non–ST-segment elevation MI), I23 (i.e., certain current complications following ST-segment elevation and non–ST-segment elevation MI), or I25 (i.e., chronic ischemic heart disease) and was ascertained from local or national records as previously described.

From the MDC-CC reexamination were randomly selected 316 controls (i.e., individuals without DM or MI), 171 DM events (101 prevalent cases and 54 incident cases), and 99 MI events (79 prevalent cases and 11 incident cases). A total of 10 individuals displayed both end points. Clinical characteristics of the study samples are presented in Tables 1 and 2.

Serum Lipidomics

Lipid extraction of never thawed, overnight fasted serum samples stored at −80°C upon collection was performed at Lipotype GmbH using high throughput Shotgun Lipidomics (Dresden, Germany) technology as previously described. In short, 2 μL of blood serum were extracted with MTBE/MetOH 7:2 with a fully automated liquid handling station (Hamilton) in a 96 well format. Shotgun MS analysis was conducted on a QExactive mass spectrometer (Thermo Fisher Scientific, Waltham, MA) coupled to a TriVersa NanoMate robotic nanoflow ion source (Advion BioSciences, Ithaca, NY).

Lipids were identified and quantified using the proprietary LipotypeXplorer software, which is based on LipidXplorer. Lipid intensities were normalized to lipid class–specific internal standards and data reported as molar amounts. Analytical quality was assessed by the inclusion of reference and blank samples. Data were corrected for batch effects and drift based on reference samples. Median technical variation was 7.2% (coefficient of variation). A total of 357 lipid species belonging to 16 major lipid classes were identified and quantified. Lipid species present in <50% of all samples were excluded, leaving 255 lipid species for further analysis.

Multivariate Data Analysis

Orthogonal projections to latent structures (OPLS) methods were adopted to analyze the correlation between lipid molecular species and clinical parameters. OPLS is a...
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supervised multivariate method where the systematic variation in X matrix is divided into two parts—one that is linearly related to Y (and therefore predictive) and one that is unrelated (orthogonal) to Y.\(^{17,18}\) Data were mean-centered and unit variance scaled prior to the analysis. The model complexity was estimated according to cross-validation.\(^{19}\) The software used for multivariate models was Simca p\(^+\) (Umetrics). OPLS has previously been used to analyze gene/isofrom expression and metabolomics as well as protein expression data.\(^{20–22}\)

In the present study, two separate OPLS analyses were performed: one with 16 clinical parameters as Y matrix for DM (Table 1) and one with 27 clinical parameters as Y matrix for MI (Table 2). A total of 487 and 415 individuals were originally included in the DM and MI analysis, respectively. Individuals with >50% missing data were excluded, resulting in 448 and 383 individuals in the DM and MI groups, respectively, in the final analyses. For the controls and MI events, there were no differences in any of the clinical characteristics between the included individuals and the one excluded (Tables S1 and S2). For DM events, all clinical characteristics between included and excluded individuals were similar, except for urinary creatinine, which was lower in the included versus the excluded individuals, and the percentage of individuals taking antihypertensive medicine, which was higher in the included versus the included individuals (Table S3).

Additional OPLS analyses were performed for both DM and MI, excluding the 10 individuals displaying both DM and MI. The results show very similar OPLS model parameters compared with the analyses with the 10 individuals included (Table S4). Therefore, the 10 individuals were subsequently included in the analyses. The significance of lipid species related to correlation between lipid species levels and clinical parameters in DM and MI separately was analyzed by means of the predictive loadings in the OPLS models. An OPLS model including several Y vectors will in most cases result in several predictive components (showing correlation to the Y vectors) and maybe one or several orthogonal components (showing systematic variation in the X matrix that is not related to Y). In order to analyze the importance of each X variable for all the predictive projections resulting from the performed OPLS analyses, a variable influence on projection (VIP) parameter was used, which summarizes the importance of the predictive principal components calculated by cross-validation.\(^{18,23}\) Variables with VIP >1 were considered to be significant. All parameters from both the DM and MI models derived from 7-fold cross-validation are shown in Table S4. Calculated VIPs from the OPLS models for DM and MI are shown in Tables S5 through S7.

**Estimation of Desaturases and Elongase Activities**

Delta-5 desaturase (D5D), encoded by *FADS1*, delta-6 desaturase (D6D), encoded by *FADS2*, and elongation of very long chain fatty acid 5 (ELOVL5), encoded by *ELOVL5*, are required for the de novo synthesis of long-chain polyunsaturated fatty acids (PUFAs). We calculated product to precursor ratios of PUFAs contained in complex lipids (glycerophospholipids and diacylglycerides [DAGs]) from the DM or MI model, respectively, as a surrogate measure for these desaturases and elongase activities,\(^{24}\) which reflects both transcription level and catalytic capacity of these enzymes. The ratio of C20:4 to C20:3 was used to estimate D5D activity as previously

**Table 2. Y Variables in the MI Model**

| Variable                        | Controls  | MI          |
|---------------------------------|-----------|-------------|
| No.                             | 293       | 90          |
| Incidents, %                    | 0         | 11          |
| Age, y                          | 72.8±5.8  | 75.1±4.9    |
| Women, %                        | 67.9      | 33.3        |
| BMI, kg/m²                      | 26.4±4.2  | 26.6±3.9    |
| Waist, cm                       | 90.0±12.3 | 94.3±12.0   |
| Waist to hip ratio              | 0.9±0.08  | 0.9±0.08    |
| Systolic blood pressure, mm Hg | 143.0±18.6| 143.6±18.1  |
| Diastolic blood pressure, mm Hg | 83.2±9.9  | 80.2±9.0    |
| Heart rate                      | 67.7±11.1 | 65.3±10.4   |
| Total triglycerides, mmol/L     | 1.1±0.6   | 1.1±0.5     |
| Total cholesterol, mmol/L       | 5.4±1.1   | 4.2±0.9     |
| HDL cholesterol, mmol/L         | 1.5±0.5   | 1.3±0.4     |
| LDL cholesterol, mmol/L         | 3.4±1.0   | 2.5±0.8     |
| Fasting glucose, mmol/L         | 5.7±0.6   | 6.0±0.8     |
| 2-h glucose (OGTT), mmol/L      | 6.8±2.1   | 7.5±1.9     |
| Plaque score                    | 3.1±1.8   | 4.0±1.4     |
| Plaque area, mm²                | 20.8±11.8 | 23.0±12.4   |
| Blood flow velocity, max        | 0.7±0.3   | 0.7±0.4     |
| Blood flow velocity, diastolic   | 0.2±0.1   | 0.2±0.1     |
| Lumen diameter, mean CCA         | 6.3±0.8   | 6.6±0.9     |
| Lumen diameter, max CCA         | 6.6±0.8   | 6.9±0.9     |
| Stenosis                        | 1.9±10.8  | 5.5±17.4    |
| IMT, mean CCA                   | 0.9±0.2   | 1.0±0.3     |
| IMT, max CCA                    | 1.0±0.2   | 1.2±0.5     |
| IMT, max CCA bifurcation         | 1.8±0.7   | 2.1±0.7     |
| Statins, %                      | 20.1      | 80          |
| Antihypertensive medication, %   | 39.2      | 89          |
| Diabetes medication, %           | 0         | 3.3         |

Values are mean±SD or percentage. BMI indicates body mass index; CCA, common carotid artery; HDL, high-density lipoprotein; IMT, intima-media thickness; LDL, low-density lipoprotein; MI, myocardial infarction; OGTT, oral glucose tolerance test.
performed,\textsuperscript{25} ratio of C18:3 to C18:2 for D\&D activity, ratio of C20:4 to C18:2 for combined elongase-desaturase activity,\textsuperscript{26} and ratio of C20:3 to C18:3 for ELOVL5 activity.

**SNP Selection**

Genotype information on 11 \textit{FADS} single nucleotide polymorphisms (SNPs), which were previously genotyped in the current dataset using an Illumina Infinium HumanOmniExpressExome BeadChip array (San Diego, CA) and that were previously shown to associate with DM at nominal significance (0.002 $\leq$ $P$ $\leq$ 0.02) in DIAGRAM v3 genome-wide association study (GWAS) meta-analysis,\textsuperscript{27} was available for 525 of the participants (list given in Table S8). Eight of the 11 gene variants were in linkage disequilibrium ($r^2$ $>$ 0.8 and $D^\prime$ $>$ 0.9) and rs174550 was used as representative of the linkage disequilibrium block, which gave 4 gene variants left.

**Statistical Methods**

Additional statistical analyses were conducted in SPSS version 22 (SPSS Inc, Chicago, IL). Welch’s t test was used to test whether the product to precursor ratios of PUFAs contained in glycerophospholipids and DAGs differed between DM and controls or MI and controls because of the uneven sample size between groups.

We tested the association of \textit{FADS1-2} gene variants with Z scores of complex lipid levels or ratios using linear regression models adjusted for age and sex. We used Bonferroni correction to handle false discovery rates from multiple testing and set a cutoff at $P$ $<$ 0.0025 [(0.05 / 4 SNPs $\times$ 5 phenotypes)]. For other tests, data were considered significant if $P$ $<$ 0.05.

Figures with lipid molecular species were constructed in GraphPad Prism version 6 (GraphPad Software, La Jolla, CA).

**Results**

**A PCs and TAGs Signature Associates With DM**

OPLS was applied to simultaneously analyze the correlations between 255 lipid molecular species belonging to 12 major lipid classes (X variables) and 16 clinical parameters describing MI (Y variables) in 383 individuals, of which 90 were MI and 293 controls. The clinical parameters were comprised of known risk factors for MI, including measurements of the intima-media thickness in the common carotid artery and bifurcation (Table 2). OPLS resulted in 6 predictive components explaining 50% of the variation between the lipid species and the clinical parameters (Table S4). Figure 3 shows OPLS score and loading plots illustrating the predictive components 1 to 3 (pq 1–pq 3) in the MI model. A trend for separation between MI and controls is observed in the score plots (Figure 3A and 3B). A total of 143 lipid species were found to significantly contribute to the separation between MI and controls (ie, VIP $>$ 1) (Table S6). Among the lipid species with the highest VIP values (ie, VIP $\geq$ 1.2), 29 of 31 are TAG lipid species (Figure 4A). The majority of the top VIP TAGs display higher levels in MI versus controls (Figure 4A) and are mainly composed of SFAs or MUFAs (ie, total double bound number $\leq$ 3) (Figure 4B). In the OPLS loading plots, the TAGs cluster together (Figure 3C and 3D, colored in green) and exhibit a good correlation with the traditionally measured total TAGs concentration.

**A TAGs Signature Associates With MI**

Similarly, OPLS was applied to simultaneously analyze correlations between 255 lipid molecular species (X variables) belonging to 12 major lipid classes and 27 clinical parameters describing MI (Y variables) in 383 individuals, of which 90 were MI and 293 controls. The clinical parameters were comprised of known risk factors for MI, including measurements of the intima-media thickness in the common carotid artery and bifurcation (Table 2). OPLS resulted in 6 predictive components explaining 50% of the variation between the lipid species and the clinical parameters (Table S4). Figure 3 shows OPLS score and loading plots illustrating the predictive components 1 to 3 (pq 1–pq 3) in the MI model. A trend for separation between MI and controls is observed in the score plots (Figure 3A and 3B). A total of 143 lipid species were found to significantly contribute to the separation between MI and controls (ie, VIP $>$ 1) (Table S6). Among the lipid species with the highest VIP values (ie, VIP $\geq$ 1.2), 29 of 31 are TAG lipid species (Figure 4A). The majority of the top VIP TAGs display higher levels in MI versus controls (Figure 4A) and are mainly composed of SFAs or MUFAs (ie, total double bound number $\leq$ 3) (Figure 4B). In the OPLS loading plots, the TAGs cluster together (Figure 3C and 3D, colored in green) and exhibit a good correlation with the traditionally measured total TAGs concentration.
Altered PUFAs Metabolism in DM and MI

In the DM model, all top VIP PCs that contained a C18:2 fatty acid were less abundant in DM versus controls (Figure 2C). This could reflect dietary intake and/or altered endogenous PUFAs metabolism. In a next step, we thus investigated the de novo synthesis of long-chain PUFAs by calculating product to precursor ratios of PUFAs contained in complex lipids from the DM model to estimate desaturase and elongase activities. Levels of C18:2 in complex lipids were lower in DM versus controls ($P=0.004$) and levels of C20:4 were higher but not statistically significant ($P=0.12$) (Table 3). The ratio of C18:3 to C18:2 was unchanged ($P=0.48$) while the ratio of C20:3 to C18:3 (ELOVL5 activity) was higher in DM ($P=0.02$) and the ratio of C20:4 to C20:3 (D5D activity) was also higher in DM but not statistically significant ($P=0.17$). Combined elongase-desaturase activity as estimated by the C20:4 to C18:2 ratio was significantly increased in DM versus controls ($P=3.0E-06$).

Product to precursor ratios of PUFAs incorporated in glycerophospholipids and DAGs from the MI model were also calculated in MI and controls. Levels of C18:2 in complex lipids were lower in MI versus controls ($P=6.0E-06$) but levels of C20:4 were similar ($P=0.66$) (Table 3). Estimated D6D activity was unchanged ($P=0.79$) while ELOVL5 activity was higher in MI ($P=0.04$), and D5D activity was also higher in MI but only marginally statistically significant ($P=0.07$). Combined elongase-desaturase activity was significantly increased in MI versus controls ($P=2.0E-06$).

FADS Genotypes are Associated With Altered Levels of PUFAs in Serum Complex Lipids and Altered Desaturase Activity

Next, we examined the association of 4 genetic variants in the FADS gene cluster previously shown to associate with DM in the Diagram GWAS [27] (Table S8) with the levels and the product to precursor ratios of serum glycerophospholipids and DAGs PUFAs. rs174550 and rs174611 minor alleles were associated with increased levels of C18:2 ($P=0.007$ and
Rs174550 and rs174570 minor allele were associated significantly decreased levels of C20:4 (P=9.5E-07 and 1.2E-05). Only the rs174570 minor allele was significantly associated with decreased C18:3 to C18:2 ratio (D6D activity) (P=0.001). The minor allele for all 4 SNPs was associated with decreased ratio of C20:4 to C20:3 (D5D activity) (9.1E-16 ≤ P ≤ 0.002) and decreased C20:4 to C18:2 ratio (combined elongase-desaturase activity) (2.4E-21 ≤ P ≤ 6.0E-06) (Table 4).

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Figure 2. Characteristics of the top loadings from the diabetes mellitus (DM) model. Ratios in DM vs controls for the lipid species that contribute the most to the separation between DM and controls (variable influence on projection ≥ 1.2) (A and B). Graph of lipid classes and fatty acid acyl chain length (A). Graph of lipid classes and fatty acid acyl chain double bound number (B). Acyl chain characteristics of the significant phosphatidylcholine lipid species. Fatty acids less abundant in DM vs controls are indicated in blue and more abundant in DM vs controls are indicated in red (C). LPE indicates lysophosphatidylethanolamine; PC, phosphatidylcholine; PC O, phosphatidylcholine ether; SE, steryl ester; TAG, triacylglyceride.

0.001) (Table 4). Rs174550 and rs174570 minor allele were associated with significantly decreased levels of C20:4 (P=9.5E-07 and 1.2E-05). Only the rs174570 minor allele was significantly associated with decreased C18:3 to C18:2 ratio (D6D activity) (P=0.001). The minor allele for all 4 SNPs was associated with decreased ratio of C20:4 to C20:3 (D5D activity) (9.1E-16 ≤ P ≤ 0.002) and decreased C20:4 to C18:2 ratio (combined elongase-desaturase activity) (2.4E-21 ≤ P ≤ 6.0E-06) (Table 4).

Lipidomic Profile Shows Differences and Similarities Between DM and MI

We next compared the lipid species contributing to the DM model with the ones important for the MI model (ie, lipids with VIP >1). Some lipid species are unique for DM (17 lipid species) or MI (19 lipid species). Many are common to both models (123 lipid species), of which one third displayed opposite regulation between the DM and the MI models and two thirds are similarly regulated (Figure 5).

The majority of the lipid species unique for DM are glycerophospholipids, including phosphatidylinositols and plasmalogen glycerophospholipids (PC-O and PE-O) (Figures S1A and S2A), while the lipid species that are unique for MI are mainly sphingolipids, including ceramides, sphingomyelins, and LysoPC16:0 (Figures S1D and S2D). Among the common discordant lipid species, several TAGs that are decreased in DM versus controls are increased in MI versus controls while several PCs and sphingomyelins that are increased in DM versus controls are decreased in MI versus controls (Figure S1B and S1E).

Discussion

In the present study, we used a lipidomics approach combined with OPLS to establish the detailed high coverage lipid
A molecular pattern associated with DM and MI in serum. Both DM and MI were associated with changes in lipid classes as well as in lipid species. The lipid classes PC and TAG contributed the most to discriminate DM from controls. The TAG lipid class as a whole has previously been shown to positively significantly associate with the presence of DM and prediabetes in the AusDiab (Australian Diabetes, Obesity and Lifestyle) study cohort but no significant association was seen.

Figure 3. Orthogonal projections to latent structures score (A through C) and loading (B through D) plots of lipid species and clinical parameters in myocardial infarction (MI). The analyses were performed on 383 individuals, 255 lipid species, and 27 clinical parameters. Two-dimensional score plots showing predictive component 1 to 2 (pq1–pq2) and predictive component 2 to 3 (pq 2–pq 3) (A through C). The black color indicates controls (CN) and the red color indicates individuals with MI. The analysis was performed on lipid species as X and clinical parameters describing MI as Y matrix. Two-dimensional loading plots showing predictive loading components 1 to 2 and 2 to 3 (Loading pq 1–Loading pq 2, and Loading pq 2–Loading pq 3) (B through D). All lipid species are marked in grey filled circles except triacylglyceride (TAG) (green filled circles) and phosphatidylcholine (PC) (violet filled circles). Clinical parameters are marked in black filled circles with each individual abbreviated clinical parameter name denoted.

Figure 4. Characteristics of the top loadings from the myocardial infarction (MI) model. Ratios in MI vs controls for the lipid species that contribute the most to the separation between MI and controls (variable influence on projection ≥1.2) (A and B). Graph of lipid classes and fatty acid acyl chain length (A). Graph of lipid classes and fatty acid acyl chain double bound number (B). DAG indicates diacylglyceride; SM, sphingomyelin; TAG, triacylglyceride.
for the PC lipid class. However, both the TAG and PC lipid classes were significantly positively associated with DM and prediabetes in the SAFHS (San Antonio Family Heart Study) cohort, which has a more similar sex structure to our MDC-CC subcohort than to the AusDiab cohort.9

Palmitic acid (C16:0) and stearic acid (C18:0) containing discriminating PC species were elevated in serum from DM versus controls, except for the one containing linoleic acid (C18:2) as the second fatty acid, which were decreased. In a small cohort of 20 individuals per group, a similar relative increase of PC containing C16:0 and C18:0 in isolated very LDL (VLDL) and LDL particles from dyslipidemic type 2 diabetic women versus controls was previously reported.28 PC species with C18:2 were not measured in this study but several C18:2 containing TAG species were decreased in VLDL and LDL particles from dyslipidemic type 2 diabetic individuals.

We also showed that lipid species belonging to the TAG lipid class played a dominating role to separate MI from controls and that the majority of the discriminating TAG lipid species were upregulated in MI versus controls. This, together with recent genetic evidence in support of a causal role of raised circulating concentrations of TAGs in CVD,3–6 further strengthens the role of TAGs in the pathogenesis of CVD.

Levels of C18:2 containing serum glycerophospholipids and diacylglycerides were lower in DM versus controls. Prospective studies have previously shown an inverse association between the proportion of linoleic acid in plasma and erythrocyte membrane phospholipids and diabetes mellitus risk29,30 and our data indicate that this imbalance remains with overt DM. A decrease of the levels of C18:2 containing serum glycerophospholipids and diacylglycerides was also observed in MI versus controls. This is consistent with results from the Verona Heart Study where lower concentrations of linoleic acid (C18:2) in serum phospholipids and in red blood cell membranes were reported in coronary artery disease (CAD) patients versus controls.26

Table 3. PUFA Metabolism in DM and MI

|             | Controls (n=293) | DM (n=155) | P Value | Controls (n=293) | MI (n=90) | P Value |
|-------------|-----------------|------------|---------|-----------------|----------|---------|
| C18:2, nmol| 1.79±0.66       | 1.61±0.60  | 0.004*  | 1.78±0.66       | 1.46±0.54| 6.0E-06*|
| C20:4, nmol| 0.51±0.20       | 0.54±0.23  | 0.12    | 0.52±0.20       | 0.53±0.21| 0.66    |
| C18:3/C18:2 (D6D)| 0.02±0.01 | 0.02±0.01 | 0.48 | 0.02±0.01 | 0.02±0.01 | 0.79 |
| C20:3/C18:3 (ELOVL5)| 7.30±4.29 | 8.18±3.65 | 0.02* | 7.30±4.29 | 8.20±3.34 | 0.04* |
| C20:4/C20:3 (D5D)| 2.74±0.92 | 2.87±1.00 | 0.17 | 2.80±0.92 | 3.00±0.90 | 0.07 |
| C20:4/C18:2 (combined elongase-desaturase) | 0.30±0.10 | 0.36±0.14 | 3.0E-06* | 0.30±0.10 | 0.38±0.13 | 2.0E-06* |

Absolute levels or ratios of polyunsaturated fatty acids (PUFAs) contained in glycerophospholipids and diacylglycerides. D5D indicates delta-5 desaturase; D6D, delta-6 desaturase; DM, diabetes mellitus; ELOVL5, elongation of very long chain fatty acid protein 5; MI, myocardial infarction. *Statistically significant associations (P<0.05) by Welch’s t test.

Table 4. FADS Gene Variants Associated With DM Associate With Serum Complex Lipid PUFA Levels

|             | rs174550 | rs174570 | rs174593 | rs174611 |
|-------------|----------|----------|----------|----------|
| C18:2       | 0.18 (0.06) | 0.007 | 0.10 (0.09) | 0.23 | 0.11 (0.07) | 0.12 | 0.23 (0.07) | 0.001* |
| C20:4       | 0.32 (0.06) | 9.5E-07* | 0.37 (0.08) | 1.2E-05* | 0.15 (0.07) | 0.04 | 0.09 (0.07) | 0.17 |
| C18:3/C18:2 (D6D) | -0.08 (0.07) | 0.23 | -0.30 (0.09) | 0.001* | -0.02 (0.08) | 0.83 | -0.08 (0.07) | 0.25 |
| C20:4/C20:3 (D5D) | -0.53 (0.06) | 9.1E-16* | -0.38 (0.09) | 1.2E-05* | -0.30 (0.08) | 9.0E-05* | -0.22 (0.07) | 0.002* |
| C20:4/C18:2 (combined elongase-desaturase) | -0.62 (0.06) | 2.4E-21* | -0.59 (0.09) | 1.3E-11* | -0.35 (0.08) | 6.0E-06* | -0.36 (0.07) | 3.1E-07* |

Linear regressions were performed with Z scores of levels or ratios of polyunsaturated fatty acids (PUFAs) contained in glycerophospholipids and diacylglycerides adjusting for age and sex (n=525). β-correlation coefficients represent the change in PUFA levels or ratios, expressed as multiples of 1-SD, per effect allele. D5D indicates delta-5 desaturase; D6D, delta-6 desaturase; DM, diabetes mellitus; FADS, fatty acid desaturases.

*Statistically significant associations (P<0.0025).
Next, we investigated whether an abnormality of PUFA levels in complex lipids was due to alterations in the pathway for de novo synthesis of PUFAs. Our data indicate that elongation of PUFAs is accelerated both in DM and MI patients and there was also a tendency for an accelerated desaturation process through increased D5D activity both in DM and MI patients, albeit not statistically significant. Overall, our study suggests that there was an acceleration in the metabolic flux from C18:2 to C20:4 in DM and MI.

Because polymorphisms in the FADS gene cluster have been shown to associate with PUFA levels in plasma and erythrocyte membrane phospholipids, we next tested whether FADS gene variants have a functional effect on desaturase activity. Minor allele carriers of the investigated FADS genotypes tended to be associated with increased levels of C18:2 containing serum glycerophospholipids and DAGs and decreased levels of C20:4 containing lipid species, all were significantly associated with lower estimated D5D activity, as previously reported.

A negative correlation of D5D activity with diabetes mellitus risk has previously been reported. However, in a meta-analyses of GWAS, FADS1 rs174550 major allele was shown to be associated with increased fasting glucose at genome-wide significance ($P=8.3E-09$) and increased DM risk at nominal significance ($P=2.9E-03$ and $2.3E-04$), thus indicating that the genetically determined high D5D activity is associated with increased DM risk, which could support a causal relationship between decreased levels of C18:2 containing complex lipids and DM in our study.

No significant association between FADS gene variants and CAD has been identified in GWAS ($0.16 \leq P \leq 0.7$). However, by using an additive model of FADS SNPs, FADS haplotypes, or both, a significant effect on a person’s susceptibility to CAD was reported. Carriers of a higher number of unfavorable FADS gene variants, ie, associated with an elevated desaturase activity, more often experienced CAD than those with less unfavorable alleles. This could indicate a possible causal relationship between decreased levels of C18:2 containing complex lipids and MI in our study.

Because of the close relationship between DM and MI, we compared the discriminating lipid species pattern for both end points. Of interest, LysoPC16:0, for which we previously found low levels to predict the risk of future CVD, was only important in the MI model and was decreased in MI versus controls in the current study. Although several TAG lipid species were similarly increased in the DM and MI models, there were nonetheless several TAG lipid species that were decreased in DM while increased in MI in the respective models, indicating opposite roles of these TAG species in the pathogenesis of DM and MI. Of note, we observed similar cholesteryl ester profiles in the DM and MI models despite the well-known role of cholesterol in MI development. Most
probably, this is because a large proportion of individuals with MI take statins medication.

**Study Limitations**

The present study has several limitations. Although all of the patients with DM were older than 50 years, we did not have data to specifically exclude individuals with type 1 DM. Thus, there may be sporadic cases of type 1 DM among the DM group. In addition, with the technique used, it is not possible to identify the position of the double bounds on the acyl chains; hence, we are not able to distinguish between omega-6 PUFAs and omega-3 PUFAs, and measured their sum only. However, since it is well known that omega-6 fatty acids predominate in the contemporary Western diet, the impact of omega-3 PUFAs on our results should be minimal. Moreover, by estimating desaturases and elongase activities by calculating product to precursor ratios, we cannot distinguish between activity changes due to altered transcription levels and changes due to modified intrinsic enzymatic capacity.

As expected, MI patients and, to a lesser extent, DM patients were more commonly taking statin therapy than controls; therefore, there are limitations to what we can conclude about cholesteryl esters. However, our study is representative of current DM and MI patients.

**Conclusions**

Using shotgun lipidomics and OPLS, we were able to identify a PC and TAG lipid molecular species signature in DM patients and a TAGs-based signature in MI patients. We also report altered PUFAs metabolism both in DM and MI patients with an increased flux from C18:2 to C20:4. We confirm a genetic role, via the FADS gene cluster, in affecting serum PUFA levels through modulation of desaturase activity. In addition, we demonstrate a possible causal relationship between decreased levels of C18:2 containing complex lipids and DM or MI. Overall, our study highlights the importance of lipid molecular species as potential etiological factors and treatment targets in DM and MI patients, although further investigations are needed to establish the pathophysiological consequences of lipid profile alterations.

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**Disclosures**

None.

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### Table S1. Clinical characteristics of the study samples.

| Clinical characteristics of the controls | Included Controls | Excluded Controls |
|------------------------------------------|-------------------|-------------------|
| n                                       | 293               | 23                |
| Age                                     | 72.8 ± 5.8        | 73.0 ± 5.0        |
| Women (%)                                | 67.9              | 75.0              |
| BMI (kg/m2)                              | 26.4 ± 4.2        | 25.4 ± 3.6        |
| Systolic blood pressure (mm Hg)          | 143.0 ± 18.6      | 138.3 ± 18.5      |
| Total Triglycerides (mmol/L)             | 1.1 ± 0.6         | 1.0 ± 0.4         |
| Total cholesterol (mmol/L)               | 5.4 ± 1.1         | 5.4 ± 0.9         |
| HDL cholesterol (mmol/L)                 | 1.5 ± 0.5         | 1.5 ± 0.4         |
| LDL cholesterol (mmol/L)                 | 3.4 ± 1.0         | 3.4 ± 0.7         |
| Fasting glucose (mmol/L)                 | 5.7 ± 0.6         | 5.8 ± 0.7         |
| Waist (cm)                               | 90.0 ± 12.3       | 86.5 ± 11.6       |
| Waist to hip ratio                       | 0.9 ± 0.1         | 0.8 ± 0.1         |
| 2-h glucose (OGTT) (mmol/L)              | 6.8 ± 2.1         | 7.4 ± 2.8         |
| U-Albumin (g/L)                          | 0.02 ± 0.1        | 0.01 ± 0.01       |
| U-Creatinine (mmol/L)                    | 8.2 ± 4.0         | 7.8 ± 4.0         |
| Diastolic blood pressure (mm Hg)         | 83.2 ± 9.9        | 79.8 ± 7.1        |
| Heart rate                               | 67.7 ± 11.1       | 67.3 ± 9.9        |
| Plaque score                             | 3.1 ± 1.8         | 2.4 ± 1.9         |
| Plaque area (mm2)                        | 20.8 ± 11.8       | 16.0 ± 4.9        |
| Blood flow velocity. max                 | 0.7 ± 0.3         | 0.6 ± 0.1         |
| Blood flow velocity. diastolic           | 0.2 ± 0.1         | 0.2 ± 0.1         |
| Lumen diameter. mean CCA                 | 6.3 ± 0.8         | 6.3 ± 0.7         |
| Lumen diameter. max CCA                  | 6.6 ± 0.8         | 6.6 ± 0.8         |
| Stenosis                                 | 1.8 ± 10.8        | 0.0 ± 0.0         |
| IMT mean CCA                             | 0.9 ± 0.2         | 0.9 ± 0.1         |
| IMT max CCA                              | 1.0 ± 0.2         | 1.0 ± 0.2         |
| IMT max CCA bifurcation                  | 1.8 ± 0.7         | 1.6 ± 0.5         |
| % statin therapy                         | 20.1              | 16.7              |
| % anti-hypertensive medicine             | 39.2              | 30.4              |
| % diabetes medicine                      | 0.0               | 0.0               |

Values are mean ± standard deviation or percentage. P values were calculated by comparing included controls versus excluded controls, using a t test for continuous variables and Pearson Chi-Square for binary variables. BMI, body mass index; CCA, common carotid artery; HDL, high-density lipoproteins; IMT, intima media thickness; LDL, low-density lipoproteins; OGTT, oral glucose tolerance test.
|                            | Included MI | Excluded MI |
|---------------------------|-------------|-------------|
| n                         | 90          | 9           |
| Age                       | 75.1 ± 5.0  | 72.1 ± 7.7  |
| Women (%)                 | 33.3        | 33.3        |
| BMI (kg/m^2)              | 26.6 ± 3.9  | 24.6 ± 3.2  |
| Systolic blood pressure (mm Hg) | 143.6 ± 18.1 | 140.3 ± 15.6 |
| Total Triglycerides (mmol/L) | 1.1 ± 0.5   | 1.0 ± 0.4   |
| Total cholesterol (mmol/L) | 4.2 ± 0.9   | 3.9 ± 0.6   |
| HDL cholesterol (mmol/L)  | 1.3 ± 0.4   | 1.3 ± 0.2   |
| LDL cholesterol (mmol/L)  | 2.5 ± 0.8   | 2.1 ± 0.4   |
| Fasting glucose (mmol/L)  | 6.0 ± 0.8   | 6.1 ± 0.7   |
| Waist (cm)                | 94.3 ± 12.0 | 91.9 ± 9.1  |
| Waist to hip ratio        | 0.9 ± 0.08  | 0.9 ± 0.1   |
| 2-h glucose (OGTT) (mmol/L) | 7.5 ± 1.9   | 8.4 ± 1.6   |
| Diastolic blood pressure (mm Hg) | 80.2 ± 9.0  | 80.0 ± 9.8  |
| Heart rate                | 65.3 ± 10.4 | 59.7 ± 11.6 |
| Plaque score              | 4.0 ± 1.4   | 3.9 ± 1.2   |
| Plaque area (mm^2)        | 23.0 ± 12.4 | 25.0 ± 24.0 |
| Blood flow velocity. max  | 0.7 ± 0.4   | 0.6 ± 0.2   |
| Blood flow velocity. diastolic | 0.2 ± 0.16  | 0.2 ± 0.1   |
| Lumen diameter. mean CCA  | 6.6 ± 0.9   | 6.8 ± 0.5   |
| Lumen diameter. max CCA   | 6.9 ± 0.9   | 7.0 ± 0.6   |
| Stenosis                  | 5.5 ± 17.4  | 0.0 ± 0.0   |
| IMT mean CCA              | 1.0 ± 0.3   | 1.0 ± 0.2   |
| IMT max CCA               | 1.2 ± 0.5   | 1.2 ± 0.3   |
| IMT max CCA bifurcation   | 2.1 ± 0.7   | 2.0 ± 0.4   |
| % statin therapy          | 80.0        | 89.0        |
| % anti-hypertensive medicine | 89.0        | 89.0        |
| % diabetes medicine       | 3.3         | 0.0         |

Values are mean ± standard deviation or percentage. P values were calculated by comparing included MI versus excluded MI, using a t test for continuous variables and Pearson Chi-Square for binary variables. BMI, body mass index; CCA, common carotid artery; HDL, high-density lipoproteins; IMT, intima media thickness; LDL, low-density lipoproteins; OGTT, oral glucose tolerance test.
|                        | Included DM | Excluded DM |
|------------------------|-------------|-------------|
| n                      | 155         | 16          |
| Age                    | 72.6 ± 5.3  | 72.8 ± 5.3  |
| Women (%)              | 54.8        | 75.0        |
| BMI (kg/m2)            | 27.9 ± 4.8  | 29.5 ± 6.6  |
| Systolic blood pressure (mm Hg) | 147.8 ± 16.7 | 141.9 ± 19.1 |
| Total Triglycerides (mmol/L) | 1.3 ± 0.6   | 1.1 ± 0.4   |
| Total cholesterol (mmol/L) | 4.7 ± 1.0   | 4.5 ± 0.5   |
| HDL cholesterol (mmol/L) | 1.3 ± 0.4   | 1.3 ± 0.3   |
| LDL cholesterol (mmol/L) | 2.9 ± 0.9   | 2.8 ± 0.5   |
| Fasting glucose (mmol/L) | 7.4 ± 1.4   | 8.0 ± 2.4   |
| Waist (cm)             | 96.3 ± 12.9 | 97.9 ± 17.1 |
| Waist to hip ratio     | 0.9 ± 0.09  | 0.9 ± 0.09  |
| 2-h glucose (OGTT) (mmol/L) | 10.2 ± 3.2  | 9.2 ± 2.6   |
| U-Albumin (g/L)        | 0.02 ± 0.06 | 0.01 ± 0.01 |
| U-Creatinine (mmol/L)  | 8.6 ± 3.9   | 6.3 ± 2.9 * |
| % statin therapy       | 49.0        | 50.0        |
| % anti-hypertensive medicine | 72.3        | 100 *       |
| % diabetes medicine    | 33.0        | 37.5        |

Values are mean ± standard deviation or percentage. P values were calculated by comparing included DM versus excluded DM excluded, using a t test for continuous variables and Pearson Chi-Square for binary variables. BMI, body mass index; HDL, high-density lipoproteins; LDL, low-density lipoproteins; OGTT, oral glucose tolerance test.
Table S4. Model quality parameters tables.
OPLS models for DM and MI with clinical parameters as Y. Number of principal components (PCs) refers to the optimal number of PCs for a particular multivariate data model according to cross-validation. $R_X^2$ accounts for the explained variance while $Q_Y^2$ accounts for the cumulative fraction of the total variation of Y that can be predicted by the model. $R_Y^2$ accounts for the explained variance for the Y component. Predictive components explain the variation accounted for by each predictive component. Orthogonal variation explains variation for each orthogonal component where applicable.

| Principal components | $R_X^2$ | $Q_Y^2$ | $R_Y^2$ |
|----------------------|---------|---------|---------|
| DM (n=448)           |         |         |         |
| Model summary        | 0.637   | 0.243   | 0.724   |
| Predictive           | 0.519   | 0.243   | 0.724   |
| P1                   | 0.19    | 0.106   | 0.236   |
| P2                   | 0.343   | 0.173   | 0.364   |
| P3                   | 0.383   | 0.191   | 0.471   |
| P4                   | 0.415   | 0.197   | 0.545   |
| P5                   | 0.464   | 0.215   | 0.607   |
| P6                   | 0.494   | 0.227   | 0.675   |
| P7                   | 0.519   | 0.243   | 0.724   |
| Orthogonal in X      | 0.117   |         |         |
| O1                   | 0.117   |         |         |

| Principal components | $R_X^2$ | $Q_Y^2$ | $R_Y^2$ |
|----------------------|---------|---------|---------|
| DM (n=438) without 10 individuals displaying both DM and MI |         |         |         |
| Model summary        | 0.639   | 0.235   | 0.726   |
| Predictive           | 0.521   | 0.235   | 0.726   |
| P1                   | 0.199   | 0.0969  | 0.232   |
| P2                   | 0.347   | 0.164   | 0.362   |
| P3                   | 0.387   | 0.182   | 0.471   |
| P4                   | 0.419   | 0.189   | 0.543   |
| P5                   | 0.466   | 0.202   | 0.604   |
| P6                   | 0.495   | 0.219   | 0.674   |
| P7                   | 0.521   | 0.235   | 0.726   |
| Orthogonal in X      | 0.117   |         |         |
| O1                   | 0.117   |         |         |
| Principal components | $R_X^2$  | $Q_Y^2$  | $R_Y^2$  |
|----------------------|---------|---------|---------|
| Model summary        | 0.604   | 0.113   | 0.503   |

Predictive

| Component | $R_X^2$  | $Q_Y^2$  | $R_Y^2$  |
|-----------|---------|---------|---------|
| P1        | 0.304   | 0.0384  | 0.15    |
| P2        | 0.435   | 0.0816  | 0.243   |
| P3        | 0.492   | 0.0833  | 0.325   |
| P4        | 0.532   | 0.084   | 0.403   |
| P5        | 0.576   | 0.0959  | 0.441   |
| P6        | 0.604   | 0.113   | 0.503   |

| Principal components | $R_X^2$  | $Q_Y^2$  | $R_Y^2$  |
|----------------------|---------|---------|---------|
| Model summary        | 0.605   | 0.113   | 0.521   |

Predictive

| Component | $R_X^2$  | $Q_Y^2$  | $R_Y^2$  |
|-----------|---------|---------|---------|
| P1        | 0.315   | 0.0366  | 0.151   |
| P2        | 0.44    | 0.0808  | 0.248   |
| P3        | 0.492   | 0.0781  | 0.331   |
| P4        | 0.535   | 0.0849  | 0.416   |
| P5        | 0.576   | 0.0973  | 0.453   |
| P6        | 0.605   | 0.113   | 0.521   |
| Lipid species       | Total length | Total db | Total oh | Ratio DM vs CN | VIP value DM Model |
|--------------------|--------------|----------|----------|----------------|-------------------|
| PC-38:2:0(18:0:0-20:2:0) | 38           | 2        | 0        | 1.18           | 1.31              |
| PC-35:2:0(18:2:0-17:0:0) | 35           | 2        | 0        | 0.99           | 1.29              |
| PC-36:3:0(18:2:0-18:1:0) | 36           | 3        | 0        | 0.79           | 1.28              |
| PC-36:5:0(20:5:0-16:0:0) | 36           | 5        | 0        | 1.62           | 1.27              |
| PC-32:1:0(16:1:0-16:0:0) | 32           | 1        | 0        | 1.64           | 1.27              |
| PC-38:5:0(20:5:0-18:0:0) | 38           | 5        | 0        | 1.27           | 1.26              |
| SE-43:2:0(27:1:0-16:1:0) | 43           | 2        | 0        | 1.69           | 1.25              |
| TAG-48:4:0 | 48           | 1        | 0        | 1.25           | 1.25              |
| PC-36:2:0(18:2:0-18:0:0) | 36           | 2        | 0        | 0.81           | 1.25              |
| PC-36:1:0(18:1:0-18:0:0) | 36           | 1        | 0        | 1.36           | 1.24              |
| TAG-50:2:0 | 50           | 2        | 0        | 1.18           | 1.24              |
| PC-34:2:0(16:0:0-18:2:0) | 34           | 2        | 0        | 0.94           | 1.23              |
| PC-30:0:0(14:0:0-16:0:0) | 30           | 0        | 0        | 1.30           | 1.23              |
| TAG-54:7:0 | 54           | 7        | 0        | 1.26           | 1.22              |
| TAG-54:4:0 | 54           | 4        | 0        | 0.80           | 1.23              |
| PC O--34:3:0 | 34           | 3        | 0        | 0.99           | 1.22              |
| TAG-48:2:0 | 48           | 2        | 0        | 1.10           | 1.22              |
| TAG-54:5:0 | 54           | 5        | 0        | 0.83           | 1.22              |
| TAG-50:1:0 | 50           | 1        | 0        | 1.38           | 1.22              |
| PC-36:4:0(18:2:0-18:2:0) | 36           | 4        | 0        | 0.78           | 1.22              |
| TAG-53:4:0 | 53           | 4        | 0        | 0.92           | 1.22              |
| PC-34:1:0(16:0:0-18:1:0) | 34           | 1        | 0        | 1.36           | 1.22              |
| TAG-50:3:0 | 50           | 3        | 0        | 1.02           | 1.21              |
| TAG-52:4:0 | 52           | 4        | 0        | 0.84           | 1.21              |
| LPE-18:2:0(18:2:0) | 18           | 2        | 0        | 1.00           | 1.21              |
| SE-45:3:0(27:1:0-18:2:0) | 45           | 3        | 0        | 0.87           | 1.21              |
| PC-36:3:0(16:0:0-20:3:0) | 36           | 3        | 0        | 1.41           | 1.21              |
| PC-32:0:0(16:0:0-16:0:0) | 32           | 0        | 0        | 1.25           | 1.21              |
| TAG-52:6:0 | 52           | 6        | 0        | 1.03           | 1.20              |
| TAG-52:5:0 | 52           | 5        | 0        | 0.86           | 1.20              |
| PC-36:3:0(18:3:0-18:0:0) | 36           | 3        | 0        | 0.89           | 1.20              |
| TAG-52:3:0 | 52           | 3        | 0        | 0.93           | 1.20              |
| PC-34:3:0(18:3:0-16:0:0) | 34           | 3        | 0        | 1.18           | 1.20              |
| TAG-54:6:0 | 54           | 6        | 0        | 1.01           | 1.20              |
| PC O--38:6:0 | 38           | 6        | 0        | 0.99           | 1.20              |
| SE-47:6:0(27:1:0-20:5:0) | 47           | 6        | 0        | 1.49           | 1.20              |
| TAG-51:3:0 | 51           | 3        | 0        | 1.04           | 1.19              |
| PC-32:1:0(14:0:0-18:1:0) | 32           | 1        | 0        | 1.36           | 1.19              |
| Name              | Value1 | Value2 | Value3 | Value4 |
|-------------------|--------|--------|--------|--------|
| PC O--34:2:0      | 34     | 2      | 0      | 0.87   | 1.19   |
| PC-35:1:0(17:0:0-18:1:0) | 35   | 1      | 0      | 1.40   | 1.19   |
| TAG-50:4:0        | 50     | 4      | 0      | 0.92   | 1.19   |
| PC O--36:3:0      | 36     | 3      | 0      | 0.71   | 1.19   |
| TAG-49:2:0        | 49     | 2      | 0      | 1.14   | 1.19   |
| PC-38:3:0(20:3:0-18:0:0) | 38   | 3      | 0      | 1.44   | 1.19   |
| PI-34:1:0(18:1:0-16:0:0) | 34   | 1      | 0      | 1.40   | 1.18   |
| TAG-49:1:0        | 49     | 1      | 0      | 1.26   | 1.18   |
| TAG-56:8:0        | 56     | 8      | 0      | 1.33   | 1.18   |
| DAG-36:3:0(18:1:0-18:2:0) | 36   | 3      | 0      | 0.84   | 1.18   |
| PC O--34:1:0      | 34     | 1      | 0      | 1.20   | 1.18   |
| TAG-51:2:0        | 51     | 2      | 0      | 1.23   | 1.18   |
| TAG-53:3:0        | 53     | 3      | 0      | 1.01   | 1.18   |
| TAG-52:2:0        | 52     | 2      | 0      | 1.10   | 1.18   |
| TAG-54:3:0        | 54     | 3      | 0      | 0.98   | 1.18   |
| PC-34:3:0(16:1:0-18:2:0) | 34   | 3      | 0      | 1.04   | 1.17   |
| TAG-56:4:0        | 56     | 4      | 0      | 1.00   | 1.17   |
| TAG-56:7:0        | 56     | 7      | 0      | 1.44   | 1.16   |
| PC-36:2:0(18:1:0-18:1:0) | 36   | 2      | 0      | 0.90   | 1.16   |
| PC-38:4:0(18:1:0-20:3:0) | 38   | 4      | 0      | 1.28   | 1.16   |
| SE-41:1:0(27:1:0-14:0:0) | 41   | 1      | 0      | 1.48   | 1.16   |
| SE-44:2:0(27:1:0-17:1:0) | 44   | 2      | 0      | 1.46   | 1.16   |
| PC-32:2:0(14:0:0-18:2:0) | 32   | 2      | 0      | 1.13   | 1.16   |
| LPC-18:2:0(18:2:0) | 18     | 2      | 0      | 0.85   | 1.16   |
| SE-45:4:0(27:1:0-18:3:0) | 45   | 4      | 0      | 1.41   | 1.16   |
| PC-38:6:0(16:0:0-22:6:0) | 38   | 6      | 0      | 1.22   | 1.16   |
| TAG-54:2:0        | 54     | 2      | 0      | 1.04   | 1.16   |
| PC-40:5:0(22:5:0-18:0:0) | 40   | 5      | 0      | 1.09   | 1.15   |
| PI-36:1:0(18:0:0-18:1:0) | 36   | 1      | 0      | 1.01   | 1.15   |
| SE-43:1:0(27:1:0-16:0:0) | 43   | 1      | 0      | 1.09   | 1.15   |
| TAG-53:2:0        | 53     | 2      | 0      | 0.98   | 1.15   |
| SE-45:2:0(27:1:0-18:1:0) | 45   | 2      | 0      | 1.20   | 1.15   |
| TAG-58:8:0        | 58     | 8      | 0      | 1.47   | 1.15   |
| TAG-48:3:0        | 48     | 3      | 0      | 0.91   | 1.15   |
| TAG-51:4:0        | 51     | 4      | 0      | 0.86   | 1.15   |
| SM-32:1:2         | 32     | 1      | 2      | 1.16   | 1.15   |
| TAG-51:1:0        | 51     | 1      | 0      | 1.21   | 1.14   |
| TAG-48:0:0        | 48     | 0      | 0      | 1.09   | 1.14   |
| PC O--40:7:0      | 40     | 7      | 0      | 1.29   | 1.14   |
| PC-34:2:0(16:1:0-18:1:0) | 34   | 2      | 0      | 1.21   | 1.14   |
| PE-36:2:0(18:2:0-18:0:0) | 36   | 2      | 0      | 1.13   | 1.14   |
| Compound      | M/Z   | Charge | Retention Time (min) | Relative Abundance | Area Ratio |
|---------------|-------|--------|----------------------|--------------------|------------|
| TAG-56:5:0    | 56    | 5      | 0                    | 0.95               | 1.13       |
| TAG-46:0:0    | 46    | 0      | 0                    | 0.90               | 1.13       |
| PC-34:0:0(16:0:0-18:0:0) | 34 | 0      | 0                    | 0.95               | 1.13       |
| TAG-58:7:0    | 58    | 7      | 0                    | 1.45               | 1.13       |
| SM-33:1:2     | 33    | 1      | 2                    | 1.09               | 1.12       |
| TAG-58:9:0    | 58    | 9      | 0                    | 1.03               | 1.12       |
| TAG-50:5:0    | 50    | 5      | 0                    | 0.80               | 1.12       |
| PC-38:5:0(16:0:0-22:5:0) | 38 | 5      | 0                    | 1.17               | 1.11       |
| LPE-20:5:0(20:5:0) | 20 | 5      | 0                    | 1.63               | 1.11       |
| PI-34:2:0(18:2:0-16:0:0) | 34 | 2      | 0                    | 1.64               | 1.10       |
| TAG-46:1:0    | 46    | 1      | 0                    | 0.93               | 1.10       |
| SE-47:4:0(27:1:0-20:3:0) | 47 | 4      | 0                    | 1.27               | 1.10       |
| SM-34:1:2     | 34    | 1      | 2                    | 0.97               | 1.10       |
| LPC-17:2:0(17:2:0) | 17 | 2      | 0                    | 1.05               | 1.09       |
| SM-40:1:2     | 40    | 1      | 2                    | 0.98               | 1.09       |
| PC-40:6:0(22:6:0-18:0:0) | 40 | 6      | 0                    | 1.02               | 1.09       |
| SM-41:2:2     | 41    | 2      | 2                    | 1.12               | 1.09       |
| PE O--38:7:0  | 38    | 7      | 0                    | 1.46               | 1.09       |
| SM-40:2:2     | 40    | 2      | 2                    | 1.03               | 1.09       |
| PC O--36:2:0  | 36    | 2      | 0                    | 0.77               | 1.09       |
| TAG-56:6:0    | 56    | 6      | 0                    | 1.06               | 1.08       |
| SE-45:5:0(27:1:0-18:4:0) | 45 | 5      | 0                    | 2.36               | 1.08       |
| PC-38:5:0(20:4:0-18:1:0) | 38 | 5      | 0                    | 0.95               | 1.08       |
| PE O--36:6:0  | 36    | 6      | 0                    | 1.79               | 1.08       |
| SM-41:1:2     | 41    | 1      | 2                    | 0.89               | 1.08       |
| PC O--32:1:0  | 32    | 1      | 0                    | 1.20               | 1.08       |
| PC-36:4:0(16:0:0-20:4:0) | 36 | 4      | 0                    | 0.96               | 1.08       |
| PC O--36:4:0  | 36    | 4      | 0                    | 0.95               | 1.07       |
| PC-38:4:0(20:4:0-18:0:0) | 38 | 4      | 0                    | 0.86               | 1.07       |
| SM-39:1:2     | 39    | 1      | 2                    | 1.12               | 1.07       |
| LPC-20:5:0(20:5:0) | 20 | 5      | 0                    | 1.53               | 1.07       |
| Cer-42:1:2    | 42    | 1      | 2                    | 1.12               | 1.07       |
| ST-27:1:0     | 27    | 1      | 0                    | 1.14               | 1.07       |
| PC O--38:5:0  | 38    | 5      | 0                    | 0.89               | 1.06       |
| Cer-40:1:2    | 40    | 1      | 2                    | 1.15               | 1.06       |
| LPE-18:1:0(18:1:0) | 18 | 1      | 0                    | 1.00               | 1.05       |
| TAG-46:2:0    | 46    | 2      | 0                    | 0.79               | 1.05       |
| PI-36:2:0(18:0:0-18:2:0) | 36 | 2      | 0                    | 1.10               | 1.05       |
| PE O--40:8:0  | 40    | 8      | 0                    | 1.18               | 1.05       |
| PC-37:4:0(20:4:0-17:0:0) | 37 | 4      | 0                    | 1.33               | 1.05       |
| Cer-41:1:2    | 41    | 1      | 2                    | 1.21               | 1.05       |
|            | SM   | LPC-18:1(18:1;0) | SE-42:1(27:1;0-15:0;0) | SM-38:1:2 | PC O--36:1;0 | SE-43:3(27:1;0-16:2;0) | SM-39:2;2 | PC O--38:4;0 | PE O--36:3;0 | PC O--40:6;0 | SM-34:2;2 | PI-38:3(18:0;0-20:3;0) | SM-35:1;2 | SM-40:3;2 | PE O--40:7;0 | PC O--32:2;0 | PI-36:2(18:1;0-18:1;0) | PI-36:4(20:4;0-16:0;0) |
|------------|------|-----------------|------------------------|-----------|--------------|------------------------|-----------|--------------|--------------|--------------|-----------|------------------------|-----------|-----------|--------------|--------------|------------------------|------------------------|
|            | 32   | 18              | 42                     | 38        | 36           | 43                     | 39        | 38           | 36           | 40           | 34        | 38                     | 35        | 40        | 40           | 32           | 36                     | 36                     |
|            | 2    | 1               | 1                      | 1         | 1            | 3                      | 2         | 4            | 3            | 6            | 2         | 3                      | 1         | 3         | 7            | 2            | 2                      | 4                      |
|            | 2    | 0               | 0                      | 2         | 0            | 0                      | 2         | 0            | 0            | 0            | 2         | 0                      | 2         | 2         | 0            | 0            | 0                      | 0                      |
|            |      |                 | 1.09                   | 1.06      | 0.97         | 2.20                   | 1.31      | 0.74         | 0.76         | 0.83         | 0.97      | 1.31                   | 1.04      | 1.04      | 1.23          | 1.11         | 0.86                    | 2.03                    |

In bold, lipid species with VIP ≥ 1.2. CN, controls; db, double bound. Cer, ceramide; DAG, diacylglyceride; LPC, lysophosphatidylcholine; LPE, lysophosphatidylethanolamine; LPE O, lysophosphatidylethanolamine ether; PC, phosphatidylcholine; PC O, phosphatidylcholine ether; PE, phosphatidylethanolamine; PE O, phosphatidylethanolamine ether; PI, phosphatidylinositol; SE, steryl ester; SM, sphingomyelin; TAG, triacylglyceride.
| Lipid specie | Total length | Total db | Total oh | Ratio MI vs CN | VIP value MI Model |
|-------------|-------------|----------|---------|---------------|------------------|
| **TAG-50:3;0** | 50 | 3 | 0 | 1.37 | 1.32 |
| **TAG-50:2;0** | 50 | 2 | 0 | 1.24 | 1.32 |
| **TAG-51:3;0** | 51 | 3 | 0 | 1.16 | 1.32 |
| **TAG-52:3;0** | 52 | 3 | 0 | 1.38 | 1.30 |
| **TAG-53:4;0** | 53 | 4 | 0 | 1.22 | 1.30 |
| **TAG-51:2;0** | 51 | 2 | 0 | 1.13 | 1.30 |
| **TAG-52:4;0** | 52 | 4 | 0 | 1.28 | 1.28 |
| **TAG-52:2;0** | 52 | 2 | 0 | 1.33 | 1.27 |
| **TAG-49:2;0** | 49 | 2 | 0 | 1.30 | 1.26 |
| **TAG-48:2;0** | 48 | 2 | 0 | 1.24 | 1.25 |
| **TAG-52:5;0** | 52 | 5 | 0 | 1.42 | 1.25 |
| **TAG-48:1;0** | 48 | 1 | 0 | 1.52 | 1.25 |
| **TAG-53:2;0** | 53 | 2 | 0 | 0.90 | 1.25 |
| **TAG-50:1;0** | 50 | 1 | 0 | 1.45 | 1.24 |
| **TAG-54:5;0** | 54 | 5 | 0 | 1.21 | 1.24 |
| **TAG-54:4;0** | 54 | 4 | 0 | 1.06 | 1.23 |
| **TAG-54:2;0** | 54 | 2 | 0 | 1.03 | 1.23 |
| **TAG-54:6;0** | 54 | 6 | 0 | 1.58 | 1.23 |
| **TAG-56:5;0** | 56 | 5 | 0 | 0.99 | 1.22 |
| **DAG-36:3;0(18:1;0-18:2;0)** | 36 | 3 | 0 | 1.27 | 1.22 |
| **TAG-49:1;0** | 49 | 1 | 0 | 1.17 | 1.22 |
| **TAG-52:6;0** | 52 | 6 | 0 | 1.67 | 1.22 |
| **TAG-56:4;0** | 56 | 4 | 0 | 1.16 | 1.21 |
| **TAG-56:6;0** | 56 | 6 | 0 | 1.49 | 1.21 |
| **TAG-51:4;0** | 51 | 4 | 0 | 1.15 | 1.21 |
| **TAG-48:3;0** | 48 | 3 | 0 | 1.69 | 1.20 |
| **TAG-54:3;0** | 54 | 3 | 0 | 0.92 | 1.20 |
| **SM-41:2;2** | 41 | 2 | 2 | 0.86 | 1.20 |
| **TAG-51:1;0** | 51 | 1 | 0 | 1.09 | 1.20 |
| **SM-40:2;2** | 40 | 2 | 2 | 0.82 | 1.19 |
| **TAG-56:7;0** | 56 | 7 | 0 | 1.86 | 1.18 |
| **SE-43:1;0(27:1;0-16:0;0)** | 43 | 1 | 0 | 1.01 | 1.17 |
| **SM-33:1;2** | 33 | 1 | 2 | 0.80 | 1.17 |
| **PE-36:2;0(18:2;0-18:0;0)** | 36 | 2 | 0 | 1.11 | 1.17 |
| **PC-34:1;0(16:0;0-18:1;0)** | 34 | 1 | 0 | 0.93 | 1.17 |
| **PC-35:2;0(18:2;0-17:0;0)** | 35 | 2 | 0 | 0.83 | 1.17 |
| Fatty Acid | m/z | Charge | Ratio | Retention Time (min) |
|------------|-----|--------|-------|---------------------|
| PC-32:1:0(16:1:0-16:0:0) | 32 | 1 | 0 | 1.22 | 1.16 |
| TAG-54:7:0 | 54 | 7 | 0 | 1.80 | 1.16 |
| TAG-50:5:0 | 50 | 5 | 0 | 1.32 | 1.16 |
| LPE-18:2:0(18:2:0) | 18 | 2 | 0 | 0.94 | 1.15 |
| PC-38:2:0(18:0:0-20:2:0) | 38 | 2 | 0 | 1.17 | 1.15 |
| SM-40:1:2 | 40 | 1 | 2 | 1.01 | 1.15 |
| SE-45:3:0(27:1:0-18:2:0) | 45 | 3 | 0 | 0.93 | 1.15 |
| PC-36:3:0(18:2:0-18:1:0) | 36 | 3 | 0 | 0.63 | 1.15 |
| SM-38:1:2 | 38 | 1 | 2 | 0.90 | 1.15 |
| LPC-18:2:0(18:2:0) | 18 | 2 | 0 | 0.90 | 1.15 |
| SM-39:2:2 | 39 | 2 | 2 | 0.97 | 1.14 |
| PC-36:1:0(18:1:0-18:0:0) | 36 | 1 | 0 | 0.86 | 1.14 |
| SM-34:1:2 | 34 | 1 | 2 | 0.73 | 1.13 |
| PC O--34:3:0 | 34 | 3 | 0 | 0.76 | 1.13 |
| PC-32:0:0(16:0:0-16:0:0) | 32 | 0 | 0 | 0.76 | 1.13 |
| SM-35:1:2 | 35 | 1 | 2 | 0.78 | 1.13 |
| PC-32:1:0(14:0:0-18:1:0) | 32 | 1 | 0 | 0.94 | 1.13 |
| PC O--38:6:0 | 38 | 6 | 0 | 0.87 | 1.13 |
| PC-34:2:0(16:0:0-18:2:0) | 34 | 2 | 0 | 0.76 | 1.13 |
| PC-36:3:0(16:0:0-20:3:0) | 36 | 3 | 0 | 1.03 | 1.13 |
| SM-36:1:2 | 36 | 1 | 2 | 0.78 | 1.13 |
| SE-43:2:0(27:1:0-16:1:0) | 43 | 2 | 0 | 1.34 | 1.12 |
| Cer-40:1:2 | 40 | 1 | 2 | 0.87 | 1.12 |
| TAG-46:2:0 | 46 | 2 | 0 | 1.28 | 1.12 |
| SM-34:2:2 | 34 | 2 | 2 | 0.77 | 1.12 |
| SM-39:1:2 | 39 | 1 | 2 | 0.87 | 1.12 |
| Cer-42:2:2 | 42 | 2 | 2 | 0.84 | 1.12 |
| LPC-18:1:0(18:1:0) | 18 | 1 | 0 | 0.93 | 1.12 |
| PC-40:5:0(22:5:0-18:0:0) | 40 | 5 | 0 | 1.16 | 1.11 |
| PC-37:4:0(20:4:0-17:0:0) | 37 | 4 | 0 | 1.16 | 1.11 |
| SM-37:1:2 | 37 | 1 | 2 | 0.81 | 1.11 |
| TAG-46:0:0 | 46 | 0 | 0 | 2.46 | 1.11 |
| SM-41:3:2 | 41 | 3 | 2 | 0.90 | 1.11 |
| Cer-40:2:2 | 40 | 2 | 2 | 0.75 | 1.11 |
| SE-45:2:0(27:1:0-18:1:0) | 45 | 2 | 0 | 1.03 | 1.11 |
| PE-38:4:0(20:4:0-18:0:0) | 38 | 4 | 0 | 1.08 | 1.11 |
| SM-38:2:2 | 38 | 2 | 2 | 0.82 | 1.11 |
| PC-36:2:0(18:0:0-18:0:0) | 36 | 2 | 0 | 0.67 | 1.10 |
| TAG-58:7:0 | 58 | 7 | 0 | 1.50 | 1.10 |
| PC O--36:3:0 | 36 | 3 | 0 | 0.55 | 1.10 |
| Cer-41:1:2 | 41 | 1 | 2 | 0.89 | 1.10 |
| Compound | Retention Time (min) | Peak Area | d3 | d4 | d5 |
|----------|---------------------|-----------|----|----|----|
| PC O--34:2:0 | 34 | 2 | 0 | 0.90 | 1.10 |
| PC-34:2:0(16:1:0-18:1:0) | 34 | 2 | 0 | 0.83 | 1.10 |
| PC-32:2:0(14:0:0-18:2:0) | 32 | 2 | 0 | 1.38 | 1.10 |
| SM-42:3:2 | 42 | 3 | 2 | 0.77 | 1.10 |
| PC-36:2:0(18:1:0-18:1:0) | 36 | 2 | 0 | 0.50 | 1.09 |
| PC O--34:1:0 | 34 | 1 | 0 | 0.80 | 1.09 |
| PC-35:1:0(17:0:0-18:1:0) | 35 | 1 | 0 | 0.92 | 1.09 |
| SM-41:1:2 | 41 | 1 | 2 | 0.86 | 1.09 |
| SM-36:2:2 | 36 | 2 | 2 | 0.76 | 1.09 |
| PC-38:5:0(16:0:0-22:5:0) | 38 | 5 | 0 | 1.26 | 1.09 |
| Cer-41:2:2 | 41 | 2 | 2 | 0.77 | 1.09 |
| Cer-42:1:2 | 42 | 1 | 2 | 1.04 | 1.09 |
| ST-27:1:0 | 27 | 1 | 0 | 1.09 | 1.09 |
| SE-44:2:0(27:1:0-17:1:0) | 44 | 2 | 0 | 1.07 | 1.09 |
| PC-34:3:0(16:1:0-18:2:0) | 34 | 3 | 0 | 0.78 | 1.09 |
| TAG-48:0:0 | 48 | 0 | 0 | 2.03 | 1.09 |
| PC-30:0:0(14:0:0-16:0:0) | 30 | 0 | 0 | 1.04 | 1.09 |
| TAG-46:1:0 | 46 | 1 | 0 | 1.34 | 1.08 |
| SM-32:1:2 | 32 | 1 | 2 | 0.58 | 1.08 |
| SM-42:2:2 | 42 | 2 | 2 | 0.88 | 1.08 |
| SE-47:6:0(27:1:0-20:5:0) | 47 | 6 | 0 | 1.88 | 1.08 |
| PC-36:4:0(18:2:0-18:2:0) | 36 | 4 | 0 | 0.58 | 1.08 |
| LPE-18:0:0(18:0:0) | 18 | 0 | 0 | 1.00 | 1.08 |
| PC O--32:1:0 | 32 | 1 | 0 | 0.81 | 1.08 |
| PC-34:3:0(18:3:0-16:0:0) | 34 | 3 | 0 | 0.93 | 1.07 |
| TAG-56:8:0 | 56 | 8 | 0 | 1.90 | 1.07 |
| PI-34:1:0(18:1:0-16:0:0) | 34 | 1 | 0 | 1.41 | 1.07 |
| SE-41:1:0(27:1:0-14:0:0) | 41 | 1 | 0 | 1.10 | 1.07 |
| PC O--38:5:0 | 38 | 5 | 0 | 0.76 | 1.07 |
| PC-38:3:0(20:3:0-18:0:0) | 38 | 3 | 0 | 1.06 | 1.07 |
| LPE-18:1:0(18:1:0) | 18 | 1 | 0 | 0.81 | 1.07 |
| Cer-42:3:2 | 42 | 3 | 2 | 0.83 | 1.07 |
| PE O--38:7:0 | 38 | 7 | 0 | 1.52 | 1.07 |
| PE O--38:6:0 | 38 | 6 | 0 | 1.23 | 1.07 |
| SM-40:3:2 | 40 | 3 | 2 | 0.76 | 1.07 |
| SE-45:4:0(27:1:0-18:3:0) | 45 | 4 | 0 | 1.15 | 1.07 |
| PC-38:5:0(20:4:0-18:1:0) | 38 | 5 | 0 | 0.88 | 1.06 |
| PE O--40:7:0 | 40 | 7 | 0 | 1.07 | 1.06 |
| PC O--37:5:0 | 37 | 5 | 0 | 0.65 | 1.06 |
| PE O--40:8:0 | 40 | 8 | 0 | 1.15 | 1.05 |
| Cer-38:1:2 | 38 | 1 | 2 | 0.80 | 1.05 |
In bold, lipid species with VIP ≥ 1.2. In bold and italic, lipid species with saturated or monounsaturated aliphatic fatty acid chains and VIP ≥ 1.2. CN, controls; db, double bound. er, ceramide; DAG, diacylglyceride; LPC, lysophosphatidylcholine; LPE, lysophosphatidylethanolamine; LPE O, lysophosphatidylethanolamine ether; PC, phosphatidylcholine; PC O, phosphatidylcholine ether; PE, phosphatidylethanolamine; PE O, phosphatidylethanolamine ether; PI, phosphatidylinositol; SE, steryl ester; SM, sphingomyelin; TAG, triacylglyceride.

| Lipid Species       | VIP | 10| 11| 12| 13|
|---------------------|-----|---|---|---|---|
| PC O--32:2:0        | 32  | 2 | 0 | 1.08 | 1.05 |
| PC-34:0:0(16:0:0-18:0:0) | 34  | 0 | 0 | 0.79 | 1.04 |
| SE-49:6:0(27:1:0-22:5:0) | 49  | 6 | 0 | 1.31 | 1.04 |
| PC-38:4:0(18:1:0-20:3:0) | 38  | 4 | 0 | 0.89 | 1.04 |
| LPC-18:0:0(18:0:0)  | 18  | 0 | 0 | 0.84 | 1.04 |
| PC O--40:7:0        | 40  | 7 | 0 | 0.86 | 1.04 |
| LPC-16:0:0(16:0:0)  | 16  | 0 | 0 | 0.88 | 1.04 |
| PC-36:4:0(16:0:0-20:4:0) | 36  | 4 | 0 | 0.82 | 1.04 |
| LPC-17:2:0(17:2:0)  | 17  | 2 | 0 | 1.35 | 1.04 |
| PC O--36:4:0        | 36  | 4 | 0 | 0.72 | 1.04 |
| TAG-58:8:0          | 58  | 8 | 0 | 1.37 | 1.03 |
| PE O--36:3:0        | 36  | 3 | 0 | 0.71 | 1.03 |
| PC-38:6:0(16:0:0-22:6:0) | 38  | 6 | 0 | 1.10 | 1.03 |
| PI-38:3:0(18:0:0-20:3:0) | 38  | 3 | 0 | 0.93 | 1.03 |
| Cer-39:1:2          | 39  | 1 | 2 | 0.85 | 1.03 |
| SM-42:1:2           | 42  | 1 | 2 | 1.29 | 1.02 |
| PC-36:5:0(20:5:0-16:0:0) | 36  | 5 | 0 | 1.63 | 1.02 |
| PI-34:2:0(18:2:0-16:0:0) | 34  | 2 | 0 | 1.03 | 1.02 |
| PC-38:4:0(20:4:0-18:0:0) | 38  | 4 | 0 | 0.88 | 1.01 |
| LPC-20:5:0(20:5:0)  | 20  | 5 | 0 | 1.72 | 1.01 |
| PC-36:3:0(18:3:0-18:0:0) | 36  | 3 | 0 | 0.72 | 1.01 |
| PI-36:4:0(20:4:0-16:0:0) | 36  | 4 | 0 | 0.55 | 1.01 |
Table S7. All lipid species analyzed and ratios in DM versus controls or MI versus controls and respective VIP values obtained from the DM OPLS model and the MI OPLS model

| Lipid specie       | Total length | Total db | Total oh | FA1 length | FA1 db | FA2 length | FA2 db | Ratio DM vs CN | VIP value DM Model | Ratio MI vs CN | VIP value MI Model |
|--------------------|--------------|----------|----------|------------|--------|------------|--------|----------------|-------------------|----------------|--------------------|
| Cer-32:1:2         | 32           | 1        | 2        | 14         | 0      | 1.12       |        | 0.69          | 0.81              | 0.60            |                    |
| Cer-33:1:2         | 33           | 1        | 2        | 15         | 0      | 1.39       |        | 0.64          | 0.76              | 0.63            |                    |
| Cer-34:1:2         | 34           | 1        | 2        | 16         | 0      | 1.13       |        | 0.65          | 1.17              | 0.74            |                    |
| Cer-34:2:2         | 34           | 2        | 2        | 16         | 1      | 0.83       |        | 0.75          | 0.74              | 0.73            |                    |
| Cer-36:1:2         | 36           | 1        | 2        | 18         | 0      | 1.30       |        | 0.85          | 0.86              | 0.92            |                    |
| Cer-36:2:2         | 36           | 2        | 2        | 18         | 1      | 1.63       |        | 0.52          | 1.70              | 0.31            |                    |
| Cer-37:1:2         | 37           | 1        | 2        | 19         | 0      | 1.77       |        | 0.53          | 1.13              | 0.61            |                    |
| Cer-38:1:2         | 38           | 1        | 2        | 20         | 0      | 1.37       |        | 0.92          | 0.80              | 1.05            |                    |
| Cer-39:1:2         | 39           | 1        | 2        | 21         | 0      | 1.46       |        | 0.92          | 0.85              | 1.03            |                    |
| Cer-40:1:2         | 40           | 1        | 2        | 22         | 0      | 1.15       |        | 1.06          | 0.87              | 1.12            |                    |
| Cer-40:2:2         | 40           | 2        | 2        | 22         | 1      | 1.20       |        | 0.96          | 0.75              | 1.11            |                    |
| Cer-41:1:2         | 41           | 1        | 2        | 23         | 0      | 1.21       |        | 1.05          | 0.89              | 1.10            |                    |
| Cer-41:2:2         | 41           | 2        | 2        | 23         | 1      | 1.25       |        | 0.92          | 0.77              | 1.09            |                    |
| Cer-42:1:2         | 42           | 1        | 2        | 24         | 0      | 1.12       |        | 1.07          | 1.04              | 1.09            |                    |
| Cer-42:2:2         | 42           | 2        | 2        | 24         | 1      | 1.12       |        | 0.92          | 0.84              | 1.12            |                    |
| Cer-43:2:2         | 42           | 3        | 2        | 24         | 2      | 1.19       |        | 0.84          | 0.83              | 1.07            |                    |
| DAG-32:0:0(16:0:0-16:0:0) | 32 | 0 | 0 | 16 | 0 | 0.90 | | 0.57 | 2.91 | 0.39 |
| DAG-34:0:0(18:0:0-16:0:0) | 34 | 0 | 0 | 18 | 0 | 0.73 | | 0.68 | 1.54 | 0.56 |
| DAG-34:1:0(18:1:0-16:0:0) | 34 | 1 | 0 | 18 | 1 | 0.97 | | 0.59 | 1.36 | 0.52 |
| DAG-34:2:0(18:2:0-16:0:0) | 34 | 2 | 0 | 18 | 2 | 1.24 | | 0.72 | 1.92 | 0.91 |
| DAG-36:2:0(18:1:0-18:1:0) | 36 | 2 | 0 | 18 | 1 | 18 | 1 | | 0.94 | 0.62 | 1.22 | 0.56 |
| DAG-36:3:0(18:1:0-18:2:0) | 36 | 3 | 0 | 18 | 1 | 18 | 2 | | 0.84 | 1.18 | 1.27 | 1.22 |
| DAG-36:4:0(18:2:0-18:2:0) | 36 | 4 | 0 | 18 | 2 | 18 | 2 | | 0.76 | 0.72 | 1.62 | 0.82 |
| HexCer-34:1:2      | 34           | 1        | 2        | 16         | 0      | 0.93       |        | 0.88          | 0.82              | 0.84            |                    |
| HexCer-40:1:2      | 40           | 1        | 2        | 22         | 0      | 0.53       |        | 0.90          | 0.86              | 0.93            |                    |
| HexCer-42:1:2      | 42           | 1        | 2        | 24         | 0      | 0.62       |        | 0.89          | 1.08              | 0.88            |                    |
| HexCer-42:2:2      | 42           | 2        | 2        | 24         | 1      | 0.44       |        | 0.86          | 0.45              | 0.87            |                    |
| LPA-16:0:0(16:0:0) | 16           | 0        | 0        | 16         | 0      | 1.22       |        | 0.98          | 0.97              | 0.82            |                    |
| LPA-16:1:0(16:1:0) | 16           | 1        | 0        | 16         | 1      | 0.90       |        | 0.49          | 1.12              | 0.42            |                    |
| LPA-18:1:0(18:1:0) | 18           | 1        | 0        | 18         | 1      | 0.77       |        | 0.66          | 0.56              | 0.73            |                    |
| LPA-18:2:0(18:2:0) | 18           | 2        | 0        | 18         | 2      | 0.92       |        | 0.77          | 0.88              | 0.75            |                    |
| LPA-20:4:0(20:4:0) | 20           | 4        | 0        | 20         | 4      | 1.01       |        | 0.31          | 1.32              | 0.44            |                    |
| LPC-14:0:0(14:0:0) | 14           | 0        | 0        | 14         | 0      | 1.24       |        | 0.81          | 1.01              | 0.86            |                    |
| LPC-15:0:0(15:0:0) | 15 0 0 15 0 | 1.14 0.79 1.21 0.93 |
| LPC-16:0:0(16:0:0) | 16 0 0 16 0 | 0.98 0.86 0.88 1.04 |
| LPC-16:1:0(16:1:0) | 16 1 0 16 1 | 1.35 0.89 1.20 0.94 |
| LPC-17:1:0(17:1:0) | 17 1 0 17 1 | 1.43 0.76 1.38 0.78 |
| LPC-17:2:0(17:2:0) | 17 2 0 17 2 | 1.05 1.09 1.35 1.04 |
| LPC-18:0:0(18:0:0) | 18 0 0 18 0 | 0.92 0.98 0.84 1.04 |
| LPC-18:1:0(18:1:0) | 18 1 0 18 1 | 1.09 1.04 0.93 1.12 |
| LPC-18:2:0(18:2:0) | 18 2 0 18 2 | 0.85 1.16 0.90 1.15 |
| LPC-18:3:0(18:3:0) | 18 3 0 18 3 | 1.11 0.96 0.85 0.97 |
| LPC-19:3:0(19:3:0) | 19 3 0 19 3 | 0.90 0.82 0.94 0.69 |
| LPC-20:3:0(20:3:0) | 20 3 0 20 3 | 1.72 0.85 1.21 0.74 |
| LPC-20:4:0(20:4:0) | 20 4 0 20 4 | 0.92 0.72 1.01 0.77 |
| LPC-20:5:0(20:5:0) | 20 5 0 20 5 | 1.53 1.07 1.72 1.01 |
| LPC-22:6:0(22:6:0) | 22 6 0 22 6 | 1.19 0.80 1.25 0.96 |
| LPC-16:0:0(16:0:0) | 16 0 0 16 0 | 1.08 0.88 1.03 0.98 |
| LPC-18:0:0(18:0:0) | 18 0 0 18 0 | 1.02 0.93 1.00 1.08 |
| LPC-18:1:0(18:1:0) | 18 1 0 18 1 | 1.00 1.05 0.81 1.07 |
| LPC-18:2:0(18:2:0) | 18 2 0 18 2 | 1.00 1.21 0.94 1.15 |
| LPC-20:2:0(20:2:0) | 20 2 0 20 2 | 0.53 0.88 0.45 0.87 |
| LPC-20:3:0(20:3:0) | 20 3 0 20 3 | 1.44 0.81 0.97 0.89 |
| LPC-20:4:0(20:4:0) | 20 4 0 20 4 | 0.96 0.78 0.90 0.83 |
| LPC-20:5:0(20:5:0) | 20 5 0 20 5 | 1.63 1.11 2.28 0.95 |
| LPC-22:5:0(22:5:0) | 22 5 0 22 5 | 1.13 0.80 0.60 0.88 |
| LPC-22:6:0(22:6:0) | 22 6 0 22 6 | 1.34 0.78 1.12 0.86 |
| LPC-16:1:0(16:1:0) | 16 1 0 16 1 | 0.99 0.31 0.52 0.25 |
| LPC-18:1:0(18:1:0) | 18 1 0 18 1 | 0.61 0.43 0.35 0.41 |
| LPC-18:2:0(18:2:0) | 18 2 0 18 2 | 1.43 0.57 1.02 0.51 |
| LPC-20:3:0(20:3:0) | 20 3 0 20 3 | 1.58 0.52 1.40 0.60 |
| LPC-20:4:0(20:4:0) | 20 4 0 20 4 | 1.21 0.62 0.95 0.63 |
| PC-30:0:0(14:0:0-16:0:0) | 30 0 0 14 0 16 0 | 1.30 1.23 1.04 1.09 |
| PC-31:0:0(14:0:0-17:0:0) | 31 0 0 14 0 17 0 | 1.51 0.55 0.67 0.58 |
| PC-32:0:0(16:0:0-16:0:0) | 32 0 0 16 0 16 0 | 1.25 1.21 0.76 1.13 |
| PC-32:1:0(14:0:0-18:1:0) | 32 1 0 14 0 18 1 | 1.36 1.19 0.94 1.13 |
| PC-32:2:0(16:0:0-16:0:0) | 32 1 0 16 1 16 0 | 1.64 1.27 1.22 1.16 |
| PC-33:0:0(14:0:0-18:2:0) | 32 2 0 14 0 18 2 | 1.13 1.16 1.38 1.10 |
| PC-33:1:0(16:0:0-17:1:0) | 33 1 0 16 0 17 1 | 1.27 0.73 2.70 0.68 |
| PC-34:0:0(16:0:0-18:0:0) | 34 0 0 16 0 18 0 | 0.95 1.13 0.79 1.04 |
| PC-34:1:0(16:0:0-18:1:0) | 34 1 0 16 0 18 1 | 1.36 1.22 0.93 1.17 |
| PC-34:2:0(16:0:0-18:2:0) | 34 2 0 16 0 18 2 | 0.94 1.23 0.76 1.13 |
| Compound                     | Mass (Da) | retention time (min) | peak area (nA s) |
|------------------------------|-----------|----------------------|------------------|
| PC-34:2:0(16:1:0-18:1:0)     | 34        | 2                    | 16               |
| PC-34:3:0(16:1:0-18:2:0)     | 34        | 3                    | 18               |
| PC-34:3:0(18:3:0-16:0:0)     | 34        | 3                    | 18               |
| PC-35:1:0(17:0:0-18:1:0)     | 35        | 1                    | 17               |
| PC-35:2:0(18:2:0-17:0:0)     | 35        | 2                    | 18               |
| PC-36:1:0(16:0:0-20:1:0)     | 36        | 1                    | 16               |
| PC-36:1:0(18:1:0-18:0:0)     | 36        | 1                    | 18               |
| PC-36:2:0(16:0:0-20:2:0)     | 36        | 2                    | 16               |
| PC-36:2:0(18:1:0-18:1:0)     | 36        | 2                    | 18               |
| PC-36:2:0(18:2:0-18:0:0)     | 36        | 2                    | 18               |
| PC-36:3:0(16:0:0-20:3:0)     | 36        | 3                    | 16               |
| PC-36:3:0(18:2:0-18:1:0)     | 36        | 3                    | 18               |
| PC-36:3:0(18:3:0-18:0:0)     | 36        | 3                    | 18               |
| PC-36:4:0(16:0:0-20:4:0)     | 36        | 4                    | 16               |
| PC-36:4:0(18:2:0-18:2:0)     | 36        | 4                    | 18               |
| PC-36:5:0(20:5:0-16:0:0)     | 36        | 5                    | 20               |
| PC-37:4:0(20:4:0-17:0:0)     | 37        | 4                    | 20               |
| PC-38:2:0(18:0:0-20:2:0)     | 38        | 2                    | 18               |
| PC-38:3:0(20:3:0-18:0:0)     | 38        | 3                    | 20               |
| PC-38:4:0(18:1:0-20:3:0)     | 38        | 4                    | 18               |
| PC-38:4:0(20:4:0-18:0:0)     | 38        | 4                    | 20               |
| PC-38:5:0(16:0:0-22:5:0)     | 38        | 5                    | 16               |
| PC-38:5:0(20:4:0-18:1:0)     | 38        | 5                    | 20               |
| PC-38:5:0(20:5:0-18:0:0)     | 38        | 5                    | 20               |
| PC-38:6:0(16:0:0-22:6:0)     | 38        | 6                    | 16               |
| PC-40:5:0(22:5:0-18:0:0)     | 40        | 5                    | 22               |
| PC-40:6:0(22:6:0-18:0:0)     | 40        | 6                    | 22               |
| PC O-30:0:0                   | 30        | 0                    | 16               |
| PC O-30:1:0                   | 30        | 1                    | 18               |
| PC O-32:0:0                   | 32        | 0                    | 18               |
| PC O-32:1:0                   | 32        | 1                    | 20               |
| PC O-32:2:0                   | 32        | 2                    | 22               |
| PC O-34:1:0                   | 34        | 1                    | 16               |
| PC O-34:2:0                   | 34        | 2                    | 18               |
| PC O-34:3:0                   | 34        | 3                    | 20               |
| PC O-35:3:0                   | 35        | 3                    | 22               |
| PC O-35:4:0                   | 35        | 4                    | 16               |
| PC O-36:1:0                   | 36        | 1                    | 18               |
| PC O-36:2:0                   | 36        | 2                    | 20               |
| PC O-36:3:0                   | 36        | 3                    | 22               |
| PC O-36:4:0                   | 36        | 4                    | 30               |
| Compound   | Retention Time | Peak Height | Area | Width |
|------------|----------------|-------------|------|-------|
| PC O--37:5:0 | 37 5 0 | 0.95 | 0.99 | 0.65 | 1.06 |
| PC O--38:4:0 | 38 4 0 | 0.74 | 1.03 | 0.61 | 0.93 |
| PC O--38:5:0 | 38 5 0 | 0.89 | 1.06 | 0.76 | 1.07 |
| PC O--38:6:0 | 38 6 0 | 0.99 | 1.20 | 0.87 | 1.13 |
| PC O--40:5:0 | 40 5 0 | 1.33 | 0.88 | 0.54 | 0.90 |
| PC O--40:6:0 | 40 6 0 | 0.83 | 1.03 | 0.68 | 1.00 |
| PC O--40:7:0 | 40 7 0 | 1.29 | 1.14 | 0.86 | 1.04 |
| PC O--42:5:0 | 42 5 0 | 0.80 | 0.74 | 0.46 | 0.76 |
| PE-34:2:0(16:0:0-18:2:0) | 34 2 0 | 16 0 | 18 2 | 1.19 | 0.95 | 1.21 | 0.97 |
| PE-36:2:0(18:1:0-18:1:0) | 36 2 0 | 18 1 | 18 1 | 0.54 | 0.21 | 0.56 | 0.22 |
| PE-36:2:0(18:2:0-18:0:0) | 36 2 0 | 18 2 | 18 0 | 1.13 | 1.14 | 1.11 | 1.17 |
| PE-38:4:0(20:4:0-18:0:0) | 38 4 0 | 20 4 | 18 0 | 1.14 | 0.96 | 1.08 | 1.11 |
| PE O--34:2:0 | 34 2 0 | 0.77 | 0.82 | 0.72 | 0.84 |
| PE O--34:3:0 | 34 3 0 | 0.80 | 0.92 | 0.68 | 0.94 |
| PE O--36:2:0 | 36 2 0 | 0.43 | 0.68 | 0.43 | 0.77 |
| PE O--36:3:0 | 36 3 0 | 0.76 | 1.03 | 0.71 | 1.03 |
| PE O--36:4:0 | 36 4 0 | 0.76 | 0.82 | 0.64 | 0.85 |
| PE O--36:5:0 | 36 5 0 | 0.99 | 0.77 | 0.97 | 0.91 |
| PE O--36:6:0 | 36 6 0 | 1.79 | 1.08 | 2.36 | 0.93 |
| PE O--38:4:0 | 38 4 0 | 0.85 | 0.80 | 0.66 | 0.81 |
| PE O--38:5:0 | 38 5 0 | 0.63 | 0.73 | 1.15 | 0.85 |
| PE O--38:6:0 | 38 6 0 | 1.16 | 1.00 | 1.23 | 1.07 |
| PE O--38:7:0 | 38 7 0 | 1.46 | 1.09 | 1.52 | 1.07 |
| PE O--39:7:0 | 39 7 0 | 0.89 | 0.83 | 1.58 | 0.81 |
| PE O--40:5:0 | 40 5 0 | 0.96 | 0.64 | 1.18 | 0.77 |
| PE O--40:6:0 | 40 6 0 | 1.24 | 0.87 | 0.92 | 0.92 |
| PE O--40:7:0 | 40 7 0 | 1.23 | 1.01 | 1.07 | 1.06 |
| PE O--40:8:0 | 40 8 0 | 1.18 | 1.05 | 1.15 | 1.05 |
| PI-34:1:0(18:1:0-16:0:0) | 34 1 0 | 18 1 | 16 0 | 1.40 | 1.18 | 1.41 | 1.07 |
| PI-34:2:0(18:2:0-16:0:0) | 34 2 0 | 18 2 | 16 0 | 1.64 | 1.10 | 1.03 | 1.02 |
| PI-36:1:0(18:0:0-18:1:0) | 36 1 0 | 18 0 | 18 1 | 1.01 | 1.15 | 0.67 | 0.99 |
| PI-36:2:0(18:0:0-18:2:0) | 36 2 0 | 18 0 | 18 2 | 1.10 | 1.05 | 0.94 | 0.92 |
| PI-36:2:0(18:1:0-18:1:0) | 36 2 0 | 18 1 | 18 1 | 0.86 | 1.01 | 0.37 | 0.81 |
| PI-36:3:0(18:1:0-18:2:0) | 36 3 0 | 18 1 | 18 2 | 0.65 | 0.86 | 0.42 | 0.60 |
| PI-36:4:0(20:4:0-16:0:0) | 36 4 0 | 20 4 | 16 0 | 2.03 | 1.01 | 0.55 | 1.01 |
| PI-38:3:0(18:0:0-20:3:0) | 38 3 0 | 18 0 | 20 3 | 1.31 | 1.02 | 0.93 | 1.03 |
| PI-38:4:0(18:0:0-20:4:0) | 38 4 0 | 18 0 | 20 4 | 0.88 | 0.85 | 0.75 | 1.00 |
| SE-41:1:0(27:1:0-14:0:0) | 41 1 0 | 27 1 | 14 0 | 1.48 | 1.16 | 1.10 | 1.07 |
| SE-41:2:0(27:1:0-14:1:0) | 41 2 0 | 27 1 | 14 1 | 1.12 | 0.87 | 2.25 | 0.79 |
| SE-42:1:0(27:1:0-15:0:0) | 42 1 0 | 27 1 | 15 0 | 1.06 | 1.04 | 0.68 | 0.96 |
| SE-43:1:0(27:1:0-16:0:0) | 43 1 0 | 27 1 | 16 0 | 1.09 | 1.15 | 1.01 | 1.17 |
| SM-32:1,2 | 32 | 1 | 2 | 14 | 0 | 1,16 | 1,15 | 0,58 | 1,08 |
| SM-32:2,2 | 32 | 2 | 2 | 14 | 1 | 0,99 | 1,04 | 0,49 | 0,98 |
| SM-33:1,2 | 33 | 1 | 2 | 15 | 0 | 1,09 | 1,12 | 0,80 | 1,17 |
| SM-33:2,2 | 33 | 2 | 2 | 15 | 1 | 1,39 | 0,71 | 0,95 | 0,77 |
| SM-34:0,2 | 34 | 0 | 2 | 16 | 0 | 1,12 | 0,85 | 1,55 | 0,87 |
| SM-34:1,2 | 34 | 1 | 2 | 16 | 0 | 0,97 | 1,10 | 0,73 | 1,13 |
| SM-34:1,3 | 34 | 1 | 3 | 16 | 0 | 0,94 | 0,74 | 0,61 | 0,72 |
| SM-34:2,2 | 34 | 2 | 2 | 16 | 1 | 0,97 | 1,02 | 0,77 | 1,12 |
| SM-35:1,2 | 35 | 1 | 2 | 17 | 0 | 1,04 | 1,02 | 0,78 | 1,13 |
| SM-35:2,2 | 35 | 2 | 2 | 17 | 1 | 1,42 | 1,06 | 0,68 | 1,18 | 0,86 |
| SM-36:1,2 | 36 | 1 | 2 | 18 | 0 | 1,06 | 1,00 | 0,78 | 1,13 |
| SM-36:2,2 | 36 | 2 | 2 | 18 | 1 | 0,97 | 0,92 | 0,76 | 1,09 |
| SM-36:3,2 | 36 | 3 | 2 | 18 | 2 | 0,80 | 0,83 | 0,47 | 0,86 |
| SM-37:1,2 | 37 | 1 | 2 | 19 | 0 | 1,15 | 0,97 | 0,81 | 1,11 |
| SM-37:2,2 | 37 | 2 | 2 | 19 | 1 | 1,04 | 0,80 | 1,07 | 0,95 |
| SM-38:1,2 | 38 | 1 | 2 | 20 | 0 | 1,16 | 1,04 | 0,90 | 1,15 |
| SHE-36:1,0 | 36 | 1 | 0 | | | 0,78 | 0,38 | 0,74 | 0,45 |
| TAG   | 1   | 2   | 3   | 4   | 5   | 6   | 7   | 8   |
|-------|-----|-----|-----|-----|-----|-----|-----|-----|
| SM-38:2:2 | 38  | 2   | 2   | 20  | 1   | 1.03| 0.92| 0.82|
| SM-39:2:2 | 39  | 1   | 2   | 21  | 0   | 1.12| 1.07| 0.87|
| SM-40:2:2 | 40  | 1   | 2   | 22  | 0   | 0.98| 1.09| 1.01|
| SM-41:2:2 | 41  | 1   | 2   | 23  | 0   | 0.89| 1.08| 0.86|
| SM-42:2:2 | 42  | 1   | 2   | 24  | 0   | 0.98| 1.06| 0.87|
| SM-43:2:2 | 43  | 2   | 2   | 25  | 1   | 1.13| 0.95| 0.76|
| ST-27:1:0 | 27  | 1   | 0   |     |     | 1.14| 1.07| 1.09|
| TAG-46:0:0 | 46  | 0   | 0   |     |     | 0.90| 1.13| 2.46|
| TAG-47:0:0 | 47  | 0   | 0   |     |     | 0.93| 1.10| 1.34|
| TAG-48:0:0 | 48  | 0   | 0   |     |     | 0.79| 1.05| 1.28|
| TAG-49:0:0 | 49  | 0   | 0   |     |     | 0.93| 1.10| 1.34|
| TAG-50:0:0 | 50  | 2   | 0   |     |     | 1.09| 1.14| 2.03|
| TAG-51:0:0 | 51  | 1   | 0   |     |     | 1.18| 1.24| 1.32|
| TAG-52:0:0 | 52  | 3   | 0   |     |     | 1.02| 1.21| 1.37|
| TAG-53:0:0 | 53  | 4   | 0   |     |     | 0.92| 1.19| 1.30|
| TAG-54:0:0 | 54  | 5   | 0   |     |     | 0.80| 1.12| 1.32|
| TAG-55:0:0 | 55  | 6   | 0   |     |     | 1.21| 1.14| 1.09|
| TAG-56:0:0 | 56  | 7   | 0   |     |     | 1.23| 1.18| 1.13|
| TAG-57:0:0 | 57  | 8   | 0   |     |     | 1.04| 1.19| 1.16|
| TAG-58:0:0 | 58  | 9   | 0   |     |     | 0.86| 1.15| 1.21|
| TAG-59:0:0 | 59  | 10  | 0   |     |     | 1.10| 1.18| 1.33|
| TAG-60:0:0 | 60  | 11  | 0   |     |     | 0.93| 1.20| 1.38|
| TAG-61:0:0 | 61  | 12  | 0   |     |     | 0.84| 1.21| 1.40|
| TAG-62:0:0 | 62  | 13  | 0   |     |     | 0.86| 1.20| 1.42|
| TAG-63:0:0 | 63  | 14  | 0   |     |     | 1.03| 1.20| 1.67|
| TAG-64:0:0 | 64  | 15  | 0   |     |     | 0.98| 1.15| 0.90|
| TAG-65:0:0 | 65  | 16  | 0   |     |     | 1.01| 1.18| 1.01|
| TAG-66:0:0 | 66  | 17  | 0   |     |     | 1.01| 1.18| 1.01|
| TAG     | CN  | db | HexCer | LPA | LPC | LPE | LPE O | LPI | PC | PC O | PE | PE O | PI  | SE | SM | TAG |
|---------|-----|----|--------|-----|-----|-----|-------|-----|----|------|----|------|-----|----|----|-----|
| 53:4;0  | 53  | 4  | 0      | 0.92| 1.22| 1.22| 1.30  |     |    |      |    |      |     |    |    |     |
| 54:2;0  | 54  | 2  | 0      | 1.04| 1.16| 1.03| 1.23  |     |    |      |    |      |     |    |    |     |
| 54:3;0  | 54  | 3  | 0      | 0.98| 1.18| 0.92| 1.20  |     |    |      |    |      |     |    |    |     |
| 54:4;0  | 54  | 4  | 0      | 0.80| 1.23| 1.06| 1.23  |     |    |      |    |      |     |    |    |     |
| 54:5;0  | 54  | 5  | 0      | 0.83| 1.22| 1.21| 1.24  |     |    |      |    |      |     |    |    |     |
| 54:6;0  | 54  | 6  | 0      | 1.01| 1.20| 1.58| 1.23  |     |    |      |    |      |     |    |    |     |
| 54:7;0  | 54  | 7  | 0      | 1.26| 1.22| 1.80| 1.16  |     |    |      |    |      |     |    |    |     |
| 54:8;0  | 54  | 8  | 0      | 1.33| 1.18| 1.90| 1.07  |     |    |      |    |      |     |    |    |     |
| 56:2;0  | 56  | 2  | 0      | 0.80| 0.87| 1.05| 0.89  |     |    |      |    |      |     |    |    |     |
| 56:3;0  | 56  | 3  | 0      | 1.24| 0.85| 1.32| 0.74  |     |    |      |    |      |     |    |    |     |
| 56:4;0  | 56  | 4  | 0      | 1.00| 1.17| 1.16| 1.21  |     |    |      |    |      |     |    |    |     |
| 56:5;0  | 56  | 5  | 0      | 0.95| 1.13| 0.99| 1.22  |     |    |      |    |      |     |    |    |     |
| 56:6;0  | 56  | 6  | 0      | 1.06| 1.08| 1.49| 1.21  |     |    |      |    |      |     |    |    |     |
| 56:7;0  | 56  | 7  | 0      | 1.44| 1.16| 1.86| 1.18  |     |    |      |    |      |     |    |    |     |
| 56:8;0  | 56  | 8  | 0      | 1.33| 1.18| 1.90| 1.07  |     |    |      |    |      |     |    |    |     |
| 58:7;0  | 58  | 7  | 0      | 1.45| 1.13| 1.50| 1.10  |     |    |      |    |      |     |    |    |     |
| 58:8;0  | 58  | 8  | 0      | 1.47| 1.15| 1.37| 1.03  |     |    |      |    |      |     |    |    |     |
| 58:9;0  | 58  | 9  | 0      | 1.03| 1.12| 1.32| 0.91  |     |    |      |    |      |     |    |    |     |

CN, controls; db, double bound. Cer, ceramide; DAG, diacylglyceride; HexCer, very long chain monoglycosylated ceramide; LPA, lysophosphatidic acid; LPC, lysophosphatidylcholine; LPE, lysophosphatidylethanolamine; LPE O, lysophosphatidylethanolamine ether; LPI, lysophosphatidylinositol; PC, phosphatidylcholine; PC O, phosphatidylcholine ether; PE, phosphatidylethanolamine; PE O, phosphatidylethanolamine ether; PI, phosphatidylinositol; SE, steryl ester; SM, sphingomyelin; TAG, triacylglyceride.
### Table S8. FADS gene variants genotyped in MDC-CC and results for the association with DM in DIAGRAM (1)

| SNP     | Gene | Ch | Genotype MDC-CC | Risk Allele | Other Allele | P       | OR    | OR_95L | OR_95U |
|---------|------|----|-----------------|-------------|--------------|---------|-------|--------|--------|
| rs174550| FADS1| 11 | 231/238/54      | T           | C            | 2.9E-03 | 1.06  | 1.02   | 1.10   |
| rs174546| FADS1| 11 | 233/238/54      | T           | C            | 3.2E-03 | 1.06  | 1.02   | 1.10   |
| rs174547| FADS1| 11 | 233/238/54      | T           | C            | 3.3E-03 | 1.05  | 1.02   | 1.09   |
| rs174548| FADS1| 11 | 255/223/46      | C           | G            | 1.6E-03 | 1.06  | 1.02   | 1.10   |
| rs1535  | FADS1| 11 | 232/238/53      | A           | G            | 3.0E-03 | 1.06  | 1.02   | 1.10   |
| rs174576| FADS2| 11 | 233/237/55      | C           | A            | 4.2E-03 | 1.06  | 1.02   | 1.10   |
| rs174577| FADS2| 11 | 233/237/55      | C           | A            | 1.1E-02 | 1.05  | 1.01   | 1.08   |
| rs174583| FADS2| 11 | 233/234/56      | C           | T            | 6.5E-03 | 1.05  | 1.01   | 1.09   |
| rs174570| FADS2| 11 | 387/125/12      | C           | T            | 1.1E-02 | 1.06  | 1.01   | 1.12   |
| rs174593| FADS2| 11 | 303/199/23      | T           | C            | 2.1E-02 | 1.06  | 1.01   | 1.11   |
| rs174611| FADS2| 11 | 260/226/39      | T           | C            | 1.3E-02 | 1.05  | 1.01   | 1.09   |

Gene variants in italic are in LD with the gene variant in bold ($r^2 > 0.8$).

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Figure S1.
Figure S2.
Supplemental Figure Legends:

**Figure S1.** Comparison between significant loadings acyl chain length for DM and MI from OPLS models. Lipid species unique for DM (A), for MI (D); lipid species common for DM and MI but with discordant loadings according to fold change (B-E); lipid species common for DM and MI but with concordant loadings according to fold change (C-F).

**Figure S2.** Comparison between significant loadings acyl chain double bound numbers for DM and MI from OPLS models. Lipid species unique for DM (A), for MI (D); lipid species common for DM and MI but with discordant loadings according to fold change (B-E); lipid species common for DM and MI but with concordant loadings according to fold change (C-F).