Chapter 7

The effects of Roux-en-Y gastric bypass surgery on the plasma lipidome largely overlap with the effects of calorie restriction

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ABSTRACT

Objective

Disturbances in lipid metabolism are strongly associated with obesity and type 2 diabetes (T2DM). The aim of this study was to characterize the lipidome, associated with obesity in presence of normal glucose tolerance (NGT) and T2DM, and to determine the early effects of a very low calorie diet (VLCD), gastric banding (GB) or roux-en-Y-gastric bypass (RYGB) on the lipidome.

Methods

We included 30 obese NGT, 32 obese T2DM and 12 Lean controls. Obese subjects underwent GB or RYGB surgery, or a very-low-calorie-diet (VLCD) and were seen before and 3 weeks after the intervention. Fasting blood samples were taken and serum was analyzed using liquid chromatography coupled to mass spectrometry. In total 128 lipid species could be identified and quantified.

Results

At baseline, serum total triglyceride (TG) level was higher in T2DM, whereas total lyso-phospahtidylcholine (LPC), phopsphatidylethanolamine (PE) and lyso-phosphatidylethanolamine (LPE) levels were lower in all obese. In NGT, GB barely affected total levels of grouped lipid species, whereas RYGB significantly decreased total PC, sphingomyelin (SM), LPC and PE levels. In T2DM subjects, RYGB and VLCD decreased total TG, LPC and PE level. Total PC level was decreased only by VLCD.

Conclusions

Our data indicate that the lipidomes of obese NGT and obese T2DM differ significantly from Lean, predominantly in TG species between T2DM and Lean. The changes in lipidomes after GB, RYGB and VLCD interventions demonstrate a significant overlap and indicate that the common denominator of all interventions, caloric restriction, may underlie the majority of the observed effects on the lipidome.

INTRODUCTION

The pathogenesis of type 2 diabetes (T2DM) involves complex metabolic and inflammatory adaptations to over-nutrition and inactivity (1). During the development of over-nutrition-induced T2DM, the capacity of adipose tissue to store fatty acids is exceeded, and excess nutrients are diverted to muscle and liver which, alike adipose tissue, become insulin resistant (2). The induced disturbances in metabolism lead to lipotoxicity, glucotoxicity and inflammation. More specifically, lipid derived metabolites such as ceramides, triglycerides and diacylglycerols have the capacity to interfere negatively with insulin resistance (3-8). The serum lipid profile observed in obesity and insulin resistance is characterized by a relative increase in short chain saturated fatty acids (9;10), reflective of impaired elongation and desaturation (11-13) Furthermore, some specific lipid species are associated with traits of the metabolic syndrome (14;15). Lysophosphatidylcholines (LPCs), products of phosphatidylcholines (PCs), upregulate pro-inflammatory cytokines and have pro-atherogenic capacity (16). Sphingolipid derivatives (Ceramides (CEs) and Sphingomyelines (SMs)) are also associated with inflammation and insulin sensitivity (17-19).

Thus far, few studies addressed differences between obese normal glucose tolerant (NGT) and T2DM subjects. Moreover, the direct effect of distinct weight loss strategies, used in treatment of obesity and T2DM, on circulating lipid profiles, has not been evaluated. Very low calorie diets (20) and bariatric surgery (21;22) are effective means to improve glucose and lipid metabolism on the short term. In addition to calorie restriction, the gastro-intestinal rearrangements of the Roux-en-Y Gastric Bypass procedure are suggested to convey additional effects on glucose and lipid metabolism (23). Lipidomic profiling is a new tool providing an integrated profile of an individual's complete circulating lipid make-up, including the lipotoxic metabolites that are potentially responsible for the development of diabetes (24-26). At the population level, genome-wide association studies are identifying genetic loci linking lipidomic profiles with disease pathogenesis.

These studies have shown that the ratio between precursor and products of certain enzymatic reactions (used as a proxy of enzymatic activity) is a powerful measure to detect loci encoding these enzymes (27). Moreover, the enzyme activity of one of these enzymes (SCD1), for example, has been related to glucose tolerance (28;29).

The current study was performed to characterize the lipidomes of healthy subjects and of obese NGT or T2DM subjects at baseline and after different weigh loss interventions.

We hypothesized that the concentration of certain lipid species, specifically those thought to interfere with insulin signaling pathways, would be increased in T2DM as compared to NGT obese subjects. Furthermore, we hypothesized that the lipidomes of these groups would be affected more by Roux-en-Y Gastric Bypass as compared to pure calorie restriction (gastric banding or very low calorie diet), given the suggested additional effects of the gastrointestinal rearrangements on glucose and lipid metabolism.

SUBJECTS AND METHODS

Study design

The research design and methods have been described in detail elsewhere (30). In short, we included obese females eligible for both dietary and surgical treatment. The subjects had either normal fasting glucose (NGT) or T2DM (treated with oral medication only) according to WHO standards. Control subjects were lean, healthy females. The protocol was approved by the medical ethics committee of the Leiden University Medical Center, and all subjects provided written informed consent before participation.

Subjects were studied (after an overnight (10h) fast) within a month before surgery and between 2 and 3 weeks after surgery. Anthropometric measurements were and a fasting blood sample was taken. EDTA, heparin and citrate tubes were immediately put on ice. All blood samples, and serum samples when clotted, were centrifuged promptly (2000 g at 4 ºC, for 10 minutes) and subsequently plasma or serum was divided in separate plastic tubes and frozen (-80 ºC) until assay.

Interventions

Standard operating procedures were followed for GB and RYGB and patients were prescribed a staged meal plan after surgery (30). VLCD subjects were prescribed commercially available Prodimed® (Prodimed Benelux BV, Valkenswaard, The Netherlands), a high-protein-low-calorie meal replacement plan (VLCD) (30).

Assays

Serum glucose, triglycerides (TG) and C-Reactive Protein (CRP) were measured on a Modular Analytics P-800 system (Roche Diagnostics, Mannheim, Germany). Insulin was measured with an immunometric assay on an automated Immulite 2500 (Siemens, Breda, The Netherlands). HbA1c was measured in whole blood samples using a

High Performance Liquid Chromatography Integra 800 analyzer (Roche Diagnostics Mannheim, Germany). A commercial kit was employed for the assay of non-esterified fatty acids (Wako).

Lipids were extracted from 10 µL human plasma using isopropyl alcohol. In short, IPA containing internal standards are added to serum to precipitate proteins. After centrifugation the supernatant is transferred to vials for LC-MS analysis similar to the method reported by Hu *et al.* (31) and Castro-Perez *et al.* (32). In total 2.5 µL were injected into an Acquity UPLC-System (Waters, Milford, USA). The temperature of the autosampler was kept at 25°C. and the lipids were separated by reversed phase LC using an HSS-T3 column (Waters, Milford, USA). Analysis was performed at a flow rate of 0.4 milliliters/min at 45°C of column temperature using solvent A (40:60 H_2O-acetonitrile with 10mM ammonium formate) and solvent B (10:90 acetonitrile-isopropanol with 10mM ammonium formate) run in a gradient starting at 50% B and ramping to 97% B in 10 min with a 3 min hold at 97%B before reequilibration.

The UPLC system was coupled to an Accurate-Mass Quadrupole Time-of-Flight (Q-ToF) (Agilent 6530) equipped with an ESI source (Jet Stream Technology). The separated lipids were detected in the full scan positive ion mode. The capillary voltage was 3.5 kV, the gas temperature was kept at 325°C, the gas flow was 10 L/min; the sheath gas temperature was 400°C and the sheath gas flow 12 L/min, the nebulizer 35 psi. Stop time was 13 min. The MS was scanned from 350–1650 m/z. In order to cope with the dynamic range and the number of points across the peak the system was operated in the 2GHz mode.

The samples were measured in random order in sample batches of 76 or 86 samples, each. Each sample was analyzed only once. For QC samples a pooled plasma sample of all individual samples was prepared and spiked with the set of internal standards as well as calibration standards at a specific concentration level. In addition, calibration samples were prepared from these pooled plasma aliquots with a fixed concentration of internal standards and different concentrations of spiked calibration standards. Blank samples were prepared from water without standards and passed the whole procedure of sample preparation. QC and Blank samples were included every 12 samples representing a block of 3 volunteers. The samples of one block were randomized. The QC sample was injected a second time after the blank sample. In the beginning and the end of each batch, calibration samples were measured. Determination of peak areas of internal standards as well as target compounds were performed with Mass Hunter Quantification (version B.04.00 SP2; Agilent).

The data were measured in two separate batches. Batch to batch differences in sensitivity were corrected using corresponding baseline group samples. The peak areas were corrected for background using the blank samples. After that the areas of target compounds were normalized to appropriate internal standards as follows: lyso-phosphatidylcholines (LPCs) to LPC (17:0/0:0), phosphatidylcholines (PCs), sphingomyelines (SMs) and diacylglycerols (DGs) to (PC) (17:0/17:0), lyso-phosphatidylethanolamines (LPEs) and phosphatidylethanolamines (PEs) to (PE) (17:0/17:0) and cholesterol esters (CEs) and triacylglycerides (TGs) to TG (17:0/17:0/17:0).

Correction using the pooled QC samples as described before (33) was applied to compensate for shifts in the sensitivity of the mass spectrometers.

Data processing and statistics

Lipid levels are presented as normalized to internal standard. Also, we calculated lipid levels relative to summed lipid levels of one class. Differences between obese subjects groups and lean controls at baseline and the effects of the different interventions within each group were calculated with a mixed-effects model, with the patient groups and diabetes as fixed effects and the subject specific deviances modelled with random intercepts. Lipid levels were log transformed before statistical analysis. A p-value <0,05 was considered statistically significant for a single test, while for multiple tests the level of statistical significance was determined using Bonferroni's method. The statistical threshold for the derived measures (sum of individual lipids and ratios) was set at *p<0,0004202* (=p<0,05 divided by 17, the number of parameters tested, and by 7, the number of hypotheses tested). Galwey's method (34) was used to calculate the effective number of independent tests for the individual lipid levels, yielding 26 individual components. The statistical threshold for these analyses was set at *p<0,000275*(=p<0,05 divided by 26, the effective number of independent components, and by 7, the number of hypotheses tested). Graphs were developed in Prism Graph Pad 5.

Activity of Stearoyl-CoA desaturase (SCD), fatty acid desaturase (FADS-1) and elongases (ELOVLs) was estimated by calculating product/precursor ratios of the values of individual fatty acids according to the following equations: FADS1 = PC36:4/PC36:3 and PC38:4/PC38:3, Δ5 desaturase = LPC20:4/LCP20:3, Δ6 desaturase = LPC18:3/LPC18:2, Stearyl Co-A desaturase (SCD1) = LPC18:1/LPC18:0 and elongases (ELOVL-1s) = LPC18:0/LPC16:0 and LPC18:1/LPC16:1.

RESULTS

Baseline characteristics of subjects

Baseline subject characteristics are shown in table 1. All obese subjects and healthy controls were Caucasian females, with a mean age of 49.4 ± 0.6 yrs. We included 32 subjects with T2DM and 30 NGT obese individuals. Eight subjects dropped out during the course of the study because they were not able to comply with the VLCD (n=2), because of logistic issues (n=3); and because of mild postoperative complications (n=3) associated with the RYGB procedure. None of the subjects reported any problems adhering to the VLCD or the prescribed meal plan.

Baseline comparison of lean, NGT and T2DM subjects

Summed levels per lipid class

The levels of the individual lipid species belonging to one class were summed to arrive at an approximate measure for the total levels of grouped lipid species (table 2). We observed that, at baseline, TG level was higher in T2DM as compared to Lean, whereas LPC, PE and LPE levels were lower in T2DM subjects as compared to Lean.

Individual lipid levels

Levels of all lipids are shown in supplementary table 1a. The lipidome of T2DM subjects as compared to Lean is characterized by significantly different levels in 34 lipid species, 22 of which are increased TGs. The lipidome of NGT subjects differs from Lean subjects in 7 lipid species, 1 of which is a TG species. No major differences were observed between the lipidomes of NGT and T2DM subjects.

Relative lipid abundances per lipid class

To determine whether the relative abundance of lipid species relative to summed lipid levels differed between the Lean and Obese subjects, we determined the percentage contribution of every individual lipid to the total summed lipid species level. The majority of these relative to summed lipid levels of individual lipid species were comparable between Lean, NGT and T2DM subjects. Nevertheless, relative to summed lipid levels of polyunsaturated PCs (PC38:3 and PC38:4,) were higher in NGT and T2DM as compared to Lean (supplementary table 2a). Furthermore, we observed that within the SMs the level of SM18:1/16:0 was significantly lower in NGT and T2DM.

Effect of intervention

Three weeks after the initiation of the different interventions, weight loss was similar in all treatment groups. Moreover, there was a comparable effect of the VLCD and RYGB on glucose levels in T2DM subjects (data shown elsewhere (30)).

Table 1 - Baseline characteristics of study groups.

	NGT (30)	T2DM (32)	Controls (12)	P value
Age (yrs)	47.7 ± 6.4	51.0 ± 7.1	49.2 ± 6.22	p=ns
Weight (kg)	124.3 ± 11.7	117.2 ± 17.1	64.4 ± 7.2*	*
BMI (kg/m²)	43.8 ± 3.2	42.0 ± 5.5	21.7 ± 1.6*	*
Fasting glucose (mmol)	5.0 ± 0.6	8.7 ± 2.5#	4.7 ± 0.3	#
Fasting insulin (mU)	10.5 ± 7.9	12.0 ± 7.8	1.6 ± 0.2	*
HbA1c (mmol/mol)	36.1 ± 7.8	49.6 ± 12.0#	31.9 ± 2.5	#
Homa-ir (%)	2.3 ± 0.3	5.1 ± 0.1	0.3 ± 0.0*	*
Triglycerides (mmol/L)	1.5 ± 0.2	1.8 ± 0.1	1.0 ± 0.1	%
FFA (mmol/L)	1.0 ± 0.4	1.2 ± 0.3	0.9 ± 0.3	p=ns
CRP (mg/L)	7.1 ± 1.2	7.8 ± 1.1	1.9 ± 0.4*	*

Values are presented as mean ± sd.Differences between subject groups (NGT vs T2DM) and lean controls at baseline were compared with a mixed-effects model, with the patient groups and diabetes as fixed effects and the subject specific deviances modelled with random intercepts. The Bonferroni posthoc test was used to correct for multiple testing. *A p-value <0.0017* was considered statistically significant (= 0,05 divided by 10, the number of parameters tested, and by 3, the number of hypotheses tested). *= significant difference between NGT/T2DM and Lean; #=significant difference between Lean/NGT and T2DM; %=significant difference between T2DM and Lean.

Summed levels per lipid class

Again, after intervention, levels of the individual lipid species belonging to one class were summed to arrive at an approximate measure for the total levels of grouped lipid species (table 3). Only small differences were observed after GB. The levels of PCs, LPCs, PEs and Cer decreased significantly after RYGB or VLCD. Of note, in T2DM subjects there was a trend towards decreased total TG level after VLCD, and as compared to RYGB, the effect of VLCD on PCs was stronger.

Individual lipid levels

Changes in the levels of individual lipid species after intervention are presented in supplementary table 1b. In NGT subjects, GB affected 30 individual lipid species (of which 12 PCs and 12 SMs), whereas RYGB affected 69 individual lipids (of which 24 PCs, 18 TGs, and 14 SMs), 27 of which overlap between the interventions (supplementary figure 1). Virtually all lipid species that changed significantly showed a decrease. In T2DM subjects RYGB affected 69 individual lipid species (of which 22 PCs, 17 TG, 14 SMs) whereas VLCD affected 80 individual lipid species (of which 27 TGs, 25 PCs, and

Table 2 - Baseline absolute values of lipids (cumulative value of individual lipids within species).

	NGT	sd	T2DM	sd	Control	sd	NGT vs C	T2DM vs C	T2DM vs NGT
PC	115.73	± 18.50	118.32	± 23.75	120.22	± 18.60	5.128E-01	7.319E-01	6.860E-01
TG	106.04	± 43.16	140.96	± 53.02	74.63	± 23.53	1.365E-02	**4.854E-06**	3.455E-03
SM	21.74	± 2.64	19.98	± 1.75	20.23	± 2.00	4.452E-02	7.349E-01	3.014E-03
LPC	11.58	± 1.99	10.92	± 1.92	14.64	± 2.65	7.086E-04	**2.582E-05**	2.529E-01
PE	3.30	± 0.68	3.01	± 0.67	4.37	± 1.05	6.616E-04	**9.883E-06**	1.482E-01
DG	0.56	± 0.25	0.70	± 0.28	0.47	± 0.18	1.975E-01	1.845E-03	1.680E-02
CE	0.42	± 0.09	0.37	± 0.08	0.40	± 0.06	6.141E-01	1.152E-01	8.532E-03
Ceramides	0,33	± 0.08	0.33	± 0.06	0.32	± 0.07	6.233E-01	6.562E-01	9.502E-01
LPE	0.12	± 0.03	0.10	± 0.03	0.19	± 0.05	7.750E-04	**3.648E-06**	7.279E-02

Values are presented as normalized to internal standard and mean ± sd. Differences between subject groups (NGT vs T2DM) and lean controls at baseline were compared with a mixed-effects model, with the patient groups and diabetes as fixed effects and the subject specific deviances modelled with random intercepts. The Bonferroni posthoc test was used to correct for multiple testing. *A p-value <0.0004204* (indicated in bold) was considered statistically significant (= 0,05 divided by 17, the number of parameters tested, and by 7, the number of hypotheses tested).

Table 3 - Absolute values of lipids (cumulative value of individual lipids within species) before and after intervention.

	NGT-GB					NGT-RYGB				
	pre	sd	post	sd	p-value	pre	sd	post	sd	p-value
PC	**116.87**	± 16.6	**104.5**	± 14.56	5.13E-03	**114.95**	± 20.174	**91.35**	± 18.20	**2.39E-10**
TG	**105.92**	± 30.0	**120.9**	± 38.69	9.93E-02	**106.12**	± 51.263	**116.35**	± 39.35	6.18E-02
SM	**21.16**	± 2.38	**20.96**	± 2.07	4.69E-01	**22.14**	± 2.813	**19.88**	± 1.79	**5.89E-07**
LPC	**11.65**	± 1.96	**10.44**	± 2.39	4.22E-02	**11.54**	± 2.068	**9.00**	± 1.75	**1.58E-06**
PE	**3.38**	± 0.63	**2.97**	± 0.65	3.93E-02	**3.24**	± 0.731	**2.45**	± 0.66	**5.16E-08**
DG	**0.52**	± 0.15	**0.71**	± 0.19	2.52E-03	**0.58**	± 0.307	**0.66**	± 0.23	2.54E-02
CE	**0.42**	± 0.09	**0.41**	± 0.07	8.13E-01	**0.43**	± 0.102	**0.36**	± 0.07	2.42E-03
Cer	**0.32**	± 0.07	**0.27**	± 0.07	**3.05E-04**	**0.34**	± 0.086	**0.22**	± 0.06	**2.74E-13**
LPE	**0.12**	± 0.03	**0.11**	± 0.04	2.44E-01	**0.12**	± 0.031	**0.09**	± 0.03	4.42E-03

Values are presented as normalized to internal standard and mean ± sd. Differences within groups before and after intervention were calculated by mixed model analysis, with the patient groups and diabetes as fixed effects and the subject specific deviances modelled with random intercepts. The Bonferroni posthoc test was used to correct for multiple testing. *A p-value <0.0004204* (indicated in bold) was considered statistically significant (= 0,05 divided by 17, the number of parameters tested, and by 7, the number of hypotheses tested).

12 SMs), 62 of which overlap. Summarizing, the effects of all interventions in NGT and T2DM subjects, changes in 27 individual lipid overlap. Several lipids however, increased after GB and RYGB (i.e. PC36:4, TG52:2, TG52:3, TG52:4) in contrast to a decrease after the VLCD.

Relative lipid abundances per lipid class

The direction of change in abundance of lipid species relative to summed lipid levels was similar among all treatment groups (supplementary table 2b), independent of baseline disease status or intervention type (supplementary figure 2). However, the relative abundance of specific lipid species was affected by the interventions. Within the ceramides species, there was a decrease in abundance of Cer18:1/24:0 relative to the summed Cer level, coinciding with an increase in Cer18:1/24:1. Abundance of LPC16:0 relative to the summed LPC levels significantly increased, whereas LPC18:0 decreased after all interventions. Abundance of PC36:2, PC36:3 relative to summed PC level decreased, whereas PC36:4 abundance increased after all interventions. Similarly, a decrease in abundance of PC38:3 and an increase in abundance of PC38:4 was observed, and these effects were most pronounced after the VLCD. There was an increase in abundance of Sphingomyelines SM18:1/18:0, SM18:1/18:1, SM18:1/24:1 and

T2DM-RYGB					T2DM-VLCD				
pre	sd	post	sd	p-value	pre	sd	post	sd	p-value
117.04	± 14.92	**98.11**	± 12.70	**6.60E-07**	**119.78**	± 31.70	**89.70**	± 20.54	**1.30E-11**
144.85	± 47.08	**138.90**	± 39.98	**8.34E-01**	**136.47**	± 60.82	**102.68**	± 44.51	**7.39E-04**
19.60	± 1.69	**18.75**	± 1.67	**7.89E-03**	**20.41**	± 1.78	**19.72**	± 1.73	**1.45E-01**
10.91	± 2.03	**8.67**	± 1.82	**1.06E-05**	**10.93**	± 1.87	**8.18**	± 2.35	**1.52E-07**
2.95	± 0.55	**2.06**	± 0.38	**8.17E-10**	**3.08**	± 0.80	**2.01**	± 0.54	**4.76E-11**
0.76	± 0.30	**0.88**	± 0.30	**2.06E-02**	**0.64**	± 0.25	**0.62**	± 0.29	**3.95E-01**
0.35	± 0.08	**0.37**	± 0.05	**3.89E-01**	**0.39**	± 0.07	**0.35**	± 0.06	**1.59E-01**
0.32	± 0.06	**0.24**	± 0.07	**2.55E-08**	**0.33**	± 0.07	**0.23**	± 0.08	**1.25E-10**
0.10	± 0.03	**0.06**	± 0.03	**1.31E-08**	**0.11**	± 0.04	**0.07**	± 0.03	**4.62E-05**

SM18:1/24:2 and a decrease in abundance of SM18:1/22:0, SM18:1/22:1, SM18:1/23:0, SM18:1/24:0. In the TG species, there was a decrease in TG50:1 and TG50:2, whereas there was an increase in TG52:2 and TG52:3, these effects seemed more pronounced after the RYGB and the VLCD.

Enzyme pathway analysis / Lipid-ratios

Baseline estimated activity of Stearoyl-CoA desaturase (SCD), fatty acid desaturase (FADS-1) and elongases (ELOVLs) was obtained by calculating product:precursor ratios of the values of individual fatty acids (figure 1). No significant differences between groups were observed at baseline. FADS1 (PC 36:4/PC36:3 and PC 38:4/PC38:3) estimated activity significantly increased after all interventions. Δ5 desaturase (LPC20:4/LCP20:3) significantly increased after all interventions, whereas Δ6 desaturase (LPC 18:3/LPC18:2) significantly decreased after all interventions.

SCD (LPC18:1/LPC18:0) estimated activity significantly increased after all interventions. ELOVL-1 estimated activity based on the LPC18:0/LPC16:0 ratio significantly decreased after all interventions, whereas the change in ELOVL-1 estimated activity based on the LPC18:1/LPC16:1 ratio was not consistent (figure 2).

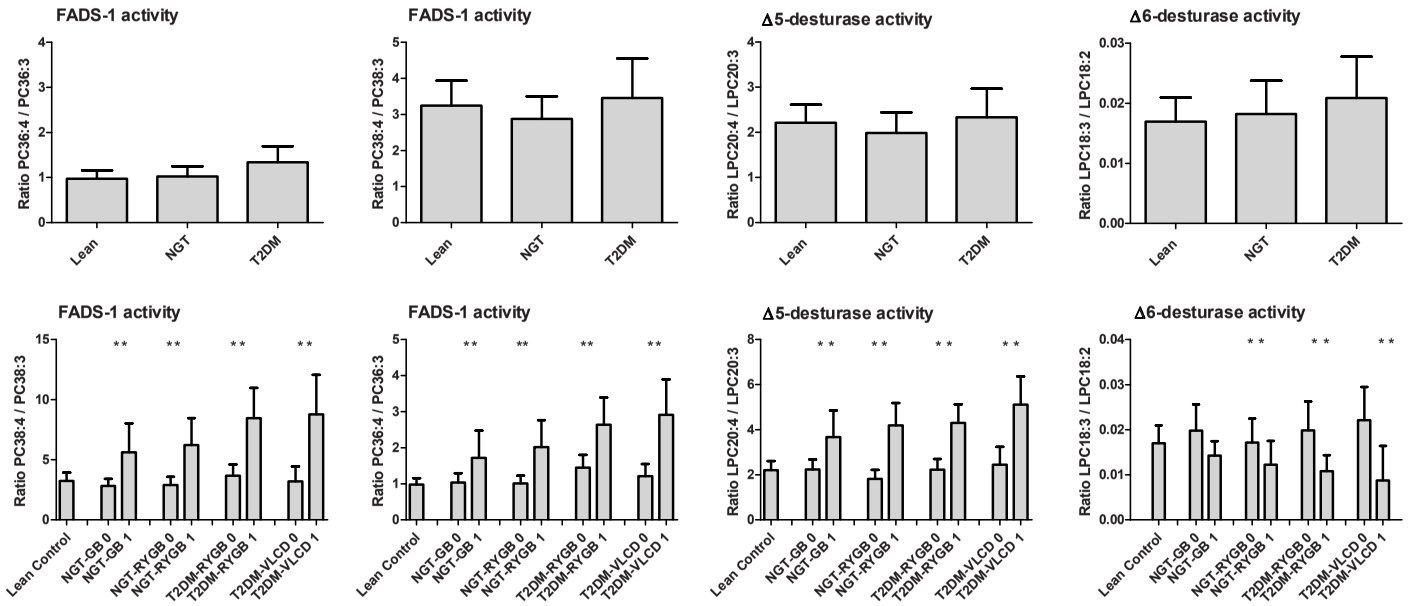

Figure 1. Lipid ratios reflecting FADS-1, D5-desaturase, D6-desaturase enzyme activity.

Enzyme activity is estimated by calculating product/precursor ratios of the values of individual fatty acids according to the following equations: FADS1 (PC 36:4/PC36:3) and (PC 38:4/PC38:3), D5 desaturase (LPC20:4/LCP20:3), D6 desaturase (LPC 18:3/LPC18:2). Values are shown as means ± sd. Differences within groups before and after intervention were calculated by mixed model analysis, with the patient groups and diabetes as fixed effects and the subject specific deviances modelled with random intercepts. The Bonferroniposthoc test was used to correct for multiple testing. A p-value <0.0004204 was considered statistically significant (= 0,05 divided by 17, the number of parameters tested, and by 7, the number of hypotheses tested. “Group name 0”=baseline, “Group name 1”= after intervention. **=significant effect of intervention after correction.

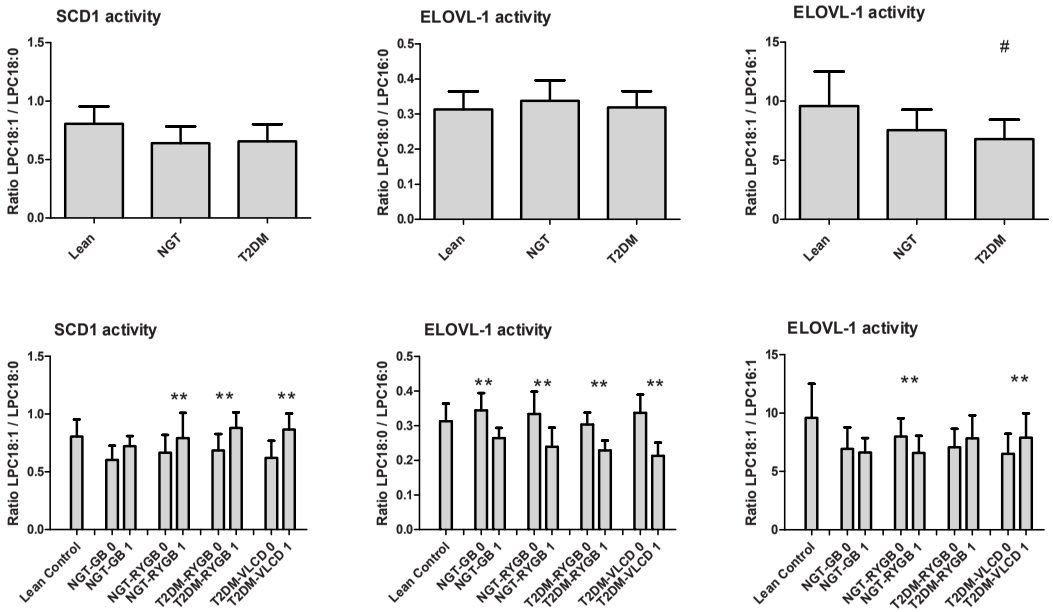

Figure 2. Lipid ratios reflecting SCD1, ELOVL enzyme activity.

Enzyme activity is estimated by calculating product/precursor ratios of the values of individual fatty acids according to the following equations: Stearyl Co-A desatrurase (SCD1): (LPC18:1/LPC18:0) and elongases (ELOVL-1s) (LPC18:0/LPC16:0) and (LPC18:1/LPC16:1). Values are shown as means ± sd. Differences within groups before and after intervention were calculated by mixed model analysis, with the patient. The Bonferroniposthoc test was used to correct for multiple testing. A p-value <0.0004204 was considered statistically significant (= 0,05 divided by 17, the number of parameters tested, and by 7, the number of hypotheses tested. "Group name 0"=baseline, "Group name 1"= after intervention. **=significant effect of intervention after correction, #=significant difference between Lean and T2DM at baseline after correction.

DISCUSSION

To the best of our knowledge, we are the first to report the short term effects of RYGB as compared to calorie restrictive weight loss interventions in equally obese subjects with NGT or T2DM on circulating lipid profiles in serum. An important finding of this study is that lipid profiles at baseline were very similar in T2DM and NGT subjects. We only observed a significantly higher total TG level and lower LPCs, PEs and LPEs levels in the T2DM subjects as compared to Lean, whereas differences between NGT and Lean subjects did not reach significance. Apparently, a lipid profile containing higher levels of TGs and lower levels of LPCs, PEs and LPCs characterizes obesity in general, whereas the development of T2DM is associated with a further, significant, increase in TG levels and significantly lower levels of LPCs, PEs and LPCs. This suggests a gradual process leading from metabolic disturbances, i.e. insulin resistance, in obesity towards more significant disturbances in T2DM. Furthermore, whereas total lipid concentrations differ, the relative levels of different individual lipid species remain similar, suggesting a certain equilibrium between components of each lipid class, which remains unaffected by obesity and T2DM.

A specific TG profile, characterized by TGs with shorter FA chain length and increased double bonds, reflective of impaired elongation and desaturation of fatty acids, was associated previously with an increased risk for development of T2DM in the general population (12). Accordingly, we found a higher total TG level, and moreover, a higher level of several saturated TG species in T2DM as compared to lean. In monozygotic twin pairs discordant for obesity, but without T2DM, increases in TGs have been associated with insulin resistance (15). Although still glucose tolerant, our NGT subjects were insulin resistant as measured by HOMAir. Also, they showed a trend towards a higher TG level as compared to lean. Thus, the quantitative and qualitative differences in TG concentrations between our 3 study populations may reflect distinct levels of insulin sensitivity.

Another important aspect of our study is the comparison of the effect of different weight loss strategies on lipid profiles. Absolute lipid levels of PCs, LPCs, PEs and Cer decreased significantly after RYGB and the VLCD, independent of baseline metabolic state (NGT or T2DM); which suggests an effect of short term calorie restriction *or* an effect of minimal weight loss. PCs and LPCs have been associated with inflammatory processes and have been found elevated in obesity and insulin resistance (15). Apparently, very short periods of calorie restriction or altered calorie intake reduce

the inflammatory state. Of note, we did not find significant effects of the weight loss strategies on SM levels, which were shown to be affected by weight loss before.

One previous study applied metabolic profiling to elucidate the effects of bariatric surgery in a small group of NGT and T2DM subjects. They revealed distinct changes in lipid classes and attributed those to the effects of the RYGB procedure (35). Similar to their study and as mentioned above, we found decreased PCs, LPCs PEs and Cers after RYGB. However, parallel comparison of the effects of RYGB to the effects induced by VLCD in our study shows a similar but somewhat more pronounced effect after the VLCD. This suggests that instead of RYGB specific mechanisms, calorie restriction and weight loss may be the major determinants of changes in circulating lipids following RYGB.

Six months of calorie restriction in obese subjects was also associated with decreases in TGs and phospholipids (PCs and LPCs), even though in this study relatively little weight was lost (9). Nevertheless, it was shown that weight loss primarily reduced the saturated fatty acids, which was associated with an increase in insulin sensitivity. Indeed, inasmuch as saturated fatty acids decrease insulin sensitivity (10), decreased saturation and enhanced elongation of fatty acids may add to the mechanisms by which weight loss improves insulin sensitivity. In this context, we suggest that the relative increase in circulating poly-unsaturated TGs (ie TG 52:2, TG52:3, TG54:3, TG54:4) we observed after both RYGB and VLCD is a beneficial effect of calorie restriction and/or weight loss.

Interestingly, there was a trend (after correction for multiple testing) towards a decreased total TG level after the VLCD, whereas RYGB or GB did not affect total TG. This change in total TG level was mainly caused by small and sometimes insignificant reductions in some of the most abundant TG species (i.e. TG52:2, TG52:3, TG54:3, TG54:4, TG54:5) after the VLCD, while some small increases were noted after RYGB. We have no explanation for this; however, we speculate that this might be a time dependent difference in effect of the two procedures. Whereas RYGB induces starvation and surgical stress, which is associated with a temporary decrease in insulin sensitivity (36;37), the VLCD very effectively reduces insulin resistance (30). Also, we cannot exclude an effect of different dietary intakes after the surgical procedures and the VLCD. The fact that weight loss was similar in surgical and dietary groups, however, suggests that calorie intake after the procedures was equivalent, but there might have been differences in macronutrient composition, which triggered the decline of TG level after the diet.

As we were able to analyze plasma samples only, we cannot report on definite changes in the expression of genes and proteins important in fatty acid metabolism influenced by the interventions. However, plasma concentrations of product: precursor ratios have been shown to correlate with ratios measured in hepatic tissue (9;38). Moreover, GWAS studies showed that these ratios are strong signals to detect genetic loci encoding enzymes and that they associate with gene expression profiles (39;40). Previous reports suggested a general effect of obesity on desaturase and elongase activity (10). We cannot confirm a general effect of obesity in our subjects on estimated FADS1 activity at baseline; however, we found a very strong and consistent effect of the different interventions, suggesting that the common parameter calorie restriction increases the capacity to desaturate long chain fatty acids (increase in PC36:4/PC36:3 ratio and PC38:4/PC38:3 ratio). A comparable effect was seen in Δ5-desaturase and SCD-1 activity, which were estimated by respectively the LPC20:4/LCP20:3 and LPC18:1/LPC18:0 ratio, and consistently increased after all interventions. In contrary, Δ6-desaturase (LPC 18:3/LPC18:2 ratio) estimated activity significantly decreased after all interventions. These findings correspond to earlier reports, describing an inverse correlation of Δ5-desaturase but a positive correlation of Δ6-desaturase with obesity and insulin resistance (13;41). Changes in desaturase activity may be a direct consequence of altered dietary intake after surgery or during the VLCD or could have been influenced by endogenous factors, such as a decrease in leptin levels (42;43). The exact meaning of the altered desaturase activities remains to be established, but it is tempting to speculate that an increase in Δ5-desaturase and FADS is associated with the development of a healthier lipid profile after weight loss.

In summary, by applying a lipidomics approach to study the differences between equally obese NGT and T2DM obese subjects, we have found that total levels of grouped lipid species are increased in T2DM relative to the overall decrease of LPCs, PEs and LPEs in obesity. Moreover, our data describe a general change in circulating lipid profile after calorie restriction and RYGB, suggesting that calorie restriction may be the major component of the RYGB procedure affecting lipid levels.

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Supplementary Table 1a. Levels of individual lipids at baseline (NGT, DM, Control).

Lipid	NGT		DM		Control		p-value (correction p<0.000275)		
	mean	sd	mean	sd	mean	sd	NGTvs C	DM vs C	DM vs NGT
Cer(d18:0/24:0)	**0.02**	0.01	**0.01**	0.01	**0.01**	0.00	4.36E-03	2.54E-02	3.95E-01
Cer(d18:1/16:0)	**0.02**	0.00	**0.02**	0.00	**0.02**	0.00	2.73E-01	6.24E-02	3.22E-01
Cer(d18:1/24:0)	**0.18**	0.05	**0.18**	0.04	**0.18**	0.05	8.21E-01	9.61E-01	8.20E-01
Cer(d18:1/24:1)	**0.12**	0.03	**0.12**	0.02	**0.11**	0.02	8.52E-01	6.45E-01	7.27E-01
DG(36:2)	**0.56**	0.25	**0.70**	0.28	**0.47**	0.18	1.97E-01	1.85E-03	1.68E-02
LPC(14:0)	**0.07**	0.02	**0.07**	0.03	**0.09**	0.02	8.83E-02	4.90E-02	7.38E-01
LPC(16:0)	**5.79**	0.89	**5.61**	1.09	**7.02**	1.17	3.49E-03	4.99E-04	4.52E-01
LPC(16:1)	**0.17**	0.04	**0.18**	0.06	**0.19**	0.05	2.27E-01	4.28E-01	5.87E-01
LPC(18:0)	**1.97**	0.50	**1.77**	0.33	**2.18**	0.41	1.76E-01	1.83E-02	1.91E-01
LPC(18:1)	**1.23**	0.33	**1.15**	0.30	**1.76**	0.45	**1.61E-04**	**1.04E-05**	3.64E-01
LPC(18:2)	**1.70**	0.48	**1.44**	0.40	**2.63**	1.02	**2.60E-04**	**8.41E-07**	6.49E-02
LPC(18:3)	**0.03**	0.01	**0.03**	0.02	**0.04**	0.02	2.75E-02	1.77E-02	8.34E-01
LPC(20:3)	**0.15**	0.03	**0.16**	0.03	**0.17**	0.05	2.21E-01	2.73E-01	8.61E-01
LPC(20:4)	**0.30**	0.11	**0.35**	0.09	**0.38**	0.12	1.92E-02	4.58E-01	3.71E-02
LPC(20:5)	**0.03**	0.01	**0.03**	0.01	**0.03**	0.01	6.50E-01	9.50E-01	5.07E-01
LPC(22:6)	**0.06**	0.02	**0.07**	0.02	**0.07**	0.02	6.60E-01	9.22E-01	6.60E-01
LPC(O-16:1)	**0.05**	0.01	**0.04**	0.01	**0.05**	0.01	5.07E-01	4.73E-03	5.47E-03
LPC(O-18:1)	**0.03**	0.01	**0.02**	0.00	**0.02**	0.00	4.40E-01	4.19E-02	4.64E-04
LPE(18:0)	**0.12**	0.03	**0.10**	0.03	**0.19**	0.05	7.75E-04	**3.65E-06**	7.28E-02
PC(32:0)	**0.84**	0.18	**0.89**	0.30	**0.98**	0.16	5.34E-02	1.16E-01	6.28E-01
PC(32:1)	**1.34**	0.66	**1.88**	1.30	**1.38**	0.51	5.62E-01	1.85E-01	1.60E-02
PC(32:2)	**0.22**	0.08	**0.21**	0.08	**0.26**	0.08	1.91E-01	8.64E-02	6.03E-01
PC(34:1)	**15.33**	3.51	**16.81**	4.14	**17.17**	3.39	1.10E-01	6.82E-01	1.25E-01
PC(34:2)	**26.37**	3.99	**25.02**	5.19	**29.05**	4.68	1.71E-01	2.67E-02	2.70E-01
PC(34:3)	**0.96**	0.26	**0.96**	0.32	**1.07**	0.28	3.22E-01	2.62E-01	8.70E-01
PC(34:4)	**0.06**	0.02	**0.07**	0.03	**0.07**	0.02	3.92E-01	6.68E-01	1.01E-01
PC(36:1)	**2.62**	0.82	**2.72**	0.83	**2.59**	0.62	9.43E-01	7.55E-01	6.24E-01
PC(36:2)	**17.48**	2.51	**16.13**	3.25	**18.20**	3.51	7.00E-01	1.56E-01	1.86E-01
PC(36:3)	**12.24**	2.73	**11.57**	4.44	**13.39**	3.37	4.17E-01	1.13E-01	3.19E-01
PC(36:4)	**12.34**	3.12	**14.65**	3.74	**12.76**	2.75	5.83E-01	8.98E-02	4.76E-03
PC(36:5)	**1.17**	0.55	**1.38**	0.65	**1.25**	0.45	5.53E-01	6.56E-01	1.84E-01
PC(36:6)	**0.03**	0.01	**0.03**	0.01	**0.04**	0.01	1.44E-01	2.29E-01	7.28E-01
PC(38:2)	**0.29**	0.07	**0.25**	0.07	**0.26**	0.06	2.87E-01	2.81E-01	6.87E-03
PC(38:3)	**2.78**	0.74	**2.81**	1.01	**1.99**	0.43	6.48E-03	7.51E-03	9.32E-01
PC(38:4)	**7.83**	2.24	**8.96**	1.94	**6.29**	1.15	1.17E-02	**1.84E-05**	1.42E-02
PC(38:5)	**3.81**	1.08	**4.16**	1.07	**3.75**	0.79	9.66E-01	2.48E-01	1.27E-01
PC(38:6)	**4.10**	1.30	**4.20**	1.43	**4.24**	1.19	6.28E-01	8.36E-01	7.20E-01
PC(40:4)	**0.12**	0.04	**0.13**	0.03	**0.10**	0.03	1.45E-01	5.15E-03	7.94E-02
PC(40:5)	**0.58**	0.18	**0.63**	0.15	**0.48**	0.11	5.41E-02	3.61E-03	1.92E-01
PC(40:6)	**1.45**	0.50	**1.49**	0.43	**1.07**	0.27	1.28E-02	3.63E-03	5.77E-01
PC(40:7)	**0.25**	0.07	**0.23**	0.06	**0.26**	0.05	3.52E-01	8.39E-02	3.04E-01
PC(40:8)	**0.04**	0.01	**0.04**	0.01	**0.06**	0.01	3.31E-04	1.39E-03	5.62E-01
PC(O-34:1)	**0.28**	0.05	**0.23**	0.04	**0.29**	0.04	4.50E-01	**6.04E-05**	**2.83E-05**
PC(O-34:3)	**0.37**	0.10	**0.28**	0.08	**0.46**	0.11	8.01E-03	**1.87E-07**	3.42E-04

Lipid	NGT		DM		Control		p-value (correction p<0.000275)		
	mean	sd	mean	sd	mean	sd	NGTvs C	DM vs C	DM vs NGT
PC(O-36:2)	**0.16**	0.03	**0.13**	0.02	**0.17**	0.03	5.65E-01	**1.53E-06**	**7.99E-08**
PC(O-36:3)	**0.09**	0.02	**0.08**	0.02	**0.12**	0.02	**1.28E-04**	**1.46E-08**	6.36E-03
PC(O-36:4)	**0.62**	0.12	**0.56**	0.13	**0.59**	0.18	3.11E-01	5.60E-01	4.23E-02
PC(O-36:5)	**0.50**	0.11	**0.49**	0.13	**0.50**	0.11	8.95E-01	8.70E-01	7.05E-01
PC(O-36:6)	**0.03**	0.01	**0.03**	0.01	**0.03**	0.01	7.72E-01	2.87E-01	3.22E-01
PC(O-38:4)	**0.26**	0.06	**0.23**	0.05	**0.25**	0.06	5.46E-01	2.35E-01	2.30E-02
PC(O-38:5)	**0.65**	0.15	**0.57**	0.12	**0.62**	0.20	3.88E-01	4.05E-01	3.15E-02
PC(O-38:6)	**0.31**	0.07	**0.28**	0.07	**0.28**	0.05	2.42E-01	7.92E-01	6.68E-02
PC(O-38:7)	**0.11**	0.03	**0.10**	0.03	**0.11**	0.02	8.09E-01	3.06E-01	3.18E-01
PC(O-42:6)	**0.02**	0.00	**0.02**	0.00	**0.02**	0.00	5.42E-01	1.16E-01	2.16E-01
PC(O-44:5)	**0.08**	0.02	**0.08**	0.02	**0.08**	0.01	7.87E-01	5.54E-01	6.81E-01
PE(34:2)	**0.28**	0.20	**0.32**	0.26	**0.34**	0.14	1.02E-01	4.89E-01	2.18E-01
PE(36:3)	**0.19**	0.00	**0.19**	0.00	**0.19**	0.01	1.28E-01	7.82E-02	7.64E-01
PE(38:2)	**2.28**	0.46	**1.94**	0.44	**3.31**	0.91	**1.10E-04**	**5.80E-08**	2.15E-02
PE(38:4)	**0.21**	0.08	**0.22**	0.06	**0.24**	0.06	7.39E-02	3.49E-01	2.64E-01
PE(O-36:5)	**0.21**	0.07	**0.22**	0.08	**0.18**	0.07	1.64E-01	1.54E-01	9.74E-01
PE(O-38:7)	**0.12**	0.04	**0.11**	0.04	**0.11**	0.03	3.87E-01	9.86E-01	2.76E-01
CE(18:2)	**0.24**	0.06	**0.20**	0.04	**0.24**	0.04	9.10E-01	5.28E-03	6.88E-04
CE(20:4)	**0.13**	0.03	**0.13**	0.03	**0.12**	0.03	3.27E-01	1.78E-01	6.39E-01
CE(20:5)	**0.03**	0.01	**0.02**	0.01	**0.03**	0.01	8.20E-01	6.31E-01	3.50E-01
CE(22:6)	**0.02**	0.01	**0.02**	0.01	**0.02**	0.01	9.38E-01	1.31E-02	2.31E-03
SM(d18:1/14:0)	**0.50**	0.09	**0.48**	0.09	**0.57**	0.09	1.81E-02	2.29E-03	3.53E-01
SM(d18:1/15:0)	**0.32**	0.03	**0.30**	0.03	**0.35**	0.03	3.10E-03	**2.58E-06**	1.19E-02
SM(d18:1/16:0)	**6.43**	0.96	**5.78**	0.64	**6.56**	0.48	4.81E-01	1.79E-03	1.84E-03
SM(d18:1/16:1)	**0.84**	0.15	**0.74**	0.09	**0.68**	0.07	**3.82E-05**	7.75E-02	1.29E-03
SM(d18:1/18:0)	**1.51**	0.24	**1.57**	0.23	**1.27**	0.19	1.65E-03	**1.06E-04**	3.12E-01
SM(d18:1/18:1)	**0.71**	0.15	**0.72**	0.13	**0.53**	0.07	**5.72E-06**	**2.48E-06**	8.16E-01
SM(d18:1/18:2)	**0.05**	0.01	**0.04**	0.01	**0.05**	0.01	8.85E-01	5.38E-02	8.66E-03
SM(d18:1/20:0)	**0.93**	0.16	**0.90**	0.13	**0.86**	0.18	1.39E-01	3.35E-01	4.98E-01
SM(d18:1/20:1)	**0.40**	0.07	**0.37**	0.05	**0.34**	0.06	5.40E-03	2.05E-01	4.40E-02
SM(d18:1/21:0)	**0.27**	0.05	**0.25**	0.04	**0.27**	0.06	9.81E-01	3.23E-01	1.96E-01
SM(d18:1/22:0)	**1.74**	0.25	**1.64**	0.27	**1.46**	0.26	2.54E-03	5.27E-02	1.41E-01
SM(d18:1/22:1)	**1.40**	0.21	**1.23**	0.16	**1.28**	0.18	9.08E-02	4.42E-01	2.04E-03
SM(d18:1/23:0)	**0.65**	0.08	**0.60**	0.08	**0.59**	0.11	3.97E-02	5.59E-01	5.61E-02
SM(d18:1/23:1)	**0.49**	0.07	**0.44**	0.07	**0.50**	0.08	9.37E-01	1.05E-02	1.69E-03
SM(d18:1/24:0)	**0.97**	0.17	**0.91**	0.16	**0.86**	0.15	4.21E-02	3.44E-01	1.55E-01
SM(d18:1/24:1)	**2.96**	0.41	**2.69**	0.38	**2.67**	0.38	3.64E-02	8.82E-01	1.28E-02
SM(d18:1/24:2)	**1.50**	0.28	**1.26**	0.21	**1.31**	0.18	2.53E-02	4.75E-01	**2.30E-04**
SM(d18:1/25:0)	**0.05**	0.01	**0.04**	0.01	**0.05**	0.01	8.39E-01	1.51E-01	3.72E-02
TG(44:1)	**0.11**	0.30	**0.12**	0.08	**0.07**	0.05	5.48E-01	2.67E-01	3.00E-02
TG(44:2)	**0.04**	0.08	**0.05**	0.04	**0.04**	0.04	5.54E-01	4.07E-01	7.04E-02
TG(46:0)	**0.34**	0.68	**0.50**	0.51	**0.17**	0.13	5.12E-01	2.34E-03	2.16E-03
TG(46:1)	**0.52**	1.02	**0.65**	0.45	**0.31**	0.19	9.28E-01	3.10E-02	8.55E-03
TG(46:2)	**0.21**	0.31	**0.25**	0.16	**0.18**	0.12	6.70E-01	2.53E-01	4.62E-02
TG(48:0)	**0.85**	1.00	**1.50**	1.33	**0.51**	0.26	4.51E-01	4.54E-04	3.91E-04

Supplementary Table 1a. Continued.

Lipid	NGT		DM		Control		p-value (correction p<0.000275)		
	mean	sd	mean	sd	mean	sd	NGTvs C	DM vs C	DM vs NGT
TG(48:1)	**2.59**	2.67	**4.17**	2.94	**1.83**	1.21	5.23E-01	3.19E-03	2.99E-03
TG(48:2)	**1.52**	1.58	**2.08**	1.23	**1.00**	0.57	3.27E-01	4.79E-03	1.70E-02
TG(48:3)	**0.36**	0.30	**0.44**	0.23	**0.28**	0.17	4.06E-01	3.39E-02	9.60E-02
TG(48:4)	**0.07**	0.05	**0.08**	0.04	**0.06**	0.05	9.49E-01	2.86E-01	1.52E-01
TG(50:0)	**0.65**	0.74	**1.24**	1.03	**0.33**	0.14	2.12E-01	**6.44E-05**	3.16E-04
TG(50:1)	**7.64**	4.44	**11.98**	6.28	**5.17**	2.44	7.48E-02	**1.42E-05**	5.75E-04
TG(50:2)	**9.16**	5.01	**13.35**	6.40	**5.91**	2.88	2.11E-02	**7.85E-06**	2.91E-03
TG(50:3)	**3.77**	2.13	**5.03**	2.59	**2.52**	1.14	4.80E-02	3.20E-04	2.92E-02
TG(50:4)	**0.63**	0.35	**0.77**	0.35	**0.41**	0.21	2.43E-02	4.28E-04	8.63E-02
TG(50:5)	**0.11**	0.06	**0.14**	0.06	**0.08**	0.04	1.06E-01	1.31E-03	3.53E-02
TG(51:1)	**0.44**	0.36	**0.64**	0.34	**0.38**	0.18	8.88E-01	1.02E-02	2.03E-03
TG(51:2)	**0.66**	0.43	**0.85**	0.41	**0.48**	0.20	1.34E-01	1.31E-03	2.39E-02
TG(51:3)	**0.35**	0.18	**0.42**	0.17	**0.29**	0.09	3.32E-01	2.08E-02	8.25E-02
TG(51:4)	**0.10**	0.04	**0.11**	0.04	**0.08**	0.03	6.45E-02	5.11E-03	2.09E-01
TG(52:0)	**0.09**	0.10	**0.18**	0.16	**0.05**	0.02	4.27E-01	4.70E-04	4.97E-04
TG(52:1)	**3.00**	2.21	**5.17**	2.85	**1.81**	0.58	1.25E-01	**1.98E-05**	2.90E-04
TG(52:2)	**20.72**	6.50	**26.29**	7.97	**15.64**	5.54	1.10E-02	**7.34E-06**	6.77E-03
TG(52:3)	**19.15**	6.39	**23.06**	8.46	**13.45**	5.13	4.06E-03	**3.60E-05**	7.58E-02
TG(52:4)	**7.14**	3.20	**8.46**	3.90	**4.29**	1.91	2.06E-03	**8.36E-05**	2.30E-01
TG(52:5)	**1.17**	0.55	**1.48**	0.70	**0.63**	0.33	**2.68E-04**	**1.13E-06**	7.11E-02
TG(52:6)	**0.17**	0.08	**0.23**	0.11	**0.11**	0.06	3.14E-03	**5.02E-06**	2.27E-02
TG(53:1)	**0.08**	0.06	**0.11**	0.06	**0.07**	0.03	6.85E-01	4.95E-02	2.82E-03
TG(54:1)	**0.18**	0.15	**0.32**	0.26	**0.10**	0.03	1.75E-01	**8.95E-05**	7.57E-04
TG(54:2)	**2.76**	1.26	**3.98**	1.57	**2.05**	0.73	1.07E-01	**6.77E-05**	1.60E-03
TG(54:3)	**6.55**	2.46	**7.96**	2.73	**5.44**	2.33	1.25E-01	2.37E-03	4.69E-02
TG(54:4)	**5.39**	2.14	**6.39**	2.58	**4.04**	1.53	3.87E-02	1.69E-03	1.51E-01
TG(54:5)	**3.19**	1.35	**4.23**	1.80	**2.26**	0.91	1.79E-02	**3.33E-05**	1.41E-02
TG(54:6)	**1.27**	0.57	**1.78**	0.82	**0.79**	0.42	2.16E-03	**7.64E-07**	6.95E-03
TG(54:7)	**0.32**	0.14	**0.41**	0.19	**0.18**	0.11	6.39E-04	**1.82E-06**	4.78E-02
TG(55:1)	**0.05**	0.04	**0.09**	0.05	**0.03**	0.02	8.61E-02	**1.01E-04**	2.85E-03
TG(55:2)	**0.39**	0.08	**0.43**	0.08	**0.32**	0.07	7.05E-03	**3.67E-05**	4.57E-02
TG(55:3)	**0.45**	0.10	**0.49**	0.12	**0.37**	0.11	7.42E-03	4.42E-04	2.50E-01
TG(56:3)	**0.22**	0.10	**0.27**	0.11	**0.20**	0.11	6.10E-01	3.45E-02	3.96E-02
TG(56:5)	**0.84**	0.34	**1.31**	0.56	**0.73**	0.21	3.89E-01	**6.87E-05**	**5.67E-05**
TG(56:6)	**1.18**	0.44	**1.79**	0.74	**0.89**	0.28	3.09E-02	**5.51E-07**	**9.24E-05**
TG(56:7)	**1.16**	0.53	**1.58**	0.69	**0.79**	0.30	2.66E-02	**3.78E-05**	9.37E-03
TG(56:8)	**0.37**	0.17	**0.47**	0.23	**0.21**	0.10	1.64E-03	**1.26E-05**	8.25E-02
TG(57:2)	**0.04**	0.01	**0.06**	0.02	**0.03**	0.01	5.45E-02	**4.44E-06**	3.18E-04
TG(58:10)	**0.05**	0.02	**0.06**	0.04	**0.03**	0.02	1.17E-02	**5.35E-05**	3.69E-02

Levels of individual lipids at baseline (NGT, DM, Control). Values are presented as mean ± sd. Means are bold larger font, sds are smaller font.) Differences between subject groups (NGT vs T2DM) and lean controls at baseline were compared with a mixed-effects model, with the patient groups and diabetes as fixed effects and the subject specific deviances modelled with random intercepts. The Bonferroni posthoc test was used to correct for multiple testing. A p-value <0.000275 was considered statistically significant (= (0,05 divided by 26, the effective number of independent lipid species, and by 7, the number of hypotheses tested). Significant p-values are bold.

Supplementary Table 1b. Levels of individual lipids at baseline and after different interventions per group (NGT_GB, NGT_RYGB, DM_RYGB, DM_VLCD).

Lipid	NGT_GB 0		NGT_GB 1		p-value	NGT_RYGB 0		NGT_RYGB 1		p-value	DM_RYGB 0		DM_RYGB 1		p-value	DM_VLCD 0		DM_VLCD 1		p-value
	mean	sd	mean	sd	*<0.000275*	mean	sd	mean	sd	*<0.000275*	mean	sd	mean	sd	*<0.000275*	mean	sd	mean	sd	*<0.000275*
Cer(d18:0/24:0)	**0.02**	0.01	**0.01**	0.01	7.28E-03	**0.02**	0.01	**0.01**	0.00	3.00E-03	**0.01**	0.01	**0.01**	0.01	**1.95E-05**	**0.01**	0.01	**0.01**	0.00	3.20E-03
Cer(d18:1/16:0)	**0.02**	0.01	**0.02**	0.00	5.65E-02	**0.02**	0.01	**0.02**	0.00	4.06E-01	**0.02**	0.00	**0.02**	0.01	9.67E-01	**0.02**	0.00	**0.02**	0.01	2.82E-01
Cer(d18:1/24:0)	**0.18**	0.04	**0.12**	0.04	**1.52E-08**	**0.18**	0.05	**0.08**	0.03	**3.29E-20**	**0.17**	0.04	**0.10**	0.03	**4.62E-14**	**0.18**	0.04	**0.10**	0.04	**1.90E-13**
Cer(d18:1/24:1)	**0.11**	0.03	**0.12**	0.03	3.42E-01	**0.11**	0.03	**0.11**	0.03	1.30E-01	**0.12**	0.02	**0.12**	0.03	9.38E-01	**0.12**	0.03	**0.10**	0.04	4.28E-03
DG(36:2)	**0.52**	0.15	**0.71**	0.19	2.52E-03	**0.54**	0.26	**0.66**	0.23	2.54E-02	**0.76**	0.30	**0.88**	0.30	2.06E-02	**0.64**	0.25	**0.62**	0.29	3.95E-01
LPC(14:0)	**0.07**	0.02	**0.04**	0.02	**3.97E-05**	**0.07**	0.02	**0.03**	0.01	**1.70E-12**	**0.07**	0.02	**0.02**	0.01	**3.35E-18**	**0.08**	0.03	**0.02**	0.01	**4.16E-16**
LPC(16:0)	**5.85**	0.95	**5.63**	1.16	4.43E-01	**5.63**	1.25	**5.09**	1.00	5.08E-03	**5.64**	1.05	**4.82**	0.99	1.38E-03	**5.57**	1.18	**4.63**	1.12	**2.43E-04**
LPC(16:1)	**0.18**	0.05	**0.16**	0.04	4.76E-01	**0.16**	0.05	**0.15**	0.05	6.19E-02	**0.17**	0.05	**0.13**	0.04	**4.83E-05**	**0.19**	0.08	**0.11**	0.05	**1.53E-08**
LPC(18:0)	**2.00**	0.37	**1.49**	0.34	**1.13E-04**	**1.91**	0.57	**1.22**	0.38	**3.39E-11**	**1.71**	0.37	**1.10**	0.28	**1.76E-10**	**1.84**	0.29	**1.00**	0.42	**3.06E-14**
LPC(18:1)	**1.22**	0.35	**1.09**	0.34	6.62E-02	**1.25**	0.32	**0.91**	0.23	**1.51E-06**	**1.17**	0.33	**0.96**	0.24	2.20E-03	**1.14**	0.28	**0.85**	0.28	**4.53E-06**
LPC(18:2)	**1.65**	0.42	**1.37**	0.50	1.22E-02	**1.65**	0.52	**1.00**	0.29	**1.20E-09**	**1.45**	0.39	**0.97**	0.30	**9.57E-07**	**1.43**	0.42	**0.90**	0.42	**4.06E-08**
LPC(18:3)	**0.03**	0.01	**0.02**	0.01	**1.32E-04**	**0.03**	0.01	**0.01**	0.01	**8.24E-11**	**0.03**	0.02	**0.01**	0.00	**5.10E-14**	**0.03**	0.01	**0.01**	0.01	**1.21E-09**
LPC(20:3)	**0.15**	0.03	**0.11**	0.03	**3.98E-05**	**0.15**	0.04	**0.09**	0.02	**3.14E-11**	**0.16**	0.03	**0.09**	0.03	**5.81E-10**	**0.15**	0.04	**0.09**	0.03	**1.95E-11**
LPC(20:4)	**0.34**	0.11	**0.37**	0.08	2.28E-02	**0.30**	0.11	**0.35**	0.07	**9.28E-05**	**0.34**	0.09	**0.40**	0.13	3.37E-02	**0.36**	0.10	**0.42**	0.14	8.46E-03
LPC(20:5)	**0.03**	0.01	**0.02**	0.02	8.77E-03	**0.03**	0.01	**0.02**	0.01	**2.58E-06**	**0.04**	0.02	**0.02**	0.01	**1.06E-04**	**0.03**	0.01	**0.01**	0.01	**2.62E-07**
LPC(22:6)	**0.07**	0.02	**0.08**	0.03	1.10E-01	**0.06**	0.02	**0.07**	0.02	4.13E-01	**0.07**	0.02	**0.09**	0.04	7.61E-04	**0.06**	0.01	**0.07**	0.03	7.50E-01
LPC(O-16:1)	**0.05**	0.01	**0.04**	0.01	3.15E-01	**0.05**	0.01	**0.04**	0.01	9.99E-04	**0.04**	0.01	**0.04**	0.01	3.73E-01	**0.04**	0.01	**0.04**	0.01	2.25E-01
LPC(O-18:1)	**0.03**	0.01	**0.03**	0.00	6.02E-01	**0.03**	0.01	**0.02**	0.01	2.16E-02	**0.02**	0.00	**0.02**	0.01	9.96E-02	**0.02**	0.00	**0.02**	0.00	4.23E-01
LPE(18:0)	**0.12**	0.03	**0.11**	0.04	2.44E-01	**0.12**	0.03	**0.09**	0.03	4.42E-03	**0.10**	0.03	**0.06**	0.03	**1.31E-08**	**0.11**	0.04	**0.07**	0.03	**4.62E-05**
PC(32:0)	**0.87**	0.19	**0.92**	0.19	1.12E-01	**0.82**	0.21	**0.84**	0.15	5.42E-01	**0.85**	0.17	**0.81**	0.22	1.69E-01	**0.93**	0.41	**0.84**	0.23	1.55E-01
PC(32:1)	**1.40**	0.64	**1.14**	0.42	1.55E-01	**1.32**	0.65	**1.09**	0.68	3.27E-02	**1.68**	0.65	**1.08**	0.42	**4.12E-06**	**2.11**	1.79	**0.88**	0.45	**5.86E-11**
PC(32:2)	**0.22**	0.07	**0.13**	0.05	**4.30E-08**	**0.22**	0.08	**0.10**	0.05	**1.67E-16**	**0.19**	0.06	**0.08**	0.03	**4.04E-16**	**0.23**	0.09	**0.07**	0.03	**5.22E-22**
PC(34:1)	**15.70**	3.40	**15.01**	3.25	5.38E-01	**14.93**	4.05	**14.08**	3.45	1.16E-01	**16.46**	2.58	**15.06**	1.91	7.38E-02	**17.22**	5.51	**13.85**	3.08	3.38E-04

Supplementary Table 1b. Continued.

Lipid	NGT_GB 0		NGT_GB 1		p-value	NGT_RYGB 0		NGT_RYGB 1		p-value	DM_RYGB 0		DM_RYGB 1		p-value	DM_VLCD 0		DM_VLCD 1		p-value
	mean	sd	mean	sd	*<0.000275*	mean	sd	mean	sd	*<0.000275*	mean	sd	mean	sd	*<0.000275*	mean	sd	mean	sd	*<0.000275*
PC(34:2)	**26.97**	4.73	**25.14**	4.77	1.44E-01	**25.64**	5.57	**21.73**	5.35	**1.28E-06**	**24.66**	2.82	**21.41**	3.47	3.75E-04	**25.44**	7.14	**19.49**	5.15	**2.76E-08**
PC(34:3)	**1.00**	0.28	**0.72**	0.21	3.60E-04	**0.93**	0.28	**0.56**	0.22	**5.31E-11**	**0.90**	0.25	**0.46**	0.13	**5.45E-14**	**1.02**	0.40	**0.38**	0.14	**5.45E-19**
PC(34:4)	**0.06**	0.02	**0.04**	0.01	**2.23E-04**	**0.06**	0.02	**0.03**	0.01	**9.28E-13**	**0.07**	0.02	**0.03**	0.01	**2.06E-14**	**0.07**	0.03	**0.02**	0.01	**2.93E-19**
PC(36:1)	**2.43**	0.53	**1.50**	0.39	**8.65E-09**	**2.54**	0.88	**1.23**	0.43	**1.79E-17**	**2.74**	0.88	**1.42**	0.33	**2.53E-13**	**2.71**	0.81	**1.15**	0.42	**5.05E-18**
PC(36:2)	**17.59**	1.31	**12.63**	2.55	**2.30E-06**	**16.92**	3.86	**9.66**	3.24	**6.72E-17**	**15.66**	2.57	**9.77**	2.41	**2.74E-12**	**16.68**	3.94	**7.84**	2.88	**3.13E-19**
PC(36:3)	**12.16**	2.25	**9.12**	2.58	**9.04E-06**	**11.90**	3.22	**7.40**	2.63	**3.31E-14**	**10.69**	2.18	**6.58**	1.73	**5.08E-13**	**12.59**	6.06	**6.59**	3.06	**1.03E-15**
PC(36:4)	**12.51**	3.36	**14.24**	3.39	2.64E-03	**12.04**	3.44	**13.54**	2.71	4.16E-03	**15.02**	2.75	**16.33**	1.86	1.09E-02	**14.23**	4.73	**17.11**	4.00	**2.04E-05**
PC(36:5)	**1.31**	0.53	**1.05**	0.85	1.83E-02	**1.16**	0.55	**0.77**	0.43	2.92E-04	**1.46**	0.76	**0.81**	0.39	**4.37E-06**	**1.29**	0.51	**0.69**	0.23	**9.45E-07**
PC(36:6)	**0.03**	0.01	**0.02**	0.01	3.71E-04	**0.03**	0.01	**0.02**	0.01	**2.33E-10**	**0.03**	0.01	**0.02**	0.01	**5.41E-07**	**0.03**	0.01	**0.01**	0.01	**2.14E-12**
PC(38:2)	**0.28**	0.04	**0.19**	0.04	**2.98E-09**	**0.28**	0.08	**0.15**	0.03	**5.06E-18**	**0.24**	0.06	**0.13**	0.03	**2.75E-16**	**0.25**	0.08	**0.13**	0.03	**1.54E-16**
PC(38:3)	**2.75**	0.50	**1.45**	0.42	**6.28E-10**	**2.70**	0.83	**1.16**	0.52	**1.41E-17**	**2.63**	0.60	**1.09**	0.33	**2.75E-17**	**3.01**	1.34	**0.98**	0.50	**1.50E-20**
PC(38:4)	**7.82**	2.36	**7.37**	1.73	3.67E-01	**7.64**	2.39	**6.34**	1.16	**7.72E-06**	**9.27**	1.70	**8.58**	1.71	9.23E-02	**8.62**	2.21	**7.32**	1.73	**2.43E-04**
PC(38:5)	**3.72**	0.96	**3.29**	0.85	3.07E-02	**3.71**	1.17	**3.02**	0.55	**1.70E-05**	**4.39**	1.16	**3.52**	0.63	**2.32E-04**	**3.90**	0.94	**3.07**	0.66	**6.28E-06**
PC(38:6)	**4.15**	1.20	**5.07**	1.63	1.34E-03	**4.00**	1.37	**4.79**	1.41	1.55E-03	**4.43**	1.36	**5.64**	1.31	**3.83E-06**	**3.93**	1.52	**4.72**	1.47	2.92E-03
PC(40:4)	**0.11**	0.02	**0.07**	0.01	**5.00E-07**	**0.11**	0.04	**0.08**	0.03	**5.91E-09**	**0.13**	0.03	**0.08**	0.01	**2.00E-11**	**0.13**	0.04	**0.07**	0.02	**1.74E-13**
PC(40:5)	**0.55**	0.14	**0.39**	0.07	**1.42E-06**	**0.57**	0.20	**0.40**	0.13	**1.48E-09**	**0.64**	0.15	**0.42**	0.10	**7.97E-10**	**0.62**	0.15	**0.34**	0.08	**2.09E-14**
PC(40:6)	**1.51**	0.50	**1.52**	0.51	6.71E-01	**1.42**	0.52	**1.34**	0.50	2.12E-01	**1.57**	0.45	**1.67**	0.47	2.16E-01	**1.39**	0.40	**1.16**	0.36	1.02E-03
PC(40:7)	**0.25**	0.07	**0.27**	0.06	1.66E-01	**0.24**	0.08	**0.22**	0.07	3.52E-02	**0.24**	0.07	**0.26**	0.06	1.14E-01	**0.21**	0.04	**0.20**	0.06	1.19E-01
PC(40:8)	**0.04**	0.01	**0.04**	0.01	3.42E-02	**0.04**	0.01	**0.03**	0.01	**1.49E-07**	**0.04**	0.01	**0.03**	0.01	**2.90E-08**	**0.04**	0.02	**0.03**	0.01	**1.05E-08**
PC(O-34:1)	**0.27**	0.04	**0.29**	0.04	1.30E-01	**0.27**	0.06	**0.25**	0.03	**7.28E-06**	**0.23**	0.04	**0.24**	0.04	2.18E-01	**0.23**	0.04	**0.24**	0.05	3.25E-01
PC(O-34:3)	**0.36**	0.05	**0.29**	0.04	4.20E-03	**0.35**	0.11	**0.22**	0.07	**5.83E-13**	**0.29**	0.09	**0.21**	0.06	**1.84E-06**	**0.27**	0.06	**0.21**	0.05	**2.72E-05**
PC(O-36:2)	**0.15**	0.02	**0.13**	0.02	**5.61E-05**	**0.16**	0.04	**0.11**	0.01	**1.86E-16**	**0.13**	0.02	**0.10**	0.01	**5.26E-07**	**0.13**	0.02	**0.10**	0.01	**1.65E-07**
PC(O-36:3)	**0.09**	0.01	**0.08**	0.01	1.28E-03	**0.09**	0.02	**0.06**	0.01	**9.49E-12**	**0.08**	0.02	**0.06**	0.01	**1.37E-07**	**0.08**	0.02	**0.06**	0.01	**2.67E-06**
PC(O-36:4)	**0.61**	0.08	**0.55**	0.10	5.59E-02	**0.60**	0.15	**0.45**	0.08	**5.23E-08**	**0.55**	0.11	**0.48**	0.05	2.51E-02	**0.56**	0.14	**0.44**	0.09	**6.19E-05**
PC(O-36:5)	**0.51**	0.08	**0.48**	0.10	5.22E-01	**0.49**	0.13	**0.41**	0.07	9.32E-04	**0.50**	0.12	**0.46**	0.09	3.50E-01	**0.49**	0.15	**0.44**	0.10	1.15E-01
PC(O-36:6)	**0.04**	0.01	**0.03**	0.02	2.08E-03	**0.03**	0.01	**0.02**	0.01	**6.90E-08**	**0.03**	0.02	**0.02**	0.01	**2.10E-06**	**0.03**	0.01	**0.02**	0.01	**7.33E-07**
PC(O-38:4)	**0.25**	0.05	**0.21**	0.06	8.48E-04	**0.25**	0.07	**0.19**	0.04	**1.96E-07**	**0.22**	0.04	**0.18**	0.03	1.27E-03	**0.24**	0.06	**0.19**	0.04	3.28E-03
PC(O-38:5)	**0.66**	0.14	**0.67**	0.07	4.04E-01	**0.63**	0.17	**0.67**	0.16	3.40E-01	**0.56**	0.10	**0.62**	0.12	2.87E-02	**0.58**	0.15	**0.65**	0.11	1.70E-02
PC(O-38:6)	**0.31**	0.06	**0.29**	0.08	3.66E-01	**0.30**	0.08	**0.24**	0.04	**2.93E-06**	**0.28**	0.07	**0.24**	0.05	2.82E-02	**0.28**	0.08	**0.25**	0.06	2.72E-02
PC(O-38:7)	**0.12**	0.03	**0.11**	0.04	3.14E-01	**0.11**	0.03	**0.08**	0.02	**2.21E-04**	**0.10**	0.03	**0.09**	0.02	1.13E-01	**0.10**	0.03	**0.08**	0.03	3.04E-03

Lipid	NGT_GB 0		NGT_GB 1		p-value	NGT_RYGB 0		NGT_RYGB 1		p-value	DM_RYGB 0		DM_RYGB 1		p-value	DM_VLCD 0		DM_VLCD 1		p-value
	mean	sd	mean	sd	*<0.000275*	mean	sd	mean	sd	*<0.000275*	mean	sd	mean	sd	*<0.000275*	mean	sd	mean	sd	*<0.000275*
PC(O-42:6)	**0.02**	0.00	**0.02**	0.00	**2.59E-05**	**0.02**	0.00	**0.02**	0.00	3.29E-04	**0.02**	0.00	**0.02**	0.00	**1.50E-06**	**0.02**	0.00	**0.02**	0.01	**2.16E-04**
PC(O-44:5)	**0.07**	0.01	**0.09**	0.02	**4.85E-05**	**0.07**	0.02	**0.09**	0.02	8.33E-04	**0.07**	0.02	**0.09**	0.02	**2.38E-05**	**0.08**	0.02	**0.09**	0.03	**1.63E-04**
PE(34:2)	**0.30**	0.22	**0.28**	0.27	2.51E-01	**0.28**	0.19	**0.25**	0.18	4.05E-01	**0.28**	0.12	**0.17**	0.09	**4.17E-07**	**0.38**	0.35	**0.19**	0.10	**3.94E-06**
PE(36:3)	**0.19**	0.01	**0.19**	0.01	8.72E-01	**0.19**	0.03	**0.19**	0.01	5.56E-01	**0.19**	0.00	**0.20**	0.00	3.57E-01	**0.19**	0.01	**0.19**	0.01	4.28E-01
PE(38:2)	**2.34**	0.37	**2.06**	0.50	9.73E-02	**2.22**	0.57	**1.63**	0.49	**2.76E-07**	**1.92**	0.42	**1.29**	0.29	**2.81E-08**	**1.98**	0.47	**1.24**	0.39	**1.43E-09**
PE(38:4)	**0.21**	0.08	**0.20**	0.05	9.97E-01	**0.20**	0.08	**0.18**	0.05	1.02E-01	**0.22**	0.07	**0.19**	0.04	5.39E-03	**0.21**	0.06	**0.19**	0.06	8.70E-03
PE(O-36:5)	**0.22**	0.08	**0.13**	0.06	**9.24E-06**	**0.21**	0.07	**0.11**	0.03	**5.74E-10**	**0.22**	0.10	**0.14**	0.04	**2.04E-05**	**0.21**	0.07	**0.11**	0.02	**6.72E-08**
PE(O-38:7)	**0.12**	0.04	**0.11**	0.04	7.23E-02	**0.12**	0.04	**0.09**	0.04	**3.66E-05**	**0.11**	0.05	**0.08**	0.02	**2.12E-04**	**0.11**	0.03	**0.09**	0.03	1.65E-03
CE(18:2)	**0.24**	0.06	**0.22**	0.05	9.63E-02	**0.24**	0.07	**0.18**	0.04	**1.12E-05**	**0.18**	0.04	**0.16**	0.03	1.09E-02	**0.21**	0.04	**0.16**	0.04	**6.50E-05**
CE(20:4)	**0.12**	0.04	**0.15**	0.03	3.33E-02	**0.12**	0.04	**0.14**	0.03	2.33E-01	**0.12**	0.03	**0.17**	0.02	**1.90E-04**	**0.13**	0.04	**0.16**	0.04	1.67E-02
CE(20:5)	**0.03**	0.01	**0.03**	0.01	2.81E-01	**0.03**	0.01	**0.02**	0.01	1.53E-03	**0.02**	0.01	**0.02**	0.01	4.69E-02	**0.03**	0.01	**0.01**	0.01	**6.87E-06**
CE(22:6)	**0.02**	0.01	**0.02**	0.01	3.91E-01	**0.02**	0.01	**0.02**	0.01	7.11E-01	**0.02**	0.01	**0.02**	0.01	**3.99E-05**	**0.02**	0.01	**0.02**	0.01	2.11E-03
SM(d18:1/14:0)	**0.47**	0.06	**0.39**	0.04	**2.30E-10**	**0.48**	0.12	**0.37**	0.06	**7.40E-20**	**0.45**	0.07	**0.31**	0.04	**3.53E-23**	**0.51**	0.11	**0.39**	0.08	**5.73E-15**
SM(d18:1/15:0)	**0.31**	0.02	**0.30**	0.02	8.42E-03	**0.31**	0.06	**0.30**	0.02	**1.90E-05**	**0.30**	0.03	**0.26**	0.02	**9.01E-13**	**0.31**	0.03	**0.30**	0.03	9.65E-02
SM(d18:1/16:0)	**6.11**	0.87	**6.17**	0.87	7.99E-01	**6.22**	1.39	**5.95**	0.61	**1.25E-04**	**5.66**	0.63	**5.46**	0.65	6.66E-02	**5.93**	0.65	**5.70**	0.60	2.19E-01
SM(d18:1/16:1)	**0.79**	0.10	**0.81**	0.11	6.48E-01	**0.81**	0.20	**0.81**	0.11	5.72E-03	**0.74**	0.06	**0.71**	0.07	3.28E-02	**0.74**	0.12	**0.75**	0.11	5.83E-01
SM(d18:1/18:0)	**1.54**	0.23	**1.99**	0.30	**3.05E-09**	**1.47**	0.34	**2.12**	0.28	**1.56E-15**	**1.59**	0.21	**2.23**	0.32	**6.91E-15**	**1.55**	0.26	**2.04**	0.30	**2.88E-10**
SM(d18:1/18:1)	**0.71**	0.13	**0.94**	0.10	**7.52E-10**	**0.69**	0.18	**1.03**	0.15	**1.90E-16**	**0.75**	0.12	**1.03**	0.12	**3.27E-14**	**0.68**	0.14	**0.95**	0.15	**1.84E-12**
SM(d18:1/18:2)	**0.05**	0.01	**0.05**	0.01	6.02E-01	**0.04**	0.01	**0.04**	0.01	1.51E-01	**0.04**	0.01	**0.04**	0.01	4.10E-01	**0.04**	0.01	**0.04**	0.01	5.75E-01
SM(d18:1/20:0)	**0.92**	0.07	**0.69**	0.08	**1.15E-11**	**0.90**	0.22	**0.59**	0.11	**1.18E-22**	**0.86**	0.12	**0.59**	0.09	**2.09E-19**	**0.94**	0.13	**0.64**	0.11	**7.66E-18**
SM(d18:1/20:1)	**0.40**	0.05	**0.40**	0.03	8.57E-01	**0.39**	0.09	**0.38**	0.06	8.21E-02	**0.36**	0.05	**0.33**	0.06	6.24E-04	**0.37**	0.05	**0.35**	0.05	5.30E-02
SM(d18:1/21:0)	**0.25**	0.03	**0.17**	0.03	**4.68E-15**	**0.26**	0.07	**0.14**	0.03	**4.75E-28**	**0.25**	0.05	**0.14**	0.03	**2.35E-25**	**0.26**	0.04	**0.17**	0.04	**5.48E-17**
SM(d18:1/22:0)	**1.75**	0.24	**1.20**	0.21	**1.45E-13**	**1.69**	0.37	**0.92**	0.14	**2.53E-26**	**1.57**	0.26	**0.96**	0.19	**1.64E-21**	**1.71**	0.28	**1.06**	0.14	**7.79E-18**
SM(d18:1/22:1)	**1.39**	0.16	**1.17**	0.14	**6.17E-07**	**1.36**	0.31	**1.01**	0.16	**2.84E-18**	**1.16**	0.13	**0.85**	0.12	**9.02E-18**	**1.32**	0.16	**1.07**	0.15	**7.52E-09**
SM(d18:1/23:0)	**0.64**	0.08	**0.46**	0.05	**8.62E-15**	**0.63**	0.13	**0.37**	0.05	**1.09E-28**	**0.59**	0.10	**0.35**	0.06	**1.34E-26**	**0.61**	0.06	**0.42**	0.14	**1.88E-14**
SM(d18:1/23:1)	**0.48**	0.06	**0.45**	0.05	2.26E-02	**0.48**	0.10	**0.41**	0.06	**1.67E-09**	**0.42**	0.06	**0.34**	0.05	**1.24E-11**	**0.45**	0.08	**0.43**	0.06	1.28E-01
SM(d18:1/24:0)	**0.97**	0.18	**0.63**	0.12	**7.49E-15**	**0.95**	0.22	**0.47**	0.07	**4.96E-28**	**0.88**	0.17	**0.49**	0.09	**1.68E-23**	**0.95**	0.15	**0.60**	0.07	**7.54E-16**
SM(d18:1/24:1)	**2.89**	0.44	**3.34**	0.46	**3.94E-05**	**2.87**	0.62	**3.16**	0.36	3.92E-02	**2.66**	0.36	**3.13**	0.40	**1.67E-07**	**2.73**	0.43	**3.15**	0.55	**4.13E-06**

Supplementary Table 1b. Continued.

Lipid	NGT_GB 0		NGT_GB 1		p-value	NGT_RYGB 0		NGT_RYGB 1		p-value	DM_RYGB 0		DM_RYGB 1		p-value	DM_VLCD 0		DM_VLCD 1		p-value
	mean	sd	mean	sd	*<0.000275*	mean	sd	mean	sd	*<0.000275*	mean	sd	mean	sd	*<0.000275*	mean	sd	mean	sd	*<0.000275*
SM(d18:1/24:2)	**1.42**	0.22	**1.76**	0.25	**6.27E-06**	**1.46**	0.36	**1.78**	0.29	**4.68E-05**	**1.25**	0.20	**1.51**	0.19	**1.50E-06**	**1.28**	0.22	**1.65**	0.27	**2.43E-09**
SM(d18:1/25:0)	**0.05**	0.01	**0.04**	0.01	**3.23E-05**	**0.05**	0.01	**0.03**	0.01	**1.10E-16**	**0.04**	0.01	**0.03**	0.01	**7.92E-14**	**0.04**	0.01	**0.03**	0.01	**3.80E-07**
TG(44:1)	**0.05**	0.04	**0.10**	0.28	2.91E-03	**0.11**	0.29	**0.02**	0.02	**3.24E-07**	**0.10**	0.07	**0.01**	0.01	**1.89E-10**	**0.13**	0.09	**0.01**	0.02	**9.35E-13**
TG(44:2)	**0.03**	0.02	**0.07**	0.20	6.12E-02	**0.04**	0.08	**0.01**	0.01	1.06E-02	**0.04**	0.02	**0.01**	0.00	**5.62E-10**	**0.06**	0.04	**0.01**	0.01	**9.76E-06**
TG(46:0)	**0.20**	0.18	**0.21**	0.41	3.63E-02	**0.32**	0.65	**0.08**	0.11	**7.47E-06**	**0.51**	0.42	**0.10**	0.07	**2.53E-08**	**0.49**	0.61	**0.07**	0.07	**7.75E-12**
TG(46:1)	**0.26**	0.18	**0.29**	0.57	4.83E-03	**0.50**	0.99	**0.12**	0.18	**2.82E-08**	**0.64**	0.41	**0.11**	0.07	**9.62E-11**	**0.67**	0.50	**0.08**	0.11	**6.88E-15**
TG(46:2)	**0.15**	0.08	**0.16**	0.29	1.06E-02	**0.20**	0.30	**0.08**	0.08	**2.83E-05**	**0.21**	0.12	**0.05**	0.03	**2.18E-10**	**0.30**	0.18	**0.05**	0.05	**5.52E-13**
TG(48:0)	**0.72**	0.57	**0.72**	0.99	2.68E-01	**0.83**	0.96	**0.44**	0.35	8.12E-03	**1.52**	1.12	**0.63**	0.43	**3.69E-06**	**1.47**	1.59	**0.41**	0.27	**6.13E-09**
TG(48:1)	**2.19**	1.42	**1.77**	1.99	2.56E-02	**2.54**	2.59	**1.28**	1.57	**4.28E-05**	**4.05**	2.39	**1.54**	0.94	**4.58E-07**	**4.31**	3.58	**0.96**	1.08	**2.97E-13**
TG(48:2)	**1.14**	0.61	**0.94**	0.91	2.54E-02	**1.48**	1.54	**0.72**	0.80	**9.98E-06**	**2.13**	1.19	**0.83**	0.45	**8.60E-07**	**2.02**	1.32	**0.50**	0.59	**2.63E-13**
TG(48:3)	**0.29**	0.13	**0.24**	0.23	1.28E-02	**0.35**	0.29	**0.17**	0.14	**2.60E-06**	**0.41**	0.19	**0.16**	0.07	**6.41E-08**	**0.47**	0.27	**0.12**	0.12	**9.73E-14**
TG(48:4)	**0.05**	0.02	**0.04**	0.04	2.24E-02	**0.06**	0.05	**0.03**	0.02	2.46E-03	**0.07**	0.04	**0.02**	0.01	**1.59E-06**	**0.09**	0.04	**0.02**	0.02	**6.63E-10**
TG(50:0)	**0.56**	0.49	**0.55**	0.92	5.72E-02	**0.65**	0.71	**0.28**	0.26	**9.02E-05**	**1.29**	0.93	**0.45**	0.34	**5.12E-07**	**1.18**	1.17	**0.30**	0.34	**4.57E-11**
TG(50:1)	**7.42**	3.48	**7.58**	4.52	9.57E-01	**7.49**	4.35	**6.87**	3.85	6.79E-01	**12.28**	5.08	**9.46**	4.09	1.92E-02	**11.63**	7.64	**6.46**	3.60	**1.97E-06**
TG(50:2)	**8.73**	3.46	**9.18**	4.37	7.23E-01	**8.95**	4.95	**8.94**	5.40	9.87E-01	**13.90**	5.60	**11.52**	4.23	1.68E-01	**12.70**	7.39	**7.21**	4.93	**9.53E-07**
TG(50:3)	**3.88**	1.44	**3.99**	1.92	7.13E-01	**3.70**	2.10	**3.71**	2.09	5.67E-01	**4.98**	2.31	**3.81**	1.77	3.05E-02	**5.10**	2.98	**2.65**	2.13	**1.92E-07**
TG(50:4)	**0.61**	0.24	**0.53**	0.29	1.91E-01	**0.61**	0.34	**0.45**	0.24	7.72E-03	**0.76**	0.32	**0.45**	0.19	**2.82E-05**	**0.78**	0.39	**0.31**	0.25	**2.57E-11**
TG(50:5)	**0.10**	0.04	**0.09**	0.06	8.82E-02	**0.10**	0.06	**0.07**	0.03	4.73E-04	**0.13**	0.06	**0.06**	0.02	**2.35E-08**	**0.14**	0.08	**0.05**	0.03	**1.69E-10**
TG(51:1)	**0.44**	0.29	**0.38**	0.20	7.11E-01	**0.44**	0.35	**0.35**	0.23	3.18E-01	**0.64**	0.34	**0.39**	0.17	1.16E-03	**0.64**	0.34	**0.32**	0.23	**1.74E-06**
TG(51:2)	**0.61**	0.31	**0.61**	0.21	8.39E-01	**0.65**	0.42	**0.59**	0.34	4.39E-01	**0.96**	0.44	**0.75**	0.26	2.21E-01	**0.73**	0.33	**0.46**	0.31	**1.90E-05**
TG(51:3)	**0.38**	0.15	**0.40**	0.13	3.21E-01	**0.35**	0.18	**0.39**	0.16	7.23E-02	**0.43**	0.18	**0.37**	0.13	2.69E-01	**0.40**	0.17	**0.28**	0.16	3.31E-04
TG(51:4)	**0.10**	0.03	**0.10**	0.03	9.62E-01	**0.10**	0.05	**0.09**	0.03	4.94E-01	**0.12**	0.04	**0.09**	0.03	3.44E-02	**0.10**	0.04	**0.06**	0.03	**8.49E-07**
TG(52:0)	**0.07**	0.07	**0.08**	0.12	1.76E-01	**0.09**	0.10	**0.03**	0.02	**1.83E-04**	**0.19**	0.18	**0.05**	0.03	**1.39E-06**	**0.17**	0.14	**0.05**	0.07	**3.28E-09**
TG(52:1)	**2.77**	1.73	**2.61**	2.27	2.98E-01	**2.95**	2.14	**2.06**	1.44	5.81E-03	**5.43**	2.92	**3.19**	1.64	6.60E-04	**4.87**	2.85	**2.21**	2.08	**1.26E-08**
TG(52:2)	**21.10**	5.09	**25.03**	6.48	1.59E-02	**20.19**	6.91	**24.77**	7.84	1.79E-03	**27.00**	6.69	**29.84**	6.12	5.61E-02	**25.48**	9.44	**23.04**	8.81	1.33E-01
TG(52:3)	**20.72**	5.41	**25.44**	7.33	3.04E-03	**18.73**	6.68	**25.54**	7.52	**6.19E-07**	**23.23**	6.75	**26.75**	6.76	1.67E-02	**22.87**	10.37	**21.47**	8.33	6.37E-01
TG(52:4)	**7.53**	2.61	**8.70**	3.24	7.28E-02	**7.00**	3.20	**8.43**	2.80	3.05E-03	**8.88**	3.64	**9.57**	4.07	2.60E-01	**7.99**	4.27	**6.32**	2.96	4.05E-02
TG(52:5)	**1.14**	0.40	**1.11**	0.45	9.56E-01	**1.14**	0.55	**0.99**	0.37	2.24E-01	**1.59**	0.71	**1.18**	0.50	7.40E-03	**1.35**	0.69	**0.72**	0.40	**4.42E-08**
TG(52:6)	**0.17**	0.06	**0.14**	0.07	1.23E-01	**0.16**	0.08	**0.13**	0.05	2.04E-02	**0.24**	0.11	**0.13**	0.06	**2.66E-06**	**0.21**	0.10	**0.10**	0.04	**1.24E-09**

Lipid	NGT_GB 0		NGT_GB 1		p-value	NGT_RYGB 0		NGT_RYGB 1		p-value	DM_RYGB 0		DM_RYGB 1		p-value	DM_VLCD 0		DM_VLCD 1		p-value
	mean	sd	mean	sd	*<0.000275*	mean	sd	mean	sd	*<0.000275*	mean	sd	mean	sd	*<0.000275*	mean	sd	mean	sd	*<0.000275*
TG(53:1)	**0.08**	0.04	**0.07**	0.04	6.15E-01	**0.07**	0.05	**0.06**	0.03	1.44E-01	**0.10**	0.05	**0.06**	0.02	**4.96E-05**	**0.11**	0.06	**0.06**	0.05	**1.02E-05**
TG(54:1)	**0.13**	0.08	**0.12**	0.11	5.96E-02	**0.17**	0.15	**0.09**	0.07	**5.83E-05**	**0.36**	0.31	**0.15**	0.07	**7.60E-05**	**0.28**	0.18	**0.12**	0.12	**5.45E-08**
TG(54:2)	**2.64**	0.87	**2.89**	1.16	5.22E-01	**2.69**	1.26	**2.60**	1.26	4.48E-01	**3.99**	1.61	**3.60**	1.13	4.76E-01	**3.96**	1.58	**2.77**	1.79	**6.25E-05**
TG(54:3)	**6.19**	1.62	**7.85**	2.21	5.57E-03	**6.36**	2.54	**7.60**	2.56	3.53E-02	**8.40**	2.67	**10.22**	2.36	1.00E-03	**7.45**	2.82	**7.35**	3.02	6.74E-01
TG(54:4)	**5.41**	1.65	**6.86**	1.95	3.03E-03	**5.26**	2.18	**6.88**	2.21	**2.09E-04**	**6.58**	2.36	**8.01**	2.28	1.57E-03	**6.17**	2.90	**5.85**	2.00	9.40E-01
TG(54:5)	**3.40**	1.10	**4.03**	1.24	2.03E-02	**3.13**	1.36	**4.11**	1.05	**2.89E-05**	**4.27**	1.79	**4.61**	1.69	2.06E-01	**4.18**	1.88	**3.78**	1.22	6.12E-01
TG(54:6)	**1.30**	0.47	**1.46**	0.58	2.07E-01	**1.25**	0.57	**1.41**	0.44	3.98E-02	**1.91**	0.89	**1.80**	0.73	8.94E-01	**1.62**	0.74	**1.34**	0.48	8.30E-02
TG(54:7)	**0.33**	0.12	**0.34**	0.17	9.69E-01	**0.31**	0.14	**0.31**	0.14	9.31E-01	**0.45**	0.21	**0.38**	0.16	2.27E-01	**0.36**	0.15	**0.24**	0.10	**1.17E-04**
TG(55:1)	**0.05**	0.05	**0.05**	0.06	3.32E-01	**0.05**	0.04	**0.04**	0.03	9.94E-02	**0.09**	0.04	**0.06**	0.02	2.68E-01	**0.09**	0.06	**0.05**	0.05	4.12E-04
TG(55:2)	**0.40**	0.07	**0.45**	0.07	2.60E-03	**0.38**	0.09	**0.45**	0.09	**1.46E-04**	**0.45**	0.07	**0.51**	0.06	2.93E-04	**0.41**	0.09	**0.43**	0.11	6.23E-01
TG(55:3)	**0.49**	0.10	**0.58**	0.11	6.63E-04	**0.44**	0.12	**0.59**	0.11	**3.82E-09**	**0.50**	0.09	**0.58**	0.09	6.69E-04	**0.49**	0.15	**0.53**	0.12	5.32E-02
TG(56:3)	**0.20**	0.06	**0.24**	0.10	1.83E-01	**0.22**	0.11	**0.19**	0.07	2.15E-01	**0.28**	0.11	**0.24**	0.07	3.08E-01	**0.27**	0.11	**0.21**	0.12	5.10E-03
TG(56:5)	**0.89**	0.36	**1.22**	0.40	4.28E-04	**0.83**	0.34	**1.27**	0.27	**3.90E-07**	**1.40**	0.64	**1.74**	0.58	1.31E-03	**1.20**	0.45	**1.43**	0.52	8.35E-02
TG(56:6)	**1.30**	0.43	**1.58**	0.48	5.77E-03	**1.16**	0.44	**1.79**	0.35	**3.60E-09**	**1.94**	0.84	**2.37**	0.85	8.98E-04	**1.63**	0.58	**2.01**	0.66	1.50E-02
TG(56:7)	**1.27**	0.51	**1.62**	0.70	1.29E-02	**1.14**	0.52	**1.75**	0.78	**1.85E-06**	**1.74**	0.75	**2.19**	0.97	3.76E-03	**1.39**	0.58	**1.74**	0.62	4.30E-02
TG(56:8)	**0.38**	0.15	**0.49**	0.25	6.34E-02	**0.36**	0.17	**0.50**	0.28	3.33E-03	**0.55**	0.25	**0.72**	0.31	1.02E-03	**0.38**	0.17	**0.46**	0.17	1.14E-01
TG(57:2)	**0.04**	0.01	**0.05**	0.02	3.04E-02	**0.04**	0.01	**0.04**	0.02	5.95E-01	**0.06**	0.02	**0.07**	0.01	1.93E-02	**0.05**	0.02	**0.05**	0.02	9.52E-02
TG(58:10)	**0.04**	0.02	**0.05**	0.03	9.29E-01	**0.05**	0.02	**0.05**	0.03	3.13E-01	**0.07**	0.05	**0.08**	0.03	6.17E-02	**0.05**	0.02	**0.05**	0.02	8.79E-01

Levels of individual lipids at baseline and after different interventions per group (NGT_GB, NGT_RYGB, DM_RYGB, DM_VLCD).Values are presented as mean ± sd. (Means are bold larger font, sds are smaller font.) Differences between subject groups (NGT vs T2DM) and lean controls at baseline were compared with a mixed-effects model, with the patient groups and diabetes as fixed effects and the subject specific deviances modelled with random intercepts. The Bonferroni posthoc test was used to correct for multiple testing. A p-value <0.000275 was considered statistically significant (= (0,05 divided by 26, the effective number of independent lipid species, and by 7, the number of hypotheses tested). Significant p-values are bold.

Supplementary Table 2a. Relative abundance of lipid species to summed lipid levels at baseline (NGT, DM, Control).

Lipid	NGT		DM		Control		p-value (correction p<0.000275)		
	mean	sd	mean	sd	mean	sd	NGTvs C	DM vs C	DM vs NGT
Cer(d18:1/16:0)	**5.309**	1.15	**5.757**	1.39	**5.010**	1.20	4.60E-01	9.50E-02	2.32E-01
Cer(d18:1/24:0)	**54.462**	2.94	**53.726**	4.28	**55.536**	4.32	6.43E-01	3.89E-01	6.12E-01
Cer(d18:1/24:1)	**35.222**	3.39	**36.189**	3.51	**36.242**	4.00	4.16E-01	9.94E-01	3.00E-01
LPC(14:0)	**0.625**	0.18	**0.629**	0.16	**0.644**	0.17	7.70E-01	8.78E-01	8.57E-01
LPC(16:0)	**50.326**	4.43	**51.388**	3.78	**48.453**	6.03	1.49E-01	2.78E-02	3.23E-01
LPC(16:1)	**1.438**	0.27	**1.643**	0.55	**1.293**	0.21	2.05E-01	1.11E-02	9.65E-02
LPC(18:0)	**16.850**	2.39	**16.270**	1.72	**14.921**	1.18	1.68E-02	7.37E-02	4.14E-01
LPC(18:1)	**10.550**	1.62	**10.516**	1.71	**11.933**	1.93	1.26E-02	9.50E-03	9.07E-01
LPC(18:2)	**14.564**	3.23	**13.111**	2.32	**17.531**	4.39	8.78E-03	**7.17E-05**	6.27E-02
LPC(18:3)	**0.259**	0.08	**0.273**	0.10	**0.294**	0.09	3.24E-01	4.71E-01	7.28E-01
LPC(20:3)	**1.325**	0.22	**1.426**	0.25	**1.165**	0.11	6.60E-02	3.18E-03	1.44E-01
LPC(20:4)	**2.612**	0.70	**3.264**	0.90	**2.573**	0.48	9.95E-01	1.43E-02	1.89E-03
LPC(20:5)	**0.251**	0.10	**0.291**	0.12	**0.211**	0.07	3.30E-01	5.39E-02	2.18E-01
LPC(22:6)	**0.552**	0.14	**0.610**	0.19	**0.456**	0.11	4.52E-02	2.48E-03	1.72E-01
LPC(O-16:1)	**0.425**	0.08	**0.383**	0.09	**0.358**	0.08	1.42E-02	3.66E-01	4.29E-02
LPC(O-18:1)	**0.224**	0.04	**0.196**	0.04	**0.167**	0.03	**9.42E-05**	3.68E-02	1.25E-02
PC(32:0)	**0.723**	0.07	**0.740**	0.15	**0.822**	0.14	2.83E-02	4.63E-02	7.77E-01
PC(32:1)	**1.113**	0.40	**1.526**	0.84	**1.138**	0.30	6.60E-01	5.22E-02	2.73E-03
PC(32:2)	**0.189**	0.05	**0.175**	0.04	**0.214**	0.05	1.54E-01	2.80E-02	3.16E-01
PC(34:1)	**13.152**	1.50	**14.179**	1.99	**14.267**	1.39	2.61E-02	7.71E-01	1.29E-02
PC(34:2)	**22.981**	2.72	**21.229**	2.29	**24.167**	1.22	1.53E-01	7.84E-04	1.11E-02
PC(34:3)	**0.817**	0.13	**0.798**	0.17	**0.877**	0.14	3.20E-01	1.46E-01	5.59E-01
PC(34:4)	**0.052**	0.02	**0.060**	0.02	**0.056**	0.02	4.76E-01	4.65E-01	6.59E-02
PC(36:1)	**2.249**	0.52	**2.312**	0.63	**2.154**	0.38	6.65E-01	4.82E-01	7.31E-01
PC(36:2)	**15.277**	2.07	**13.725**	1.87	**15.179**	2.10	9.16E-01	8.56E-02	2.04E-02
PC(36:3)	**10.513**	1.18	**9.589**	1.62	**10.991**	1.28	4.34E-01	1.23E-02	2.63E-02
PC(36:4)	**10.586**	1.68	**12.404**	1.99	**10.581**	1.34	9.50E-01	1.38E-02	1.42E-03
PC(36:5)	**0.995**	0.38	**1.147**	0.41	**1.044**	0.35	6.88E-01	5.20E-01	1.82E-01
PC(36:6)	**0.027**	0.01	**0.028**	0.01	**0.032**	0.01	1.51E-01	2.01E-01	8.30E-01
PC(38:2)	**0.250**	0.04	**0.208**	0.04	**0.220**	0.03	2.03E-02	2.08E-01	**9.82E-06**
PC(38:3)	**2.384**	0.41	**2.348**	0.56	**1.652**	0.22	**2.96E-05**	**9.11E-05**	6.81E-01
PC(38:4)	**6.768**	1.55	**7.681**	1.59	**5.275**	0.81	1.39E-03	**1.76E-06**	2.13E-02
PC(38:5)	**3.271**	0.66	**3.531**	0.66	**3.163**	0.67	5.83E-01	7.79E-02	1.19E-01
PC(38:6)	**3.512**	0.84	**3.534**	0.84	**3.545**	0.85	8.83E-01	9.86E-01	8.68E-01
PC(40:4)	**0.100**	0.03	**0.110**	0.03	**0.084**	0.02	3.73E-02	8.71E-04	9.49E-02
PC(40:5)	**0.502**	0.12	**0.534**	0.10	**0.409**	0.12	8.03E-03	4.42E-04	2.36E-01
PC(40:6)	**1.248**	0.35	**1.269**	0.31	**0.907**	0.27	1.60E-03	5.83E-04	7.02E-01
PC(40:7)	**0.214**	0.05	**0.194**	0.04	**0.222**	0.04	5.34E-01	5.72E-02	9.99E-02
PC(40:8)	**0.035**	0.01	**0.036**	0.01	**0.047**	0.01	**3.24E-05**	**9.90E-05**	6.75E-01
PC(O-34:1)	**0.247**	0.04	**0.199**	0.03	**0.247**	0.04	9.48E-01	3.78E-04	**1.21E-05**
PC(O-34:3)	**0.319**	0.08	**0.243**	0.06	**0.388**	0.08	1.20E-02	**2.14E-08**	**1.90E-05**
PC(O-36:2)	**0.142**	0.03	**0.108**	0.02	**0.139**	0.02	9.01E-01	**1.98E-04**	**1.71E-06**
PC(O-36:3)	**0.080**	0.02	**0.068**	0.01	**0.103**	0.02	6.19E-04	**2.50E-08**	1.74E-03

Lipid	NGT		DM		Control		p-value (correction p<0.000275)		
	mean	sd	mean	sd	mean	sd	NGTvs C	DM vs C	DM vs NGT
PC(O-36:4)	**0.543**	0.11	**0.478**	0.11	**0.489**	0.12	1.20E-01	7.77E-01	1.93E-02
PC(O-36:5)	**0.435**	0.07	**0.426**	0.13	**0.417**	0.09	5.07E-01	9.14E-01	4.74E-01
PC(O-36:6)	**0.029**	0.01	**0.026**	0.01	**0.028**	0.01	9.99E-01	3.25E-01	2.10E-01
PC(O-38:4)	**0.230**	0.06	**0.196**	0.05	**0.213**	0.06	3.40E-01	4.18E-01	2.52E-02
PC(O-38:5)	**0.569**	0.15	**0.493**	0.13	**0.519**	0.16	2.37E-01	6.41E-01	3.60E-02
PC(O-38:6)	**0.267**	0.04	**0.237**	0.05	**0.235**	0.04	4.11E-02	9.94E-01	9.28E-03
PC(O-38:7)	**0.096**	0.02	**0.089**	0.03	**0.094**	0.02	8.60E-01	3.48E-01	1.55E-01
PC(O-42:6)	**0.018**	0.00	**0.017**	0.00	**0.018**	0.01	9.79E-01	2.80E-01	1.78E-01
PC(O-44:5)	**0.068**	0.02	**0.065**	0.02	**0.066**	0.02	8.62E-01	7.60E-01	5.40E-01
PE(34:2)	**7.965**	4.25	**10.230**	5.11	**7.698**	2.36	7.65E-01	1.21E-01	1.91E-02
PE(36:3)	**6.132**	1.47	**6.689**	1.33	**4.555**	1.02	4.32E-04	**5.85E-06**	1.46E-01
PE(38:2)	**69.362**	4.00	**64.620**	5.79	**75.282**	4.17	3.77E-03	**1.64E-07**	9.74E-04
PE(38:4)	**6.247**	1.93	**7.347**	1.78	**5.535**	1.15	2.43E-01	1.58E-03	9.30E-03
PE(O-36:5)	**6.495**	1.71	**7.284**	2.62	**4.340**	1.89	**7.65E-05**	**2.22E-06**	2.69E-01
PE(O-38:7)	**3.798**	1.11	**3.830**	1.19	**2.590**	0.64	2.82E-04	**2.55E-04**	9.93E-01
SM(d18:1/14:0)	**2.287**	0.29	**2.388**	0.40	**2.835**	0.31	**4.82E-05**	5.80E-04	3.42E-01
SM(d18:1/15:0)	**1.495**	0.18	**1.524**	0.17	**1.757**	0.17	**7.95E-05**	4.25E-04	5.16E-01
SM(d18:1/16:0)	**29.508**	1.60	**28.917**	1.39	**32.566**	1.79	**6.93E-07**	**5.65E-09**	1.68E-01
SM(d18:1/16:1)	**3.862**	0.52	**3.701**	0.36	**3.362**	0.25	5.66E-04	1.25E-02	1.77E-01
SM(d18:1/18:0)	**6.979**	0.96	**7.903**	1.06	**6.282**	0.57	2.47E-02	**1.83E-06**	5.37E-04
SM(d18:1/18:1)	**3.289**	0.58	**3.619**	0.67	**2.643**	0.22	**1.38E-04**	**1.18E-07**	2.53E-02
SM(d18:1/18:2)	**0.210**	0.04	**0.195**	0.04	**0.224**	0.04	4.02E-01	5.34E-02	1.58E-01
SM(d18:1/20:0)	**4.290**	0.50	**4.510**	0.52	**4.223**	0.56	6.89E-01	1.32E-01	1.57E-01
SM(d18:1/20:1)	**1.849**	0.21	**1.836**	0.22	**1.692**	0.20	3.84E-02	5.44E-02	8.34E-01
SM(d18:1/21:0)	**1.255**	0.18	**1.279**	0.22	**1.348**	0.22	2.72E-01	3.83E-01	7.65E-01
SM(d18:1/22:0)	**8.036**	0.82	**8.190**	1.15	**7.202**	0.75	2.02E-02	8.39E-03	6.87E-01
SM(d18:1/22:1)	**6.427**	0.45	**6.174**	0.58	**6.325**	0.38	6.41E-01	4.13E-01	1.02E-01
SM(d18:1/23:0)	**3.001**	0.29	**3.018**	0.36	**2.892**	0.32	4.01E-01	3.57E-01	9.20E-01
SM(d18:1/23:1)	**2.278**	0.23	**2.184**	0.29	**2.452**	0.24	7.97E-02	5.07E-03	1.63E-01
SM(d18:1/24:0)	**4.476**	0.48	**4.566**	0.66	**4.253**	0.52	2.66E-01	1.50E-01	6.78E-01
SM(d18:1/24:1)	**13.632**	1.04	**13.453**	1.30	**13.214**	1.39	2.87E-01	5.49E-01	5.45E-01
SM(d18:1/24:2)	**6.898**	0.81	**6.321**	0.85	**6.488**	0.70	1.43E-01	4.72E-01	5.85E-03
SM(d18:1/25:0)	**0.228**	0.04	**0.222**	0.05	**0.241**	0.04	4.48E-01	2.16E-01	5.40E-01
CE(18:2)	**57.831**	5.46	**53.516**	5.62	**60.143**	3.13	3.11E-01	4.21E-03	1.67E-02
CE(20:4)	**30.105**	5.38	**35.341**	5.37	**28.388**	3.53	4.30E-01	4.22E-04	4.27E-04
CE(20:5)	**6.646**	2.20	**6.668**	2.30	**5.897**	2.37	9.87E-01	9.83E-01	9.60E-01
CE(22:6)	**5.418**	1.67	**4.475**	1.84	**5.572**	1.41	7.12E-01	2.65E-02	1.80E-02
TG(44:1)	**0.078**	0.14	**0.084**	0.06	**0.106**	0.07	8.11E-02	4.41E-01	2.04E-01
TG(44:2)	**0.031**	0.04	**0.035**	0.03	**0.058**	0.06	7.55E-02	2.28E-01	4.49E-01
TG(46:0)	**0.243**	0.31	**0.322**	0.21	**0.225**	0.14	5.86E-01	1.65E-01	1.43E-02
TG(46:1)	**0.380**	0.46	**0.448**	0.24	**0.430**	0.22	2.06E-01	8.77E-01	6.95E-02
TG(46:2)	**0.166**	0.14	**0.181**	0.11	**0.257**	0.15	3.33E-02	1.07E-01	4.89E-01
TG(48:0)	**0.690**	0.49	**0.994**	0.57	**0.692**	0.26	4.41E-01	9.45E-02	2.17E-03

Supplementary Table 2a. Continued.

Lipid	NGT		DM		Control		p-value (correction p<0.000275)		
	mean	sd	mean	sd	mean	sd	NGTvs C	DM vs C	DM vs NGT
TG(48:1)	**2.128**	1.23	**2.787**	1.17	**2.409**	1.18	3.60E-01	3.33E-01	1.72E-02
TG(48:2)	**1.257**	0.68	**1.414**	0.53	**1.347**	0.58	5.91E-01	6.41E-01	1.99E-01
TG(48:3)	**0.313**	0.12	**0.307**	0.12	**0.387**	0.21	2.95E-01	2.23E-01	8.30E-01
TG(48:4)	**0.054**	0.03	**0.056**	0.03	**0.085**	0.07	1.22E-01	1.90E-01	7.45E-01
TG(50:0)	**0.533**	0.37	**0.835**	0.52	**0.480**	0.22	9.46E-01	1.27E-02	2.12E-03
TG(50:1)	**6.865**	1.87	**8.327**	2.09	**6.768**	1.70	9.62E-01	1.74E-02	3.14E-03
TG(50:2)	**8.261**	1.61	**9.255**	1.76	**7.649**	1.90	2.20E-01	4.83E-03	3.77E-02
TG(50:3)	**3.383**	0.72	**3.446**	0.68	**3.286**	0.93	5.45E-01	3.81E-01	7.31E-01
TG(50:4)	**0.573**	0.13	**0.543**	0.14	**0.552**	0.24	3.68E-01	7.37E-01	4.65E-01
TG(50:5)	**0.099**	0.03	**0.099**	0.04	**0.111**	0.06	6.78E-01	5.42E-01	8.06E-01
TG(51:1)	**0.382**	0.16	**0.447**	0.15	**0.517**	0.22	1.04E-02	3.08E-01	4.26E-02
TG(51:2)	**0.593**	0.15	**0.592**	0.13	**0.643**	0.22	4.58E-01	5.21E-01	8.93E-01
TG(51:3)	**0.325**	0.06	**0.296**	0.05	**0.390**	0.10	1.04E-02	**1.27E-04**	8.35E-02
TG(51:4)	**0.095**	0.02	**0.081**	0.02	**0.103**	0.03	4.45E-01	5.21E-03	8.75E-03
TG(52:0)	**0.074**	0.05	**0.132**	0.14	**0.075**	0.03	6.09E-01	1.07E-01	7.32E-03
TG(52:1)	**2.629**	1.08	**3.602**	1.45	**2.476**	0.51	9.59E-01	1.04E-02	1.47E-03
TG(52:2)	**20.317**	2.74	**19.121**	1.89	**21.041**	3.17	4.70E-01	4.03E-02	8.72E-02
TG(52:3)	**18.651**	2.76	**16.601**	2.86	**17.706**	2.89	2.96E-01	1.99E-01	3.44E-03
TG(52:4)	**6.766**	1.60	**5.952**	1.59	**5.611**	1.72	2.38E-02	4.72E-01	4.46E-02
TG(52:5)	**1.105**	0.29	**1.047**	0.33	**0.840**	0.38	1.92E-03	1.16E-02	4.11E-01
TG(52:6)	**0.163**	0.05	**0.166**	0.07	**0.144**	0.08	1.83E-01	2.03E-01	9.30E-01
TG(53:1)	**0.068**	0.03	**0.079**	0.04	**0.101**	0.04	2.54E-03	4.93E-02	1.50E-01
TG(54:1)	**0.153**	0.09	**0.240**	0.23	**0.139**	0.03	9.96E-01	5.29E-02	1.36E-02
TG(54:2)	**2.621**	0.65	**2.856**	0.74	**2.891**	0.96	3.64E-01	9.50E-01	2.13E-01
TG(54:3)	**6.479**	1.70	**5.753**	0.96	**7.731**	3.74	1.33E-01	7.42E-03	1.21E-01
TG(54:4)	**5.279**	1.26	**4.576**	1.14	**5.488**	1.37	6.31E-01	2.50E-02	2.40E-02
TG(54:5)	**3.055**	0.65	**2.999**	0.73	**3.032**	0.89	8.08E-01	9.42E-01	6.84E-01
TG(54:6)	**1.204**	0.28	**1.269**	0.41	**1.061**	0.53	8.07E-02	3.27E-02	6.17E-01
TG(54:7)	**0.304**	0.09	**0.301**	0.12	**0.245**	0.14	3.60E-02	6.49E-02	7.28E-01
TG(55:1)	**0.045**	0.02	**0.063**	0.03	**0.034**	0.02	2.84E-01	4.92E-03	1.97E-02
TG(55:2)	**0.403**	0.11	**0.331**	0.07	**0.453**	0.10	1.01E-01	**9.50E-05**	2.61E-03
TG(55:3)	**0.470**	0.13	**0.374**	0.10	**0.497**	0.07	2.81E-01	**2.11E-04**	6.28E-04
TG(56:3)	**0.213**	0.07	**0.195**	0.04	**0.273**	0.10	4.51E-03	4.26E-04	3.56E-01
TG(56:5)	**0.832**	0.23	**0.931**	0.22	**1.014**	0.25	2.58E-02	3.70E-01	8.13E-02
TG(56:6)	**1.169**	0.29	**1.284**	0.29	**1.228**	0.31	5.81E-01	5.88E-01	1.62E-01
TG(56:7)	**1.100**	0.29	**1.138**	0.35	**1.053**	0.24	7.72E-01	6.03E-01	7.70E-01
TG(56:8)	**0.363**	0.12	**0.351**	0.16	**0.286**	0.11	1.02E-01	2.36E-01	5.52E-01
TG(57:2)	**0.037**	0.01	**0.041**	0.01	**0.040**	0.01	5.69E-01	7.40E-01	2.49E-01
TG(58:10)	**0.049**	0.03	**0.050**	0.04	**0.043**	0.03	5.41E-01	5.98E-01	9.11E-01

Relative abundance of lipid species to summed lipid levels at baseline (NGT, DM, Control) .Values are presented as mean ± sd. (Means are bold larger font, sds are smaller font.) Differences between subject groups (NGT vs T2DM) and lean controls at baseline were compared with a mixed-effects model, with the patient groups and diabetes as fixed effects and the subject specific deviances modelled with random intercepts. The Bonferroni posthoc test was used to correct for multiple testing. A p-value <0.000275 was considered statistically significant (= (0,05 divided by 26, the effective number of independent lipid species, and by 7, the number of hypotheses tested). Significant p-values are bold.

Supplementary Table 2b. Relative abundance of lipid species to summed lipid levels at baseline and after different interventions per group.

Lipid	NGT_GB 0		NGT_GB 1		p-value	NGT_RYGB 0		NGT_RYGB 1		p-value	DM_RYGB 0		DM_RYGB 1		p-value	DM_VLCD 0		DM_VLCD 1		p-value
	mean	sd	mean	sd	*<0.000275*	mean	sd	mean	sd	*<0.000275*	mean	sd	mean	sd	*<0.000275*	mean	sd	mean	sd	*<0.000275*
Cer(d18:1/16:0)	**5.39**	1.51	**7.57**	1.66	**1.50E-05**	**5.25**	0.86	**8.52**	1.84	**1.06E-09**	**5.64**	1.14	**7.69**	2.03	**4.98E-05**	**5.89**	1.66	**8.02**	2.29	**5.35E-05**
Cer(d18:1/24:0)	**54.81**	3.21	**42.32**	5.13	**4.33E-11**	**54.22**	2.83	**36.25**	6.17	**2.02E-22**	**53.22**	4.27	**39.14**	4.47	**2.51E-16**	**54.31**	4.40	**42.64**	4.94	**8.82E-11**
Cer(d18:1/24:1)	**34.53**	3.29	**45.29**	3.93	**5.80E-14**	**35.70**	3.48	**50.10**	5.50	**1.45E-21**	**36.74**	3.59	**49.31**	3.51	**8.50E-19**	**35.56**	3.44	**44.52**	4.40	**6.64E-12**
LPC(14:0)	**0.59**	0.19	**0.39**	0.12	**7.76E-05**	**0.65**	0.18	**0.32**	0.12	**8.07E-11**	**0.58**	0.15	**0.14**	0.12	**9.59E-19**	**0.69**	0.15	**0.25**	0.08	**1.33E-14**
LPC(16:0)	**50.40**	3.91	**54.16**	2.93	**2.80E-05**	**50.28**	4.87	**56.60**	2.64	**4.00E-12**	**51.83**	3.28	**55.76**	4.20	**2.15E-06**	**50.87**	4.35	**57.18**	3.99	**2.75E-10**
LPC(16:1)	**1.54**	0.31	**1.57**	0.17	3.09E-01	**1.37**	0.22	**1.60**	0.34	1.11E-03	**1.57**	0.40	**1.49**	0.38	1.06E-01	**1.73**	0.70	**1.41**	0.49	**6.16E-05**
LPC(18:0)	**17.22**	1.80	**14.26**	1.22	**2.80E-06**	**16.59**	2.75	**13.48**	3.02	**1.07E-10**	**15.68**	1.42	**12.66**	1.02	**1.53E-10**	**16.96**	1.83	**12.05**	1.55	**2.75E-15**
LPC(18:1)	**10.32**	1.96	**10.26**	1.17	9.18E-01	**10.71**	1.38	**10.10**	1.13	2.68E-02	**10.63**	1.61	**11.07**	1.41	5.69E-02	**10.38**	1.88	**10.31**	1.19	9.30E-01
LPC(18:2)	**14.06**	2.38	**12.77**	2.00	3.83E-02	**14.91**	3.74	**11.03**	1.88	**1.19E-08**	**13.19**	1.96	**11.00**	1.72	**1.06E-04**	**13.02**	2.76	**10.74**	2.24	**7.34E-05**
LPC(18:3)	**0.27**	0.05	**0.18**	0.06	**7.61E-05**	**0.25**	0.09	**0.14**	0.06	**5.80E-10**	**0.27**	0.11	**0.12**	0.05	**9.85E-15**	**0.28**	0.09	**0.10**	0.08	**3.73E-10**
LPC(20:3)	**1.29**	0.15	**1.03**	0.18	**2.63E-05**	**1.35**	0.27	**0.99**	0.21	**6.66E-09**	**1.44**	0.22	**1.08**	0.22	**7.09E-08**	**1.41**	0.29	**1.05**	0.20	**6.59E-08**
LPC(20:4)	**2.87**	0.62	**3.73**	1.24	**1.51E-05**	**2.43**	0.72	**4.10**	1.33	**1.56E-14**	**3.22**	0.95	**4.62**	1.18	**1.02E-09**	**3.31**	0.88	**5.21**	1.05	**1.23E-12**
LPC(20:5)	**0.25**	0.09	**0.22**	0.15	4.16E-02	**0.25**	0.11	**0.19**	0.08	1.36E-03	**0.33**	0.15	**0.26**	0.15	1.79E-02	**0.25**	0.06	**0.18**	0.05	4.20E-04
LPC(22:6)	**0.56**	0.13	**0.73**	0.23	**1.41E-04**	**0.55**	0.15	**0.74**	0.18	**8.92E-08**	**0.67**	0.21	**1.04**	0.27	**1.03E-12**	**0.54**	0.12	**0.78**	0.16	**9.57E-08**
LPC(O-16:1)	**0.42**	0.10	**0.44**	0.08	4.32E-01	**0.43**	0.06	**0.45**	0.11	3.20E-01	**0.39**	0.07	**0.51**	0.09	**9.64E-07**	**0.37**	0.12	**0.46**	0.08	**1.19E-04**
LPC(O-18:1)	**0.22**	0.04	**0.26**	0.04	6.67E-03	**0.23**	0.05	**0.27**	0.07	4.70E-04	**0.19**	0.04	**0.27**	0.07	**3.48E-09**	**0.20**	0.04	**0.28**	0.06	**6.13E-10**
PC(32:0)	**0.74**	0.08	**0.88**	0.11	**1.04E-06**	**0.71**	0.06	**0.93**	0.13	**9.57E-13**	**0.72**	0.72	**0.82**	0.82	**1.46E-04**	**0.76**	0.19	**0.94**	0.18	**2.05E-09**
PC(32:1)	**1.17**	0.43	**1.07**	0.26	6.03E-01	**1.08**	0.39	**1.14**	0.46	4.40E-01	**1.41**	1.42	**1.08**	1.08	**1.41E-04**	**1.66**	1.15	**0.96**	0.41	**1.51E-08**
PC(32:2)	**0.18**	0.05	**0.12**	0.04	**1.33E-08**	**0.19**	0.05	**0.10**	0.04	**5.02E-15**	**0.16**	0.16	**0.08**	0.08	**1.32E-16**	**0.19**	0.04	**0.07**	0.02	**1.31E-21**
PC(34:1)	**13.38**	1.80	**14.25**	1.68	1.90E-02	**13.00**	1.29	**15.33**	1.18	**4.66E-08**	**14.07**	####	**15.37**	####	1.27E-03	**14.30**	2.51	**15.47**	1.24	1.99E-03
PC(34:2)	**23.14**	2.88	**24.00**	2.77	1.63E-01	**22.87**	2.69	**23.59**	2.31	1.95E-01	**21.17**	####	**21.86**	####	2.31E-01	**21.30**	2.79	**21.68**	2.92	5.04E-01
PC(34:3)	**0.85**	0.15	**0.68**	0.12	1.04E-03	**0.79**	0.12	**0.60**	0.15	**2.02E-08**	**0.77**	0.78	**0.46**	0.46	**5.18E-15**	**0.83**	0.17	**0.42**	0.10	**5.03E-19**
PC(34:4)	**0.05**	0.01	**0.04**	0.01	8.97E-04	**0.05**	0.02	**0.03**	0.01	**6.11E-10**	**0.06**	0.06	**0.03**	0.03	**1.50E-13**	**0.06**	0.02	**0.02**	0.01	**2.27E-17**
PC(36:1)	**2.10**	0.51	**1.42**	0.24	**9.35E-10**	**2.35**	0.52	**1.32**	0.29	**2.72E-16**	**2.34**	2.37	**1.44**	1.44	**7.67E-13**	**2.28**	0.54	**1.27**	0.29	**3.48E-16**
PC(36:2)	**15.27**	1.92	**12.08**	1.94	**2.55E-06**	**15.28**	2.23	**10.40**	2.43	**5.34E-15**	**13.40**	####	**9.86**	9.86	**4.34E-11**	**14.09**	2.08	**8.63**	1.85	**2.66E-17**
PC(36:3)	**10.41**	1.20	**8.65**	1.84	**1.94E-06**	**10.59**	1.21	**7.89**	1.37	**6.14E-13**	**9.10**	9.10	**6.64**	6.64	**2.03E-14**	**10.15**	1.84	**7.10**	1.76	**3.52E-14**
PC(36:4)	**10.55**	1.79	**13.75**	3.53	**3.80E-07**	**10.61**	1.65	**15.24**	3.69	**1.66E-13**	**12.84**	####	**16.82**	####	**3.12E-10**	**11.90**	2.16	**19.30**	3.24	**2.51E-17**
PC(36:5)	**1.11**	0.41	**0.98**	0.70	1.03E-01	**0.92**	0.35	**0.84**	0.42	8.14E-02	**1.22**	1.21	**0.83**	0.83	5.67E-04	**1.07**	0.25	**0.77**	0.20	1.96E-03
PC(36:6)	**0.03**	0.01	**0.02**	0.01	1.31E-03	**0.03**	0.01	**0.02**	0.01	**1.26E-07**	**0.03**	0.03	**0.02**	0.02	**3.56E-05**	**0.03**	0.01	**0.02**	0.01	**1.89E-09**

Supplementary Table 2b. Continued.

Lipid	NGT_GB 0		NGT_GB 1		p-value	NGT_RYGB 0		NGT_RYGB 1		p-value	DM_RYGB 0		DM_RYGB 1		p-value	DM_VLCD 0		DM_VLCD 1		p-value
	mean	sd	mean	sd	*<0.000275*	mean	sd	mean	sd	*<0.000275*	mean	sd	mean	sd	*<0.000275*	mean	sd	mean	sd	*<0.000275*
PC(38:2)	**0.24**	0.04	**0.18**	0.02	**1.33E-09**	**0.26**	0.04	**0.17**	0.02	**1.51E-14**	**0.21**	0.21	**0.13**	0.13	**3.33E-15**	**0.21**	0.03	**0.15**	0.02	**2.08E-11**
PC(38:3)	**2.35**	0.27	**1.38**	0.34	**1.34E-11**	**2.41**	0.49	**1.23**	0.36	**2.42E-17**	**2.24**	2.23	**1.09**	1.09	**7.08E-19**	**2.47**	0.67	**1.06**	0.42	**1.16E-20**
PC(38:4)	**6.66**	1.61	**7.19**	2.09	1.10E-01	**6.84**	1.55	**7.14**	1.67	2.17E-01	**7.93**	7.82	**8.79**	8.79	3.40E-03	**7.39**	2.03	**8.27**	1.58	2.58E-03
PC(38:5)	**3.16**	0.63	**3.15**	0.66	7.03E-01	**3.35**	0.69	**3.35**	0.52	6.46E-01	**3.72**	3.72	**3.59**	3.59	7.17E-01	**3.31**	0.66	**3.47**	0.57	4.36E-01
PC(38:6)	**3.53**	0.87	**4.84**	1.30	**2.19E-08**	**3.50**	0.85	**5.25**	1.23	**4.51E-14**	**3.75**	3.67	**5.70**	5.70	**3.22E-15**	**3.28**	0.76	**5.24**	1.01	**1.30E-14**
PC(40:4)	**0.09**	0.02	**0.07**	0.01	**8.67E-06**	**0.10**	0.03	**0.09**	0.03	1.06E-03	**0.11**	0.11	**0.08**	0.08	**3.85E-08**	**0.11**	0.03	**0.08**	0.02	**1.35E-07**
PC(40:5)	**0.47**	0.09	**0.37**	0.06	**8.41E-06**	**0.52**	0.14	**0.44**	0.11	**1.59E-04**	**0.54**	0.54	**0.42**	0.42	**4.45E-07**	**0.53**	0.12	**0.38**	0.08	**2.98E-09**
PC(40:6)	**1.29**	0.40	**1.47**	0.46	7.91E-03	**1.22**	0.32	**1.47**	0.46	**1.09E-04**	**1.34**	1.30	**1.69**	1.69	**3.00E-07**	**1.19**	0.31	**1.29**	0.29	7.48E-02
PC(40:7)	**0.21**	0.06	**0.26**	0.06	4.20E-04	**0.21**	0.04	**0.24**	0.06	4.32E-03	**0.20**	0.20	**0.26**	0.26	**1.30E-07**	**0.18**	0.04	**0.23**	0.04	**1.35E-04**
PC(40:8)	**0.04**	0.01	**0.03**	0.01	4.77E-01	**0.03**	0.00	**0.03**	0.00	3.73E-02	**0.04**	0.04	**0.03**	0.03	**7.39E-05**	**0.04**	0.01	**0.03**	0.01	1.67E-02
PC(O-34:1)	**0.23**	0.04	**0.28**	0.03	**1.06E-04**	**0.26**	0.04	**0.28**	0.05	7.20E-03	**0.20**	0.20	**0.25**	0.25	**2.23E-08**	**0.20**	0.02	**0.27**	0.05	**1.58E-12**
PC(O-34:3)	**0.31**	0.04	**0.28**	0.02	1.26E-01	**0.33**	0.09	**0.24**	0.06	**3.20E-06**	**0.25**	0.25	**0.21**	0.21	2.22E-02	**0.23**	0.04	**0.23**	0.04	8.44E-01
PC(O-36:2)	**0.13**	0.03	**0.12**	0.02	1.49E-01	**0.15**	0.03	**0.12**	0.02	**2.05E-04**	**0.11**	0.11	**0.10**	0.10	5.48E-01	**0.11**	0.02	**0.11**	0.02	2.19E-01
PC(O-36:3)	**0.08**	0.01	**0.07**	0.01	1.18E-01	**0.08**	0.02	**0.07**	0.01	7.97E-04	**0.07**	0.07	**0.06**	0.06	1.85E-02	**0.07**	0.01	**0.07**	0.01	8.20E-01
PC(O-36:4)	**0.53**	0.06	**0.53**	0.08	8.23E-01	**0.55**	0.14	**0.51**	0.13	1.12E-01	**0.48**	0.48	**0.50**	0.50	2.66E-01	**0.48**	0.10	**0.50**	0.09	4.19E-01
PC(O-36:5)	**0.44**	0.04	**0.47**	0.11	3.48E-01	**0.43**	0.09	**0.46**	0.12	4.27E-01	**0.43**	0.42	**0.47**	0.47	3.39E-02	**0.42**	0.16	**0.50**	0.10	3.35E-03
PC(O-36:6)	**0.03**	0.01	**0.02**	0.01	2.08E-02	**0.03**	0.01	**0.02**	0.01	2.87E-04	**0.03**	0.03	**0.02**	0.02	6.77E-04	**0.03**	0.01	**0.02**	0.00	4.45E-03
PC(O-38:4)	**0.22**	0.04	**0.20**	0.07	7.07E-02	**0.24**	0.06	**0.21**	0.06	7.99E-02	**0.19**	0.19	**0.19**	0.19	7.15E-01	**0.21**	0.06	**0.21**	0.04	2.46E-01
PC(O-38:5)	**0.57**	0.13	**0.65**	0.09	1.62E-02	**0.57**	0.16	**0.76**	0.25	**7.36E-07**	**0.48**	0.49	**0.64**	0.64	**9.79E-07**	**0.51**	0.15	**0.74**	0.15	**7.75E-10**
PC(O-38:6)	**0.26**	0.04	**0.28**	0.06	3.68E-01	**0.27**	0.05	**0.26**	0.03	8.63E-01	**0.24**	0.24	**0.25**	0.25	1.90E-01	**0.24**	0.05	**0.28**	0.04	1.82E-03
PC(O-38:7)	**0.10**	0.02	**0.10**	0.03	7.33E-01	**0.09**	0.02	**0.09**	0.02	6.02E-01	**0.09**	0.09	**0.09**	0.09	3.39E-01	**0.09**	0.03	**0.09**	0.01	4.61E-01
PC(O-42:6)	**0.02**	0.00	**0.02**	0.00	**3.65E-06**	**0.02**	0.00	**0.03**	0.01	**3.82E-10**	**0.02**	0.02	**0.02**	0.02	**8.00E-10**	**0.02**	0.00	**0.03**	0.01	**3.25E-11**
PC(O-44:5)	**0.06**	0.01	**0.09**	0.02	**7.61E-07**	**0.07**	0.03	**0.10**	0.04	**2.85E-10**	**0.06**	0.06	**0.09**	0.09	**8.89E-10**	**0.06**	0.01	**0.11**	0.03	**8.14E-12**
PE(34:2)	**8.36**	4.55	**8.76**	6.64	9.03E-01	**7.69**	4.16	**9.35**	4.83	6.72E-03	**9.35**	3.33	**8.08**	3.08	4.94E-02	**11.25**	6.61	**9.35**	2.24	4.64E-01
PE(36:3)	**5.91**	1.21	**6.73**	1.32	4.82E-02	**6.29**	1.65	**8.60**	3.32	**1.47E-07**	**6.77**	1.23	**9.74**	1.73	**8.11E-10**	**6.60**	1.48	**10.06**	2.25	**2.03E-10**
PE(38:2)	**69.59**	4.45	**69.23**	6.58	7.88E-01	**69.21**	3.81	**65.85**	6.38	6.47E-03	**64.82**	5.45	**62.10**	3.97	4.81E-02	**64.39**	6.39	**60.84**	4.71	7.93E-03
PE(38:4)	**6.14**	1.65	**7.04**	2.17	4.24E-02	**6.32**	2.15	**7.62**	1.72	**7.73E-05**	**7.61**	1.90	**9.20**	1.96	**1.54E-04**	**7.05**	1.65	**9.42**	2.62	**9.89E-06**
PE(O-36:5)	**6.33**	1.54	**4.54**	1.80	**1.29E-04**	**6.61**	1.85	**4.67**	1.75	**7.43E-05**	**7.60**	3.04	**6.80**	2.08	4.81E-01	**6.92**	2.10	**5.79**	1.03	5.39E-02
PE(O-38:7)	**3.68**	0.87	**3.70**	1.15	8.10E-01	**3.88**	1.27	**3.91**	1.24	7.85E-01	**3.86**	1.48	**4.08**	0.83	1.53E-01	**3.79**	0.80	**4.54**	0.93	1.14E-02

Lipid	NGT_GB 0		NGT_GB 1		p-value	NGT_RYGB 0		NGT_RYGB 1		p-value	DM_RYGB 0		DM_RYGB 1		p-value	DM_VLCD 0		DM_VLCD 1		p-value
	mean	sd	mean	sd	*<0.000275*	mean	sd	mean	sd	*<0.000275*	mean	sd	mean	sd	*<0.000275*	mean	sd	mean	sd	*<0.000275*
SM(d18:1/14:0)	**2.24**	0.19	**1.85**	0.16	**5.89E-11**	**2.32**	0.36	**1.88**	0.29	**7.82E-15**	**2.28**	0.31	**1.64**	0.23	**7.91E-23**	**2.51**	0.49	**1.98**	0.37	**1.80E-14**
SM(d18:1/15:0)	**1.50**	0.13	**1.45**	0.14	1.32E-01	**1.49**	0.21	**1.54**	0.17	3.13E-02	**1.53**	0.16	**1.42**	0.18	**2.57E-05**	**1.51**	0.19	**1.52**	0.18	7.84E-01
SM(d18:1/16:0)	**28.84**	1.40	**29.34**	1.62	5.12E-01	**29.97**	1.66	**29.95**	1.42	6.12E-01	**28.85**	1.46	**29.10**	1.87	5.32E-01	**28.99**	1.42	**28.85**	1.19	7.79E-01
SM(d18:1/16:1)	**3.76**	0.27	**3.87**	0.36	1.60E-01	**3.94**	0.66	**4.08**	0.49	2.78E-03	**3.78**	0.28	**3.79**	0.36	8.06E-01	**3.61**	0.44	**3.79**	0.47	7.81E-03
SM(d18:1/18:0)	**7.29**	0.93	**9.51**	1.33	**2.74E-12**	**6.77**	0.98	**10.66**	1.15	**3.59E-23**	**8.16**	1.08	**11.91**	1.43	**1.97E-20**	**7.61**	1.03	**10.31**	1.14	**8.87E-14**
SM(d18:1/18:1)	**3.38**	0.54	**4.50**	0.49	**1.04E-12**	**3.23**	0.64	**5.16**	0.52	**7.48E-24**	**3.87**	0.70	**5.53**	0.67	**2.86E-19**	**3.32**	0.56	**4.81**	0.68	**2.08E-16**
SM(d18:1/18:2)	**0.22**	0.04	**0.22**	0.06	8.47E-01	**0.20**	0.03	**0.21**	0.04	3.18E-01	**0.20**	0.03	**0.22**	0.05	3.38E-02	**0.19**	0.05	**0.20**	0.05	2.21E-01
SM(d18:1/20:0)	**4.36**	0.33	**3.33**	0.40	**3.93E-13**	**4.24**	0.61	**2.97**	0.41	**3.74E-21**	**4.40**	0.44	**3.13**	0.35	**4.21E-20**	**4.64**	0.62	**3.24**	0.54	**2.40E-19**
SM(d18:1/20:1)	**1.91**	0.24	**1.93**	0.14	4.10E-01	**1.80**	0.20	**1.90**	0.20	2.30E-02	**1.84**	0.23	**1.74**	0.24	1.31E-02	**1.83**	0.22	**1.77**	0.24	1.65E-01
SM(d18:1/21:0)	**1.21**	0.16	**0.84**	0.17	**1.55E-15**	**1.28**	0.20	**0.72**	0.12	**2.78E-26**	**1.29**	0.21	**0.74**	0.14	**3.79E-25**	**1.27**	0.24	**0.87**	0.19	**7.34E-17**
SM(d18:1/22:0)	**8.29**	0.81	**5.73**	0.87	**1.76E-14**	**7.86**	0.83	**4.61**	0.64	**1.05E-25**	**8.02**	0.97	**5.09**	0.81	**4.90E-22**	**8.39**	1.37	**5.41**	0.74	**6.83E-19**
SM(d18:1/22:1)	**6.57**	0.34	**5.61**	0.51	**6.70E-09**	**6.33**	0.50	**5.06**	0.52	**1.93E-17**	**5.91**	0.43	**4.55**	0.52	**7.56E-21**	**6.48**	0.61	**5.45**	0.64	**3.77E-10**
SM(d18:1/23:0)	**3.05**	0.28	**2.23**	0.30	**2.45E-15**	**2.97**	0.31	**1.84**	0.28	**7.49E-27**	**3.02**	0.42	**1.86**	0.31	**1.25E-26**	**3.02**	0.31	**2.13**	0.71	**3.71E-14**
SM(d18:1/23:1)	**2.26**	0.28	**2.14**	0.29	1.42E-02	**2.29**	0.21	**2.08**	0.24	**8.50E-06**	**2.15**	0.25	**1.80**	0.23	**8.46E-13**	**2.22**	0.34	**2.17**	0.30	3.90E-01
SM(d18:1/24:0)	**4.57**	0.48	**2.99**	0.43	**2.02E-16**	**4.41**	0.50	**2.35**	0.32	**2.95E-28**	**4.49**	0.66	**2.60**	0.38	**8.71E-25**	**4.65**	0.71	**3.06**	0.41	**4.23E-17**
SM(d18:1/24:1)	**13.62**	0.92	**15.87**	1.02	**4.76E-10**	**13.64**	1.17	**15.89**	1.20	**3.15E-12**	**13.55**	1.12	**16.65**	1.20	**6.55E-17**	**13.34**	1.56	**15.94**	2.09	**9.18E-13**
SM(d18:1/24:2)	**6.70**	0.62	**8.40**	0.73	**4.92E-10**	**7.03**	0.93	**8.92**	0.98	**3.05E-14**	**6.40**	0.89	**8.05**	0.71	**2.40E-13**	**6.23**	0.85	**8.32**	1.01	**2.08E-15**
SM(d18:1/25:0)	**0.23**	0.03	**0.19**	0.03	**2.17E-04**	**0.22**	0.05	**0.16**	0.03	**3.73E-12**	**0.23**	0.05	**0.16**	0.04	**4.16E-11**	**0.21**	0.06	**0.17**	0.04	**8.26E-06**
CE(18:2)	**58.52**	7.13	**52.68**	8.39	7.99E-03	**57.36**	4.15	**50.38**	4.67	**9.35E-05**	**52.57**	5.09	**43.63**	5.60	**6.69E-08**	**54.61**	6.20	**44.33**	8.18	**1.38E-07**
CE(20:4)	**29.46**	7.36	**35.96**	6.00	1.00E-03	**30.55**	3.69	**37.80**	5.39	**1.22E-05**	**36.23**	3.80	**45.45**	4.93	**3.54E-06**	**34.31**	6.78	**44.92**	8.87	**1.83E-05**
CE(20:5)	**6.85**	2.48	**5.51**	3.14	2.68E-01	**6.50**	2.06	**4.97**	2.58	2.54E-02	**6.64**	2.64	**4.89**	1.94	1.04E-02	**6.70**	1.95	**4.27**	2.36	**9.69E-06**
CE(22:6)	**5.16**	1.61	**5.84**	1.82	3.24E-01	**5.59**	1.74	**6.85**	2.77	2.51E-02	**4.56**	2.12	**6.03**	1.61	**9.90E-05**	**4.38**	1.55	**6.47**	1.85	**3.03E-05**
TG(44:1)	**0.05**	0.03	**0.07**	0.18	**8.93E-05**	**0.10**	0.18	**0.01**	0.01	**8.02E-10**	**0.07**	0.06	**0.01**	0.00	**2.25E-12**	**0.10**	0.06	**0.01**	0.01	**6.25E-13**
TG(44:2)	**0.02**	0.01	**0.05**	0.13	7.26E-03	**0.04**	0.05	**0.01**	0.01	3.97E-04	**0.03**	0.02	**0.00**	0.00	**1.70E-11**	**0.04**	0.04	**0.00**	0.00	**1.33E-05**
TG(46:0)	**0.18**	0.14	**0.14**	0.25	6.02E-04	**0.29**	0.39	**0.06**	0.05	**1.67E-09**	**0.33**	0.20	**0.07**	0.03	**1.63E-11**	**0.31**	0.21	**0.05**	0.03	**2.69E-13**
TG(46:1)	**0.24**	0.14	**0.20**	0.35	**2.08E-05**	**0.48**	0.58	**0.09**	0.08	**9.27E-13**	**0.43**	0.24	**0.08**	0.03	**1.86E-14**	**0.47**	0.23	**0.07**	0.04	**7.99E-17**
TG(46:2)	**0.14**	0.06	**0.11**	0.18	**5.49E-05**	**0.19**	0.17	**0.06**	0.03	**6.86E-09**	**0.15**	0.08	**0.04**	0.01	**6.22E-14**	**0.22**	0.12	**0.04**	0.02	**5.26E-14**
TG(48:0)	**0.64**	0.42	**0.52**	0.58	7.30E-03	**0.72**	0.55	**0.35**	0.14	**2.48E-06**	**0.99**	0.54	**0.43**	0.16	**9.76E-10**	**0.99**	0.59	**0.38**	0.09	**8.00E-10**

Supplementary Table 2b. Continued.

Lipid	NGT_GB 0		NGT_GB 1		p-value	NGT_RYGB 0		NGT_RYGB 1		p-value	DM_RYGB 0		DM_RYGB 1		p-value	DM_VLCD 0		DM_VLCD 1		p-value
	mean	sd	mean	sd	*<0.000275*	mean	sd	mean	sd	*<0.000275*	mean	sd	mean	sd	*<0.000275*	mean	sd	mean	sd	*<0.000275*
TG(48:1)	**1.98**	1.01	**1.27**	1.13	**1.41E-05**	**2.23**	1.38	**0.94**	0.69	**3.70E-11**	**2.65**	0.93	**1.05**	0.33	**4.84E-12**	**2.95**	1.34	**0.79**	0.42	**2.84E-17**
TG(48:2)	**1.04**	0.39	**0.69**	0.49	**1.38E-05**	**1.41**	0.79	**0.54**	0.34	**6.00E-12**	**1.40**	0.47	**0.58**	0.18	**2.12E-11**	**1.43**	0.57	**0.41**	0.23	**6.85E-17**
TG(48:3)	**0.27**	0.08	**0.18**	0.13	**1.94E-06**	**0.34**	0.13	**0.14**	0.06	**5.96E-13**	**0.28**	0.09	**0.12**	0.03	**5.80E-13**	**0.34**	0.14	**0.10**	0.04	**1.11E-16**
TG(48:4)	**0.05**	0.02	**0.03**	0.03	1.00E-03	**0.06**	0.03	**0.02**	0.01	**4.57E-05**	**0.05**	0.03	**0.01**	0.01	**2.13E-09**	**0.06**	0.03	**0.01**	0.01	**9.80E-10**
TG(50:0)	**0.49**	0.33	**0.39**	0.56	4.41E-04	**0.57**	0.40	**0.22**	0.12	**3.22E-09**	**0.86**	0.56	**0.30**	0.12	**1.64E-10**	**0.81**	0.44	**0.25**	0.14	**1.68E-12**
TG(50:1)	**6.84**	2.05	**5.96**	1.89	1.26E-02	**6.88**	1.80	**5.68**	1.32	**1.55E-04**	**8.35**	1.62	**6.64**	1.32	**4.80E-06**	**8.30**	2.45	**6.10**	1.17	**1.27E-07**
TG(50:2)	**8.09**	1.54	**7.33**	1.21	4.42E-02	**8.38**	1.69	**7.30**	1.71	1.97E-03	**9.42**	1.14	**8.20**	1.13	2.95E-03	**9.06**	2.20	**6.65**	1.75	**1.18E-09**
TG(50:3)	**3.60**	0.56	**3.19**	0.54	1.20E-01	**3.24**	0.80	**3.04**	0.72	1.62E-01	**3.32**	0.64	**2.67**	0.55	**3.81E-05**	**3.59**	0.66	**2.39**	0.78	**3.70E-10**
TG(50:4)	**0.56**	0.11	**0.42**	0.10	**1.43E-05**	**0.58**	0.14	**0.37**	0.10	**2.14E-10**	**0.52**	0.11	**0.32**	0.08	**8.55E-12**	**0.57**	0.16	**0.28**	0.09	**4.12E-16**
TG(50:5)	**0.09**	0.02	**0.07**	0.03	**5.25E-05**	**0.10**	0.03	**0.06**	0.02	**3.46E-10**	**0.09**	0.03	**0.05**	0.01	**1.42E-13**	**0.11**	0.05	**0.05**	0.01	**3.43E-11**
TG(51:1)	**0.39**	0.14	**0.31**	0.09	1.74E-02	**0.37**	0.17	**0.28**	0.09	5.35E-04	**0.43**	0.14	**0.28**	0.05	**2.42E-07**	**0.47**	0.15	**0.29**	0.07	**6.58E-07**
TG(51:2)	**0.56**	0.14	**0.50**	0.06	6.93E-02	**0.61**	0.16	**0.48**	0.11	4.01E-04	**0.64**	0.13	**0.54**	0.09	3.81E-02	**0.54**	0.10	**0.43**	0.09	**2.42E-05**
TG(51:3)	**0.36**	0.05	**0.33**	0.04	7.23E-01	**0.30**	0.06	**0.33**	0.06	4.17E-01	**0.29**	0.05	**0.26**	0.04	3.60E-02	**0.30**	0.05	**0.26**	0.04	2.22E-02
TG(51:4)	**0.09**	0.01	**0.08**	0.01	6.62E-03	**0.10**	0.02	**0.08**	0.02	**2.53E-05**	**0.08**	0.02	**0.07**	0.01	**8.75E-05**	**0.08**	0.02	**0.06**	0.01	**5.83E-06**
TG(52:0)	**0.06**	0.04	**0.05**	0.08	1.08E-02	**0.08**	0.06	**0.03**	0.01	**9.54E-08**	**0.14**	0.17	**0.04**	0.01	**4.13E-09**	**0.12**	0.09	**0.04**	0.03	**2.26E-09**
TG(52:1)	**2.49**	0.95	**1.97**	1.22	9.20E-04	**2.73**	1.19	**1.64**	0.72	**4.77E-09**	**3.69**	1.64	**2.21**	0.54	**9.73E-08**	**3.50**	1.12	**1.92**	0.75	**9.28E-11**
TG(52:2)	**20.30**	2.50	**21.14**	2.79	2.25E-01	**20.33**	2.98	**21.53**	1.64	2.18E-02	**19.14**	2.02	**22.00**	2.42	**6.08E-06**	**19.10**	1.64	**22.76**	1.79	**1.78E-07**
TG(52:3)	**19.75**	2.50	**21.45**	3.12	8.52E-03	**17.89**	2.75	**22.27**	1.78	**1.95E-08**	**16.32**	2.46	**19.40**	1.23	**1.52E-06**	**16.93**	3.13	**21.19**	1.96	**2.80E-09**
TG(52:4)	**7.04**	1.45	**7.24**	1.38	4.52E-01	**6.58**	1.72	**7.30**	1.16	1.38E-02	**6.08**	1.49	**6.69**	1.39	1.73E-02	**5.80**	1.62	**6.15**	0.98	1.00E-01
TG(52:5)	**1.05**	0.19	**0.91**	0.17	1.08E-02	**1.14**	0.35	**0.86**	0.19	**1.34E-06**	**1.10**	0.35	**0.84**	0.22	**2.81E-06**	**0.98**	0.29	**0.69**	0.14	**8.24E-09**
TG(52:6)	**0.15**	0.03	**0.12**	0.04	**1.28E-04**	**0.17**	0.07	**0.11**	0.03	**7.70E-07**	**0.17**	0.08	**0.10**	0.04	**5.79E-10**	**0.16**	0.06	**0.10**	0.02	**1.43E-08**
TG(53:1)	**0.07**	0.02	**0.06**	0.02	1.32E-02	**0.07**	0.03	**0.05**	0.02	**1.35E-04**	**0.07**	0.03	**0.04**	0.01	**8.09E-09**	**0.09**	0.04	**0.06**	0.02	**7.42E-05**
TG(54:1)	**0.12**	0.04	**0.09**	0.07	5.23E-04	**0.17**	0.10	**0.08**	0.05	**5.48E-09**	**0.26**	0.29	**0.10**	0.03	**8.89E-07**	**0.22**	0.13	**0.10**	0.05	**2.43E-07**
TG(54:2)	**2.50**	0.40	**2.34**	0.34	1.49E-01	**2.70**	0.78	**2.19**	0.68	**9.02E-06**	**2.75**	0.65	**2.59**	0.25	2.78E-01	**2.98**	0.79	**2.60**	0.78	4.30E-03
TG(54:3)	**6.04**	1.55	**6.64**	1.17	9.12E-02	**6.78**	1.79	**6.62**	1.17	8.79E-01	**5.84**	0.65	**7.49**	0.80	**6.19E-07**	**5.66**	1.19	**7.31**	1.76	**4.19E-06**
TG(54:4)	**5.21**	1.30	**5.81**	1.07	4.12E-02	**5.33**	1.27	**6.03**	1.05	4.22E-03	**4.55**	0.95	**5.77**	0.70	**1.94E-06**	**4.60**	1.29	**5.87**	0.96	**2.49E-06**
TG(54:5)	**3.20**	0.62	**3.38**	0.51	1.49E-01	**2.95**	0.67	**3.67**	0.59	**5.66E-05**	**2.93**	0.73	**3.27**	0.56	2.44E-02	**3.08**	0.68	**3.83**	0.77	**3.11E-05**
TG(54:6)	**1.21**	0.24	**1.22**	0.38	9.19E-01	**1.20**	0.31	**1.26**	0.31	4.12E-01	**1.33**	0.48	**1.28**	0.30	9.27E-01	**1.20**	0.27	**1.36**	0.37	1.29E-01
TG(54:7)	**0.30**	0.08	**0.29**	0.14	8.34E-02	**0.30**	0.10	**0.27**	0.10	4.34E-02	**0.33**	0.15	**0.28**	0.10	1.57E-01	**0.27**	0.06	**0.24**	0.07	6.55E-02
TG(55:1)	**0.04**	0.03	**0.03**	0.03	4.67E-02	**0.05**	0.02	**0.03**	0.02	6.19E-03	**0.06**	0.02	**0.05**	0.01	1.94E-01	**0.07**	0.03	**0.04**	0.02	3.82E-03
TG(55:2)	**0.39**	0.08	**0.40**	0.08	9.92E-01	**0.41**	0.13	**0.41**	0.08	6.75E-01	**0.33**	0.07	**0.39**	0.07	1.18E-03	**0.33**	0.08	**0.44**	0.07	**3.31E-07**

Lipid	NGT_GB 0		NGT_GB 1		p-value	NGT_RYGB 0		NGT_RYGB 1		p-value	DM_RYGB 0		DM_RYGB 1		p-value	DM_VLCD 0		DM_VLCD 1		p-value
	mean	sd	mean	sd	*<0.000275*	mean	sd	mean	sd	*<0.000275*	mean	sd	mean	sd	*<0.000275*	mean	sd	mean	sd	*<0.000275*
TG(55:3)	**0.48**	0.10	**0.50**	0.10	3.77E-01	**0.46**	0.14	**0.53**	0.10	3.00E-03	**0.36**	0.09	**0.43**	0.07	1.81E-03	**0.39**	0.11	**0.55**	0.10	**1.07E-08**
TG(56:3)	**0.19**	0.04	**0.20**	0.03	7.80E-01	**0.23**	0.08	**0.17**	0.04	3.25E-04	**0.19**	0.03	**0.18**	0.02	1.86E-01	**0.20**	0.05	**0.21**	0.07	8.67E-01
TG(56:5)	**0.84**	0.21	**1.04**	0.29	2.75E-03	**0.83**	0.25	**1.17**	0.35	**3.03E-07**	**0.94**	0.21	**1.26**	0.24	**7.76E-06**	**0.92**	0.22	**1.46**	0.38	**3.55E-09**
TG(56:6)	**1.23**	0.22	**1.37**	0.42	1.13E-01	**1.13**	0.34	**1.65**	0.46	**2.12E-08**	**1.32**	0.30	**1.70**	0.33	**1.18E-05**	**1.25**	0.26	**2.08**	0.64	**9.66E-11**
TG(56:7)	**1.18**	0.31	**1.42**	0.72	9.94E-02	**1.04**	0.27	**1.55**	0.57	**1.30E-05**	**1.21**	0.39	**1.55**	0.36	**1.18E-04**	**1.06**	0.27	**1.78**	0.52	**5.68E-08**
TG(56:8)	**0.35**	0.10	**0.43**	0.29	5.05E-01	**0.37**	0.14	**0.45**	0.22	8.30E-02	**0.40**	0.18	**0.52**	0.15	**1.54E-04**	**0.29**	0.11	**0.48**	0.15	**3.03E-05**
TG(57:2)	**0.03**	0.01	**0.04**	0.01	2.44E-01	**0.04**	0.01	**0.04**	0.01	1.06E-01	**0.04**	0.01	**0.05**	0.01	4.72E-04	**0.04**	0.01	**0.05**	0.02	4.39E-02
TG(58:10)	**0.04**	0.02	**0.05**	0.04	2.82E-01	**0.05**	0.04	**0.05**	0.03	8.53E-01	**0.06**	0.04	**0.06**	0.03	8.39E-02	**0.04**	0.02	**0.06**	0.03	2.99E-02

Relative abundance of lipid species to summed lipid levels at baseline and after different interventions per group (NGT_GB, NGT_RYGB, DM_RYGB, DM_VLCD).Values are presented as mean ± sd. (Means are bold larger font, sds are smaller font.) Differences between subject groups (NGT vs T2DM) and lean controls at baseline were compared with a mixed-effects model, with the patient groups and diabetes as fixed effects and the subject specific deviances modelled with random intercepts. The Bonferroni posthoc test was used to correct for multiple testing. A p-value <0.000275 was considered statistically significant (= (0,05 divided by 26, the effective number of independent lipid species, and by 7, the number of hypotheses tested). Significant p-values are bold.