# Genome-wide analysis of blood lipid metabolites in over 5000 South Asians reveals biological insights at cardiometabolic disease loci

#### SUPPLEMENTARY MATERIAL

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#### SUPPLEMENTARY FIGURES

**Supplementary Figure 1.** Extended heat map showing associations of significant loci from conditional analyses in PROMIS with all lipid metabolites, major lipids, and lipid-related diseases/disorders



#### Caption for Supplementary Figure 1 (previous page):

The effect estimates of the associations between significant variants with all lipid metabolites in PROMIS are plotted as a heat map. Results are shown for the association of all lipid metabolites (rows) with the most strongly associated genetic variant within each locus (columns). The associations with major lipids from the GLGC (total cholesterol, HDL-C, LDL-C, and triglycerides), DIAGRAM Consortium (type 2 diabetes), and CARDIoGRAMplusC4D Consortium (coronary artery disease) are also shown. The magnitude and direction of the effect estimates (standardised per 1-SD) are indicated by a colour scale, with blue indicating a negative association and red indicating a positive association with respect to the SNP effect on the trait. Asterisks indicates the degree of significance of the *P*-values of association.  $* = P < 1 \times 10^{-4}$ ;  $** = P < 5 \times 10^{-8}$ ;  $*** = P < 8.9 \times 10^{-10}$ . **Note:** A high-resolution version of this figure is available as Additional file 3.



Supplementary Figure 2. Genetic architecture of serum lipid levels in PROMIS

n = 5,662 participants from PROMIS. (a) Number of significantly associated loci per lipid. (b) Number of conditionally significant associations within each lipid QTL. (c) Histogram of variance explained by conditionally independent variants. (d) Effect size versus MAF.



Supplementary Figure 3. Comparison of associations in PROMIS and INTERVAL

(a) Beta estimates in INTERVAL vs PROMIS. (b) -log<sub>10</sub> *P*-values in INTERVAL vs PROMIS.



Supplementary Figure 4. Number of lipids in PROMIS associated with each variant

Results are shown for the number of lipids in PROMIS associated with each variant at genome-wide significance ( $P < 8.9 \times 10^{-10}$ ).

**Supplementary Figure 5.** Increased *de novo* lipogenesis in lipodystrophy and NAFLD patients



Increased *de novo* lipogenesis in lipodystrophy patients (left panel based on Eiden et al 2015) [49] and NAFLD patients (right panel based on Sanders et al 2018) [50] both show an increase in TAG(48:1) and TG(50:1) originating from the liver, leading to lower levels of TG(52:4) and other triglycerides associated with *APOA5-C3* variants.

Supplementary Figure 6. Flow diagram outlining strategy for mediating gene prioritisation



The flow diagram shows how the "bottom-up" and "top-down" approaches were used and then integrated to identify probable causal genes for each significantly associated variant. A proxy is defined as those variants with  $r^2 \ge 0.8$  with the lead (EUR population, 1000 Genomes). **Abbreviations: eQTL** = Expression Quantitative Trait Locus; **GO** = Gene Ontology; **GTEx** = Genotype-Tissue Expression; **KEGG** = Kyoto Encyclopedia of Genes and Genomes; **Lipid MAPS** = Lipid Metabolites and Pathways Strategy; **MGI** = Mouse Genome Informatics; **OMIM** = Online Inheritance in Man. Adapted from Stacey et al [14].

# **Supplementary Figure 7.** Association of lipids in PROMIS with significantly associated loci from conditional analyses

#### (a) ANGPTL3

| Lipid                                 | Lipid           |                      |                 |
|---------------------------------------|-----------------|----------------------|-----------------|
| name                                  | m/z             | Beta (95% CI)        | <i>P</i> -value |
|                                       | 1               |                      |                 |
| CE(16:1)_[M+NH4]1+                    | 640.6024        | 0.03 (0.01, 0.05)    | 1.09e-03        |
| SM(42:2)_[M+OAc]1-                    | 871.6911        | 0.02 (0.01, 0.04)    | 5.15e-04*       |
| CE(18:3)_[M+NH4]1+                    | 664.6026        | 0.02 (0.01, 0.03)    | 1.04e-03        |
| SM(36:1)_[M+H]1+                      | 731.6062        | 0.02 (0.01, 0.03)    | 1.13e-04*       |
| SM(36:1)_[M-CH3]1-                    | 715.5761        | 0.02 (0.01, 0.03)    | 2.02e-03        |
| SM(36:0)_[M+H]1+                      | 733.6219        | 0.02 (0.01, 0.03)    | 4.65e-04*       |
| SM(38:1)_[M+H]1+                      | 759.6372        | 0.02 (0.01, 0.03)    | 3.42e-04*       |
| CE(18:0)_[M+NH4]1+                    | 670.6496        | 0.02 (0.01, 0.03)    | 1.14e-03        |
| CE(18:1)_[M+NH4]1+                    | 668.6339        | 0.02 (0.01, 0.02)    | 5.71e-04*       |
| PI(36:4)_[M-H]1-                      | 857.5186        | -0.03 (-0.04, -0.01) | 2.75e-04*       |
| PI(38:4)_[M-H]1-                      | 885.5498        | -0.03 (-0.04, -0.02) | 1.21e-06*       |
| PI(40:6)_[M-H]1-                      | 909.5498        | -0.03 (-0.04, -0.01) | 5.39e-04*       |
| PI(40:5)_[M-H]1-                      | 911.5655        | -0.03 (-0.04, -0.01) | 8.40e-05*       |
| PI(34:1)_[M-H]1-                      | 835.5341        | -0.03 (-0.05, -0.02) | 7.31e-05*       |
| PI(38:5)_[M-H]1-                      | 883.5343        | -0.03 (-0.05, -0.02) | 6.14e-06*       |
| PI(34:2)_[M-H]1-                      | 833.5186        | -0.04 (-0.05, -0.02) | 9.38e-08*       |
| PA(44:6)_[M+OAc]1- / PG(43:6)_[M-H]1- | 863.5806        | -0.04 (-0.06, -0.03) | 1.88e-07*       |
| PI(36:2)_[M-H]1-                      | 861.5498        | -0.04 (-0.06, -0.03) | 1.63e-13***     |
| PI(34:0)_[M-H]1-                      | 837.5498        | -0.05 (-0.07, -0.02) | 4.58e-05*       |
| PI(35:2)_[M-H]1-                      | 847.5343        | -0.05 (-0.07, -0.03) | 5.58e-06*       |
|                                       |                 |                      |                 |
|                                       |                 | 1                    |                 |
|                                       | 4321 0 .1 .2 .3 | 4                    |                 |

Beta (95% CI) for ANGPTL3 (rs6657050, chr1:63105253)

#### (b) APOA5-APOC3

| Lipid                   | Lipid    |                                       |                      |             |
|-------------------------|----------|---------------------------------------|----------------------|-------------|
| name                    | m/z      |                                       | Beta (95% CI)        | P-value     |
|                         |          |                                       |                      |             |
| CE(18:3)_[M+NH4]1+      | 664.6026 | -                                     | 0.08 (0.07, 0.10)    | 4.28e-23*** |
| SM(41:2)_[M+H]1+        | 799.6685 |                                       | 0.07 (0.06, 0.09)    | 2.57e-21*** |
| SM(42:3)_[M+H]1+        | 811.6688 |                                       | 0.07 (0.06, 0.09)    | 6.88e-21*** |
| SM(36:1)_[M+H]1+        | 731.6062 |                                       | 0.07 (0.05, 0.08)    | 3.92e-26*** |
| SM(34:0)_[M+H]1+        | 705.5906 |                                       | 0.07 (0.05, 0.08)    | 1.08e-26*** |
| SM(36:0)_[M+H]1+        | 733.6219 |                                       | 0.07 (0.05, 0.08)    | 1.43e-22*** |
| SM(34:1)_[M+H]1+        | 703.5747 |                                       | 0.07 (0.05, 0.08)    | 2.85e-27*** |
| SM(38:1)_[M+H]1+        | 759.6372 |                                       | 0.07 (0.05, 0.08)    | 1.56e-24*** |
| CE(18:0)_[M+NH4]1+      | 670.6496 |                                       | 0.06 (0.05, 0.08)    | 1.53e-24*** |
| CE(18:1)_[M+NH4]1+      | 668.6339 |                                       | 0.06 (0.05, 0.07)    | 9.12e-24*** |
| Cholesterol_[M+H-H2O]1+ | 369.3514 |                                       | 0.06 (0.05, 0.07)    | 6.74e-25*** |
| DG(34:2)_[M+H-H2O]1+    | 575.5039 |                                       | -0.08 (-0.10, -0.07) | 1.07e-20*** |
| DG(36:2)_[M+H-H2O]1+    | 603.5352 |                                       | -0.09 (-0.10, -0.07) | 2.06e-24*** |
| TG(52:2)_[M+NH4]1+      | 876.8016 |                                       | -0.09 (-0.11, -0.07) | 5.29e-19*** |
| TG(52:1)_[M+NH4]1+      | 878.8172 |                                       | -0.09 (-0.11, -0.07) | 2.68e-21*** |
| TG(53:3)_[M+NH4]1+      | 888.8016 |                                       | -0.09 (-0.11, -0.07) | 6.95e-20*** |
| TG(52:3)_[M+NH4]1+      | 874.7859 |                                       | -0.09 (-0.11, -0.07) | 4.17e-25*** |
| DG(36:3)_[M+H-H2O]1+    | 601.5195 |                                       | -0.10 (-0.11, -0.08) | 1.20e-22*** |
| TG(54:3)_[M+NH4]1+      | 902.8175 |                                       | -0.10 (-0.12, -0.08) | 3.18e-23*** |
| TG(54:4)_[M+NH4]1+      | 900.8015 |                                       | -0.10 (-0.12, -0.08) | 4.74e-22*** |
|                         |          |                                       |                      |             |
|                         |          | + $+$ $+$ $+$ $+$ $+$ $+$ $+$ $+$ $+$ | 1                    |             |
|                         | 4321     | 0 .1 .2 .3                            | .4                   |             |



#### (c) APOE-APOC1-APOC2-APOC4

| Lipid              | Lipid    |   |                      |             |
|--------------------|----------|---|----------------------|-------------|
| name               | m/z      |   | Beta (95% CI)        | P-value     |
|                    |          | I |                      |             |
| PE(36:4)_[M-H]1-   | 738.5079 | = | 0.04 (0.02, 0.07)    | 5.28e-05*   |
| SM(32:1)_[M-CH3]1- | 659.5135 |   | -0.03 (-0.05, -0.02) | 5.28e-05*   |
| SM(36:1)_[M-CH3]1- | 715.5761 |   | -0.04 (-0.05, -0.02) | 5.21e-05*   |
| SM(38:1)_[M+CH3]1- | 743.6075 |   | -0.05 (-0.06, -0.03) | 3.14e-07*   |
| SM(36:0)_[M-CH3]1- | 717.5918 | - | -0.05 (-0.07, -0.03) | 2.46e-06*   |
| SM(34:1)_[M-CH3]1- | 687.5448 |   | -0.05 (-0.06, -0.03) | 4.64e-08**  |
| SM(40:2)_[M-CH3]1- | 769.6231 |   | -0.05 (-0.06, -0.03) | 1.05e-07*   |
| PC(36:0)_[M+OAc]1- | 848.6385 | = | -0.05 (-0.07, -0.03) | 1.28e-05*   |
| SM(40:0)_[M+OAc]1- | 847.6911 | • | -0.05 (-0.07, -0.03) | 1.74e-07*   |
| SM(34:0)_[M-CH3]1- | 689.5604 |   | -0.05 (-0.07, -0.03) | 4.68e-08**  |
| SM(40:1)_[M-CH3]1- | 771.6386 |   | -0.05 (-0.07, -0.03) | 2.47e-08**  |
| SM(41:2)_[M-CH3]1- | 783.6387 | - | -0.05 (-0.07, -0.03) | 8.38e-08*   |
| SM(40:3)_[M+OAc]1- | 841.6442 | = | -0.05 (-0.08, -0.03) | 9.04e-06*   |
| SM(42:2)_[M+OAc]1- | 871.6911 | - | -0.05 (-0.07, -0.03) | 4.94e-07*   |
| SM(41:0)_[M+OAc]1- | 861.7068 | - | -0.05 (-0.08, -0.03) | 8.88e-06*   |
| SM(41:1)_[M-CH3]1- | 785.6543 | - | -0.06 (-0.08, -0.03) | 2.08e-06*   |
| SM(42:1)_[M+OAc]1- | 873.7067 | - | -0.06 (-0.08, -0.04) | 5.20e-09**  |
| SM(42:0)_[M+OAc]1- | 875.7224 | • | -0.06 (-0.08, -0.04) | 8.24e-10*** |
| SM(40:0)_[M-CH3]1- | 773.6543 | = | -0.06 (-0.08, -0.04) | 6.39e-09**  |
| SM(42:1)_[M-CH3]1- | 799.67   | - | -0.06 (-0.08, -0.04) | 1.20e-09**  |
|                    |          |   |                      |             |
|                    |          |   | [                    |             |

-.4 -.3 -.2 -.1 0 .1 .2 .3 .4

Beta (95% CI) for APOE-APOC1-APOC2-APOC4 (rs75627662, chr19:45413576)

# (d) *C19orf80*

| Lipid  | Lipid                                |                      |             |
|--|--------------------------------------|----------------------|-------------|
| name   | m/z                                  | Beta (95% CI)        | P-value     |
| SM(42:2)_[M+OAc]1-   | 871.6911                             | 0.04 (0.02, 0.06)    | 1.41e-05*   |
| PC-O(34:1)_[M+H]1+ / PC-P(34:0)_[M+H]1+ / PE-O(37:1)_[M+H]1+ | 746.6061                             | 0.03 (0.01, 0.05)    | 2.24e-04*   |
| SM(34:0)_[M+H]1+   | 705.5906                             | 0.02 (0.01, 0.04)    | 4.02e-04*   |
| SM(34:1)_[M+H]1+   | 703.5747                             | 0.02 (0.01, 0.04)    | 3.86e-04*   |
| PA(44:6)_[M+OAc]1- / PG(43:6)_[M-H]1-                        | 863.5806                             | -0.04 (-0.06, -0.02) | 5.51e-04*   |
| PI(36:3)_[M-H]1-   | 859.5343                             | -0.04 (-0.06, -0.02) | 1.00e-04*   |
| PI(34:2)_[M-H]1-   | 833.5186                             | -0.04 (-0.06, -0.02) | 3.76e-05*   |
| TG(53:3)_[M+NH4]1+   | 888.8016                             | -0.04 (-0.06, -0.02) | 1.48e-04*   |
| PI(36:2)_[M-H]1-   | 861.5498                             | -0.04 (-0.06, -0.03) | 5.26e-07*   |
| TG(50:4)_[M+NH4]1+   | 844.739                              | -0.04 (-0.07, -0.02) | 7.67e-04*   |
| PI(36:4)_[M-H]1-   | 857.5186                             | -0.05 (-0.07, -0.03) | 1.70e-06*   |
| PI(38:4)_[M-H]1-   | 885.5498                             | -0.05 (-0.06, -0.03) | 3.56e-10*** |
| PI(38:5)_[M-H]1-   | 883.5343                             | -0.05 (-0.07, -0.03) | 4.23e-06*   |
| TG(51:3)_[M+NH4]1+   | 860.7703 🖶                           | -0.05 (-0.07, -0.03) | 2.52e-05*   |
| PI(40:7)_[M+OAc]1-   | 967.5553 -                           | -0.05 (-0.08, -0.02) | 9.18e-04*   |
| PI(40:5)_[M-H]1-   | 911.5655 🖶                           | -0.05 (-0.07, -0.03) | 3.47e-07*   |
| TG(53:4)_[M+NH4]1+   | 886.7859 🖶                           | -0.06 (-0.08, -0.03) | 3.55e-06*   |
| TG(49:3)_[M+NH4]1+   | 832.739                              | -0.08 (-0.12, -0.03) | 7.21e-04*   |
| PI(35:2)_[M-H]1-   | 847.5343                             | -0.08 (-0.11, -0.05) | 5.88e-07*   |
| TG(51:4)_[M+NH4]1+   | 858.7544                             | -0.08 (-0.12, -0.05) | 6.56e-06*   |
|  |                                      |                      |             |
|  | 4321 0 .1 .2 .3                      | .4                   |             |
| Beta (95% CI) for  | C19orf80 (rs8101801, cbr19:11335477) |                      |             |

# (e) *CERS4*

| Lipid                                   | Lipid    |            |                   |                 |
|---|----------|------------|-------------------|-----------------|
| name                                    | m/z      |            | Beta (95% CI)     | <i>P</i> -value |
| TG(59:12)_[M+NH4]1+                     | 954.754  | _ <b>_</b> | 0.18 (0.04, 0.32) | 1.29e-02        |
| TG(57:9)_[M+NH4]1+                      | 932.7697 | <b></b>    | 0.08 (0.01, 0.15) | 2.67e-02        |
| SM(42:8)_[M+OAc]1-                      | 859.5972 | -          | 0.05 (0.02, 0.08) | 1.52e-03        |
| SM(38:1)_[M+H]1+                        | 759.6372 |            | 0.04 (0.03, 0.05) | 1.65e-12***     |
| SM(38:1)_[M+CH3]1-                      | 743.6075 |            | 0.04 (0.02, 0.05) | 6.76e-09**      |
| SM(38:0)_[M+H]1+                        | 761.6532 |            | 0.04 (0.02, 0.05) | 2.43e-07*       |
| SM(37:1)_[M+H]1+                        | 745.6216 |            | 0.03 (0.02, 0.05) | 1.41e-07*       |
| SM(37:1)_[M-CH3]1-                      | 729.5917 |            | 0.03 (0.02, 0.05) | 1.16e-05*       |
| SM(36:2)_[M-CH3]1-                      | 713.5605 |            | 0.03 (0.02, 0.05) | 5.28e-07*       |
| PS(41:5)_[M+OAc]1-                      | 910.5816 | -          | 0.03 (0.01, 0.06) | 1.48e-02        |
| SM(36:2)_[M+H]1+                        | 729.5906 |            | 0.03 (0.02, 0.04) | 2.41e-08**      |
| SM(36:0)_[M-CH3]1-                      | 717.5918 |            | 0.03 (0.02, 0.04) | 6.89e-06*       |
| SM(36:1)_[M-CH3]1-                      | 715.5761 |            | 0.03 (0.02, 0.04) | 8.75e-07*       |
| SM(36:1)_[M+H]1+                        | 731.6062 | i 🖬        | 0.03 (0.02, 0.04) | 4.88e-08**      |
| PC-O(33:2)_[M+H]1+ / PC-P(33:1)_[M+H]1+ | 730.5747 |            | 0.03 (0.01, 0.04) | 4.11e-04*       |
| SM(36:0)_[M+H]1+                        | 733.6219 | <b>•</b>   | 0.02 (0.01, 0.03) | 7.01e-06*       |
| SM(36:3)_[M+OAc]1-                      | 785.5816 | •          | 0.02 (0.00, 0.04) | 4.87e-02        |
| SM(39:1)_[M-CH3]1-                      | 757.623  | <b>•</b>   | 0.02 (0.00, 0.03) | 3.78e-02        |
| PC(40:4)_[M+OAc]1-                      | 900.6698 | <b>•</b>   | 0.02 (0.00, 0.03) | 3.70e-02        |
| SM(39:1)_[M+H]1+                        | 773.6531 | <b>H</b>   | 0.01 (0.00, 0.03) | 3.39e-02        |

-.4 -.3 -.2 -.1 0 .1 .2 .3 .4

Beta (95% CI) for CERS4 (rs11666866, chr19:8285607)



#### (f) CETP

| Lipid  | Lipid    |   |                      |             |
|--|----------|---|----------------------|-------------|
| name   | m/z      |   | Beta (95% CI)        | P-value     |
|  |          | 1 |                      |             |
| CE(20:5)_[M+NH4]1+                                       | 688.6026 | = | 0.04 (0.02, 0.06)    | 1.47e-04*   |
| PC(36:5)_[M+OAc]1- / PS(40:4)_[M-H]1-                    | 838.5602 | = | 0.03 (0.01, 0.05)    | 1.02e-03    |
| PE(38:5)_[M-H]1-   | 764.5236 |   | 0.02 (0.01, 0.04)    | 1.40e-03    |
| PC(40:5)_[M+OAc]1- / PS(44:4)_[M-H]1-                    | 894.6229 |   | 0.02 (0.01, 0.03)    | 7.57e-04*   |
| PA(43:4)_[M-H]1-   | 793.5752 |   | 0.02 (0.01, 0.03)    | 2.44e-03    |
| PC(38:5)_[M+H]1+ / PE(41:5)_[M+H]1+ / PA(43:6)_[M+NH4]1+ | 808.5851 |   | 0.02 (0.01, 0.02)    | 2.62e-04*   |
| PG(36:0)_[M-H]1-   | 777.5649 |   | 0.02 (0.01, 0.02)    | 2.51e-03    |
| PG(34:1)_[M-H]1-   | 747.518  |   | -0.02 (-0.03, -0.01) | 2.66e-03    |
| PG(36:2)_[M-H]1-   | 773.5337 |   | -0.02 (-0.04, -0.01) | 3.97e-04*   |
| PC-O(40:7)_[M+H]1+ / PC-P(40:6)_[M+H]1+                  | 818.6057 |   | -0.02 (-0.04, -0.01) | 5.81e-04*   |
| PI(38:1)_[M-H]1-   | 891.5967 |   | -0.02 (-0.04, -0.01) | 1.69e-03    |
| PC(40:7)_[M+OAc]1- / PS(44:6)_[M-H]1-                    | 890.5916 |   | -0.02 (-0.04, -0.01) | 4.99e-04*   |
| PC(37:6)_[M+H]1+ / PE(40:6)_[M+H]1+ / PA(42:7)_[M+NH4]1+ | 792.5537 |   | -0.03 (-0.04, -0.01) | 2.21e-04*   |
| PC(39:6)_[M+OAc]1- / PS(43:5)_[M-H]1-                    | 878.5916 |   | -0.03 (-0.04, -0.01) | 5.31e-04*   |
| PC(38:6)_[M+H]1+ / PE(41:6)_[M+H]1+                      | 806.5694 |   | -0.03 (-0.04, -0.02) | 2.86e-09**  |
| PI(38:6)_[M-H]1-   | 881.5186 |   | -0.03 (-0.05, -0.02) | 1.12e-04*   |
| PC(40:6)_[M+OAc]1- / PS(44:5)_[M-H]1-                    | 892.6072 |   | -0.03 (-0.05, -0.02) | 1.05e-05*   |
| PC(40:6)_[M+H]1+ / PE(43:6)_[M+H]1+                      | 834.6006 |   | -0.03 (-0.05, -0.02) | 8.50e-08*   |
| FA(22:6)_[M-H]1-   | 327.233  |   | -0.04 (-0.06, -0.03) | 1.68e-08**  |
| PI(40:6)_[M-H]1-   | 909.5498 |   | -0.05 (-0.06, -0.03) | 1.43e-10*** |

-.4 -.3 -.2 -.1 0 .1 .2 .3 .4 Beta (95% CI) for *ELOVL2* (rs6920155, chr6:11047956)

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17

# (g) *ELOVL2*

#### (h) FADS1-FADS2-FADS3

Lipid

| P(36:3)_[M-H]1-    859.534      PC(36:3)_[M+OAc]1- / PS(40:2)_[M-H]1-    842.591      PC(36:3)_[M+H]1+ / PE(39:3)_[M+H]1+ / PA(41:4)_[M+NH4]1+    784.585      PC(38:5)_[M+H]1+ / PE(41:5)_[M+H]1+ / PA(43:6)_[M+NH4]1+    808.585      PC(38:5)_[M+H]1+ / PE(41:5)_[M+H]1+ / PA(43:6)_[M+NH4]1+    793.575      PC-O(38:5)_[M+H]1+ / PC-P(38:4)_[M+H]1+    794.605      PC(35:4)_[M+H]1+ / PE(38:4)_[M+H]1+ / PA(40:5)_[M+NH4]1+    768.554      PC(36:4)_[M+H]1+ / PE(38:4)_[M+H]1+ / PA(40:5)_[M+NH4]1+    768.564      PC(36:4)_[M+H]1+ / PE(39:4)_[M+H]1+ / PA(41:5)_[M+NH4]1+    782.569      PC-O(36:5)_[M+H]1+ / PC-P(36:4)_[M+H]1+    766.574      P(36:1)_[M+OAc]1-    923.566      _PC(20:4)_[M+H]1+    544.340      PC(20:4)_[M+H]1+    544.340      PC(20:4)_[M+H]1+    868.607      PC(36:4)_[M+OAc]1-    868.607      PC(36:4)_[M+OAc]1- / PS(42:3)_[M-H]1-    868.607  | 43<br>16<br>55<br>51<br>52<br>58<br>43<br>3<br>63<br>99<br>45<br>65<br>04 |   |   |   | • | 0.12 (0.10, 0.13)<br>0.08 (0.07, 0.09)<br>0.07 (0.06, 0.08)<br>-0.08 (-0.09, -0.07)<br>-0.09 (-0.11, -0.08)<br>-0.09 (-0.10, -0.08)<br>-0.10 (-0.11, -0.09)<br>-0.11 (-0.12, -0.09)<br>-0.11 (-0.12, -0.09)<br>-0.13 (-0.14, -0.12)<br>-0.13 (-0.14, -0.11) | 3.57e-36***<br>3.15e-35***<br>9.96e-62***<br>4.12e-48***<br>4.33e-33***<br>2.61e-43***<br>6.43e-45***<br>8.10e-41***<br>2.15e-47***<br>4.8e-130***<br>4.38e-77*** |
|--|---|---|---|---|---|---|---|
| PI(36:3)_[M-H]1-      859.534        PC(36:3)_[M+OAc]1- / PS(40:2)_[M-H]1-      842.591        PC(36:3)_[M+H]1+ / PE(39:3)_[M+H]1+ / PA(41:4)_[M+NH4]1+      784.585        PC(38:5)_[M+H]1+ / PE(41:5)_[M+H]1+ / PA(43:6)_[M+NH4]1+      808.585        PA(43:4)_[M-H]1-      793.575        PC-O(38:5)_[M+H]1+ / PC-P(38:4)_[M+H]1+      794.605        PC-O(38:5)_[M+H]1+ / PC-P(38:4)_[M+H]1+      768.554        PC(35:4)_[M+H]1+ / PE(38:4)_[M+H]1+ / PA(40:5)_[M+NH4]1+      768.554        PC(20:5,_[M+H]1+      836.616        PCC(36:4)_[M+H]1+ / PC-P(36:4)_[M+H]1+ / PA(41:5)_[M+NH4]1+      762.569        PCC-O(36:5)_[M+H]1+ / PC-P(36:4)_[M+H]1+      766.574        PC(36:4)_[M+H]1+ / PC-P(36:4)_[M+H]1+      766.574        PC(36:1)_[M+OAc]1-      923.586        PC(20:4)_[M+H]1+      544.340        PC(20:4)_[M+H]1+      868.607        PC(38:4)_[M+OAc]1- / PS(42:3)_[M-H]1-      868.607        PC(44:6)_[M+OAc]1- / PS(42:3)_[M-H]1-      950.612   | 43<br>16<br>55<br>51<br>52<br>58<br>43<br>3<br>63<br>99<br>45<br>65<br>04 |   |   |   | • | 0.12 (0.10, 0.13)<br>0.08 (0.07, 0.09)<br>0.07 (0.06, 0.08)<br>-0.08 (-0.09, -0.07)<br>-0.09 (-0.11, -0.08)<br>-0.09 (-0.10, -0.08)<br>-0.10 (-0.11, -0.09)<br>-0.11 (-0.12, -0.09)<br>-0.11 (-0.12, -0.09)<br>-0.13 (-0.14, -0.12)<br>-0.13 (-0.14, -0.11) | 3.57e-36***<br>3.15e-35***<br>9.96e-62***<br>4.12e-48***<br>4.33e-33***<br>2.61e-43***<br>6.43e-45***<br>8.10e-41***<br>2.15e-47***<br>4.8e-130***<br>4.38e-77*** |
| PC(36:3)_[M+OAc]1- / PS(40:2)_[M-H]1-      842.591        PC(36:3)_[M+H]1+ / PE(39:3)_[M+H]1+ / PA(41:4)_[M+NH4]1+      784.585        PC(38:5)_[M+H]1+ / PE(41:5)_[M+H]1+ / PA(43:6)_[M+NH4]1+      808.585        PC(38:5)_[M+H]1+ / PE(41:5)_[M+H]1+ / PA(43:6)_[M+NH4]1+      808.585        PC-0(38:5)_[M+H]1+ / PC-P(38:4)_[M+H]1+      793.575        PC-0(38:5)_[M+H]1+ / PC-P(38:4)_[M+H]1+      794.605        PC-0(38:5)_[M+H]1+ / PC-P(38:4)_[M+H]1+ / PA(40:5)_[M+NH4]1+      768.554        FA(20:4)_[M-H]1-      303.233        PC(40:5)_[M+H]1+ / PE(39:4)_[M+H]1+ / PA(41:5)_[M+NH4]1+      762.569        PC-0(36:5)_[M+H]1+ / PC-P(36:4)_[M+H]1+ / PA(41:5)_[M+NH4]1+      766.574        PC(36:4)_[M+H]1+ / PC-P(36:4)_[M+H]1+      766.574        PC(36:1)_[M+OAc]1-      923.586       PC(20:4)_[M+H]1+      544.340        PC(38:4)_[M+OAc]1- / PS(42:3)_[M-H]1-      868.607        PC(38:4)_[M+OAc]1- / PS(42:3)_[M-H]1-      868.607        PC(44:6)_[M+OAc]1- / PS(42:3)_[M-H]1-      868.607 | 16<br>55<br>51<br>52<br>58<br>43<br>3<br>63<br>99<br>45<br>65<br>65       |   |   | • |   | 0.08 (0.07, 0.09)<br>0.07 (0.06, 0.08)<br>-0.08 (-0.09, -0.07)<br>-0.09 (-0.11, -0.08)<br>-0.09 (-0.10, -0.08)<br>-0.10 (-0.11, -0.09)<br>-0.11 (-0.12, -0.09)<br>-0.11 (-0.12, -0.09)<br>-0.13 (-0.14, -0.12)<br>-0.13 (-0.14, -0.11)                      | 3.15e-35***<br>9.96e-62***<br>4.12e-48***<br>4.33e-33***<br>2.61e-43***<br>6.43e-45***<br>8.10e-41***<br>2.15e-47***<br>4.8e-130***<br>4.38e-77***                |
| PC(36:3)_[M+H]1+ / PE(39:3)_[M+H]1+ / PA(41:4)_[M+NH4]1+    784.585      PC(36:3)_[M+H]1+ / PE(41:5)_[M+H]1+ / PA(43:6)_[M+NH4]1+    808.585      PA(43:4)_[M-H]1-    793.575      PC-O(38:5)_[M+H]1+ / PC-P(38:4)_[M+H]1+    794.605      PC-O(38:5)_[M+H]1+ / PC-P(38:4)_[M+H]1+    794.605      PC-O(38:5)_[M+H]1+ / PC-P(38:4)_[M+H]1+    768.554      FA(20:4)_[M-H]1-    303.233      PC(40:5)_[M+H]1+ / PE(39:4)_[M+H]1+ / PA(41:5)_[M+NH4]1+    782.569      PC-O(36:5)_[M+H]1+ / PC-P(36:4)_[M+H]1+    766.574      PC(36:4)_[M+H]1+ / PC-P(36:4)_[M+H]1+    766.574      PC(36:1)_[M+OAc]1-    923.586     PC(20:4)_[M+H]1+    544.340      PC(38:4)_[M+OAc]1- / PS(42:3)_[M-H]1-    868.607      PC(38:4)_[M+OAc]1- / PS(42:3)_[M-H]1-    868.607   | 55<br>51<br>52<br>58<br>43<br>3<br>63<br>99<br>45<br>65<br>04             |   |   | - |   | 0.07 (0.06, 0.08)<br>-0.08 (-0.09, -0.07)<br>-0.09 (-0.11, -0.08)<br>-0.09 (-0.10, -0.08)<br>-0.10 (-0.11, -0.09)<br>-0.11 (-0.12, -0.09)<br>-0.11 (-0.12, -0.09)<br>-0.13 (-0.14, -0.12)<br>-0.13 (-0.14, -0.11)   | 9.96e-62***<br>4.12e-48***<br>4.33e-33***<br>2.61e-43***<br>6.43e-45***<br>8.10e-41***<br>2.15e-47***<br>4.8e-130***<br>4.38e-77***                               |
| PC(38:5)_[M+H]1+ / PE(41:5)_[M+H]1+ / PA(43:6)_[M+NH4]1+      808.585        PA(43:4)_[M-H]1-      793.575        PC-O(38:5)_[M+H]1+ / PC-P(38:4)_[M+H]1+      794.605        PC(35:4)_[M+H]1+ / PC-P(38:4)_[M+H]1+      784.605        PC(35:4)_[M+H]1+ / PC-P(38:4)_[M+H]1+ / PA(40:5)_[M+NH4]1+      768.554        FA(20:4)_[M-H]1-      303.233        PC(40:5)_[M+H]1+      836.616        PC(36:4)_[M+H]1+ / PE(39:4)_[M+H]1+ / PA(41:5)_[M+NH4]1+      782.569        PC-O(36:5)_[M+H]1+ / PC-P(36:4)_[M+H]1+      766.574        PI(36:1)_[M+OAc]1-      923.586       PC(20:4)_[M+H]1+      544.340        PC(38:4)_[M+OAc]1- / PS(42:3)_[M-H]1-      868.607        PS(44:6)_[M+OAc]1- / PS(42:3)_[M-H]1-      868.607  | 51<br>52<br>58<br>43<br>3<br>63<br>99<br>45<br>65<br>65                   |   |   |   |   | -0.08 (-0.09, -0.07)<br>-0.09 (-0.11, -0.08)<br>-0.09 (-0.10, -0.08)<br>-0.10 (-0.11, -0.09)<br>-0.11 (-0.12, -0.09)<br>-0.11 (-0.12, -0.09)<br>-0.13 (-0.14, -0.12)<br>-0.13 (-0.14, -0.11)  | 4.12e-48***<br>4.33e-33***<br>2.61e-43***<br>6.43e-45***<br>8.10e-41***<br>2.15e-47***<br>4.8e-130***<br>4.38e-77***  |
| PA(43:4)_[M-H]1-  793.575    PC-O(38:5)_[M+H]1+ / PC-P(38:4)_[M+H]1+  794.605    PC(35:4)_[M+H]1+ / PE(38:4)_[M+H]1+ / PA(40:5)_[M+NH4]1+  768.554    PC(40:5)_[M+H]1-  303.233    PC(40:5)_[M+H]1+  836.616    PC(36:4)_[M+H]1+ / PE(39:4)_[M+H]1+ / PA(41:5)_[M+NH4]1+  782.569    PC-O(36:5)_[M+H]1+ / PC-P(36:4)_[M+H]1+  766.574    PC(36:1)_[M+OAc]1-  923.586   PC(20:4)_[M+H]1+  544.340    PC(38:4)_[M+OAc]1- / PS(42:3)_[M-H]1-  868.607    PS(44:6)_[M+OAc]1-  950.612  | 52<br>58<br>43<br>3<br>63<br>99<br>45<br>65<br>04                         |   |   |   |   | -0.09 (-0.11, -0.08)<br>-0.09 (-0.10, -0.08)<br>-0.10 (-0.11, -0.09)<br>-0.11 (-0.12, -0.09)<br>-0.11 (-0.12, -0.09)<br>-0.13 (-0.14, -0.12)<br>-0.13 (-0.14, -0.11)  | 4.33e-33***<br>2.61e-43***<br>6.43e-45***<br>8.10e-41***<br>2.15e-47***<br>4.8e-130***<br>4.38e-77***   |
| PC-O(38:5)_[M+H]1+ / PC-P(38:4)_[M+H]1+      794.605        PC(35:4)_[M+H]1+ / PE(38:4)_[M+H]1+ / PA(40:5)_[M+NH4]1+      768.554        FA(20:4)_[M-H]1-      303.233        PC(40:5)_[M+H]1+      836.616        PC(36:4)_[M+H]1+ / PE(39:4)_[M+H]1+ / PA(41:5)_[M+NH4]1+      782.569        PC-O(36:5)_[M+H]1+ / PC-P(36:4)_[M+H]1+      766.574        P(36:1)_[M+OAc]1-      923.586        _PC(20:4)_[M+H]1+      544.340        PC(38:4)_[M+OAc]1- / PS(42:3)_[M-H]1-      868.607        PS(44:6)_[M+OAc]1-      950.612  | 58<br>43<br>3<br>63<br>99<br>45<br>65<br>04                               |   |   |   |   | -0.09 (-0.10, -0.08)<br>-0.10 (-0.11, -0.09)<br>-0.11 (-0.12, -0.09)<br>-0.11 (-0.12, -0.09)<br>-0.13 (-0.14, -0.12)<br>-0.13 (-0.14, -0.11)  | 2.61e-43***<br>6.43e-45***<br>8.10e-41***<br>2.15e-47***<br>4.8e-130***<br>4.38e-77***  |
| PC(35:4)_[M+H]1+ / PE(38:4)_[M+H]1+ / PA(40:5)_[M+NH4]1+      768.554        FA(20:4)_[M-H]1-      303.233        PC(40:5)_[M+H]1+      836.616        PC(36:4)_[M+H]1+      PE(39:4)_[M+H]1+ / PA(41:5)_[M+NH4]1+        PC-036:5)_[M+H]1+ / PC-P(36:4)_[M+H]1+ / PA(41:5)_[M+NH4]1+      768.574        PC(36:1)_[M+OAc]1-      923.586        _PC(20:4)_[M+H]1+      544.340        PC(38:4)_[M+OAc]1- / PS(42:3)_[M-H]1-      868.607        PS(44:6)_[M+OAc]1-      950.612   | 43<br>3<br>63<br>99<br>45<br>65<br>04                                     |   |   |   |   | -0.10 (-0.11, -0.09)<br>-0.11 (-0.12, -0.09)<br>-0.11 (-0.12, -0.09)<br>-0.13 (-0.14, -0.12)<br>-0.13 (-0.14, -0.11)  | 6.43e-45***<br>8.10e-41***<br>2.15e-47***<br>4.8e-130***<br>4.38e-77***   |
| FA(20:4)_[M-H]1-      303.233        PC(40:5)_[M+H]1+      836.616        PC(36:4)_[M+H]1+ / PE(39:4)_[M+H]1+ / PA(41:5)_[M+NH4]1+      782.569        PC-0(36:5)_[M+H]1+ / PC-P(36:4)_[M+H]1+      766.574        P(36:1)_[M+OAc]1-      923.586        PC(20:4)_[M+H]1+      544.340        PC(38:4)_[M+OAc]1- / PS(42:3)_[M-H]1-      868.607        PS(44:6)_[M+OAc]1-      950.612  | 3<br>63<br>99<br>45<br>65<br>04   |   | : |   |   | -0.11 (-0.12, -0.09)<br>-0.11 (-0.12, -0.09)<br>-0.13 (-0.14, -0.12)<br>-0.13 (-0.14, -0.11)  | 8.10e-41***<br>2.15e-47***<br>4.8e-130***<br>4.38e-77***  |
| PC(40:5)_[M+H]1+      836.616        PC(40:5)_[M+H]1+ / PE(39:4)_[M+H]1+ / PA(41:5)_[M+NH4]1+      782.569        PC-O(36:5)_[M+H]1+ / PC-P(36:4)_[M+H]1+      766.574        PP(36:1)_[M+OAc]1-      923.586        .PC(20:4)_[M+H]1+      544.340        PC(38:4)_[M+OAc]1- / PS(42:3)_[M-H]1-      868.607        PS(44:6)_[M+OAc]1-      950.612   | 63<br>99<br>45<br>65<br>04  |   |   |   |   | -0.11 (-0.12, -0.09)<br>-0.13 (-0.14, -0.12)<br>-0.13 (-0.14, -0.11)  | 2.15e-47***<br>4.8e-130***<br>4.38e-77***   |
| PC(36:4)_[M+H]1+ / PE(39:4)_[M+H]1+ / PA(41:5)_[M+NH4]1+      782.569        PC-O(36:5)_[M+H]1+ / PC-P(36:4)_[M+H]1+      766.574        Pl(36:1)_[M+OAc]1-      923.586        .PC(20:4)_[M+H]1+      544.340        PC(38:4)_[M+OAc]1- / PS(42:3)_[M-H]1-      868.607        PS(44:6)_[M+OAc]1-      950.612  | 99<br>45<br>65<br>04  |   | : |   |   | -0.13 (-0.14, -0.12)<br>-0.13 (-0.14, -0.11)  | 4.8e-130***<br>4.38e-77***  |
| PC-O(36:5)_[M+H]1+ / PC-P(36:4)_[M+H]1+      766.574        Pl(36:1)_[M+OAc]1-      923.586       PC(20:4)_[M+H]1+      544.340        PC(38:4)_[M+OAc]1- / PS(42:3)_[M-H]1-      868.607        PS(44:6)_[M+OAc]1-      950.612   | 45<br>65<br>04  |   |   |   |   | -0.13 (-0.14, -0.11)  | 4.38e-77***   |
| Pl(36:1)_[M+OAc]1-  923.586    _PC(20:4)_[M+H]1+  544.340    PC(38:4)_[M+OAc]1- / PS(42:3)_[M-H]1-  868.607    PS(44:6)_[M+OAc]1-  950.612   | 65<br>04  |   | - |   |   |   |   |
| _PC(20:4)_[M+H]1+      544.340        PC(38:4)_[M+OAc]1- / PS(42:3)_[M-H]1-      868.607        PS(44:6)_[M+OAc]1-      950.612  | 04  |   |   |   |   | -0.13 (-0.16, -0.11)  | 6.63e-36***   |
| PC(38:4)_[M+OAc]1- / PS(42:3)_[M-H]1- 868.607<br>PS(44:6)_[M+OAc]1- 950.612  |   |   | • |   |   | -0.14 (-0.16, -0.12)  | 1.10e-38***   |
| PS(44:6)_[M+OAc]1- 950.612   | 72  |   |   |   |   | -0.14 (-0.16, -0.13)  | 4.82e-74***   |
|  | 28  | ł | - |   |   | -0.15 (-0.17, -0.12)  | 2.63e-36***   |
| PC(38:4)_[M+H]1+ / PE(41:4)_[M+H]1+ 810.601  | 12  | I |   |   |   | -0.15 (-0.16, -0.13)  | 7.2e-115***   |
| SM(44:9)_[M+H]1- 825.591   | 18  | 1 |   |   |   | -0.15 (-0.17, -0.13)  | 1.06e-74***   |
| PC(37:4)_[M+H]1+ / PE(40:4)_[M+H]1+ / PA(42:5)_[M+NH4]1+ 796.585   | 56  |   | - |   |   | -0.15 (-0.17, -0.13)  | 3.30e-56***   |
| CE(20:4)_[M+NH4]1+ 690.618   | 83  | - |   |   |   | -0.20 (-0.21, -0.18)  | 1.2e-112***   |
| CE(20:5)_[M+NH4]1+ 688.602   | 26  | - |   |   |   | -0.20 (-0.23, -0.18)  | 1.88e-46***   |

Lipid

Beta (95% CI) for FADS1-FADS2-FADS3 (rs174546, chr11:61569830)

# (i) *GAL3ST1*

| Lipid  | Lipid                                  |                      |             |
|--|--|----------------------|-------------|
| name   | m/z                                    | Beta (95% CI)        | P-value     |
|  |  |                      |             |
| TG(46:0)_[M+NH4]1+                                       | 796.7393                               | 0.06 (0.01, 0.11)    | 1.24e-02    |
| DG(30:1)_[M+H-H2O]1+                                     | 521.4569                               | 0.05 (0.01, 0.09)    | 2.01e-02    |
| TG(46:2)_[M+NH4]1+                                       | 792.7077                               | 0.05 (0.01, 0.08)    | 1.59e-02    |
| DG(34:2)_[M+NH4]1+                                       | 610.541                                | 0.03 (0.01, 0.05)    | 1.57e-03    |
| DG(34:1)_[M+NH4]1+                                       | 612.5564                               | 0.03 (0.01, 0.05)    | 5.77e-03    |
| TG(50:2)_[M+NH4]1+                                       | 848.77                                 | 0.03 (0.01, 0.05)    | 1.50e-02    |
| TG(50:3)_[M+NH4]1+                                       | 846.7546                               | 0.02 (0.00, 0.04)    | 1.34e-02    |
| DG(36:2)_[M+NH4]1+                                       | 638.5723                               | 0.02 (0.01, 0.04)    | 9.90e-03    |
| DG(34:2)_[M+H-H2O]1+                                     | 575.5039                               | 0.02 (0.00, 0.04)    | 1.37e-02    |
| PC(36:4)_[M+H]1+ / PE(39:4)_[M+H]1+ / PA(41:5)_[M+NH4]1+ | 782.5699                               | -0.01 (-0.02, -0.00) | 1.29e-02    |
| SM(38:1)_[M+H]1+   | 759.6372                               | -0.01 (-0.03, -0.00) | 9.46e-03    |
| PC(38:4)_[M+H]1+ / PE(41:4)_[M+H]1+                      | 810.6012                               | -0.02 (-0.03, -0.00) | 7.18e-03    |
| CE(18:3)_[M+NH4]1+                                       | 664.6026                               | -0.02 (-0.03, -0.00) | 2.42e-02    |
| PC(37:4)_[M+H]1+ / PE(40:3)_[M+H]1+                      | 798.6012                               | -0.02 (-0.03, -0.00) | 1.74e-02    |
| PC(35:1)_[M+H]1+ / PE(38:1)_[M+H]1+ / PA(40:2)_[M+NH4]1+ | 774.6009                               | -0.02 (-0.03, -0.00) | 1.36e-02    |
| PC(42:4)_[M+OAc]1-                                       | 924.6698                               | -0.02 (-0.04, -0.00) | 1.64e-02    |
| PC(37:4)_[M+H]1+ / PE(40:4)_[M+H]1+ / PA(42:5)_[M+NH4]1+ | 796.5856                               | -0.03 (-0.04, -0.01) | 4.34e-03    |
| SM(38:0)_[M+H]1+   | 761.6532                               | -0.03 (-0.04, -0.01) | 4.86e-04*   |
| PS(40:1)_[M+OAc]1-                                       | 904.6284 -                             | -0.07 (-0.11, -0.04) | 6.76e-05*   |
| PG(32:1)_[M+OAc]1-                                       | 779.5078                               | -0.12 (-0.16, -0.08) | 4.86e-10*** |
|  |  |                      |             |
|  |  | í                    |             |
|  | 4321 0 .1 .2 .3 .                      | 4                    |             |
| Beta (95% CI) f  | or GAL3ST1 (rs2267161, chr22:30953295) |                      |             |



#### (j) GCKR

| name   | m/z          | Beta (95% CI)        | P-value     |
|--|--------------|----------------------|-------------|
|  | 1            |                      |             |
| PE(34:2)_[M+H]1+   | 716.523      | 0.15 (0.13, 0.17)    | 9.25e-43*** |
| PE(36:4)_[M+H]1+   | 740.5229     | 0.14 (0.12, 0.15)    | 3.17e-54*** |
| PE(36:4)_[M-H]1-   | 738.5079     | 0.13 (0.11, 0.14)    | 1.97e-53*** |
| Cer(42:11)_[M+OAc]1-                                     | 688.4947 -   | 0.11 (0.07, 0.16)    | 1.84e-06*   |
| PC(33:3)_[M+H]1+ / PE(36:3)_[M+H]1+ / PA(38:4)_[M+NH4]1+ | 742.5386     | 0.11 (0.09, 0.13)    | 1.35e-23*** |
| PE(40:7)_[M-H]1-   | 788.5236     | 0.09 (0.07, 0.11)    | 7.10e-16*** |
| PC(35:4)_[M+H]1+ / PE(38:4)_[M+H]1+ / PA(40:5)_[M+NH4]1+ | 768.5543     | 0.09 (0.07, 0.10)    | 4.07e-41*** |
| PC(37:6)_[M+H]1+ / PE(40:6)_[M+H]1+ / PA(42:7)_[M+NH4]1+ | 792.5537     | 0.07 (0.06, 0.09)    | 8.49e-19*** |
| PE(38:5)_[M-H]1-   | 764.5236     | 0.06 (0.05, 0.08)    | 1.29e-12*** |
| PC(33:2)_[M+H]1+ / PE(36:2)_[M+H]1+ / PA(38:3)_[M+NH4]1+ | 744.5543     | 0.05 (0.04, 0.06)    | 8.03e-16*** |
| PA(43:6)_[M+OAc]1-                                       | 849.565      | 0.04 (0.02, 0.07)    | 3.55e-04*   |
| Cer(44:11)_[M+OAc]1-                                     | 716.526      | 0.04 (0.02, 0.06)    | 2.39e-05*   |
| PE(34:1)_[M-H]1-   | 716.5235     | 0.04 (0.02, 0.06)    | 2.39e-05*   |
| PA(39:1)_[M+H]1+   | 745.5746     | 0.03 (0.02, 0.04)    | 1.78e-07*   |
| Cholesterol_[M+H-H2O]1+                                  | 369.3514     | -0.02 (-0.03, -0.01) | 6.70e-04*   |
| SM(38:1)_[M+H]1+   | 759.6372     | -0.02 (-0.03, -0.01) | 6.99e-05*   |
| SM(41:2)_[M+H]1+   | 799.6685     | -0.02 (-0.04, -0.01) | 8.35e-04*   |
| CE(20:3)_[M+NH4]1+                                       | 692.6339     | -0.02 (-0.04, -0.01) | 5.05e-04*   |
| SM(39:1)_[M+H]1+   | 773.6531     | -0.03 (-0.04, -0.01) | 8.34e-04*   |
| SM(38:0)_[M+H]1+   | 761.6532     | -0.03 (-0.04, -0.01) | 8.08e-04*   |
|  |              |                      |             |
|  | ····         |                      |             |
|  | 4321 0 .1 .2 | .3 .4                |             |

Lipid

# (k) *LIPC*

Lipid

# (I) *LPL*

| Lipid                | Lipid      |                      |             |
|----------------------|------------|----------------------|-------------|
| name                 | m/z        | Beta (95% CI)        | P-value     |
|                      |            |                      |             |
| SM(42:4)_[M+H]1+     | 809.6531   | 0.08 (0.05, 0.10)    | 7.51e-11*** |
| CE(20:3)_[M+NH4]1+   | 692.6339   | 0.07 (0.04, 0.09)    | 1.35e-09**  |
| SM(42:3)_[M+H]1+     | 811.6688   | 0.06 (0.04, 0.08)    | 9.36e-09**  |
| CE(18:0)_[M+NH4]1+   | 670.6496   | 0.05 (0.03, 0.07)    | 4.70e-09**  |
| SM(36:0)_[M+H]1+     | 733.6219   | 0.05 (0.03, 0.07)    | 5.53e-08*   |
| CE(18:1)_[M+NH4]1+   | 668.6339   | 0.05 (0.03, 0.06)    | 6.92e-09**  |
| SM(34:1)_[M+H]1+     | 703.5747   | 0.05 (0.03, 0.06)    | 4.36e-08**  |
| DG(36:2)_[M+H-H2O]1+ | 603.5352 🖶 | -0.07 (-0.09, -0.05) | 3.63e-09**  |
| DG(36:2)_[M+NH4]1+   | 638.5723 🖶 | -0.07 (-0.09, -0.04) | 3.85e-08**  |
| DG(34:2)_[M+H-H2O]1+ | 575.5039 🖶 | -0.07 (-0.10, -0.05) | 6.57e-09**  |
| DG(34:1)_[M+H-H2O]1+ | 577.5193 🖶 | -0.07 (-0.10, -0.05) | 3.18e-08**  |
| TG(52:2)_[M+NH4]1+   | 876.8016 🖶 | -0.08 (-0.10, -0.05) | 2.75e-08**  |
| TG(53:3)_[M+NH4]1+   | 888.8016 🖶 | -0.08 (-0.10, -0.05) | 3.63e-08**  |
| TG(54:3)_[M+NH4]1+   | 902.8175 🖶 | -0.08 (-0.10, -0.05) | 2.48e-08**  |
| TG(52:3)_[M+NH4]1+   | 874.7859 🖶 | -0.08 (-0.10, -0.05) | 2.23e-10*** |
| DG(36:3)_[M+H-H2O]1+ | 601.5195 🖶 | -0.08 (-0.10, -0.05) | 1.17e-08**  |
| DG(36:1)_[M+H-H2O]1+ | 605.5508 - | -0.08 (-0.11, -0.05) | 3.28e-08**  |
| TG(54:4)_[M+NH4]1+   | 900.8015 - | -0.08 (-0.11, -0.05) | 3.62e-08**  |
| TG(52:4)_[M+NH4]1+   | 872.7702 - | -0.08 (-0.11, -0.05) | 6.15e-08*   |
| TG(54:2)_[M+NH4]1+   | 904.8326 - | -0.09 (-0.13, -0.06) | 3.32e-08**  |
|                      |            |                      |             |
|                      |            |                      |             |
|                      |            |                      |             |

-.4 -.3 -.2 -.1 0 .1 .2 .3 .4

Beta (95% CI) for LPL (rs9644639, chr8:19884947)

# (m) *MBOAT7*

| Lipid                                 | Lipid    |                      |             |
|---------------------------------------|----------|----------------------|-------------|
| name                                  | m/z      | Beta (95% CI)        | P-value     |
|                                       | 1        |                      |             |
| PI(33:0)_[M-H]1-                      | 823.5341 | 0.14 (0.08, 0.21)    | 1.59e-05*   |
| PI(35:2)_[M-H]1-                      | 847.5343 | 0.12 (0.10, 0.15)    | 7.88e-29*** |
| PI(32:1)_[M-H]1-                      | 807.5028 | 0.12 (0.10, 0.15)    | 1.29e-21*** |
| PI(34:0)_[M-H]1-                      | 837.5498 | 0.12 (0.10, 0.14)    | 1.08e-27*** |
| PI(40:6)_[M-H]1-                      | 909.5498 | 0.10 (0.09, 0.12)    | 1.98e-43*** |
| PA(40:5)_[M+OAc]1- / PG(39:5)_[M-H]1- | 809.5337 | 0.10 (0.08, 0.12)    | 3.31e-20*** |
| PI(34:2)_[M-H]1-                      | 833.5186 | 0.10 (0.08, 0.11)    | 8.71e-45*** |
| PI(34:1)_[M-H]1-                      | 835.5341 | 0.09 (0.08, 0.11)    | 2.56e-31*** |
| PS(42:8)_[M+OAc]1-                    | 918.5502 | 0.09 (0.04, 0.14)    | 2.80e-04*   |
| PI(36:2)_[M-H]1-                      | 861.5498 | 0.09 (0.08, 0.10)    | 6.80e-49*** |
| PI(40:5)_[M-H]1-                      | 911.5655 | 0.08 (0.07, 0.09)    | 5.26e-30*** |
| PI(38:6)_[M-H]1-                      | 881.5186 | 0.08 (0.06, 0.09)    | 2.47e-20*** |
| PS(33:0)_[M+OAc]1-                    | 808.5345 | 0.07 (0.04, 0.11)    | 2.81e-06*   |
| PA(44:6)_[M+OAc]1- / PG(43:6)_[M-H]1- | 863.5806 | 0.06 (0.05, 0.08)    | 3.01e-15*** |
| PA(43:6)_[M+OAc]1-                    | 849.565  | 0.06 (0.04, 0.08)    | 4.87e-08**  |
| PI(36:3)_[M-H]1-                      | 859.5343 | 0.04 (0.02, 0.05)    | 1.00e-06*   |
| PE(36:4)_[M-H]1-                      | 738.5079 | 0.02 (0.01, 0.04)    | 8.98e-04*   |
| PI(40:7)_[M+OAc]1-                    | 967.5553 | -0.04 (-0.06, -0.02) | 1.68e-04*   |
| PI(36:4)_[M-H]1-                      | 857.5186 | -0.04 (-0.06, -0.03) | 3.53e-10*** |
| PI(38:4)_[M-H]1-                      | 885.5498 | -0.05 (-0.06, -0.04) | 5.50e-25*** |
|                                       |          |                      |             |
|                                       |          |                      |             |

-.4 -.3 -.2 -.1 0 .1 .2 .3 .4

Beta (95% CI) for MBOAT7 (rs8736, chr19:54677189)

| name   | m/z      |             | Beta (95% CI)     | P-value     |
|--|----------|-------------|-------------------|-------------|
|  |          | 1           |                   |             |
| PC-O(34:3)_[M+H]1+ / PE-P(37:2)_[M+H]1+                      | 742.5748 | -           | 0.06 (0.04, 0.09) | 4.52e-09**  |
| SM(34:0)_[M-CH3]1-   | 689.5604 |             | 0.06 (0.04, 0.08) | 6.02e-10*** |
| SM(42:1)_[M-CH3]1-   | 799.67   | -           | 0.06 (0.04, 0.08) | 9.27e-08*   |
| SM(34:1)_[M-CH3]1-   | 687.5448 |             | 0.06 (0.04, 0.08) | 7.76e-10*** |
| PC-O(36:2)_[M+H]1+ / PE-P(39:1)_[M+H]1+                      | 772.6219 | -           | 0.06 (0.03, 0.08) | 2.50e-06*   |
| SM(42:4)_[M+H]1+   | 809.6531 | -           | 0.06 (0.03, 0.08) | 2.31e-07*   |
| SM(42:2)_[M+OAc]1-   | 871.6911 | -           | 0.06 (0.03, 0.08) | 8.61e-07*   |
| PC-O(34:2)_[M+H]1+ / PE-O(37:2)_[M+H]1+                      | 744.5904 | =           | 0.05 (0.03, 0.07) | 7.93e-07*   |
| SM(42:0)_[M+OAc]1-   | 875.7224 | =           | 0.05 (0.03, 0.07) | 1.26e-06*   |
| SM(42:1)_[M+OAc]1-   | 873.7067 | -           | 0.05 (0.03, 0.07) | 1.96e-06*   |
| SM(38:1)_[M+CH3]1-   | 743.6075 |             | 0.05 (0.03, 0.07) | 5.73e-07*   |
| SM(42:3)_[M+H]1+   | 811.6688 | -           | 0.05 (0.03, 0.07) | 1.22e-06*   |
| SM(40:2)_[M-CH3]1-   | 769.6231 |             | 0.05 (0.03, 0.07) | 5.30e-07*   |
| PC-O(36:3)_M+H]1+ / PC-P(36:2)_M+H]1+                        | 770.6063 | -           | 0.05 (0.03, 0.07) | 2.43e-06*   |
| PC-O(34:1)_[M+H]1+ / PC-P(34:0)_[M+H]1+ / PE-O(37:1)_[M+H]1+ | 746.6061 | -           | 0.05 (0.03, 0.07) | 2.29e-06*   |
| SM(36:1)_[M-CH3]1-   | 715.5761 |             | 0.05 (0.03, 0.07) | 1.48e-06*   |
| SM(33:1)_[M-CH3]1-   | 673.5291 |             | 0.05 (0.03, 0.07) | 1.68e-06*   |
| SM(34:0)_[M+H]1+   | 705.5906 |             | 0.05 (0.03, 0.06) | 5.83e-09**  |
| SM(34:1)_[M+H]1+   | 703.5747 |             | 0.04 (0.03, 0.06) | 6.48e-09**  |
| PC-O(39:1)_[M+H]1+ / PE-P(39:0)_[M+H]1+                      | 816.6845 |             | 0.04 (0.02, 0.05) | 2.31e-06*   |
|  |          |             |                   |             |
|  | I        |             | 1 1               |             |
|  | 43 -     | .21 0 .1 .2 | .3 .4             |             |

Beta (95% CI) for *MLXIPL* (chr7:73042302:D, chr7:73042302)

# (n) *MLXIPL*

# (o) PAQR9

Lipid

| name   | m/z          | Beta (95% CI)        | P-value  |
|--|--------------|----------------------|----------|
|  | I            |                      |          |
| PA(44:6)_[M+OAc]1- / PG(43:6)_[M-H]1-                    | 863.5806     | 0.08 (0.05, 0.10)    | 3.71e-10 |
| PI(34:0)_[M-H]1-   | 837.5498     | 0.06 (0.03, 0.10)    | 6.81e-04 |
| PI(34:1)_[M-H]1-   | 835.5341     | 0.05 (0.02, 0.07)    | 2.59e-04 |
| CE(18:0)_[M+NH4]1+                                       | 670.6496     | 0.02 (0.01, 0.04)    | 3.07e-03 |
| CE(18:1)_[M+NH4]1+                                       | 668.6339     | 0.02 (0.01, 0.04)    | 3.36e-03 |
| CE(16:0)_[M+NH4]1+                                       | 642.6183     | 0.01 (0.00, 0.03)    | 4.60e-02 |
| PC(36:3)_[M+OAc]1- / PS(40:2)_[M-H]1-                    | 842.5916     | -0.02 (-0.03, -0.00) | 3.80e-02 |
| PC(34:3)_[M+H]1+ / PE(37:3)_[M+H]1+ / PA(39:4)_[M+NH4]1+ | 756.5541     | -0.02 (-0.04, -0.00) | 3.18e-02 |
| PG(35:3)_[M-H]1-   | 757.5024     | -0.02 (-0.04, 0.00)  | 5.23e-02 |
| PA(43:6)_[M-H]1-   | 789.5439     | -0.02 (-0.04, -0.00) | 5.09e-02 |
| PA(45:6)_[M-H]1-   | 817.5752     | -0.02 (-0.04, -0.00) | 1.58e-02 |
| PI(36:4)_[M-H]1-   | 857.5186     | -0.02 (-0.04, -0.00) | 2.62e-02 |
| PE(38:5)_[M-H]1-   | 764.5236     | -0.03 (-0.05, -0.00) | 2.04e-02 |
| DG(34:3)_[M+H-H2O]1+                                     | 573.488      | -0.03 (-0.06, -0.00) | 2.90e-0  |
| PC(32:1)_[M+OAc]1-                                       | 790.5602 -   | -0.03 (-0.06, -0.00) | 4.14e-02 |
| PE(36:4)_[M-H]1-   | 738.5079     | -0.03 (-0.06, -0.01) | 3.42e-03 |
| PE(40:7)_[M-H]1-   | 788.5236     | -0.03 (-0.06, -0.01) | 2.16e-02 |
| PA(40:5)_[M+OAc]1- / PG(39:5)_[M-H]1-                    | 809.5337 -   | -0.04 (-0.07, -0.00) | 3.19e-02 |
| PS(38:3) _[M+OAc]1-                                      | 872.5659     | -0.04 (-0.08, -0.01) | 2.46e-02 |
| PS(40:5) _[M+OAc]1-                                      | 896.5659     | -0.05 (-0.08, -0.01) | 8.69e-0  |
|  |              |                      |          |
|  |              |                      |          |
|  | 4321 0 .1 .2 | .3 .4                |          |

Lipid

# (p) *PCTP*

|   | Lipid    |                      |            |
|---|----------|----------------------|------------|
| name                                    | m/z      | Beta (95% CI)        | P-value    |
| PC-O(46:1)_[M+H]1+ / PC-P(46:0)_[M+H]1+ | 914.7941 | - 0.04 (-0.01, 0.08) | 9.62e-02   |
| CEoxid(20:4)_[M+NH4]1+                  | 706.6132 | 0.02 (-0.00, 0.05)   | 1.01e-01   |
| Cer(42:2)_[M+OAc]1-                     | 706.6355 | 0.01 (-0.00, 0.03)   | 9.67e-02   |
| PA(39:1)_[M+H]1+                        | 745.5746 | 0.01 (-0.00, 0.02)   | 6.78e-02   |
| CE(16:1)_[M+NH4]1+                      | 640.6024 | -0.02 (-0.03, 0.00)  | 9.80e-02   |
| CE(17:1)_[M+NH4]1+                      | 654.618  | -0.02 (-0.04, 0.00)  | 9.93e-02   |
| PS(40:2) _[M+OAc]1-                     | 902.6128 | -0.02 (-0.03, 0.00)  | 6.91e-02   |
| PA(34:1)_[M-H]1-                        | 673.4812 | -0.02 (-0.04, 0.00)  | 9.71e-02   |
| FA(21:0)_[M-H]1-                        | 325.3113 | -0.02 (-0.04, 0.00)  | 6.20e-02   |
| SM(37:1)_[M-CH3]1-                      | 729.5917 | -0.02 (-0.03, -0.00) | 1.84e-02   |
| PA(44:6)_[M+OAc]1- / PG(43:6)_[M-H]1-   | 863.5806 | -0.02 (-0.04, -0.01) | 6.58e-03   |
| PI(34:1)_[M-H]1-                        | 835.5341 | -0.02 (-0.04, -0.01) | 4.41e-03   |
| PS(41:5)_[M+OAc]1-                      | 910.5816 | -0.03 (-0.05, 0.00)  | 5.64e-02   |
| PI(34:0)_[M-H]1-                        | 837.5498 | -0.03 (-0.05, -0.01) | 1.45e-02   |
| PI(32:1)_[M-H]1-                        | 807.5028 | -0.03 (-0.06, -0.00) | 3.45e-02   |
| PI-O(33:0)_[M-H]1-                      | 809.5548 | -0.04 (-0.07, -0.00) | 3.78e-02   |
| PG(32:1)_[M+OAc]1-                      | 779.5078 | -0.04 (-0.08, -0.01) | 1.20e-02   |
| PA(40:5)_[M+OAc]1- / PG(39:5)_[M-H]1-   | 809.5337 | -0.07 (-0.09, -0.05) | 1.98e-10** |
| PI(33:0) [M-H]1-                        | 823.5341 | -0.08 (-0.15, -0.02) | 1.51e-02   |
|   |          |                      |            |

Beta (95% CI) for *PCTP* (rs11079173, chr17:53487664)

#### (q) PIGH-TMEM229B

| Lipia                                   | Lipid      |                      |             |
|---|------------|----------------------|-------------|
| name                                    | m/z        | Beta (95% CI)        | P-value     |
| SM(40:7)_[M+H]1+                        | 775.5743   | 0.06 (-0.01, 0.13)   | 8.71e-02    |
| PC(34:5)_[M+OAc]1- / PE(37:5)_[M+OAc]1- | 810.529    | 0.02 (-0.00, 0.05)   | 5.98e-02    |
| PC-O(32:0)_[M+H]1+ / PE-O(35:0)_[M+H]1+ | 720.5906   | 0.02 (0.00, 0.03)    | 8.36e-03    |
| DG(34:2)_[M+NH4]1+                      | 610.541    | 0.02 (0.00, 0.03)    | 3.37e-02    |
| PA(34:2)_[M-H]1-                        | 671.4656   | 0.02 (0.00, 0.03)    | 3.92e-02    |
| PA(34:1)_[M-H]1-                        | 673.4812   | 0.02 (-0.00, 0.04)   | 9.12e-02    |
| PI(38:5)_[M-H]1-                        | 883.5343   | 0.02 (0.00, 0.03)    | 3.05e-02    |
| DG(34:1)_[M+NH4]1+                      | 612.5564   | 0.02 (-0.00, 0.03)   | 6.38e-02    |
| PC(40:4)_[M+OAc]1- / PS(44:3)_[M-H]1-   | 896.6385   | 0.01 (-0.00, 0.03)   | 8.78e-02    |
| PC-O(38:4)_[M+H]1+ / PC-P(38:3)_[M+H]1+ | 796.6219   | 0.01 (0.00, 0.03)    | 2.75e-02    |
| PI(38:4)_[M-H]1-                        | 885.5498   | 0.01 (-0.00, 0.02)   | 6.50e-02    |
| PC-O(33:2)_[M+H]1+ / PC-P(33:1)_[M+H]1+ | 730.5747   | -0.01 (-0.03, 0.00)  | 8.49e-02    |
| SM(38:0)_[M+H]1+                        | 761.6532   | -0.02 (-0.03, -0.01) | 1.95e-03    |
| PA(38:1)_[M+H]1+                        | 731.5587   | -0.02 (-0.05, 0.00)  | 7.40e-02    |
| PC-O(34:3)_[M+H]1+ / PE-P(37:2)_[M+H]1+ | 742.5748   | -0.03 (-0.04, -0.01) | 1.69e-04*   |
| PS(40:1)_[M+OAc]1-                      | 904.6284 - | -0.04 (-0.07, -0.01) | 9.54e-03    |
| PI-O(36:0)_[M-H]1- / PG(37:0)_[M+OAc]1- | 851.6017   | -0.05 (-0.06, -0.03) | 1.41e-11*** |
| PC-O(40:9)_[M+H]1+ / PE-P(40:8)_[M+H]1+ | 814.5744 - | -0.06 (-0.11, -0.02) | 9.27e-03    |
| PC-O(36:5)_[M+H]1+ / PC-P(36:4)_[M+H]1+ | 766.5745   | -0.07 (-0.08, -0.06) | 6.45e-42**  |
| SM(44:9)_[M+H]1-                        | 825.5918   | -0.08 (-0.09, -0.07) | 4.98e-35*** |

Beta (95% CI) for PIGH-TMEM229B (rs1885041, chr14:67976325)

#### (r) PLA2G10-NTAN1-NPIPA5

| цра  | Lipid    |                      |            |
|--|----------|----------------------|------------|
| name   | m/z      | Beta (95% CI)        | P-value    |
| PA(39:1)_[M+H]1+   | 745.5746 | 0.02 (0.01, 0.03)    | 3.18e-05*  |
| PC-O(34:3)_[M+H]1+ / PE-P(37:2)_[M+H]1+                  | 742.5748 | 0.02 (0.00, 0.03)    | 9.23e-03   |
| PA(39:0)_[M+H]1+   | 747.5903 | 0.02 (0.00, 0.03)    | 5.62e-03   |
| PC(33:2)_[M+H]1+ / PE(36:2)_[M+H]1+ / PA(38:3)_[M+NH4]1+ | 744.5543 | 0.01 (0.00, 0.02)    | 6.96e-03   |
| PC(36:2)_[M+H]1+ / PE(39:2)_[M+H]1+ / PA(41:3)_[M+NH4]1+ | 786.6012 | 0.01 (0.00, 0.02)    | 2.21e-03   |
| PC(34:2)_[M+H]1+ / PE(37:2)_[M+H]1+ / PA(39:3)_[M+NH4]1+ | 758.57   | 0.01 (0.00, 0.02)    | 6.27e-03   |
| PC(35:3)_[M+H]1+ / PE(38:3)_[M+H]1+ / PA(40:4)_[M+NH4]1+ | 770.5697 | -0.02 (-0.03, -0.00) | 7.82e-03   |
| PC(38:4)_[M+OAc]1- / PS(42:3)_[M-H]1-                    | 868.6072 | -0.02 (-0.03, -0.00) | 5.93e-03   |
| PC(38:4)_[M+H]1+ / PE(41:4)_[M+H]1+                      | 810.6012 | -0.02 (-0.03, -0.01) | 1.96e-04*  |
| PC(36:3)_[M+H]1+ / PE(39:3)_[M+H]1+ / PA(41:4)_[M+NH4]1+ | 784.5855 | -0.02 (-0.03, -0.02) | 1.85e-11** |
| CE(18:3)_[M+NH4]1+                                       | 664.6026 | -0.02 (-0.04, -0.01) | 4.94e-04*  |
| PC(36:3)_[M+OAc]1- / PS(40:2)_[M-H]1-                    | 842.5916 | -0.02 (-0.03, -0.01) | 1.28e-06*  |
| FA(20:3)_[M-H]1-   | 305.2487 | -0.03 (-0.04, -0.02) | 1.98e-06*  |
| PC(37:4)_[M+H]1+ / PE(40:3)_[M+H]1+                      | 798.6012 | -0.03 (-0.05, -0.02) | 1.61e-07*  |
| CE(20:3)_[M+NH4]1+                                       | 692.6339 | -0.04 (-0.05, -0.02) | 7.47e-10** |
| PI(38:0)_[M+OAc]1-                                       | 953.6335 | -0.05 (-0.07, -0.03) | 1.86e-06*  |
| PC(38:3)_[M+H]1+ / PE(41:3)_[M+H]1+ / PA(43:4)_[M+NH4]1+ | 812.6168 | -0.05 (-0.06, -0.04) | 5.53e-24** |
| PC(38:3)_[M+OAc]1- / PS(42:2)_[M-H]1-                    | 870.6229 | -0.06 (-0.07, -0.04) | 3.92e-16** |
| PC(38:2)_[M+H]1+ / PE(41:2)_[M+H]1+                      | 814.6322 | -0.06 (-0.07, -0.05) | 6.75e-23** |
| PE(40:2)_[M-H]1-   | 798.6017 | -0.06 (-0.08, -0.05) | 7.22e-14** |
|  |          |                      |            |
|  |          |                      |            |

Beta (95% CI) for PLA2G10-NTAN1-NPIPA5 (rs34955778, chr16:15139594)

# (s) PNPLA3

| Lipid                                   | Lipid        |                      |             |
|---|--------------|----------------------|-------------|
| name                                    | m/z          | Beta (95% CI)        | P-value     |
| TG(57:10)_[M+NH4]1+                     | 930.754      | 0.16 (0.09, 0.23)    | 2.74e-06*   |
| TG(57:9)_[M+NH4]1+                      | 932.7697     | 0.15 (0.07, 0.23)    | 4.26e-04*   |
| TG(58:9)_[M+NH4]1+                      | 946.7854     | 0.08 (0.04, 0.13)    | 6.93e-05*   |
| TG(56:6)_[M+NH4]1+                      | 924.801      | 0.07 (0.05, 0.09)    | 3.37e-14*** |
| TG(55:8)_[M+NH4]1+                      | 906.7543     | 0.07 (0.03, 0.10)    | 9.66e-05*   |
| TG(56:5)_[M+NH4]1+                      | 926.817      | 0.07 (0.05, 0.08)    | 5.85e-14*** |
| TG(56:4)_[M+NH4]1+                      | 928.8329     | 0.06 (0.04, 0.08)    | 3.90e-07*   |
| TG(56:7)_[M+NH4]1+                      | 922.7853     | 0.06 (0.03, 0.08)    | 4.56e-07*   |
| TG(54:4)_[M+NH4]1+                      | 900.8015     | 0.04 (0.02, 0.06)    | 1.53e-04*   |
| PI(36:3)_[M-H]1-                        | 859.5343     | 0.04 (0.02, 0.05)    | 6.10e-05*   |
| PC-O(40:6)_[M+H]1+ / PC-P(40:5)_[M+H]1+ | 820.6214     | 0.02 (0.01, 0.04)    | 2.70e-04*   |
| PG(36:0)_[M-H]1-                        | 777.5649     | 0.02 (0.01, 0.03)    | 3.51e-04*   |
| DG(34:0)_[M+H-H2O]1+                    | 579.5352     | -0.04 (-0.07, -0.02) | 5.79e-05*   |
| TG(50:1)_[M+NH4]1+                      | 850.7859     | -0.05 (-0.08, -0.02) | 2.95e-04*   |
| DG(32:0)_[M+H-H2O]1+                    | 551.5038 -   | -0.05 (-0.08, -0.02) | 3.71e-04*   |
| TG(48:1)_[M+NH4]1+                      | 822.7546     | -0.06 (-0.09, -0.03) | 4.20e-04*   |
| TG(51:1)_[M+NH4]1+                      | 864.8016 -   | -0.07 (-0.10, -0.03) | 1.30e-04*   |
| TG(48:0)_[M+NH4]1+                      | 824.7706 -   | -0.09 (-0.13, -0.05) | 3.02e-05*   |
| TG(52:0)_[M+NH4]1+                      | 880.8331 -   | -0.09 (-0.13, -0.05) | 4.26e-06*   |
| TG(46:0)_[M+NH4]1+                      | 796.7393 -   | -0.10 (-0.15, -0.05) | 1.82e-04*   |
|   |              |                      |             |
|   |              |                      |             |
|   | 4321 0 .1 .2 | .3 .4                |             |



| name   | m/z      |   | Beta (95% CI)        | P-value     |
|--|----------|---|----------------------|-------------|
|  |          | 1 |                      |             |
| TG(48:0)_[M+NH4]1+                                       | 824.7706 |   | 0.07 (0.03, 0.10)    | 1.82e-04*   |
| DG(32:0)_[M+H-H2O]1+                                     | 551.5038 | = | 0.04 (0.02, 0.06)    | 6.69e-04*   |
| FA(16:0)_[M-H]1-   | 255.233  |   | 0.02 (0.01, 0.04)    | 7.34e-04*   |
| PC-O(38:4)_[M+H]1+ / PC-P(38:3)_[M+H]1+                  | 796.6219 | - | 0.02 (0.01, 0.03)    | 9.67e-04*   |
| SM(37:1)_[M-CH3]1-                                       | 729.5917 |   | -0.02 (-0.04, -0.01) | 7.80e-04*   |
| PG(36:2)_[M-H]1-   | 773.5337 |   | -0.03 (-0.04, -0.02) | 1.82e-05*   |
| Cer(44:11)_[M+OAc]1-                                     | 716.526  |   | -0.03 (-0.05, -0.01) | 2.82e-04*   |
| PE(34:1)_[M-H]1-   | 716.5235 |   | -0.03 (-0.05, -0.01) | 2.82e-04*   |
| PS(38:1) _[M+OAc]1-                                      | 876.5971 |   | -0.03 (-0.05, -0.01) | 6.39e-04*   |
| TG(50:3)_[M+NH4]1+                                       | 846.7546 |   | -0.03 (-0.05, -0.02) | 2.42e-05*   |
| PC(40:7)_[M+OAc]1- / PS(44:6)_[M-H]1-                    | 890.5916 |   | -0.03 (-0.05, -0.02) | 1.28e-06*   |
| DG(34:3)_[M+H-H2O]1+                                     | 573.488  |   | -0.04 (-0.05, -0.02) | 2.66e-05*   |
| PC(32:1)_[M+H]1+ / PE(35:1)_[M+H]1+ / PA(37:2)_[M+NH4]1+ | 732.5541 |   | -0.04 (-0.05, -0.02) | 1.22e-04*   |
| PE(40:7)_[M-H]1-   | 788.5236 | - | -0.04 (-0.05, -0.02) | 1.62e-04*   |
| PI(38:1)_[M-H]1-   | 891.5967 |   | -0.04 (-0.05, -0.02) | 1.26e-06*   |
| PC(32:1)_[M+OAc]1-                                       | 790.5602 | - | -0.04 (-0.06, -0.02) | 5.81e-05*   |
| LPC(16:1)_[M+H]1+ / LPE(19:1)_[M+H]1+                    | 494.3245 |   | -0.05 (-0.06, -0.03) | 3.60e-11*** |
| CE(16:1)_[M+NH4]1+                                       | 640.6024 |   | -0.05 (-0.07, -0.03) | 2.46e-08**  |
| FA(16:1)_[M-H]1-   | 253.2174 | - | -0.07 (-0.10, -0.05) | 5.80e-10*** |
| Cer(42:11)_[M+OAc]1-                                     | 688.4947 |   | -0.08 (-0.12, -0.04) | 4.20e-05*   |

Lipid

Beta (95% CI) for SCD (rs603424, chr10:102075479)

# (t) *SCD*

Lipid



#### (u) SGPP1

# (v) *SPTLC3*

Lipid

| name   | m/z                                  | Beta (95% CI)        | P-value     |
|--|--------------------------------------|----------------------|-------------|
|  |                                      |                      |             |
| SM(33:1)_[M-CH3]1-   | 673.5291                             | -0.04 (-0.05, -0.02) | 8.58e-09**  |
| SM(38:1)_[M+CH3]1-   | 743.6075                             | -0.04 (-0.05, -0.03) | 1.17e-10*** |
| SM(41:2)_[M+H]1+   | 799.6685                             | -0.04 (-0.05, -0.03) | 1.96e-10*** |
| SM(38:1)_[M+H]1+   | 759.6372                             | -0.05 (-0.06, -0.03) | 1.95e-17*** |
| SM(32:1)_[M-CH3]1-   | 659.5135                             | -0.05 (-0.06, -0.03) | 1.31e-14*** |
| SM(38:0)_[M+H]1+   | 761.6532                             | -0.05 (-0.06, -0.03) | 2.01e-11*** |
| SM(32:1)_[M+H]1+   | 675.5434                             | -0.05 (-0.06, -0.04) | 2.67e-20*** |
| SM(37:1)_[M+H]1+   | 745.6216                             | -0.07 (-0.09, -0.06) | 4.02e-29*** |
| SM(37:1)_[M-CH3]1-   | 729.5917                             | -0.07 (-0.09, -0.06) | 3.67e-21*** |
| SM(39:1)_[M-CH3]1-   | 757.623                              | -0.08 (-0.09, -0.06) | 1.72e-22*** |
| Cer(40:1)_[M-H]1-  | 620.5987                             | -0.08 (-0.10, -0.06) | 9.77e-20*** |
| SM(39:1)_[M+H]1+   | 773.6531                             | -0.08 (-0.10, -0.07) | 1.66e-30*** |
| Cer(42:0)_[M-H]1-  | 650.6457                             | -0.08 (-0.10, -0.06) | 8.19e-17*** |
| Cer(41:1)_[M-H]1-  | 634.6144                             | -0.09 (-0.11, -0.07) | 2.09e-17*** |
| SM(43:2)_[M-CH3]1-   | 811.67                               | -0.09 (-0.11, -0.07) | 1.09e-20*** |
| Cer(40:2)_[M-H]1-  | 618.5831                             | -0.09 (-0.12, -0.07) | 1.31e-16*** |
| Cer(41:2)_[M-H]1-  | 632.5987                             | -0.11 (-0.13, -0.08) | 2.81e-18*** |
| PC-O(36:1)_[M+H]1+ / PE-O(39:1)_[M+H]1+ / PC-P(36:0)_[M+H]1+ | 774.6376                             | -0.11 (-0.13, -0.09) | 1.80e-21*** |
| Cer(40:0)_[M-H]1-  | 622.6144                             | -0.12 (-0.14, -0.09) | 7.97e-20*** |
| Cer(41:0)_[M-H]1-  | 636.6301 -                           | -0.13 (-0.16, -0.10) | 1.95e-17*** |
|  |                                      |                      |             |
|  |                                      |                      |             |
|  | 4321 0 .1 .2 .3 .4                   | t.                   |             |
| Beta (95% CI) fo   | or SPTLC3 (rs438568, chr20:12958687) |                      |             |

Lipid



Lipid

Beta (95% CI) for UGT8 (rs28870381, chr4:115478499)

#### (w) *UGT8*

Lipid

#### (x) *XBP1*

|  | Lipia      |                      |             |
|--|------------|----------------------|-------------|
| name   | m/z        | Beta (95% CI)        | P-value     |
| PC(36:2)_[M+H]1+ / PE(39:2)_[M+H]1+ / PA(41:3)_[M+NH4]1+ | 786.6012   | -0.05 (-0.08, -0.02) | 3.60e-04*   |
| PC-O(39:1)_[M+H]1+ / PE-P(39:0)_[M+H]1+                  | 816.6845 - | -0.09 (-0.14, -0.04) | 1.10e-04*   |
| SM(36:1)_[M+H]1+   | 731.6062 - | -0.10 (-0.15, -0.05) | 8.79e-05*   |
| SM(32:1)_[M-CH3]1-                                       | 659.5135 - | -0.10 (-0.15, -0.05) | 1.60e-04*   |
| SM(34:1)_[M+H]1+   | 703.5747 - | -0.10 (-0.15, -0.05) | 1.79e-05*   |
| SM(32:1)_[M+H]1+   | 675.5434 - | -0.11 (-0.16, -0.06) | 2.68e-05*   |
| SM(34:2)_[M+H]1+   | 701.5593   | -0.12 (-0.17, -0.07) | 6.63e-06*   |
| SM(42:1)_[M+OAc]1-                                       | 873.7067 - | -0.12 (-0.18, -0.05) | 4.32e-04*   |
| SM(40:0)_[M+OAc]1-                                       | 847.6911 - | -0.12 (-0.18, -0.05) | 2.79e-04*   |
| SM(42:0)_[M+OAc]1-                                       | 875.7224   | -0.12 (-0.19, -0.06) | 2.83e-04*   |
| PC-O(34:3)_[M+H]1+ / PE-P(37:2)_[M+H]1+                  | 742.5748   | -0.13 (-0.20, -0.06) | 3.46e-04*   |
| SM(41:2)_[M+H]1+   | 799.6685 — | -0.13 (-0.19, -0.07) | 1.17e-05*   |
| SM(34:0)_[M+H]1+   | 705.5906 - | -0.13 (-0.18, -0.08) | 5.05e-07*   |
| SM(41:1)_[M+H]1+   | 801.6844 - | -0.13 (-0.19, -0.07) | 1.03e-05*   |
| PC-O(36:3)_M+H]1+ / PC-P(36:2)_M+H]1+                    | 770.6063 - | -0.15 (-0.21, -0.08) | 7.02e-06*   |
| PC(35:1)_[M+H]1+ / PE(38:1)_[M+H]1+ / PA(40:2)_[M+NH4]1+ | 774.6009   | -0.17 (-0.24, -0.10) | 1.19e-06*   |
| SM(39:1)_[M+H]1+   | 773.6531   | -0.18 (-0.24, -0.11) | 7.14e-08*   |
| PC(35:2)_[M+H]1+ / PE(38:2)_[M+H]1+ / PA(40:3)_[M+NH4]1+ | 772.5856   | -0.18 (-0.25, -0.12) | 5.71e-08*   |
| LPC(17:0)_[M+H]1+ / LPE(20:0)_[M+H]1+                    | 510.356    | -0.22 (-0.33, -0.12) | 3.26e-05*   |
| SM(37:1) [M+H]1+   | 745.6216   | -0.23 (-0.30, -0.16) | 2.67e-11*** |

Beta (95% CI) for XBP1 (rs71661463, chr22:29339470)

Forest plots showing the association of the top 20 most significantly associated lipids in PROMIS with the lead variant in each significant locus from the conditional analyses. **Note:** \* = P < 0.001;  $** = P < 5 \times 10^{-8}$ ;  $*** = P < 8.9 \times 10^{-10}$ .



**Supplementary Figure 8.** Comparison of genetic associations with lipids pre- and post-adjustment for clinical lipid measures

Comparison of  $-\log_{10} P$ -values in PROMIS from conditional analyses (pre-adjustment) and after adjustment for several clinical lipid measures (total cholesterol, HDL cholesterol, and triglycerides). Association estimates are shown coloured by (a) lipid subclass and (b) genetic locus.