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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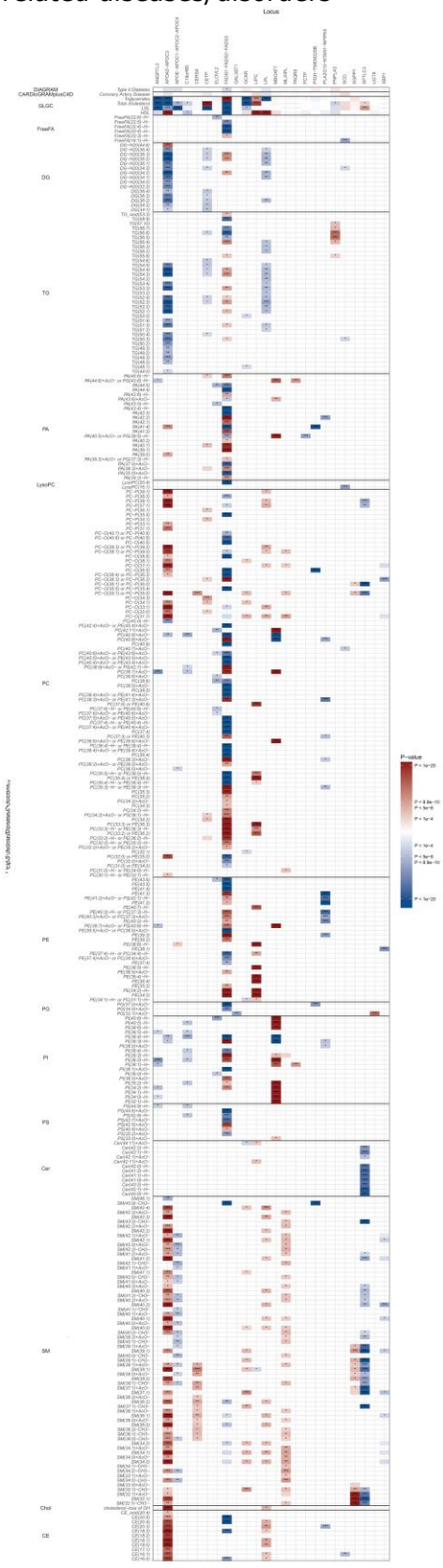
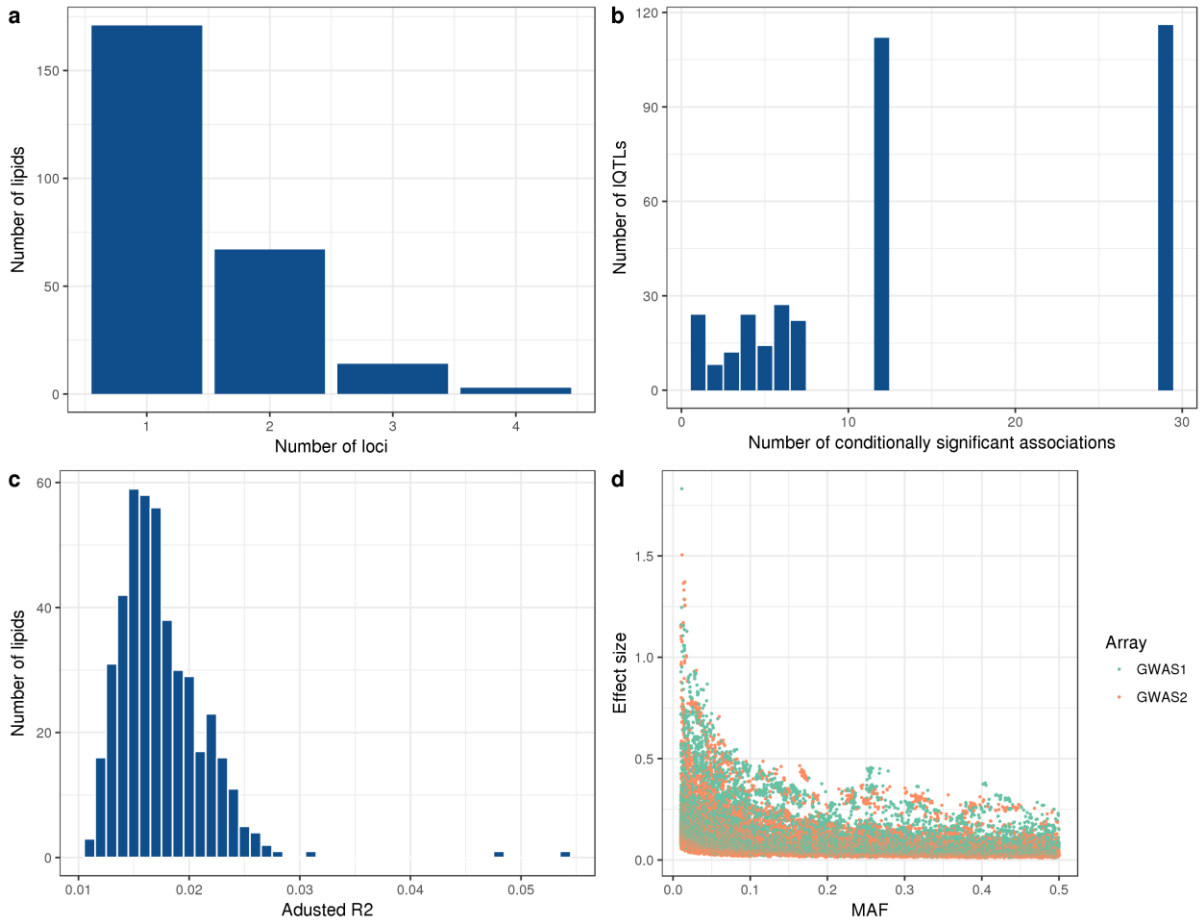
SUPPLEMENTARY FIGURES

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



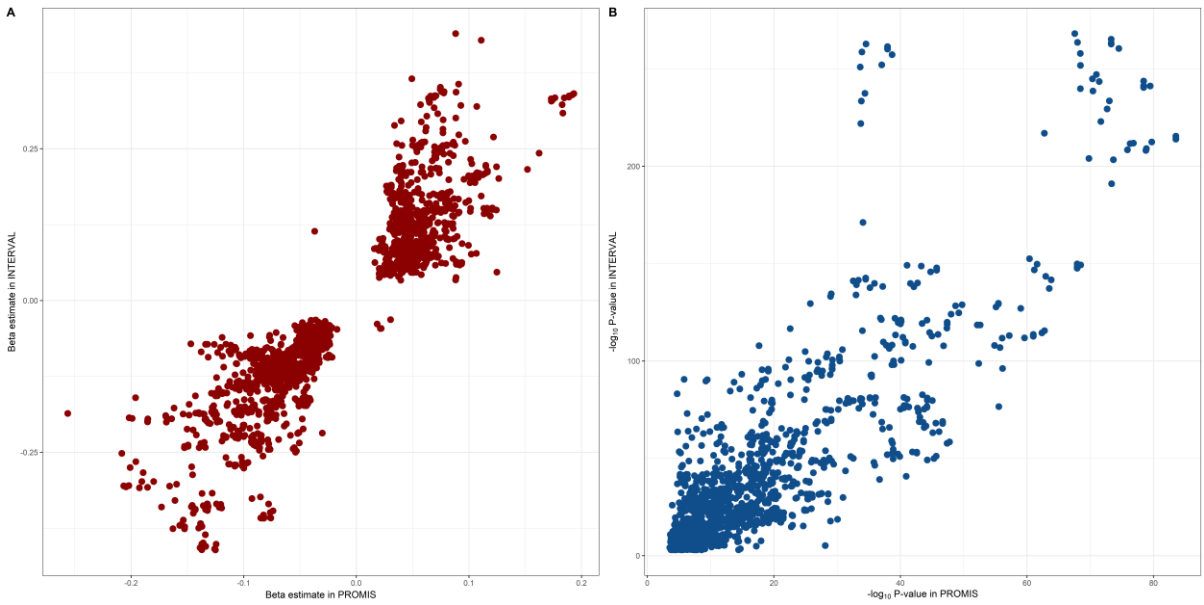
Caption for Supplementary Figure 1 (previous page):
The effect estimates of the associations between significant variants with all lipid metabolites in PROMIS are plotted as a heat map. Results are shown for the association of all lipid metabolites (rows) with the most strongly associated genetic variant 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



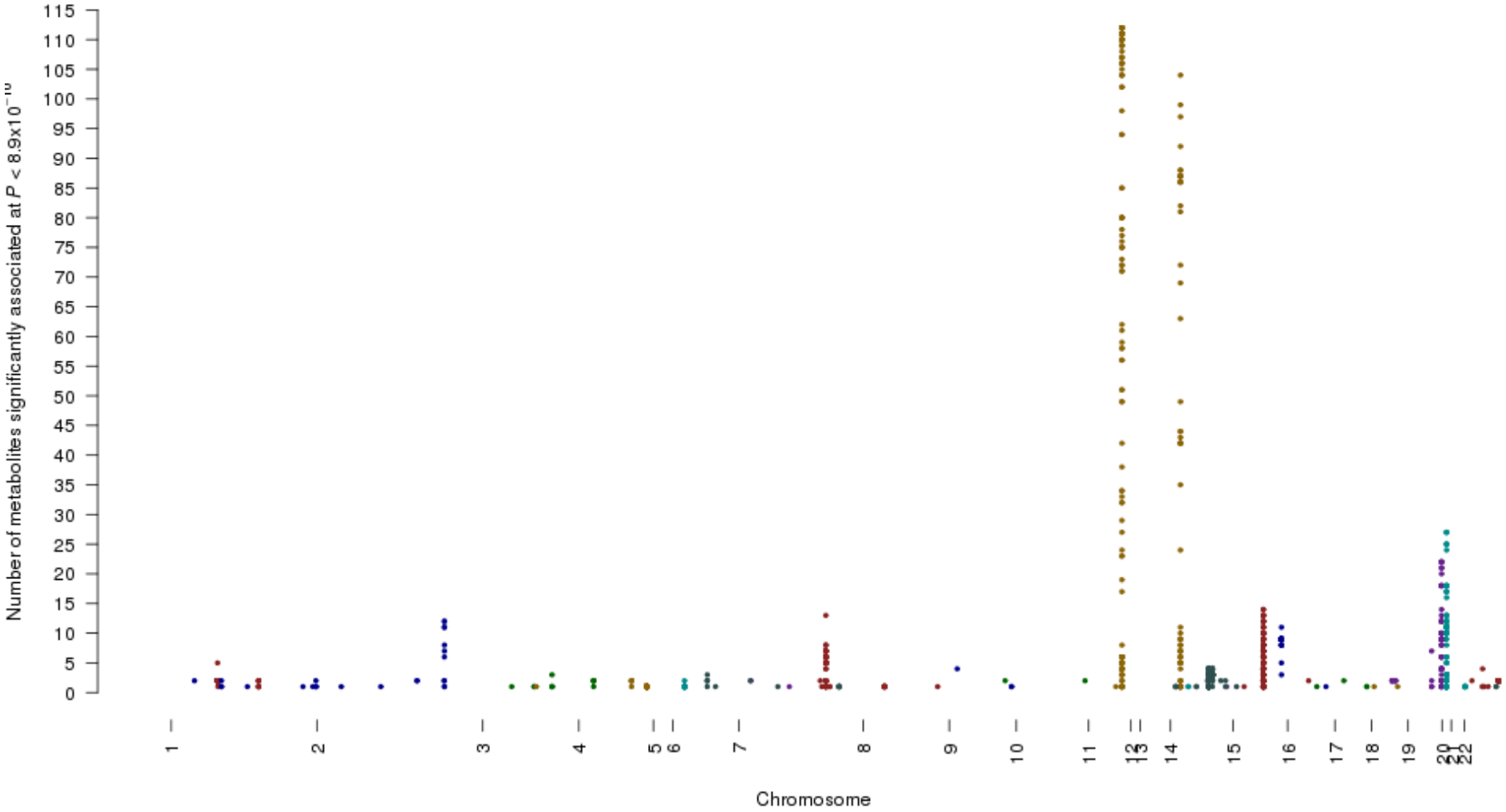
n = 5,662 participants from PROMIS. (a) Number of significantly associated loci per lipid. (b) Number of conditionally significant associations within each lipid QTL. (c) Histogram of variance explained by conditionally independent variants. (d) Effect size versus MAF.

Supplementary Figure 3. Comparison of associations in PROMIS and INTERVAL



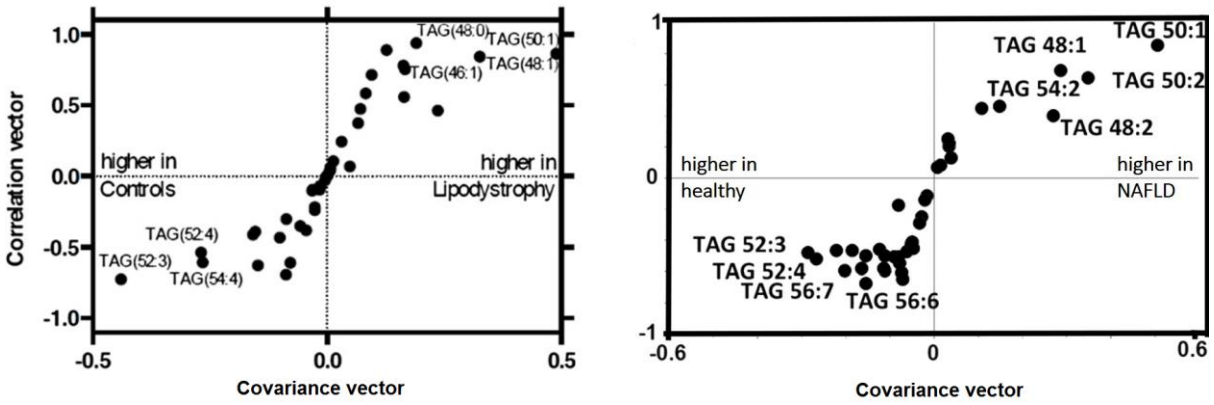
(a) Beta estimates in INTERVAL vs PROMIS. (b) $-\log_{10}$ *P*-values in INTERVAL vs PROMIS.

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



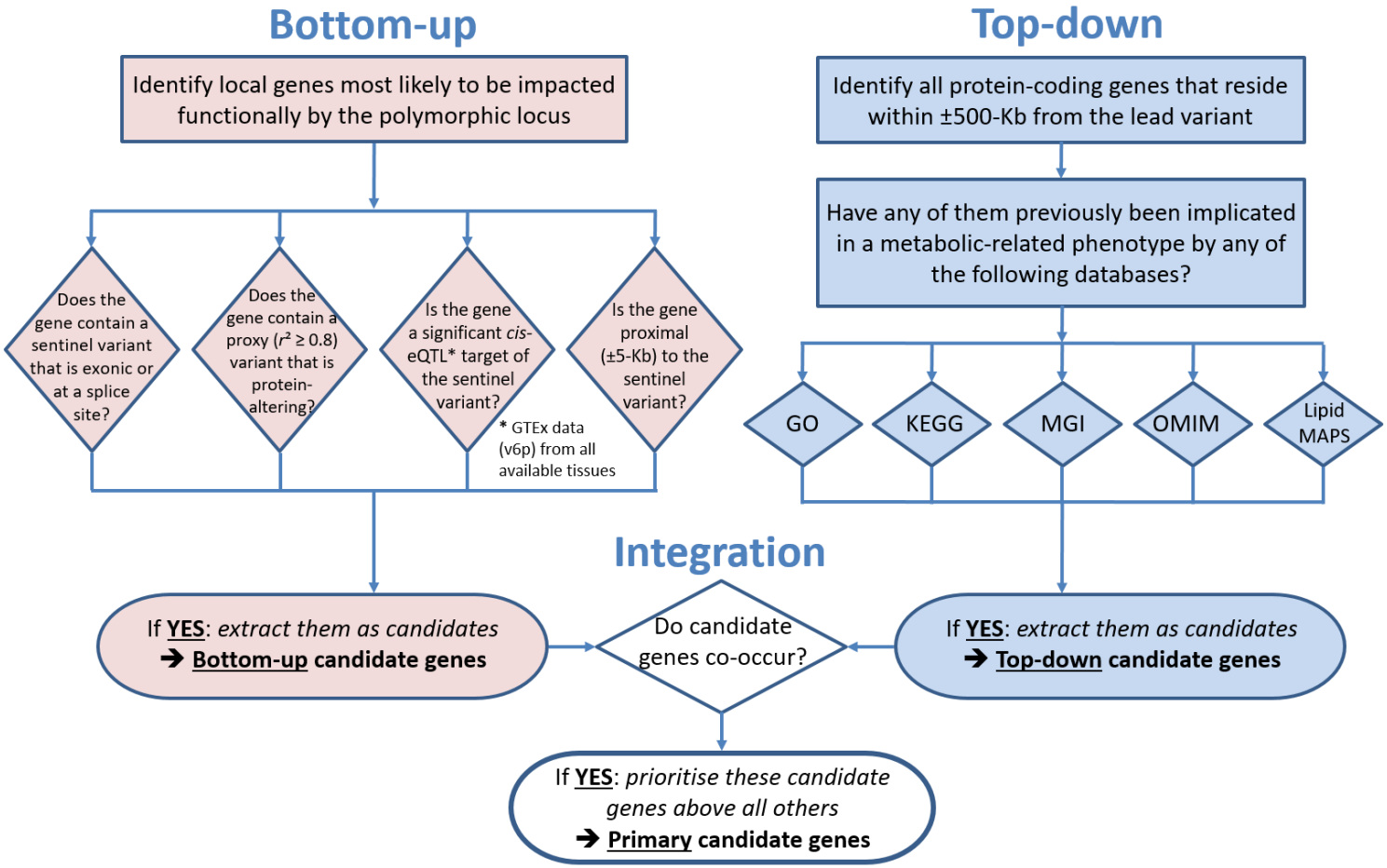
Results are shown for the number of lipids in PROMIS associated with each variant at genome-wide significance ($P < 8.9 \times 10^{-10}$).

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.

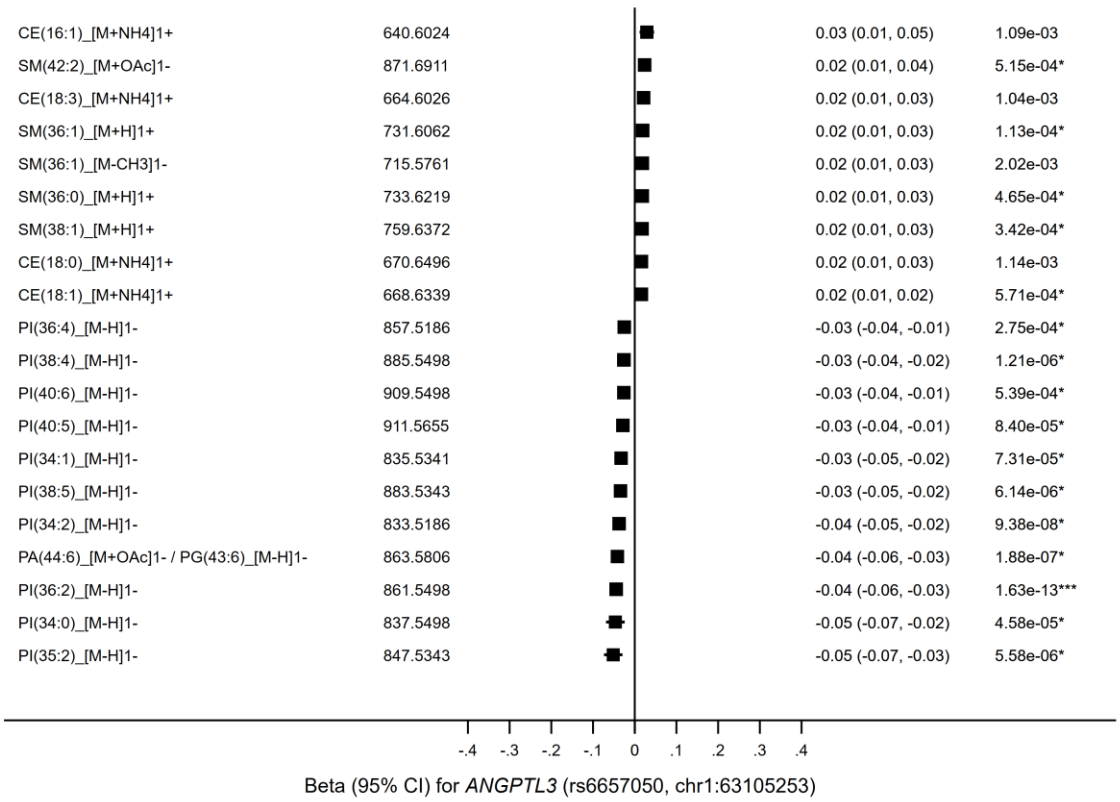
Supplementary Figure 6. Flow diagram outlining strategy for mediating gene prioritisation



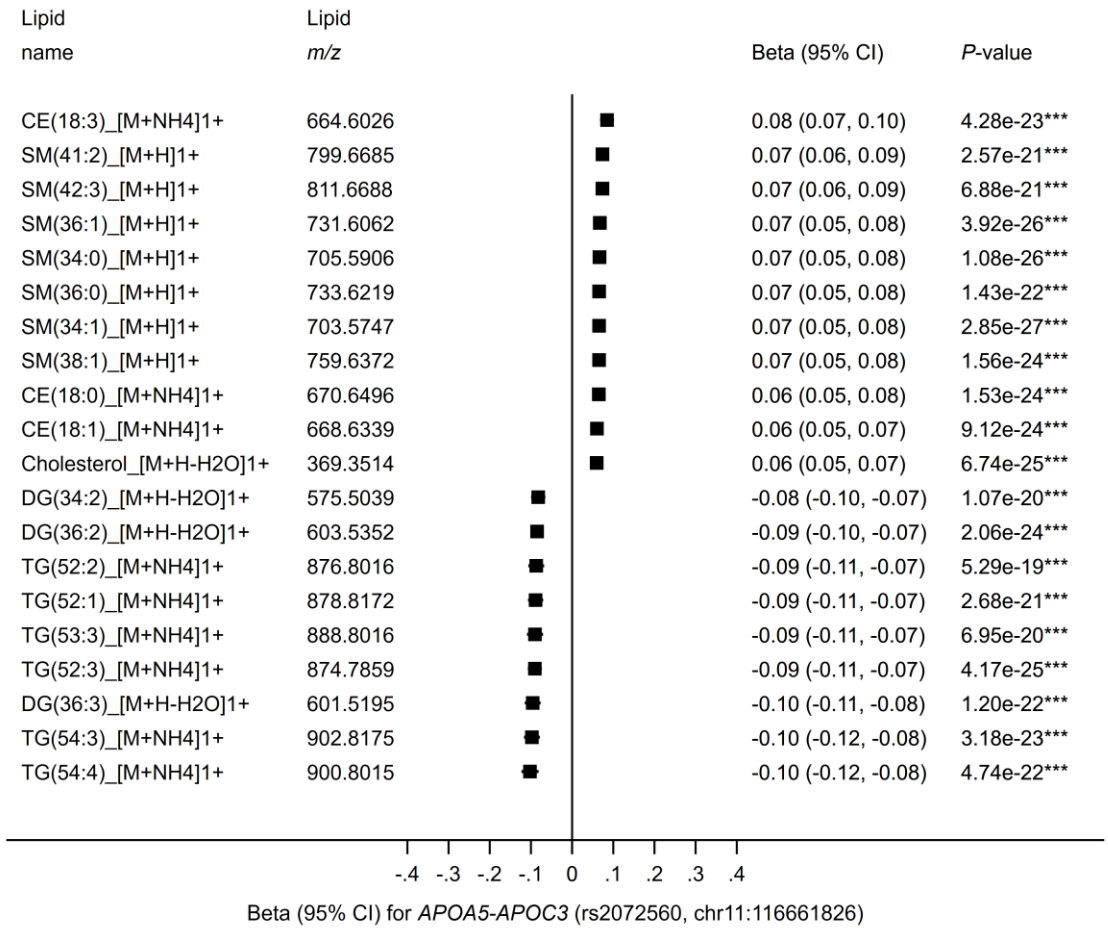
The flow diagram shows how the "bottom-up" and "top-down" approaches were used and then integrated to identify probable causal genes for each significantly associated variant. A proxy is defined as those variants with $r^2 \geq 0.8$ with the lead (EUR population, 1000 Genomes). **Abbreviations: eQTL** = 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

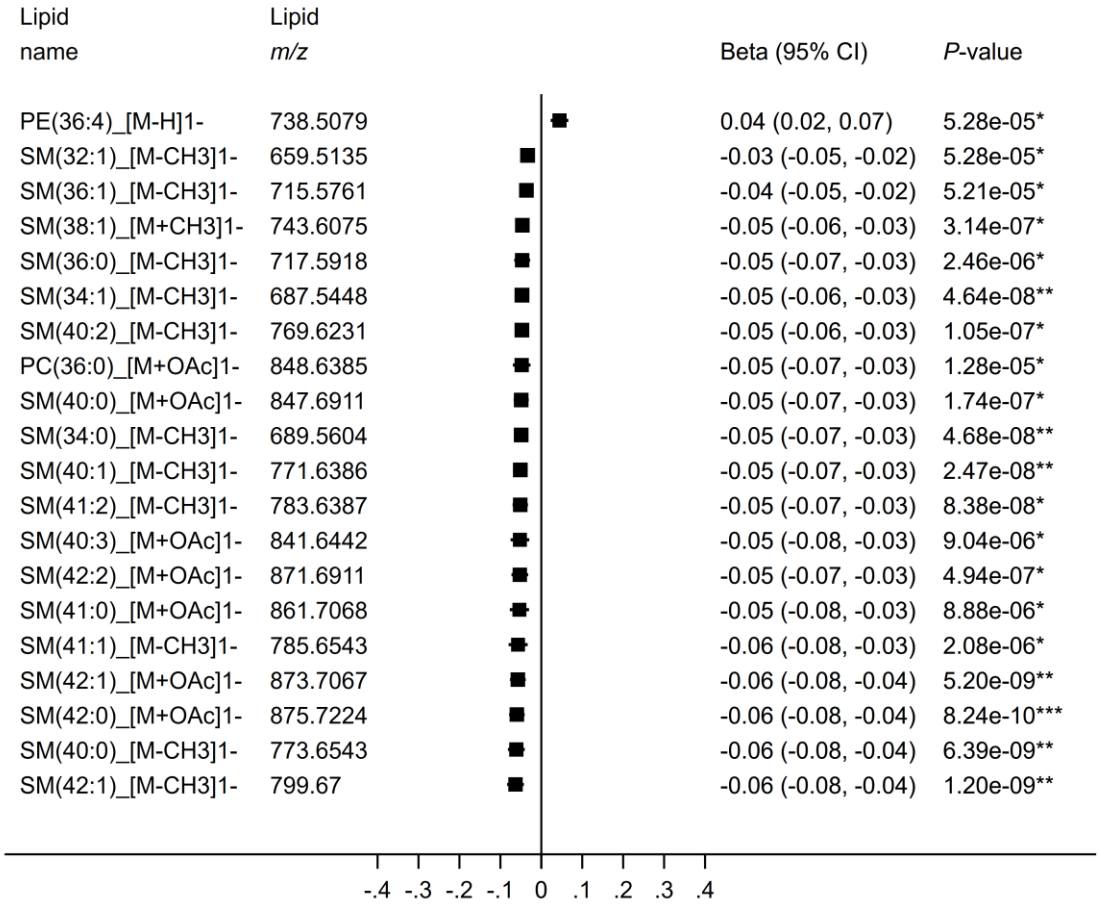
(a) *ANGPTL3*



(b) *APOA5-APOC3*

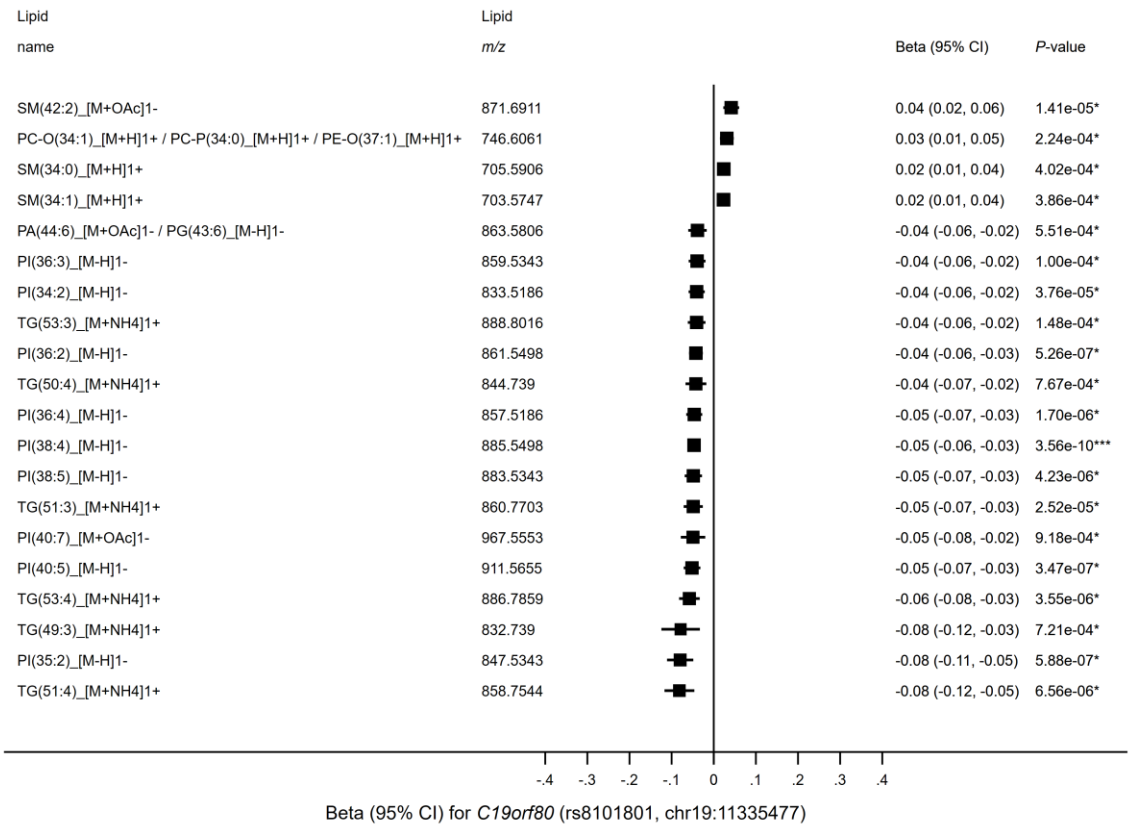


(c) *APOE-APOC1-APOC2-APOC4*



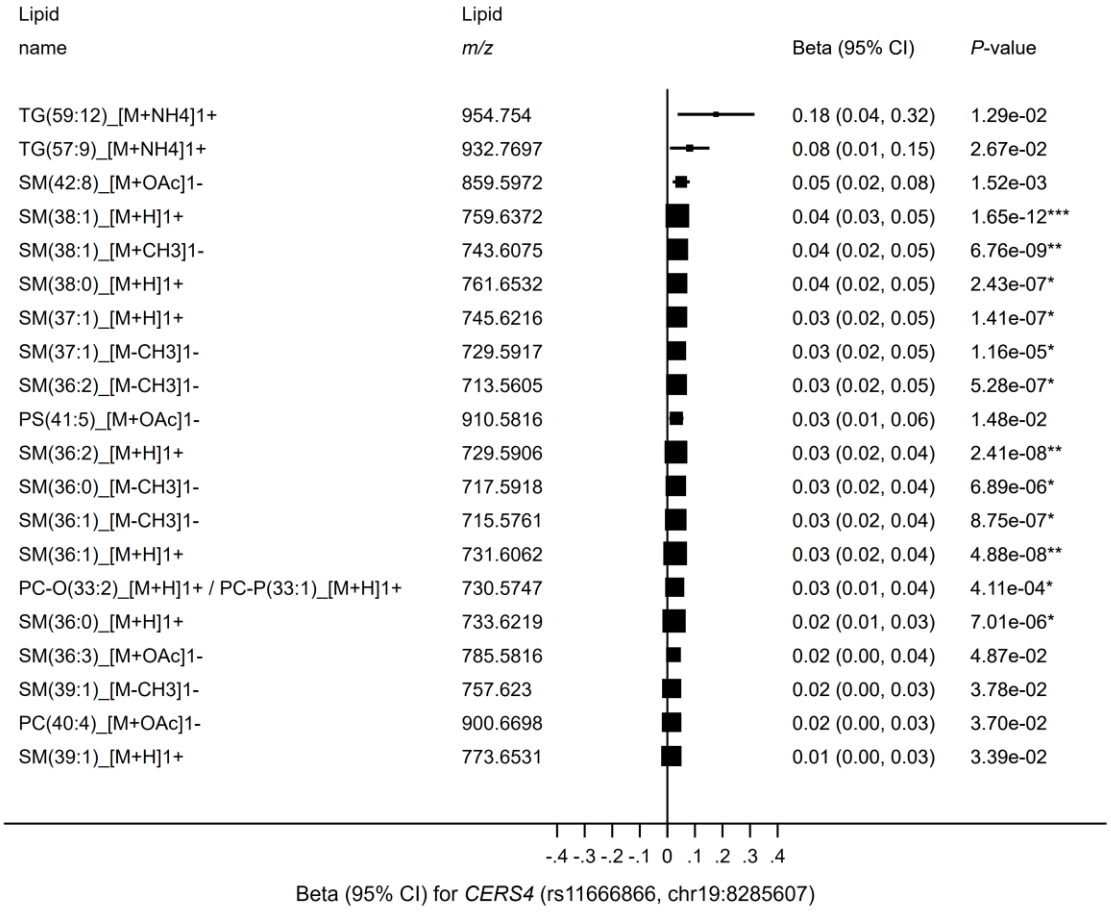
Beta (95% CI) for *APOE-APOC1-APOC2-APOC4* (rs75627662, chr19:45413576)

(d) *C19orf80*

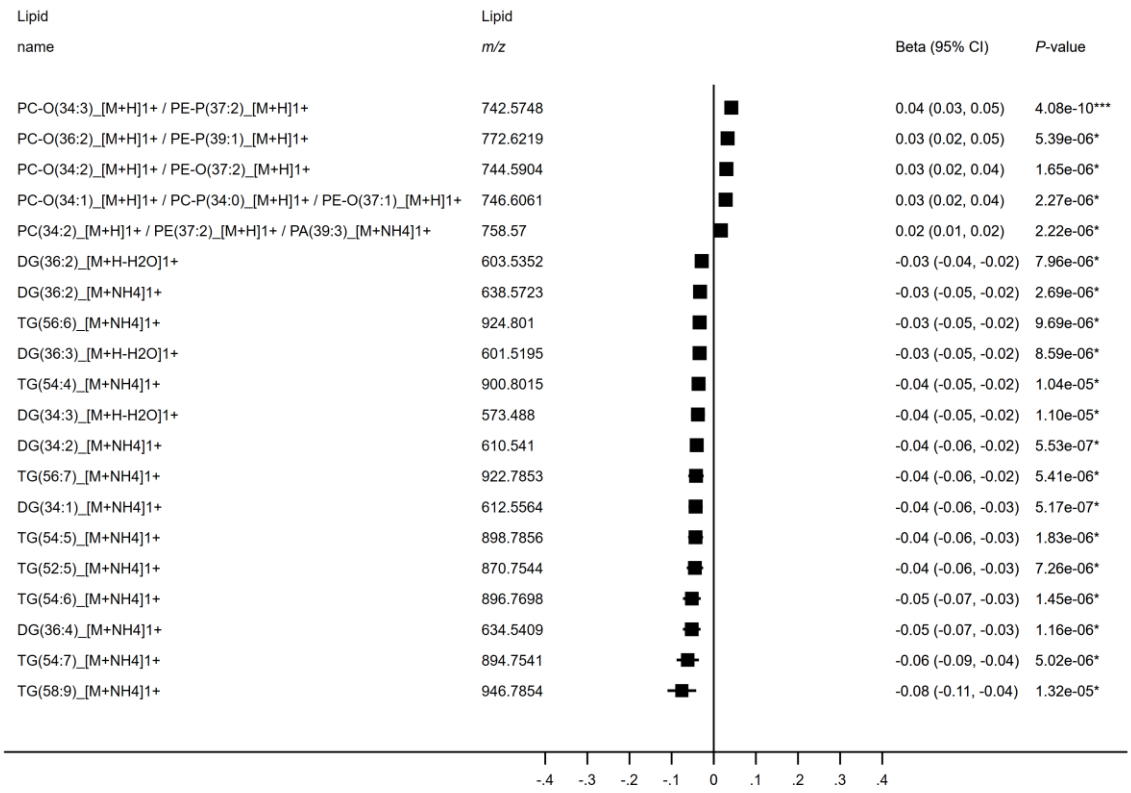


Beta (95% CI) for *C19orf80* (rs8101801, chr19:11335477)

(e) *CERS4*

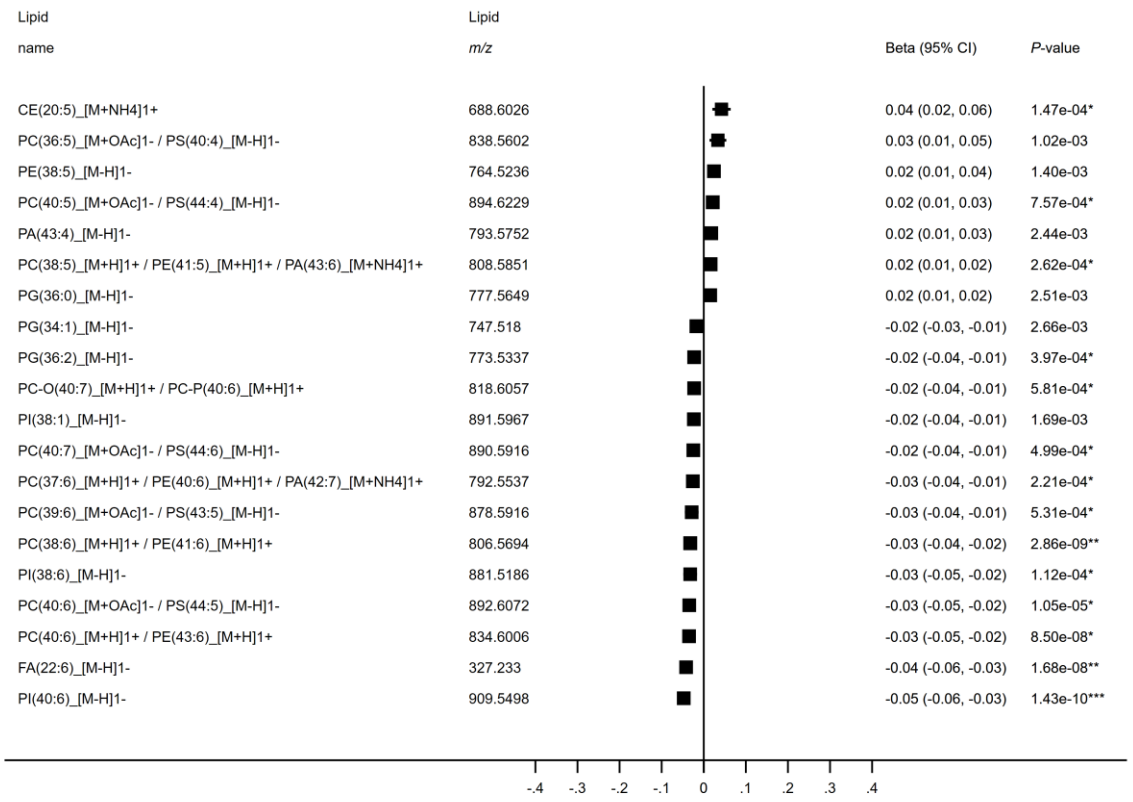

Lipid name
Lipid m/z
Beta (95% CI)
P-value
TG(59:12)_[M+NH4]1+ 954.754 0.18 (0.04, 0.32) 1.29e-02
TG(57:9)_[M+NH4]1+ 932.7697 0.08 (0.01, 0.15) 2.67e-02
SM(42:8)_[M+OAc]1- 859.5972 0.05 (0.02, 0.08) 1.52e-03
SM(38:1)_[M+H]1+ 759.6372 0.04 (0.03, 0.05) 1.65e-12***
SM(38:1)_[M+CH3]1- 743.6075 0.04 (0.02, 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 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 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 0.02 (0.00, 0.03) 3.78e-02
PC(40:4)_[M+OAc]1- 900.6698 0.02 (0.00, 0.03) 3.70e-02
SM(39:1)_[M+H]1+ 773.6531 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*



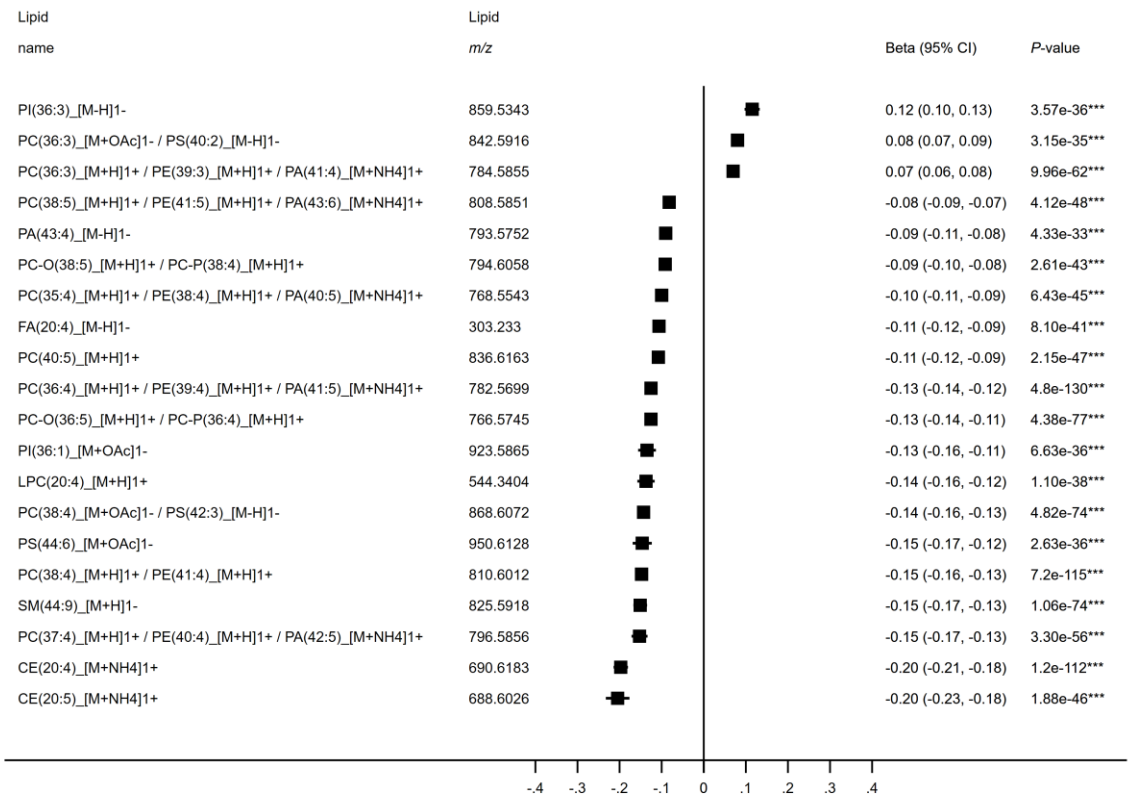
Beta (95% CI) for *CETP* (rs711752, chr16:56996211)

(g) *ELOVL2*



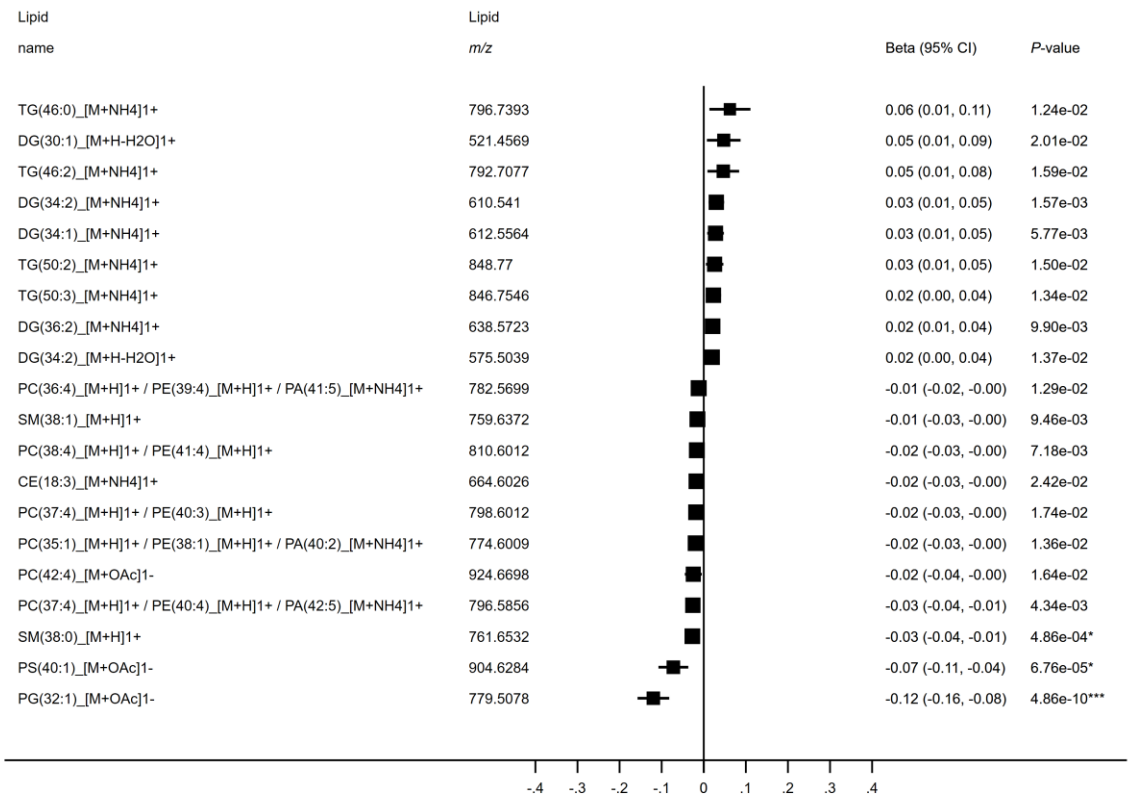
Beta (95% CI) for *ELOVL2* (rs6920155, chr6:11047956)

(h) *FADS1-FADS2-FADS3*



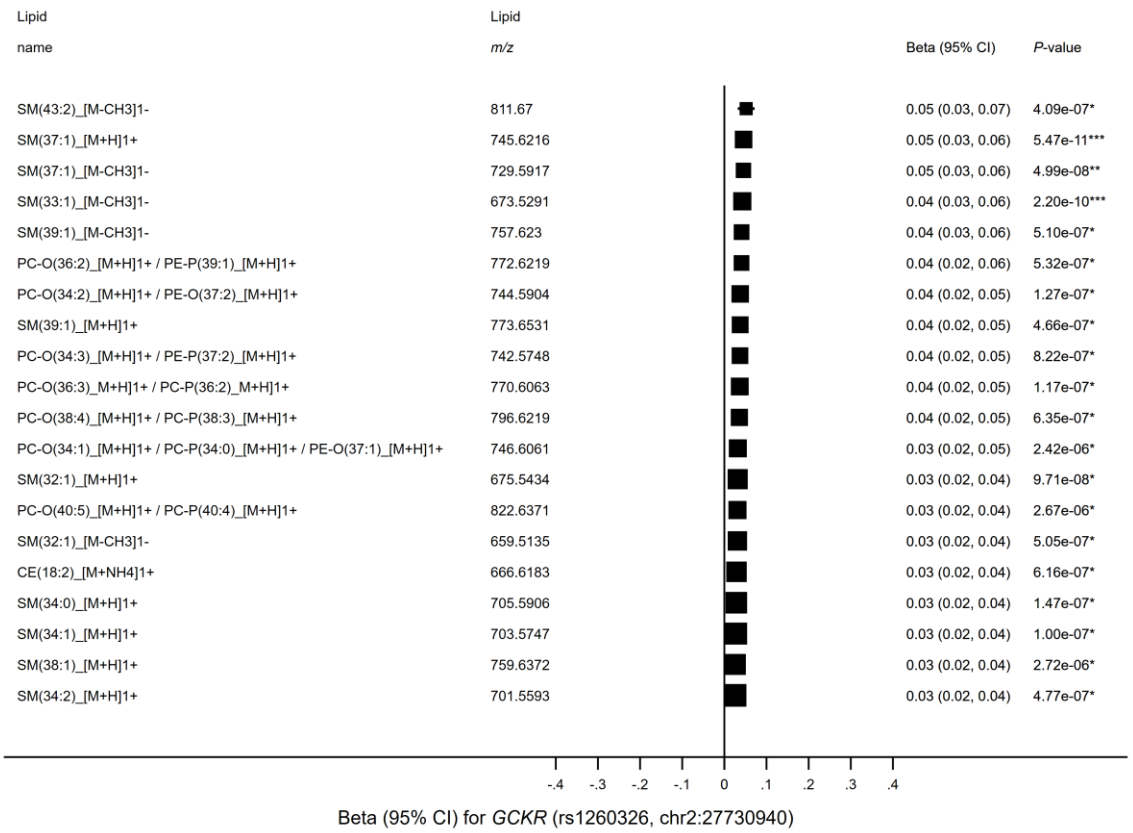
Beta (95% CI) for *FADS1-FADS2-FADS3* (rs174546, chr11:61569830)

(i) *GAL3ST1*

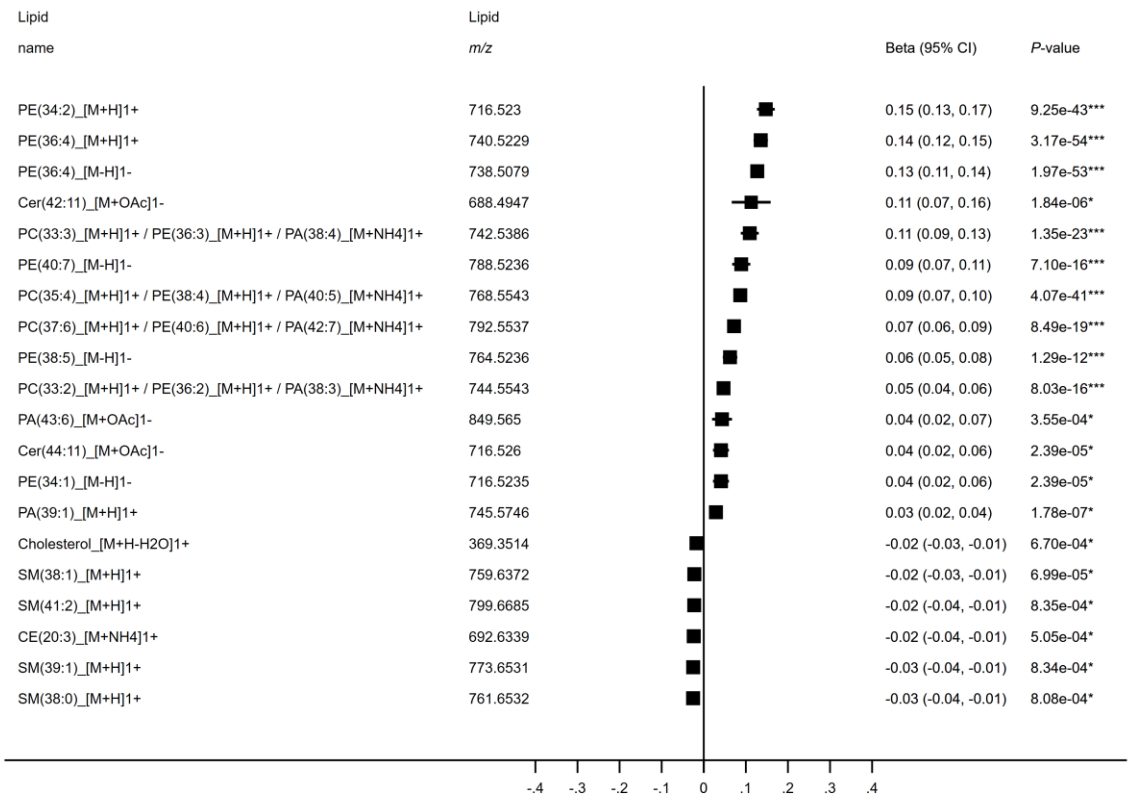


Beta (95% CI) for *GAL3ST1* (rs2267161, chr22:30953295)

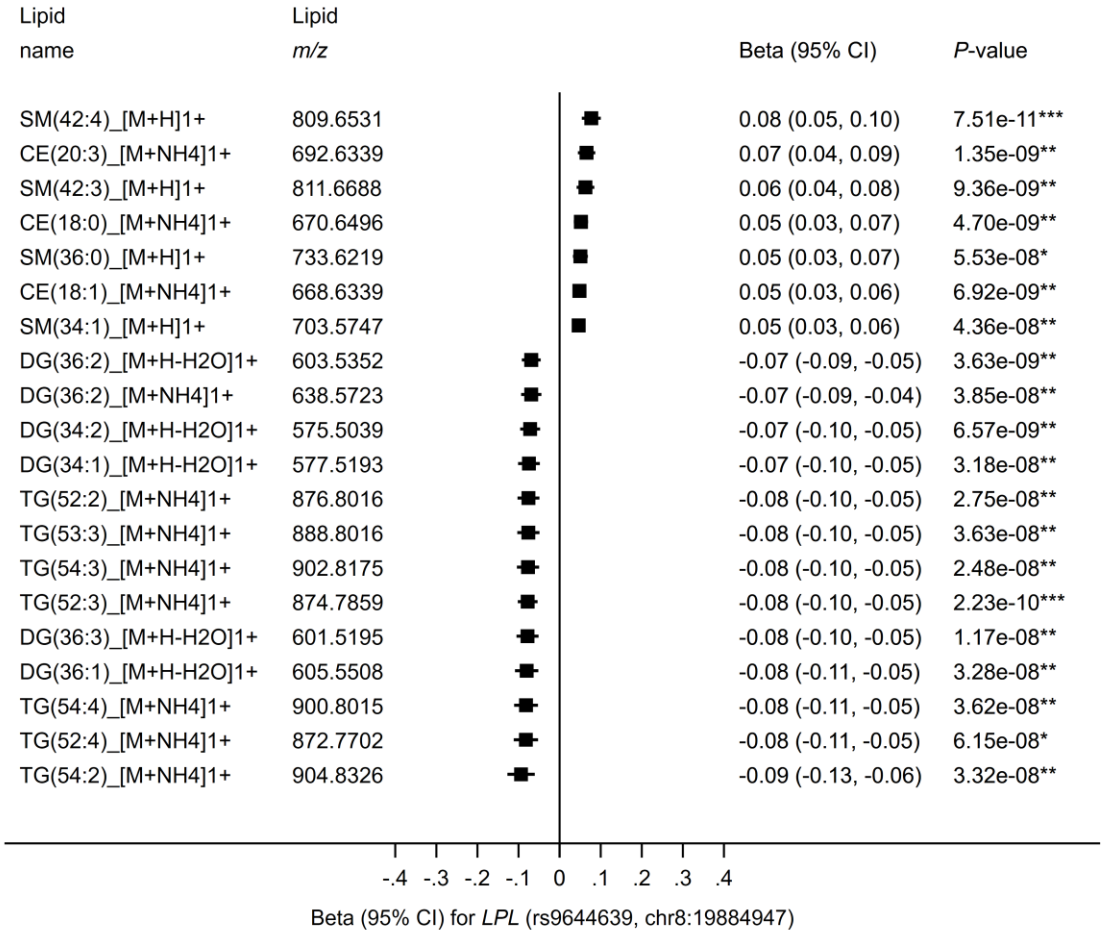
(j) *GCKR*


Lipid name
Lipid m/z
Beta (95% CI)
P-value
SM(43:2)_[M-CH3]1- 811.67 0.05 (0.03, 0.07) 4.09e-07*
SM(37:1)_[M+H]1+ 745.6216 0.05 (0.03, 0.06) 5.47e-11***
SM(37:1)_[M-CH3]1- 729.5917 0.05 (0.03, 0.06) 4.99e-08**
SM(33:1)_[M-CH3]1- 673.5291 0.04 (0.03, 0.06) 2.20e-10***
SM(39:1)_[M-CH3]1- 757.623 0.04 (0.03, 0.06) 5.10e-07*
PC-O(36:2)_[M+H]1+ / PE-P(39:1)_[M+H]1+ 772.6219 0.04 (0.02, 0.06) 5.32e-07*
PC-O(34:2)_[M+H]1+ / PE-O(37:2)_[M+H]1+ 744.5904 0.04 (0.02, 0.05) 1.27e-07*
SM(39:1)_[M+H]1+ 773.6531 0.04 (0.02, 0.05) 4.66e-07*
PC-O(34:3)_[M+H]1+ / PE-P(37:2)_[M+H]1+ 742.5748 0.04 (0.02, 0.05) 8.22e-07*
PC-O(36:3)_M+H]1+ / PC-P(36:2)_M+H]1+ 770.6063 0.04 (0.02, 0.05) 1.17e-07*
PC-O(38:4)_[M+H]1+ / PC-P(38:3)_[M+H]1+ 796.6219 0.04 (0.02, 0.05) 6.35e-07*
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 (0.02, 0.05) 2.42e-06*
SM(32:1)_[M+H]1+ 675.5434 0.03 (0.02, 0.04) 9.71e-08*
PC-O(40:5)_[M+H]1+ / PC-P(40:4)_[M+H]1+ 822.6371 0.03 (0.02, 0.04) 2.67e-06*
SM(32:1)_[M-CH3]1- 659.5135 0.03 (0.02, 0.04) 5.05e-07*
CE(18:2)_[M+NH4]1+ 666.6183 0.03 (0.02, 0.04) 6.16e-07*
SM(34:0)_[M+H]1+ 705.5906 0.03 (0.02, 0.04) 1.47e-07*
SM(34:1)_[M+H]1+ 703.5747 0.03 (0.02, 0.04) 1.00e-07*
SM(38:1)_[M+H]1+ 759.6372 0.03 (0.02, 0.04) 2.72e-06*
SM(34:2)_[M+H]1+ 701.5593 0.03 (0.02, 0.04) 4.77e-07*
-.4 -.3 -.2 -.1 0 .1 .2 .3 .4
Beta (95% CI) for GCKR (rs1260326, chr2:27730940)

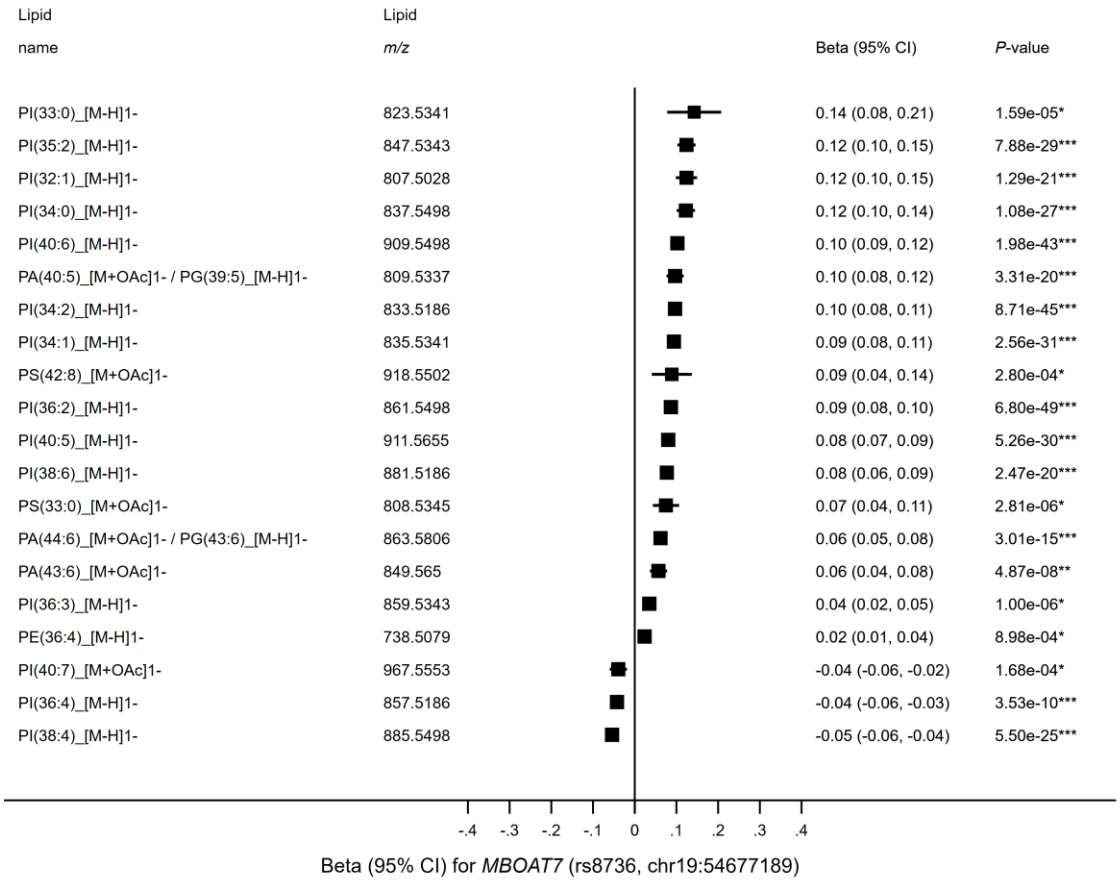
(k) *LIPC*


Lipid name
Lipid m/z
Beta (95% CI)
P-value
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*
-.4 -.3 -.2 -.1 0 .1 .2 .3 .4
Beta (95% CI) for *LIPC* (rs2070895, chr15:58723939)

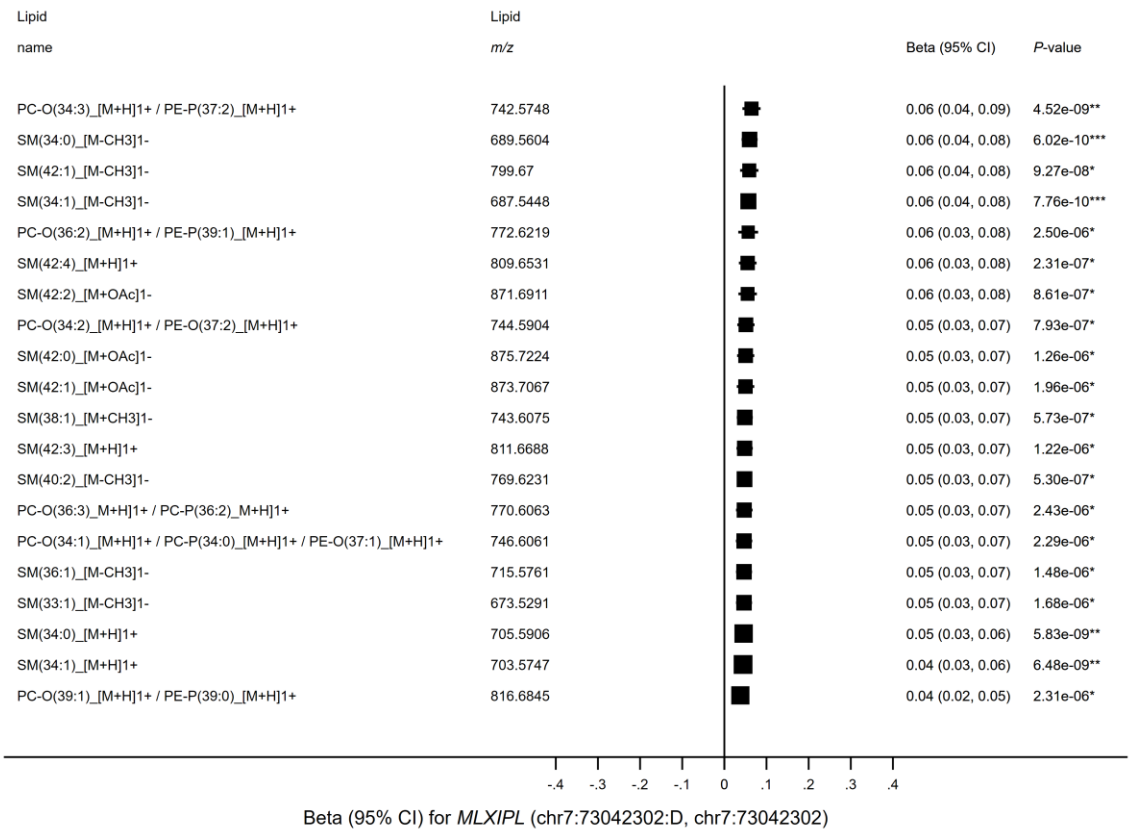
(I) *LPL*


Lipid name
Lipid 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*

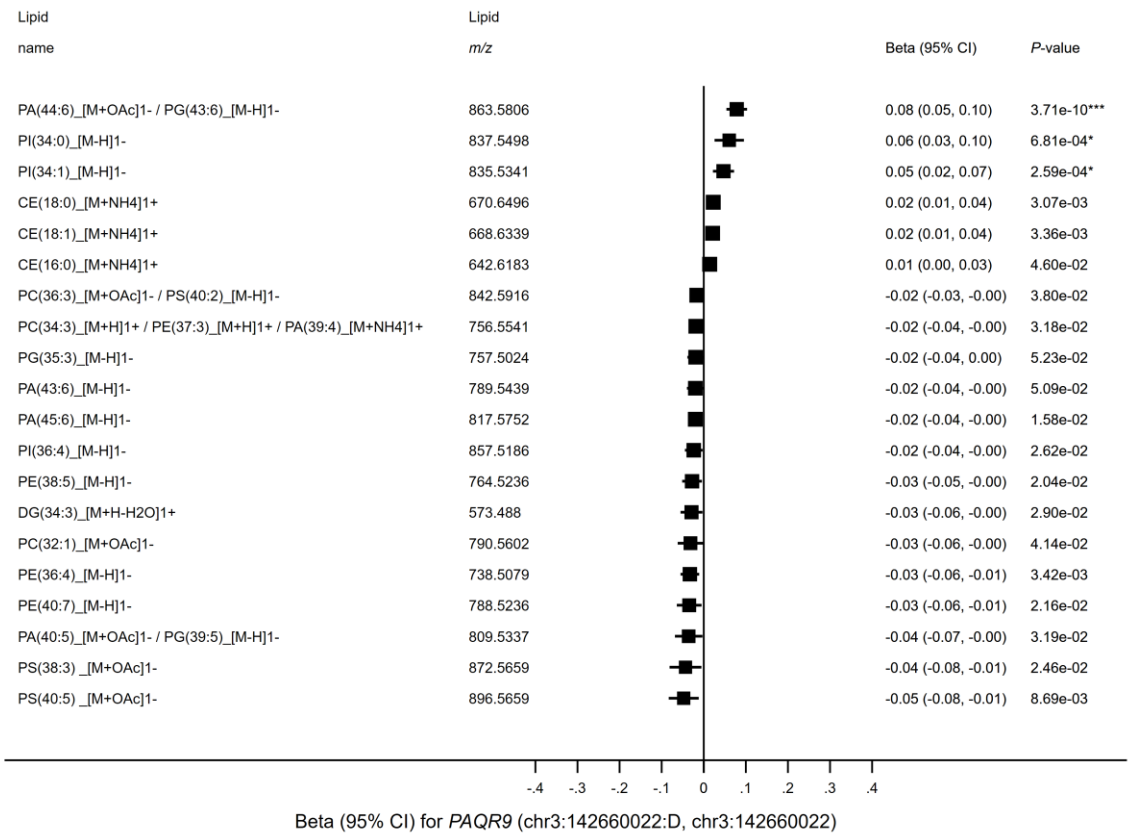

Lipid name
Lipid m/z
Beta (95% CI)
P-value
PI(33:0)_[M-H]1- 823.5341 0.14 (0.08, 0.21) 1.59e-05*
PI(35:2)_[M-H]1- 847.5343 0.12 (0.10, 0.15) 7.88e-29***
PI(32:1)_[M-H]1- 807.5028 0.12 (0.10, 0.15) 1.29e-21***
PI(34:0)_[M-H]1- 837.5498 0.12 (0.10, 0.14) 1.08e-27***
PI(40:6)_[M-H]1- 909.5498 0.10 (0.09, 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)

(n) *MLXIPL*

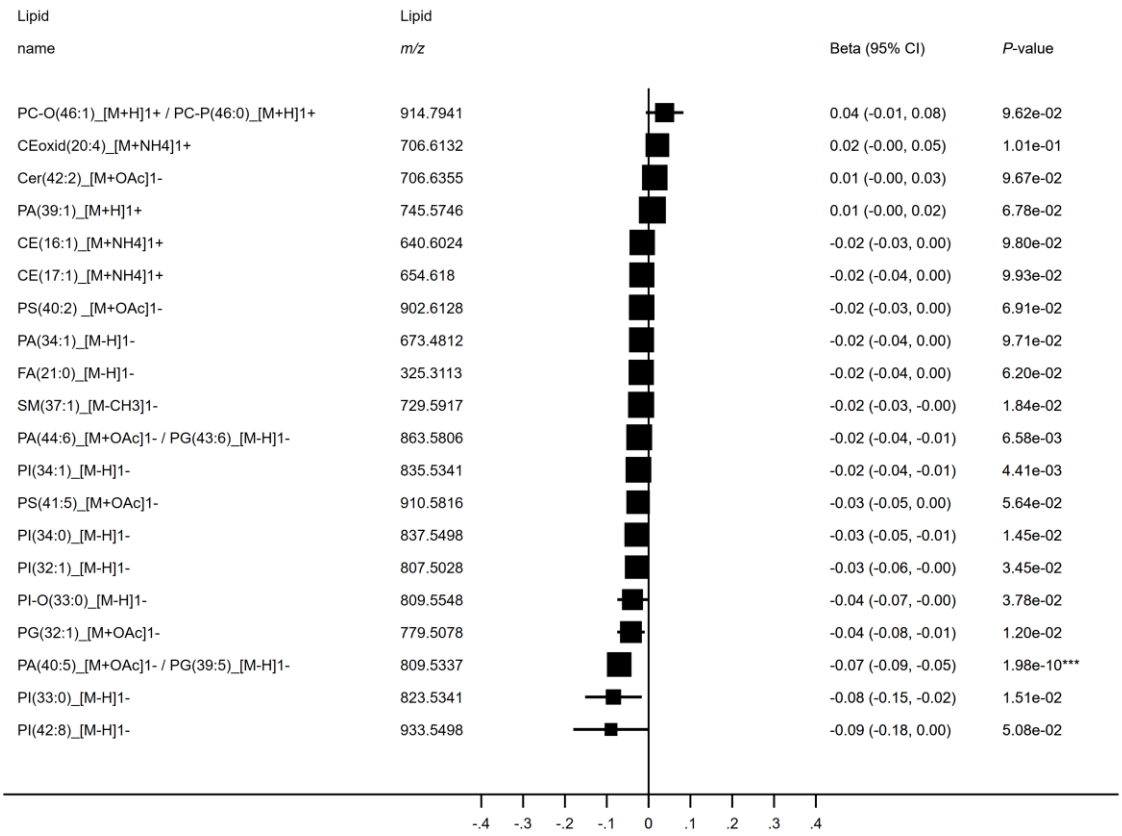


Beta (95% CI) for *MLXIPL* (chr7:73042302:D, chr7:73042302)

(o) *PAQR9*

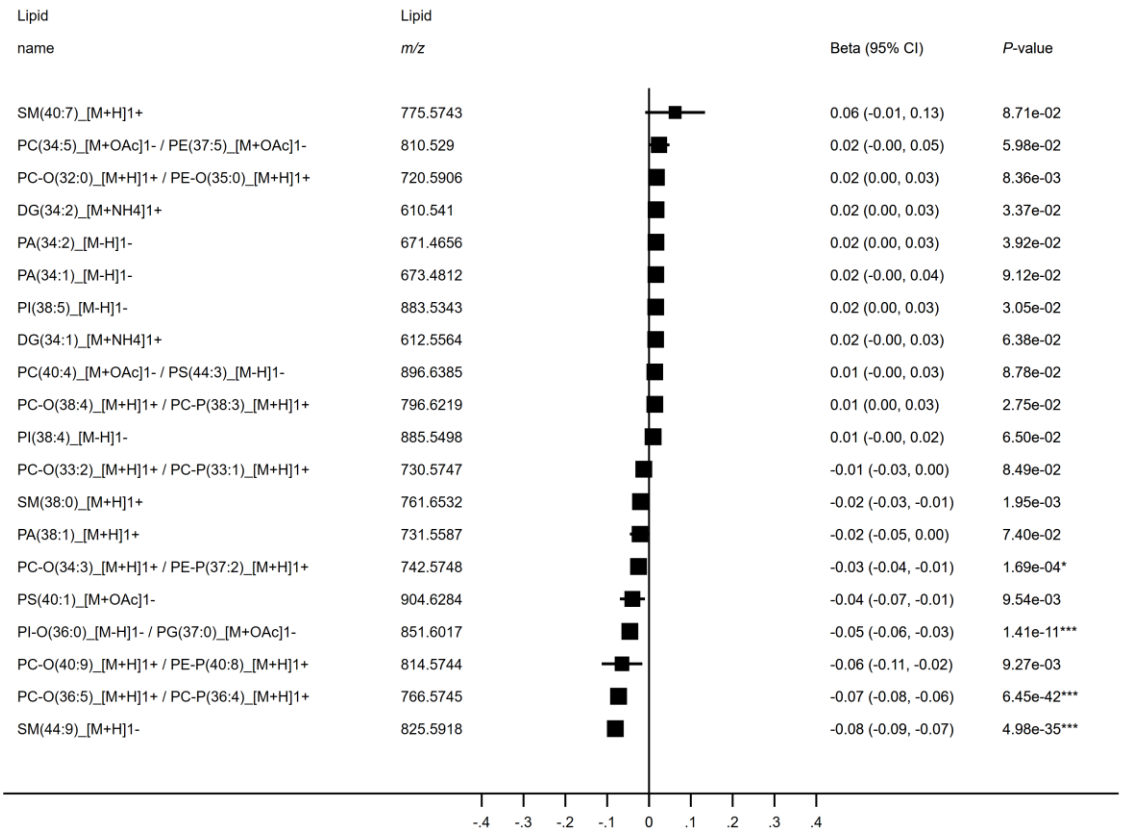

Lipid name
Lipid m/z
Beta (95% CI)
P-value
PA(44:6)_[M+OAc]1- / PG(43:6)_[M-H]1- 863.5806 0.08 (0.05, 0.10) 3.71e-10***
PI(34:0)_[M-H]1- 837.5498 0.06 (0.03, 0.10) 6.81e-04*
PI(34:1)_[M-H]1- 835.5341 0.05 (0.02, 0.07) 2.59e-04*
CE(18:0)_[M+NH4]1+ 670.6496 0.02 (0.01, 0.04) 3.07e-03
CE(18:1)_[M+NH4]1+ 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-02
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-03
-.4 -.3 -.2 -.1 0 .1 .2 .3 .4
Beta (95% CI) for PAQR9 (chr3:142660022:D, chr3:142660022)

(p) *PCTP*



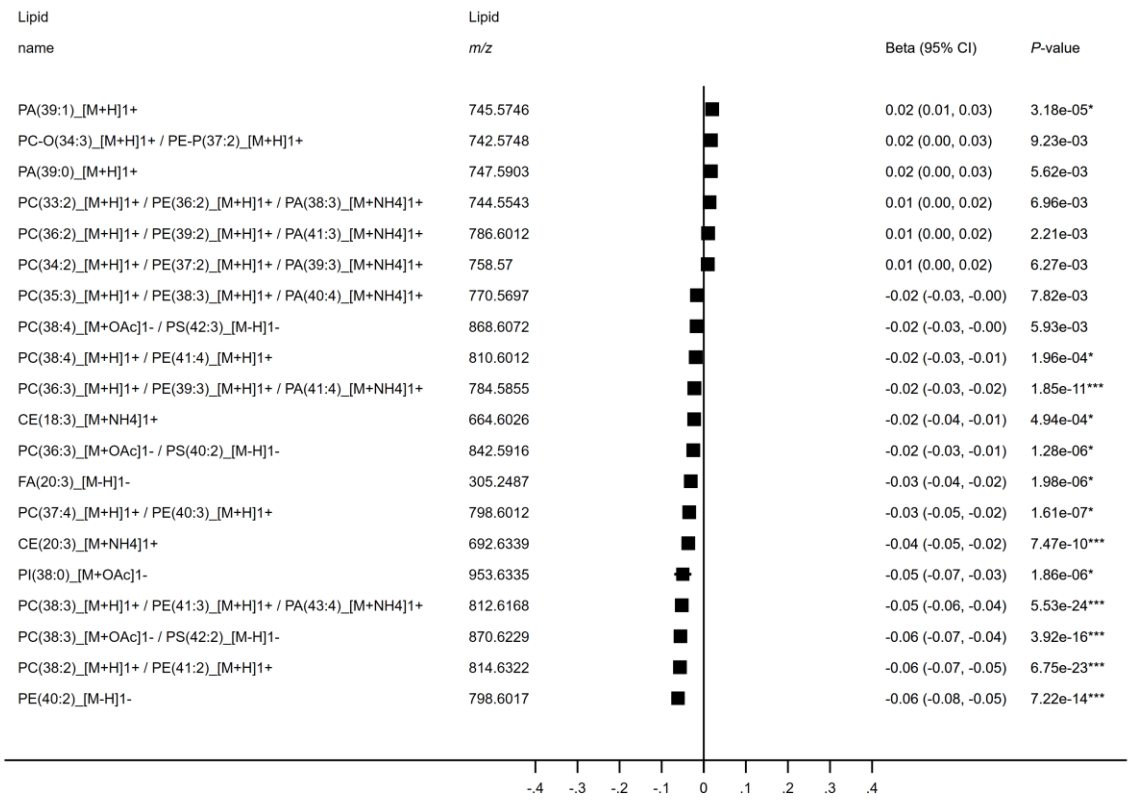
Beta (95% CI) for *PCTP* (rs11079173, chr17:53487664)

(q) *PIGH-TMEM229B*



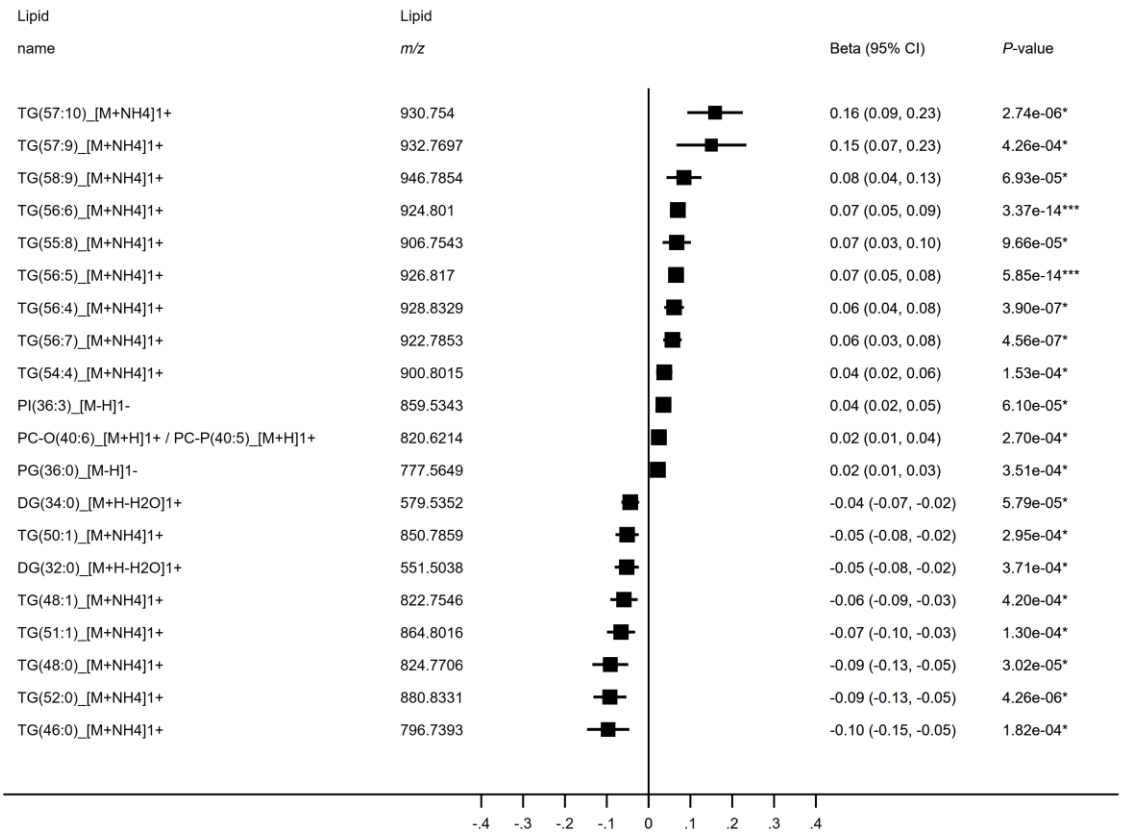
Beta (95% CI) for *PIGH-TMEM229B* (rs1885041, chr14:67976325)

(r) *PLA2G10-NTAN1-NPIPA5*



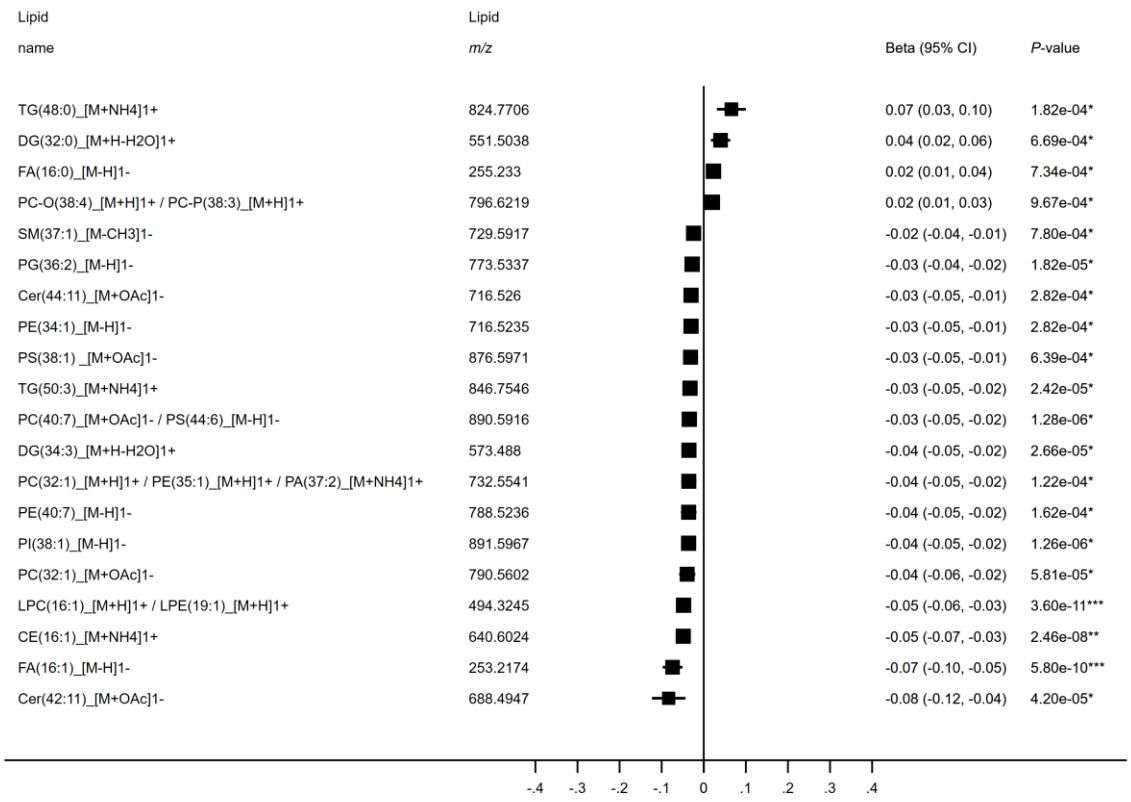
Beta (95% CI) for *PLA2G10-NTAN1-NPIPA5* (rs34955778, chr16:15139594)

(s) *PNPLA3*



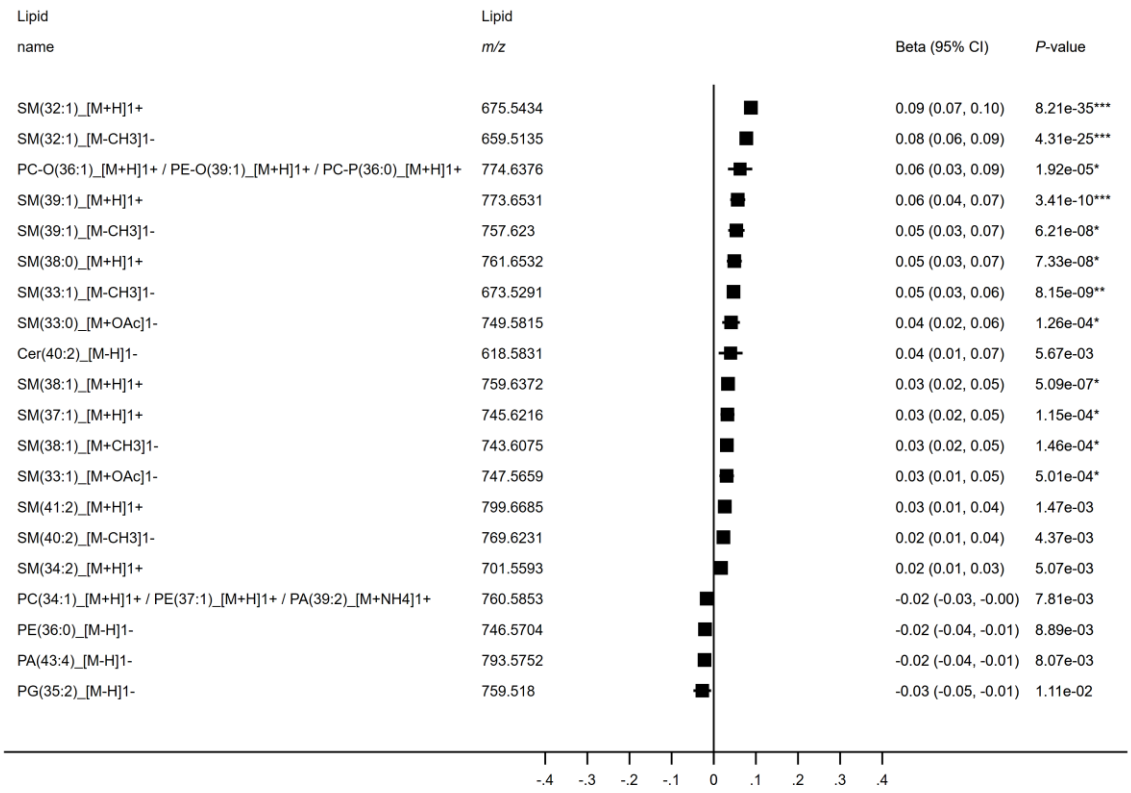
Beta (95% CI) for *PNPLA3* (rs12484809, chr22:44325631)

(t) *SCD*



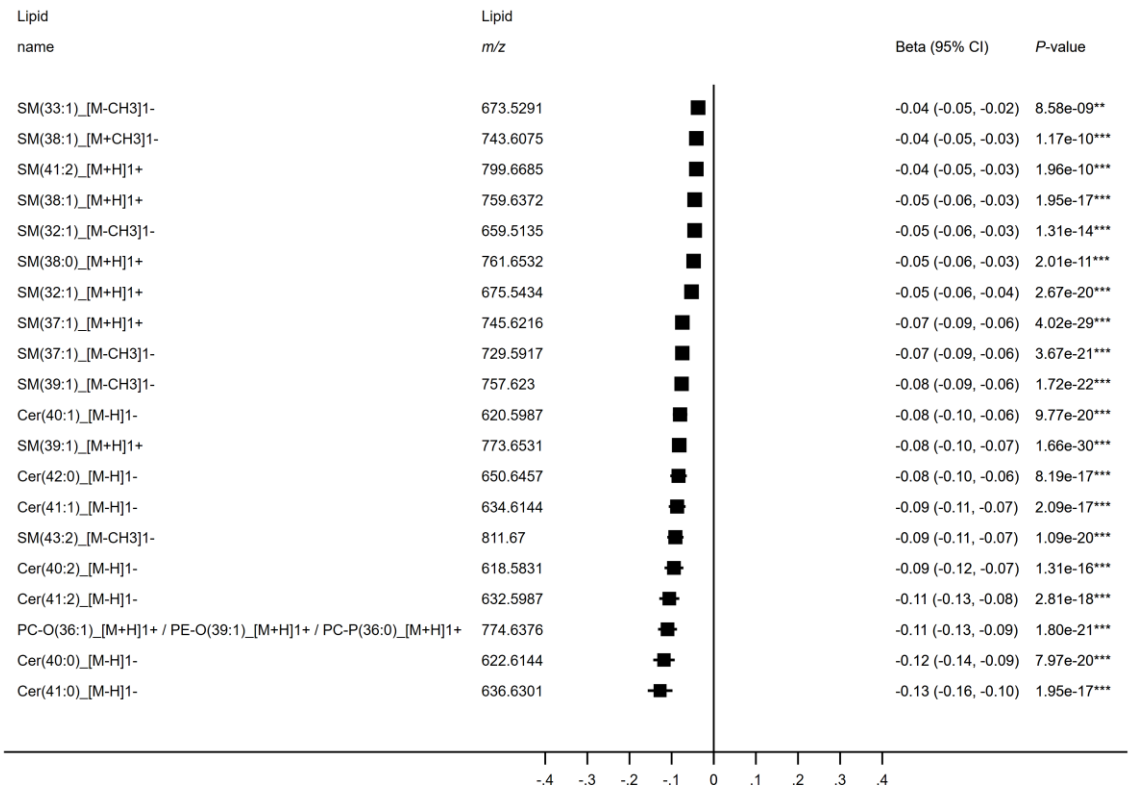
Beta (95% CI) for *SCD* (rs603424, chr10:102075479)

(u) *SGPP1*



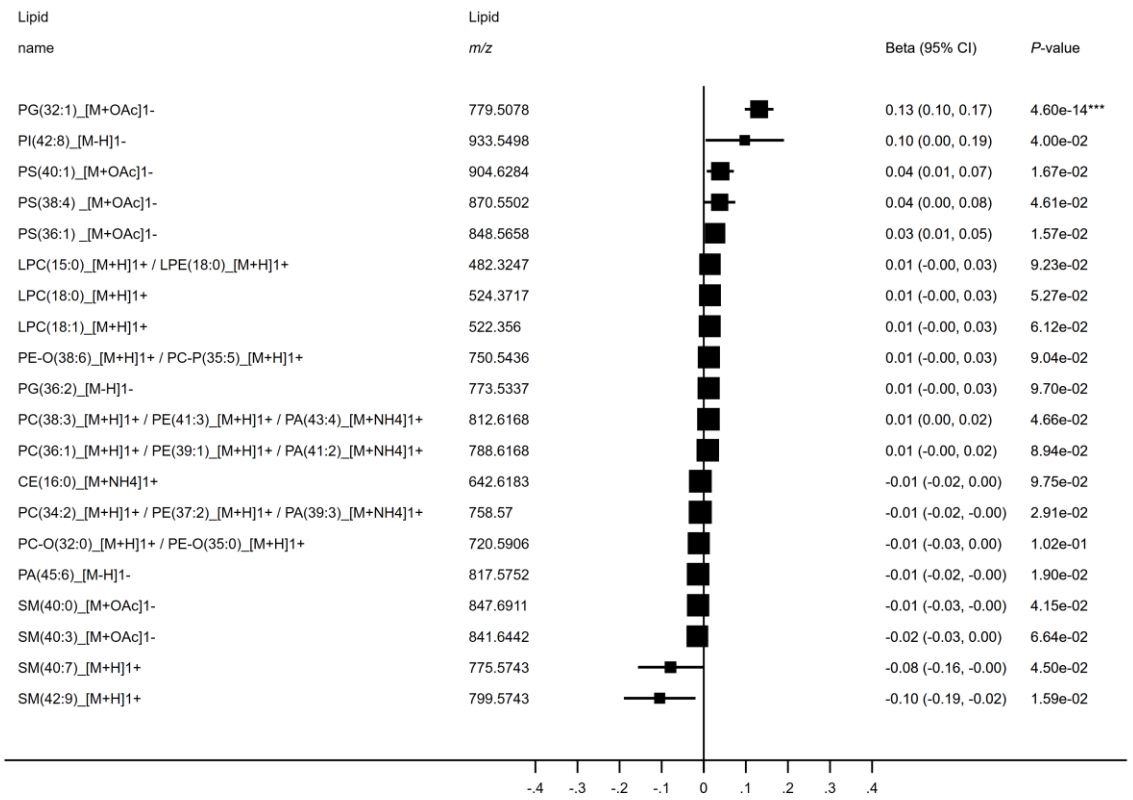
Beta (95% CI) for *SGPP1* (rs7157785, chr14:64235556)

(v) *SPTLC3*



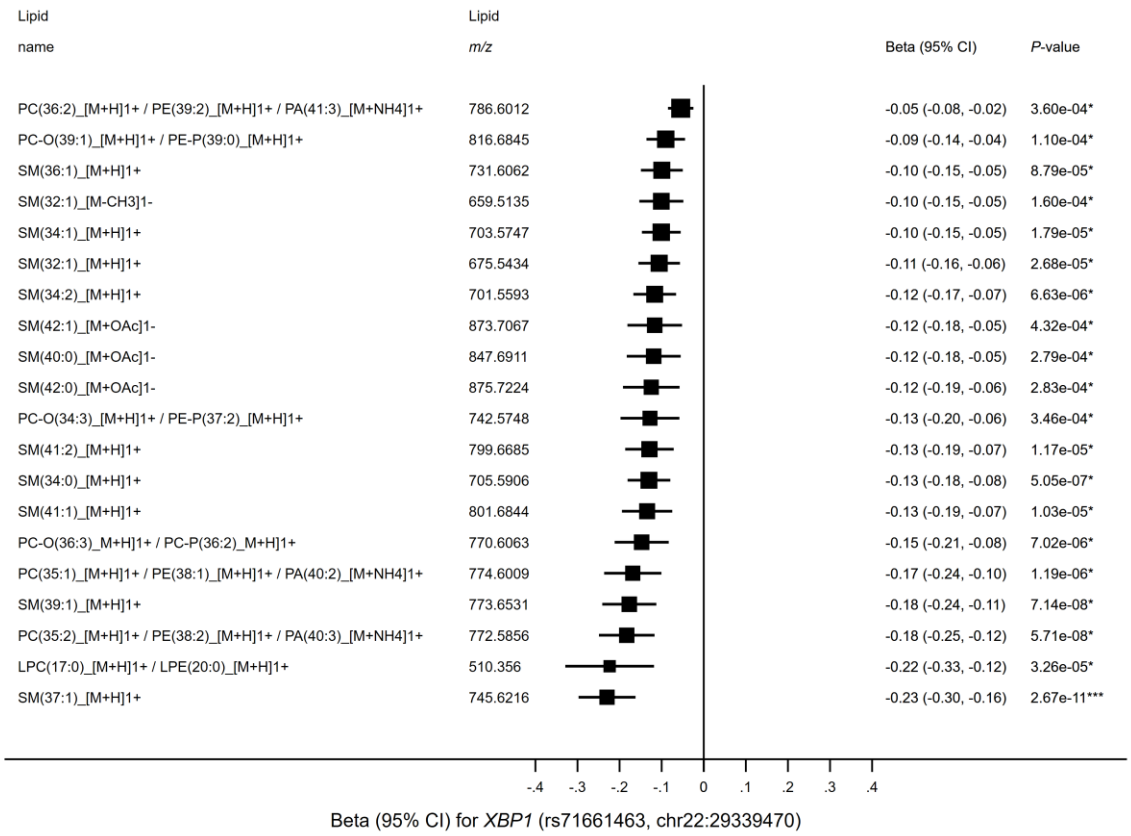
Beta (95% CI) for *SPTLC3* (rs438568, chr20:12958687)

(w) *UGT8*



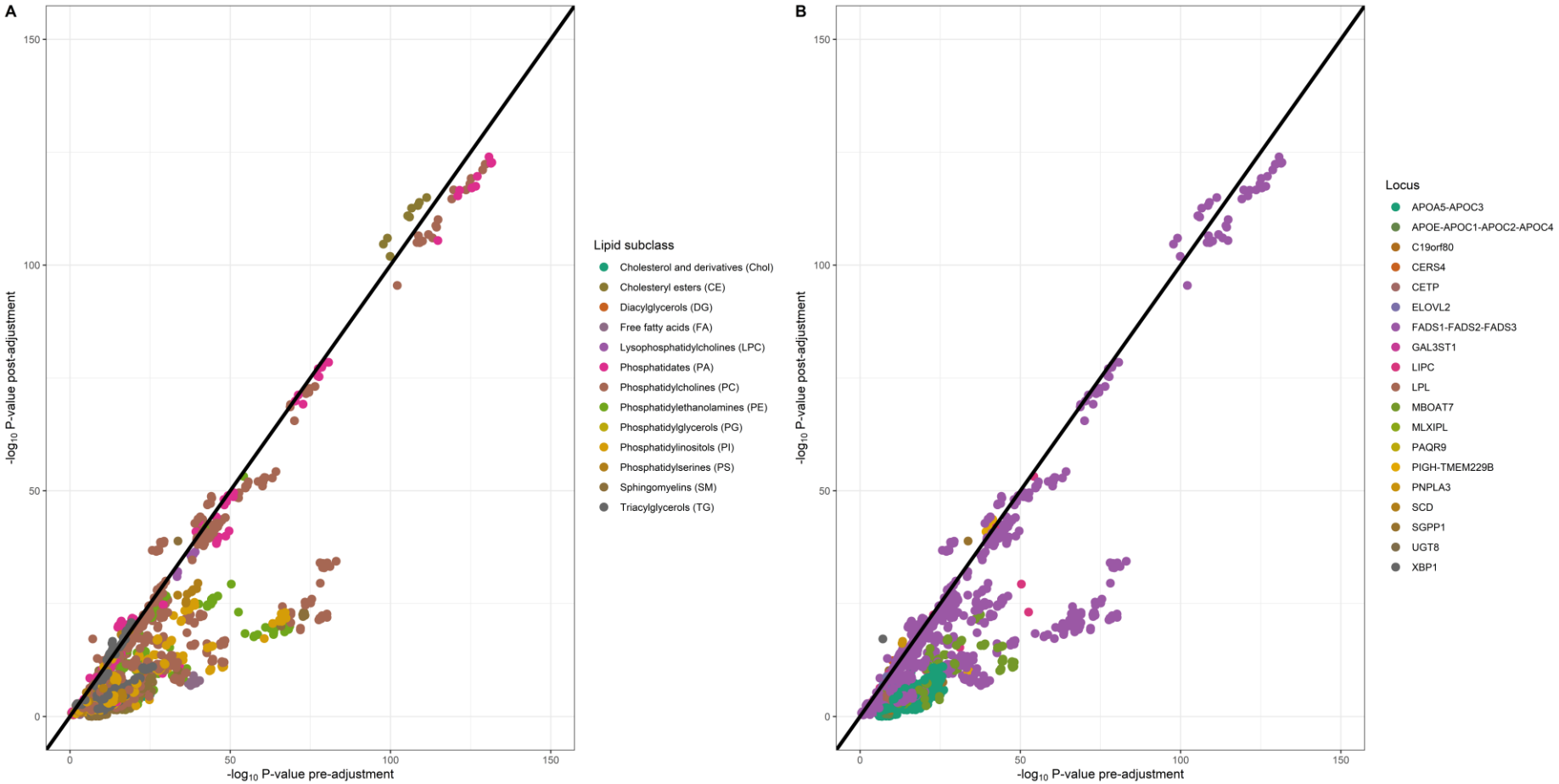
Beta (95% CI) for *UGT8* (rs28870381, chr4:115478499)

(x) *XBP1*



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.