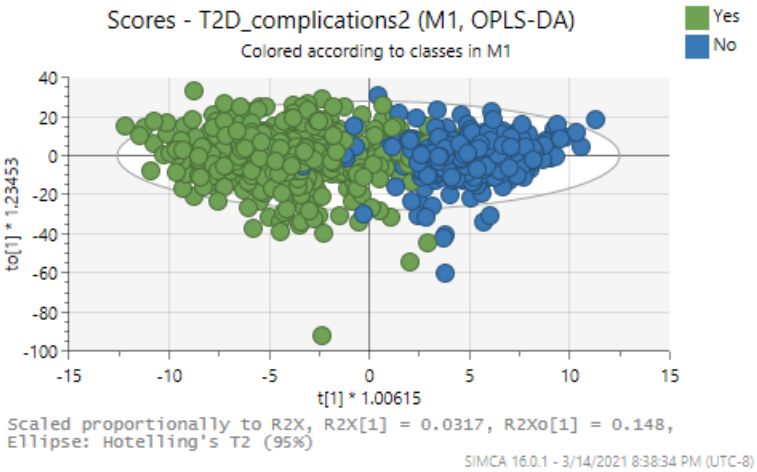
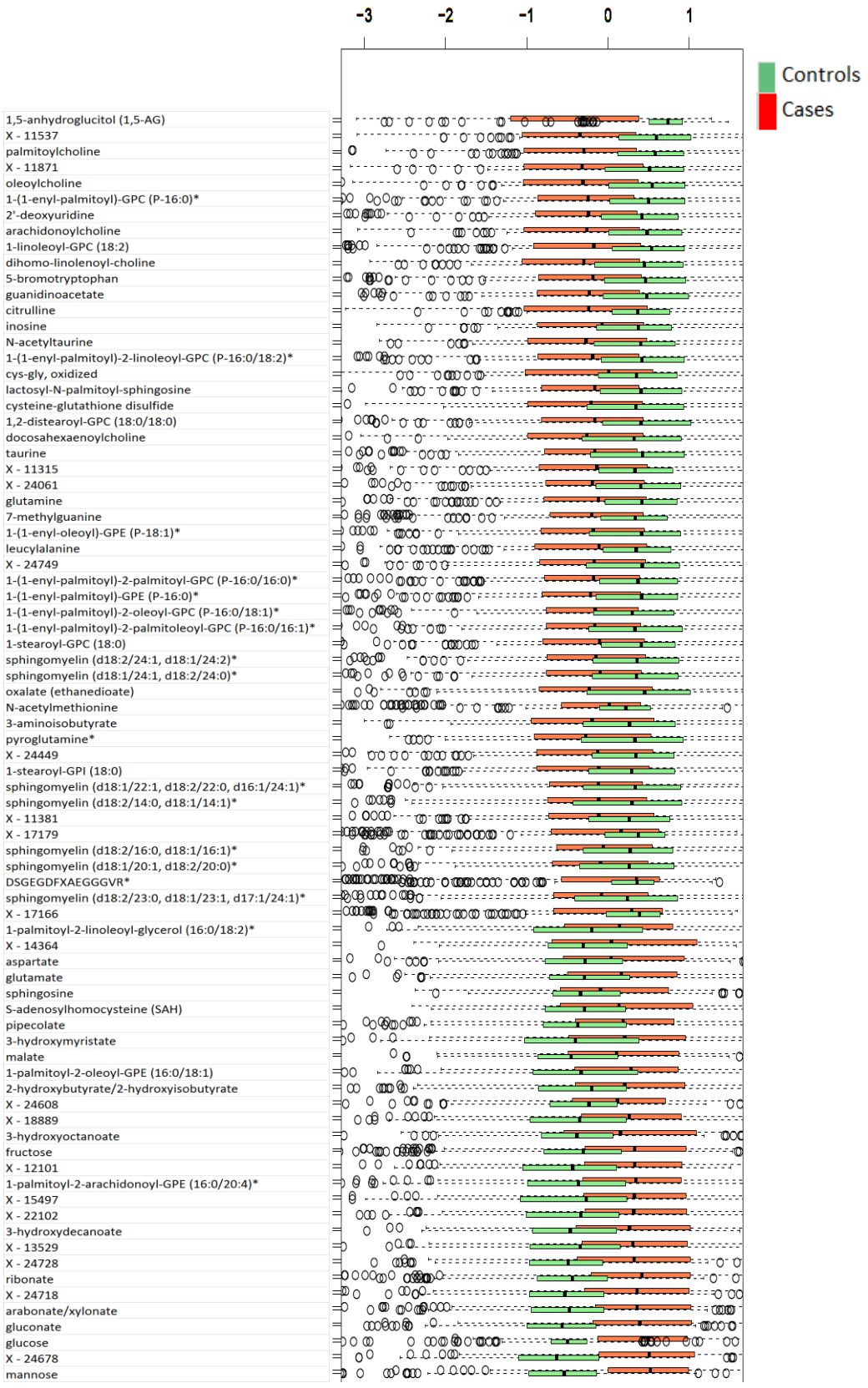


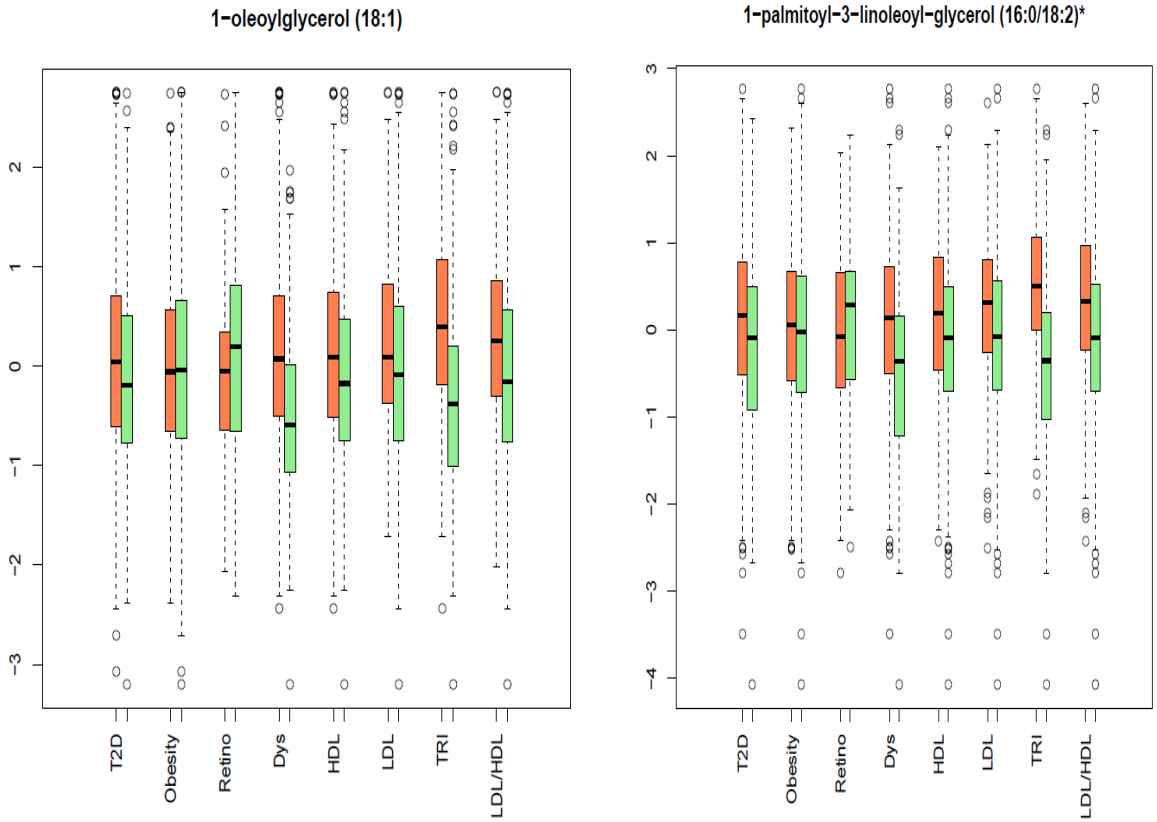
Supplementary Figure 1: OPLS-DA classification results. Score plot for 996 samples of T2D using metabolomics data to classify T2D patients from controls.“Yes” indicatesT2D patients and “No” indicates controls.


-3
-2
-1
0
1
Controls
Cases
1,5-anhydroglucitol (1,5-AG)
X - 11537
palmitoylcholine
X - 11871
oleoylcholine
1-(1-enyl-palmitoyl)-GPC (P-16:0)*
2'-deoxyuridine
arachidonoylcholine
1-linoleoyl-GPC (18:2)
dihomo-linolenoyl-choline
5-bromotryptophan
guanidinoacetate
citrulline
inosine
N-acetyltaurine
1-(1-enyl-palmitoyl)-2-linoleoyl-GPC (P-16:0/18:2)*
cys-gly, oxidized
lactosyl-N-palmitoyl-sphingosine
cysteine-glutathione disulfide
1,2-distearoyl-GPC (18:0/18:0)
docosahexaenoylcholine
taurine
X - 11315
X - 24061
glutamine
7-methylguanine
1-(1-enyl-oleoyl)-GPE (P-18:1)*
leucylalanine
X - 24749
1-(1-enyl-palmitoyl)-2-palmitoyl-GPC (P-16:0/16:0)*
1-(1-enyl-palmitoyl)-GPE (P-16:0)*
1-(1-enyl-palmitoyl)-2-oleoyl-GPC (P-16:0/18:1)*
1-(1-enyl-palmitoyl)-2-palmitoleoyl-GPC (P-16:0/16:1)*
1-stearoyl-GPC (18:0)
sphingomyelin (d18:2/24:1, d18:1/24:2)*
sphingomyelin (d18:1/24:1, d18:2/24:0)*
oxalate (ethanedioate)
N-acetylmethionine
3-aminoisobutyrate
pyroglutamine*
X - 24449
1-stearoyl-GPI (18:0)
sphingomyelin (d18:1/22:1, d18:2/22:0, d16:1/24:1)*
sphingomyelin (d18:2/14:0, d18:1/14:1)*
X - 11381
X - 17179
sphingomyelin (d18:2/16:0, d18:1/16:1)*
sphingomyelin (d18:1/20:1, d18:2/20:0)*
DSGEGDFXAEGGGVR*
sphingomyelin (d18:2/23:0, d18:1/23:1, d17:1/24:1)*
X - 17166
1-palmitoyl-2-linoleoyl-glycerol (16:0/18:2)*
X - 14364
aspartate
glutamate
sphingosine
S-adenosylhomocysteine (SAH)
pipecolate
3-hydroxymyristate
malate
1-palmitoyl-2-oleoyl-GPE (16:0/18:1)
2-hydroxybutyrate/2-hydroxyisobutyrate
X - 24608
X - 18889
3-hydroxyoctanoate
fructose
X - 12101
1-palmitoyl-2-arachidonoyl-GPE (16:0/20:4)*
X - 15497
X - 22102
3-hydroxydecanoate
X - 13529
X - 24728
ribonate
X - 24718
arabonate/xylonate
gluconate
glucose
X - 24678
mannose

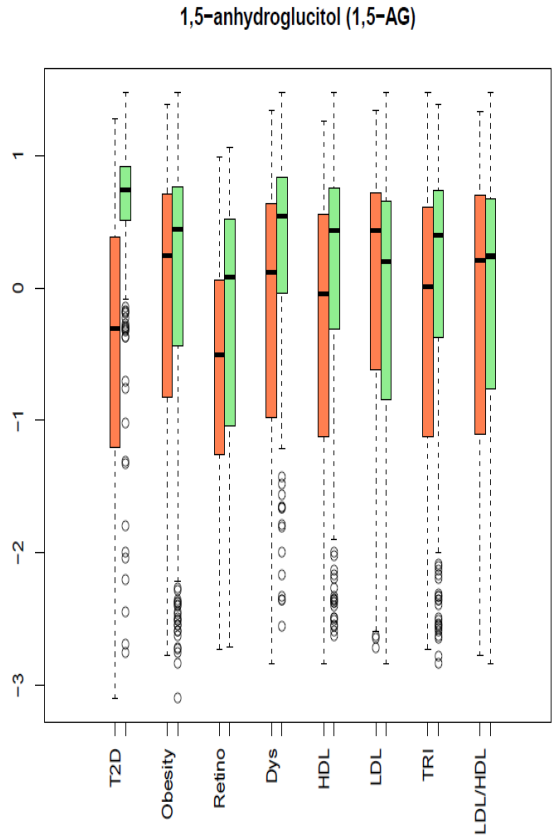
Supplementary Figure 2: Boxplots of the 80 most significant metabolites associated with T2D sorted on their beta values of regression. The y-axis is the metabolite name, and the x-axis is the metabolite value. Black circles are outliers.

	BMI	Retinopathy	LDL/HDL	HDL	LDL	TRI	Dyslipidemia
T2D	0.176005	-0.12613	0.082466	-0.38771	-0.21402	0.294968	0.344756
BMI		-0.20787	0.147036	-0.33574	-0.05467	0.208565	0.291359
Retinopathy			-0.24464	0.06353	-0.158	-0.17971	-0.14818
LDL/HDL				-0.38981	0.71815	0.570698	0.50559
HDL					0.258981	-0.67185	-0.79574
LDL						0.058548	-0.03268
TRI							0.882566

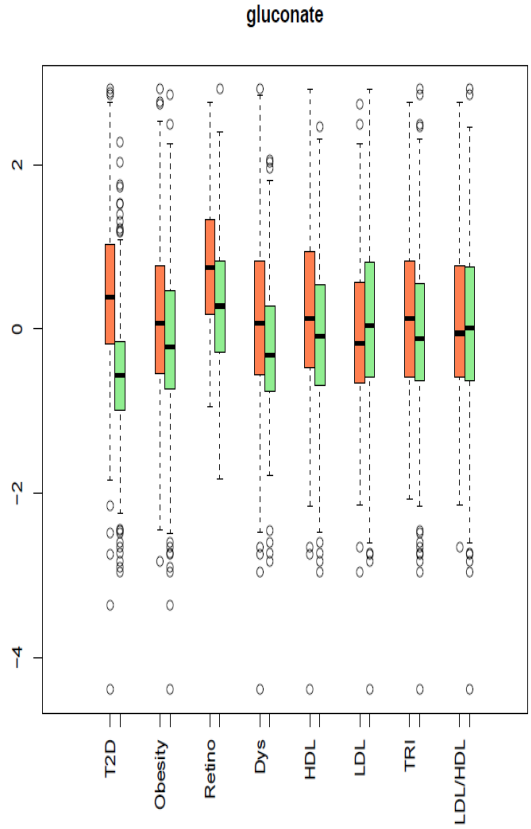
Supplementary Figure 3. Pairwise correlations of clinical variables based on their associations with metabolites.



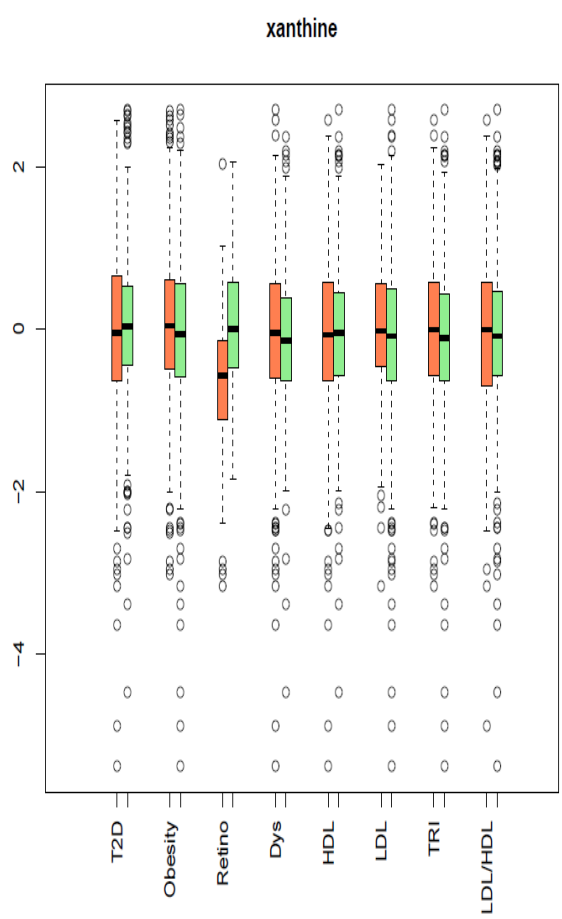
(a) (b)


1,5−anhydroglucitol (1,5−AG)
1
0
−1
−2
−3
T2D
Obesity
Retino
Dys
HDL
LDL
TRI
LDL/HDL

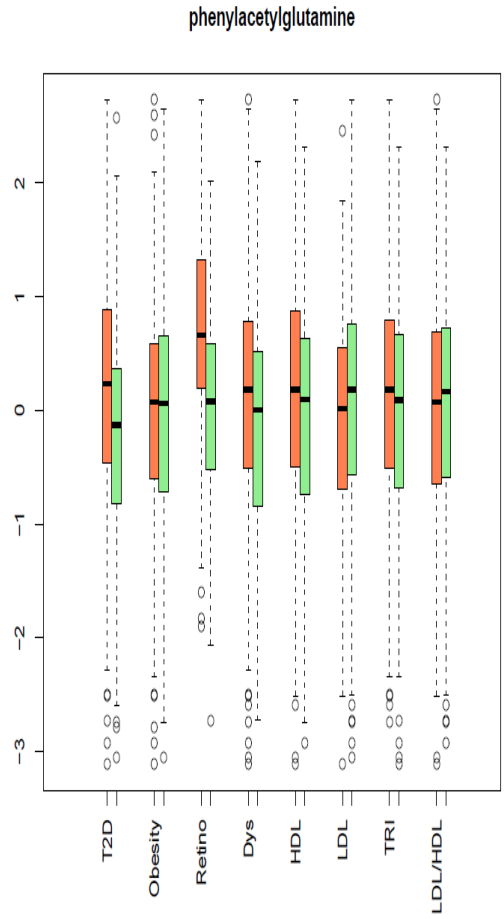
(c)


gluconate
2
0
−2
−4
T2D
Obesity
Retino
Dys
HDL
LDL
TRI
LDL/HDL

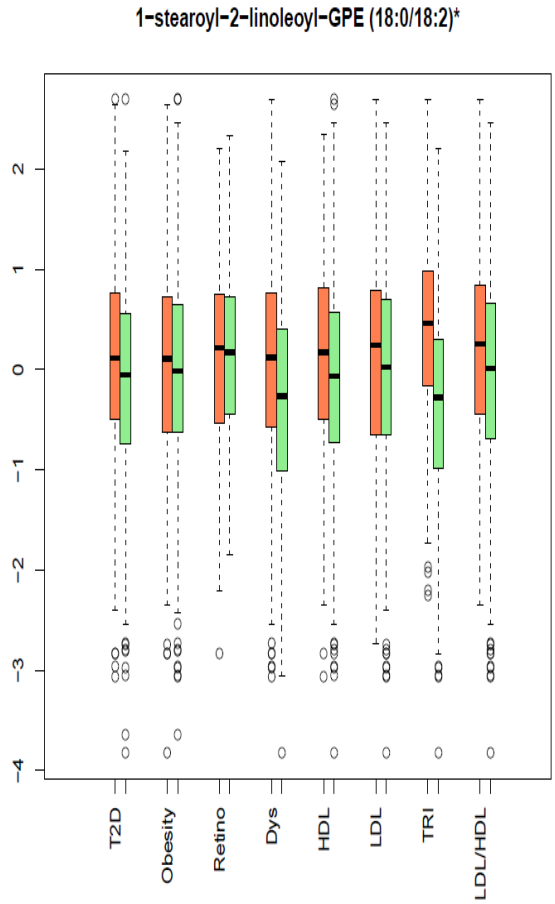
(d)


xanthine
2
0
−2
−4
T2D
Obesity
Retino
Dys
HDL
LDL
TRI
LDL/HDL

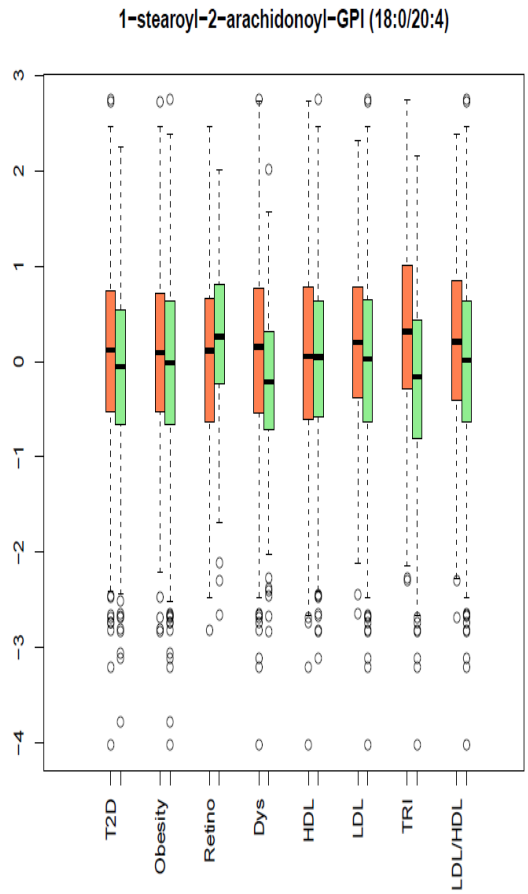
(e)


phenylacetylglutamine
2
1
0
−1
−2
−3
T2D
Obesity
Retino
Dys
HDL
LDL
TRI
LDL/HDL

(f)

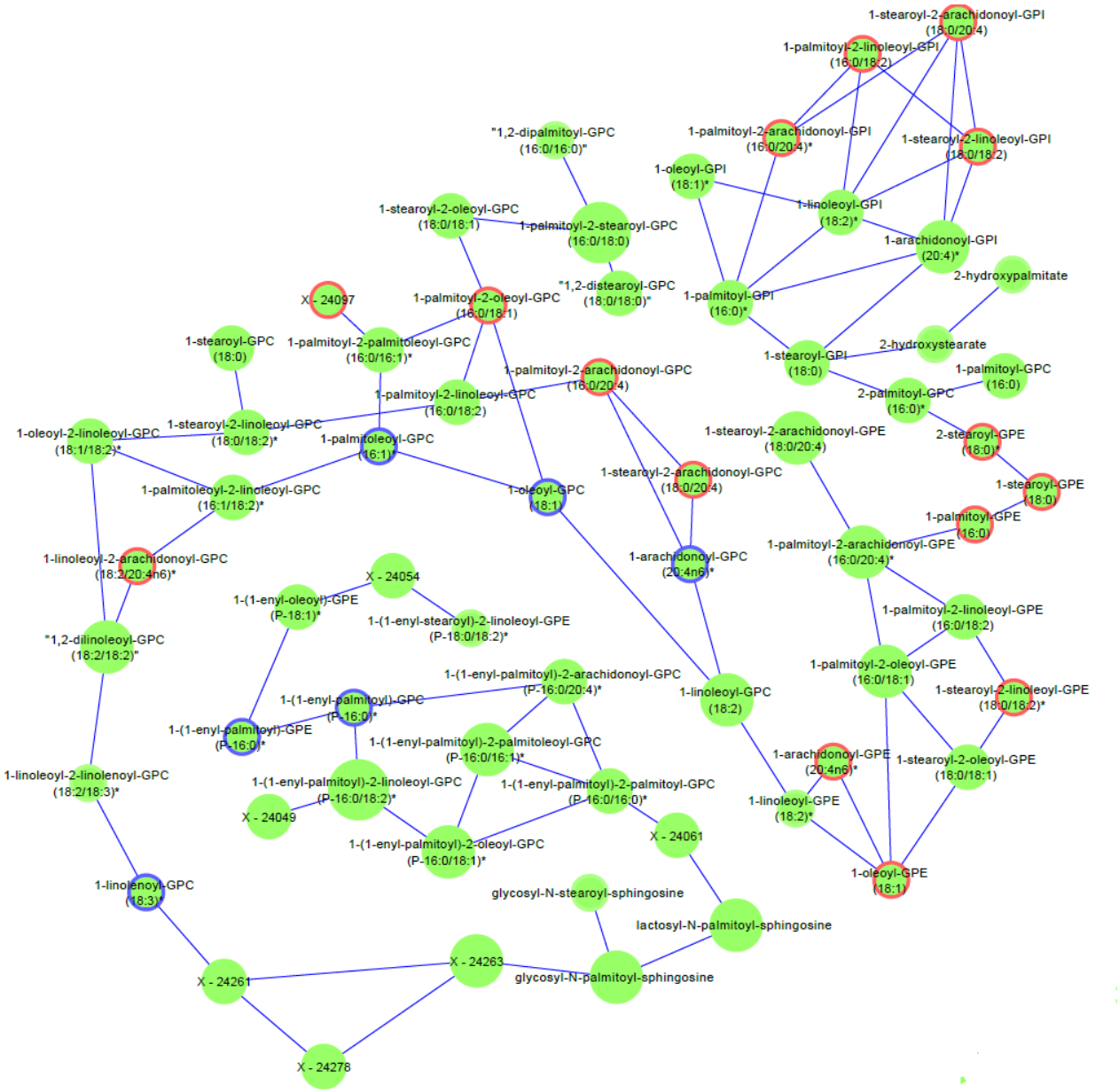


(g)

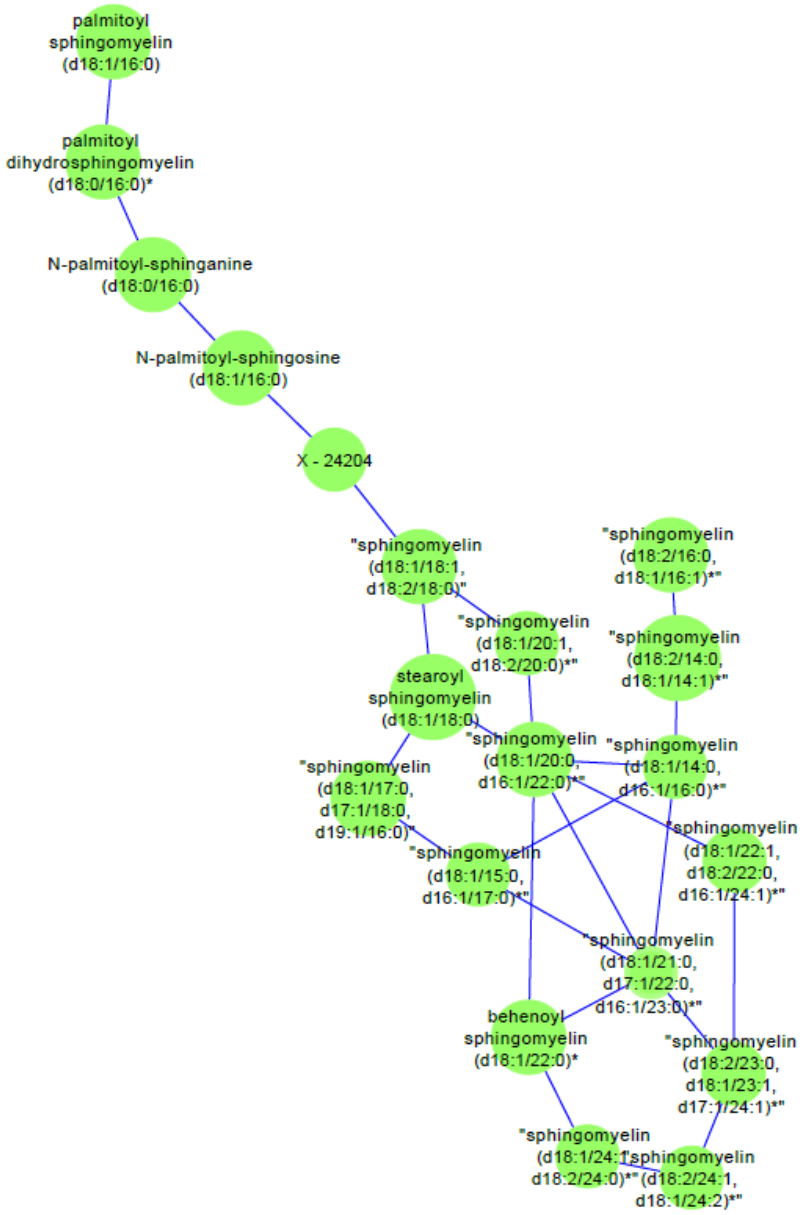


(h)

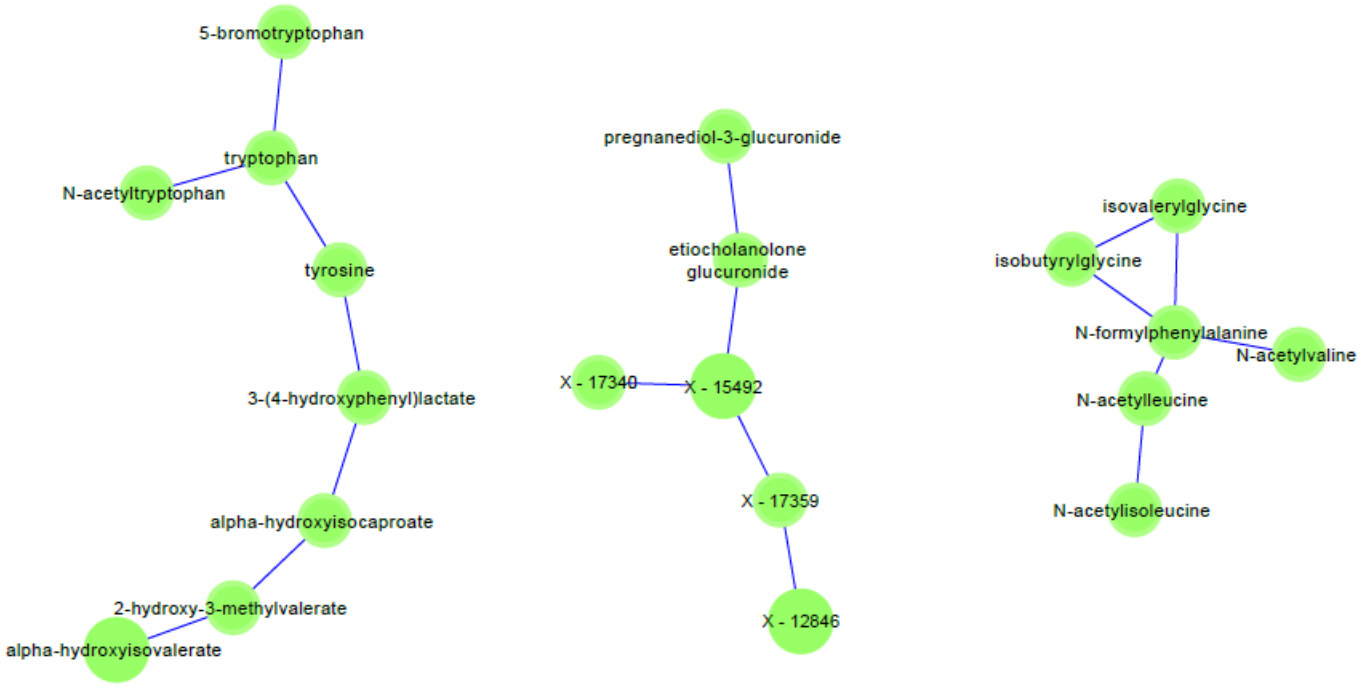
Supplementary Figure 4: Boxplots of metabolites associated with five or more variables (a, b) or associated only with T2D (c, d), retinopathy (e, f), or TRI (g, h). Red represents the case (T2D, obesity, retinopathy, dyslipidemia [Dys], and levels above/below threshold for quantitative variables), and green represents the controls. Y-axes are levels of the metabolites.


1-stearoyl-2-arachidonoyl-GPI (18:0/20:4)
1-palmitoyl-2-linoleoyl-GPI (16:0/18:2)
1-palmitoyl-2-arachidonoyl-GPI (16:0/20:4)*
1-stearoyl-2-linoleoyl-GPI (18:0/18:2)
"1,2-dipalmitoyl-GPC (16:0/16:0)"
1-oleoyl-GPI (18:1)*
1-linoleoyl-GPI (18:2)*
1-stearoyl-2-oleoyl-GPC (18:0/18:1)
1-palmitoyl-2-stearoyl-GPC (16:0/18:0)
1-arachidonoyl-GPI (20:4)*
"1,2-distearoyl-GPC (18:0/18:0)*
1-palmitoyl-GPI (16:0)*
2-hydroxypalmitate
X - 24097
1-palmitoyl-2-oleoyl-GPC (16:0/18:1)
1-stearoyl-GPC (18:0)
1-palmitoyl-2-palmitoleoyl-GPC (16:0/16:1)*
1-stearoyl-GPI (18:0)
2-hydroxystearate
1-palmitoyl-2-arachidonoyl-GPC (16:0/20:4)
1-palmitoyl-GPC (16:0)
1-palmitoyl-2-linoleoyl-GPC (16:0/18:2)
2-palmitoyl-GPC (16:0)*
1-stearoyl-2-arachidonoyl-GPE (18:0/20:4)
1-oleoyl-2-linoleoyl-GPC (18:1/18:2)*
1-stearoyl-2-linoleoyl-GPC (18:0/18:2)*
1-palmitoleoyl-GPC (16:1)*
2-stearoyl-GPE (18:0)*
1-stearoyl-2-arachidonoyl-GPC (18:0/20:4)
1-stearoyl-GPE (18:0)
1-palmitoyl-GPE (16:0)
1-palmitoleoyl-2-linoleoyl-GPC (16:1/18:2)*
1-oleoyl-GPC (18:1)
1-palmitoyl-2-arachidonoyl-GPE (16:0/20:4)*
1-linoleoyl-2-arachidonoyl-GPC (18:2/20:4n6)*
1-arachidonoyl-GPC (20:4n6)*
X - 24054
1-(1-enyl-oleoyl)-GPE (P-18:1)*
1-palmitoyl-2-linoleoyl-GPE (16:0/18:2)
1-(1-enyl-stearoyl)-2-linoleoyl-GPE (P-18:0/18:2)*
"1,2-dilinoleoyl-GPC (18:2/18:2)"
1-palmitoyl-2-oleoyl-GPE (16:0/18:1)
1-(1-enyl-palmitoyl)-2-arachidonoyl-GPC (P-16:0/20:4)*
1-linoleoyl-GPC (18:2)
1-stearoyl-2-linoleoyl-GPE (18:0/18:2)*
1-(1-enyl-palmitoyl)-GPC (P-16:0)*
1-(1-enyl-palmitoyl)-GPE (P-16:0)*
1-(1-enyl-palmitoyl)-2-palmitoleoyl-GPC (P-16:0/16:1)*
1-arachidonoyl-GPE (20:4n6)*
1-stearoyl-2-oleoyl-GPE (18:0/18:1)
1-linoleoyl-2-linolenoyl-GPC (18:2/18:3)*
1-(1-enyl-palmitoyl)-2-linoleoyl-GPC (P-16:0/18:2)*
1-(1-enyl-palmitoyl)-2-palmitoyl-GPC (P-16:0/16:0)*
1-linoleoyl-GPE (18:2)*
X - 24049
X - 24061
1-(1-enyl-palmitoyl)-2-oleoyl-GPC (P-16:0/18:1)*
1-oleoyl-GPE (18:1)*
1-linolenoyl-GPC (18:3)*
glycosyl-N-stearoyl-sphingosine
lactosyl-N-palmitoyl-sphingosine
X - 24263
X - 24261
glycosyl-N-palmitoyl-sphingosine
X - 24278

(a)

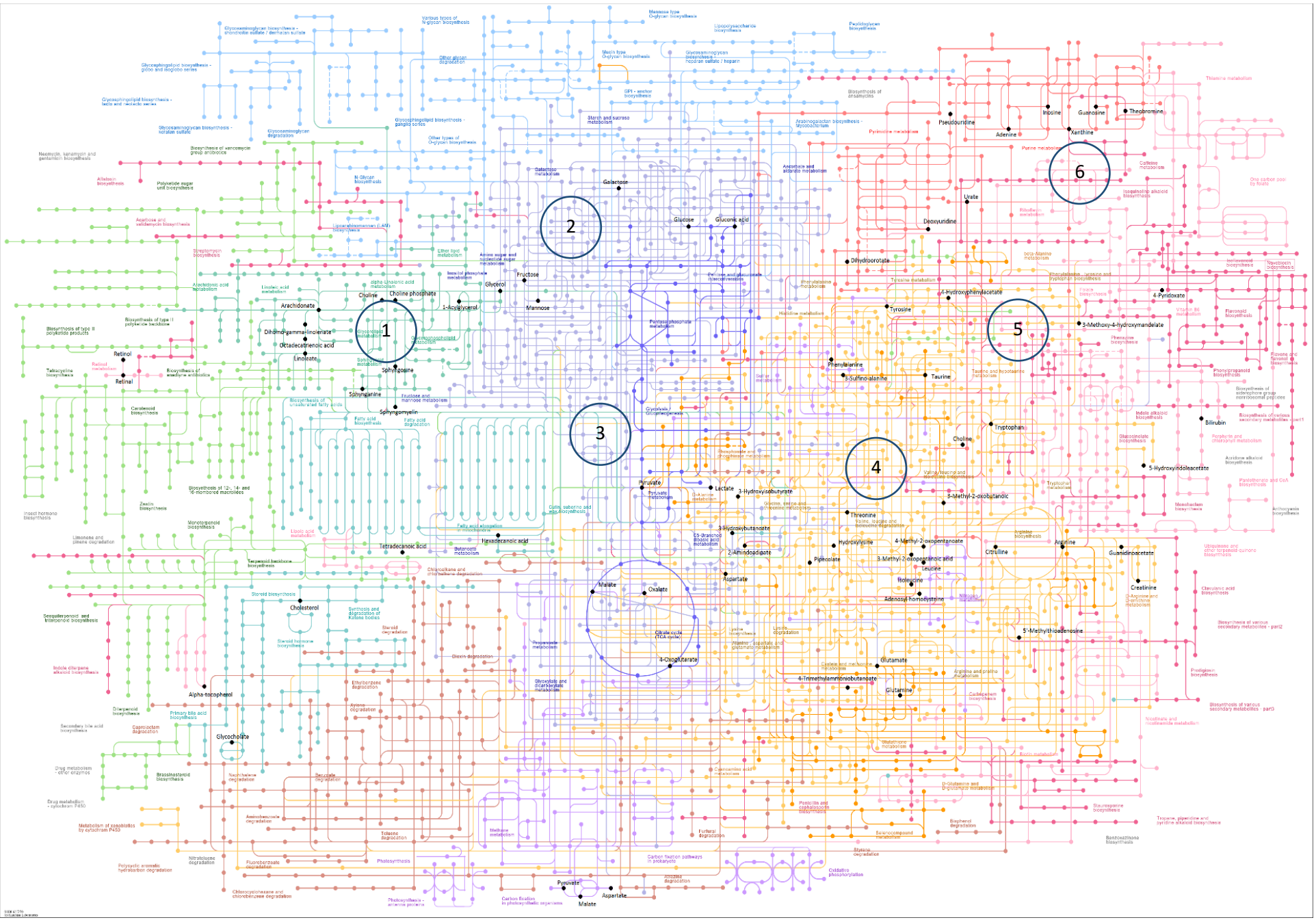

palmitoyl sphingomyelin (d18:1/16:0)
palmitoyl dihydrosphingomyelin (d18:0/16:0)*
N-palmitoyl-sphinganine (d18:0/16:0)
N-palmitoyl-sphingosine (d18:1/16:0)
X - 24204
"sphingomyelin (d18:1/18:1, d18:2/18:0)"
"sphingomyelin (d18:1/20:1, d18:2/20:0)*"
stearoyl sphingomyelin (d18:1/18:0)
"sphingomyelin (d18:1/17:0, d17:1/18:0, d19:1/16:0)"
"sphingomyelin (d18:1/20:0, d16:1/22:0)*"
"sphingomyelin (d18:1/15:0, d16:1/17:0)*"
"sphingomyelin (d18:2/16:0, d18:1/16:1)*"
"sphingomyelin (d18:2/14:0, d18:1/14:1)*"
"sphingomyelin (d18:1/14:0, d16:1/16:0)*"
"sphingomyelin (d18:1/22:1, d18:2/22:0, d16:1/24:1)*"
"sphingomyelin (d18:1/21:0, d17:1/22:0, d16:1/23:0)*"
behenoyl sphingomyelin (d18:1/22:0)*
"sphingomyelin (d18:2/23:0, d18:1/23:1, d17:1/24:1)*"
"sphingomyelin (d18:1/24:1, d18:2/24:0)*"
"sphingomyelin (d18:2/24:1, d18:1/24:2)*"

(b)



(c) (d) (e)

Supplementary Figure 5: Additional GGM subnetworks from the 11 largest subnetworks presented in Figure 3. The larger the node, the more phenotypes are associated with the metabolite (up to six phenotypes can be associated with metabolites). If four or more metabolites are associated only with a single clinical variable, the border of the node is colored: a red border indicates association with TRI only, and a blue border indicates association with T2D only. (a) Lipid subnetwork (palmitoyls/stearoyl/ arachidonoyl/oleoyl/linoleoyl– GPC/GPE/GPI) with 65 metabolites; (b) sphingomyelin subnetwork (20 metabolites); (c,e) branched chain Amino Acids (BCAAs)/phenylalanine and tyrosine; (d) glucoronides/unknowns subnetworks.


1
2
3
4
5
6
Choline
Choline phosphate
Arachidonate
Dihomo-gamma-linolenate
Octadecatrienoic acid
Linoleate
Retinol
Retinal
Sphingosine
Sphinganine
Sphingomyelin
1-Acylglycerol
Glycerol
Fructose
Mannose
Galactose
Glucose
Gluconic acid
Dihydroorotate
Deoxyuridine
Urate
Pseudouridine
Adenine
Xanthine
Inosine
Guanosine
Theobromine
4-Hydroxyphenylacetate
Tyrosine
3-Methoxy-4-hydroxymandelate
4-Pyridoxate
Phenylalanine
3-Sulfino-alanine
Taurine
Tryptophan
5-Hydroxyindoleacetate
Bilirubin
Choline
Pyruvate
Lactate
3-Hydroxyisobutyrate
3-Methyl-2-oxobutanoic
3-Hydroxybutanoate
2-Aminoadipate
Threonine
Hydroxylysine
Pipecolate
4-Methyl-2-oxopentanoate
3-Methyl-2-oxopentanoic acid
Leucine
Isoleucine
Adenosyl homocysteine
5'-Methylthioadenosine
Citrulline
Arginine
Guanidinoacetate
Creatinine
Malate
Oxalate
Aspartate
Glutamate
4-Trimethylammoniobutanoate
Glutamine
4-Oxoglutarate
Hexadecanoic acid
Tetradecanoic acid
Cholesterol
Alpha-tocopherol
Glycocholate
Pyruvate
Aspartate
Malate

Supplementary Figure 6: KEGG pathways with metabolites mapped from 373 metabolites are labelled with black dots. 1-(linoleic acid metabolism, arachidonic acid metabolism, sphingolipid metabolism, alpha-linolenic, glycerophospholipid). 2-(amino sugar and nucleotide sugar, starch and sucrose metabolism, and galactose metabolism). 3-(pantose phosphate metabolism, glycolysis, and TCA cycle). 4-(arginine, aspartate and glutamate metabolism, serine, glycine and threonine metabolism, leucine-valine-isoleucine [BCAA] metabolism). 5-(taurine and hypotaurine metabolism, phenylalanine-tyrosine-tryptophan metabolism). 6-(pyrimidine, purine and caffeine metabolism).