Serum orotidine: a novel biomarker of increased CVD risk in type 2 diabetes discovered through metabolomics studies.

Short Title: Orotidine increases CVD risk in T2D

ONLINE SUPPLEMENT

Supplemental Material

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Online Supplemental Material

Assessment of renal function

Serum creatinine and cystatin C. In the Discovery Set, serum creatinine concentrations at enrollment and during follow-up were measured at the Advanced Research and Diagnostic Laboratory, University of Minnesota in 2013-2015, using Roche enzymatic assay (Product # 11775685) on a Roche/Hitachi Mod P analyzer (Roche Diagnostics, Indianapolis, IN). In the Validation Set, serum creatinine was measured in baseline samples at the Joslin Clinical Laboratory using the Jaffe modified picrate method on the Beckman CX9 Chemistry Analyzer (Beckman, Brea, CA), for samples collected prior to 2007, the VITROS CREA Slide method on the VITROS 5.1 Chemistry Analyzer (Ortho Diagnostics, Raritan, NJ), for samples collected in 2007-2011, or the Jaffe modified picrate method on the Roche Integra 800 Chemistry Analyzer (Roche Diagnostics, Indianapolis, IN), for samples collected in 2011-2014. Baseline serum cystatin C concentrations were measured in the Discovery and Validation Sets at the Advanced Research and Diagnostic Laboratory, University of Minnesota, MN set in 2017-2018 and 2019-2020, respectively. Measurements were carried out on the Roche COBAS 6000 chemistry analyzer (Roche Diagnostics, Indianapolis, IN) using Gentian Cystatin C Immunoassay (Gentian AS, Moss, Norway), which is an FDA-approved Particle-Enhanced Turbidimetric Immunoassay (PETIA) with a detection limit of 0.32 mg/L, coefficient of variations of 4.3% at 0.75 mg/L and 3.2% at 3.83 mg/L, and a reference range of 0.51-1.05 mg/L. Calibrators for the assay are standardized against the international calibrator standard ERM-DA471/IFCC[40]. The Chronic Kidney Disease Epidemiology (CKD-EPI) Collaboration formulas[41] were used to estimate creatinine-derived (SCre-eGFR) and cystatin C-derived (SCys-eGFR) glomerular filtration rates for both study populations.

AccuGFR. In a randomly selected subset of 225 individuals (112 controls and 113 cases) of the Discovery Set, accuGFR™ (Metabolon, Durham, NC) was estimated from an equation based on a panel of four novel metabolites, including, pseudouridine, acetylthreonine, phenylacethylglutamine, and tryptophan,

which were quantitatively measured in baseline serum samples using Ultrahigh Performance Liquid Chromatography-Tandem Mass Spectroscopy (UPLC-MS/MS) methods as described previously[42]. This accuGFR algorithm does not include creatinine, cystatin C, or demographic variables, and has been shown to have a greater degree of accuracy in assessing glomerular filtration than either SCre-eGFR or SCys-eGFR estimations as it had a higher concordance with mGFR[42].

***Urinary Albumin Creatinine Ratio*.** In the Discovery Set, Albumin-Creatinine Ratios (ACRs) were assessed in urine at baseline and during follow-up as previously described[43, 44]. Albumin concentrations were measured in spot urines at the Joslin Clinical Laboratory by immunonephelometry on a BN ProSpec System (Dade Behring, Newark, DE) with N-albumin kits. Urinary creatinine was assayed by the Jaffe modified picrate method on a Ciba Corning 550 Express Plus Chemistry Analyzer. Normoalbuminuria (ACR<30 mg/g), microalbuminuria (ACR 30-300 mg/g) and macroalbuminuria (ACR >300 mg/g) were determined using the geometric mean ACR for the preceding 2-year interval of the baseline exam for each patient. Quantitative assessments of urine albumin in baseline samples of the Validation Set were performed at the Joslin Clinical Laboratory as follows: prior to 2007, by immunonephelometry on a BN ProSpec System (Dade Behring, Newark, DE) with N-albumin kits; between 2007-2011, using the VITROS Chemistry Products mALB Reagent on the VITROS 5.1 Chemistry Analyzer (Ortho Diagnostics, Raritan, NJ); and between 2011-2014, using the COBAS INTEGRA Albumin Gen.2 reagent on the Roche Integra 800 Chemistry Analyzer (Roche Diagnostics, Indianapolis, IN). Urinary creatinine concentrations were measured as described above for serum creatinine.

Targeted metabolite assays

For validation of methods and replication of findings from the global metabolomics study of the Discovery set (JKS), targeted quantitative assays for the top metabolites, orotidine and 2-piperidinone, were developed at the Molecular Phenotyping and Metabolomics Core at the University of Michigan.

Serum samples from the Validation set (JHS) (n=599) as well as 20 replicates from the Discovery Set (JKS) were then assayed for these two metabolites.

Sample Preparation. Samples were thawed for 1.5 to 2 hours at 4 °C. Aliquots (50 µL) were centrifuged (10 min @ 4 °C and 17,100 x g), and 25 µL from each sample were dispensed into 100 µL ice-cold 0.1% acetic acid in methanol to extract the metabolites. The supernatants were dried, and then reconstituted in 50 µL 50 mM sodium carbonate and vortexed, followed by an addition of 25 µL 1% benzoyl chloride in acetonitrile. An internal standard solution (175 µL; 143 nM $^{13}C_5$-uridine, 714 nM 2-piperidone-d4 in 0.014% acetic acid in 85.7:14.3 water:acetonitrile) was then added. Samples were then filtered via filter vials (0.2 µm PTFE).

UPHLC-MS/MS Parameters. All UHPLC-MS/MS experiments were performed on an Agilent 6495 triple quadrupole LC-MS system (Agilent Technologies, Inc.; Santa Clara, CA, USA) equipped with a thermostat, autosampler, binary pump (all 1290 Infinity series), a thermostatted column compartment (1260 Infinity series), and an Agilent Zorbax Bonus-RP LC column (2.1x50 mm, 1.8 µm). Mobile phases A and B consisted of 5 mM ammonium acetate in water (pH 5.30 ± 0.02) and 50:50 ACN:MeOH, respectively. The instrumental parameters were as follows: needle wash solvent: 80:20 ACN:water; autosampler temperature, 4 °C; injection volume, 2 µL; column compartment temperature, 30 °C; drying gas temperature, 150 °C; drying gas flow rate, 11 L/ min.; nebulizer pressure, 60 psi; sheath gas temperature, 400 °C; sheath gas flow rate, 11 L/ min.; capillary voltage, + 3,000 V/ - 2,500 V; nozzle voltage; 0 V; dwell time, 50 msec.

<u>Gradient/ Flow Program:</u>

(min.): 0 → 2 → 5 →5.01→6.50→6.51→ 8 →8.01→ 9

(%B): 5 → 5 → 95 → 95 → 95 → 5 → 5 → 5 → 5

(mL/ min.): 0.2 → 0.2 → 0.2 → 0.5 → 0.5 → 0.5 → 0.5 → 0.2 → 0.

Retention times and MRM parameters for Validation assays

Compound	Retention Time (min)	MRM Transition*
Oro	1.04	- 287.2 → 111.1
		- 287.2 → 42.0
13C5-Uri	1.05	- 248.1 → 205.1
		- 248.1 → 112.1
2-Pip	1.47	+ 100.2 → 55.9
		+ 100.2 → 82.0
2-Pip-d4	1.44	+ 104.2 → 76.1
		+ 104.2 → 71.9

* The first and second lines per compound correspond to the quantifier and qualifier MRM transition, respectively

Method Validation. Method validation was conducted as follows. Selectivity was assessed by verifying that the retention times and the relative peak areas of the quantitative and qualitative MRM transitions for each analyte and were within 10% and 15% of those values measured in 500 nM calibration standard solutions, respectively. In addition, blanks consisting of water prepared in the same manner as samples were also analyzed to ensure that the reagents and internal standard solution did not contribute to the MS response of samples. Accuracy was assessed by verifying that the analyte concentrations in serum calculated from the calibration curve and those obtained by standard addition differed by <15%.

***Batch Setup*.** Two sets of clinical samples were run (N_1=319, N_2=300). A commercial pooled human serum sample (Innovative Research; IPLA-SER-27540) and pooled serum from respective sets of clinical samples ("test pool") were ran with each batch (typically 40 samples) to normalize for instrumental drift and minimize batch effects. Averaged test pool values (N=5 per batch) was used to normalize measurements for "batch effects."

***Quantitation*.** Agilent MassHunter Quantitative Analysis for QQQ (version B.07.00) was used to integrate chromatographic peaks. Weighted least squares were used for calibration. The reported concentrations accounted for the dilution factor (x12.5), recovery (69.8% and 73.8% for orotidine and 2-piperidone, respectively), and batch effects.

Limit of Detection (LoD), and Limit of Quantitation (LoQ)

	LOD	LOQ
2-Piperidone	2.5 nM	10 nM
Orotidine	100 pM	250 pM

Supplementary Table 1: Baseline eGFRs and accuGFR in Discovery subset (n=225)

	Controls (n=112)	Cases (n=113)	P-value
SCre-eGFR (ml/min/1.73 m²)	73.7 ± 19.4	71.2 ± 21.5	3.60E-01
accuGFR (ml/min/1.73 m²)	81.7 ± 23.5	71.2 ± 26.0	1.80E-03
SCys-eGFR (ml/min/1.73 m²)	75.2 ± 24.3	65.9 ± 28.6	9.60E-03

Means±SD presented. P-value obtained from t-test for difference in means between cases and controls.
SCre-eGFR and SCys-eGFR were derived using creatinine or cystatin-C, respectively, from CKD-EPI equations (Inker et al., NEJM 2012)
accuGFR™ (Metabolon, Durham, NC) was estimated from an equation based on a panel of four novel metabolites, including, pseudouridine, acetylthreonine, phenylacethylglutamine, and tryptophan

Supplementary Table 2: Dropped metabolites (>20% sample missingness) that had significantly different undetectability rates between cases and controls

BIOCHEMICAL	SUPER_PATHWAY	SUB_PATHWAY	Controls	Cases	Pvalue
metoprolol	Xenobiotics	Drug	259 (88.1)	77 (67)	5.19E-07
metoprolol acid metabolite	Xenobiotics	Drug	221 (75.2)	67 (58.3)	8.00E-04
N-acetylkynurenine (2)	Amino Acid	Tryptophan Metabolism	149 (50.7)	38 (33)	1.30E-03
valsartan	Xenobiotics	Drug	253 (86.1)	86 (74.8)	6.50E-03
oxypurinol	Xenobiotics	Drug	290 (98.6)	108 (93.9)	7.90E-03
Glycohyocholate*	Lipid	Secondary Bile Acid Metabolism	81 (27.6)	47 (40.9)	9.00E-03
allopurinol	Xenobiotics	Drug	293 (99.7)	111 (96.5)	9.40E-03
guaifenesin	Xenobiotics	Drug	293 (99.7)	111 (96.5)	9.40E-03
pregabalin	Xenobiotics	Drug	293 (99.7)	111 (96.5)	9.40E-03
tauro-beta-muricholate*	Lipid	Primary Bile Acid Metabolism	137 (46.6)	70 (60.9)	9.50E-03
N-acetylproline	Amino Acid	Urea cycle; Arginine and Proline Metabolism	88 (29.9)	20 (17.4)	9.70E-03
atorvastatin lactone	Xenobiotics	Drug	292 (99.3)	110 (95.7)	1.01E-02
indolin-2-one	Xenobiotics	Food Component/Plant	70 (23.8)	15 (13)	1.58E-02
furosemide	Xenobiotics	Drug	274 (93.2)	99 (86.1)	2.25E-02
carbamazepine	Xenobiotics	Drug	294 (100)	113 (98.3)	2.34E-02
o-hydroxyatorvastatin lactone	Xenobiotics	Drug	294 (100)	113 (98.3)	2.34E-02
p-hydroxyatorvastatin	Xenobiotics	Drug	275 (93.5)	100 (87)	3.02E-02
2-ethylphenylsulfate	Xenobiotics	Benzoate Metabolism	202 (68.7)	66 (57.4)	3.04E-02
atorvastatin (lipitor)	Xenobiotics	Drug	263 (89.5)	94 (81.7)	3.52E-02
benzoylecgonine	Xenobiotics	Drug	293 (99.7)	112 (97.4)	3.61E-02
topiramate	Xenobiotics	Drug	293 (99.7)	112 (97.4)	3.61E-02
4-hydroxyphenylacetate	Amino Acid	Phenylalanine and Tyrosine Metabolism	125 (42.5)	36 (31.3)	3.69E-02
sucrose	Carbohydrate	Disaccharides and Oligosaccharides	68 (23.1)	16 (13.9)	3.81E-02
3-methylurate	Xenobiotics	Xanthine Metabolism	191 (65)	62 (53.9)	3.86E-02
Guanosine*	Nucleotide	Purine Metabolism, Guanine containing	82 (27.9)	44 (38.3)	4.11E-02
I-urobilinogen	Cofactors an	Hemoglobin and Porphyrin Metabolism	283 (96.3)	105 (91.3)	4.13E-02
alpha-CEHC sulfate*	Cofactors an	Tocopherol Metabolism	94 (32)	49 (42.6)	4.26E-02
Paroxetine*	Xenobiotics	Drug	284 (96.6)	115 (100)	4.52E-02

Frequency, n (%) of undetectability of metabolite in cases and controls reported with chi-square probabilities for difference in proportions.

*Metabolites that had significantly higher undetectability in cases compared to controls.

Supplementary Table 3: Metabolites attaining q<0.05 in Primary metabolomic analysis

								Model 1				Model 2 (Model 1+ SCre-eGFR)				Model 3 (Model 1+ SCys-eGFR)			
BIOCHEMICAL	PUBCHEM	CHEMSPIDER	KEGG	HMDB_ID	SUPER_PATHWAY	SUB_PATHWAY	Uremic solute	BETA	SE	P-value	Q-value	BETA	SE	P-value	Q-value	BETA	SE	P-value	Q-value
orotidine	92751	83729	C01103	HMDB00788	Nucleotide	Pyrimidine Metabolism, Orotate containing	Yes	0.7834	0.1441	5.46E-08	3.63E-05	0.8166	0.1542	1.17E-07	7.91E-05	0.6639	0.1724	1.17E-04	3.35E-02
N6-carbamoylthreonyladenosine	161466	141829		HMDB41623	Nucleotide	Purine Metabolism, Adenine containing	Yes	0.7325	0.1508	1.19E-06	3.98E-04	0.8162	0.1722	2.14E-06	7.22E-04	0.6091	0.2285	7.76E-03	3.25E-01
N-acetylthreonine	152204	3841173			Amino Acid	Glycine, Serine and Threonine Metabolism	Yes	0.7027	0.1522	3.92E-06	8.70E-04	0.7599	0.1708	8.51E-06	1.92E-03	0.5023	0.1877	7.41E-03	3.25E-01
pseudouridine	15047	21403010	C02067	HMDB00767	Nucleotide	Pyrimidine Metabolism, Uracil containing	Yes	0.6751	0.1532	1.05E-05	1.52E-03	0.7821	0.1837	2.09E-05	2.77E-03	0.4437	0.2495	7.59E-02	5.10E-01
tartronate (hydroxymalonate)	45	44	C02287	HMDB35227	Xenobiotics	Bacterial/Fungal	No	-0.5605	0.1277	1.14E-05	1.52E-03	-0.5507	0.1279	1.66E-05	2.77E-03	-0.472	0.1304	2.95E-04	4.96E-02
C-glycosyltryptophan	10981970	9157171			Amino Acid	Tryptophan Metabolism	Yes	0.6261	0.1468	2.00E-05	2.08E-03	0.6643	0.1654	5.89E-05	5.16E-03	0.3679	0.2202	9.55E-02	5.47E-01
N-acetylputrescine	122356	109095	C02714	HMDB02064	Amino Acid	Polyamine Metabolism	Yes	0.5569	0.1312	2.18E-05	2.08E-03	0.5431	0.1355	6.17E-05	5.16E-03	0.4105	0.1402	3.39E-03	2.78E-01
2-piperidinone	12665	12144			Xenobiotics	Food Component/Plant	No	0.5226	0.1244	2.65E-05	2.20E-03	0.5152	0.1249	3.72E-05	4.15E-03	0.4845	0.1275	1.45E-04	3.35E-02
O-sulfo-L-tyrosine	514186	448617			Xenobiotics	Chemical	Yes	0.6095	0.1464	3.12E-05	2.31E-03	0.6342	0.1629	1.00E-04	7.39E-03	0.3671	0.1829	4.47E-02	4.59E-01
N1-methylinosine	65095	513976		HMDB02721	Nucleotide	Purine Metabolism, (Hypo)Xanthine/Inosine containing	Yes	0.5766	0.1415	4.63E-05	3.08E-03	0.5876	0.1557	1.62E-04	9.80E-03	0.3216	0.1784	7.08E-02	5.10E-01
N-acetylhistidine	75619	68142	C02997	HMDB32055	Amino Acid	Histidine Metabolism	Yes	0.5465	0.1384	7.80E-05	4.35E-03	0.5466	0.1488	2.40E-04	1.32E-02	0.3661	0.1528	1.66E-02	3.98E-01
glycerophosphoinositol*					Lipid	Phospholipid Metabolism	No	-0.4742	0.1205	8.35E-05	4.35E-03	-0.4663	0.1207	1.12E-04	7.46E-03	-0.4719	0.1245	1.51E-04	3.35E-02
N-acetylalanine	88064	79449	C02847	HMDB00766	Amino Acid	Alanine and Aspartate Metabolism	Yes	0.5865	0.1492	8.48E-05	4.35E-03	0.6051	0.1655	2.57E-04	1.32E-02	0.3012	0.1905	1.15E-01	5.63E-01
N6-acetyllysine	92832	83801	C02727	HMDB00206	Amino Acid	Lysine Metabolism	Yes	0.5063	0.1299	9.73E-05	4.63E-03	0.4919	0.1355	2.82E-04	1.36E-02	0.3502	0.1411	1.32E-02	3.52E-01
homostachydrine*	441447	390180	C08283	HMDB33433	Xenobiotics	Food Component/Plant	No	0.4629	0.121	1.31E-04	5.82E-03	0.4445	0.1236	3.24E-04	1.44E-02	0.3388	0.1278	7.94E-03	3.25E-01
N-acetylserine	65249	58744		HMDB02931	Amino Acid	Glycine, Serine and Threonine Metabolism	Yes	0.5159	0.1364	1.55E-04	6.10E-03	0.502	0.1436	4.79E-04	1.52E-02	0.2949	0.1592	6.46E-02	4.94E-01
N-acetyltaurine	159864	140553			Amino Acid	Methionine, Cysteine, SAM and Taurine Metabolism	Yes	0.5185	0.1371	1.56E-04	6.10E-03	0.4983	0.141	4.07E-04	1.52E-02	0.3349	0.1516	2.69E-02	4.49E-01
N-acetylvaline	66789	60154		HMDB11757	Amino Acid	Leucine, Isoleucine and Valine Metabolism	Yes	0.5003	0.133	1.69E-04	6.10E-03	0.4839	0.139	5.01E-04	1.52E-02	0.3018	0.1514	4.68E-02	4.59E-01
2-methylbutyrylcarnitine (C5)	6426901	4932320		HMDB00378	Amino Acid	Leucine, Isoleucine and Valine Metabolism	Yes	0.5178	0.1385	1.86E-04	6.10E-03	0.5029	0.1465	5.89E-04	1.52E-02	0.31	0.1539	4.37E-02	4.59E-01
N2,N2-dimethylguanosine	92919	83878		HMDB04824	Nucleotide	Purine Metabolism, Guanine containing	Yes	0.5256	0.1407	1.87E-04	6.10E-03	0.5417	0.1583	6.17E-04	1.52E-02	0.1715	0.2064	4.07E-01	7.80E-01
4-acetamidobutanoate	18189	17180	C02946	HMDB03681	Amino Acid	Polyamine Metabolism	Yes	0.511	0.137	1.92E-04	6.10E-03	0.5032	0.1466	6.03E-04	1.52E-02	0.2798	0.1566	7.41E-02	5.10E-01
propionylcarnitine (C3)	107738	96904	C03017	HMDB00824	Lipid	Fatty Acid Metabolism (also BCAA Metabolism)	Yes	0.4773	0.1288	2.10E-04	6.25E-03	0.456	0.1307	4.79E-04	1.52E-02	0.3797	0.133	4.27E-03	2.78E-01
2-methylcitrate/homocitrate					Energy	TCA Cycle	Yes	0.4892	0.1322	2.16E-04	6.25E-03	0.4677	0.1359	5.75E-04	1.52E-02	0.3501	0.1397	1.23E-02	3.52E-01
glycerol	753	733	C00116	HMDB00131	Lipid	Glycerolipid Metabolism	No	0.4478	0.1226	2.60E-04	7.20E-03	0.4374	0.123	3.80E-04	1.48E-02	0.3835	0.1256	2.24E-03	2.53E-01
N-carbamoylaspartate	93072	4573859	C00438	HMDB00828	Nucleotide	Pyrimidine Metabolism, Orotate containing	Yes	0.4351	0.1207	3.12E-04	7.80E-03	0.4167	0.1217	6.17E-04	1.52E-02	0.3164	0.1244	1.10E-02	3.52E-01
o-cresol sulfate	11615528	9790277			Amino Acid	Phenylalanine and Tyrosine Metabolism	Yes	0.441	0.1225	3.20E-04	7.80E-03	0.44	0.1231	3.47E-04	1.47E-02	0.4106	0.1252	1.05E-03	1.40E-01
4-hydroxyphenylacetylglutamine					Peptide	Acetylated Peptides	Yes	0.4397	0.1225	3.31E-04	7.80E-03	0.422	0.1278	9.55E-04	2.14E-02	0.2667	0.1336	4.57E-02	4.59E-01
N-acetyl-1-methylhistidine*				HMDB00001	Amino Acid	Histidine Metabolism	Yes	0.3664	0.1021	3.34E-04	7.80E-03	0.352	0.1066	9.55E-04	2.14E-02	0.2296	0.1087	3.47E-02	4.53E-01
quinolinate	1066	1037	C03722	HMDB00232	Cofactors and Vitami	Nicotinate and Nicotinamide Metabolism	Yes	0.4664	0.1303	3.44E-04	7.80E-03	0.4486	0.1374	1.10E-03	2.23E-02	0.1899	0.1626	2.45E-01	6.75E-01
stearoylcarnitine (C18)	6426855	21233653		HMDB00848	Lipid	Fatty Acid Metabolism(Acyl Carnitine)	No	0.4319	0.1208	3.51E-04	7.80E-03	0.4151	0.1215	6.31E-04	1.52E-02	0.3681	0.1241	3.02E-03	2.78E-01
1-stearoyl-GPG (18:0)		21403138			Lipid	Lysolipid	No	0.3724	0.1046	3.68E-04	7.91E-03	0.3642	0.1046	5.01E-04	1.52E-02	0.3023	0.108	5.13E-03	2.78E-01
3-hydroxy-3-methylglutarate	1662	4573695	C03761	HMDB00355	Lipid	Mevalonate Metabolism	Yes	0.4565	0.1289	3.97E-04	8.26E-03	0.4378	0.136	1.29E-03	2.54E-02	0.2672	0.1402	5.62E-02	4.81E-01
N-acetylneuraminate	439197	10292217	C00270	HMDB00230	Carbohydrate	Aminosugar Metabolism	Yes	0.4698	0.1334	4.29E-04	8.65E-03	0.4565	0.1425	1.35E-03	2.60E-02	0.228	0.1607	1.55E-01	6.22E-01
kynurenine	161166	141580	C00328	HMDB00684	Amino Acid	Tryptophan Metabolism	Yes	0.4514	0.1303	5.34E-04	1.05E-02	0.4369	0.1398	1.78E-03	3.14E-02	0.1771	0.1601	2.69E-01	6.94E-01
gluconate	10690	10240	C00257	HMDB00625	Xenobiotics	Food Component/Plant	Yes	0.3972	0.116	6.21E-04	1.18E-02	0.383	0.1163	9.77E-04	2.14E-02	0.3074	0.1172	8.71E-03	3.25E-01
N6-succinyladenosine				HMDB00912	Nucleotide	Purine Metabolism, Adenine containing	No	0.4505	0.1322	6.56E-04	1.21E-02	0.4393	0.1426	2.09E-03	3.47E-02	0.2148	0.1556	1.66E-01	6.25E-01
N-acetylaspartate (NAA)	65065	58576	C01042	HMDB00812	Amino Acid	Alanine and Aspartate Metabolism	Yes	0.4121	0.1218	7.20E-04	1.30E-02	0.3907	0.1243	1.66E-03	3.04E-02	0.2977	0.1268	1.91E-02	4.22E-01
acetylcarnitine (C2)	1	5406074	C02571	HMDB00201	Lipid	Fatty Acid Metabolism(Acyl Carnitine)	No	0.4334	0.1287	7.60E-04	1.33E-02	0.4096	0.1318	1.91E-03	3.25E-02	0.2978	0.135	2.75E-02	4.49E-01
dimethylarginine (SDMA + ADMA)	123831	110375	C03626	HMDB01539	Amino Acid	Urea cycle; Arginine and Proline Metabolism	Yes	0.4568	0.1361	7.87E-04	1.34E-02	0.4454	0.1484	2.69E-03	4.00E-02	0.1594	0.1692	3.47E-01	7.38E-01
succinate	1110	1078	C00042	HMDB00254	Energy	TCA Cycle	Yes	0.4216	0.1259	8.15E-04	1.34E-02	0.416	0.1269	1.05E-03	2.18E-02	0.3667	0.13	4.79E-03	2.78E-01
palmitoylcarnitine (C16)	461	448	C02990	HMDB00222	Lipid	Fatty Acid Metabolism(Acyl Carnitine)	No	0.4036	0.1207	8.25E-04	1.34E-02	0.3866	0.1214	1.45E-03	2.69E-02	0.3198	0.125	1.05E-02	3.52E-01
6-hydroxyindole sulfate					Xenobiotics	Chemical	Yes	0.4273	0.1283	8.67E-04	1.37E-02	0.4029	0.1325	2.34E-03	3.80E-02	0.2766	0.135	4.07E-02	4.53E-01
urea	1176	1143	C00086	HMDB00294	Amino Acid	Urea cycle; Arginine and Proline Metabolism	Yes	0.4865	0.1464	8.90E-04	1.38E-02	0.483	0.1634	3.09E-03	4.46E-02	0.2451	0.1634	1.35E-01	5.86E-01
succinylcarnitine (C4-DC)				HMDB61717	Energy	TCA Cycle	No	0.4359	0.1325	1.00E-03	1.51E-02	0.4211	0.1435	3.31E-03	4.67E-02	0.1891	0.1564	2.29E-01	6.68E-01
N-acetylcitrulline	656979	571213	C15532	HMDB00856	Amino Acid	Urea cycle; Arginine and Proline Metabolism	Yes	0.4024	0.1233	1.09E-03	1.62E-02	0.3815	0.1255	2.40E-03	3.80E-02	0.2733	0.1293	3.47E-02	4.53E-01
O-methylcatechol sulfate	22473	21078			Xenobiotics	Benzoate Metabolism	Yes	0.4133	0.1293	1.40E-03	2.02E-02	0.3911	0.1313	2.88E-03	4.21E-02	0.2756	0.1376	4.57E-02	4.59E-01
7-methylguanine	11361	10883	C02242	HMDB00897	Nucleotide	Purine Metabolism, Guanine containing	Yes	0.4135	0.13	1.47E-03	2.08E-02	0.391	0.1382	4.68E-03	5.91E-02	0.1713	0.1514	2.57E-01	6.89E-01
3-indoxyl sulfate	10258	9840		HMDB00682	Amino Acid	Tryptophan Metabolism	Yes	0.4023	0.1277	1.64E-03	2.27E-02	0.3763	0.1325	4.47E-03	5.83E-02	0.2437	0.1353	7.24E-02	5.10E-01
1-methylhistidine	92105	83153	C01152	HMDB00001	Amino Acid	Histidine Metabolism	Yes	0.4675	0.1487	1.67E-03	2.27E-02	0.4651	0.1693	6.03E-03	6.82E-02	0.1722	0.1743	3.24E-01	7.38E-01
imidazole propionate	70630	63798		HMDB02271	Amino Acid	Histidine Metabolism	Yes	0.3575	0.1141	1.72E-03	2.30E-02	0.3362	0.1181	4.37E-03	5.80E-02	0.237	0.1208	5.01E-02	4.69E-01
N6,N6,N6-trimethyllysine	440120	140379	C03793	HMDB01325	Amino Acid	Lysine Metabolism	Yes	0.4035	0.13	1.91E-03	2.49E-02	0.3765	0.1345	5.13E-03	6.05E-02	0.2545	0.1374	6.46E-02	4.94E-01
1-palmitoyl-GPE (16:0)	9547069	7826019		HMDB11503	Lipid	Lysolipid	No	0.3648	0.1182	2.03E-03	2.60E-02	0.3559	0.1185	2.69E-03	4.00E-02	0.3198	0.1218	8.71E-03	3.25E-01
arabitol/xylitol					Carbohydrate	Pentose Metabolism	Yes	0.4126	0.1366	2.53E-03	3.17E-02	0.3924	0.1496	8.71E-03	8.45E-02	0.1161	0.165	4.79E-01	8.18E-01
margaroylcarnitine*					Lipid	Fatty Acid Metabolism(Acyl Carnitine)	No	0.3508	0.1172	2.77E-03	3.37E-02	0.3309	0.1182	5.13E-03	6.05E-02	0.2784	0.1214	2.19E-02	4.40E-01
allantoin	204	199	C02350	HMDB00462	Nucleotide	Purine Metabolism, (Hypo)Xanthine/Inosine containing	Yes	0.3583	0.1199	2.80E-03	3.37E-02	0.3337	0.1234	6.76E-03	7.39E-02	0.2011	0.1304	1.23E-01	5.73E-01
beta-hydroxyisovalerate	69362	62571		HMDB00754	Amino Acid	Leucine, Isoleucine and Valine Metabolism	No	0.3761	0.126	2.84E-03	3.37E-02	0.3517	0.1283	6.17E-03	6.82E-02	0.3109	0.1285	1.55E-02	3.87E-01
palmitoyl-linoleoyl-glycerol (16:0/18:2) [2]*					Lipid	Diacylglycerol	No	0.3583	0.1204	2.92E-03	3.41E-02	0.35	0.1211	3.80E-03	5.25E-02	0.2813	0.1249	2.45E-02	4.40E-01
1-linoleoyl-2-linolenoyl-GPC (18:2/18:3)*		24766802			Lipid	Phospholipid Metabolism	No	-0.2899	0.0976	2.99E-03	3.42E-02	-0.2962	0.0984	2.63E-03	4.00E-02	-0.2937	0.1016	3.80E-03	2.78E-01
pyroglutamine*	134508	118562			Amino Acid	Glutamate Metabolism	Yes	0.4073	0.1374	3.03E-03	3.42E-02	0.382	0.1483	1.00E-02	8.94E-02	0.1609	0.1553	3.02E-01	7.12E-01
1-stearoyl-GPE (18:0)	9547068	7826018		HMDB11130	Lipid	Lysolipid	No	0.3419	0.1163	3.28E-03	3.65E-02	0.3331	0.1168	4.37E-03	5.80E-02	0.2794	0.1195	1.95E-02	4.22E-01
2-palmitoleoylglycerol (16:1)*					Lipid	Monoacylglycerol	No	0.2625	0.0901	3.59E-03	3.88E-02	0.2531	0.0904	5.13E-03	6.05E-02	0.2292	0.0919	1.26E-02	3.52E-01
threonylphenylalanine	4099799;4099798	3313819			Peptide	Dipeptide	No	-0.3287	0.1132	3.67E-03	3.88E-02	-0.3161	0.1137	5.50E-03	6.30E-02	-0.2621	0.1176	2.57E-02	4.49E-01

urate	1175		C00366	HMDB00289	Nucleotide	Purine Metabolism, (Hypo)Xanthine/Inosine containing	Yes	0.3913	0.1345	3.61E-03	3.88E-02	0.361	0.1423	1.12E-02	9.63E-02	0.1425	0.1534	3.55E-01	7.38E-01
N-acetylleucine	70912	64075	C02710	HMDB11756	Amino Acid	Leucine, Isoleucine and Valine Metabolism	Yes	0.3446	0.1192	3.82E-03	3.98E-02	0.3236	0.121	7.41E-03	7.97E-02	0.2437	0.1256	5.25E-02	4.81E-01
N-acetylglutamine	182230	158492	C02716	HMDB06029	Amino Acid	Glutamate Metabolism	Yes	0.3718	0.1299	4.20E-03	4.30E-02	0.3436	0.1336	1.02E-02	8.94E-02	0.2194	0.1385	1.12E-01	5.63E-01
p-cresol sulfate	4615423	3806480	C01468	HMDB11635	Amino Acid	Phenylalanine and Tyrosine Metabolism	Yes	0.3342	0.1177	4.54E-03	4.58E-02	0.3107	0.1196	9.33E-03	8.79E-02	0.1999	0.1235	1.05E-01	5.63E-01
5-(galactosylhydroxy)-L-lysine					Amino Acid	Lysine Metabolism	Yes	0.3373	0.1192	4.66E-03	4.62E-02	0.3124	0.1272	1.41E-02	1.09E-01	0.0484	0.1369	7.24E-01	9.12E-01
erythritol	222285	13835932	C00503	HMDB02994	Xenobiotics	Food Component/Plant	Yes	0.3834	0.1357	4.72E-03	4.62E-02	0.3565	0.1473	1.55E-02	1.15E-01	0.0462	0.1708	7.94E-01	9.44E-01
2-hydroxylaurate	97783	88259			Lipid	Fatty Acid, Monohydroxy	No	-0.3352	0.1195	5.03E-03	4.85E-02	-0.3138	0.1209	9.33E-03	8.79E-02	-0.217	0.1239	7.94E-02	5.10E-01
palmitoyl-linoleoyl-glycerol (16:0/18:2	9543695	7822645		HMDB05207	Lipid	Diacylglycerol	No	0.335	0.1197	5.15E-03	4.90E-02	0.3264	0.1202	6.61E-03	7.25E-02	0.2575	0.1244	3.80E-02	4.53E-01
1-palmitoleoylglycerol (16:1)*					Lipid	Monoacylglycerol	No	0.3359	0.1203	5.22E-03	4.90E-02	0.3214	0.1207	7.76E-03	8.00E-02	0.2712	0.1244	2.95E-02	4.53E-01
sphinganine	3126	3014	C00836	HMDB00269	Lipid	Sphingolipid Metabolism	No	0.312	0.1119	5.31E-03	4.91E-02	0.3159	0.1127	5.13E-03	6.05E-02	0.2914	0.1148	1.12E-02	3.52E-01

Beta estimates, standard errors and p-values obtained from conditional logistic regression models with CVD outcome as dependent variable, matching variables (sex, storage time, Scre-eGFR, HbA1c) included in stratum statement, and metabolite as predictors adjusted by eGFR as indicated.

The Q-values are derived from Benjamin-Hochberg False Discovery Rate corrections for multiple comparisons involving the whole panel of 671 metabolites.

Supplementary Table 4: Effects of orotidine on case and component outcomes in Discovery cohort

				Model 1- Unadjusted by eGFR		Model 2- adjusted by SCre-eGFR		Model 3- adjusted by SCys-eGFR	
Outcome	**Ntotal**	**Ncases**	**Ncontrols**	**OR (95% CI)**	**P**	**OR (95% CI)**	**P**	**OR (95% CI)**	**P**
Total CVD	409	115	294	2.19 (1.65-2.90)	5.46E-08	2.26 (1.67-3.06)	1.17E-07	1.94 (1.39-2.72)	1.17E-04
CV events	373	79	294	1.92 (1.42-2.61)	2.65E-05	2.04 (1.47-2.82)	1.69E-05	1.83 (1.28-2.63)	9.00E-04
CV deaths	330	36	294	2.76 (1.74-4.39)	1.64E-05	2.65 (1.63-4.31)	8.74E-05	2.01 (1.14-3.54)	1.50E-02
MI	321	27	294	1.60 (1.00-2.57)	5.00E-02	1.72 (1.05-2.81)	3.20E-02	1.78 (1.03-3.07)	3.90E-02
PTCA	332	38	294	1.59 (1.08-2.35)	2.00E-02	1.60 (1.05-2.42)	2.90E-02	1.63 (1.03-2.58)	3.80E-02
CABG	313	19	294	1.58 (0.90-2.79)	1.10E-01	1.75 (1.00-3.09)	5.00E-02	1.56 (0.84-2.88)	1.60E-01
Stroke	313	19	294	2.47 (1.39-4.39)	2.00E-03	2.40 (1.31-4.39)	4.00E-03	1.61 (0.77-3.35)	2.10E-01

*Base model (Model 1) is conditional logistic regression analysis conditioned on matching variables

Supplementary Table 5: Effects of orotidine on incident CVD, stratified by baseline CVD status

Model	No Prior CVD (N=48/289 events)		Prior CVD + (N=30/76 events)		P for orotidine*prior cvd interaction
	OR (95% CI)	P	OR (95% CI)	P	
Model 1: Unadjusted by eGFR	2.33 (1.58-3.45)	2.36E-05	1.21 (0.69-2.11)	5.11E-01	1.10E-01
Model 2: adjusted by SCre-eGFR	2.40 (1.59-3.63)	3.07E-05	1.04 (0.99-1.09)	2.70E-01	1.10E-01
Model 3: adjusted by SCys-eGFR	2.21 (1.41-3.44)	5.03E-04	1.11 (0.58-2.11)	7.50E-01	1.04E-01
Model 4: Ful model	2.26 (1.25-4.09)	7.00E-03	0.86 (0.22-3.32)	8.30E-01	4.00E-02

Supplementary Table 6: Previously reported CV risk metabolites

BIOCHEMICAL	SUB_PATHWAY	Model 1				Model 2 (Model 1+ SCre-eGFR)				Model 3 (Model 1+ SCys-eGFR)			
		beta	SE	P	Q	beta	SE	P	Q	beta	SE	P	Q
stearoylcarnitine (C18)	Fatty Acid Metabolism(Acyl Carnitine)	0.4319	0.1208	3.51E-04	7.80E-03	0.4151	0.1215	6.31E-04	1.52E-02	0.3681	0.1241	3.02E-03	2.78E-01
kynurenine	Tryptophan Metabolism	0.4514	0.1303	5.34E-04	1.05E-02	0.4369	0.1398	1.78E-03	3.14E-02	0.1771	0.1601	2.69E-01	6.94E-01
acetylcarnitine (C2)	Fatty Acid Metabolism(Acyl Carnitine)	0.4334	0.1287	7.60E-04	1.33E-02	0.4096	0.1318	1.91E-03	3.25E-02	0.2978	0.135	2.75E-02	4.49E-01
dimethylarginine (SDMA + ADMA)	Urea cycle; Arginine and Proline Metabolism	0.4568	0.1361	7.87E-04	1.34E-02	0.4454	0.1484	2.69E-03	4.00E-02	0.1594	0.1692	3.47E-01	7.38E-01
palmitoylcarnitine (C16)	Fatty Acid Metabolism(Acyl Carnitine)	0.4036	0.1207	8.25E-04	1.34E-02	0.3866	0.1214	1.45E-03	2.69E-02	0.3198	0.125	1.05E-02	3.52E-01
oleoylcarnitine (C18:1)	Fatty Acid Metabolism(Acyl Carnitine)	0.3275	0.1189	5.89E-03	5.16E-02	0.3104	0.1194	9.33E-03	8.79E-02	0.2246	0.1238	6.92E-02	5.10E-01
isobutyrylcarnitine (C4)	Leucine, Isoleucine and Valine Metabolism	0.3123	0.128	1.47E-02	9.52E-02	0.2805	0.1314	3.31E-02	1.92E-01	0.1605	0.135	2.34E-01	6.68E-01
butyrylcarnitine (C4)	Fatty Acid Metabolism (also BCAA Metabolism)	0.2698	0.117	2.12E-02	1.25E-01	0.2607	0.1174	2.63E-02	1.69E-01	0.1958	0.1185	9.77E-02	5.49E-01
myristoylcarnitine (C14)	Fatty Acid Metabolism(Acyl Carnitine)	0.257	0.1144	2.47E-02	1.38E-01	0.2337	0.1158	4.37E-02	2.18E-01	0.1536	0.1188	1.95E-01	6.48E-01
1-stearoyl-GPC (18:0)	Lysolipid	0.2432	0.1142	3.31E-02	1.59E-01	0.2495	0.1147	2.95E-02	1.80E-01	0.2032	0.1181	8.51E-02	5.19E-01
glutamine	Glutamate Metabolism	-0.2325	0.116	4.51E-02	1.95E-01	-0.2239	0.1164	5.50E-02	2.53E-01	-0.2109	0.1174	7.24E-02	5.10E-01
1-linoleoyl-GPC (18:2)	Lysolipid	-0.2289	0.1147	4.60E-02	1.96E-01	-0.2229	0.1147	5.25E-02	2.48E-01	-0.171	0.1171	1.45E-01	6.01E-01
phenylalanine	Phenylalanine and Tyrosine Metabolism	0.225	0.1147	4.99E-02	2.03E-01	0.2171	0.1151	5.89E-02	2.66E-01	0.1484	0.117	2.04E-01	6.48E-01
linoleoylcarnitine (C18:2)*	Fatty Acid Metabolism(Acyl Carnitine)	0.2243	0.1164	5.40E-02	2.13E-01	0.2198	0.117	6.03E-02	2.66E-01	0.1427	0.1207	2.34E-01	6.71E-01
3-hydroxybutyrylcarnitine (1)	Fatty Acid Metabolism(Acyl Carnitine)	0.2286	0.1211	5.92E-02	2.23E-01	0.1966	0.1241	1.12E-01	3.58E-01	0.0921	0.1276	4.68E-01	8.18E-01
glutarylcarnitine (C5-DC)	Lysine Metabolism	0.1885	0.1069	7.77E-02	2.66E-01	0.1477	0.1141	1.95E-01	4.63E-01	0.0093	0.1144	9.33E-01	9.88E-01
ornithine	Urea cycle; Arginine and Proline Metabolism	0.1937	0.1165	9.63E-02	2.90E-01	0.1933	0.1167	9.77E-02	3.31E-01	0.1777	0.1196	1.38E-01	5.88E-01
tryptophan	Tryptophan Metabolism	-0.162	0.1169	1.66E-01	3.96E-01	-0.1437	0.1173	2.19E-01	4.85E-01	-0.0274	0.1241	8.32E-01	9.44E-01
laurylcarnitine (C12)	Fatty Acid Metabolism(Acyl Carnitine)	0.1542	0.1148	1.79E-01	4.11E-01	0.1272	0.116	2.75E-01	5.34E-01	0.0155	0.1212	8.91E-01	9.68E-01
1-palmitoleoyl-GPC (16:1)*	Lysolipid	0.1619	0.1199	1.77E-01	4.11E-01	0.1656	0.1193	1.66E-01	4.38E-01	0.134	0.1231	2.75E-01	6.94E-01
glutamate	Glutamate Metabolism	0.1509	0.1143	1.87E-01	4.18E-01	0.1512	0.1143	1.86E-01	4.60E-01	0.1552	0.116	1.82E-01	6.39E-01
glycine	Glycine, Serine and Threonine Metabolism	0.1584	0.1213	1.91E-01	4.24E-01	0.151	0.1215	2.14E-01	4.73E-01	0.0837	0.1258	5.01E-01	8.20E-01
asparagine	Alanine and Aspartate Metabolism	-0.1495	0.1152	1.95E-01	4.26E-01	-0.1435	0.1157	2.14E-01	4.74E-01	-0.0764	0.12	5.25E-01	8.21E-01
cis-4-decenoylcarnitine (C10:1)	Fatty Acid Metabolism(Acyl Carnitine)	0.1532	0.1197	2.01E-01	4.33E-01	0.1117	0.1238	3.63E-01	6.06E-01	-0.0541	0.1313	6.76E-01	8.94E-01
leucine	Leucine, Isoleucine and Valine Metabolism	0.1426	0.1118	2.02E-01	4.34E-01	0.1368	0.112	2.24E-01	4.85E-01	0.2012	0.1168	8.51E-02	5.19E-01
alanine	Alanine and Aspartate Metabolism	0.1333	0.1123	2.35E-01	4.67E-01	0.1325	0.1128	2.40E-01	5.02E-01	0.1618	0.117	1.66E-01	6.25E-01
histidine	Histidine Metabolism	-0.1344	0.1145	2.41E-01	4.76E-01	-0.1204	0.1147	2.95E-01	5.51E-01	0.0191	0.1209	8.71E-01	9.57E-01
valine	Leucine, Isoleucine and Valine Metabolism	0.1282	0.1123	2.53E-01	4.91E-01	0.1277	0.1124	2.57E-01	5.22E-01	0.1807	0.1169	1.23E-01	5.73E-01
beta-alanine	Pyrimidine Metabolism, Uracil containing	-0.1232	0.112	2.71E-01	5.05E-01	-0.1357	0.1128	2.29E-01	4.93E-01	-0.1008	0.1171	3.89E-01	7.74E-01
serine	Glycine, Serine and Threonine Metabolism	0.1213	0.1151	2.92E-01	5.24E-01	0.146	0.1161	2.09E-01	4.72E-01	0.1766	0.1189	1.38E-01	5.88E-01
octanoylcarnitine (C8)	Fatty Acid Metabolism(Acyl Carnitine)	0.1188	0.1158	3.05E-01	5.33E-01	0.0852	0.1184	4.68E-01	6.88E-01	-0.022	0.1224	8.51E-01	9.54E-01
decanoylcarnitine (C10)	Fatty Acid Metabolism(Acyl Carnitine)	0.0916	0.115	4.26E-01	6.33E-01	0.0583	0.1172	6.17E-01	7.85E-01	-0.0427	0.1209	7.24E-01	9.12E-01
isoleucine	Leucine, Isoleucine and Valine Metabolism	0.0869	0.1121	4.39E-01	6.38E-01	0.0795	0.1124	4.79E-01	6.92E-01	0.1252	0.1169	2.82E-01	6.94E-01
tyrosine	Phenylalanine and Tyrosine Metabolism	-0.0824	0.1124	4.64E-01	6.56E-01	-0.0784	0.1129	4.90E-01	6.99E-01	-0.0529	0.1159	6.46E-01	8.85E-01
stearoyl sphingomyelin (d18:1/18:0)	Sphingolipid Metabolism	0.0854	0.1201	4.77E-01	6.68E-01	0.0887	0.1207	4.57E-01	6.86E-01	0.111	0.1237	3.72E-01	7.58E-01
trans-4-hydroxyproline	Urea cycle; Arginine and Proline Metabolism	0.038	0.1158	7.43E-01	8.62E-01	0.0167	0.1172	8.91E-01	9.44E-01	-0.0224	0.1207	8.51E-01	9.52E-01
1-oleoyl-GPC (18:1)	Lysolipid	0.0311	0.113	7.83E-01	8.82E-01	0.0302	0.1128	7.94E-01	8.99E-01	-0.004	0.1157	9.77E-01	9.96E-01
citrulline	Urea cycle; Arginine and Proline Metabolism	-0.0042	0.1169	9.71E-01	9.89E-01	-0.0333	0.1185	7.76E-01	8.92E-01	-0.1402	0.1242	2.57E-01	6.89E-01

Beta estimates, standard errors and p-values obtained from conditional logistic regression models with CVD outcome as dependent variable, matching variables (sex, storage time, Scre-eGFR, HbA1c) included in stratum statement, and metabolite as predictors adjusted by eGFR as indicated.

The Q-values are derived from Benjamin-Hochberg False Discovery Rate corrections for multiple comparisons involving this panel of 38 metabolites.

Supplementary Table 7: Clinical characteristics of Cases and Controls in the Validation Set.

Characteristic	Controls (n=299)	Cases (n=300)	P
Females*	105 (35.1%)	73 (24.3%)	4.00E-03
Age (yrs)	63.48±5.43	64.9±6.9	5.00E-03
Age at diagnosis (yrs)	51.06±7.39	53.5±9.87	7.00E-04
Duration of diabetes (yrs)	12.5±5.95	11.42±8.52	7.60E-02
Sample storage time (yrs)	8.48±1.67	8.82±1.7	1.50E-02
BMI (kg/m2)	32.7±5.67	32.72±5.76	9.60E-01
HbA1C (%)	7.55±1.27	7.37±1.28	9.60E-02
Systolic BP (mmHg)	128.13±16.38	128.85±15.37	5.80E-01
Diastolic BP (mmHg)	74.96±9.76	70.63±10.91	<1.00E-04
Total Cholesterol (mg/dl)	164.91±34.83	153.33±36.75	<1.00E-04
Triglycerides (mg/dl)	170.14±105.53	172.34±112.77	8.10E-01
HDL-C (mg/dl)	49.33±14.62	40.74±12.27	<1.00E-04
LDL-C (mg/dl)	85.98±28.58	80.03±28.3	1.20E-02
SerCr eGFR (ml/min/1.73 m2)	77.56±18.35	73.35±20.52	8.00E-03
SerCys eGFR (ml/min/1.73 m2)	71.45±22.19	64.89±24.22	6.00E-04
History of smoking*	155 (54.2%)	195 (65.7%)	5.00E-03
Urinary ACR (mg/g)#	10.49 [5.24-32.58]	13.83 [6.05-57.70]	2.00E-02
Urinary ACR category (%)*			1.60E-02
Normoalbuminuria	212 (73.4%)	167 (62.6%)	
Microalbuminuria	65 (22.5%)	79 (29.6%)	
Macroalbuminuria	12 (4.2%)	21 (7.9%)	
Diabetes treatment (%)*			4.00E-03
Diet alone	2 (0.69%)	18 (6.0%)	
Oral	159 (54.8%)	164 (54.7%)	
Oral + Insulin	51 (17.6%)	47 (15.7%)	
Insulin	78 (26.9%)	71 (23.7%)	
RASB (%)*	228 (77.0%)	215 (72.6%)	2.00E-01
Calcium channel blockers (%)*	39 (13.1%)	62 (21.0%)	1.00E-02
Beta blockers (%)*	74 (25.0%)	245 (83.1%)	<1.00E-04
Alpha blockers (%)*	7 (2.4%)	13 (4.5%)	1.60E-01
Diuretics (%)*	64 (21.6%)	100 (33.8%)	9.00E-04
Statins (%)*	222 (75.0%)	266 (89.9%)	<1.00E-04
Thiazolidinediones (%)*	37 (12.5%)	22 (7.4%)	4.00E-02
Aspirin (%)*	173 (58.3%)	260 (87.8%)	<1.00E-04
Allopurinol (%)*	18 (6.0%)	12 (4.0%)	2.60E-01

Means (SD) or Median (IQR) presented for continuous variables and n,% frequencies presented for categorical variables (*). Two-sample independent t-test p-values for difference in means between cases and controls presented for continuous variables, and chi-square probabilities for categorical variables. #Kruskal-Wallis p-values for non-parametric variables.

Supplementary Table 8: Validation of significant metabolites associated with increased CV risk in T2D

Metabolite	Model	Validation Set [n=599]	
		OR (95% CI)	***P***
Orotidine	***Model 1: storage time + sex***	1.54 (1.28-1.86)	4.3E-06
	Model 2: SCre-eGFR + Model 1	1.53 (1.23-1.89)	1.0E-04
	Model 3: SCys-eGFR + Model 1	1.39 (1.11-1.75)	4.60E-03
2-piperidinone	***Model 1: storage time + sex***	1.14 (0.97-1.35)	1.10E-01
	Model 2: SCre-eGFR + Model 1	1.12 (0.95-1.33)	1.70E-01
	Model 3: SCys-eGFR + Model 1	1.10 (0.93 -1.30)	2.60E-01

Supplementary Table 9: Lipids detected in the Metabolon panel and their associations with CVD in the Discovery Set

			Model 1				Model 2 (Model 1+ SCre-eGFR)				Model 3 (Model 1+ SCys-eGFR)			
BIOCHEMICAL	SUPER_PATHWAY	SUB_PATHWAY	BETA	SE	P-value	Q-value	BETA	SE	P-value	Q-value	BETA	SE	P-value	Q-value
glycerophosphoinositol*	Lipid	Phospholipid Metabolism	-0.4742	0.1205	8.35E-05	4.35E-03	-0.4663	0.1207	1.12E-04	7.46E-03	-0.4719	0.1245	1.51E-04	3.35E-02
propionylcarnitine (C3)	Lipid	Fatty Acid Metabolism (also BCAA Metabolism)	0.4773	0.1288	2.10E-04	6.25E-03	0.456	0.1307	4.79E-04	1.52E-02	0.3797	0.133	4.27E-03	2.78E-01
glycerol	Lipid	Glycerolipid Metabolism	0.4478	0.1226	2.60E-04	7.20E-03	0.4374	0.123	3.80E-04	1.48E-02	0.3835	0.1256	2.24E-03	2.53E-01
stearoylcarnitine (C18)	Lipid	Fatty Acid Metabolism(Acyl Carnitine)	0.4319	0.1208	3.51E-04	7.80E-03	0.4151	0.1215	6.31E-04	1.52E-02	0.3681	0.1241	3.02E-03	2.78E-01
1-stearoyl-GPG (18:0)	Lipid	Lysolipid	0.3724	0.1046	3.68E-04	7.91E-03	0.3642	0.1046	5.01E-04	1.52E-02	0.3023	0.108	5.13E-03	2.78E-01
3-hydroxy-3-methylglutarate	Lipid	Mevalonate Metabolism	0.4565	0.1289	3.97E-04	8.26E-03	0.4378	0.136	1.29E-03	2.54E-02	0.2672	0.1402	5.62E-02	4.81E-01
acetylcarnitine (C2)	Lipid	Fatty Acid Metabolism(Acyl Carnitine)	0.4334	0.1287	7.60E-04	1.33E-02	0.4096	0.1318	1.91E-03	3.25E-02	0.2978	0.135	2.75E-02	4.49E-01
palmitoylcarnitine (C16)	Lipid	Fatty Acid Metabolism(Acyl Carnitine)	0.4036	0.1207	8.25E-04	1.34E-02	0.3866	0.1214	1.45E-03	2.69E-02	0.3198	0.125	1.05E-02	3.52E-01
1-palmitoyl-GPE (16:0)	Lipid	Lysolipid	0.3648	0.1182	2.03E-03	2.60E-02	0.3559	0.1185	2.69E-03	4.00E-02	0.3198	0.1218	8.71E-03	3.25E-01
margaroylcarnitine*	Lipid	Fatty Acid Metabolism(Acyl Carnitine)	0.3508	0.1172	2.77E-03	3.37E-02	0.3309	0.1182	5.13E-03	6.05E-02	0.2784	0.1214	2.19E-02	4.40E-01
palmitoyl-linoleoyl-glycerol (16:0/18:2) [2]*	Lipid	Diacylglycerol	0.3583	0.1204	2.92E-03	3.41E-02	0.35	0.1211	3.80E-03	5.25E-02	0.2813	0.1249	2.45E-02	4.40E-01
1-linoleoyl-2-linolenoyl-GPC (18:2/18:3)*	Lipid	Phospholipid Metabolism	-0.2899	0.0976	2.99E-03	3.42E-02	-0.2962	0.0984	2.63E-03	4.00E-02	-0.2937	0.1016	3.80E-03	2.78E-01
1-stearoyl-GPE (18:0)	Lipid	Lysolipid	0.3419	0.1163	3.28E-03	3.65E-02	0.3331	0.1168	4.37E-03	5.80E-02	0.2794	0.1195	1.95E-02	4.22E-01
2-palmitoleoylglycerol (16:1)*	Lipid	Monoacylglycerol	0.2625	0.0901	3.59E-03	3.88E-02	0.2531	0.0904	5.13E-03	6.05E-02	0.2292	0.0919	1.26E-02	3.52E-01
2-hydroxylaurate	Lipid	Fatty Acid, Monohydroxy	-0.3352	0.1195	5.03E-03	4.85E-02	-0.3138	0.1209	9.33E-03	8.79E-02	-0.217	0.1239	7.94E-02	5.10E-01
palmitoyl-linoleoyl-glycerol (16:0/18:2) [1]*	Lipid	Diacylglycerol	0.335	0.1197	5.15E-03	4.90E-02	0.3264	0.1202	6.61E-03	7.25E-02	0.2575	0.1244	3.80E-02	4.53E-01
1-palmitoleoylglycerol (16:1)*	Lipid	Monoacylglycerol	0.3359	0.1203	5.22E-03	4.90E-02	0.3214	0.1207	7.76E-03	8.00E-02	0.2712	0.1244	2.95E-02	4.53E-01
sphinganine	Lipid	Sphingolipid Metabolism	0.312	0.1119	5.31E-03	4.91E-02	0.3159	0.1127	5.13E-03	6.05E-02	0.2914	0.1148	1.12E-02	3.52E-01
1-margaroylglycerol (17:0)	Lipid	Monoacylglycerol	0.2574	0.0932	5.77E-03	5.13E-02	0.2477	0.0938	8.32E-03	8.15E-02	0.2161	0.0952	2.34E-02	4.40E-01
N-stearoyl-sphinganine (d18:0/18:0)*	Lipid	Sphingolipid Metabolism	0.3197	0.1158	5.76E-03	5.13E-02	0.309	0.1165	7.94E-03	8.08E-02	0.2427	0.1181	3.98E-02	4.53E-01
oleoylcarnitine (C18:1)	Lipid	Fatty Acid Metabolism(Acyl Carnitine)	0.3275	0.1189	5.89E-03	5.16E-02	0.3104	0.1194	9.33E-03	8.79E-02	0.2246	0.1238	6.92E-02	5.10E-01
2-stearoyl-GPE (18:0)*	Lipid	Lysolipid	0.3181	0.1165	6.34E-03	5.43E-02	0.3097	0.1169	8.13E-03	8.08E-02	0.2572	0.1194	3.16E-02	4.53E-01
palmitoyl-oleoyl-glycerol (16:0/18:1) [2]*	Lipid	Diacylglycerol	0.2398	0.0887	6.87E-03	5.65E-02	0.2371	0.0889	7.76E-03	8.00E-02	0.1828	0.0915	4.57E-02	4.59E-01
1-arachidonylglycerol (20:4)	Lipid	Monoacylglycerol	0.3082	0.1147	7.22E-03	5.79E-02	0.2978	0.1151	9.77E-03	8.91E-02	0.2546	0.1175	3.02E-02	4.53E-01
carnitine	Lipid	Carnitine Metabolism	0.3366	0.1262	7.65E-03	6.06E-02	0.3154	0.1271	1.32E-02	1.03E-01	0.2489	0.1297	5.50E-02	4.81E-01
dihomo-linolenoylcarnitine (20:3n3 or 6)*	Lipid	Fatty Acid Metabolism(Acyl Carnitine)	0.2333	0.0899	9.42E-03	7.37E-02	0.2282	0.0903	1.15E-02	9.73E-02	0.1761	0.0922	5.62E-02	4.81E-01
pregn steroid monosulfate*	Lipid	Steroid	-0.3555	0.1371	9.51E-03	7.37E-02	-0.3383	0.138	1.41E-02	1.09E-01	-0.2726	0.1428	5.62E-02	4.81E-01
1-stearoyl-2-arachidonoyl-GPE (18:0/20:4)	Lipid	Phospholipid Metabolism	0.3005	0.1173	1.04E-02	7.79E-02	0.2818	0.1186	1.74E-02	1.26E-01	0.2046	0.1216	9.33E-02	5.44E-01
palmitoyl-arachidonoyl-glycerol (16:0/20:4) [2]*	Lipid	Diacylglycerol	0.2863	0.1122	1.07E-02	7.93E-02	0.2781	0.1127	1.38E-02	1.07E-01	0.2437	0.115	3.39E-02	4.53E-01
docosadioate	Lipid	Fatty Acid, Dicarboxylate	-0.2949	0.116	1.10E-02	8.03E-02	-0.2998	0.1165	1.00E-02	8.94E-02	-0.2642	0.117	2.40E-02	4.40E-01
myo-inositol	Lipid	Inositol Metabolism	0.3413	0.1352	1.16E-02	8.29E-02	0.3056	0.1462	3.63E-02	2.01E-01	0.1205	0.1509	4.27E-01	7.87E-01
trimethylamine N-oxide	Lipid	Phospholipid Metabolism	0.2929	0.1175	1.27E-02	8.88E-02	0.2622	0.1226	3.24E-02	1.91E-01	0.1196	0.1282	3.55E-01	7.38E-01
1-oleoylglycerol (18:1)	Lipid	Monoacylglycerol	0.294	0.1193	1.37E-02	9.43E-02	0.2804	0.1199	1.95E-02	1.32E-01	0.2365	0.1236	5.62E-02	4.81E-01
choline	Lipid	Phospholipid Metabolism	0.2797	0.1141	1.42E-02	9.51E-02	0.2776	0.1151	1.58E-02	1.17E-01	0.2108	0.1202	7.94E-02	5.10E-01
1-palmitoylglycerol (16:0)	Lipid	Monoacylglycerol	0.2863	0.1169	1.43E-02	9.51E-02	0.276	0.117	1.82E-02	1.28E-01	0.2473	0.1199	3.89E-02	4.53E-01
sphingosine	Lipid	Sphingolipid Metabolism	0.2766	0.1127	1.41E-02	9.51E-02	0.2841	0.1132	1.20E-02	9.74E-02	0.2357	0.1146	3.98E-02	4.53E-01
1-palmitoyl-GPC (16:0)	Lipid	Lysolipid	0.2858	0.1173	1.49E-02	9.52E-02	0.2961	0.1175	1.17E-02	9.74E-02	0.2466	0.1194	3.89E-02	4.53E-01
taurolithocholate 3-sulfate	Lipid	Secondary Bile Acid Metabolism	-0.2655	0.1089	1.48E-02	9.52E-02	-0.2756	0.1093	1.17E-02	9.74E-02	-0.3096	0.1113	5.37E-03	2.78E-01
deoxycarnitine	Lipid	Carnitine Metabolism	0.3209	0.1323	1.53E-02	9.62E-02	0.287	0.137	3.63E-02	2.01E-01	0.178	0.1395	2.04E-01	6.48E-01
1-palmitoyl-2-arachidonoyl-GPE (16:0/20:4)*	Lipid	Phospholipid Metabolism	0.2774	0.1169	1.77E-02	1.08E-01	0.2582	0.1183	2.88E-02	1.77E-01	0.1848	0.1216	1.29E-01	5.80E-01
1-myristoylglycerol (14:0)	Lipid	Monoacylglycerol	0.2749	0.1183	2.02E-02	1.20E-01	0.2714	0.1186	2.19E-02	1.48E-01	0.2547	0.1215	3.63E-02	4.53E-01
butyrylcarnitine (C4)	Lipid	Fatty Acid Metabolism (also BCAA Metabolism)	0.2698	0.117	2.12E-02	1.25E-01	0.2607	0.1174	2.63E-02	1.69E-01	0.1958	0.1185	9.77E-02	5.49E-01
sphingomyelin (d18:0/18:0, d19:0/17:0)*	Lipid	Sphingolipid Metabolism	0.2686	0.1179	2.27E-02	1.32E-01	0.2642	0.1183	2.57E-02	1.65E-01	0.2234	0.1197	6.17E-02	4.94E-01
stearidonate (18:4n3)	Lipid	Polyunsaturated Fatty Acid (n3 and n6)	0.2607	0.1156	2.42E-02	1.38E-01	0.2611	0.1158	2.40E-02	1.57E-01	0.2907	0.12	1.55E-02	3.87E-01
myristoylcarnitine (C14)	Lipid	Fatty Acid Metabolism(Acyl Carnitine)	0.257	0.1144	2.47E-02	1.38E-01	0.2337	0.1158	4.37E-02	2.18E-01	0.1536	0.1188	1.95E-01	6.48E-01
1-palmitoyl-2-oleoyl-GPE (16:0/18:1)	Lipid	Phospholipid Metabolism	0.256	0.1154	2.65E-02	1.46E-01	0.2354	0.1166	4.37E-02	2.18E-01	0.1538	0.1208	2.04E-01	6.48E-01
1-(1-enyl-palmitoyl)-2-linoleoyl-GPC (P-16:0/18:2)*	Lipid	Plasmalogen	-0.258	0.1167	2.70E-02	1.46E-01	-0.2522	0.1165	3.02E-02	1.82E-01	-0.1742	0.1199	1.48E-01	6.02E-01
N-oleoyltaurine	Lipid	Endocannabinoid	0.2354	0.1062	2.67E-02	1.46E-01	0.2251	0.1064	3.47E-02	1.94E-01	0.1851	0.1075	8.51E-02	5.19E-01
linoleoyl-arachidonoyl-glycerol (18:2/20:4) [1]*	Lipid	Diacylglycerol	0.2513	0.1143	2.78E-02	1.48E-01	0.2429	0.1147	3.39E-02	1.94E-01	0.2063	0.1168	7.76E-02	5.10E-01
1-palmitoyl-GPA (16:0)	Lipid	Lysolipid	0.2644	0.1201	2.77E-02	1.48E-01	0.2759	0.1205	2.19E-02	1.48E-01	0.2039	0.1236	1.00E-01	5.49E-01
behenoyl dihydrosphingomyelin (d18:0/22:0)*	Lipid	Sphingolipid Metabolism	0.2561	0.1167	2.82E-02	1.48E-01	0.2582	0.1169	2.69E-02	1.70E-01	0.2696	0.1186	2.29E-02	4.40E-01
sphingomyelin (d18:0/20:0, d16:0/22:0)*	Lipid	Sphingolipid Metabolism	0.2579	0.1178	2.86E-02	1.48E-01	0.2533	0.1182	3.24E-02	1.91E-01	0.2619	0.1203	2.95E-02	4.53E-01
diacylglycerol (16:1/18:2 [2], 16:0/18:3 [1])*	Lipid	Diacylglycerol	0.24	0.1101	2.92E-02	1.50E-01	0.223	0.111	4.47E-02	2.21E-01	0.1573	0.114	1.66E-01	6.25E-01

oleoyl-linoleoyl-glycerol (18:1/18:2) [2]	Lipid	Diacylglycerol	0.2528	0.1171	3.09E-02	1.53E-01	0.2311	0.1187	5.13E-02	2.47E-01	0.1376	0.1236	2.63E-01	6.92E-01
1-linolenoylglycerol (18:3)	Lipid	Monoacylglycerol	0.2471	0.1153	3.22E-02	1.57E-01	0.2345	0.1158	4.27E-02	2.18E-01	0.2089	0.1178	7.59E-02	5.10E-01
1-stearoyl-GPC (18:0)	Lipid	Lysolipid	0.2432	0.1142	3.31E-02	1.59E-01	0.2495	0.1147	2.95E-02	1.80E-01	0.2032	0.1181	8.51E-02	5.19E-01
1-oleoyl-2-arachidonoyl-GPE (18:1/20:4)*	Lipid	Phospholipid Metabolism	0.2434	0.1155	3.51E-02	1.67E-01	0.2218	0.1171	5.89E-02	2.66E-01	0.1158	0.1217	3.39E-01	7.38E-01
2-palmitoylglycerol (16:0)	Lipid	Monoacylglycerol	0.2039	0.0975	3.65E-02	1.73E-01	0.1992	0.0978	4.17E-02	2.15E-01	0.1614	0.1004	1.07E-01	5.63E-01
1-palmitoyl-GPG (16:0)*	Lipid	Lysolipid	0.1936	0.0932	3.79E-02	1.74E-01	0.1905	0.0934	4.17E-02	2.15E-01	0.1499	0.0955	1.17E-01	5.63E-01
palmitoleate (16:1n7)	Lipid	Long Chain Fatty Acid	0.2414	0.1176	4.01E-02	1.83E-01	0.2374	0.1177	4.37E-02	2.18E-01	0.2082	0.1205	8.32E-02	5.19E-01
2-oleoylglycerol (18:1)	Lipid	Monoacylglycerol	0.2315	0.1138	4.20E-02	1.88E-01	0.2206	0.1141	5.37E-02	2.50E-01	0.2037	0.1163	7.94E-02	5.10E-01
10-heptadecenoate (17:1n7)	Lipid	Long Chain Fatty Acid	0.2357	0.1155	4.12E-02	1.86E-01	0.2276	0.1157	4.90E-02	2.39E-01	0.2089	0.1189	7.94E-02	5.10E-01
1,2-dilinoleoyl-GPC (18:2/18:2)	Lipid	Phospholipid Metabolism	-0.2338	0.1152	4.23E-02	1.88E-01	-0.2414	0.1159	3.72E-02	2.04E-01	-0.2534	0.1195	3.39E-02	4.53E-01
eicosanodioate	Lipid	Fatty Acid, Dicarboxylate	-0.2292	0.1132	4.29E-02	1.89E-01	-0.2334	0.1133	3.98E-02	2.10E-01	-0.22	0.1142	5.37E-02	4.81E-01
5alpha-pregnan-3beta,20alpha-diol monosulfate (2)	Lipid	Steroid	-0.2268	0.1127	4.41E-02	1.92E-01	-0.2178	0.1134	5.50E-02	2.53E-01	-0.1976	0.1179	9.33E-02	5.47E-01
1-dihomo-linolenylglycerol (20:3)	Lipid	Monoacylglycerol	0.2299	0.1143	4.42E-02	1.92E-01	0.214	0.1148	6.17E-02	2.70E-01	0.1674	0.1171	1.51E-01	6.22E-01
1-dihomo-linoleoylglycerol (20:2)	Lipid	Fatty Acid, Keto	0.2348	0.1174	4.54E-02	1.95E-01	0.2178	0.118	6.46E-02	2.72E-01	0.1785	0.1202	1.38E-01	5.88E-01
1-linoleoyl-GPC (18:2)	Lipid	Lysolipid	-0.2289	0.1147	4.60E-02	1.96E-01	-0.2229	0.1147	5.25E-02	2.48E-01	-0.171	0.1171	1.45E-01	6.01E-01
hexanoylcarnitine (C6)	Lipid	Fatty Acid Metabolism(Acyl Carnitine)	0.2328	0.1181	4.88E-02	2.02E-01	0.2012	0.1209	9.55E-02	3.31E-01	0.0821	0.1241	5.13E-01	8.20E-01
oleoyl-oleoyl-glycerol (18:1/18:1) [1]*	Lipid	Diacylglycerol	0.1882	0.0963	5.07E-02	2.04E-01	0.174	0.0965	7.08E-02	2.92E-01	0.1185	0.0991	2.29E-01	6.68E-01
4-cholesten-3-one	Lipid	Sterol	0.2403	0.1234	5.15E-02	2.04E-01	0.2316	0.1238	6.17E-02	2.70E-01	0.167	0.1265	1.86E-01	6.46E-01
dehydroisoandrosterone sulfate (DHEA-S)	Lipid	Steroid	-0.2337	0.1199	5.13E-02	2.04E-01	-0.2124	0.1209	7.94E-02	3.05E-01	-0.1395	0.1247	2.63E-01	6.92E-01
sphingomyelin (d18:2/16:0, d18:1/16:1)*	Lipid	Sphingolipid Metabolism	0.2481	0.1274	5.15E-02	2.04E-01	0.2275	0.1273	7.41E-02	2.97E-01	0.0888	0.1364	5.13E-01	8.20E-01
linoleoylcarnitine (C18:2)*	Lipid	Fatty Acid Metabolism(Acyl Carnitine)	0.2243	0.1164	5.40E-02	2.13E-01	0.2198	0.117	6.03E-02	2.66E-01	0.1427	0.1207	2.34E-01	6.71E-01
cerotoylcarnitine (C26)*	Lipid	Fatty Acid Metabolism(Acyl Carnitine)	0.2275	0.1185	5.48E-02	2.13E-01	0.2331	0.1192	5.01E-02	2.44E-01	0.2155	0.1204	7.41E-02	5.10E-01
1-pentadecanoylglycerol (15:0)	Lipid	Monoacylglycerol	0.1812	0.0943	5.48E-02	2.13E-01	0.1756	0.0947	6.31E-02	2.70E-01	0.137	0.0972	1.58E-01	6.22E-01
oleoyl-linoleoyl-glycerol (18:1/18:2) [1]	Lipid	Diacylglycerol	0.2233	0.1167	5.57E-02	2.13E-01	0.2004	0.1183	8.91E-02	3.22E-01	0.1049	0.1236	3.98E-01	7.75E-01
2-linoleoylglycerol (18:2)	Lipid	Monoacylglycerol	0.2174	0.1143	5.72E-02	2.18E-01	0.205	0.1144	7.24E-02	2.96E-01	0.1867	0.1167	1.10E-01	5.63E-01
etiocholanolone glucuronide	Lipid	Steroid	0.2249	0.1184	5.76E-02	2.18E-01	0.2036	0.1198	8.91E-02	3.22E-01	0.1237	0.1214	3.09E-01	7.18E-01
3-hydroxybutyrylcarnitine (1)	Lipid	Fatty Acid Metabolism(Acyl Carnitine)	0.2286	0.1211	5.92E-02	2.23E-01	0.1966	0.1241	1.12E-01	3.58E-01	0.0921	0.1276	4.68E-01	8.18E-01
1-linoleoylglycerol (18:2)	Lipid	Monoacylglycerol	0.2163	0.1158	6.18E-02	2.29E-01	0.2008	0.1164	8.51E-02	3.13E-01	0.162	0.1185	1.70E-01	6.28E-01
pregnenolone sulfate	Lipid	Steroid	-0.2074	0.1112	6.21E-02	2.29E-01	-0.1842	0.1125	1.02E-01	3.41E-01	-0.1478	0.1154	2.00E-01	6.48E-01
N-palmitoyl-sphinganine (d18:0/16:0)	Lipid	Sphingolipid Metabolism	0.2081	0.1144	6.88E-02	2.50E-01	0.2027	0.1154	7.94E-02	3.05E-01	0.1762	0.1187	1.38E-01	5.88E-01
pentadecanoate (15:0)	Lipid	Long Chain Fatty Acid	0.2067	0.1145	7.09E-02	2.56E-01	0.203	0.1146	7.59E-02	3.02E-01	0.1966	0.1179	9.55E-02	5.47E-01
3-methylglutarate/2-methylglutarate	Lipid	Fatty Acid, Dicarboxylate	0.2051	0.1146	7.36E-02	2.59E-01	0.1929	0.115	9.33E-02	3.27E-01	0.1273	0.1184	2.82E-01	6.94E-01
myristate (14:0)	Lipid	Long Chain Fatty Acid	0.2063	0.1154	7.39E-02	2.59E-01	0.2064	0.1156	7.41E-02	2.97E-01	0.2272	0.1199	5.75E-02	4.85E-01
ximenoylcarnitine (C26:1)*	Lipid	Fatty Acid Metabolism(Acyl Carnitine)	0.2018	0.1135	7.54E-02	2.60E-01	0.1996	0.1136	7.94E-02	3.05E-01	0.123	0.1167	2.95E-01	7.02E-01
octadecanedioate	Lipid	Fatty Acid, Dicarboxylate	-0.2013	0.114	7.75E-02	2.66E-01	-0.2021	0.1143	7.76E-02	3.02E-01	-0.2071	0.1158	7.41E-02	5.10E-01
caproate (6:0)	Lipid	Medium Chain Fatty Acid	0.1984	0.1128	7.85E-02	2.66E-01	0.2045	0.1133	7.08E-02	2.92E-01	0.176	0.1151	1.26E-01	5.80E-01
myristoleate (14:1n5)	Lipid	Long Chain Fatty Acid	0.2018	0.1153	8.01E-02	2.69E-01	0.191	0.1156	9.77E-02	3.32E-01	0.1818	0.1193	1.29E-01	5.80E-01
1-(1-enyl-stearoyl)-2-linoleoyl-GPE (P-18:0/18:2)*	Lipid	Plasmalogen	-0.2005	0.1157	8.33E-02	2.79E-01	-0.198	0.1165	8.91E-02	3.22E-01	-0.1702	0.119	1.51E-01	6.22E-01
glycodeoxycholate sulfate	Lipid	Secondary Bile Acid Metabolism	-0.1818	0.1052	8.41E-02	2.80E-01	-0.1879	0.1056	7.59E-02	2.99E-01	-0.2248	0.1086	3.80E-02	4.53E-01
glycolithocholate sulfate*	Lipid	Secondary Bile Acid Metabolism	-0.1922	0.1117	8.53E-02	2.81E-01	-0.1944	0.1118	8.13E-02	3.13E-01	-0.233	0.1146	4.17E-02	4.59E-01
2-aminoheptanoate	Lipid	Fatty Acid, Amino	0.2046	0.1198	8.76E-02	2.82E-01	0.1718	0.123	1.62E-01	4.34E-01	0.0004	0.1312	1.00E+00	9.98E-01
arachidonate (20:4n6)	Lipid	Polyunsaturated Fatty Acid (n3 and n6)	0.1989	0.1161	8.66E-02	2.81E-01	0.2121	0.1165	6.92E-02	2.85E-01	0.1899	0.1194	1.12E-01	5.63E-01
palmitic amide	Lipid	Fatty Acid, Amide	0.1874	0.1095	8.72E-02	2.82E-01	0.1829	0.1103	9.77E-02	3.31E-01	0.1399	0.1126	2.14E-01	6.54E-01
1-arachidonoyl-GPE (20:4n6)*	Lipid	Lysolipid	0.1915	0.1123	8.82E-02	2.82E-01	0.1835	0.1123	1.02E-01	3.41E-01	0.1829	0.1142	1.10E-01	5.63E-01
palmitoleoylcarnitine (C16:1)*	Lipid	Fatty Acid Metabolism(Acyl Carnitine)	0.1923	0.1132	8.92E-02	2.82E-01	0.1671	0.1146	1.45E-01	4.11E-01	0.0633	0.1192	5.89E-01	8.66E-01
5-hydroxyhexanoate	Lipid	Fatty Acid, Monohydroxy	0.1909	0.1131	9.13E-02	2.85E-01	0.1764	0.114	1.23E-01	3.73E-01	0.1	0.1162	3.89E-01	7.74E-01
eicosapentaenoate (EPA; 20:5n3)	Lipid	Polyunsaturated Fatty Acid (n3 and n6)	0.1919	0.1146	9.38E-02	2.88E-01	0.1989	0.1151	8.32E-02	3.13E-01	0.2694	0.1211	2.63E-02	4.49E-01
eicosenoylcarnitine (C20:1)*	Lipid	Fatty Acid Metabolism(Acyl Carnitine)	0.1679	0.1008	9.60E-02	2.90E-01	0.148	0.102	1.48E-01	4.14E-01	0.0893	0.105	3.98E-01	7.75E-01
linoleamide (18:2n6)	Lipid	Fatty Acid, Amide	0.1827	0.1107	9.87E-02	2.94E-01	0.1764	0.1113	1.12E-01	3.58E-01	0.1235	0.1144	2.82E-01	6.94E-01
N-palmitoyl-sphingosine (d18:1/16:0)	Lipid	Sphingolipid Metabolism	0.1904	0.1149	9.74E-02	2.91E-01	0.181	0.1151	1.15E-01	3.61E-01	0.1111	0.1173	3.47E-01	7.38E-01
1-arachidonoyl-GPI (20:4)*	Lipid	Lysolipid	-0.1839	0.1133	1.05E-01	3.04E-01	-0.183	0.1133	1.07E-01	3.48E-01	-0.2157	0.1164	6.46E-02	4.94E-01
linoleoyl ethanolamide	Lipid	Endocannabinoid	0.1828	0.1128	1.05E-01	3.04E-01	0.1798	0.1131	1.12E-01	3.58E-01	0.1691	0.1152	1.41E-01	5.96E-01
1-palmitoyl-2-linoleoyl-GPI (16:0/18:2)	Lipid	Phospholipid Metabolism	0.1818	0.1131	1.08E-01	3.08E-01	0.181	0.1132	1.10E-01	3.52E-01	0.1264	0.115	2.69E-01	6.94E-01
oleoyl-oleoyl-glycerol (18:1/18:1) [2]*	Lipid	Diacylglycerol	0.1807	0.1118	1.06E-01	3.05E-01	0.1629	0.1126	1.48E-01	4.14E-01	0.0908	0.1174	4.37E-01	7.97E-01
palmitoleoyl-arachidonoyl-glycerol (16:1/20:4) [2]*	Lipid	Diacylglycerol	0.1489	0.094	1.13E-01	3.17E-01	0.1364	0.0941	1.48E-01	4.14E-01	0.0987	0.0959	3.02E-01	7.13E-01
2-hydroxyoctanoate	Lipid	Fatty Acid, Monohydroxy	0.1798	0.1146	1.17E-01	3.23E-01	0.1466	0.1178	2.14E-01	4.73E-01	0.0401	0.1213	7.41E-01	9.18E-01
androstenediol (3beta,17beta) monosulfate (1)	Lipid	Steroid	-0.1894	0.1213	1.18E-01	3.25E-01	-0.1697	0.1225	1.66E-01	4.38E-01	-0.1011	0.1264	4.27E-01	7.87E-01

dihomo-linoleoylcarnitine (C20:2)*	Lipid	Fatty Acid Metabolism(Acyl Carnitine)	0.1612	0.1027	1.17E-01	3.23E-01	0.1483	0.1035	1.51E-01	4.18E-01	0.0765	0.106	4.68E-01	8.18E-01
palmitoyl dihydrosphingomyelin (d18:0/16:0)*	Lipid	Sphingolipid Metabolism	0.1847	0.118	1.17E-01	3.25E-01	0.1915	0.1179	1.05E-01	3.45E-01	0.1706	0.121	1.58E-01	6.22E-01
1-(1-enyl-palmitoyl)-GPE (P-16:0)*	Lipid	Lysoplasmalogen	0.1799	0.1156	1.20E-01	3.27E-01	0.1885	0.1169	1.07E-01	3.48E-01	0.2333	0.1216	5.50E-02	4.81E-01
N-stearoyl-sphingosine (d18:1/18:0)*	Lipid	Sphingolipid Metabolism	0.1779	0.1146	1.21E-01	3.27E-01	0.1655	0.1153	1.51E-01	4.18E-01	0.1131	0.1175	3.39E-01	7.38E-01
stearoyl-arachidonoyl-glycerol (18:0/20:4) [1]*	Lipid	Diacylglycerol	0.1802	0.1161	1.21E-01	3.27E-01	0.1668	0.1168	1.51E-01	4.19E-01	0.1422	0.1197	2.34E-01	6.68E-01
linoleoyl-arachidonoyl-glycerol (18:2/20:4) [2]*	Lipid	Diacylglycerol	0.1751	0.1132	1.22E-01	3.29E-01	0.1686	0.1137	1.38E-01	4.01E-01	0.1438	0.116	2.14E-01	6.54E-01
1-arachidonoyl-GPA (20:4)	Lipid	Lysolipid	0.1788	0.117	1.27E-01	3.39E-01	0.2045	0.1182	8.32E-02	3.13E-01	0.189	0.1213	1.20E-01	5.66E-01
dihomo-linolenate (20:3n3 or n6)	Lipid	Polyunsaturated Fatty Acid (n3 and n6)	0.1752	0.1149	1.27E-01	3.40E-01	0.1762	0.115	1.26E-01	3.78E-01	0.1481	0.1181	2.09E-01	6.54E-01
1-(1-enyl-oleoyl)-GPE (P-18:1)*	Lipid	Lysoplasmalogen	0.1816	0.121	1.33E-01	3.50E-01	0.1913	0.1223	1.17E-01	3.66E-01	0.2091	0.1265	9.77E-02	5.49E-01
adrenate (22:4n6)	Lipid	Polyunsaturated Fatty Acid (n3 and n6)	0.1703	0.1141	1.36E-01	3.51E-01	0.1702	0.1138	1.35E-01	3.94E-01	0.1495	0.117	2.00E-01	6.48E-01
arachidoylcarnitine (C20)*	Lipid	Fatty Acid Metabolism(Acyl Carnitine)	0.1498	0.1007	1.37E-01	3.51E-01	0.1353	0.1012	1.82E-01	4.52E-01	0.1208	0.1033	2.40E-01	6.75E-01
laurate (12:0)	Lipid	Medium Chain Fatty Acid	0.1696	0.114	1.37E-01	3.51E-01	0.1751	0.1145	1.26E-01	3.78E-01	0.2171	0.1203	7.08E-02	5.10E-01
N-stearoyltaurine	Lipid	Endocannabinoid	0.124	0.0851	1.45E-01	3.67E-01	0.1281	0.0851	1.32E-01	3.90E-01	0.1039	0.0866	2.29E-01	6.68E-01
1,2-dipalmitoyl-GPE (16:0/16:0)*	Lipid	Phospholipid Metabolism	0.1161	0.0803	1.48E-01	3.69E-01	0.1126	0.0804	1.62E-01	4.34E-01	0.0707	0.0828	3.89E-01	7.75E-01
docosahexaenoylcarnitine (C22:6)*	Lipid	Fatty Acid Metabolism(Acyl Carnitine)	-0.1879	0.1299	1.48E-01	3.69E-01	-0.1795	0.1303	1.70E-01	4.39E-01	-0.1516	0.1349	2.63E-01	6.90E-01
docosapentaenoate (n3 DPA; 22:5n3)	Lipid	Polyunsaturated Fatty Acid (n3 and n6)	0.1657	0.1144	1.48E-01	3.69E-01	0.1686	0.1148	1.41E-01	4.05E-01	0.2141	0.1195	7.24E-02	5.10E-01
1-palmitoyl-2-arachidonoyl-GPI (16:0/20:4)*	Lipid	Phospholipid Metabolism	0.1566	0.1111	1.59E-01	3.90E-01	0.1535	0.1116	1.70E-01	4.39E-01	0.123	0.1142	2.82E-01	6.94E-01
dodecanedioate	Lipid	Fatty Acid, Dicarboxylate	0.1573	0.1126	1.62E-01	3.94E-01	0.1671	0.1135	1.41E-01	4.04E-01	0.1232	0.1159	2.88E-01	6.97E-01
oleamide	Lipid	Fatty Acid, Amide	0.1539	0.1099	1.61E-01	3.92E-01	0.1489	0.1106	1.78E-01	4.52E-01	0.0918	0.1138	4.17E-01	7.87E-01
1-stearoyl-2-oleoyl-GPE (18:0/18:1)	Lipid	Phospholipid Metabolism	0.1596	0.1138	1.61E-01	3.92E-01	0.1375	0.1153	2.34E-01	4.98E-01	0.0906	0.1176	4.37E-01	7.97E-01
glycosyl-N-palmitoyl-sphingosine (d18:1/16:0)	Lipid	Sphingolipid Metabolism	0.1571	0.1145	1.70E-01	4.04E-01	0.1601	0.1143	1.62E-01	4.34E-01	0.0721	0.1172	5.37E-01	8.28E-01
adipate	Lipid	Fatty Acid, Dicarboxylate	0.1554	0.1146	1.75E-01	4.11E-01	0.1672	0.1155	1.48E-01	4.14E-01	0.1203	0.1171	3.02E-01	7.13E-01
1-stearoyl-2-arachidonoyl-GPC (18:0/20:4)	Lipid	Phospholipid Metabolism	0.1552	0.1144	1.75E-01	4.11E-01	0.1493	0.1147	1.95E-01	4.63E-01	0.095	0.1165	4.17E-01	7.86E-01
13-HODE + 9-HODE	Lipid	Fatty Acid, Monohydroxy	0.1856	0.1381	1.79E-01	4.11E-01	0.1786	0.1387	2.00E-01	4.68E-01	0.1808	0.1406	2.00E-01	6.48E-01
docosapentaenoate (n6 DPA; 22:5n6)	Lipid	Polyunsaturated Fatty Acid (n3 and n6)	0.1524	0.113	1.77E-01	4.11E-01	0.1478	0.113	1.91E-01	4.63E-01	0.1239	0.1151	2.82E-01	6.94E-01
laurylcarnitine (C12)	Lipid	Fatty Acid Metabolism(Acyl Carnitine)	0.1542	0.1148	1.79E-01	4.11E-01	0.1272	0.116	2.75E-01	5.34E-01	0.0155	0.1212	8.91E-01	9.68E-01
leukotriene B4	Lipid	Eicosanoid	0.1405	0.1041	1.77E-01	4.11E-01	0.1432	0.1048	1.70E-01	4.45E-01	0.128	0.1074	2.34E-01	6.68E-01
1-palmitoleoyl-GPC (16:1)*	Lipid	Lysolipid	0.1619	0.1199	1.77E-01	4.11E-01	0.1656	0.1193	1.66E-01	4.38E-01	0.134	0.1231	2.75E-01	6.94E-01
pimelate (heptanedioate)	Lipid	Fatty Acid, Dicarboxylate	0.1524	0.1134	1.79E-01	4.11E-01	0.163	0.1142	1.55E-01	4.19E-01	0.1245	0.1157	2.82E-01	6.94E-01
5alpha-pregnan-3beta,20alpha-diol disulfate	Lipid	Steroid	-0.1528	0.1142	1.81E-01	4.14E-01	-0.1468	0.1145	2.00E-01	4.70E-01	-0.1878	0.1194	1.15E-01	5.63E-01
stearoyl-arachidonoyl-glycerol (18:0/20:4) [2]*	Lipid	Diacylglycerol	0.1457	0.1093	1.83E-01	4.15E-01	0.143	0.1096	1.91E-01	4.63E-01	0.1361	0.1117	2.24E-01	6.68E-01
lignoceroylcarnitine (C24)*	Lipid	Fatty Acid Metabolism(Acyl Carnitine)	0.1515	0.115	1.88E-01	4.18E-01	0.1617	0.1155	1.62E-01	4.34E-01	0.1583	0.1173	1.78E-01	6.32E-01
myristoyl dihydrosphingomyelin (d18:0/14:0)*	Lipid	Sphingolipid Metabolism	0.1563	0.1191	1.89E-01	4.20E-01	0.1438	0.1198	2.29E-01	4.94E-01	0.1065	0.1234	3.89E-01	7.74E-01
heptanoate (7:0)	Lipid	Medium Chain Fatty Acid	0.146	0.1122	1.93E-01	4.26E-01	0.1466	0.1128	1.95E-01	4.63E-01	0.093	0.1149	4.17E-01	7.87E-01
linoleoylcholine*	Lipid	Fatty Acid Metabolism (Acyl Choline)	-0.1444	0.1116	1.95E-01	4.26E-01	-0.1506	0.112	1.78E-01	4.52E-01	-0.2087	0.1156	7.08E-02	5.10E-01
5alpha-pregnan-3beta,20beta-diol monosulfate (1)	Lipid	Steroid	-0.1156	0.0899	1.99E-01	4.30E-01	-0.1134	0.0907	2.09E-01	4.73E-01	-0.1309	0.0951	1.70E-01	6.26E-01
cis-4-decenoylcarnitine (C10:1)	Lipid	Fatty Acid Metabolism(Acyl Carnitine)	0.1532	0.1197	2.01E-01	4.33E-01	0.1117	0.1238	3.63E-01	6.06E-01	-0.0541	0.1313	6.76E-01	8.94E-01
1-palmitoyl-2-linoleoyl-GPC (16:0/18:2)	Lipid	Phospholipid Metabolism	-0.1443	0.1148	2.09E-01	4.45E-01	-0.1511	0.1152	1.91E-01	4.63E-01	-0.1629	0.1176	1.66E-01	6.25E-01
hexanoylglutamine	Lipid	Fatty Acid Metabolism (Acyl Glutamine)	0.1367	0.1104	2.16E-01	4.51E-01	0.1118	0.112	3.16E-01	5.66E-01	0.0226	0.116	8.51E-01	9.50E-01
linolenate [alpha or gamma; (18:3n3 or 6)]	Lipid	Polyunsaturated Fatty Acid (n3 and n6)	0.1426	0.1145	2.13E-01	4.49E-01	0.1348	0.1147	2.40E-01	5.02E-01	0.1552	0.1176	1.86E-01	6.46E-01
undecanedioate	Lipid	Fatty Acid, Dicarboxylate	0.1389	0.112	2.15E-01	4.51E-01	0.1461	0.1127	1.95E-01	4.63E-01	0.1072	0.1146	3.47E-01	7.38E-01
sphingomyelin (d18:2/14:0, d18:1/14:1)*	Lipid	Sphingolipid Metabolism	0.1665	0.1349	2.17E-01	4.51E-01	0.1487	0.1359	2.75E-01	5.34E-01	0.0509	0.1413	7.24E-01	9.08E-01
N-stearoyl-sphingadienine (d18:2/18:0)*	Lipid	Sphingolipid Metabolism	0.1398	0.1154	2.26E-01	4.63E-01	0.1257	0.1163	2.82E-01	5.42E-01	0.0569	0.1197	6.31E-01	8.84E-01
N-behenoyl-sphingadienine (d18:2/22:0)*	Lipid	Sphingolipid Metabolism	0.1365	0.1132	2.28E-01	4.65E-01	0.1182	0.1139	3.02E-01	5.54E-01	0.058	0.1154	6.17E-01	8.77E-01
N-palmitoylglycine	Lipid	Fatty Acid Metabolism(Acyl Glycine)	0.1398	0.1164	2.30E-01	4.67E-01	0.1238	0.1167	2.88E-01	5.49E-01	0.0737	0.1187	5.37E-01	8.26E-01
alpha-hydroxycaproate	Lipid	Fatty Acid, Monohydroxy	0.1244	0.104	2.32E-01	4.67E-01	0.1238	0.1047	2.34E-01	5.02E-01	0.0715	0.1075	5.01E-01	8.20E-01
caprylate (8:0)	Lipid	Medium Chain Fatty Acid	0.1358	0.1138	2.33E-01	4.67E-01	0.144	0.1143	2.09E-01	4.72E-01	0.1483	0.1174	2.09E-01	6.51E-01
1-linoleoyl-GPA (18:2)*	Lipid	Lysolipid	0.1362	0.1146	2.35E-01	4.67E-01	0.1495	0.115	1.95E-01	4.63E-01	0.1047	0.1176	3.72E-01	7.59E-01
1-linoleoyl-GPE (18:2)*	Lipid	Lysolipid	-0.1352	0.1135	2.33E-01	4.67E-01	-0.1424	0.1141	2.14E-01	4.73E-01	-0.1207	0.1165	3.02E-01	7.12E-01
linoleoyl-linolenoyl-glycerol (18:2/18:3) [2]*	Lipid	Diacylglycerol	0.1346	0.1132	2.35E-01	4.67E-01	0.1199	0.114	2.95E-01	5.50E-01	0.0763	0.1168	5.13E-01	8.20E-01
sphingomyelin (d18:2/18:1)*	Lipid	Sphingolipid Metabolism	0.1449	0.1214	2.33E-01	4.67E-01	0.1262	0.1227	3.02E-01	5.58E-01	-0.0188	0.1317	8.91E-01	9.65E-01
21-hydroxypregnenolone disulfate	Lipid	Steroid	-0.1397	0.1209	2.48E-01	4.86E-01	-0.1425	0.1208	2.40E-01	5.02E-01	-0.2094	0.1244	9.33E-02	5.44E-01
glycerophosphoserine*	Lipid	Phospholipid Metabolism	0.1314	0.1133	2.46E-01	4.84E-01	0.1218	0.1139	2.88E-01	5.46E-01	0.0743	0.118	5.25E-01	8.22E-01
1-palmitoyl-2-arachidonoyl-GPC (16:0/20:4n6)	Lipid	Phospholipid Metabolism	0.1311	0.114	2.50E-01	4.87E-01	0.1301	0.1138	2.51E-01	5.19E-01	0.1235	0.1157	2.88E-01	6.94E-01
2-palmitoyl-GPC (16:0)*	Lipid	Lysolipid	0.1315	0.1154	2.54E-01	4.91E-01	0.1397	0.1155	2.29E-01	4.92E-01	0.1252	0.1185	2.88E-01	7.01E-01
1-docosahexaenoylglycerol (22:6)	Lipid	Monoacylglycerol	0.0958	0.0844	2.56E-01	4.92E-01	0.0834	0.0853	3.31E-01	5.70E-01	0.0862	0.0875	3.24E-01	7.38E-01
stearate (18:0)	Lipid	Long Chain Fatty Acid	0.1288	0.1134	2.56E-01	4.92E-01	0.1372	0.1136	2.29E-01	4.92E-01	0.1257	0.1165	2.82E-01	6.94E-01

16-hydroxypalmitate	Lipid	Fatty Acid, Monohydroxy	0.125	0.1122	2.65E-01	4.99E-01	0.1223	0.1124	2.75E-01	5.38E-01	0.0984	0.1157	3.98E-01	7.75E-01
1-(1-enyl-palmitoyl)-2-oleoyl-GPC (P-16:0/18:1)*	Lipid	Plasmalogen	-0.1274	0.1137	2.62E-01	4.97E-01	-0.127	0.1136	2.63E-01	5.30E-01	-0.0886	0.117	4.47E-01	8.04E-01
myristoleoylcarnitine (C14:1)*	Lipid	Fatty Acid Metabolism(Acyl Carnitine)	0.1271	0.1143	2.66E-01	4.99E-01	0.0911	0.1171	4.37E-01	6.59E-01	-0.0318	0.1222	7.94E-01	9.44E-01
1-stearoyl-2-linoleoyl-GPC (18:0/18:2)*	Lipid	Phospholipid Metabolism	-0.1287	0.1145	2.61E-01	4.95E-01	-0.1333	0.1149	2.45E-01	5.08E-01	-0.1778	0.1173	1.29E-01	5.80E-01
1-linoleoyl-GPI (18:2)*	Lipid	Lysolipid	-0.1254	0.1133	2.68E-01	5.02E-01	-0.1195	0.1132	2.88E-01	5.49E-01	-0.1524	0.116	1.91E-01	6.48E-01
linoleoyl-linoleoyl-glycerol (18:2/18:2) [1]*	Lipid	Diacylglycerol	0.1222	0.1113	2.72E-01	5.05E-01	0.1051	0.112	3.47E-01	5.89E-01	0.0538	0.1151	6.46E-01	8.84E-01
glycocholenate sulfate*	Lipid	Secondary Bile Acid Metabolism	0.1221	0.1121	2.76E-01	5.08E-01	0.1239	0.1117	2.69E-01	5.30E-01	0.1169	0.1123	2.95E-01	7.12E-01
15-methylpalmitate	Lipid	Fatty Acid, Branched	0.1219	0.1131	2.81E-01	5.12E-01	0.1162	0.1135	3.09E-01	5.58E-01	0.1252	0.1172	2.88E-01	6.94E-01
sphingomyelin (d18:1/18:1, d18:2/18:0)	Lipid	Sphingolipid Metabolism	0.1316	0.1228	2.84E-01	5.15E-01	0.1226	0.1228	3.16E-01	5.66E-01	0.0698	0.1258	5.75E-01	8.54E-01
1-(1-enyl-palmitoyl)-2-linoleoyl-GPE (P-16:0/18:2)*	Lipid	Plasmalogen	-0.1191	0.114	2.96E-01	5.26E-01	-0.1163	0.1148	3.09E-01	5.63E-01	-0.0791	0.1171	5.01E-01	8.20E-01
campesterol	Lipid	Sterol	0.117	0.1121	2.96E-01	5.26E-01	0.1121	0.1125	3.16E-01	5.66E-01	0.1798	0.1167	1.23E-01	5.73E-01
hexadecanedioate	Lipid	Fatty Acid, Dicarboxylate	-0.1191	0.1131	2.92E-01	5.24E-01	-0.1257	0.1133	2.69E-01	5.30E-01	-0.146	0.1146	2.04E-01	6.48E-01
ceramide (d18:1/20:0, d16:1/22:0, d20:1/18:0)*	Lipid	Ceramides	0.1166	0.1137	3.05E-01	5.33E-01	0.1019	0.1146	3.72E-01	6.13E-01	0.0668	0.1168	5.62E-01	8.48E-01
maleate	Lipid	Fatty Acid, Dicarboxylate	-0.095	0.0923	3.03E-01	5.33E-01	-0.1082	0.0931	2.45E-01	5.08E-01	-0.149	0.0968	1.23E-01	5.73E-01
octanoylcarnitine (C8)	Lipid	Fatty Acid Metabolism(Acyl Carnitine)	0.1188	0.1158	3.05E-01	5.33E-01	0.0852	0.1184	4.68E-01	6.88E-01	-0.022	0.1224	8.51E-01	9.54E-01
taurodeoxycholate	Lipid	Secondary Bile Acid Metabolism	-0.1077	0.1045	3.03E-01	5.33E-01	-0.1121	0.1049	2.88E-01	5.46E-01	-0.1381	0.1069	1.95E-01	6.48E-01
1-stearoyl-2-oleoyl-GPC (18:0/18:1)	Lipid	Phospholipid Metabolism	0.1161	0.1124	3.02E-01	5.33E-01	0.11	0.1125	3.31E-01	5.70E-01	0.0837	0.1135	4.57E-01	8.07E-01
1-palmitoyl-2-oleoyl-GPI (16:0/18:1)*	Lipid	Phospholipid Metabolism	0.1151	0.1129	3.08E-01	5.34E-01	0.1102	0.1132	3.31E-01	5.70E-01	0.0899	0.1149	4.37E-01	7.91E-01
1-palmitoyl-2-stearoyl-GPC (16:0/18:0)	Lipid	Phospholipid Metabolism	0.114	0.1119	3.08E-01	5.34E-01	0.12	0.1126	2.88E-01	5.46E-01	0.0856	0.115	4.57E-01	8.06E-01
1-(1-enyl-palmitoyl)-2-palmitoleoyl-GPC (P-16:0/16:1)*	Lipid	Plasmalogen	-0.1156	0.115	3.15E-01	5.40E-01	-0.1118	0.1151	3.31E-01	5.70E-01	-0.1361	0.1187	2.51E-01	6.83E-01
sphingomyelin (d17:2/16:0, d18:2/15:0)*	Lipid	Sphingolipid Metabolism	0.1277	0.127	3.15E-01	5.40E-01	0.1053	0.1284	4.17E-01	6.49E-01	-0.0023	0.1343	9.77E-01	9.96E-01
pregnen-diol disulfate*	Lipid	Steroid	-0.1246	0.1269	3.26E-01	5.56E-01	-0.1265	0.127	3.16E-01	5.66E-01	-0.1674	0.1317	2.04E-01	6.48E-01
2-hydroxyglutarate	Lipid	Fatty Acid, Dicarboxylate	0.1102	0.1127	3.28E-01	5.56E-01	0.1185	0.1135	2.95E-01	5.53E-01	0.1011	0.1148	3.80E-01	7.61E-01
beta-sitosterol	Lipid	Sterol	0.1098	0.1125	3.29E-01	5.56E-01	0.109	0.1131	3.39E-01	5.75E-01	0.184	0.118	1.17E-01	5.66E-01
1-stearoyl-2-linoleoyl-GPE (18:0/18:2)*	Lipid	Phospholipid Metabolism	0.1102	0.1132	3.31E-01	5.56E-01	0.0915	0.1147	4.27E-01	6.56E-01	0.0296	0.1185	7.94E-01	9.44E-01
12-HETE	Lipid	Eicosanoid	0.087	0.0892	3.29E-01	5.56E-01	0.0913	0.0895	3.09E-01	5.58E-01	0.0844	0.0916	3.55E-01	7.41E-01
3-hydroxybutyrate (BHBA)	Lipid	Ketone Bodies	-0.1072	0.1121	3.39E-01	5.60E-01	-0.1128	0.1126	3.16E-01	5.66E-01	-0.0864	0.1145	4.47E-01	8.04E-01
1-(1-enyl-stearoyl)-GPE (P-18:0)*	Lipid	Lysoplasmalogen	0.1094	0.1144	3.39E-01	5.60E-01	0.1157	0.1152	3.16E-01	5.66E-01	0.1668	0.1196	1.62E-01	6.25E-01
cholesterol	Lipid	Sterol	0.1108	0.1155	3.38E-01	5.60E-01	0.0918	0.1163	4.27E-01	6.57E-01	0.032	0.1186	7.94E-01	9.44E-01
1-palmitoyl-2-linoleoyl-GPE (16:0/18:2)	Lipid	Phospholipid Metabolism	0.1096	0.1138	3.35E-01	5.60E-01	0.0896	0.1154	4.37E-01	6.59E-01	0.015	0.1196	8.91E-01	9.68E-01
suberate (octanedioate)	Lipid	Fatty Acid, Dicarboxylate	0.1065	0.1117	3.40E-01	5.60E-01	0.1148	0.1123	3.09E-01	5.58E-01	0.0814	0.1142	4.79E-01	8.18E-01
5alpha-androstan-3alpha,17beta-diol monosulfate (1)	Lipid	Steroid	-0.0985	0.1046	3.46E-01	5.64E-01	-0.0878	0.1051	4.07E-01	6.40E-01	-0.0552	0.1073	6.03E-01	8.69E-01
9,10-DiHOME	Lipid	Fatty Acid, Dihydroxy	0.0839	0.0902	3.52E-01	5.71E-01	0.0798	0.0903	3.80E-01	6.17E-01	0.0914	0.092	3.24E-01	7.38E-01
androstenediol (3beta,17beta) monosulfate (2)	Lipid	Steroid	-0.1012	0.1092	3.54E-01	5.72E-01	-0.091	0.1098	4.07E-01	6.42E-01	-0.0828	0.1114	4.57E-01	8.06E-01
1-(1-enyl-palmitoyl)-2-oleoyl-GPE (P-16:0/18:1)*	Lipid	Plasmalogen	-0.1043	0.1139	3.59E-01	5.74E-01	-0.1044	0.1144	3.63E-01	6.05E-01	-0.0556	0.1166	6.31E-01	8.84E-01
epiandrosterone sulfate	Lipid	Steroid	-0.1113	0.1214	3.59E-01	5.74E-01	-0.104	0.1213	3.89E-01	6.33E-01	-0.0581	0.1224	6.31E-01	8.84E-01
sebacate (decanedioate)	Lipid	Fatty Acid, Dicarboxylate	0.1036	0.113	3.59E-01	5.74E-01	0.1113	0.1137	3.31E-01	5.70E-01	0.0748	0.1161	5.25E-01	8.20E-01
adipoylcarnitine (C6-DC)	Lipid	Fatty Acid Metabolism(Acyl Carnitine)	0.0915	0.1024	3.72E-01	5.85E-01	0.0511	0.1058	6.31E-01	7.92E-01	-0.1901	0.1208	1.15E-01	5.63E-01
10-undecenoate (11:1n1)	Lipid	Medium Chain Fatty Acid	-0.1009	0.1122	3.68E-01	5.83E-01	-0.1072	0.1128	3.39E-01	5.82E-01	-0.0554	0.1163	6.31E-01	8.84E-01
androstenediol (3beta,17beta) disulfate (1)	Lipid	Steroid	-0.1088	0.1238	3.79E-01	5.95E-01	-0.106	0.1244	3.98E-01	6.33E-01	-0.1222	0.1278	3.39E-01	7.38E-01
ceramide (d18:1/17:0, d17:1/18:0)*	Lipid	Ceramides	0.0949	0.1078	3.78E-01	5.94E-01	0.0796	0.1087	4.68E-01	6.86E-01	0.0339	0.1119	7.59E-01	9.36E-01
3-hydroxysebacate	Lipid	Fatty Acid, Monohydroxy	-0.0782	0.0915	3.93E-01	6.08E-01	-0.0898	0.092	3.31E-01	5.70E-01	-0.1366	0.0937	1.45E-01	6.01E-01
8-hydroxyoctanoate	Lipid	Fatty Acid, Monohydroxy	0.0978	0.1129	3.86E-01	6.01E-01	0.1029	0.1138	3.63E-01	6.06E-01	0.0772	0.1157	5.01E-01	8.20E-01
7-alpha-hydroxy-3-oxo-4-cholestenoate (7-Hoca)	Lipid	Sterol	-0.0939	0.1106	3.96E-01	6.11E-01	-0.0999	0.1112	3.72E-01	6.08E-01	-0.1321	0.1143	2.45E-01	6.83E-01
1-stearoyl-2-oleoyl-GPS (18:0/18:1)	Lipid	Phosphatidylserine (PS)	0.0888	0.1058	4.01E-01	6.18E-01	0.0837	0.1062	4.27E-01	6.57E-01	0.0729	0.1104	5.13E-01	8.20E-01
10-nonadecenoate (19:1n9)	Lipid	Long Chain Fatty Acid	0.0951	0.1135	4.02E-01	6.18E-01	0.0893	0.1137	4.37E-01	6.58E-01	0.0903	0.1173	4.47E-01	7.97E-01
glycocholate	Lipid	Primary Bile Acid Metabolism	-0.0926	0.1115	4.06E-01	6.23E-01	-0.0939	0.112	3.98E-01	6.40E-01	-0.0955	0.1131	3.98E-01	7.77E-01
glycodeoxycholate	Lipid	Secondary Bile Acid Metabolism	-0.0831	0.1008	4.09E-01	6.27E-01	-0.087	0.1014	3.89E-01	6.33E-01	-0.0974	0.1032	3.47E-01	7.38E-01
1-palmitoyl-2-oleoyl-GPC (16:0/18:1)	Lipid	Phospholipid Metabolism	0.0916	0.1116	4.12E-01	6.29E-01	0.0845	0.1113	4.47E-01	6.69E-01	0.0795	0.1125	4.79E-01	8.18E-01
1-(1-enyl-palmitoyl)-GPC (P-16:0)*	Lipid	Lysoplasmalogen	0.0909	0.1126	4.19E-01	6.33E-01	0.0962	0.113	3.98E-01	6.33E-01	0.1158	0.117	3.24E-01	7.38E-01
ceramide (d18:2/24:1, d18:1/24:2)*	Lipid	Ceramides	0.0942	0.1153	4.14E-01	6.31E-01	0.0666	0.1171	5.75E-01	7.56E-01	-0.0204	0.1188	8.71E-01	9.56E-01
palmitoylcholine	Lipid	Fatty Acid Metabolism (Acyl Choline)	-0.0909	0.1117	4.16E-01	6.31E-01	-0.0961	0.1121	3.89E-01	6.33E-01	-0.1523	0.1154	1.86E-01	6.46E-01
13-methylmyristate	Lipid	Fatty Acid, Branched	0.0895	0.1131	4.29E-01	6.33E-01	0.0878	0.1134	4.37E-01	6.60E-01	0.0975	0.117	4.07E-01	7.80E-01
3-hydroxylaurate	Lipid	Fatty Acid, Monohydroxy	-0.0914	0.1144	4.24E-01	6.33E-01	-0.0891	0.1145	4.37E-01	6.59E-01	-0.05	0.1177	6.76E-01	8.93E-01
1-arachidonoyl-GPC (20:4n6)*	Lipid	Lysolipid	0.0881	0.1113	4.29E-01	6.33E-01	0.0901	0.1114	4.17E-01	6.53E-01	0.0995	0.1126	3.80E-01	7.59E-01
decanoylcarnitine (C10)	Lipid	Fatty Acid Metabolism(Acyl Carnitine)	0.0916	0.115	4.26E-01	6.33E-01	0.0583	0.1172	6.17E-01	7.85E-01	-0.0427	0.1209	7.24E-01	9.12E-01
glycerophosphorylcholine (GPC)	Lipid	Phospholipid Metabolism	-0.0932	0.1168	4.25E-01	6.33E-01	-0.0699	0.1186	5.50E-01	7.50E-01	-0.0568	0.1207	6.31E-01	8.84E-01

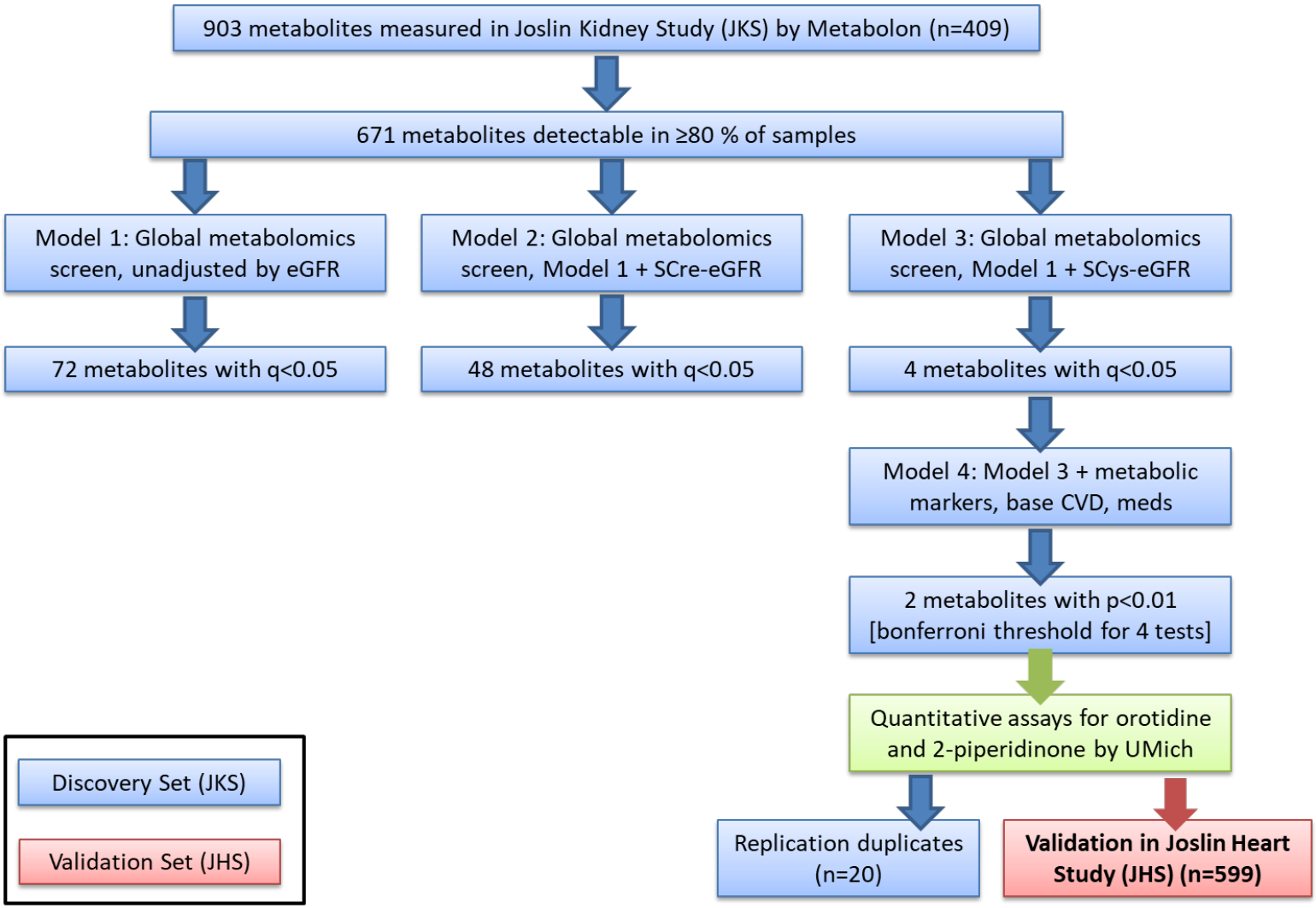
glycochenodeoxycholate sulfate	Lipid	Primary Bile Acid Metabolism	-0.0861	0.1092	4.30E-01	6.34E-01	-0.1039	0.1102	3.47E-01	5.88E-01	-0.196	0.1154	8.91E-02	5.36E-01
N-palmitoyl-sphingadienine (d18:2/16:0)*	Lipid	Sphingolipid Metabolism	0.095	0.1201	4.29E-01	6.33E-01	0.0852	0.1198	4.79E-01	6.91E-01	0.0279	0.1225	8.13E-01	9.44E-01
1-palmitoyl-2-palmitoleoyl-GPC (16:0/16:1)*	Lipid	Phospholipid Metabolism	0.0881	0.1122	4.32E-01	6.34E-01	0.091	0.112	4.17E-01	6.53E-01	0.0896	0.1141	4.37E-01	7.91E-01
androstenediol (3alpha, 17alpha) monsulfate (3)	Lipid	Steroid	-0.0987	0.1291	4.44E-01	6.39E-01	-0.0804	0.1301	5.37E-01	7.38E-01	-0.0442	0.1335	7.41E-01	9.18E-01
androsterone sulfate	Lipid	Steroid	-0.0897	0.117	4.43E-01	6.39E-01	-0.0803	0.1172	4.90E-01	7.01E-01	-0.0464	0.1185	6.92E-01	9.03E-01
16a-hydroxy DHEA 3-sulfate	Lipid	Steroid	-0.0892	0.1198	4.56E-01	6.51E-01	-0.0971	0.1202	4.17E-01	6.53E-01	-0.1685	0.1248	1.78E-01	6.32E-01
1,2-dipalmitoyl-GPC (16:0/16:0)	Lipid	Phospholipid Metabolism	0.0825	0.1121	4.62E-01	6.56E-01	0.0875	0.1125	4.37E-01	6.59E-01	0.0341	0.1152	7.59E-01	9.38E-01
dihomo-linoleate (20:2n6)	Lipid	Polyunsaturated Fatty Acid (n3 and n6)	0.0833	0.1125	4.59E-01	6.54E-01	0.0811	0.1124	4.68E-01	6.88E-01	0.077	0.1155	5.01E-01	8.20E-01
palmitoyl ethanolamide	Lipid	Endocannabinoid	0.0915	0.1229	4.56E-01	6.51E-01	0.0906	0.1228	4.57E-01	6.85E-01	0.1195	0.1242	3.39E-01	7.38E-01
3-hydroxydecanoate	Lipid	Fatty Acid, Monohydroxy	-0.0824	0.1132	4.67E-01	6.58E-01	-0.0785	0.1135	4.90E-01	6.99E-01	-0.039	0.116	7.41E-01	9.18E-01
sphingomyelin (d18:1/24:1, d18:2/24:0)*	Lipid	Sphingolipid Metabolism	0.0848	0.1168	4.68E-01	6.59E-01	0.0928	0.1169	4.27E-01	6.56E-01	0.0682	0.1194	5.62E-01	8.48E-01
behenoyl sphingomyelin (d18:1/22:0)*	Lipid	Sphingolipid Metabolism	0.0833	0.1165	4.75E-01	6.67E-01	0.1011	0.117	3.89E-01	6.33E-01	0.1388	0.119	2.45E-01	6.75E-01
stearoyl sphingomyelin (d18:1/18:0)	Lipid	Sphingolipid Metabolism	0.0854	0.1201	4.77E-01	6.68E-01	0.0887	0.1207	4.57E-01	6.86E-01	0.111	0.1237	3.72E-01	7.58E-01
5-dodecenoate (12:1n7)	Lipid	Medium Chain Fatty Acid	0.0755	0.1104	4.94E-01	6.79E-01	0.0708	0.1101	5.25E-01	7.21E-01	0.0689	0.113	5.37E-01	8.28E-01
1-linolenoyl-GPC (18:3)*	Lipid	Lysolipid	-0.0783	0.1121	4.85E-01	6.76E-01	-0.0719	0.1122	5.25E-01	7.21E-01	-0.028	0.1144	8.13E-01	9.44E-01
docosadienoate (22:2n6)	Lipid	Polyunsaturated Fatty Acid (n3 and n6)	0.0787	0.1133	4.87E-01	6.78E-01	0.0768	0.1134	5.01E-01	7.04E-01	0.0671	0.1164	5.62E-01	8.48E-01
linoleate (18:2n6)	Lipid	Polyunsaturated Fatty Acid (n3 and n6)	-0.0778	0.1123	4.89E-01	6.78E-01	-0.0774	0.1128	4.90E-01	7.01E-01	-0.0812	0.1152	4.79E-01	8.18E-01
sphinganine-1-phosphate	Lipid	Sphingolipid Metabolism	-0.0797	0.114	4.84E-01	6.76E-01	-0.0669	0.1147	5.62E-01	7.52E-01	-0.0515	0.1174	6.61E-01	8.92E-01
1-oleoyl-GPG (18:1)*	Lipid	Lysolipid	0.0673	0.1011	5.05E-01	6.88E-01	0.0544	0.1011	5.89E-01	7.65E-01	-0.0273	0.1051	7.94E-01	9.44E-01
3-hydroxyoctanoate	Lipid	Fatty Acid, Monohydroxy	-0.0736	0.1129	5.15E-01	6.95E-01	-0.079	0.1135	4.90E-01	6.99E-01	-0.0797	0.1152	4.90E-01	8.20E-01
glycosyl-N-stearoyl-sphingosine (d18:1/18:0)	Lipid	Sphingolipid Metabolism	0.078	0.1177	5.08E-01	6.88E-01	0.0775	0.1177	5.13E-01	7.12E-01	0.0456	0.1195	7.08E-01	9.03E-01
sphingomyelin (d18:1/20:0, d16:1/22:0)*	Lipid	Sphingolipid Metabolism	-0.0753	0.1158	5.16E-01	6.95E-01	-0.0648	0.1164	5.75E-01	7.56E-01	0.0157	0.1211	8.91E-01	9.68E-01
1-lignoceroyl-GPC (24:0)	Lipid	Lysolipid	-0.0731	0.1149	5.25E-01	7.04E-01	-0.0646	0.1161	5.75E-01	7.56E-01	-0.0452	0.1197	7.08E-01	9.03E-01
lactosyl-N-palmitoyl-sphingosine (d18:1/16:0)	Lipid	Sphingolipid Metabolism	0.0721	0.1141	5.27E-01	7.04E-01	0.0822	0.1145	4.68E-01	6.88E-01	0.022	0.118	8.51E-01	9.52E-01
sphingomyelin (d18:1/14:0, d16:1/16:0)*	Lipid	Sphingolipid Metabolism	0.0754	0.1198	5.29E-01	7.04E-01	0.0565	0.1209	6.46E-01	8.01E-01	0.0012	0.125	1.00E+00	9.96E-01
arachidonoylcholine	Lipid	Phospholipid Metabolism	-0.0674	0.1087	5.35E-01	7.09E-01	-0.0707	0.109	5.13E-01	7.19E-01	-0.1232	0.1119	2.69E-01	6.94E-01
lactosyl-N-nervonoyl-sphingosine (d18:1/24:1)*	Lipid	Sphingolipid Metabolism	0.0694	0.1141	5.43E-01	7.16E-01	0.0764	0.1143	5.01E-01	7.07E-01	0.0244	0.1173	8.32E-01	9.44E-01
oleoylcholine	Lipid	Fatty Acid Metabolism (Acyl Choline)	-0.0658	0.1077	5.41E-01	7.15E-01	-0.0745	0.1082	4.90E-01	7.01E-01	-0.1386	0.1117	2.14E-01	6.54E-01
9-hydroxystearate	Lipid	Fatty Acid, Monohydroxy	-0.0533	0.0901	5.54E-01	7.28E-01	-0.0611	0.0901	5.01E-01	7.04E-01	-0.0607	0.0916	5.13E-01	8.20E-01
2-hydroxystearate	Lipid	Fatty Acid, Monohydroxy	-0.0632	0.1083	5.60E-01	7.32E-01	-0.0555	0.1091	6.17E-01	7.82E-01	-0.0683	0.1117	5.37E-01	8.28E-01
3beta,7alpha-dihydroxy-5-cholestenoate	Lipid	Sterol	-0.0617	0.1075	5.66E-01	7.38E-01	-0.0548	0.1075	6.17E-01	7.82E-01	-0.0746	0.108	4.90E-01	8.20E-01
3beta-hydroxy-5-cholestenoate	Lipid	Sterol	-0.0649	0.1122	5.63E-01	7.35E-01	-0.0587	0.1127	6.03E-01	7.76E-01	0.022	0.1155	8.51E-01	9.51E-01
docosahexaenoate (DHA; 22:6n3)	Lipid	Polyunsaturated Fatty Acid (n3 and n6)	0.0637	0.1117	5.69E-01	7.40E-01	0.0634	0.1125	5.75E-01	7.56E-01	0.1206	0.1169	3.02E-01	7.13E-01
glycosyl ceramide (d18:1/20:0, d16:1/22:0)*	Lipid	Ceramides	0.0641	0.1163	5.82E-01	7.54E-01	0.0661	0.1161	5.75E-01	7.56E-01	0.0549	0.1182	6.46E-01	8.84E-01
sphingomyelin (d18:2/21:0, d16:2/23:0)*	Lipid	Sphingolipid Metabolism	0.0715	0.1317	5.87E-01	7.55E-01	0.0528	0.1329	6.92E-01	8.40E-01	-0.0529	0.1397	7.08E-01	9.03E-01
1-stearoyl-2-arachidonoyl-GPI (18:0/20:4)	Lipid	Phospholipid Metabolism	-0.0608	0.114	5.94E-01	7.59E-01	-0.069	0.1145	5.50E-01	7.43E-01	-0.109	0.1174	3.55E-01	7.38E-01
taurochenodeoxycholate	Lipid	Primary Bile Acid Metabolism	-0.0595	0.1103	5.89E-01	7.56E-01	-0.0657	0.1111	5.50E-01	7.50E-01	-0.106	0.113	3.47E-01	7.38E-01
caprate (10:0)	Lipid	Medium Chain Fatty Acid	0.0598	0.1147	6.02E-01	7.65E-01	0.0641	0.1152	5.75E-01	7.56E-01	0.0885	0.1194	4.57E-01	8.06E-01
deoxycholate	Lipid	Secondary Bile Acid Metabolism	-0.0587	0.1117	5.99E-01	7.63E-01	-0.0478	0.1127	6.76E-01	8.26E-01	0.0091	0.1153	9.33E-01	9.89E-01
pelargonate (9:0)	Lipid	Medium Chain Fatty Acid	0.0606	0.1177	6.07E-01	7.69E-01	0.0695	0.1188	5.62E-01	7.52E-01	0.0279	0.1205	8.13E-01	9.44E-01
5alpha-androstan-3beta,17beta-diol disulfate	Lipid	Steroid	-0.0688	0.1396	6.22E-01	7.78E-01	-0.0629	0.1397	6.46E-01	8.10E-01	-0.0415	0.1424	7.76E-01	9.39E-01
androstenediol (3beta,17beta) disulfate (2)	Lipid	Steroid	-0.0642	0.1267	6.12E-01	7.73E-01	-0.0667	0.1267	6.03E-01	7.72E-01	-0.1382	0.1289	2.82E-01	6.94E-01
sphingomyelin (d18:1/20:1, d18:2/20:0)*	Lipid	Sphingolipid Metabolism	0.0614	0.1244	6.21E-01	7.78E-01	0.0625	0.1244	6.17E-01	7.84E-01	0.0384	0.128	7.59E-01	9.37E-01
sphingomyelin (d18:2/24:2)*	Lipid	Sphingolipid Metabolism	-0.0655	0.1285	6.10E-01	7.72E-01	-0.0768	0.1287	5.50E-01	7.47E-01	-0.2215	0.1365	1.05E-01	5.63E-01
1-stearoyl-GPI (18:0)	Lipid	Lysolipid	-0.0606	0.1192	6.11E-01	7.72E-01	-0.0603	0.1192	6.17E-01	7.83E-01	-0.0826	0.1204	4.90E-01	8.20E-01
1-(1-enyl-palmitoyl)-2-arachidonoyl-GPE (P-16:0/20:4)*	Lipid	Plasmalogen	-0.055	0.1137	6.29E-01	7.84E-01	-0.0514	0.1145	6.61E-01	8.10E-01	0.0047	0.1181	9.77E-01	9.96E-01
androstenediol (3alpha, 17alpha) monsulfate (2)	Lipid	Steroid	-0.0545	0.1126	6.28E-01	7.84E-01	-0.0299	0.1141	7.94E-01	8.99E-01	-0.0054	0.1163	9.55E-01	9.96E-01
valerate	Lipid	Short Chain Fatty Acid	0.0478	0.1049	6.49E-01	8.03E-01	0.0701	0.1059	5.13E-01	7.11E-01	0.0143	0.1074	8.91E-01	9.68E-01
sphingosine 1-phosphate	Lipid	Sphingolipid Metabolism	-0.051	0.1178	6.65E-01	8.19E-01	-0.0339	0.1188	7.76E-01	8.91E-01	-0.0403	0.1209	7.41E-01	9.18E-01
1-(1-enyl-stearoyl)-2-oleoyl-GPE (P-18:0/18:1)	Lipid	Plasmalogen	-0.0471	0.1137	6.79E-01	8.28E-01	-0.0577	0.1143	6.17E-01	7.83E-01	-0.0185	0.1153	8.71E-01	9.57E-01
1-(1-enyl-stearoyl)-2-arachidonoyl-GPE (P-18:0/20:4)*	Lipid	Plasmalogen	-0.0455	0.1154	6.93E-01	8.33E-01	-0.0421	0.1163	7.24E-01	8.64E-01	0.0248	0.1209	8.32E-01	9.44E-01
azelate (nonanedioate)	Lipid	Fatty Acid, Dicarboxylate	0.0434	0.1112	6.96E-01	8.34E-01	0.0397	0.1117	7.24E-01	8.65E-01	0.0108	0.1141	9.33E-01	9.82E-01
ceramide (d18:1/14:0, d16:1/16:0)*	Lipid	Ceramides	0.0444	0.1147	6.99E-01	8.34E-01	0.035	0.1152	7.59E-01	8.81E-01	0.0207	0.1166	8.51E-01	9.55E-01
palmitoyl sphingomyelin (d18:1/16:0)	Lipid	Sphingolipid Metabolism	0.0472	0.1195	6.93E-01	8.33E-01	0.0545	0.1193	6.46E-01	8.10E-01	0.0032	0.1217	9.77E-01	9.96E-01
sphingomyelin (d18:1/25:0, d19:0/24:1, d20:1/23:0, d19	Lipid	Sphingolipid Metabolism	0.045	0.1132	6.91E-01	8.33E-01	0.0389	0.1132	7.24E-01	8.74E-01	0.091	0.1162	4.37E-01	7.91E-01
3-carboxy-4-methyl-5-propyl-2-furanpropanoate (CMPF)	Lipid	Fatty Acid, Dicarboxylate	0.0423	0.1132	7.09E-01	8.41E-01	0.0285	0.1139	7.94E-01	9.05E-01	0.1035	0.1169	3.80E-01	7.59E-01
3-hydroxyhexanoate	Lipid	Fatty Acid, Monohydroxy	0.0415	0.1126	7.13E-01	8.43E-01	0.0187	0.1139	8.71E-01	9.34E-01	-0.0258	0.1157	8.32E-01	9.44E-01

1-linoleoyl-2-arachidonoyl-GPC (18:2/20:4n6)*	Lipid	Phospholipid Metabolism	-0.0428	0.1142	7.08E-01	8.41E-01	-0.0407	0.1145	7.24E-01	8.65E-01	-0.0059	0.1175	9.55E-01	9.96E-01
docosatrienoate (22:3n3)	Lipid	Polyunsaturated Fatty Acid (n3 and n6)	0.0298	0.0804	7.11E-01	8.42E-01	0.0311	0.0806	6.92E-01	8.48E-01	0.0306	0.0824	7.08E-01	9.06E-01
1-stearoyl-2-oleoyl-GPI (18:0/18:1)*	Lipid	Phospholipid Metabolism	0.0419	0.1117	7.08E-01	8.41E-01	0.0383	0.1122	7.41E-01	8.75E-01	0.001	0.1137	1.00E+00	9.96E-01
chenodeoxycholate	Lipid	Primary Bile Acid Metabolism	-0.0395	0.1095	7.18E-01	8.44E-01	-0.0333	0.1097	7.59E-01	8.81E-01	0.0189	0.1111	8.71E-01	9.56E-01
sphingomyelin (d18:1/20:2, d18:2/20:1, d16:1/22:2)*	Lipid	Sphingolipid Metabolism	0.044	0.1235	7.22E-01	8.45E-01	0.0233	0.1249	8.51E-01	9.31E-01	-0.1517	0.135	2.63E-01	6.90E-01
sphingomyelin (d18:1/21:0, d17:1/22:0, d16:1/23:0)*	Lipid	Sphingolipid Metabolism	-0.0428	0.1206	7.23E-01	8.45E-01	-0.0492	0.1215	6.92E-01	8.35E-01	-0.0205	0.1254	8.71E-01	9.56E-01
taurocholate	Lipid	Primary Bile Acid Metabolism	0.0312	0.0895	7.28E-01	8.49E-01	0.0275	0.09	7.59E-01	8.81E-01	0.0024	0.0917	9.77E-01	9.96E-01
eicosenoate (20:1)	Lipid	Long Chain Fatty Acid	0.0357	0.1119	7.50E-01	8.64E-01	0.0303	0.1121	7.94E-01	8.98E-01	0.0491	0.1159	6.76E-01	8.93E-01
glycerophosphoethanolamine	Lipid	Phospholipid Metabolism	0.0401	0.1226	7.44E-01	8.62E-01	0.0564	0.1242	6.46E-01	8.10E-01	0.1145	0.1294	3.80E-01	7.59E-01
oleate/vaccenate (18:1)	Lipid	Long Chain Fatty Acid	-0.0376	0.1133	7.40E-01	8.60E-01	-0.03	0.1137	7.94E-01	8.99E-01	-0.0253	0.1158	8.32E-01	9.44E-01
undecanoate (11:0)	Lipid	Medium Chain Fatty Acid	0.0407	0.1222	7.39E-01	8.60E-01	0.0505	0.1236	6.76E-01	8.34E-01	0.0286	0.1261	8.13E-01	9.44E-01
17-methylstearate	Lipid	Fatty Acid, Branched	0.0355	0.1122	7.52E-01	8.65E-01	0.0343	0.1128	7.59E-01	8.81E-01	0.0521	0.1165	6.61E-01	8.86E-01
2-hydroxyadipate	Lipid	Fatty Acid, Dicarboxylate	0.0313	0.1049	7.65E-01	8.72E-01	0.0329	0.1052	7.59E-01	8.79E-01	-0.0041	0.107	9.77E-01	9.96E-01
choline phosphate	Lipid	Phospholipid Metabolism	0.035	0.1184	7.67E-01	8.72E-01	0.0636	0.1204	6.03E-01	7.72E-01	0.2181	0.1282	8.91E-02	5.36E-01
isoursodeoxycholate	Lipid	Secondary Bile Acid Metabolism	-0.0328	0.1109	7.68E-01	8.72E-01	-0.0372	0.1115	7.41E-01	8.76E-01	-0.0316	0.1128	7.76E-01	9.43E-01
1-oleoyl-GPC (18:1)	Lipid	Lysolipid	0.0311	0.113	7.83E-01	8.82E-01	0.0302	0.1128	7.94E-01	8.99E-01	-0.004	0.1157	9.77E-01	9.96E-01
1-oleoyl-GPE (18:1)	Lipid	Lysolipid	0.031	0.112	7.82E-01	8.82E-01	0.0197	0.1126	8.71E-01	9.34E-01	0.002	0.1159	9.77E-01	9.96E-01
2-aminooctanoate	Lipid	Fatty Acid, Amino	0.0299	0.11	7.86E-01	8.83E-01	0.0078	0.1114	9.55E-01	9.74E-01	-0.0728	0.115	5.25E-01	8.21E-01
1-(1-enyl-palmitoyl)-2-palmitoyl-GPC (P-16:0/16:0)*	Lipid	Plasmalogen	-0.0285	0.1123	8.00E-01	8.91E-01	-0.0203	0.1123	8.51E-01	9.33E-01	-0.0125	0.1148	9.12E-01	9.74E-01
erucate (22:1n9)	Lipid	Long Chain Fatty Acid	0.0299	0.1134	7.92E-01	8.85E-01	0.023	0.1138	8.32E-01	9.25E-01	0.0741	0.1173	5.25E-01	8.21E-01
palmitate (16:0)	Lipid	Long Chain Fatty Acid	0.0298	0.1119	7.90E-01	8.84E-01	0.0359	0.1121	7.41E-01	8.78E-01	0.0578	0.114	6.17E-01	8.74E-01
andro steroid monosulfate (1)*	Lipid	Steroid	-0.0241	0.1055	8.20E-01	9.05E-01	-0.028	0.1057	7.94E-01	8.99E-01	-0.0972	0.1093	3.72E-01	7.59E-01
arachidate (20:0)	Lipid	Long Chain Fatty Acid	0.0252	0.1115	8.21E-01	9.05E-01	0.0233	0.1117	8.32E-01	9.25E-01	0.0779	0.1144	5.01E-01	8.20E-01
sphingomyelin (d18:1/17:0, d17:1/18:0, d19:1/16:0)	Lipid	Sphingolipid Metabolism	0.0282	0.1164	8.08E-01	8.97E-01	0.0194	0.1168	8.71E-01	9.34E-01	0.0143	0.1194	9.12E-01	9.68E-01
sphingomyelin (d18:2/24:1, d18:1/24:2)*	Lipid	Sphingolipid Metabolism	0.0292	0.1239	8.14E-01	9.00E-01	0.0267	0.1239	8.32E-01	9.23E-01	-0.0543	0.1282	6.76E-01	8.93E-01
cholate	Lipid	Primary Bile Acid Metabolism	0.0182	0.0883	8.37E-01	9.08E-01	0.0149	0.0886	8.71E-01	9.34E-01	0.0059	0.0912	9.55E-01	9.93E-01
1-oleoyl-2-linoleoyl-GPE (18:1/18:2)*	Lipid	Phospholipid Metabolism	0.0231	0.1124	8.37E-01	9.08E-01	0.0037	0.1141	9.77E-01	9.90E-01	-0.0629	0.1184	5.89E-01	8.66E-01
lignoceroyl sphingomyelin (d18:1/24:0)	Lipid	Sphingolipid Metabolism	0.0258	0.1174	8.26E-01	9.07E-01	0.0493	0.1181	6.76E-01	8.29E-01	0.1399	0.1221	2.51E-01	6.83E-01
sphingomyelin (d18:1/22:1, d18:2/22:0, d16:1/24:1)*	Lipid	Sphingolipid Metabolism	0.0262	0.1244	8.33E-01	9.08E-01	0.0256	0.1243	8.32E-01	9.25E-01	0.0266	0.1274	8.32E-01	9.44E-01
sphingomyelin (d18:2/23:1)*	Lipid	Sphingolipid Metabolism	0.0271	0.1304	8.35E-01	9.08E-01	0.0022	0.1319	9.77E-01	9.93E-01	-0.1287	0.1389	3.55E-01	7.38E-01
tetradecanedioate	Lipid	Fatty Acid, Dicarboxylate	0.0244	0.1123	8.28E-01	9.07E-01	0.0189	0.1124	8.71E-01	9.34E-01	-0.0403	0.1152	7.24E-01	9.13E-01
nonadecanoate (19:0)	Lipid	Long Chain Fatty Acid	-0.0222	0.113	8.44E-01	9.14E-01	-0.0199	0.1133	8.51E-01	9.34E-01	0.027	0.117	8.13E-01	9.44E-01
taurocholenate sulfate	Lipid	Secondary Bile Acid Metabolism	-0.0215	0.1128	8.49E-01	9.18E-01	-0.0373	0.113	7.41E-01	8.76E-01	-0.0493	0.1139	6.61E-01	8.93E-01
1-(1-enyl-palmitoyl)-2-arachidonoyl-GPC (P-16:0/20:4)*	Lipid	Plasmalogen	-0.0186	0.1139	8.70E-01	9.32E-01	-0.0149	0.114	8.91E-01	9.47E-01	0.0252	0.1177	8.32E-01	9.44E-01
2-hydroxypalmitate	Lipid	Fatty Acid, Monohydroxy	-0.0175	0.1123	8.76E-01	9.37E-01	-0.0103	0.1125	9.33E-01	9.67E-01	-0.0563	0.1155	6.31E-01	8.84E-01
sphingomyelin (d18:1/19:0, d19:1/18:0)*	Lipid	Sphingolipid Metabolism	-0.0197	0.1195	8.69E-01	9.32E-01	-0.0309	0.1207	7.94E-01	9.03E-01	-0.0345	0.1244	7.76E-01	9.43E-01
2-hydroxydecanoate	Lipid	Fatty Acid, Monohydroxy	0.0142	0.1115	8.99E-01	9.49E-01	-0.0034	0.1127	9.77E-01	9.90E-01	0.0066	0.1143	9.55E-01	9.96E-01
5-hydroxydecanoate	Lipid	Fatty Acid, Monohydroxy	0.0145	0.1101	8.95E-01	9.49E-01	0.0207	0.1109	8.51E-01	9.31E-01	-0.013	0.1127	9.12E-01	9.70E-01
pregnanediol-3-glucuronide	Lipid	Steroid	0.0119	0.1044	9.09E-01	9.53E-01	0.007	0.1048	9.55E-01	9.74E-01	-0.0394	0.1087	7.24E-01	9.08E-01
sphingomyelin (d18:1/22:2, d18:2/22:1, d16:1/24:2)*	Lipid	Sphingolipid Metabolism	-0.0134	0.1306	9.18E-01	9.62E-01	-0.0317	0.1315	8.13E-01	9.07E-01	-0.1853	0.1397	1.86E-01	6.46E-01
glycerol 3-phosphate	Lipid	Glycerolipid Metabolism	-0.0091	0.1141	9.37E-01	9.70E-01	0.0068	0.1151	9.55E-01	9.77E-01	0.0644	0.1193	5.89E-01	8.63E-01
glycochenodeoxycholate glucuronide (1)	Lipid	Primary Bile Acid Metabolism	0.0107	0.1124	9.24E-01	9.67E-01	0.01	0.1124	9.33E-01	9.67E-01	-0.0492	0.116	6.76E-01	8.93E-01
glycoursodeoxycholate	Lipid	Secondary Bile Acid Metabolism	-0.0085	0.1123	9.40E-01	9.70E-01	-0.015	0.1128	8.91E-01	9.47E-01	-0.0192	0.1149	8.71E-01	9.56E-01
propionylglycine	Lipid	Fatty Acid Metabolism (also BCAA Metabolism)	-0.0083	0.1035	9.36E-01	9.70E-01	-0.0147	0.1036	8.91E-01	9.44E-01	0.0054	0.1062	9.55E-01	9.96E-01
sphingomyelin (d18:2/23:0, d18:1/23:1, d17:1/24:1)*	Lipid	Sphingolipid Metabolism	-0.0116	0.1262	9.27E-01	9.67E-01	-0.0192	0.1267	8.71E-01	9.41E-01	-0.0341	0.1305	7.94E-01	9.44E-01
glycochenodeoxycholate	Lipid	Primary Bile Acid Metabolism	0.0063	0.1123	9.55E-01	9.77E-01	0.0045	0.1126	9.77E-01	9.89E-01	-0.0255	0.1141	8.32E-01	9.44E-01
sphingomyelin (d18:1/15:0, d16:1/17:0)*	Lipid	Sphingolipid Metabolism	-0.0072	0.1185	9.52E-01	9.75E-01	-0.0241	0.1193	8.32E-01	9.25E-01	-0.082	0.1231	5.01E-01	8.20E-01
5alpha-androstan-3beta,17beta-diol monosulfate (2)	Lipid	Steroid	0.002	0.0869	9.82E-01	9.94E-01	0.0085	0.0873	9.12E-01	9.65E-01	0.0367	0.0889	6.76E-01	8.94E-01
1-palmitoyl-GPI (16:0)	Lipid	Lysolipid	-0.0049	0.1165	9.67E-01	9.86E-01	-0.0017	0.1166	9.77E-01	9.93E-01	-0.043	0.1194	7.24E-01	9.08E-01
1-stearoyl-2-linoleoyl-GPI (18:0/18:2)	Lipid	Phospholipid Metabolism	-0.0037	0.1143	9.74E-01	9.91E-01	-0.002	0.1145	9.77E-01	9.93E-01	-0.0607	0.1166	6.03E-01	8.67E-01
cortisone	Lipid	Steroid	-0.0016	0.1168	9.89E-01	9.96E-01	0.0297	0.1189	7.94E-01	9.05E-01	0.0878	0.1217	4.68E-01	8.18E-01
1-linoleoyl-GPG (18:2)*	Lipid	Lysolipid	0.0006	0.1028	9.95E-01	9.96E-01	-0.0133	0.1039	8.91E-01	9.47E-01	-0.0501	0.1059	6.31E-01	8.84E-01
glycosyl ceramide (d18:2/24:1, d18:1/24:2)*	Lipid	Ceramides	-0.0013	0.1183	9.91E-01	9.96E-01	-0.005	0.1179	9.77E-01	9.88E-01	-0.0721	0.121	5.50E-01	8.39E-01
tricosanoyl sphingomyelin (d18:1/23:0)*	Lipid	Sphingolipid Metabolism	0.0007	0.1209	9.95E-01	9.96E-01	0.0167	0.1213	8.91E-01	9.45E-01	0.0561	0.1234	6.46E-01	8.85E-01

Beta estimates, standard errors and p-values obtained from conditional logistic regression models with CVD outcome as dependent variable, matching variables (sex, storage time, Scre-eGFR, HbA1c) included in stratum statement, and metabolite as predictors adjusted by eGFR as indicated.

The Q-values are derived from Benjamin-Hochberg False Discovery Rate corrections for multiple comparisons involving the whole panel of 671 metabolites.

Supplementary Fig.1. Flowchart for Metabolite analysis



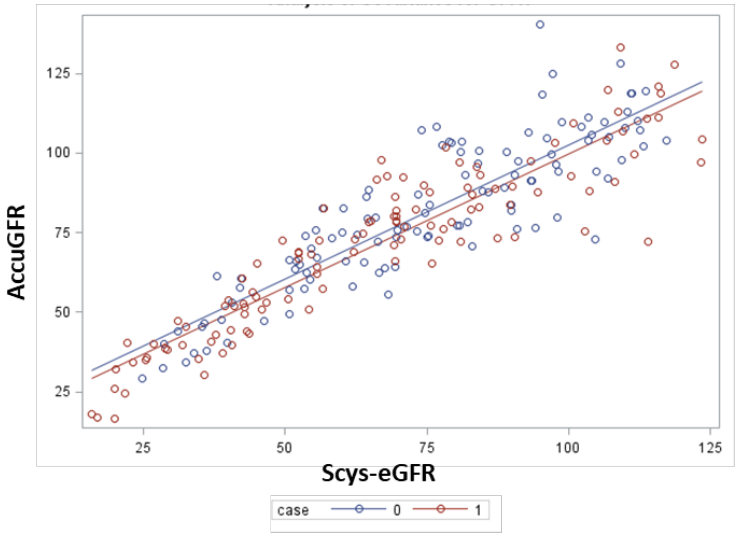
Supplementary Fig.2. Precision of GFR estimates (n=225)

Fig.2A. AccuGFR vs. creatinine-eGFR

Controls R^2 = 0.63

Cases R^2 = 0.62

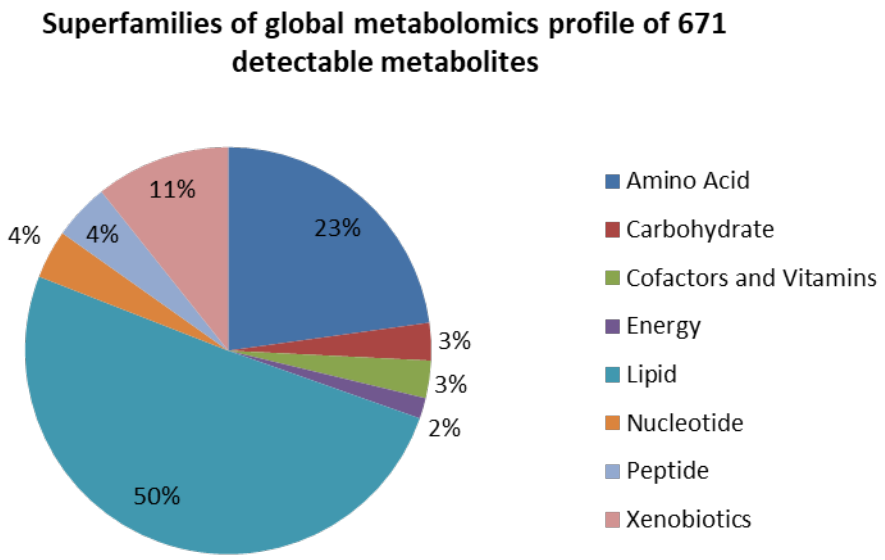
Fig.2B. AccuGFR vs. cystatin-eGFR



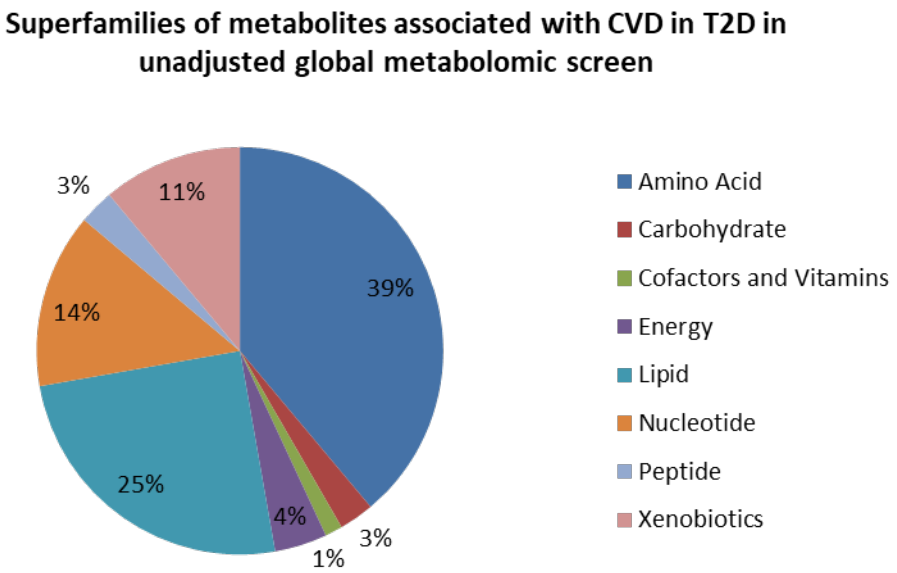
Controls R^2 = 0.76

Cases R^2 = 0.84

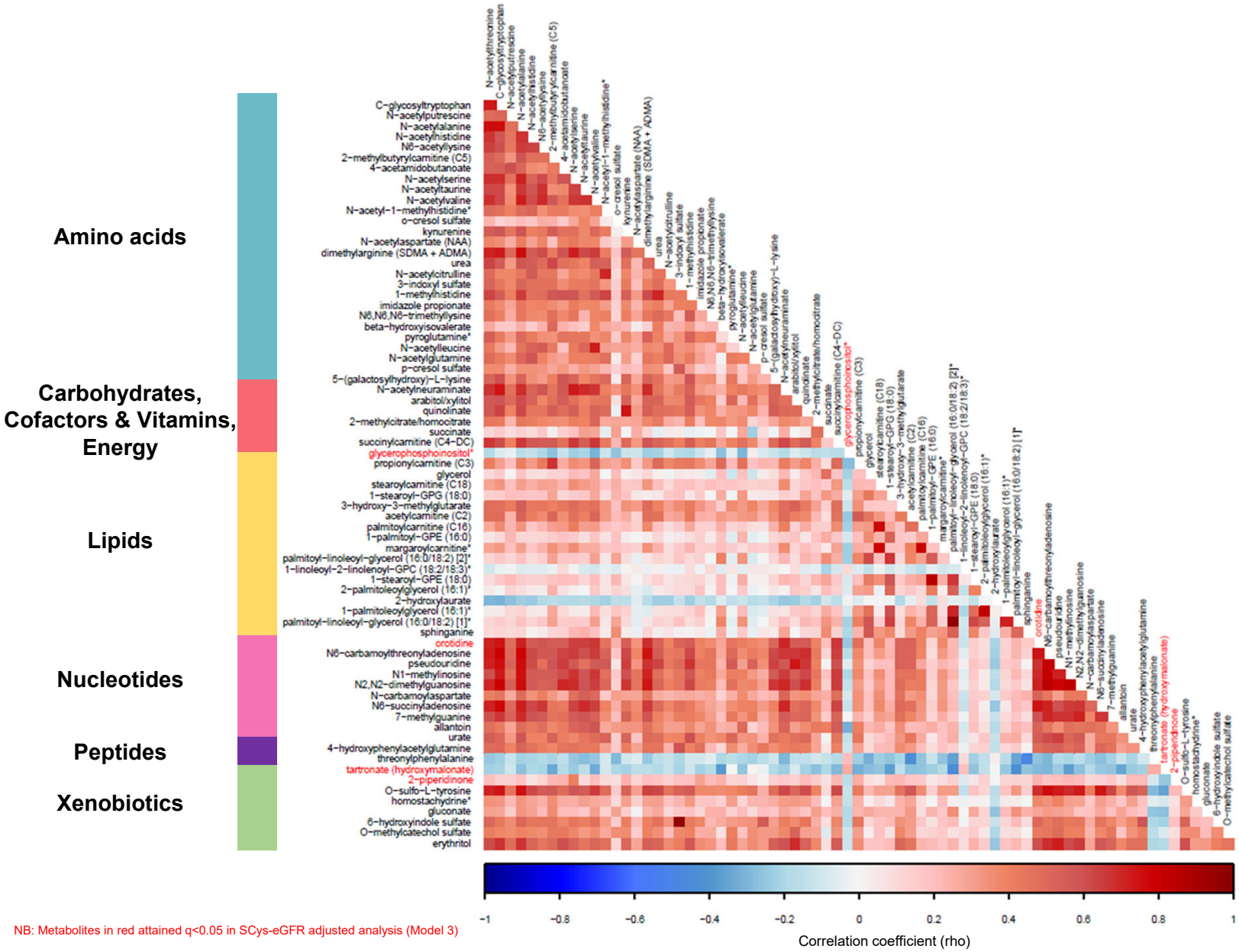
Supplementary Fig.3A. Profile of 671 metabolites detectable in 80% of samples

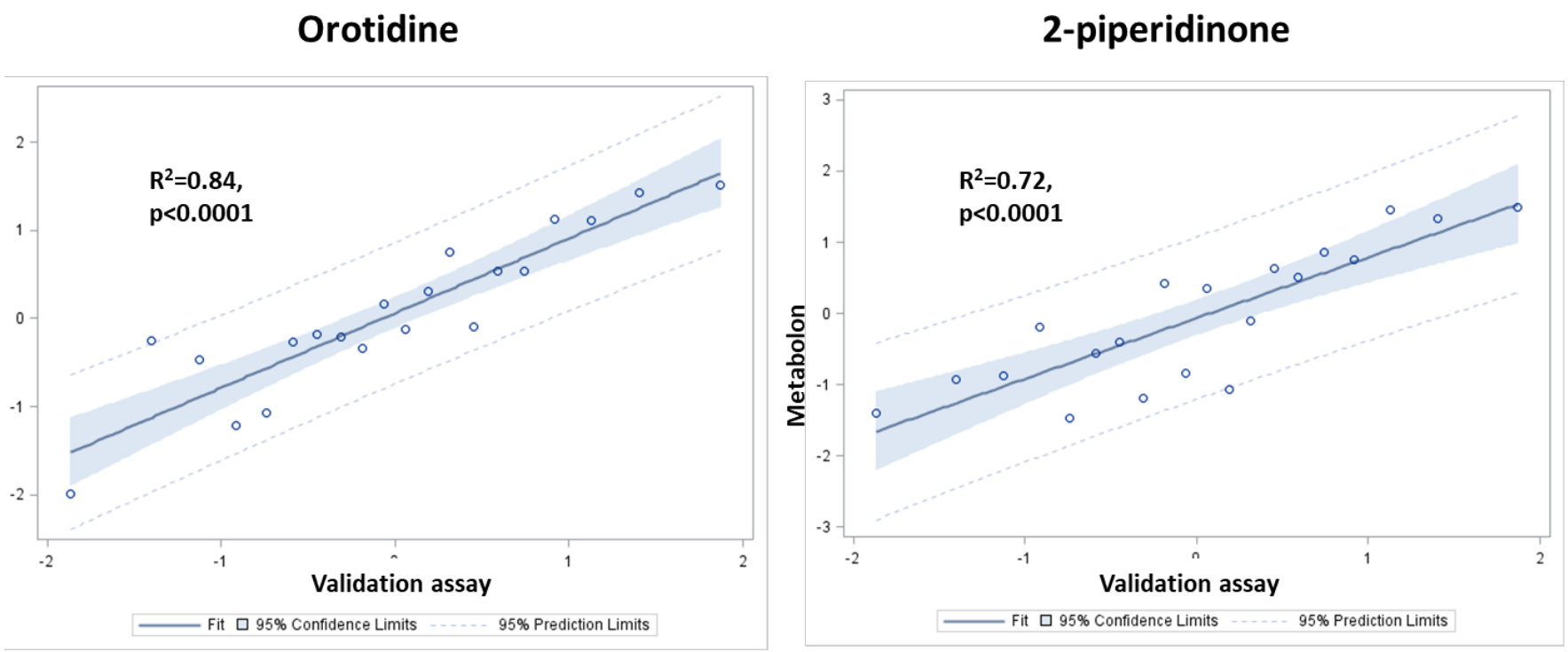


Supplementary Fig.3B. Profile of 72 metabolites associated with CVD in T2D [FDR<0.05]



Supplementary Fig.4: Correlations between 72 metabolites that attained q<0.05 for associations with CVD in the primary analysis (Model 1) in the Discovery Set



NB: Metabolites in red attained q<0.05 in SCys-eGFR adjusted analysis (Model 3)

Supplementary Fig.5: Correlation of significant metabolites measured by Metabolon versus validation assay methods among 20 replicates of Discovery set