

SUPPLEMENTARY MATERIAL

METABOLIC PROFILING OF OBESITY WITH AND WITHOUT THE METABOLIC SYNDROME – A MULTI-SAMPLE EVALUATION

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Supplementary Table 1. An overview of metabolite differences between certain groups; obese (OB) subjects without MetS vs normal-weight (NW) without MetS, overweight (OW) without MetS vs normal-weight (NW) without MetS, OB with vs OB without MetS, and to the right metabolites vs insulin resistance (Matsuda index). A positive beta denote that the metabolite is higher in obese subjects without MetS compared to normal-weight without MetS etc. Only metabolites with $FDR < 0.05$ are shown. A p-value of 0 denotes that $p < e-25$.

This table is given in a separate Excel file: Lind L, Salihovic S, Sundström J, Elmståhl S, Hammar U, Dekkers K, Ärnlöv J, Smith JG, Engström G, Fall T. Data from: Supplementary Table 1. An overview of metabolite differences between certain groups. 2021. Deposited 01 December 2021. <http://urn.kb.se/resolve?urn=urn:nbn:se:uu:diva-460027>.

Supplementary Table 2. Pathway enrichment and topographical analysis for the 427 validated metabolites that differed between obese subjects without MetS and normal-weight without MetS. Only pathways with $p < 0.05$ are given. Data on all 427 metabolites are given in Suppl Table 1. * = $FDR < 0.05$.

Pathway	Total	Expected	Hits	<i>p</i> -value
Alanine, aspartate and glutamate metabolism	28	2.87	12	6.43e-06*
Valine, leucine and isoleucine biosynthesis	8	.82	6	.000025*
Phenylalanine, tyrosine and tryptophan biosynthesis	4	.41	4	.00010*
Arginine biosynthesis	14	1.43	7	.00019*
Histidine metabolism	16	1.64	7	.00054*
Aminoacyl-tRNA biosynthesis	48	4.92	13	.00067*
Sphingolipid metabolism	21	2.15	7	.0035*
Glycine, serine and threonine metabolism	33	3.38	9	.0044*
Phenylalanine metabolism	10	1.02	4	.013
Cysteine and methionine metabolism	33	3.38	8	.015
Pantothenate and CoA biosynthesis	19	1.94	5	.037
Citrate cycle (TCA cycle)	20	2.05	5	.046

Supplementary Table 3. Pathway enrichment and topographical analysis for the 196 validated metabolites that differed between obese subjects with and without MetS. Only pathways with $p < 0.05$ are given. Data on all 196 metabolites are given in Suppl Table 1. * = $FDR < 0.05$.

Pathway	Total	Expected	Hits	p-value
Valine, leucine and isoleucine biosynthesis	8	.33	6	1.03e-07*
Aminoacyl-tRNA biosynthesis	48	1.98	10	.000013*
Arginine biosynthesis	14	.57	5	.00015*
Alanine, aspartate and glutamate metabolism	28	1.15	6	.00072*
Valine, leucine and isoleucine degradation	40	1.65	7	.00093*
Sphingolipid metabolism	21	.86	5	.0012*
Glycine, serine and threonine metabolism	33	1.362	6	.0018*
Histidine metabolism	16	.66	4	.0033*
Pantothenate and CoA biosynthesis	19	.784	4	.0064
D-Glutamine and D-glutamate metabolism	6	.24	2	.022
Glyoxylate and dicarboxylate metabolism	32	1.32	4	.039

Supplementary Table 4. Relationships between metabolites and BMI and number of MetS components in the continuous analysis. Only metabolites with FDR<0.05 for both BMI and number of MetS components are given. The direction of the associations could be seen in Suppl table 1.

Super pathway	Sub pathway	Chemical name	p-value for MetS components	p-value for BMI
Amino Acid	Alanine and Aspartate Metabolism	hydroxyasparagine	.0075129	<1.00e-25
Amino Acid	Alanine and Aspartate Metabolism	alanine	9.35e-21	.0032375
Amino Acid	Alanine and Aspartate Metabolism	N-acetylaspartate (NAA)	6.42e-07	.0079234
Amino Acid	Alanine and Aspartate Metabolism	aspartate	2.76e-11	2.85e-11
Amino Acid	Creatine Metabolism	guanidinoacetate	3.65e-13	5.26e-06
Amino Acid	Creatine Metabolism	creatine	.0017725	5.62e-08
Amino Acid	Glutamate Metabolism	glutamine	.0057657	.0165151
Amino Acid	Glutamate Metabolism	N-acetyl-aspartyl-glutamate (NAAG)	.0141565	.0218621
Amino Acid	Glutamate Metabolism	beta-citrylglutamate	3.89e-07	1.69e-07
Amino Acid	Glutamate Metabolism	glutamate	2.55e-24	1.59e-28
Amino Acid	Glutamate Metabolism	N-acetylglutamate	5.40e-06	2.52e-11
Amino Acid	Glutamate Metabolism	4-hydroxyglutamate	1.20e-35	1.37e-36
Amino Acid	Glutathione Metabolism	2-aminobutyrate	.0087878	2.70e-09
Amino Acid	Glutathione Metabolism	cysteine-glutathione disulfide	5.33e-16	.002181
Amino Acid	Glutathione Metabolism	cysteinylglycine disulfide	.0002293	2.67e-13
Amino Acid	Glutathione Metabolism	2-hydroxybutyrate/2-hydroxyisobutyrate	1.94e-15	5.56e-07
Amino Acid	Glutathione Metabolism	5-oxoproline	.020589	.0096886
Amino Acid	Glycine, Serine and Threonine Metabolism	glycine	1.65e-26	1.71e-07

Amino Acid	Glycine, Serine and Threonine Metabolism	N-acetylglycine	6.90e-22	3.06e-13
Amino Acid	Histidine Metabolism	1-methyl-4-imidazoleacetate	.0121934	.0002715
Amino Acid	Histidine Metabolism	formiminoglutamate	6.77e-19	2.62e-26
Amino Acid	Histidine Metabolism	hydantoin-5-propionate	.0074574	7.03e-11
Amino Acid	Histidine Metabolism	imidazole lactate	.0004074	.0113722
Amino Acid	Histidine Metabolism	histidine	3.44e-08	2.67e-11
Amino Acid	Leucine, Isoleucine and Valine Metabolism	3-hydroxy-2-ethylpropionate	.0006434	.0000594
Amino Acid	Leucine, Isoleucine and Valine Metabolism	2-hydroxy-3-methylvalerate	3.10e-16	.02694
Amino Acid	Leucine, Isoleucine and Valine Metabolism	isovalerate (i5:0)	.0004062	.0000447
Amino Acid	Leucine, Isoleucine and Valine Metabolism	alpha-hydroxyisovalerate	4.42e-09	.0052401
Amino Acid	Leucine, Isoleucine and Valine Metabolism	3-methyl-2-oxobutyrate	2.29e-19	8.78e-07
Amino Acid	Leucine, Isoleucine and Valine Metabolism	1-carboxyethylleucine	<1.00e-25	6.10e-07
Amino Acid	Leucine, Isoleucine and Valine Metabolism	isovalerylcarnitine (C5)	.0122559	5.60e-16
Amino Acid	Leucine, Isoleucine and Valine Metabolism	tigloylglycine	.0008098	.0004868
Amino Acid	Leucine, Isoleucine and Valine Metabolism	1-carboxyethylisoleucine	<1.00e-25	.001904
Amino Acid	Leucine, Isoleucine and Valine Metabolism	1-carboxyethylvaline	<1.00e-25	1.18e-07
Amino Acid	Leucine, Isoleucine and Valine Metabolism	2,3-dihydroxy-2-methylbutyrate	.0167624	.0008331

Amino Acid	Leucine, Isoleucine and Valine Metabolism	isoleucine	4.26e-35	7.28e-17
Amino Acid	Leucine, Isoleucine and Valine Metabolism	3-methyl-2-oxovalerate	<1.00e-25	.0051857
Amino Acid	Leucine, Isoleucine and Valine Metabolism	N-acetylleucine	2.99e-11	.0011692
Amino Acid	Leucine, Isoleucine and Valine Metabolism	2-ketocaprylate	.0099326	.0039478
Amino Acid	Leucine, Isoleucine and Valine Metabolism	alpha-hydroxyisocaproate	.0000113	.000389
Amino Acid	Leucine, Isoleucine and Valine Metabolism	valine	1.97e-18	7.44e-25
Amino Acid	Leucine, Isoleucine and Valine Metabolism	4-methyl-2-oxopentanoate	6.00e-23	.0173347
Amino Acid	Leucine, Isoleucine and Valine Metabolism	ethylmalonate	.0078657	.0007957
Amino Acid	Leucine, Isoleucine and Valine Metabolism	leucine	2.57e-24	4.06e-14
Amino Acid	Lysine Metabolism	fructosyllsine	1.41e-25	9.36e-10
Amino Acid	Lysine Metabolism	glutaryl carnitine (C5-DC)	.0155275	.0053935
Amino Acid	Lysine Metabolism	2-aminoadipate	2.29e-20	1.97e-06
Amino Acid	Lysine Metabolism	N6,N6,N6-trimethyllysine	5.76e-07	5.00e-08
Amino Acid	Lysine Metabolism	5-hydroxylysine	.0001513	1.33e-38
Amino Acid	Methionine, Cysteine, SAM and Taurine Metabolism	2,3-dihydroxy-5-methylthio-4-pentenoate (DMTPA)	2.45e-11	1.63e-29
Amino Acid	Methionine, Cysteine, SAM and Taurine Metabolism	N-acetylmethionine	.0035339	.0027502

Amino Acid	Methionine, Cysteine, SAM and Taurine Metabolism	alpha-ketobutyrate	4.48e-11	2.81e-10
Amino Acid	Methionine, Cysteine, SAM and Taurine Metabolism	hypotaurine	.0003286	5.54e-09
Amino Acid	Methionine, Cysteine, SAM and Taurine Metabolism	S-methylcysteine sulfoxide	1.28e-11	.0014681
Amino Acid	Methionine, Cysteine, SAM and Taurine Metabolism	2-hydroxy-4-(methylthio)butanoic acid	.0047484	4.00e-10
Amino Acid	Methionine, Cysteine, SAM and Taurine Metabolism	S-adenosylhomocysteine (SAH)	.0115256	5.82e-06
Amino Acid	Methionine, Cysteine, SAM and Taurine Metabolism	cystathionine	1.77e-06	.0000118
Amino Acid	Phenylalanine Metabolism	N-acetylphenylalanine	.0009742	.0000184
Amino Acid	Phenylalanine Metabolism	phenyllactate (PLA)	.0247303	.0001496
Amino Acid	Phenylalanine Metabolism	1-carboxyethylphenylalanine	<1.00e-25	.0001184
Amino Acid	Polyamine Metabolism	5-methylthioadenosine (MTA)	8.32e-08	2.27e-23
Amino Acid	Tryptophan Metabolism	C-glycosyltryptophan	.0239477	8.10e-14
Amino Acid	Tryptophan Metabolism	3-indoxyl sulfate	.0000936	.027536
Amino Acid	Tryptophan Metabolism	tryptophan betaine	.0009804	.0149031
Amino Acid	Tryptophan Metabolism	indolepropionate	.0000205	4.96e-06
Amino Acid	Tryptophan Metabolism	8-methoxykynurenate	3.11e-06	9.04e-08
Amino Acid	Tryptophan Metabolism	oxindolylalanine	.0062575	.0000544
Amino Acid	Tryptophan Metabolism	tryptophan	.0181204	.0031215
Amino Acid	Tyrosine Metabolism	4-hydroxyphenylacetyl carnitine	.0015791	.0000402

Amino Acid	Tyrosine Metabolism	1-carboxyethyltyrosine	<1.00e-25	4.00e-09
Amino Acid	Tyrosine Metabolism	homovanillate (HVA)	.0034728	.0320509
Amino Acid	Tyrosine Metabolism	3-(4-hydroxyphenyl)lactate	.0124515	6.27e-11
Amino Acid	Tyrosine Metabolism	4-hydroxyphenylpyruvate	.000264	.0004026
Amino Acid	Tyrosine Metabolism	3-methoxytyrosine	.0000169	.0124249
Amino Acid	Urea cycle; Arginine and Proline Metabolism	arginine	1.33e-10	.0000844
Amino Acid	Urea cycle; Arginine and Proline Metabolism	dimethylarginine (SDMA + ADMA)	6.25e-12	4.86e-06
Amino Acid	Urea cycle; Arginine and Proline Metabolism	N,N,N-trimethyl-alanylproline betaine (TMAP)	.0006935	.0011629
Amino Acid	Urea cycle; Arginine and Proline Metabolism	3-amino-2-piperidone	.025986	.0279599
Amino Acid	Urea cycle; Arginine and Proline Metabolism	N2,N5-diacetylornithine	.0115424	.0020041
Amino Acid	Urea cycle; Arginine and Proline Metabolism	2-oxoarginine	.0008115	2.45e-08
Amino Acid	Urea cycle; Arginine and Proline Metabolism	homocitrulline	.0028927	.0292491
Amino Acid	Urea cycle; Arginine and Proline Metabolism	N-acetylcitrulline	.0003588	2.85e-06
Amino Acid	Urea cycle; Arginine and Proline Metabolism	proline	6.45e-08	.002951
Amino Acid	Urea cycle; Arginine and Proline Metabolism	ornithine	.0056888	.0123024
Carbohydrate	Aminosugar Metabolism	erythronate	2.90e-23	.0041227
Carbohydrate	Aminosugar Metabolism	N-acetylglucosamine/N-acetylgalactosamine	.0039585	1.94e-13
Carbohydrate	Fructose, Mannose and Galactose Metabolism	fructose	4.57e-12	.0002289

Carbohydrate	Fructose, Mannose and Galactose Metabolism	mannose	5.86e-35	1.17e-23
Carbohydrate	Glycolysis, Gluconeogenesis, and Pyruvate Metabolism	pyruvate	1.80e-24	.0017732
Carbohydrate	Glycolysis, Gluconeogenesis, and Pyruvate Metabolism	1,5-anhydroglucitol (1,5-AG)	2.98e-23	6.12e-09
Carbohydrate	Glycolysis, Gluconeogenesis, and Pyruvate Metabolism	glucose	<1.00e-25	.0035022
Carbohydrate	Glycolysis, Gluconeogenesis, and Pyruvate Metabolism	lactate	<1.00e-25	.0113982
Carbohydrate	Glycolysis, Gluconeogenesis, and Pyruvate Metabolism	glycerate	1.96e-10	.0028877
Carbohydrate	Pentose Metabolism	ribitol	2.16e-18	3.38e-07
Carbohydrate	Pentose Metabolism	xylose	.0004221	.0172044
Carbohydrate	Pentose Metabolism	arabitol/xylitol	.0001869	.0001361
Carbohydrate	Pentose Metabolism	arabinose	.0178268	.0249052
Cofactors and Vitamins	Ascorbate and Aldarate Metabolism	oxalate (ethanedioate)	9.66e-10	.0007906
Cofactors and Vitamins	Ascorbate and Aldarate Metabolism	2-O-methylascorbic acid	2.14e-17	6.20e-23
Cofactors and Vitamins	Hemoglobin and Porphyrin Metabolism	bilirubin (Z,Z)	1.69e-07	.000991
Cofactors and Vitamins	Hemoglobin and Porphyrin Metabolism	bilirubin (E,Z or Z,E)	1.76e-08	.0062686

Cofactors and Vitamins	Nicotinate and Nicotinamide Metabolism	quinolinate	.0000144	<1.00e-25
Cofactors and Vitamins	Nicotinate and Nicotinamide Metabolism	N1-Methyl-2-pyridone-5-carboxamide	.0073374	2.38e-17
Cofactors and Vitamins	Nicotinate and Nicotinamide Metabolism	trigonelline (N'-methylnicotinate)	.000073	.0006371
Cofactors and Vitamins	Pantothenate and CoA Metabolism	pantothenate	.0214155	5.17e-07
Cofactors and Vitamins	Tocopherol Metabolism	gamma-tocopherol/beta-tocopherol	1.33e-12	.0081553
Cofactors and Vitamins	Tocopherol Metabolism	alpha-tocopherol	2.38e-06	.0000114
Cofactors and Vitamins	Vitamin A Metabolism	carotene diol (2)	2.71e-21	5.94e-19
Cofactors and Vitamins	Vitamin A Metabolism	carotene diol (3)	2.34e-14	9.34e-06
Cofactors and Vitamins	Vitamin A Metabolism	beta-cryptoxanthin	9.21e-22	9.08e-11
Cofactors and Vitamins	Vitamin A Metabolism	retinol (Vitamin A)	2.53e-08	4.65e-12
Cofactors and Vitamins	Vitamin A Metabolism	carotene diol (1)	2.33e-14	1.33e-18
Cofactors and Vitamins	Vitamin A Metabolism	4-oxo-retinoic acid	.0034338	.0044362
Cofactors and Vitamins	Vitamin B6 Metabolism	pyridoxate	.014549	.0156544
Energy	Oxidative Phosphorylation	phosphate	.0073466	4.28e-10
Energy	TCA Cycle	succinylcarnitine (C4-DC)	.0001333	5.14e-06
Energy	TCA Cycle	citrate	.0003602	1.99e-13
Energy	TCA Cycle	aconitate [cis or trans]	3.49e-11	1.57e-10

Energy	TCA Cycle	malate	.0034171	1.69e-15
Energy	TCA Cycle	alpha-ketoglutarate	1.86e-19	1.59e-15
Lipid	Androgenic Steroids	etiocholanolone glucuronide	.0037358	.0000501
Lipid	Androgenic Steroids	11beta-hydroxyetiocholanolone glucuronide	.0044986	.0007129
Lipid	Androgenic Steroids	5alpha-androstan-3beta,17beta-diol monosulfate (2)	.0000771	.0053195
Lipid	Androgenic Steroids	androstenediol (3beta,17beta) monosulfate (1)	.0002527	.0041342
Lipid	Androgenic Steroids	androstenediol (3beta,17beta) disulfate (1)	7.00e-12	.0143099
Lipid	Ceramide PEs	palmitoyl-sphingosine-phosphoethanolamine (d18:1/16:0)	<1.00e-25	.0015176
Lipid	Ceramides	N-palmitoyl-sphingadienine (d18:2/16:0)	.0000814	.0000535
Lipid	Ceramides	N-stearoyl-sphingosine (d18:1/18:0)	3.72e-28	6.54e-16
Lipid	Ceramides	N-stearoyl-sphingadienine (d18:2/18:0)	.0033895	4.50e-12
Lipid	Corticosteroids	tetrahydrocortisone glucuronide (5)	5.50e-14	4.85e-21
Lipid	Corticosteroids	cortolone glucuronide (1)	6.64e-12	0
Lipid	Corticosteroids	cortisol	.0012902	3.06e-22
Lipid	Corticosteroids	tetrahydrocortisol glucuronide	5.48e-25	1.02e-07
Lipid	Diacylglycerol	oleoyl-linoleoyl-glycerol (18:1/18:2) [2]	<1.00e-25	.0000705
Lipid	Diacylglycerol	oleoyl-arachidonoyl-glycerol (18:1/20:4) [2]	<1.00e-25	1.48e-07
Lipid	Diacylglycerol	oleoyl-linoleoyl-glycerol (18:1/18:2) [1]	<1.00e-25	6.58e-06
Lipid	Diacylglycerol	linoleoyl-arachidonoyl-glycerol (18:2/20:4) [2]	<1.00e-25	.000314
Lipid	Diacylglycerol	linoleoyl-linoleoyl-glycerol (18:2/18:2) [1]	3.52e-35	.0031657
Lipid	Dihydroceramides	N-palmitoyl-sphinganine (d18:0/16:0)	3.18e-12	.0063155
Lipid	Dihydroceramides	N-stearoyl-sphinganine (d18:0/18:0)	5.24e-25	5.94e-22
Lipid	Dihydrosphingomyelins	behenoyl dihydrosphingomyelin (d18:0/22:0)	7.05e-08	8.97e-20
Lipid	Dihydrosphingomyelins	myristoyl dihydrosphingomyelin (d18:0/14:0)	2.61e-19	.0131765
Lipid	Dihydrosphingomyelins	sphingomyelin (d18:0/20:0, d16:0/22:0)	.0008339	1.97e-16
Lipid	Dihydrosphingomyelins	sphingomyelin (d18:0/18:0, d19:0/17:0)	.0000144	4.77e-27
Lipid	Endocannabinoid	N-oleoylserine	1.44e-06	.0010202

Lipid	Fatty Acid Metabolism (Acyl Carnitine, Dicarboxylate)	pimeloylcarnitine/3-methyladipoylcarnitine (C7-DC)	1.37e-13	3.11e-07
Lipid	Fatty Acid Metabolism (Acyl Carnitine, Dicarboxylate)	octadecanedioylcarnitine (C18-DC)	.0123333	.0295103
Lipid	Fatty Acid Metabolism (Acyl Carnitine, Hydroxy)	(S)-3-hydroxybutyrylcarnitine	.0000388	1.54e-06
Lipid	Fatty Acid Metabolism (Acyl Carnitine, Hydroxy)	3-hydroxyhexanoylcarnitine (1)	.0146929	.0000979
Lipid	Fatty Acid Metabolism (Acyl Carnitine, Hydroxy)	3-hydroxydecanoylcarnitine	.0000995	1.38e-06
Lipid	Fatty Acid Metabolism (Acyl Carnitine, Hydroxy)	3-hydroxyoctanoylcarnitine (1)	.0002946	8.60e-07
Lipid	Fatty Acid Metabolism (Acyl Carnitine, Hydroxy)	(R)-3-hydroxybutyrylcarnitine	.0003277	3.44e-08
Lipid	Fatty Acid Metabolism (Acyl Carnitine, Long Chain Saturated)	arachidoylcarnitine (C20)	4.79e-13	1.04e-31
Lipid	Fatty Acid Metabolism (Acyl Carnitine, Long Chain Saturated)	margaroylcarnitine (C17)	.0005067	.011527
Lipid	Fatty Acid Metabolism (Acyl Carnitine, Long Chain Saturated)	stearoylcarnitine (C18)	.0002067	1.38e-12
Lipid	Fatty Acid Metabolism (Acyl Carnitine, Medium Chain)	cis-3,4-methyleneheptanoylcarnitine	.0026675	3.09e-15

Lipid	Fatty Acid Metabolism (Acyl Carnitine, Medium Chain)	laurylcarnitine (C12)	.0202209	.0000126
Lipid	Fatty Acid Metabolism (Acyl Carnitine, Monounsaturated)	5-dodecenoylcarnitine (C12:1)	7.50e-06	.0000153
Lipid	Fatty Acid Metabolism (Acyl Carnitine, Monounsaturated)	eicosenoylcarnitine (C20:1)	1.50e-11	2.29e-06
Lipid	Fatty Acid Metabolism (Acyl Carnitine, Monounsaturated)	palmitoleoylcarnitine (C16:1)	.0125414	.0179456
Lipid	Fatty Acid Metabolism (Acyl Carnitine, Monounsaturated)	myristoleoylcarnitine (C14:1)	.0128396	.0055832
Lipid	Fatty Acid Metabolism (Acyl Carnitine, Polyunsaturated)	dihomo-linoleoylcarnitine (C20:2)	8.81e-06	.0118856
Lipid	Fatty Acid Metabolism (Acyl Choline)	stearoylcholine	.0021804	.0310259
Lipid	Fatty Acid Metabolism (Acyl Choline)	linoleoylcholine	6.88e-12	5.97e-08
Lipid	Fatty Acid Metabolism (Acyl Choline)	oleoylcholine	1.67e-07	1.83e-06
Lipid	Fatty Acid Metabolism (Acyl Choline)	palmitoylcholine	2.78e-08	1.06e-06
Lipid	Fatty Acid Metabolism (Acyl Glycine)	2-butenoylglycine	.0064531	5.64e-07
Lipid	Fatty Acid Metabolism (Acyl Glycine)	trans-2-hexenoylglycine	.0008208	.000071

Lipid	Fatty Acid Metabolism (Acyl Glycine)	picolinoylglycine	4.24e-09	1.35e-22
Lipid	Fatty Acid Metabolism (also BCAA Metabolism)	propionylcarnitine (C3)	3.87e-06	1.06e-16
Lipid	Fatty Acid Metabolism (also BCAA Metabolism)	butyrylcarnitine (C4)	8.11e-06	9.61e-10
Lipid	Fatty Acid Metabolism (also BCAA Metabolism)	propionylglycine	.0000189	.0003918
Lipid	Fatty Acid, Amino	2-aminooctanoate	5.45e-06	.0041683
Lipid	Fatty Acid, Amino	2-aminoheptanoate	.0030455	.0074178
Lipid	Fatty Acid, Dicarboxylate	branched chain 14:0 dicarboxylic acid	.0265081	1.96e-17
Lipid	Fatty Acid, Dicarboxylate	3-carboxy-4-methyl-5-pentyl-2-furanpropionate (3-CMPFP)	.0000372	.0010147
Lipid	Fatty Acid, Dicarboxylate	maleate	2.45e-11	.022581
Lipid	Fatty Acid, Dicarboxylate	octadecadienedioate (C18:2-DC)	.0100029	5.32e-07
Lipid	Fatty Acid, Dicarboxylate	3-hydroxyadipate	.0021028	.0026051
Lipid	Fatty Acid, Dicarboxylate	hydroxy-CMPF	5.61e-15	.0003137
Lipid	Fatty Acid, Dihydroxy	2R,3R-dihydroxybutyrate	4.72e-11	.0055407
Lipid	Fatty Acid, Dihydroxy	3,4-dihydroxybutyrate	1.10e-14	3.24e-07
Lipid	Fatty Acid, Dihydroxy	9,10-DiHOME	3.00e-06	9.27e-09
Lipid	Fatty Acid, Monohydroxy	16-hydroxypalmitate	.0024173	.0000677
Lipid	Fatty Acid, Monohydroxy	3-hydroxysebacate	.0020798	2.95e-10
Lipid	Fatty Acid, Monohydroxy	9-hydroxystearate	4.65e-07	5.13e-10
Lipid	Fatty Acid, Monohydroxy	2-hydroxydecanoate	.0002054	1.68e-06
Lipid	Hexosylceramides (HCER)	glycosyl ceramide (d18:1/20:0, d16:1/22:0)	1.15e-16	.0288581
Lipid	Hexosylceramides (HCER)	glycosyl ceramide (d18:2/24:1, d18:1/24:2)	<1.00e-25	.0081201
Lipid	Ketone Bodies	3-hydroxybutyrate (BHBA)	.0167485	.0000251
Lipid	Lactosylceramides (LCER)	lactosyl-N-behenoyl-sphingosine (d18:1/22:0)	2.04e-17	.0056111
Lipid	Lactosylceramides (LCER)	lactosyl-N-nervonoyl-sphingosine (d18:1/24:1)	<1.00e-25	.0000521

Lipid	Long Chain Monounsaturated Fatty Acid	myristoleate (14:1n5)	.0009957	9.73e-14
Lipid	Long Chain Polyunsaturated Fatty Acid (n3 and n6)	dihomo-linolenate (20:3n3 or n6)	8.13e-07	.0003194
Lipid	Long Chain Polyunsaturated Fatty Acid (n3 and n6)	stearidonate (18:4n3)	.0003444	.0016324
Lipid	Long Chain Polyunsaturated Fatty Acid (n3 and n6)	docosapentaenoate (n3 DPA; 22:5n3)	.0070452	.0071901
Lipid	Long Chain Polyunsaturated Fatty Acid (n3 and n6)	docosatrienoate (22:3n3)	.0004599	.0011791
Lipid	Long Chain Polyunsaturated Fatty Acid (n3 and n6)	docosadienoate (22:2n6)	.0012097	.0001164
Lipid	Long Chain Polyunsaturated Fatty Acid (n3 and n6)	dihomo-linoleate (20:2n6)	.0214391	.0048885
Lipid	Long Chain Polyunsaturated Fatty Acid (n3 and n6)	adrenate (22:4n6)	2.09e-07	5.52e-06
Lipid	Long Chain Saturated Fatty Acid	palmitate (16:0)	.0000672	.0002322
Lipid	Long Chain Saturated Fatty Acid	stearate (18:0)	.0000223	.0004472
Lipid	Lysophospholipid	1-oleoyl-GPC (18:1)	3.23e-12	<1.00e-25
Lipid	Lysophospholipid	2-stearoyl-GPE (18:0)	.0001421	2.74e-18

Lipid	Lysophospholipid	1-oleoyl-GPE (18:1)	.0002234	7.09e-26
Lipid	Lysophospholipid	1-palmitoleoyl-GPC (16:1)	.0009945	.0019495
Lipid	Lysophospholipid	1-lignoceroyl-GPC (24:0)	1.11e-20	2.74e-16
Lipid	Lysophospholipid	1-cerotoyl-GPC (26:0)	2.84e-10	5.79e-08
Lipid	Lysophospholipid	1-stearoyl-GPE (18:0)	.0131522	<1.00e-25
Lipid	Lysophospholipid	1-stearoyl-GPC (18:0)	.0094899	4.66e-23
Lipid	Lysophospholipid	1-linoleoyl-GPC (18:2)	5.25e-25	<1.00e-25
Lipid	Lysophospholipid	1-arachidonoyl-GPE (20:4n6)	.0000961	1.74e-10
Lipid	Lysophospholipid	1-linoleoyl-GPG (18:2)*	8.46e-07	.0000112
Lipid	Lysoplasmalogen	1-(1-enyl-stearoyl)-GPE (P-18:0)	5.52e-06	5.49e-12
Lipid	Lysoplasmalogen	1-(1-enyl-palmitoyl)-GPC (P-16:0)	<1.00e-25	1.26e-16
Lipid	Medium Chain Fatty Acid	5-dodecenoate (12:1n7)	.0007586	4.56e-11
Lipid	Medium Chain Fatty Acid	heptanoate (7:0)	.0271446	1.10e-08
Lipid	Medium Chain Fatty Acid	caprate (10:0)	.0005224	3.97e-16
Lipid	Mevalonate Metabolism	3-hydroxy-3-methylglutarate	1.15e-14	1.93e-08
Lipid	Monoacylglycerol	2-linoleoylglycerol (18:2)	3.44e-14	.0046965
Lipid	Monoacylglycerol	1-oleoylglycerol (18:1)	<1.00e-25	.0173411
Lipid	Monoacylglycerol	2-oleoylglycerol (18:1)	1.66e-37	.0203284
Lipid	Monoacylglycerol	1-linolenoylglycerol (18:3)	1.68e-35	.0277316
Lipid	Phosphatidylcholine (PC)	1-palmitoyl-2-arachidonoyl-GPC (16:0/20:4n6)	1.51e-06	.0000746
Lipid	Phosphatidylcholine (PC)	1-stearoyl-2-linoleoyl-GPC (18:0/18:2)	5.14e-06	1.24e-06
Lipid	Phosphatidylcholine (PC)	1-palmitoyl-2-palmitoleoyl-GPC (16:0/16:1)	4.74e-23	.0248628
Lipid	Phosphatidylcholine (PC)	1-stearoyl-2-arachidonoyl-GPC (18:0/20:4)	.000938	1.06e-07
Lipid	Phosphatidylcholine (PC)	1-palmitoyl-2-dihomo-linolenoyl-GPC (16:0/20:3n3 or 6)	2.03e-15	.0001622
Lipid	Phosphatidylcholine (PC)	1,2-dilinoleoyl-GPC (18:2/18:2)	2.06e-21	3.92e-20
Lipid	Phosphatidylcholine (PC)	1-palmitoleoyl-2-linolenoyl-GPC (16:1/18:3)	.0089226	.0228165
Lipid	Phosphatidylcholine (PC)	1-palmitoyl-2-stearoyl-GPC (16:0/18:0)	.0000512	9.46e-16
Lipid	Phosphatidylcholine (PC)	1-linoleoyl-2-arachidonoyl-GPC (18:2/20:4n6)	.0000887	.0002434

Lipid	Phosphatidylcholine (PC)	1-linoleoyl-2-linolenoyl-GPC (18:2/18:3)	4.50e-06	6.70e-13
Lipid	Phosphatidylcholine (PC)	1-palmitoyl-2-oleoyl-GPC (16:0/18:1)	1.87e-09	3.57e-06
Lipid	Phosphatidylcholine (PC)	1-stearoyl-2-docosahexaenoyl-GPC (18:0/22:6)	5.87e-06	.0099218
Lipid	Phosphatidylcholine (PC)	1-stearoyl-2-oleoyl-GPC (18:0/18:1)	1.13e-06	1.47e-07
Lipid	Phosphatidylcholine (PC)	1-oleoyl-2-docosahexaenoyl-GPC (18:1/22:6)	6.20e-06	1.99e-23
Lipid	Phosphatidylcholine (PC)	1-myristoyl-2-arachidonoyl-GPC (14:0/20:4)	1.20e-09	3.15e-06
Lipid	Phosphatidylethanolamine (PE)	1-palmitoyl-2-linoleoyl-GPE (16:0/18:2)	2.73e-38	3.47e-15
Lipid	Phosphatidylethanolamine (PE)	1-palmitoyl-2-oleoyl-GPE (16:0/18:1)	<1.00e-25	.0016973
Lipid	Phosphatidylethanolamine (PE)	1-oleoyl-2-linoleoyl-GPE (18:1/18:2)	4.98e-27	4.32e-21
Lipid	Phosphatidylethanolamine (PE)	1-palmitoyl-2-arachidonoyl-GPE (16:0/20:4)	<1.00e-25	2.88e-11
Lipid	Phosphatidylethanolamine (PE)	1-stearoyl-2-docosahexaenoyl-GPE (18:0/22:6)	<1.00e-25	.0000124
Lipid	Phosphatidylethanolamine (PE)	1-stearoyl-2-linoleoyl-GPE (18:0/18:2)	<1.00e-25	1.02e-08
Lipid	Phosphatidylethanolamine (PE)	1-stearoyl-2-arachidonoyl-GPE (18:0/20:4)	<1.00e-25	.0003034
Lipid	Phosphatidylethanolamine (PE)	1-oleoyl-2-arachidonoyl-GPE (18:1/20:4)	5.92e-37	1.63e-19
Lipid	Phosphatidylethanolamine (PE)	1-oleoyl-2-docosahexaenoyl-GPE (18:1/22:6)	6.49e-07	.0000142
Lipid	Phosphatidylethanolamine (PE)	1-palmitoyl-2-docosahexaenoyl-GPE (16:0/22:6)	<1.00e-25	1.62e-15
Lipid	Phosphatidylethanolamine (PE)	1-stearoyl-2-oleoyl-GPE (18:0/18:1)	<1.00e-25	.0002048
Lipid	Phosphatidylinositol (PI)	1-palmitoyl-2-linoleoyl-GPI (16:0/18:2)	4.71e-12	.0000249
Lipid	Phosphatidylinositol (PI)	1-palmitoyl-2-oleoyl-GPI (16:0/18:1)	.000084	.0004897

Lipid	Phospholipid Metabolism	glycerophosphorylcholine (GPC)	.0000615	3.40e-22
Lipid	Phospholipid Metabolism	phosphoethanolamine	.0020306	.0133496
Lipid	Plasmalogen	1-(1-enyl-palmitoyl)-2-oleoyl-GPC (P-16:0/18:1)	<1.00e-25	3.35e-18
Lipid	Plasmalogen	1-(1-enyl-palmitoyl)-2-arachidonoyl-GPC (P-16:0/20:4)	7.84e-26	.0001181
Lipid	Plasmalogen	1-(1-enyl-stearoyl)-2-linoleoyl-GPE (P-18:0/18:2)	1.03e-18	5.06e-06
Lipid	Plasmalogen	1-(1-enyl-palmitoyl)-2-palmitoleoyl-GPC (P-16:0/16:1)	<1.00e-25	4.29e-07
Lipid	Plasmalogen	1-(1-enyl-stearoyl)-2-oleoyl-GPE (P-18:0/18:1)	.0032043	.0029556
Lipid	Plasmalogen	1-(1-enyl-palmitoyl)-2-arachidonoyl-GPE (P-16:0/20:4)	.0161718	4.18e-06
Lipid	Plasmalogen	1-(1-enyl-palmitoyl)-2-palmitoyl-GPC (P-16:0/16:0)	<1.00e-25	.0000411
Lipid	Plasmalogen	1-(1-enyl-palmitoyl)-2-linoleoyl-GPC (P-16:0/18:2)	<1.00e-25	4.85e-10
Lipid	Pregnenolone Steroids	pregnenetriol disulfate	8.05e-07	.0069844
Lipid	Pregnenolone Steroids	pregnenetriol sulfate	.0024778	.0056578
Lipid	Pregnenolone Steroids	pregnenolone sulfate	.0226391	.0002025
Lipid	Primary Bile Acid Metabolism	glycochenodeoxycholate glucuronide (1)	.0008755	.0333554
Lipid	Primary Bile Acid Metabolism	glyco-beta-muricholate	.0001087	.0080154
Lipid	Primary Bile Acid Metabolism	cholic acid glucuronide	.0270194	.0011957
Lipid	Progestin Steroids	pregnanediol-3-glucuronide	.0015079	9.86e-07
Lipid	Secondary Bile Acid Metabolism	taurodeoxycholate	.0000106	.0030538
Lipid	Secondary Bile Acid Metabolism	glycoursodeoxycholic acid sulfate (1)	1.67e-06	3.31e-06

Lipid	Secondary Bile Acid Metabolism	tauroolithocholate 3-sulfate	.0040355	.0100654
Lipid	Secondary Bile Acid Metabolism	isoursodeoxycholate	2.85e-09	.0190076
Lipid	Secondary Bile Acid Metabolism	ursodeoxycholate	.0000903	.005667
Lipid	Secondary Bile Acid Metabolism	deoxycholic acid glucuronide	.0007661	5.04e-06
Lipid	Secondary Bile Acid Metabolism	deoxycholate	9.63e-12	.0238089
Lipid	Secondary Bile Acid Metabolism	glycohyocholate	7.86e-10	7.39e-08
Lipid	Secondary Bile Acid Metabolism	deoxycholic acid 12-sulfate	1.47e-20	.000807
Lipid	Sphingolipid Synthesis	sphinganine-1-phosphate	.001247	.0230432
Lipid	Sphingomyelins	sphingomyelin (d18:1/18:1, d18:2/18:0)	4.62e-13	<1.00e-25
Lipid	Sphingomyelins	tricosanoyl sphingomyelin (d18:1/23:0)	2.20e-22	.0172073
Lipid	Sphingomyelins	stearoyl sphingomyelin (d18:1/18:0)	5.43e-09	4.61e-20
Lipid	Sphingomyelins	sphingomyelin (d18:1/14:0, d16:1/16:0)	1.75e-20	.0232516
Lipid	Sphingomyelins	sphingomyelin (d18:2/24:2)	<1.00e-25	2.51e-23
Lipid	Sphingomyelins	sphingomyelin (d18:1/22:1, d18:2/22:0, d16:1/24:1)	<1.00e-25	1.09e-18
Lipid	Sphingomyelins	sphingomyelin (d18:2/23:0, d18:1/23:1, d17:1/24:1)	<1.00e-25	.0000227
Lipid	Sphingomyelins	sphingomyelin (d18:1/19:0, d19:1/18:0)	6.36e-13	1.93e-10
Lipid	Sphingomyelins	sphingomyelin (d18:1/25:0, d19:0/24:1, d20:1/23:0, d19:1/24:0)	1.34e-16	2.94e-07
Lipid	Sphingomyelins	sphingomyelin (d18:1/24:1, d18:2/24:0)	1.14e-37	4.68e-07
Lipid	Sphingomyelins	lignoceroyl sphingomyelin (d18:1/24:0)	2.80e-16	.0000256

Lipid	Sphingomyelins	sphingomyelin (d18:1/17:0, d17:1/18:0, d19:1/16:0)	1.42e-37	.0100607
Lipid	Sphingomyelins	sphingomyelin (d18:2/14:0, d18:1/14:1)	4.68e-29	<1.00e-25
Lipid	Sphingomyelins	sphingomyelin (d18:1/21:0, d17:1/22:0, d16:1/23:0)	8.77e-16	.0002057
Lipid	Sphingomyelins	hydroxypalmitoyl sphingomyelin (d18:1/16:0(OH))	<1.00e-25	.0054111
Lipid	Sphingomyelins	sphingomyelin (d17:2/16:0, d18:2/15:0)	<1.00e-25	1.01e-35
Lipid	Sphingomyelins	sphingomyelin (d18:2/23:1)	<1.00e-25	1.53e-22
Lipid	Sphingomyelins	sphingomyelin (d18:2/18:1)	<1.00e-25	1.18e-25
Lipid	Sphingomyelins	sphingomyelin (d18:1/20:0, d16:1/22:0)	4.13e-10	6.29e-10
Lipid	Sphingomyelins	sphingomyelin (d18:1/20:1, d18:2/20:0)	<1.00e-25	1.82e-34
Lipid	Sphingomyelins	sphingomyelin (d18:1/22:2, d18:2/22:1, d16:1/24:2)	<1.00e-25	9.51e-33
Lipid	Sphingomyelins	sphingomyelin (d18:2/24:1, d18:1/24:2)	<1.00e-25	5.63e-19
Lipid	Sphingomyelins	sphingomyelin (d18:1/20:2, d18:2/20:1, d16:1/22:2)	2.23e-31	1.12e-33
Lipid	Sphingomyelins	sphingomyelin (d18:2/16:0, d18:1/16:1)	<1.00e-25	3.29e-25
Lipid	Sphingomyelins	sphingomyelin (d17:1/14:0, d16:1/15:0)	2.99e-34	.0073499
Lipid	Sphingomyelins	sphingomyelin (d18:2/21:0, d16:2/23:0)	1.50e-33	1.77e-25
Lipid	Sphingomyelins	behenoyl sphingomyelin (d18:1/22:0)	.0000354	.0001578
Lipid	Sphingosines	sphingosine	.0006915	1.17e-06
Lipid	Sterol	7-alpha-hydroxy-3-oxo-4-cholestenoate (7-Hoca)	.0040725	8.95e-07
Lipid	Sterol	3beta-hydroxy-5-cholestenoate	.0006967	1.28e-23
Lipid	Sterol	cholesterol	4.77e-08	.0144541
Nucleotide	Purine Metabolism, (Hypo)Xanthine/Inosine containing	urate	1.66e-10	<1.00e-25

Nucleotide	Purine Metabolism, (Hypo)Xanthine/Inosine containing	xanthine	.0085662	1.46e-16
Nucleotide	Purine Metabolism, Adenine containing	N6-carbamoylthreonyladenosine	.0058618	1.79e-21
Nucleotide	Purine Metabolism, Adenine containing	N1-methyladenosine	.0219652	4.42e-08
Nucleotide	Purine Metabolism, Guanine containing	N2,N2-dimethylguanosine	.000073	1.05e-38
Nucleotide	Pyrimidine Metabolism, Cytidine containing	2'-O-methylcytidine	4.28e-11	.0004809
Nucleotide	Pyrimidine Metabolism, Cytidine containing	N4-acetylcytidine	2.94e-07	2.59e-08
Nucleotide	Pyrimidine Metabolism, Orotate containing	orotidine	8.90e-10	2.47e-11
Nucleotide	Pyrimidine Metabolism, Thymine containing	5,6-dihydrothymine	9.79e-09	1.37e-13
Nucleotide	Pyrimidine Metabolism, Thymine containing	3-aminoisobutyrate	5.53e-11	.0044364
Nucleotide	Pyrimidine Metabolism, Uracil containing	uridine	.002534	.0000157
Nucleotide	Pyrimidine Metabolism, Uracil containing	beta-alanine	.0098149	4.29e-07
Nucleotide	Pyrimidine Metabolism, Uracil containing	3-(3-amino-3-carboxypropyl)uridine	.0177754	7.00e-15
Nucleotide	Pyrimidine Metabolism, Uracil containing	5-methyluridine (ribothymidine)	1.71e-07	.0044427
Partially Characterized Molecules	Partially Characterized Molecules	glutamine_degradant	7.72e-06	.0006912

Partially Characterized Molecules	Partially Characterized Molecules	glycine conjugate of C10H12O2	.0094102	.0000541
Partially Characterized Molecules	Partially Characterized Molecules	branched-chain, straight-chain, or cyclopropyl 10:1 fatty acid (1)	7.29e-17	1.81e-13
Partially Characterized Molecules	Partially Characterized Molecules	metabolonic lactone sulfate	3.23e-28	<1.00e-25
Partially Characterized Molecules	Partially Characterized Molecules	glycine conjugate of C10H14O2 (1)	.0000173	1.52e-07
Peptide	Acetylated Peptides	4-hydroxyphenylacetylglutamine	.0000206	.0002263
Peptide	Dipeptide	isoleucylglycine	3.07e-06	.0097674
Peptide	Gamma-glutamyl Amino Acid	gamma-glutamylglutamate	1.01e-08	1.32e-17
Peptide	Gamma-glutamyl Amino Acid	gamma-glutamylphenylalanine	.0000458	7.92e-22
Peptide	Gamma-glutamyl Amino Acid	gamma-glutamylcitrulline	1.61e-16	.0161739
Peptide	Gamma-glutamyl Amino Acid	gamma-glutamylvaline	1.18e-18	1.25e-23
Peptide	Gamma-glutamyl Amino Acid	gamma-glutamylleucine	3.50e-24	7.17e-16
Peptide	Gamma-glutamyl Amino Acid	gamma-glutamylisoleucine	<1.00e-25	8.51e-22
Peptide	Gamma-glutamyl Amino Acid	gamma-glutamyltyrosine	.0013151	3.97e-25
Peptide	Gamma-glutamyl Amino Acid	gamma-glutamylglycine	3.05e-16	.0001682

Supplementary Table 5. Pathway enrichment and topographical analysis for the 371 validated metabolites that differed between overweight subjects without MetS and normal-weight without MetS. Only pathways with $p < 0.05$ are given. Data on all 371 metabolites are given in Suppl Table 1. * = FDR < 0.05.

Pathway	Total	Expected	Hits	<i>p</i> -value
Valine, leucine and isoleucine biosynthesis	8	.676	7	1.97e-07*
Alanine, aspartate and glutamate metabolism	28	2.366	10	.000046*
Arginine biosynthesis	14	1.18	7	.000054*
Aminoacyl-tRNA biosynthesis	48	4.05	12	.00039*
Phenylalanine, tyrosine and tryptophan biosynthesis	4	.33	3	.0022*
Glycine, serine and threonine metabolism	33	2.78	8	.0047
Cysteine and methionine metabolism	33	2.78	7	.017
Pantothenate and CoA biosynthesis	19	1.60	5	.017
Citrate cycle (TCA cycle)	20	1.69	5	.021
Nicotinate and nicotinamide metabolism	15	1.26	4	.031
Histidine metabolism	16	1.35	4	.039
Phenylalanine metabolism	10	.84	3	.045

Supplementary Table 6. Pathway enrichment and topographical analysis for the 417 metabolites being related to BMI in subjects with no MetS components. Only pathways with $p < 0.05$ are given. * = FDR < 0.05.

Pathway	Total	Expected	Hits	<i>p</i> -value
Arginine biosynthesis	14	1.3458	9	7.33e-07*
Alanine, aspartate and glutamate metabolism	28	2.6916	10	.0001436*
Histidine metabolism	16	1.5381	6	.0025328
Valine, leucine and isoleucine biosynthesis	8	.76903	4	.0042237
Aminoacyl-tRNA biosynthesis	48	4.6142	11	.0043881
Sphingolipid metabolism	21	2.0187	6	.011434
D-Glutamine and D-glutamate metabolism	6	.57677	3	.01401
Cysteine and methionine metabolism	33	3.1723	7	.033056
Taurine and hypotaurine metabolism	8	.76903	3	.033957
Nicotinate and nicotinamide metabolism	15	1.4419	4	.048296
Phenylalanine, tyrosine and tryptophan biosynthesis	4	.38452	2	.048378