Supplementary material

Supplementary Information on Sample Preparation: The blood samples were stored in a cooler during transport to the laboratory. The samples were centrifuged within 30 minutes (mins) after collection and plasma was stored at -80 °C. One hundred microliters (µl) of plasma were extracted with 400 µl of methanol. The extraction was performed by shaking at 1000 revolutions per minute (rpm) for 2 mins using a Geno/Grinder 2010 (SPEX SamplePrep., Metuchen, NJ, US). Then, the extract was centrifuged at 15,000 relative centrifugal force (rcf) for 5 mins at 4℃ using an Eppendorf Centrifuge 5810R (Eppendorf AG, Hamburg, Germany). The supernatant was collected into an Eppendorf tube and evaporated using an EYELA CVE-200D Centrifugal Evaporator (TOKYO RIKAKIKAI CO., Tokyo, JP). The residue was re-reconstituted in 50% methanol. The reconstituted sample was sonicated for 10 mins and centrifuged at 15,000 rcf for 5 mins at 4℃. The supernatant was filtered through a 0.2 µm Minisart RC 4 filter (Sartorius Stedim Biotech GmbH, Goettingen, Germany) and underwent liquid chromatography-mass spectrometry (LC-MS) analysis.

Metabolomics profiling was performed using an Agilent 1290 UHPLC system coupled with an Agilent 6540 Q-TOF mass spectrometry (Agilent Technologies, Santa Clara, CA). Two microliters of the plasma extract were injected into an Acquity HSS T3 analytic column (2.1x100mm, 1.8µm) (Waters, Milford, MA) that was maintained at 40°C. The mobile phase was composed of solvent A (water/0.1% formic acid) and solvent B (acetonitrile/0.1% formic acid). The gradient elution program was as follows: 0-1.5 min: 2% B; 1.5-9 min: linear gradient from 2% to 50% B; 9-14 min: linear gradient from 50% to 95% B; and 3 min maintenance of 95% B. The flow rate was 300 µL min-1.

Supplementary Table 1 – 54 metabolites tested using MetaboAnalyst

Compound name	HMDB	KEGG
(R)-3-Hydroxybutyric acid	HMDB0000011	C01089
(S)-3-Hydroxybutyric acid	HMDB0000442	C03197
1-Methyladenosine	HMDB0003331	C02494
2-Hydroxybutyric acid	HMDB0000008	C05984
2-Ketohexanoic acid	HMDB0001864	C00902
2-Oxoglutarate	HMDB0000208	C00026
3-Hydroxyisovaleric acid	HMDB0000754	
4-Methoxyphenylacetic acid	HMDB0002072	
5-Aminolevulinic acid	HMDB0001149	C00430
5-Methylcytidine	HMDB0000982	
Allose	HMDB0001151	C01487
Ascorbic Acid	HMDB0000044	C00072
Carnitine	HMDB0000062	C00318
Catechol	HMDB0000957	C00090
cis-Aconitate	HMDB0000072	C00417
citric acid	HMDB0000094	C00158
Decanoylcarnitine	HMDB0000651	
Deoxycholic acid	HMDB0000626	C04483
D-Fructose	HMDB0000660	C02336
D-Glucurono-6,3-lactone	HMDB0006355	C02670
D-Galactose	HMDB0000143	C00984
D-Mannose	HMDB0000169	C00159
D-Tagatose	HMDB0003418	C00795
D-threo-Isocitric acid	HMDB0001874	C00451
Glycerophosphocholine	HMDB0000086	C00670
Hexanoylcarnitine	HMDB0000705	
Hydroxyoctanoic acid	HMDB0000711	
Hydroxyphenyllactic acid	HMDB0000755	C03672
Hyodeoxycholic acid	HMDB0000733	
Hypoxanthine	HMDB0000157	C00262
Indolelactic acid	HMDB0000671	C02043
Ketoleucine	HMDB0000695	C00233
L-3-Phenyllactic acid	HMDB0000748	C05607
L-Acetylcarnitine	HMDB0000201	C02571

Lactate	HMDB0000190	C00186
L-Alloisoleucine	HMDB0000557	
L-Isoleucine	HMDB0000172	C00407
Levulinic acid	HMDB0000720	
L-Kynurenine	HMDB0000684	C00328
L-Norleucine	HMDB0001645	C01933
Malic Acid	HMDB0000744	C00711
Methionine	HMDB0000696	C00073
N6-Acetyl-L-lysine	HMDB0000206	C02727
Paraxanthine	HMDB0001860	C13747
Phenylalanine	HMDB0000159	C00079
Pipecolic acid	HMDB0000070	C00408
Pyroglutamic acid	HMDB0000267	C01879
Pyrrolidonecarboxylic acid	HMDB0000805	C02237
Pyruvic acid	HMDB0000243	C00022
Spermine	HMDB0001256	C00750
Succinate	HMDB0000254	C00042
Tetradecanedioic acid	HMDB0000872	C11002
Tyrosine	HMDB0000158	C00082
Uridine	HMDB0000296	C00299

Note. HMDB = Human Metabolome Database; KEGG = Kyoto Encyclopedia of Genes and Genomes

Supplementary Table 2 – Fold Change

Compound name	Marker	Fold Change	log2(FC)	KEGG	HMDB
Spermine	A	7.2889	2.8657	C00750	HMDB0001256
Pyrrolidonecarboxylic acid	B	0.32446	-1.6239	C02237	HMDB0000805
Hydroxyoctanoic acid	C	2.5006	1.3223		HMDB0000711
Paraxanthine	D	0.48379	-1.0475	C13747	HMDB0001860

Note. FC = fold change; HMDB = Human Metabolome Database; KEGG = Kyoto Encyclopedia of Genes and Genomes

Supplementary Figure 1. Illustration of the fold change analysis. The marker A is spermine, marker B is pyrrolidonecarboxylic acid, marker C is hydroxyoctanoic acid, and marker D is paraxanthine.