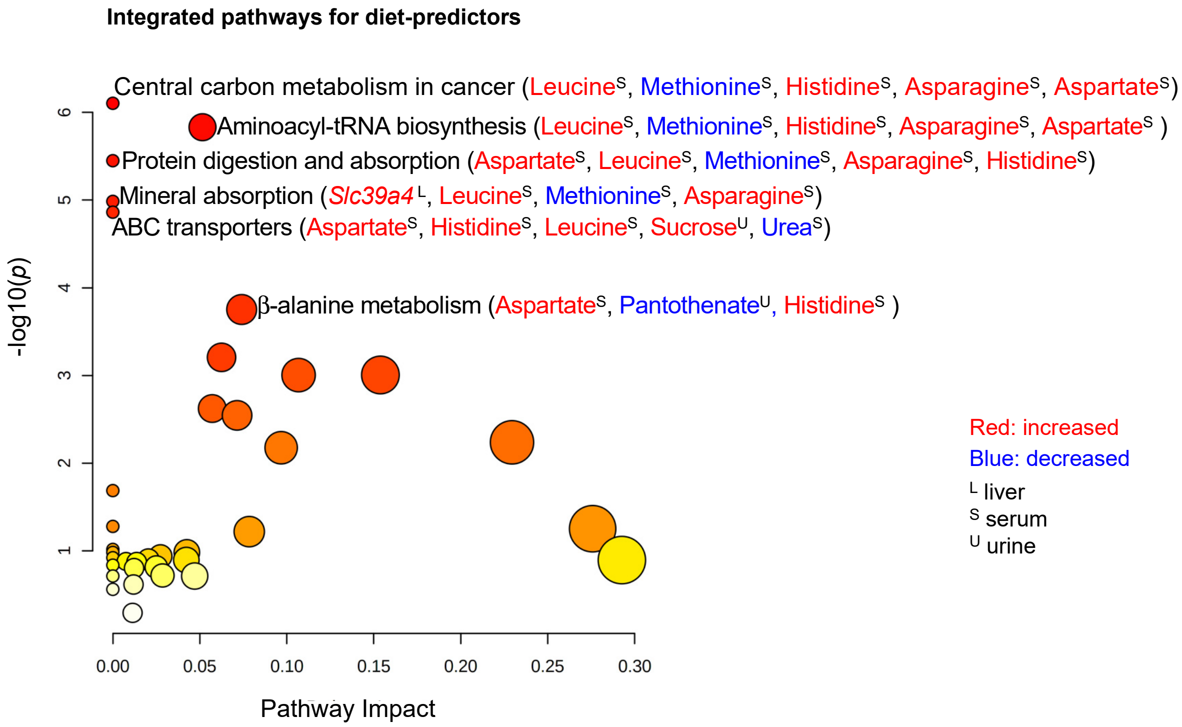
Figure S1

(A)


Integrated pathways for diet-predictors
Central carbon metabolism in cancer (Leucine^S, Methionine^S, Histidine^S, Asparagine^S, Aspartate^S)
Aminoacyl-tRNA biosynthesis (Leucine^S, Methionine^S, Histidine^S, Asparagine^S, Aspartate^S)
Protein digestion and absorption (Aspartate^S, Leucine^S, Methionine^S, Asparagine^S, Histidine^S)
Mineral absorption (Slc39a4^L, Leucine^S, Methionine^S, Asparagine^S)
ABC transporters (Aspartate^S, Histidine^S, Leucine^S, Sucrose^U, Urea^S)
β-alanine metabolism (Aspartate^S, Pantothenate^U, Histidine^S)
-log10(p)
1
2
3
4
5
6
0.00
0.05
0.10
0.15
0.20
0.25
0.30
Pathway Impact
Red: increased
Blue: decreased
L liver
S serum
U urine

(B)

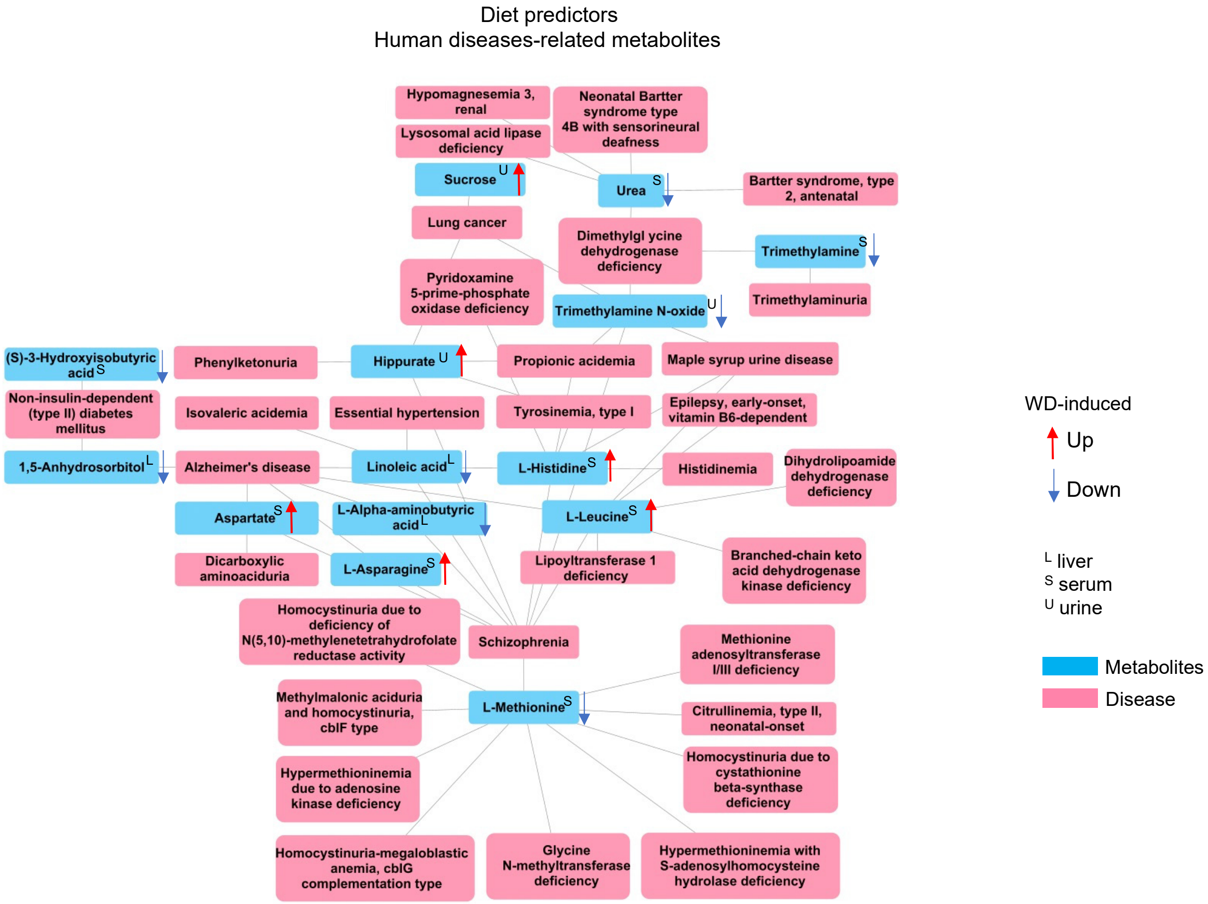
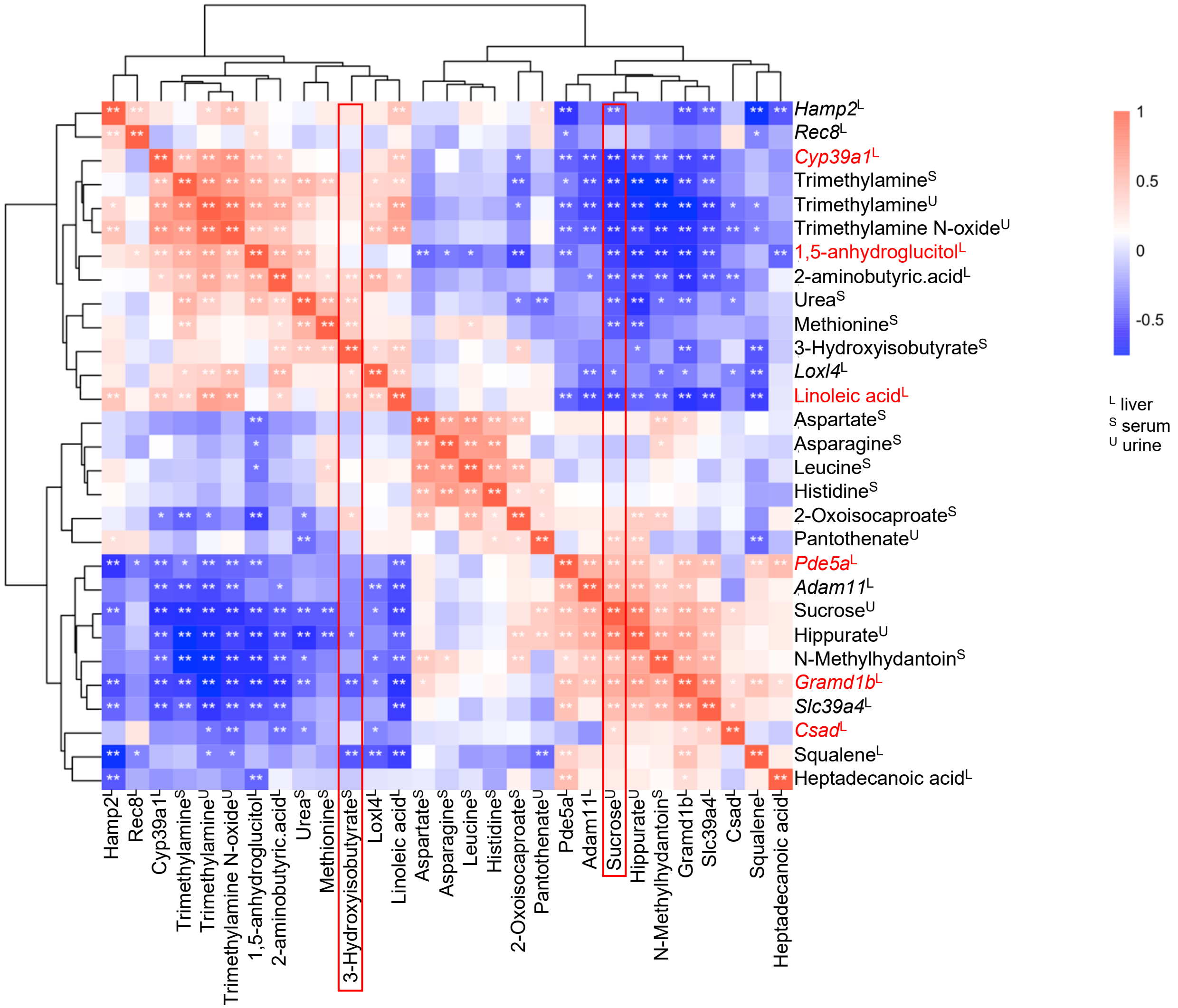

Diet predictors
Human diseases-related metabolites
Hypomagnesemia 3, renal
Neonatal Bartter syndrome type 4B with sensorineural deafness
Lysosomal acid lipase deficiency
Sucrose U
Urea S
Bartter syndrome, type 2, antenatal
Lung cancer
Dimethylgl ycine dehydrogenase deficiency
Trimethylamine S
Pyridoxamine 5-prime-phosphate oxidase deficiency
Trimethylamine N-oxide U
Trimethylaminuria
(S)-3-Hydroxyisobutyric acid S
Phenylketonuria
Hippurate U
Propionic acidemia
Maple syrup urine disease
Non-insulin-dependent (type II) diabetes mellitus
Isovaleric acidemia
Essential hypertension
Tyrosinemia, type I
Epilepsy, early-onset, vitamin B6-dependent
1,5-Anhydrosorbitol L
Alzheimer's disease
Linoleic acid L
L-Histidine S
Histidinemia
Dihydrolipoamide dehydrogenase deficiency
Aspartate S
L-Alpha-aminobutyric acid L
L-Leucine S
Dicarboxylic aminoaciduria
L-Asparagine S
Lipoyltransferase 1 deficiency
Branched-chain keto acid dehydrogenase kinase deficiency
Homocystinuria due to deficiency of N(5,10)-methylenetetrahydrofolate reductase activity
Schizophrenia
Methionine adenosyltransferase I/III deficiency
Methylmalonic aciduria and homocystinuria, cblF type
L-Methionine S
Citrullinemia, type II, neonatal-onset
Hypermethioninemia due to adenosine kinase deficiency
Homocystinuria due to cystathionine beta-synthase deficiency
Homocystinuria-megaloblastic anemia, cblG complementation type
Glycine N-methyltransferase deficiency
Hypermethioninemia with S-adenosylhomocysteine hydrolase deficiency
WD-induced
Up
Down
L liver
S serum
U urine
Metabolites
Disease

Figure S1. Functional analysis of diet predictors. (A) Integrated pathway analysis showing pathways for WD-predictors (transcripts and metabolites). The corresponding features for the important pathways are indicated. (B) The network shows that metabolomic predictors of WD intake are associated with human diseases.

Figure S2

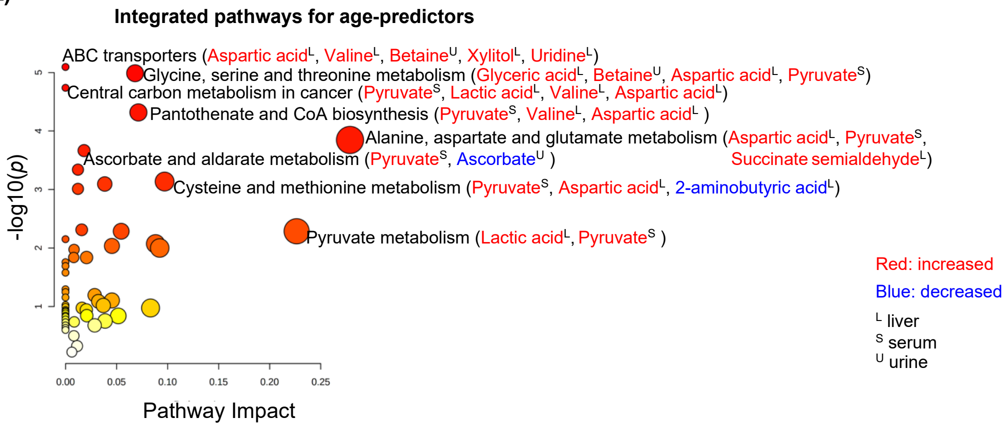


Hamp2L
Rec8L
Cyp39a1L
TrimethylamineS
TrimethylamineU
Trimethylamine N-oxideU
1,5-anhydroglucitolL
2-aminobutyric.acidL
UreaS
MethionineS
3-HydroxyisobutyrateS
Loxl4L
Linoleic acidL
AspartateS
AsparagineS
LeucineS
HistidineS
2-OxoisocaproateS
PantothenateU
Pde5aL
Adam11L
SucroseU
HippurateU
N-MethylhydantoinS
Gramd1bL
Slc39a4L
CsadL
SqualeneL
Heptadecanoic acidL
1
0.5
0
-0.5
L liver
S serum
U urine

Figure S2. Spearman's correlation for WD-predictors from the liver, serum, and urine. Spearman's correlation, *$p < 0.05$, **$p < 0.01$.

Figure S3

(A)



(B)

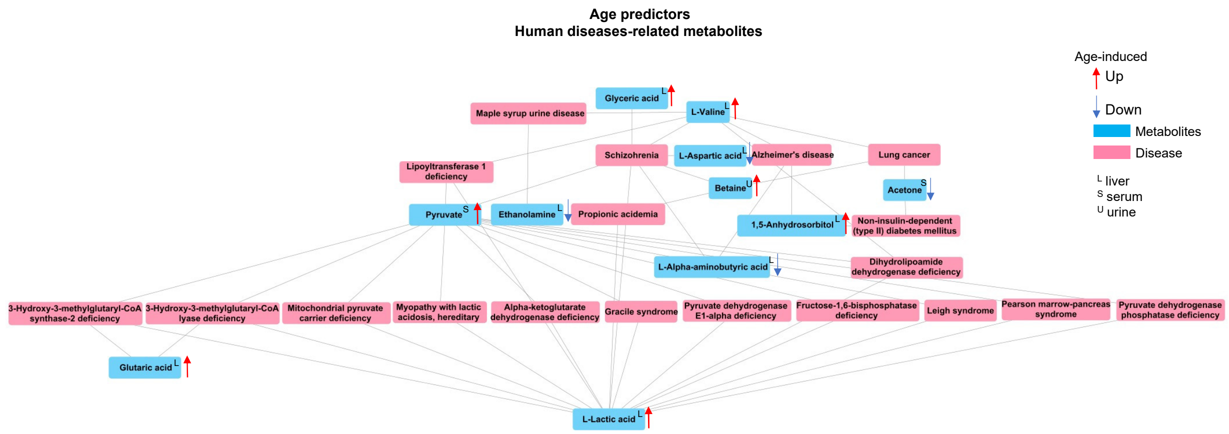
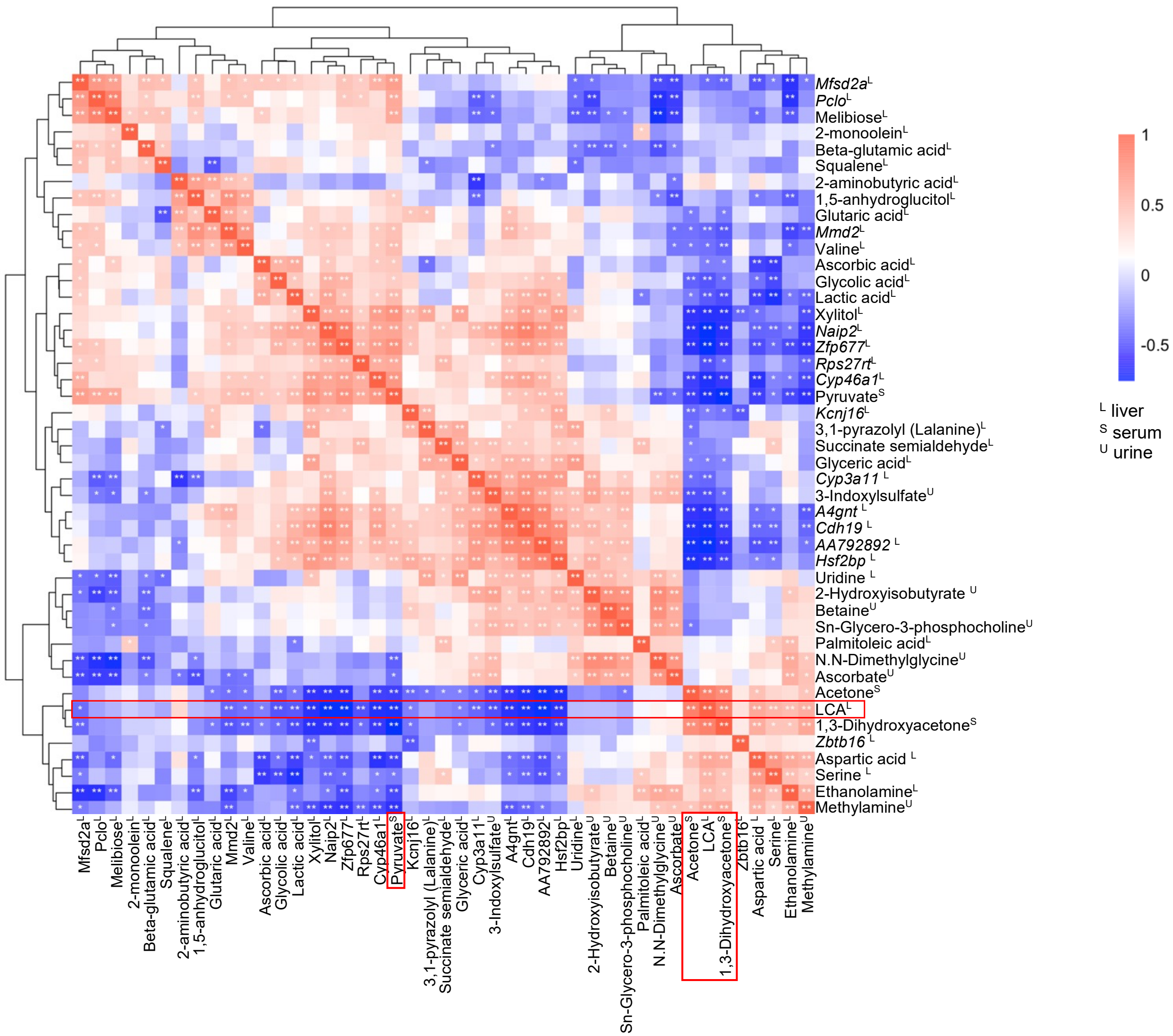


Figure S3. Functional analysis of age-predictors. (A) Integrated pathway analysis for age-predictors (metabolites). (B) Features that can classify ages in association with human diseases.

Figure S4

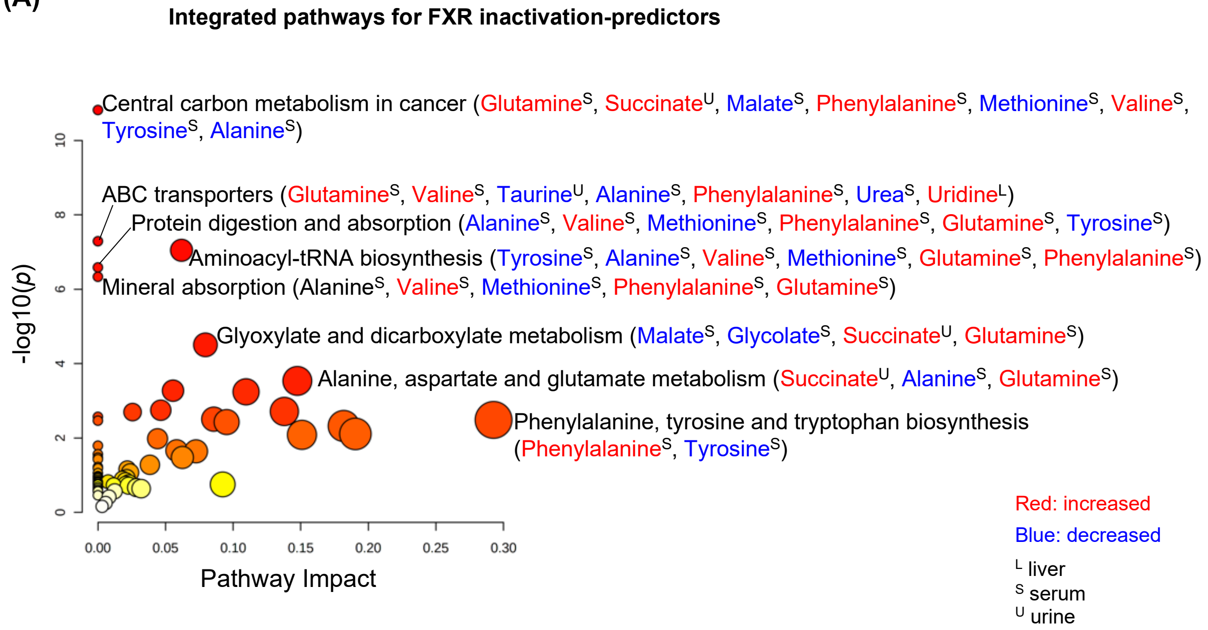


Mfsd2a L
Pclo L
Melibiose L
2-monoolein L
Beta-glutamic acid L
Squalene L
2-aminobutyric acid L
1,5-anhydroglucitol L
Glutaric acid L
Mmd2 L
Valine L
Ascorbic acid L
Glycolic acid L
Lactic acid L
Xylitol L
Naip2 L
Zfp677 L
Rps27rt L
Cyp46a1 L
Pyruvate S
Kcnj16 L
3,1-pyrazolyl (Lalanine) L
Succinate semialdehyde L
Glyceric acid L
Cyp3a11 L
3-Indoxylsulfate U
A4gnt L
Cdh19 L
AA792892 L
Hsf2bp L
Uridine L
2-Hydroxyisobutyrate U
Betaine U
Sn-Glycero-3-phosphocholine U
Palmitoleic acid L
N.N-Dimethylglycine U
Ascorbate U
Acetone S
LCA L
1,3-Dihydroxyacetone S
Zbtb16 L
Aspartic acid L
Serine L
Ethanolamine L
Methylamine U
1
0.5
0
-0.5
L liver
S serum
U urine

Figure S4. Interaction between features that can be used for chronological age prediction. Spearman's correlation, *$p < 0.05$, **$p < 0.01$.

Figure S5

(A)



(B)

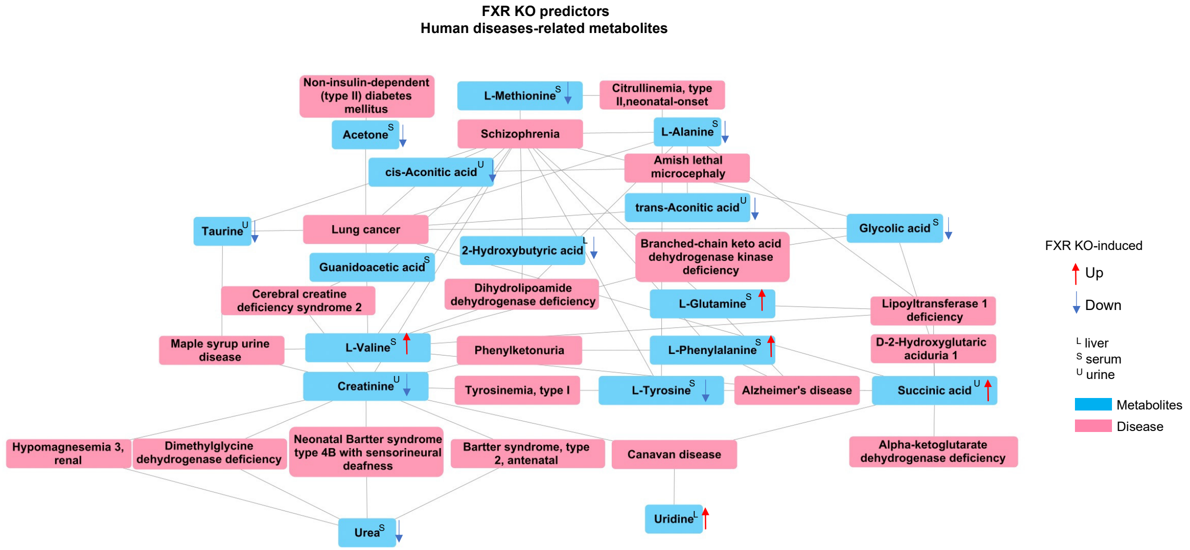
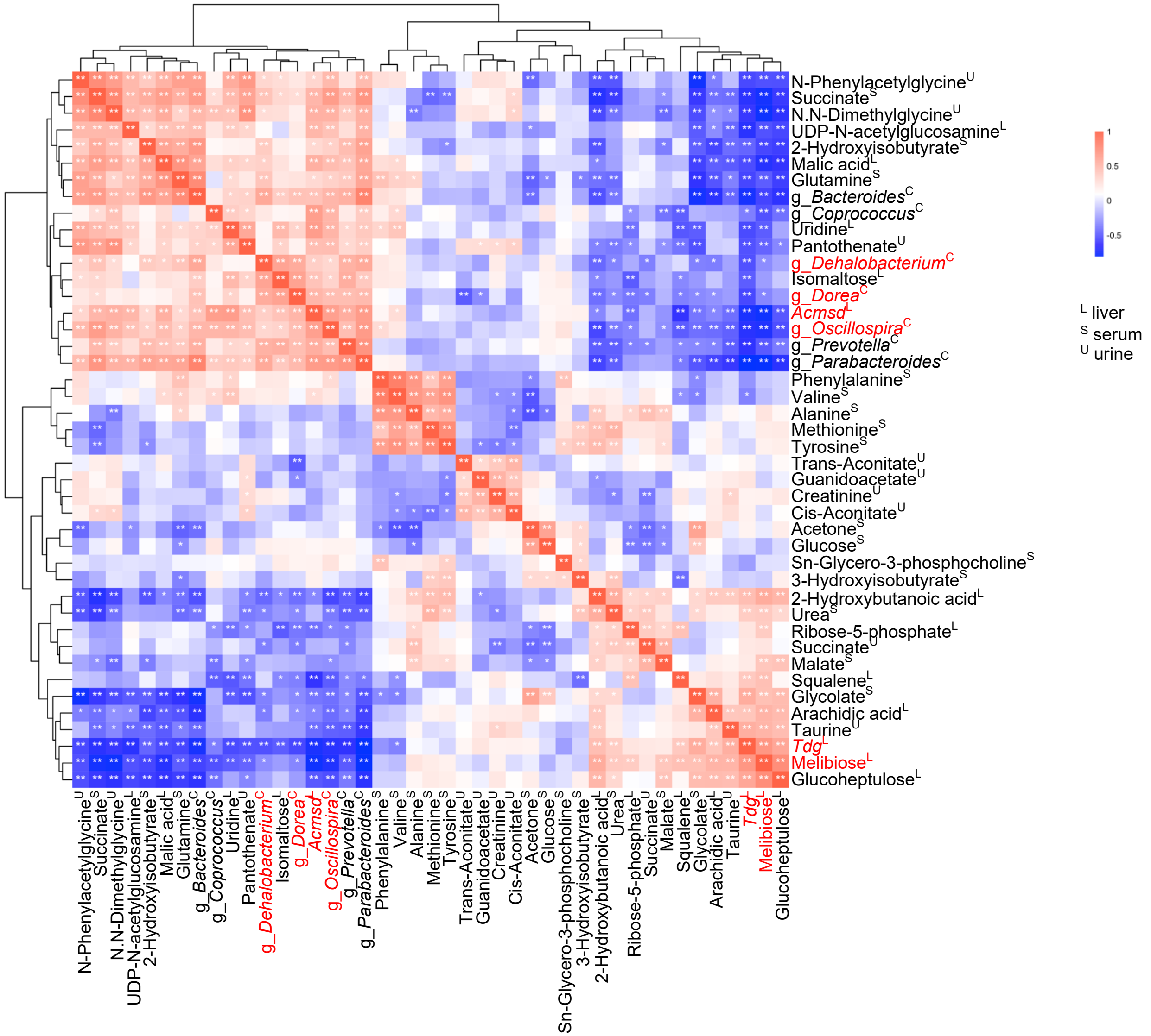


Figure S5. Functional analysis of FXR expression predictors. (A) The pathways for metabolites serve as FXR expression predictors. (B)

The network shows the interaction between metabolites and diseases for FXR expression predictors.

Figure S6



N-Phenylacetylglycine^{U}
Succinate^{S}
N.N-Dimethylglycine^{U}
UDP-N-acetylglucosamine^{L}
2-Hydroxyisobutyrate^{S}
Malic acid^{L}
Glutamine^{S}
g_*Bacteroides*^{C}
g_*Coprococcus*^{C}
Uridine^{L}
Pantothenate^{U}
g_*Dehalobacterium*^{C}
Isomaltose^{L}
g_*Dorea*^{C}
Acmsd^{L}
g_*Oscillospira*^{C}
g_*Prevotella*^{C}
g_*Parabacteroides*^{C}
Phenylalanine^{S}
Valine^{S}
Alanine^{S}
Methionine^{S}
Tyrosine^{S}
Trans-Aconitate^{U}
Guanidoacetate^{U}
Creatinine^{U}
Cis-Aconitate^{U}
Acetone^{S}
Glucose^{S}
Sn-Glycero-3-phosphocholine^{S}
3-Hydroxyisobutyrate^{S}
2-Hydroxybutanoic acid^{L}
Urea^{S}
Ribose-5-phosphate^{L}
Succinate^{U}
Malate^{S}
Squalene^{L}
Glycolate^{S}
Arachidic acid^{L}
Taurine^{U}
Tdg^{L}
Melibiose^{L}
Glucoheptulose^{L}
1
0.5
0
-0.5
^{L} liver
^{S} serum
^{U} urine

Figure S6. Interactions of FXR expression predictors. Spearman's correlation between cecal microbiota at the genus level, hepatic transcripts, and metabolites from the liver, serum, and urine. *$p < 0.05$, **$p < 0.01$.

Table S1. Samples for multi-omics data from the mouse model.

Omics	Number of mice	Age (month)	Diet	Genotype
Hepatic transcripts	48	5, 10, 15	CD, WD	WT, FXR KO
Metabolites				
Bile acids (liver)	186	5, 10, 15	CD, WD	WT, FXR KO
Liver	72	5, 10, 15	CD, WD	WT, FXR KO
Serum	122	5, 10, 15	CD, WD	WT, FXR KO
Urine	157	5, 10, 15	CD, WD	WT, FXR KO
Microbiota	163	5, 10, 15	CD, WD	WT, FXR KO

Table S2. Hepatic transcripts that classify diet, age, and FXR activity.

Transcript name	Protein name	Functions	Changes	Diseases implications
Cyp39a1	24-hydroxycholesterol 7-alpha-hydroxylase	Steroid metabolism; cholesterol degradation; lipid metabolism; bile acid biosynthesis	Western diet (Down)	CYP39A1 is an HCC suppressor in humans [1]. CYP39A1 is an HCC biomarker [2].
Pde5a	cGMP-specific 3',5'-cyclic phosphodiesterase	Purine metabolism, plays a role in signal transduction by regulating the intracellular concentration of cyclic nucleotides	Western diet (Up)	-
Csad	Cysteine sulfinic acid decarboxylase	Organosulfur biosynthesis; taurine biosynthesis	Western diet (Up)	CSAD is protective in NAFLD [3].
Gramd1b	Protein Aster-B	Cholesterol transporter that mediates non-vesicular transport of cholesterol from the plasma membrane to the endoplasmic reticulum	Western diet (Up)	-
Slc39a4	Zinc transporter ZIP4	ZIP4 (SLC39A4) may play a role in the acquisition of zinc by hepatocellular carcinomas, leading to repressed apoptosis, enhanced growth rate and enhanced invasive behavior [4].	Western diet (Up)	SLC39A4 is involved in the pathogenesis of acrodermatitis enteropathica, zinc-deficiency type [5–7]. SLC39A4 expression is activated in HCC [4].
Hamp2	Hepcidin-2	Antimicrobial	Western diet (Down)	-
Loxl4	Lysyl oxidase homolog 4	Crosslinking of collagen fibrils; Elastic fibre formation	Western diet (Down)	LOXL4 expression is increased during the liver carcinogenesis [8].

Rec8	Meiotic recombination protein REC8 homolog	Meiotic synapsis	Western diet (Down)	REC8 promotes tumor migration, invasion, and angiogenesis in human HCC [9].
Adam11	Disintegrin and metalloproteinase domain-containing protein 11	LGI (leucine-rich glioma inactivated)-ADAM interactions	Western diet (Up)	-
Zbtb16	Zinc finger and BTB domain-containing protein 16	Energy metabolism regulator	Aging (Down)	ZBTB16 associate with increased obesity-related parameters and elevated total and low-density lipoprotein cholesterol [10].
Rps27rt	Ribosomal Protein S27	RNA binding and structural constituent of ribosome	Aging (Up)	-
Naip2	Baculoviral IAP repeat-containing protein 1b	Inflammatory response; Innate immunity; Apoptosis	Aging (Up)	-
Cyp46a1	Cholesterol 24-hydroxylase	Steroid metabolism; cholesterol degradation; Lipid metabolism; C21-steroid hormone metabolism	Aging (Up)	*Cyp46* gene levels were higher in the hippocampus of elderly humans and in patients with certain pathological, neurodegenerative conditions [11].
Mmd2	Monocyte to macrophage differentiation factor 2	Positive regulation of Ras protein signal transduction	Aging (Up)	-
AA792892	Expressed sequence AA792892		Aging (Up)	-
A4gnt	Alpha-1,4-N-acetylglucosaminyltransferase	O-linked glycosylation of mucins	Aging (Up)	-

Cdh19	Cadherin-19	Wnt signaling pathway; Cadherin signaling pathway	Aging (Up)	-
Pclo	Protein piccolo	Component of the presynaptic cytoskeletal matrix, involved in regulation of presynaptic proteins and synaptic vesicles	Aging (Up)	Loss of PCLO causes pontocerebellar hypoplasia 3 in humans [12]; *Pclo* is highly mutated as cancer driver gene in hepatitis B virus-related HCC patients [13].
Zfp677	Uncharacterized protein	-	Aging (Up)	-
Cyp3a11	Cytochrome P450 3A11	Xenobiotics; Aflatoxin activation and detoxification; Biosynthesis of maresin-like SPMs	Aging (Up)	The mRNA expression of hepatic *Cyp3a11* is increased high-fat and high-sucrose induced NAFLD mouse model [14].
Hsf2bp	Heat shock factor 2-binding protein	Double-strand break repair involved in meiotic recombination	Aging (Up)	-
Kcnj16	Inward rectifier potassium channel 16	Potassium transport channels; Activation of G protein gated Potassium channels; Inhibition of voltage gated Ca2+ channels via Gbeta/gamma subunits	Aging (Up)	*Kcnj16* level is lower in HCC tumor tissues compared to adjacent tissues from HCC patients [15]. *Kcnj16* mutation cause a novel tubulopathy with hypokalemia, salt wasting, disturbed acid-base homeostasis, and sensorineural deafness [16].
Mfsd2a	Sodium-dependent lysophosphatidylcholine symporter 1	Glycerophospholipid biosynthesis	Aging (Up)	The MFSD2A level in HCC patients is lower than in healthy controls [17].

Acmsd	2-amino-3-carboxymuconate-6-semialdehyde decarboxylase	Secondary metabolite metabolism; quinolate metabolism	FXR KO (Up)	Inhibiting ACMSD protects liver injury in mouse models [18].
Tdg	G/T mismatch-specific thymine DNA glycosylase	DNA demethylation	FXR KO (Down)	Conditional knockout of Tdg causes HCC in a mouse model [19].

HCC, hepatocellular carcinoma; NAFLD, nonalcoholic liver disease; -, unknown.

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Table S3. Metabolites that classify diet, age, and FXR activity.

Metabolites (Specimens)	Source	Functions or Roles	Changes	Disease implications
1,5-anhydroglucitol (Liver)	Mainly from food, well absorbed in the intestine, and is distributed to all organs and tissues.	A glycemic marker	Western diet (Down) Aging (Up)	Serum 1,5-anhydroglucitol concentrations are lower in cirrhotic and chronic liver disease patients than those in healthy people [1,2]. Low serum 1,5-anhydroglucitol concentration is a predictor of short-term mortality in Hepatitis B virus-related acute-on-chronic liver failure patients [3].
Linoleic acid (Liver)	Hydrogenated vegetable oils	An omega-6 trans fatty acid; α-linolenic acid and linoleic acid metabolism	Western diet (Down)	Dietary conjugated linoleic acid protects the liver from NAFLD in a rat model [4].
Squalene (Liver)	Human sebum (5%), fish liver oils, yeast lipids, and many vegetable oils (e.g., palm oil, cottonseed oil, rapeseed oil)	A biochemical precursor to the whole family of steroids; An intermediate for cholesterol synthesis; A precursor to phytosterol synthesis; A bactericide	Western diet (Up) Aging (Up) FXR KO (Down)	Squalene decreases hepatic cholesterol and triglycerides [5].
Heptadecanoic acid (Liver)	Exogenous origin, such as dairy fats (milk and meat)	A saturated fatty acid	Western diet (Up)	Biomarkers for dietary food (fat) intake assessment; Biomarkers for coronary heart disease risk and type II diabetes mellitus risk [6].

2-aminobutyric acid (Liver)	Biosynthesized by transamination of oxobutyrate; A metabolite in isoleucine biosynthesis; A non-essential amino acid that is primarily derived from the catabolism of methionine, threonine, and serine.	A non-proteinogenic α-amino acid	Western diet (Down)	-
Trimethylamine (Serum)	A product of decomposition of plants and animals; A bacteria metabolite	A colorless, hygroscopic, and flammable simple amine with a typical fishy odor in low concentrations; Ammonia like odor in higher concentrations.	Western diet (Down)	NAFLD patients have increased trimethylamine in the intestine and liver [7].
3-Hydroxyisobutyrate (Serum)	An intermediate in L-valine metabolism	Valine, leucine, and isoleucine degradation	Western diet (Down) FXR KO (Down)	Plasma 3-hydroxyisobutyrate is a marker of hepatic mitochondrial fatty acid oxidation in male Wistar rats [8].
Aspartate (Serum)	Found in all organisms ranging from bacteria to plants to animals; Nonessential amino acid derived from glutamic acid by enzymes using vitamin B6.	Proteinogenic α-amino acid; Arginine and proline metabolism; Aspartate metabolism; Urea cycle	Western diet (Up)	Administration of L-aspartate in vitro or in mice efficiently ameliorates metabolic dysfunction-associated fatty liver disease [9].

Leucine (Serum)	Essential amino acid; Human dietary sources are foods that contain protein, such as meats, dairy products, soy products, beans and legumes.	A branched chain amino acid; Proteinogenic α-amino acid; Valine, leucine, and isoleucine degradation	Western diet (Up)	L-leucine supplementation is protective in patients with liver cirrhosis [10].
Histidine (Serum)	Essential amino acid; Exogenous food, such as fruits (berries)	α-amino acid; Histidine metabolism; Nitrogen metabolism; Beta-alanine metabolism; Anti-oxidant, anti-inflammatory and anti-secretory properties	Western diet (Up)	Histidine supplementation ameliorates metabolic syndrome [11].
Urea (Serum)	Exogenous food, such as berries	Urea cycle; Arginine and proline metabolism	Western diet (Down) FXR KO (Down)	Urea cycle disorders [12].
2-Oxoisocaproate (Serum)	Endogenously produced metabolite	Valine, leucine, and isoleucine degradation; A neurotoxin and a metabotoxin.	Western diet (Up)	Plasma 2-oxoisocaproate (ketoleucine) concentrations are increased in patients with metabolic stress [13].
N-Methylhydantoin (Serum)	Exogenous, such as animal foods.	A bacterial metabolite; A imidazolidine-2,4-dione that is the N-methyl-derivative of hydantoin.	Western diet (Up)	-
Methionine (Serum)	Essential amino acid; Exogenous food such as	Proteinogenic α-amino acid; Glycine, serine, and	Western diet (Down)	NAFLD patients have low liver methionine concentrations [14].

	berries; An intermediate in transmethylation reactions	threonine metabolism; Methionine metabolism	FXR KO (Down)	
Asparagine (Serum)	Non-essential amino acid, the precursor to asparagine is oxaloacetate; Exogenous food such as berries	Proteinogenic α-amino acid; Aspartate metabolism; Nitrogen metabolism; Ammonia recycling	Western diet (Up)	Upregulating asparagine synthetase is beneficial for alleviating liver injury [15].
Sucrose (Urine)	From sugarcane (Saccharum officinarum), sugar beet (Beta vulgaris), and other plants	Sucrose is a sweetener and used in food products as a preservative, antioxidant, moisture control agent, stabilizer, and thickening agent; Galactose metabolism	Western diet (Up)	Excessive sucrose intake leads to NAFLD [16].
Trimethylamine (Urine)	Decomposition of plants and animals	A uremic toxin; A marker for urinary tract infection brought on by *E. coli*.	Western diet (Down)	Trimethylamine in the intestine and liver is increased in NAFLD patients [7].
Trimethylamine N-oxide (Urine)	Biosynthesized endogenously from trimethylamine, which is derived from choline.	A uremic toxin; TMAO alters cholesterol metabolism in the intestines, in the liver and in arterial wall.	Western diet (Down)	Trimethylamine-N-oxide promotes brain aging and cognitive impairment in mice [17]. TMAO supplementation aggravates liver steatosis [18].
Hippurate (Urine)	Produced from the metabolism of benzoate, which is mainly stored in the liver mitochondria.	Reflect hepatic function	Western diet (Up)	Elevated blood hippurate associates with improved hepatic steatosis and good metabolic health [19].

Pantothenate Vitamin B5 (Urine)	From everywhere and small quantities of pantothenic acid are found in nearly every food, with high amounts in whole grain cereals, legumes, eggs, meat, and royal jelly.	A water-soluble vitamin required to sustain life; Beta-alanine metabolism; Pantothenate and CoA biosynthesis	Western diet (Down) FXR KO (Up)	-
Succinate semialdehyde (Liver)	An intermediate in the catabolism of gamma-aminobutyrate or gamma-aminobutyric acid	High levels of succinate semialdehyde function as a neurotoxin and a metabotoxin.	Aging (Up)	-
Xylitol (Liver)	Xylitol exists in all living species, ranging from bacteria to plants to humans.	Organism's growth, development, or reproduction	Aging (Up)	-
Valine (Liver)	Essential amino acid; Human dietary sources are foods that contain protein, such as meats, dairy products, soy products, beans and legumes.	Proteinogenic α-amino acid; Branched chain amino acid; Valine, leucine, and isoleucine degradation; Propanoate metabolism; Transcription/Translation	Aging (Up)	Excessive valine causes NAFLD [20].
Glyceric acid (Liver)	Obtained from oxidation of glycerol.	Glycine, serine, and threonine metabolism; Glycerolipid metabolism	Aging (Up)	Oral D-glyceric acid activates mitochondrial metabolism and reduces inflammation among 50-60-year-old healthy volunteers [21].

Aspartic acid (Liver)	Aspartic acid is found in all organisms ranging from bacteria to plants to animals.	Proteinogenic α-amino acid; Transcription/translation; Arginine and proline metabolism; Aspartate metabolism	Aging (Down)	-
Ethanolamine (Liver)	Ethanolamine exists in all living species, ranging from bacteria to plants to humans.	An initial precursor for the biosynthesis of two primary phospholipid classes, phosphatidylcholine (PC) and phosphatidylethanolamine (PE).	Aging (Down)	Ethanolamine protects against hyperlipidemia in aged mice [22].
Glutaric acid (Liver)	Glutaric acid is naturally produced in the body during the metabolism of some amino acids, including lysine and tryptophan.	Glutaric acid may cause irritation to the skin and eyes. Glutaric acid acts as an acidogen and a metabotoxin when present in sufficiently high levels.	Aging (Up)	-
Ascorbic acid (Liver)	Ascorbic acid is found naturally in citrus fruits and many	Necessary to maintain connective tissue and bone.	Aging (Up)	Ascorbic acid inhibits obesity and nonalcoholic fatty liver disease [23].

	vegetables and is an essential nutrient in human diets.	Tyrosine metabolism		
2-aminobutyric acid (Liver)	A non-essential amino acid; Biosynthesized by transamination of oxobutyrate, a metabolite in isoleucine biosynthesis.	Non-proteogenic amino acid	Aging (Down)	-
2-monoolein (Liver)	A major end product of the intestinal digestion of dietary fats in animals via the enzyme pancreatic lipase.	Act as emulsifiers, helping to mix ingredients such as oil and water that would not otherwise blend well	Aging (Up)	-
3-(1-pyrazolyl)-l-alanine (Liver)	L-alanine derivative	A non-proteinogenic L-α-amino acid	Aging (Up)	-
Glycolic acid (Liver, serum)	A metabolite in bacteria such as Acetobacter, *Escherichia*	A nephrotoxin if consumed orally; A known inhibitor of tyrosinase; Renal toxicity	Aging (Up in the liver) FXR KO (Down in serum)	-
Beta-glutamic acid (Liver)	A metabolite found in the aging mouse brain; A natural product found in Chondria armata	A marine metabolite and an algal metabolite.	Aging (Up)	-
Uridine (Liver)	Uridine can be synthesized from uracil. Uridine is found in many foods (anything containing RNA).	A nucleoside consisting of uracil and D-ribose and a component of RNA; Pyrimidine metabolism	Aging (Up) FXR KO (Up)	Uridine alleviates carbon tetrachloride-induced liver fibrosis [24].

Serine (Liver)	Serine is found in all organisms ranging from bacteria to plants to animals.	Proteinogenic amino acid; Nitrogen metabolism; Starch and sucrose metabolism; Glycine, serine, and threonine metabolism	Aging (Down)	Reduced hepatic serine contributes to the development of fatty liver disease [25].
Palmitoleic acid (Liver)	A common constituent of the glycerides of human adipose tissue; From gut bacteria, such as Akkermansia muciniphila; Macadamia oil (Macadamia integrifolia) and sea buckthorn oil (Hippophae rhamnoides) are botanical sources of palmitoleic acid, containing 22 and 40% respectively.	A monounsaturated fatty acid; Reduce hepatic gluconeogenesis	Aging (Down)	Palmitoleic acid reduces high fat diet-induced liver inflammation [26]. Palmitoleic acid improves metabolic functions in fatty liver [27]. Palmitoleic acid protects against hypertension [28].
Lactic acid (Liver)	In animals, L-lactate is constantly produced from pyruvate via the enzyme lactate dehydrogenase in a process of fermentation during normal metabolism and exercise. Exogenous food such as beverages.	Gluconeogenesis; Pyruvate metabolism	Aging (Up)	-

Lithocholic acid (Liver)	It is formed from chenodeoxycholate by bacterial action and is usually conjugated with glycine or taurine.	Secondary bile acid; It acts as a detergent to solubilize fats for absorption.	Aging (Down)	Lithocholic acid inhibits inflammation and regulates metabolism [29].
Pyruvate (Serum)	Pyruvate is found in all living organisms ranging from bacteria to plants to humans. It is intermediate compound in the metabolism of carbohydrates, proteins, and fats.	Urea cycle; Glucose-alanine cycle; Glycine, serine, and threonine metabolism	Aging (Up)	-
1.3-Dihydroxyacetone (Serum)	It is often derived from plant sources such as sugar beets and sugar cane, by the fermentation of glycerin.	In combination with naphthoquinones, it acts as a sun screening agent.	Aging (Down)	-
Acetone (Serum)	Acetone is produced and disposed of in the human body through normal metabolic processes. It is normally present in blood and urine.	Ketone body metabolism	Aging (Down) FXR KO (Down)	-
Methylamine (Urine)	Methylamine occurs endogenously from amine catabolism; Methylamines produced by microbial	Tyrosine metabolism	Aging (Down)	-

	metabolism of dietary choline and L-carnitine. Exogenous food such as teas			
N.N-Dimethylglycine (Urine)	A derivative of the amino acid glycine	A microbial metabolite; A biomarker for the consumption of legumes	Aging (Down) FXR KO (Up)	-
Betaine (Urine)	Exogenous food such as fruits (e.g., berries)	Glycine, serine, and threonine metabolism; Methionine metabolism	Aging (Up)	Betaine inhibits inflammation and apoptosis [30].
2-Hydroxyisobutyrate (Urine)	Non-essential, secondary metabolite	May serve as defense or signaling molecules.	Aging (Up) FXR KO (Up)	-
Sn-Glycero-3-phosphocholine (Urine)	Formed in the breakdown of phosphatidylcholine	One of the four major organic osmolytes in renal medullary cells, changing their intracellular osmolyte concentration in parallel with extracellular tonicity during cellular osmoadaptation. Retinol metabolism	Aging (Up) FXR KO (Up)	-
3-Indoxylsulfate (Urine)	A metabolite of the common amino acid tryptophan and is derived through the consumption, digestion, and	A uremic toxin and cardiotoxin	Aging (Up)	-

	microbial processing of protein-rich foods. Indoxyl sulfate is technically a bacterial co-metabolite, meaning that it is derived from both bacterial and host metabolism.			
Ascorbate Vitamin C (Urine)	An essential nutrient in human diets, including citrus fruits and many vegetables; A microbial metabolite produced by Ketogulonicigenium	A water-soluble vitamin; Antioxidant; An electron donor for enzymes involved in collagen hydroxylation, biosynthesis of carnitine and norepinephrine.	Aging (Down)	Ascorbate ameliorates factors linked to Alzheimer's disease pathogenesis [31].
Melibiose (Liver)	This sugar is produced and metabolized only by enteric and lactic acid bacteria and other microbes, such as *Escherichia*. It is not an endogenous metabolite but may be obtained from the consumption of partially fermented molasses, brown sugar, or honey.	Galactose metabolism	Aging (Up), FXR KO (Down)	-
Glucoheptulose (Liver)	L-arabinose	-	FXR KO (Down)	-

UDP-N-acetylglucosamine (Liver)	Exogenous, food such as animal food	Glucose sensor; Amino sugar metabolism; Elevated UDP-N-acetylglucosamine has an effect on insulin-stimulated glucose uptake.	FXR KO (Up)	-
Uridine (Liver)	Synthesized from uracil; Uridine is found in many foods (anything containing RNA).	Pyrimidine metabolism	FXR KO (Up)	Uridine alleviates carbon tetrachloride induced liver fibrosis [24].
Isomaltose (Liver)	A product of the caramelization of glucose; Exogenous, food such as beverages	Starch and sucrose metabolism; Metabolic pathways	FXR KO (Up)	Isomaltulose improves insulin resistance in NAFLD patients [32].
Ribose-5-phosphate (Liver)	Exogenous, food such as fruits; A product and an intermediate of the pentose phosphate pathway.	Purine metabolism; Pentose phosphate pathway	FXR KO (Down)	Ribose-5-phosphate isomerase A overexpression induces oncogenesis in HCC [33].
2-hydroxybutanoic acid (Liver)	Primarily produced in mammalian hepatic tissues that catabolize L-threonine or synthesize glutathione. Exogenous, food such as animal foods	An early marker for both insulin resistance and impaired glucose regulation	FXR KO (Down)	-

Arachidic acid (Liver)	A minor constituent of butter, perilla oil, peanut oil, corn oil, and cocoa butter.	Saturated, long-chain fatty acids	FXR KO (Down)	Arachidic acid induces liver dysfunction in hyperglycaemic rats [34].
Malic acid (Liver, serum)	Exogenous, food such as herbs and spices	Citric acid cycle; Gluconeogenesis; Pyruvate metabolism; Malate-aspartate shuttle	FXR KO (Up in the liver) FXR KO (Down in the serum)	Malic acid is increased in NAFLD [35]
Succinate (Serum, Urine)	Exogenous, food such as fruits	A cell signaling molecule; Succinate alters gene expression patterns, thereby modulating the epigenetic landscape or it can exhibit hormone-like signaling functions.	FXR KO (Down in serum and up in urine)	Elevated extracellular succinate in liver tissue drives inflammation [36].
Alanine (Serum)	It is formed in vivo by the degradation of dihydrouracil and carnosine.	A neurotoxin; A mitochondrial toxin; A metabotoxin; Beta-alanine metabolism	FXR KO (Down)	-
Glutamine (Serum)	Non-essential amino acid	Proteinogenic α-amino acid; Glutamate metabolism; Purine metabolism; Urea cycle	FXR KO (Up)	Glutamine is beneficial for human inflammatory bowel disease [37].
Phenylalanine (Serum)	An essential amino acid and the precursor of the amino acid tyrosine, highly concentrated in	Proteinogenic α-amino acid; A precursor for catecholamines including	FXR KO (Up)	-

	high protein foods, such as meat, cottage cheese, and wheat germ. An additional dietary source of phenylalanine is artificial sweeteners containing aspartame.	tyramine, dopamine, epinephrine, and norepinephrine; A neurotoxin and a metabotoxin.		
Tyrosine (Serum)	Exogenous, food such as fruits	Proteinogenic α-amino acid; Tyrosine metabolism	FXR KO (Down)	-
Glucose (Serum)	Exogenous, food such as fruits	Primary source of energy for all living organisms, Glycolysis; Gluconeogenesis; Lactose synthesis	FXR KO (Up)	-
Creatinine (Urine)	Exogenous, food such as herbs and spices	An amino acid derivative; A waste product and is normally eliminated in large quantities by the kidneys through urinary excretion.	FXR KO (Down)	-
Taurine (Urine)	An essential amino acid; Foods such as vegetables, animal and fish protein	A neurotransmitter in the brain; Taurine and hypotaurine metabolism; Primary bile acid biosynthesis	FXR KO (Down)	Taurine displays potential ameliorating effects against different neurological disorders [38].

N-Phenylacetylglycine (Urine)	Exogenous, food such as animal food	A surrogate biomarker for phospholipidosis	FXR KO (Up)	A biomarker for dimethylnitrosamine-induced hepatic fibrosis in a rat model [39].
Guanidoacetate (Urine)	Exists naturally in all vertebrates; Formed primarily in the kidneys by transferring the guanidine.	α-amino acid and derivatives; Arginine and proline metabolism; Glycine, serine, and threonine metabolism	FXR KO (Down)	-
trans-Aconitate (Urine)	Normally present in human urine; Detected in foods, such as garden tomato fruits, root vegetables, soybeans, and rice.	A biomarker for the consumption of soy products	FXR KO (Down)	-
Cis-Aconitate (Urine)	Cow milk	Glutaminolysis and cancer pathway; Citric acid cycle	FXR KO (Down)	-
N.N-Dimethylglycine (Urine)	Exogenous, food such as animal foods; An amino acid derivative found in the cells of all plants and animals and can be obtained in the diet in small amounts from grains and meat; A byproduct of homocysteine metabolism; A microbial metabolite	A biomarker for the consumption of legumes; Glycine, serine, and threonine metabolism; Methionine metabolism	FXR KO (Up)	Plasma N.N-Dimethylglycine is markedly decreased in Alzheimer's disease patients compared with normal controls [40].

HCC, hepatocellular carcinoma; NAFLD, nonalcoholic liver disease; -, unknown.

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