

SUPPLEMENTARY MATERIAL FOR

High-throughput metabolomics for discovering potential biomarkers and identifying metabolic mechanisms in aging and Alzheimer's disease

1. Supplementary Methods

1.1 Experimental protocol of metabolic profiling analysis for plasma by UPLC/Q-TOF-MS/MS

Chemicals and reagents

Formic acid was procured from Beijing Reagent Company (Beijing, China). Methanol and acetonitrile of HPLC grade were both procured from Honeywell Burdick & Jackson (Muskegon, MI). All reagents and chemicals (HPLC grade) were available from commercial sources. Ultrapure water was purchased from Veolia Water Solutions & Technologies (France).

Plasma sample preparation

Samples were thawed at 4°C and vortexed for 1 min. We obtained 250 µl of plasma using a 2-ml centrifuge tube, followed by addition of 750 µl of methanol, a 1 min vortex, and centrifugation performed at 12000 rpm for 10 min at 4°C. The upper phase of the mixture was collected and dried via nitrogen. Proteins were treated with a 350 µl mixture consisted of acetonitrile and water (1:2, v/v) for deproteinization, after which they were subjected to a 1 min vortex and centrifugation at 12,000 rpm for 10 min at 4°C. The collected supernatants were brought to the dried tubes for the dissolution of the residue. A final sample was obtained before a 1 min vortex, a 5 min stewing, and centrifuged at 12,000 rpm for 10 min at 4°C. Then, the metabolite-containing supernatants were placed in autosampler vials for metabolic measurement. Aliquots of 5 plasma was used as pooled quality-control (QC) sample to evaluate the repeatability and reliability of the platform, with which plasma samples were analyzed in two batches at regular intervals throughout the measurement run (n =15).

UPLC/Q-TOF-MS/MS analysis

Plasma metabolite separation was conducted using a UPLC system (ACQUITY UPLC; Waters Corp., USA) equipped with 1.7- μ m BEH C18 column [ACQUITY (HSS); Waters Corp., Milford, MA, USA; 2.1 mm $\times$ 100 mm], maintained at 35°C. The mobile phase was performed using 0.1% formic acid waters (A) and acetonitrile (B). Each plasma sample was delivered at a volume of 2 μ l and a flow rate of 0.35 ml/min. The elution gradient was 0.5 min (2% B), over 0.5 to 6.0 min (2% to 20% B), over 6.0 to 7.0 min (20% to 35% B), over 7.0 to 9.0 min (35% to 70% B), over 9.0 to 10.5 min (70% to 98% B), 2.0 min (98% B), 6.0 min (2% B). After establishing the initial settings, the column was equilibrated for 2.0 min. Samples were injected in a randomized order with acetonitrile run at regular intervals (n=4) as a blank solution.

Q-TOF MS/MS, incorporated with a mass spectrometer (Micromass Q-TOF mass spectrometer; Waters Corp., Manchester, UK), was carried out in electrospray ionization (ESI) interface under full scan monitoring mode (50~1000 m/z). The capillary voltage and source temperature of ESI⁻ and ESI⁺ were set to be 2800V, 100°C and 3000V, 110°C, respectively. The desolvation gas (nitrogen) flow was 650 L/h and the temperature was 320°C. In both modes, collision energy was 6 eV, sample cone voltage was 35 V, collision gas was selected as argon, nitrogen cone gas flow was 50 L/h, MCP detector voltage was 2400 V and acquisition rate was 0.4 s with 0.1 s interscan delay. Data were obtained in centroid MS mode using the lock spray, the frequency of which was 10s. Metabolite mass was locked by application of 200 pg/ml leucine-enkephalin (554.2615 in ESI⁻ and 556.2771 in ESI⁺) and data were averaged over 10 scans.

Data processing

MarkerLynx software coupled with Masslynx software (version 4.1 SCN714) was used to pretreat the LC-MS data, the latter of which aimed to recognize and align peak. The peak width was set at 5% height and 1 s, and peak-to-peak baseline noise was automatically calculated. Parameters of collection were as follows: 0.5-10.5 min and 0.1 min for range and tolerance of retention time, 50-1000 Da and 0.05 Da for range and tolerance of mass, 6.0 for noise elimination level, 80 for minimum intensity, and remove deisotope peak data. The intensity of ion was converted to the summed

one of each chromatogram after peak identification and alignment. The data pretreatment was accorded with the “80% rule.”

Differential metabolites identification

Metabolite annotation was performed by comparing the exact m/z values and MS/MS spectra with those in free online databases Human Metabolome Database (HMDB, <http://www.hmdb.ca/>). Additionally, the MassFragment application manager (MassLynx version 4.1, Waters) was applied to facilitate the MS/MS fragment ion analysis process via chemically intelligent peak-matching algorithms.

1.2 Systematic review of metabolomics studies of human Alzheimer’s disease

Literature search strategy

Inclusion and exclusion criteria

Previous published studies were judged to be eligible if the following items were achieved: 1) all patients were diagnosed as AD or MCI with standard criteria, and all healthy controls (CN) were confirmed to be free of AD or MCI; 2) Studies applied approaches of metabolomics such as GC-MS, LC-MS and NMR; 3) Metabolites or metabolic pathways were presented with complete names; 4) Studies focused on differentiated metabolites or metabolic pathways which were related to the progression of MCI or AD. In detail, biomarkers were identified by at least one of following six comparisons: AD VS. CN, MCI VS. CN, AD VS. MCI, CN_AD (healthy subjects who developed AD subsequently) VS. CN (healthy controls without diagnosed AD during follow-up), CN_MCI (healthy subjects who developed MCI subsequently) VS. CN (healthy controls without diagnosed MCI during the follow-up), as well as MCI_AD (patients of MCI who developed AD subsequently) VS. MCI (patients of MCI without diagnosed AD during follow-up). The exclusion criteria were as follows: 1) Genomics or proteomics studies; 2) Studies were performed on non-human models including animals, plants or cells; 3) Studies investigated pathogenesis or clinical evaluation of AD drugs; 4) Subjects mixed with other kinds of dementia, such as vascular dementia, preclinical AD.

Data extraction from included studies

We examined the selected studies in more detail and extracted relevant information, including study characteristics (year of publication, author details, study design, sample characteristics, metabolomics platform applied in different biosamples and sample size), as well as a summary of findings that comprised differentiated metabolites and pathways.

Two authors (Y.H. Y and Z.P. L) independently extracted the data and appraised the quality of each article. Divergence regarding quality evaluation or information extraction was dealt with discussion or judgment of senior investigators (F. W. and M.Q. W.).

2. Supplementary Tables

Supplementary Table 1. Demographic and clinical characteristics of population in training and testing sets

Supplementary Table 2. The characteristics and identified metabolites or pathways of included metabolomics studies.

Supplementary Table 3. Quality assessment of metabolomics studies included in this systematic review by QUADOMICS

Supplementary Table 4. Differential metabolites of Alzheimer's disease and their reported frequencies in previous studies

Supplementary Table 5. Differential metabolites of mild cognitive impairment and their reported frequencies in previous studies

Supplementary Table 6. Differential metabolites between Alzheimer's disease and mild cognitive impairment and their reported frequencies in previous studies

Supplementary Table 7. Metabolites related with Alzheimer's disease replicated in previous prospective studies

Supplementary Table 8. Metabolites related with the conversion from mild cognitive impairment to Alzheimer's disease in previous prospective studies

Supplementary Table 9. Pathways altered in mild cognitive impairment and Alzheimer's disease identified by direct extraction and pathway enrichment analysis

Supplementary Table 10. Pathways altered in Alzheimer's disease identified in brain tissue, CSF, plasma and serum

3. Supplementary Figures

Supplementary Figure 1. Variable importance for the top 30 aging-related metabolites selected by random forest. The y-axis represents retention time and mass of metabolites. The x-axis represents IncNodePurity, which indicates the importance of the variable given by the classification model.

Supplementary Figure 2. Flow diagram of the literature search of metabolomics studies in Alzheimer's disease using the PubMed, Cochrane and Embase databases.

Supplementary Figure 3. Description of the included studies' basic information. (A) year of publication; (B) race of population; (C) study design; (D) different platforms used in different biosample analyses.

Supplementary Table 1. Demographic and clinical characteristics of training set and testing set

	Training set(n=119)	Testing set(n=64)	t / χ^2 value	P-value
Age(years, mean(sd))	58.66±11.21	58.98±10.84	-0.186	0.852
Range (min-max)	32~82	25~85		
Gender(F/M)	48/71	31/33	0.80762	0.3688
BMI (kg/m2, mean(sd))	24.10±3.30	23.93±4.03	0.289	0.773
Education ^a (NO, (%))				
Primary school or below	38(31.93)	23(35.94)		
Junior high school	33(27.73)	16(25)		
Senior high school	18(15.13)	8(12.5)		
College and above	20(16.81)	10(15.63)		
Unknown	10(8.4)	7(10.94)	0.84132	0.9328
Tobacco Smoking ^b (NO, (%))				
Yes	43(36.13)	28(43.75)		
No	48(40.34)	34(53.13)	0.008022	0.9286
Alcohol drinking ^c (NO, (%))				
Yes	41(34.45)	27(42.19)		
No	50(42.02)	35(54.69)	0.00033898	0.9853
Chronic diseases ^d (NO, (%))				
No	67(56.3)	43(67.19)		
Yes				
Diabetes	17(14.29)	3(4.69)		
Hypertension	27(22.69)	5(7.81)		
Heart disease	22(18.49)	6(9.38)	0.46382	0.793
Exercise ^e (NO, (%))				
Yes	34(28.57)	18(28.13)		
No	50(42.02)	34(53.13)	0.25194	0.6157

^aEducation, missing for 10 in training set and 7 in testing set.

^bSmoking, missing for 28 in training set and 3 in testing set.

^cDrinking, missing for 28 in training set and 3 in testing set.

^dChronic diseases, missing for 6 in training set and 3 in testing set.

^eExercise, missing for 35 in training set and 12 in testing set.

Supplementary Table 2. The characteristics and identified metabolites or pathways of included metabolomics studies.

Study First Author [ref]Year	Study Type	Number of Subjects	Match or Not	Sample Source	Sample Type	Platforms	Metabolites
Varma ⁽¹⁾ 2018	Case-control study	15 AD 15 ASYMAD 14 CN	No	BLSA	brain tissue	FIA-MS/MS; HPLC-MS/MS	Arginine, Propionylcarnitine, lysoPC a C17:0, lysoPC a C18:0, PC aa C38:4, PC aa C40:4, PC aa C40:5 , PC aa C40:6, PC ae C34:0, PC ae C34:2 , PC ae C36:0, PC ae C36:3 , PC ae C36:4 , PC ae C40:1, PC ae C42:3, Serotonin, Spermidine, SM C16:0, SM C16:1, SM C18:1 , SM C24:1, SM C26:1, (SM (OH) C14:1, SM (OH) C22:1, SM (OH) C22:2, SM (OH) C24:1, H1
Marksteiner ⁽²⁾ 2018	Nested case- control study	30 CN 20 MCI 30 AD	No	Hall/Tirol State Hospital, Austria	plasma	LC-MS/MS	glycochenodeoxycholic acid, glycodeoxycholic acid, glycolithocholic acid, lithocholic acid, lithocholic acid
Pan ⁽³⁾ 2017	Case-control study	Plasma: 10 AD 10 CN Brain tissue: 10 AD 10 CN	Yes	Plasma: the Belfast City Hospital brain tissue: Brains for Dementia Research (BDR) initiative	plasma and brain tissue	LC-MS/MS	cholic acid, taurocholic acid
Oresic ⁽⁴⁾ 2017	Case-control study	37 AD 46 CN	No	Florida Hospital's NPH program	serum	GC-GC-TOFMS	Glutamic acid
Lau ⁽⁵⁾ 2017	Case-control study	20 AD 20 PD 20 CN	No	Kyungpook National University Hospital	exhaled breath samples	GC-MS and in-house fabricated exhaled breath sensor systems	Acetamide, Siloxanes, Cyclopentasiloxane, Cyclotrisiloxane, Triphenyl phosphate, 1-phenantherol, ethyl 3-cyano-2,3-bis (2,5,-dimethyl-3-thienyl)-acrylate

Proitsi ⁽⁶⁾ 2015	Case-control study	36 AD 48 MCI 40 CN	Yes	Dementia Case Register (DCR) at King's College London and the EU funded AddNeuroMed study	plasma	UPLC-MS	ChE 32:0, ChE 34:0, ChE34:6, ChE 32:4, ChE 33:6, ChE 40:4, Cholesterol,
Oberacher ⁽⁷⁾ 2017	Nested case-control study	training set: 21 AD 15 MCI 18 CN validation set: 9 AD 6 MCI 11 CN blinded follow up conversion study: 7 AD 3 CN	No	Hall/Tirol 120 State Hospital, Austria	platelets	FIA-MS/MS	PC aaC32:0, PC aeC32:2, PC aeC34:1, SM(OH) C14:1, PC ae C40:4, PC aeC32:2, PC aaC36:5, PC aeC34:1, lysoPCaC18:1, lysoPC aC16:0, SM(OH) C14:1
de Leeuw ⁽⁸⁾ 2017	Case-control study	127 AD 121 CN	No	Amsterdam Dementia Cohort	plasma	UPLC-MS; GC-MS	2-Aminoadipic , TG(51:3), 3-Hydroxyisovaleric acid , Tyrosine , TG(54:6), TG(50:4) , S-3-Hydroxyisobutyric acid , TG(56:8) , Methyl dopa, 8-iso-PGF2a , TG(48:3) , O-Acetylserine , TG(48:2), Methylmalonic acid , TG(46:2), Valine , TG(50:3) Lipids, TG(52:4) , TG(52:5) , TG(56:7) , TG(48:0) , Ornithine, SM(d18:1/23:0) , SM(d18:1/20:1) , TG(48:1) , TG(58:10) , 2-Aminoadipic acid , Tyrosine, Lysine, TG(48:2) , TG(51:3) , TG(54:6) , TG(50:3) , TG(50:2) , TG(50:1) , Leucine , LPC(18:1) , TG(46:2) , TG(50:0) ,

							TG(52:3) , TG(51:2) , Isoleucine , 2-hydroxybutyric acid , TG(51:1), TG(52:1), Proline, TG(54:5), TG(56:7), PGD2, TG(46:1), PC(O-44:5) , LPA C14:0 , PC(O-34:1) , LPC(20:4) , SM(d18:1/24:2) , 8,12-iPF2a IV , TG(46:0), 5-iPF2a VI , TG(52:2) , SM(d18:1/16:0), Ornithine , Histidine , PGD2 , Methyldopa , NO2-aLA (C18:3) , Serine , Arginine , SM(d18:1/23:0), Glyceric acid , Lysine , Glycolic acid , cLPA C18:0 , SM(d18:1/18:0) , LPA C22:4 , LPA C16 , 3-Methoxytyramine , 2,3-dinor-8-iso-PGF2a , PC(O-34:3) , Cis-Aconitic acid , LPA C14:0, PC(O-36:6) , PC(O-38:6) , Putrescine , Homoserine , TG(O-50:0), Carnosine , Sarcosine, O-Acetylserine, PE(38:2) , Gamma-glutamylalanine, 8-iso-PGF2a (15-F2t-IsoP) , LPA C18:3 , Uracil , Citrulline , Histamine , NO2-OA (C18:1) , S-3-Hydroxyisobutyric acid, 2-Aminoadipic acid, TG(50:3), TG(50:1), TG(52:5), Isoleucine, LPC(18:1), TG(52:1) , SM(d18:1/20:1), 1-Methylhistidine , 5-iPF2a VI, TG(51:2), TG(58:9), Histidine, DG(36:3) , Phenylalanine, SM(d18:1/24:2), TG(46:0) , Methionine , LPA C20:1 , TG(48:3), TG(52:3), TG(58:10), TG(58:9) , Methylmalonic acid, TG(50:0), SM(d18:1/25:0) , LPA C18 , Glyceric acid, 8-iso-PGF2a (15-F2t-IsoP), TG(O-50:0) , TG(48:0), Serine, Putrescine, 3-Methoxytyramine, cLPA C18:1 , PE(O-38:5) , LPC(20:4), Gamma-glutamylalanine , 2,3-dinor-8-iso-PGF2a, Cysteine , Carnosine, PC(O-34:2) , SM(d18:1/25:0)
Zhu ⁽⁹⁾ 2016	Case-control	7 AD	No	Karolinska Institutet	brain	LC-MS-MS	RvD5, MaR, PD1, PGD2,

	study	7 CN			tissue		
Xu ⁽¹⁰⁾ 2016	Case-control study	9 AD 9 CN	Yes	New Zealand Neurological Foundation HBB	brain tissue	GC--MS	Glucose, Glucose-6-phosphate, Sorbitol, Fructose, Fructose-6-phosphate, Pentonic acid A, Pentonic acid B, Arabinose, Ribose-5-phosphate, Erythronic acid, Butanediol , β -Hydroxybutyric acid , Lactic acid , 2-hydroxy-3-methylbutyric acid , Threitol , Xylitol , Disaccharide , N-acetylglucosamine , Myo-inositol , Myo-inositol-1-phosphate , Glycerol , Glycerol-2-phosphate , Glycerol-3-phosphate , Glyceric acid , Citric acid , Malic acid , Fumaric acid , Ornithine , Urea , N-acetylglutamic acid , Creatinine , Proline , Lysine , Glycine , Serine , Threonine , Cysteine , beta-Alanine , Aspartic acid , N-acetylaspatic acid , Glutamic acid , GABA , 4-hydroxybutyric acid , Phenylalanine , Tryptophan , Adenine , Uracil , Adenosine-5-monophosphate , Guanosine , Hypoxanthine , Ethanolamine , Methyl-phosphate , Phosphoric acid , 2-Hydroxyglutaric acid , Ascorbic acid
Paglia ⁽¹¹⁾ 2016	Case-control study	21 AD 19 CN	Yes	Banner Sun Health Research Institute	brain tissue	UPLC-HILIC-MS and LC-MS	Acetylaspatic acid, Aspartic acid, Alanine, Asparagine, Pyruvate, Glutamic acid, Glutamine, Succinic acid, Arginine, Proline, SAME, Hydroxyproline, Acetylglutamic acid, Serine, Cystine, Methionine, SAH, Threonine, Choline, Tryptophan, Pentose 5-phosphate, ADP-ribose, ADP, AMP, GMP, Guanosine, IMP, Uric acid, Xanthine, Xanthosine, Hypoxanthine, Inosine, Valine, Pantothenic acid, aspartate, malate, citrate, glutamate Arginine and proline metabolism, Alanine, aspartate and glutamate metabolism, Glycine, serine and threonine

							metabolism, Purine metabolism, Cysteine and methionine metabolism, Pantothenate and CoA biosynthesis
Nasaruddin (12)2016	Case-control study	14 AD 15 CN	Yes	Newcastle Brain Tissue Resource	brain tissue	GC-MS	Pentadecanoic acid, Palmitic acid, Palmitoleic acid, Heptadecanoic acid, Stearic acid, Elaidic acid, all-cis-11,14,17-eicosatrienoic acid, all-cis-13,16-docosadienoic acid, Docosahexanoic acid
Casanova ⁽¹³⁾ 2016	Nested case-control study	The Baltimore Longitudinal Study of Aging (BLSA): 93 AD 99 CN Age, Gene/Environment Susceptibility-Reykjavik Study (AGES-RS): 100 AD 100 CN	Yes	BLSA and AGES-RS	serum	FIA-MS/MS; HPLC-MS/MS	Propionylcarnitine, Glutaryl carnitine or Hydroxyhexanoylcarnitine, Creatinine, Methionine, Ornithine, Serine, Taurine, Threonine, Glucose, PC aa C36:4, PC aa C38:4, PC ae C30:2, PC ae C42:5, PC ae C44:4, Acetylcarnitine, C5(Isovalerylcarnitine / 2-Methylbutyrylcarnitine / Valerylcarnitine), C5:1-DC(Glutaconylcarnitine / Mesaconylcarnitine), Citrulline, Symmetric dimethylarginine, lysoPC a C16:1 (Lysophosphatidylcholine with acyl residue C16:1) , lysoPC a C18:1 (Lysophosphatidylcholine with acyl residue C18:1) , PC aa C32:3, PC aa C34:3, PC aa C36:3
Gonzalez-Do minguez (14)2016	Case-control study	75 AD 17 MCI 45 CN	Yes	Neurological Service of Hospital Juan Ramón Jiménez	serum	UPLC-MS	LPE (16:0), LPE (18:2), LPC (16:1), LPC (16:0), LPC (O-18:0), LPC (20:5), LPC (22:6), LPC (22:5), PE(16:0/18:0), PC(16:1/16:0), PC(16:0/16:0), PPC(16:0/18:2), PC(15:0/18:2), PC(15:0/18:1), PPE(16:0/22:6), PPE(18:1/20:4), PC(16:0/18:2), PC(16:0/20:3), PC(16:1/22:6), PC(18:0/20:4), PC(20:4/20:4), PC(18:1/22:6), PC(20:4/22:6), sphingosine-1-phosphate, CER(d18:1/16:0), SM(d18:1/12:0), SM(d18:1/14:0), SM(d18:1/16:0), SM(d18:1/18:2), SM(d18:1/18:1),

							SM(d18:1/18:0), Hex-CER(d18:1/16:0), Hex-CER(d18:1/18:0), SULF(d18:1/18:0), Lac-CER(d18:1/14:0), Lac-CER(d18:1/16:1), Lac-CER(d18:1/16:0), Monopalmitin, MG(18:0), palmitoyl-carnitine, inoleyl-carnitine, oleylcarnitine, stearoyl-carnitine, histidine, PAG, oleamide, PREGS
Ciavardelli, D. ⁽¹⁵⁾ 2016	Case-control study	35 AD 38 MCI 34 CN	Yes	memory clinic of the Santa Lucia Foundation (Rome, Italy)	plasma	GC-MS; LC-MS	octanoylcarnitine , decenoylcarnitine, decanoylcarnitine , dodecenoylcarnitine, lauroylcarnitine , tetradecenoylcarnitine, acetylcarnitine , 2-hydroxybutyric acid, tetradecadienoylcarnitine, oleylcarnitine, free carnitine
Yoshida ⁽¹⁶⁾ 2015	Case-control study	32 AD 22 MCI 74 CN	Yes	unknown	urine	LC-MS/MS	creatinine
Vankova ⁽¹⁷⁾ 2016	Case-control study	16 AD 22 CN	Yes	unknown	serum	GC-MS	Pregnenolone sulfate, 17-Hydroxypregnenolonea , 17-Hydroxyprogesteronea, 20 α -Dihydroprogesterone , Androstenedione , Allopregnanolone , Allopregnanolone sulfate, Isopregnanolone , Pregnanolone , Conjugated pregnanolone, Conjugated 5 β -pregnane-3 α ,20 α -diol, Conjugated 5 α -androstane-3 β ,17 β -diol , Pregnenolone, 17-Hydroxypregnenolone, 16 α -Hydroxypregnenolone, Cortisol, Allopregnanolone, Isopregnanolone, Pregnanolone, Androsterone sulfate, Epiandrosterone sulfate, Epitiocholanolone sulfate, 17-hydroxyprogesterone, 16 α -hydrox-yprogesterone, cortisol, Epiandrosterone sulfate, epitiocholanolone sulfate, conjugated 5 β -androstane-3 α ,17 β -diol, pregnenolone, pregnenolone sulfate, 16 α -hydroxypregnenolone, 16 α -hydroxyprogesterone,

							conjugated pregnanolone , 5 α -Androstane-3 β ,17 β -diol sulfate, 5 β -Androstane-3 α ,17 β -diol sulfate, Epiandrosterone sulfate
Cho ⁽¹⁸⁾ 2006	Case-control study	20 AD 20 CN	Yes	Gongju Geriatric Hospital	plasma	Column-switching HPLC with MS spectrometry	DHEAS
Koal ⁽¹⁹⁾ 2015	Case-control study	50 AD-Like 50 CN	No	unknown	CSF	FIA-MS/MS ; HPLC-MS/MS	SM (d18:1/18:0), SM (d18:1/18:1), SM(OH)C14:1, PC aa C30:0, PC aa C32:0, PC aa C34:1, PC aa C34:4, PC aa C36:1, PC aa C36:6, PC aa C38:4, PC aa C38:5, PC aa C38:6, PC ae C30:1, PC ae C34:0, PC ae C38:2, lysoPC a C16:0, C10:2, C16-OH, C3-DC-M/C5-OH, Ala, Gln, Creatinine
Klavins ⁽²⁰⁾ 2015	Case-control study	43 AD 33 MCI 35 CN	No	the memory clinics at the Department of Psychiatry of Innsbruck Medical University and Hall in Tirol State Hospital	plasma	AbsoluteIDQ p180 Kit (Biocrates Life Sciences)	PC aa C34:4, PC aa C38:3, PC aa C40:5, PC aa C36:6, PC aa C40:6, lysoPC a C18:1, lysoPC a C18:2, glycine, valine
Gonzalez-Do minguez ⁽²¹⁾ 2015	Case-control study	30 AD 30 CN	No	Neurologic service of Hospital Juan Ramón Jiménez (Huelva, Spain)	serum	FIA-APPI-QTOF MS	Palmitoleamide, Palmitamide, Linolenamide, Linoleamide, Oleamide, Stearamide, CER(d18:1/16:1), CER(d18:1/16:0), CER(d18:1/18:1), CER(d18:1/18:0), CER(d18:1/18:0)-1P, CER(d18:1/24:1), DAG(14:1/16:0), DAG(16:0/18:3), DAG(16:0/18:1), DAG(18:3/18:3), DAG(18:3/18:2), DAG(16:0/20:4), DAG(18:2/18:1), Palmitoleicacid, Palmitic acid, Oleic acid, Urea, Alanine, Taurine, Picolinic acid, Creatine, Malic acid, Dopamine, Serotonin
Cui ⁽²²⁾ 2015	Case-control study	33 AD 31 CN	No	Centre of Harbin Elderly Care Service in Heilongjiang Province of	serum	GC-MS	C14:0, C16:0, C18:0, C16:1, C18:1, C18:2, γ -C18:3, C20:2, C22:6, C18:3

				northern China.			
Ansoleaga ⁽²³⁾ 2015	Case-control study	16 AD 4 CN	No	Institute of Neuropathology HUB-ICO-IDIBELL Biobank	brain tissue	LC-MS	guanine, dGMP, glycine, xanthosine, inosine diphosphate, deoxyguanosine; purine metabolism
Wisniewski ⁽²⁴⁾)2013	Case-control study	9 AD 10 CN	Yes	BioRepository Center of NYU-Langone Medical Center	brain tissue	LC-MS	desmosterol
Gonzalez-Do minguez ⁽²⁵⁾ 2014	Case-control study	19 AD 17 CN	No	Neurologic Service of Hospital Juan Ramón Jiménez (all residents in the province of Huelva)	serum	UPLC-ESI-QTOF- MS; UPLC-ICP-MS	LPE(16:0), LPE(18:2), LPE(18:1), LPC(16:0), LPPC(18:1), LPPC(18:0), LPC(18:2), LPC(18:1), LPC(18:0), LPC(20:5), LPC(22:6), PC(16:1/16:1), PC(16:1/16:0), PC(16:0/16:0), PC(16:1/18:3), PC(16:0/18:3), PC(16:0/18:2), PC(16:0/18:1), PC(16:0/18:0), PC(16:0/20:5), PC(18:2/18:2), PC(18:2/18:1), PC(18:1/18:1), PC(18:0/18:0), PC(18:2/20:5) , PC(16:0/22:6), PC(16:0/22:5), PC(18:1/20:4), PC(18:1/20:3), PC(18:0/20:3), PC(18:0/22:6), PE(16:1/20:5), PE(16:0/20:5), PE(18:1/20:5), PE(18:1/20:4), PE(18:2/22:6), PE(18:1/22:6), PE(18:0/22:6), PE(22:6/22:5), PE(22:5/22:4), PPE(16:0/20:5), PPE(16:0/20:4), PPE(18:1/18:2), PPE(18:1/18:1), PPE(16:0/22:6), PPE(18:1/20:4), PPE(18:0/20:4), PPE(18:1/22:6), PPE(18:0/22:6), PPC(16:0/22:6), PPC(18:1/20:4), PPC(18:0/20:4), PPC(18:1/22:6), PPC(18:0/22:6)
Gonzalez-Do minguez ⁽²⁶⁾ 2014	Case-control study	42 AD 14 MCI 37 CN	Yes	Neurological Service of Hospital Juan Ram'on Jim'enez	serum	CE-ESI-TOF-MS	Choline, Creatinine, Creatine, Asparagine, Proline betaine, Methionine, Histidine, Carnitine, Gly Val, N-acetyl-spermidine, Asymmetric dimethyl-Arginine, Leu Pro, C5-Carnitine, Hcy-Cys, Glu Gln, C8-carnitine, Phe Phe, C10:1-carnitine,

							C10:0-carnitine, Tripeptide
Liu ⁽²⁷⁾ 2014	Case-control study	20 AD 20 MCI 20 CN	No	Shengjing Affiliated Hospital, China Medical University	plasma	UPLC-MS	L-phenylalanine, L-phenylalanine fragment, Tryptophan fragment, Progesterone, Phytosphingosine, Dihydrosphingosine, LPC C 18:2, LPC C 20:4, LPC C 16:0, LPC C 18: 1, LPC C 18: 0,
Gonzalez-Do minguez ⁽²⁸⁾ 2014	Case-control study	22 AD 18 CN	No	Patients were newly diagnosed of sporadic Alzheimer's disease by the Neurologic Service of Hospital Juan Ramón Jiménez	serum	DIMS	LPC(16:0), LPC(18:1), LPC(18:0), LPC(20:5), PPE(16:0/22:6), PPE(18:1/20:4), PPE(18:0/20:4), PPE(18:1/22:6), PPE(18:0/22:6), PC(16:0/18:3), PC(16:0/18:2), PC(16:0/18:1), PC(16:0/18:0), PC(16:0/20:5), PC(18:2/18:2), PC(18:2/18:1), PC(18:2/18:0), PPC(16:0/22:6), PPC(16:0/22:5), PPC(18:1/22:6), PC(16:0/22:6), PC(18:1/20:4), PC(18:0/22:6), Caprylic acid, Capric acid, Lauric acid, Myristic acid, Palmitoleic acid, Palmitic acid, Linoleic acid, Docosahexaenoic acid, Leukotriene B4, Prostaglandin, Choline, Valine, Creatine, Glutamine, Glutamate, Dopamine, Histidine, Carnitine, Arginine, N-acetyl glutamine, Glucose, GPCCh
Trushina E ⁽²⁹⁾ 2013	Case-control study	15 AD 15 MCI 15 CN	No	MCSA and ADRC	plasma and CSF	UPLC-ToF-MS	Methylglyoxal, Lactaldehyde, 2-Pyrrolidinone , Acetoin, Succinic anhydride, Indole, Vigabatrin, DL-Ornithine, N-Acetylarylamine, Urocanic acid, 1-Aminocyclohexanecarboxylic acid, Propionylglycine methyl ester, 2-oxo-4-hydroxy-hexanoic acid, 5,7-nonadienoic acid, 2-Methylbutyrylglycine , Phenylalanine, Terephthalic acid, ACECLIDINE, Hippuric acid, 2,4-DINITROPHENOL, Indoleacrylic acid, 8-Amino-7-oxononanoate, Asymmetric dimethylarginine, PYROGALLIN, Tryptophan, 10-hydroxy-11-dodecenoic

							acid, 12-amino-dodecanoic acid, EUPATORIOCHROMENE, 9,12-dioxo-dodecanoic acid, Glu Ser , 3E,13Z-octadecadien-1-ol, Ser Asp Gly, 1-Methyladenosine, 5-octadecylenic acid - 1.9778987, 1,3-DIPROPYL-8-CYCLOPENTYLXANTHINE [DPCPX], Isorhamnetin, Val Ser Lys , Anandamide (20:2, n-6), 1-octadecanoyl-rac-glycerol, Testosterone sulfate - 0.8743172, Cys Tyr Cys, 3beta,4beta-Dihydroxy-5beta-cholan-24-oic Acid, 2beta,3beta-Dihydroxy-6-oxo-5alpha-chol-7-en-24-oic Acid, Trp Gly Phe, Met His Lys, (24S)-1alpha,24-dihydroxy-22-oxa-20-epivitamin D3 / (24S)-1alpha,24-dihydroxy-22-oxa-20-epicholecalc, 3alpha,6alpha,12alpha-Trihydroxy-7-oxo-5beta-cholan-24-oic Acid, 25-hydroxy-26,27-dimethylvitamin D3 / 25-hydroxy-26,27-dimethylcholecalciferol, (17Z)-1alpha,25-dihydroxy-26,27-dimethyl-17,20,22,22,23,2 3-hexadehydrovitamin D3 / (17Z)-1alpha,25-d, 27-nor-5b-cholestane-3a,7a,12a,24,25-pentol, (23R,25R)-1alpha,25-dihydroxyvitamin D3 26,23-lactone / (23R,25R)-1alpha,25-dihydroxycholecalciferol, Glycoursodeoxycholic acid, Ritodrine glucuronide, Met Trp Gln, 6alpha-Hydroxycasterone , Netilmicin, 1beta,25-dihydroxy-2beta-(3-hydroxypropoxy)vitamin D3 / 1beta,25-dihydroxy-2beta-(3-hydroxypropoxy)c, 1-Hydroxyvitamin D3 3-D-glucopyranoside, Biliverdin IX ,
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							Bilirubin, GlcAbeta-Cer(d18:1/18:0), GPEtn(18:1(11Z)/18:1(9Z))[U] , GPEtn(20:4(5Z,8Z,11Z,14Z)/20:4(5Z,8Z,11Z,14Z))[U], GPGro(17:0/20:4(5Z,8Z,11Z,14Z)), GPEtn(O-16:0/22:5(4Z,7Z,10Z,13Z,16Z)), Acetoacetic acid, Deoxyadenosine, Fumaric acid, Proline, Pyruvic acid, Pyroglutamic acid , 2-Methylbutyrylglycine, 2-Methyl-3-ketovaleric acid, 2-Furoic acid, N-Acetyl-a-neuraminic acid, Dehydroascorbic acid , 5-(hydroxymethyl)- 2-Furancarboxylic acid , Testosterone sulfate, Diacetyl , Diethanolamine, Ne-Methyl-L-lysine, Lecanoric acid, (S)-2-Hydroxyglutarate, 4-Hydroxy-L-threonine, Acetazolamide, Isoniazid, Pyrimethamine, Pirenzepine, ETHOPROPAZINE, L-Aspartic acid b-semialdehyde, COTARNINE, 8-Amino Caprylic acid, Bis (2-hydroxypropyl) amine, Allocortol, diethyltoluamide, 20alpha-Dihydroprednisolone, Gualenate (Sodium Gualenate), N,N-Didemethylchlorpromazine, MYCOPHENOLIC ACID, TUBAIC ACID, AMBELLINE, 7alpha-(Thiomethyl)spironolactone, L-Glutamic acid dibutyl ester, BERGENIN, CITROPTEN, O-Desmethylnaproxen , Embelin , Phenoperidine, Idebenone Metabolite (Benzenehexanoic acid, 2,5-dihydroxy-3,4-dimethoxy-6-methyl-) + 5.8371787, DIALLYL SULFIDE, 4-Methylumbelliferyl beta-D-glucuronide, 1,3-Glyceryl dinitrate, Glycolate,
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							METHYL 7-DESHYDROXYPYROGALLIN-4-CARBOXYLATE, Ethosuximide, 7-hydroxy Tetranor Iloprost, Oxaloglutarate, Methoxsalen Metabolite, Met Glu Lys, Met Ala His , Iridotrial glucoside, Imidazolone, EPICATECHIN PENTAACETATE, dodecanamide, clavirin I, a-hydroxybutyrate, 6,7-DICHLORO-3-HYDROXY-2-QUINOXALINECARBOXYLIC ACID, 2-ISOPROPYL-3-METHOXYCINNAMIC ACID, 10-hydroxy-8E-Decene-2,4,6-triynoic acid, (R)-3-Methyl-2-oxobutanoate, (24S)-1 alpha,24-dihydroxy-22-oxavitamin D3 / (24S)-1 alpha,24-dihydroxy-22-oxacholecalciferol + 2.8750935, (22R)-1 alpha,22,25-trihydroxy-23,24-tetradehydro-24a,24b-dihomo-20-epivitamin D3 / (22R)-1 alpha,22,2, (22E,24E)-1 alpha,25-dihydroxy-22,23,24,24a-tetradehydro-2 4a-homovitamin D3 / (22E,24E)-1 alpha,25-dih, Azatadine, N-Acetylcadaverine, VD 2656, a-hydroxyisovalerate, Hydroxyhydroquinone, (22R)-1 alpha,22,25-trihydroxy-26,27-dimethyl-23,24-tetradehydro-24a-homo-20-epivitamin D3 / (22R)-1a + 1.1406572, L-2-Aminoadipic acid, p-Hydroxyaniline, 5-oxo-7-decynoic acid, (23R)-1 alpha,23,25-trihydroxy-24-oxovitamin D3 / (23R)-1 alpha,23,25-trihydroxy-24-oxocholecalciferol, Ala Leu, Estradiol valerate, Trp Ala Ile, Diaminopimelic acid,
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							N4-Acetylsulfapyridine, 1alpha,25-dihydroxy-11beta-phenylvitamin D3 / 1alpha,25-dihydroxy-11beta-phenylcholecalciferol, epsilon-Caprolactam , N-arachidonoyl D-serine, Purine, Phe Val Val, GPSer(16:0/18:1(11Z)), 1alpha,25-dihydroxy-3-deoxy-3-thiavitamin D3 / 1alpha,25-dihydroxy-3-deoxy-3-thiacholecalciferol, Glucosamine , Thr Ser Gln, Ophiobolin A, 1alpha,25-dihydroxy-22-oxavitamin D3 3-hemiglutarate/ 1alpha,25-dihydroxy-22-oxacholecalciferol 3-he, Glu Ser + 1.2297873, QUERCETIN TETRAMETHYL (5,7,3',4') ETHER, Visnagin, clavulone I - 10.898006, Loroxanthin ester/ Loroxanthin dodecenoate, Penicillin G, Ala Thr Pro, Isoquinoline, 5-NITRO-2-PHENYLPROPYLAMINOBENZOIC ACID [NPPB] + 1.8134243, 20-oxo-heneicosanoic acid, Arginine, Indole-3-ethanol , Ile Ser Lys, 5H-Oxireno[4,5]furo[3,2-g][1]benzopyran-5-one, 1a,8b-dihydro-3-methoxy-, Creatinine, Dimethylglycine, 4,7,10,13,16-docosapentaenoic acid, 1-Phenyl-2-(diethylamino)-1-propanol, 4-Hydroxybenzyl cyanide , EMODIC ACID - 4.837887, N-methyl-Gabapentin, Traumatic acid, Acetamide, PTERIN-6-CARBOXYLIC ACID, Asp Asn Glu, 1-eicosanoyl-rac-glycerol, glyceraldehyde, TEGASEROD, 3,6-octadecadiynoic acid, KARANJIN, Acenocoumarol, 5-(hydroxymethyl)-
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							2-Furancarboxylic acid, BEPRIDIL, 4-Pyridoxic acid , 5-octadecylenic acid, 7,12-Dioxo-5beta-cholan-24-oic Acid, Rimiterol, N'-5Z,8Z,11Z,14Z-eicosatetraenoyl-N"-diethyl-ethylenediam ine, 4-dodecynoic acid, Acetoin , 4-undecynoic acid, 5beta-Androstan-3alpha-ol-17-one sulfate - 7.384574, Leu Glu Gln, N(pai)-Methyl-L-histidine, 6-hydroxy-2-hexynoic acid, 8R-hydroxy-9Z-octadecenoic acid, guaifenesin, Biliverdin IX, Queuine, Propionylglycine methyl ester , (22S)-1alpha,22,25-trihydroxy-23,24-tetradehydro-24a,24b-d ihomo-20-epivitamin D3 / (22S)-1alpha,22,2, GPA(21:0/22:6(4Z,7Z,10Z,13Z,16Z,19Z)), Citraconic acid, threo-Isocitric acid , Pyruvic acid , Methionine, Granisetron metabolite , p-Aminobenzoic acid , N-Didesethylquinagolide, dihydro-alpha-ergocryptine, Pro Pro, L-Alanine n-butyl ester, Loratadine, bicyclo-PGE2, 4'-Hydroxyminoxidil, 7,8-Didehydroastaxanthin, ,4-Dihydroxyphenylpropionic acid, 3-Aminopropanal, S-(p-Azidophenacyl)glutathione, 3-(a-Naphthoxy)lactic acid, Adriamycinone, Valine, Isoacitretin , Bifemelane (M4), Acyclovir, 5-Hydroxytryptophan, Mebeverine, 2-Pyrrolidinone, Taurine, 2-Amino-3-methyl-1-butanol, 13,14-dihydro-15-keto-PGF2alpha, Gln Pro Lys, Dimercaprol, 6-Hydroxynicotinic acid, 3-dodecynoic acid, Leu Leu Ala, Asn Gln Gln, Ala Met Lys,
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							Dihydrolevobunolol, 9-pentadecen-1-ol, VALERYL SALYCILATE, 2,5-Dimethoxycinnamic acid, Nalidixic acid, Pyridoxamine , ethylmalonic acid, Glu Ser, alpha,alpha-Trehalose, 3-Hydroxydodecanedioic acid, 5,7-nonadienoic acid , Pyroglutamic acid, D-Biotin, Ala Ala Asp, 1a,1b-dihomo-PGJ2, 5-Hydroxyindoleacetic acid , Embelin, DALBERGIONE, 4-METHOXY-4'-HYDROXY-, (R)-(+)-Citronellal, 3-Dehydroquinic acid, S-Succinyldihydrolipoamide, Gummiferol, Tetrahydrofuran, 9-lauroleic acid, EB 1213, Urocanic acid , 4-hydroxy enanthalic acid, 2-Hydroxy-3-(4-methoxyethylphenoxy)-propanoic acid, cyclohexylammonium, cis-3-(6-Hydroxy-7-methoxy-5-benzofuranyl)acrylic acid - 0.9427811, 5-(4-hydroxy-2,5-dimethylphenoxy)-2,2-dimethyl-Pentanoic acid (Gemfibrozil M1), Tyr Pro, 2H-1-Benzopyran-6-acetic acid, 7-hydroxy-8-methoxy-2-oxo-, Fura-fylline, PURPUROGALLIN, Lorazepam , alpha-ketoglutarate, Lidocaine, Tranexamic acid, phosphatidylethanolamine(20:4(5Z,8Z,11Z,14Z)/20:4(5Z,8Z, ,11Z,14Z))[U], DIHYDROFISSINOLIDE, Met His Lys , L-Urobilin, 2,4-DICHLOROPHENOXYBUTYRIC ACID, METHYL ESTER, myo-Inositol, 5beta-Androstan-3alpha-ol-17-one sulfate, phosphatidylethanolamine(18:1(11Z)/18:1(9Z))[U] +
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						2.416716, ARECOLINE, L-gamma-Cyano-gamma-aminobutyric acid, gamma-Hydroxyphenylbutazone glucuronide, Galbeta1-4GlcNAcbeta-Sp, 3alpha,12alpha,25-trihydroxy-5beta-cholestan-7-one, Pizotyline, DL-2-Aminooctanoic acid , thyrotropin releasing hormone, Purine - 5.6426544, epsilon-Caprolactam + 6.236251, (2-Chlorophenyl)diphenylmethane, Phe Ala Arg, Met Glu Cys, CARYLOPHYLLENE OXIDE, Glutaral (Glutaraldehyde), 3-oxo-4-pentenoic acid, N-Acetylputrescine, S-Methylpenicillamine, Creatine, Val Gly, Glutaconic acid, isoamyl nitrite, Uric acid, 5-Acetyl-4-methylthiazole, Doxapram, 3-Hydroxy-4-methoxyphenylacetic acid, methyl 8-[2-(2-formyl-vinyl)-3-hydroxy-5-oxo-cyclopentyl]-octanoate, GPSer(18:0/20:4(5Z,8Z,11Z,14Z)), THIODIGLYCOL, KOBUSONE, 9-amino-nonanoic acid, Uridine, Isoquinoline N-oxide, Cilastatin, 3,3,45-Tetrahydroxystilbene , phosphatidylethanolamineNMe(18:1(9Z)/18:1(9Z))[U], Mannitol, Indole-3-ethanol, 1-(11E-octadecenoyl)-rac-glycerol, Pergolide, 1-Hydroxy-2-naphthoic acid, 3-Methyl-2-oxovaleric acid, EMODIC ACID, Flavin adenine dinucleotide (FAD), PRISTIMEROL, 10,11-epoxy-chlorovulone I, 1-(2-Pyrimidyl)piperazine, AGELASINE, Gibberellin A9, Glucoheptonic acid, 4-hydroxy pelargonic acid,
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							HYDROLYSIS PRODUCT OF BUSSEIN - 1.1705549, phosphatidylethanolamine(O-16:0/22:5(4Z,7Z,10Z,13Z,16Z)), 3-(a-Naphthoxy)lactic acid glucuronide, 9,12-dioxo-dodecanoic acid , 3beta-ACETOXYDEOXYANGOLENSIC ACID, METHYL ESTER, OXOLINIC ACID, Bilirubin , 3'-Methoxy-E,E-dienoestrol, Xanthine , Sedoheptulose, 2-Naphthaleneacetic acid, 6-hydroxy- - 2.938551, phosphatidylethanolamineNMe(18:2(9Z,12Z)/18:2(9Z,12Z)) [U], 7-Hydroxyoctanoic acid, 3,7,12-Trioxochola-1,5-dien-24-oic Acid, 9R-hydroxy-10E-octadecenoic acid, D-Leucic acid, SULBACTAM , 9-chloro-10-hydroxy-hexadecanoic acid + 1.4075756, 4-Pyridoxic acid, Galabiosylceramide (d18:1/12:0), 10-hydroxy-2E,8E-Decadiene-4,6-diynoic acid, phosphatidylethanolamine(18:0/20:4(5Z,8Z,11Z,14Z))[U] - 5.053175, (+/-)-13-HDoHE, Diglycolic acid, Urea, Nalorphine, alpha-hydroxyisobutyrate, Norcodeine, Hypoxanthine, Dehydroascorbic acid, 2-Aminopropanol, threo-Isocitric acid, Propanoic acid, 2-hydroxy-3-[(4-hydroxy-1-naphthalenyl)oxy]-, Vigabatrin , Granisetron metabolite 1, L-gamma-Cyano-gamma-aminobutyric acid , N-gamma-Acetyl-N-2-formyl-5-methoxykynurenamine, 2-Methyl-3-ketovaleric acid , Phenol, Promazine, L-Glutamic acid dibutyl ester , beta-D-Glucopyranosiduronic
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						acid, 2-(1H-indol-4-yloxy)-1-[[[(1-methylethyl)amino]methyl]ethyl - 10.241287, Tyr Tyr Thr, Isoacitrein, L-DOPA, Glucosylceramide (d18:1/20:0), GPEtn(13:0/15:0)[U], D-Leucic acid , 4-Hydroxytacrine, HAEMATOTOXYLIN, 8,13-dihydroxy-9,11-octadecadienoic acid, N2,N2-Dimethylguanosine, Ala Phe Arg, Estrone sulfate, 5-[2-(hydroxymethyl)-5-methylphenoxy]-2,2-dimethyl-Penta noic acid (Gemfibrozil M4), Cyclopentiazide, 3-oxo-dodecanoic acid, dihydroxyacetone phosphate (DHAP), 3-Amino-2-piperidone, 1-heptadecanoyl-2-(9Z-heptadecenoyl)-3-eicosanoyl-sn-glyc erol, N1-Acetylspermidine, Pyrrole-2-carboxylic acid, Catalpol, MERBROMIN, Imidazolone , Pro Lys Pro, Creatinine , 9(S)-HODE-d4, Thr Gly, Asp Glu, BENZANTHRONE , Lactate, beta-Alanine , Benzaldehyde, p-amino-, thiosemicarbazone, 4-Guanidinobutanoate, 4-Aminophenyl 1-thio-beta-D-glucuronide + 2.5971124, cysteine, beta-vinyl acrylic acid, Clonidine Metabolite 3, N1,N4-Diacetylsulfanilamide, Cys Cys Tyr, 1-(7Z,10Z,13Z,16Z-docosatetraenoyl)-2-(7Z,10Z,13Z,16Z,1 9Z-docosapentaenoyl)-sn-glycerol, Allantoin , Octane, Erythrono-1,4-lactone, 3-(Imidazol-4-yl)-2-oxopropyl phosphate, Alfentanil, 3-Hydroxyphenytoin, 1-Hexadecylamine, Arg Cys Cys, Oxazepam, 2-Naphthaleneacetic acid, 6-hydroxy, 4-Hydroxypyridine,
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							O-BENZYL-L-SERINE, (22E,24E,26E)-1alpha,26b-dihydroxy-22,23,24,25,26,26a-hexadehydro-26a,26b-dihomo-27-norvitamin D3 /, B-ureidoisobutyric acid, ANISOMYCIN, N-Acetyl-p-benzoquinonimine, 7E-decen-1-ol, Dihydrokaempferol, Hydromorphone, PGE2alpha dimethylamine, 2-Octenedioic acid, Anthracene, 3E-undecenoic acid, 5-tert-Butyl-4-hydroxymethylfuran-2-carboxylic acid, Gly His, Carbaryl, 5-Methoxyindoleacetate , BUFEXAMAC, Arg Asn Gln, (22R)-1alpha,22,25-trihydroxy-26,27-dimethyl-23,24-tetradehydro-24a-homo-20-epivitamin D3 / (22R)-1a, 3-Methylindole, Chloramphenicol alcohol, 13E,17-octadecadienoic acid , 1alpha,25-dihydroxy-2beta-(5-hydroxypentoxy)vitamin D3 / 1alpha,25-dihydroxy-2beta-(5-hydroxypentoxy, clavulone I, Urea , SULBACTAM, Phenyl sulfate, Asn Gly Ser, Succinic anhydride , DICHLORODIPHENYLTRICHLOROETHANE, Methylphenidate, Tyrosine , Caffeine, Phenytoin-N-glucuronide TCA cycle, Cholesterol and sphingolipids transport, Vitamin d2 metabolism, Polyamine metabolism, Urea cycle, Intracellular cholesterol transport, (L)-Arginine metabolism, cortisone biosynthesis and metabolism, lipid metabolism, FXR-regulated cholesterol and bile acid transport, Lysine
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						metabolism, Bile acid metabolism, Regulation of CFTR gating, Role of VDR in regulation of genes involved in osteoporosis, Vitamin D3 metabolic C-23 and C-24 pathways, Triacylglycerol biosynthesis in obesity and diabetes mellitus, type II, Mechanism of action of DGaT1 in obesity and diabetes mellitus, type II, Aminoacyl-tRNA biosynthesis in mitochondria , Triacylglycerol metabolism p.2, Muscle contraction_nNOS signaling in skeletal muscles, Aminoacyl-tRNA biosynthesis in cytoplasm , tryptophan metabolism, Regulation of lipid MB FXR-dependent negative-feedback regulation of bile acid concentration, Cortisol biosynthesis from cholesterol , Development_Activation of astroglia cell proliferation by ACM3, Fatty Acid Omega Oxidation , Prostaglandin 2 biosynthesis and metabolism, Aspartate and asparagine metabolism, Nicotine metabolism in liver, Cholesterol and sphingolipids transport/transport from Golgi, Glycolysis and gluconeogenesis, FXR-regulated cholesterol and bile acid cellular transport, Saturated fatty acids metabolism, Cortisol BS from cholesterol, saturated fatty acid metabolism, aminoacyl-tRNA biosynthesis in cytoplasm, neurophysiological process_, melatonin signaling, Nicotine MB in liver, Role of Diethylhexyl Phthalate and Tributyltin in fat differentiation, Nitrogen metabolism, Cholesterol metabolism, Arginine metabolism, Bile Acid Biosynthesis, Aminoacyl-tRNA biosynthesis in mitochondrion,
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							Histidine-glutamate-glutamine metabolism, Neurophysiological process_ GABAergic neurotransmission, tryptophan metabolism , Proline metabolism, Saturated fatty acid biosynthesis, Catecholamine metabolism, Muscle contraction_nNOS Signaling in Skeletal Muscle, Acetylcholine biosynthesis and metabolism, Development Activation of astroglial cells proliferation by ACM3, Fatty Acid Omega Oxidation, Nicotine signaling in GABAergic neurons, Neurophysiological process_ ACM1 and ACM2 in neuronal..., Serotonin modulation of dopamine release in nicotine addiction, Transport ACM3 in salivary glands, Development_ACM2 and ACM4 activation of ERK, Regulation of CFTR gating (nomal and CF), HETE and HPETE biosynthesis and metabolism, Neurophysiological process_Role of CDK5 in presynaptic signaling, Role of Diethylhexyl Phthalate and Tributyltin in fat cell differentiation, Phosphatidylinositol metabolism, Aldosterone biosynthesis and metabolism, Transcription role of VDR in regulation of genes involved in osteoporosis, Tyrosine metabolism p.1(dopamine)
Kaddurah-Daouk ⁽³⁰⁾ 2013	Case-control study	40 AD 36 MCI 38 CN	Yes	Penn Memory Center, University of Pennsylvania (Philadelphia,PA, USA) and the Maria de los Santos Health Center (Philadelphia, PA, USA),	CSF	liquid chromatography electrochemical array platform	MET, 5-HIAA, Xanthosine, GSH, VMA, Hypoxanthine, Indole-3-acetic acid, Uric acid, 5-HTP, Kynurenine, TRP

Sato ⁽³¹⁾ 2012	Case-control study	Test set: 10 AD 10 CN validation set: 41 AD 26 MCI 42 CN	Yes	PrecisionMed, Inc. (San Diego, CA)	plasma and CSF	LC/APCI-MS; GC-MS	Desmosterol
Czech ⁽³²⁾ 2012	Case-control study	53 Light to mild AD (MMSE>22) 26 Moderate to Strong AD (MMSE 14-22) 51 CN	Yes	five different clinical centres in Europe: One in Germany, one in France, one in Switzerland, and two in Sweden	CSF	GC-MS; LC-MS/MS	5-Hydroxy-3-indoleacetic acid , Noradrenaline, 3,4-Dihydroxyphenylalanine, 4-Hydroxy-3-methoxy-phenylglycol, Histamine, 21-Hydroxyprogesterone, Cortisol, Normetanephine, Citrulline, Cysteine, Methionine, Ornithine (incl. Arginine, Citrulline), Arabinose, Erythrol, Galactitol, Lyxose, myo-Inositol, Ribonic acid, Sorbitol (incl. Mannitol, Galactitol), scyllo-Inositol, Pyruvate (incl. Phosphoenolpyruvate), Carnitine, Pseudouridine, putative Tartronic acid, Quinic acid (incl. Chlorogenic acid), Salicylic acid, Uric acid, Choline, uridine, 3-methoxy-4-hydroxy phenylglycol (MHPG), dopamine, noradrenaline , normetanephine., sorbitol, tyrosine, phenylalanine, serine, pyruvate, taurine, creatinine, dopamine , ornithine
Ibanez ⁽³³⁾ 2013	Nested case-control study	21 AD 21 MCI-S 12 MCI-AD 21 CN	No	unknown	CSF	RP/UHPLC-TOF MS; HILIC/UHPLC-TOF MS	uracil, xanthine, uridine, tyrosyl-serine (or serinyl-tyrosine), methyl-salsolinol, nonanoylglycine, dopamine-quinone, caproic acid, vanlyglycol, histidine, pipelicolic acid, hydroxyphophinyl-piruvate, creatinine, taurine, C16-sphingosine-1-phosphate, tryptophan, methylthioadenosine

Wang ⁽³⁴⁾ 2012	Case-control study	46 AD 39 CN	No	Centre of Harbin Elderly Care Service	serum	GC-MS	linolenic acid, cis-4,7,10,13,16,19-docosahexaenoic acid, myristic acid, palmitic acid, oleic acid
Oresic ⁽³⁵⁾ 2011	Nested case-control study	37 AD 52 Progressive MCI 91 Stable MCI 46 CN	No	longitudinal study databases gathered in the University of Kuopio	serum	UPLC-MS ; GC GC-TOFMS	PC(16:0/18:2), PI(18:0/20:4), PC(O-18:0/18:2), PC(18:0/20:4), SM(d18:1/24:0), 2-ketobutyric acid, Sitosterol, Ketovaline, Histamine, lactic acid, PC(18:0/18:2), PC(16:0/20:4), PC (16:0/16:0), 2,4-dihydroxybutanoic acid, lysoPC (16:0), PC(16:0/20:5), PC (18:0/20:4) , PC (O-18:1/16:0), ribose-5-phosphate, pyruvic acid pentose phosphate pathway
Kaddurah-Daouk ⁽³⁶⁾ 2011	Case-control study	15 AD 15 CN	Yes	autopsy program of the Joseph and Kathleen Bryan Alzheimer Disease Research Center (Bryan ADRC)	CSF	LC/ECA	tryptophan, indoleacetic acid, Norepinephrine
Han ⁽³⁷⁾ 2011	Case-control study	26 AD 26 CN	Yes	Joseph and Kathleen Bryan Alzheimer's Disease Research Center (Bryan ADRC) and the Department of Psychiatry both at Duke University	plasma	MDMS-SL	N22:1, N20:0, N22:0, N23:0, N23:1, N24:1, N21:0, N24:0, N17:1, N24:2, N18:0, N21:0, N16:0, N26:0, OH-N24:2, OH-N24:1, N28:2, N23:0
Li ⁽³⁸⁾ 2010	Case-control study	20 AD 20 CN	No	Shengjing Affiliated Hospital China Medical University.	plasma	UPLC-MS	Dihydrosphingosine, Tryptophan fragment, LPC C18:2, LPC C18:1, LPC C16:0, LPC C18:0, LPC C20:4, phytosphingosine, hexadecasphinganine
Lee ⁽³⁹⁾ 2007	Case-control study	36 AD 34 CN	No	patients:Gongju Geriatric Hospital.	urine	LC/ESI-MS	Pseudouridine, 1-Methyladenosine, 8-Hydroxy-2'-deoxyguanosine, 3-Methyluridine, N2,

							N2-dimethylguanosine, 2-Deoxyguanosine
Paik ⁽⁴⁰⁾ 2006	Case-control study	4 AD 22 CN	No	unknown	urine	GC-SIM-MS	N1-acetylputrescine, N1-acetylcadaverine, Putrescine, Cadaverine, N1-acetylspermidine, N8-acetylspermidine, Spermidine, N1-acetylspermine, Spermine
Yoshida ⁽⁴¹⁾ 2009	Case-control study	39 AD 25 VD 24 CN	No	Aoisoranosato Geriatric Health Services Facility and the Arimakogen Hospital	plasma	GC-MS	t8-iso-PGF2, Ascorbic acid, Ubiquinol-10 , α-Tocopherol
Kim ⁽⁴²⁾ 2004	Case-control study	34 AD 20 CN	Yes	Gongju Geriatric Hospital	urine	GC-MS	PGF2α, PGF2β
Fonteh ⁽⁴³⁾ 2013	Case-control study	29 40 MCI 79 CN	Yes	The local Institutional Review Board (Huntington Hospital Pasadena CA)	CSF	LC-MS/MS	PC(32a:0), PC(34p:0/34e:1), PC(34a:1), PC(34a:0), PC(36a:1), PC(38a:5), PC(36a:0/38p:6), PC(38a:6), 1-rady1-2-acyl- sn -glycerophosphoethanolamine, 1,2-diacyl- sn -glycerophosphoserine , PE(40p:4/40e:5), PS(34a:3), PS(36a:4)
Wang ⁽⁴⁴⁾ 2005	Case-control study	8 AD 8 CN	Yes	University of Kentucky Alzheimer's Disease Research Center Clinic; All controls were followed longitudinally in the control clinic	nuclear and mitochondrial DNA of frontal, parietal, and temporal lobes and cerebellum from short	GC/MS-SIM	8-hydroxyadenine, 5-hydroxycytosine, fapyadenine, 5-hydroxyuraci, Fapyguanine, 8-hydroxyguanine

					postmortem interval AD brain		
Huang ⁽⁴⁵⁾ 2004	Case-control study	3 AD 3 CN	Yes	unknown	brain tissue	NMR; GC, GC-MS	glucose
Gonzalez-Do minguez ⁽⁴⁶⁾ 2015	Case-control study	8 AD 21 CN	Yes	Neurological Service of Hospital Juan Ramón Jiménez	serum	GC-MS	Valine, Urea, Aspartic acid, Pyroglutamic acid, Glutamine, Phenylalanine, Asparagine, Ornithine, Pipecolic acid, Histidine, Tyrosine, Palmitic acid, Uric acid, Tryptophan, Stearic acid, Cystine, Lactic acid, α-Ketoglutarate, Isocitric acid, Glucose, Adenosine, Cholesterol, Oleic acid Alanine, aspartate and glutamate metabolism, TCA cycle, tryptophan metabolism, arginine and proline metabolism, histidine metabolism, pyruvate metabolism, phenylalanine metabolism
Whiley ⁽⁴⁷⁾ 2014	Case-control study	screen phase: 10 AD 10 MCI 10 CN Validation phase: Phosphatidylcholine analysis: 42 AD 50 MCI 49 control Total plasma fatty acid analysis:	Yes	the AddNeuroMed cohort and the King's College London Dementia Case Register (DCR)	plasma	NMR; LC-MS	PC 16:0/20:5, PC16:0/22:6, PC18:0/22:6, eicosapentaenoic acid

		10 AD 10 MCI 10 control total choline: n=35					
Popp ⁽⁴⁸⁾ 2013	Case-control study	106 AD 87 CN	No	Memory Clinic at the Department of Psychiatry University of Bonn	Plasma and CSF	GC-MS and gas chromatography-flame ionization detection	Cholesterol, 24s-hydroxycholesterol, 27-hydroxycholesterol, lanosterol, lathosterol
Snowden ⁽⁴⁹⁾ 2017	Case-control study	14 AD 15 ASYMAD 14 CN	No	BLSA	brain tissue	LC-MS; GC-MS	Cholesterol, Linoleic Acid, Cholestenol, Docosahexaenoic acid, Carbamic acid, Methylheptadecadiynoic acid, Oleic acid, Palmitic acid, Hexanedioic acid, Dimethylglycine, Guanidobutanoate, Ascorbate, Aminobutanol, Gluconic acid, Cysteine, Aspartate, L-DOPA, Fumaric acid, Linolenic acid, Indoleacetic acid, Eicosapentaenoic acid, Allantoin, Hypoxanthine, Coumaric acid, Adenine, Oxoarginine, Deoxyflurouridine, Arginine, GABA, Methylstearate, Octadecanal, eicosapentaenoic acid, arachidonic acid, docosahexaenoic acid
Guiraud ⁽⁵⁰⁾ 2017	Case-control study	6 AD 6 CN	No	PrecisionMed Inc.	plasma and CSF	UPLC-MS/MS	S-adenosylhomocysteine, S-adenosylmethionine, glycine
Graham ⁽⁵¹⁾ 2015	Nested case-control study	19 MCI-AD 16 MCI 37 CN	Yes	patients: Belfast City Hospital memory clinic; Controls were recruited from groups of volunteers that have previously	plasma	HRMS	4-aminobutanol, Creatine, GABA, L-arginine, L-ornithine, Methylthioadenosine, N1 or N8-acetyl-spermidine, N1,N12-diacetylspermine, N-acetylputrescine, Putrescine, Spermidine, Spermine Lysine metabolism, Tryptophan metabolism, Polyamine

				assisted with studies of this type or were spouses of patients			metabolism, Urea cycle, Phospholipid metabolism p.1, CHOL & Sphingolipid transport, Sat fatty acid biosynthesis, Regulation of lipid metabolism, Glycolysis & GNG p.2, Transport of IC CHO, Niacin-HDL metabolism, Plasmalogen biosynthesis, UMP biosynthesis, GABA biosynthesis& metabolism, PG 2 biosynthesis & metabolism, Glycolysis GNG(short map), L-Arginine metabolism, CHOL sphingolipid transport, Transport of IC CHOL, Glycolysis & GNG p.1, Prostaglandin 2 biosynthesis and metabolism, Ascorbate metabolism, Glycolysis &GNG p.2, Tyrosine metabolism p.1, Catecholamine metabolism, NAE & PL A2 pathway
Kim ⁽⁵²⁾ 2017	Case-control study	205 AD 207 CN	No	patients: Dementia Case Register (DCR) at King's College London and the EU funded AddNeuroMed study; Normal elderly control subjects: non-related family members of AD patients care-givers' relatives social centers for the elderly or GP surgeries	plasma	UPLC-MS	PC36:5, PC38: 6, Cer24:1, Cer16:0, Cer18:0, PC40:6
Qun Liang ⁽⁵³⁾ 2015	Case-control study	256 AD 218 CN	Yes	First Affiliated Hospital Heilongjiang University of Chinese Medicine.	saliva samples	FUPLC-MS	Sphinganine-1-phosphate, Ornithine, Phenyllactic acid, Inosine, 3-Dehydrocarnitine, Hypoxanthine
Andrea	Case-control	30 AD	Yes	MCI/AD Italian prevention	plasma	LC-MS/MS	d18:1/16:0, d18:1/24:0, d18:1/24:1, d18:1/16:0, d18:1/18:0,

Armirotti ⁽⁵⁴⁾ 2014	study	30 MCI 30 CN		project			d18:1/24:1, d18:1/24:1, d18:1/16:0, d18:1/16:0, d18:1/24:1
Iltaf Shah ⁽⁵⁵⁾ 2012	Case-control study	26 untreated AD 44 trrated AD 35 CN	No	memory clinic in East Sussex UK	serum	LC-MS/MS	25OHD2, Vitamin D2, Vitamin D3
Yu Cui ⁽⁵⁶⁾ 2014	Case-control study	46 AD 47 CN	No	Centre of Harbin Elderly Care Service Heilongjiang Province in the North of China	serum	UPLC-QTOF-MS	PGE2α dimethyl amine, Monoiodothyronine, Palmitic amide, (6R)-vitamin D3 6,19- (4-phenyl-1,2,4-triazoline-3,5-dione), Trimethyltridecanoic acid, 1-Methylinosine, 16-bromo-9-hexadecenoic acid, PS(18:1/0:0), LysoPC(18:0), LysoPC(20:3), LysoPC(18:2), Dihydrosphingosine, N-Acetylglutamine, 1α,25-dihydroxy-2α-(3-hydroxypropoxy) vitamin D3, N-Acryloylglycine, Argininosuccinic acid, Dethiobiotin, Isobutyryl-L-carnitine, 2-hydroxy-N-(2-hydroxyethyl)-N,N-dimethyl-1-dodecanaminium, L-aspartyl-4-phosphate, L-glutamine, 5-L-glutamylglycine, azelaic acid, aminopterin, cytidine, acetyl-L-carnitine, stra-1,3,5(10),7-tetraene-3,17α-diol, p-cresol glucuronide, etiocholanolone glucuronide
Muguruma ⁽⁵⁷⁾ 2018	Case-control study	10 AD 10 CN	No	unknown	CSF	UHPLC-MS/MS	anthranilic acid, methionine sulfoxide, N1N8-diacetyl-spermidine, Trp, kynurenine, ornithine, 3-hydroxykyurenine, N1N12-diacetyl-spermine, anthranilate, Phe, diacetyl-spermidine, diacetyl-spermine,
van der Lee ⁽⁵⁸⁾ 2018	Cohort study	1356 AD, 23882 CN	No	ERF, RS,WHII, VUmc ADC, AgeCoDe, EGCUT, FHS, Finrisk97, and DILGOM	plasma	NMR	S-HDL-free cholesterol, M-HDL-phospholipids, DHA, Glutamine

Tukiainen (59)2008	Cohort study	unknown	No	the city of Kuopio	serum	¹ H NMR	valine, lactate, 3-hydroxybutyrate, acetate, glucose
Ellison (60)2017	Case-control study	10 CN 8 PCAD 11 MCI 10 LOAD	Yes	autopsies from the Neuropathology Core of the University of Kentucky Alzheimer's Disease Center (UK-ADC)	DNA of brain tissue	GC-MS	cytosine, 5-methylcytosine, 5-hydroxymethylcytosine
Dayon (61)2017	Case-control study	Cognitively normal (CDR 0) :n = 48 Cognitively impaired(CDR 0.5 or 1): n = 72	Yes	MCI: the memory clinics, departments of psychiatry, and the Leenaards Memory Center, Department of Clinical Neurosciences, University Hospitals of Lausanne (Switzerland). CN: the community through advertisement or among the spouses of memory clinic patients.	CSF and plasma	LC-MS / MS	cystathionine, methionine, SAH, SAM, serine, cysteine, 5-MTHF, cystathionine, glycine, methionine, SAH, SAM, serine, cysteine, Hcy
Fiandaca (62)2015	Cohort study	discovery cohort: 53 normal 18 phenoconverters internal validation: 20 normal 10 phenoconverters	Yes	participation at the University of Rochester and the University of California Irvine	plasma	MRM-SID-MS	PC ae C40:6, PC aa C40:1, PC aa C38:6, PC aa C38:0, PC aa C36:6, lysoPC a C18:2, C3, PC ae C36:4, C10:2, C9, PC ae C42:1, PC aa C38:3, C5, ADMA, Asn, PC aa C34:4, C18:1-OH, PC ae C34:0, C5-OH (C3-DC-M), PC aa C40:5, PC aa C32:0, C16:2, C12:1, C10:1

Ibanez (63)2012	Nested case control study	training set: 19 CN 23 MCI-nonAD 9 MCI-AD 23 AD test set: 4 CN 2 MCI-nonAD 4 MCI-AD 2 AD	No	Karolinska University Hospital	CSF	CE-MS	choline, valine, arginine, tripeptide, suberylglycine, carnitine, dimethy-L-arginine, creatine, serine, hisidine
Ronnemaa (64)2012	Cohort study	baseline: 2009 participants During a 35 year follow-up time: 213 dementia 91 AD 1796 control.	No	ULSAM cohort	serum	GC	Myristic acid, Palmitic acid, Stearic acid, Oleic acid, Linoleic acid
Toledo (65)2017	Cohort study	175 AD 356 MCI 199 CN	No	ADNI-1 cohort	serum	UPLC-MS/MS	PC ae C40:3, PC ae C42:4, PC ae C44:4, SM (OH) C14:1, SM C16:0, SM C20:2, PC ae C36:2
Takayama (66)2015	Case-control	unknown	No	Fukushimura Brain Bank	brain tissue	LC-ESI-MS/MS	L-phenylalanine, L-lactic acid
Shah (67)2014	Case-control	12AD 32CN	No	a memory clinic in East Sussex	serum	LC-MS/MS	24R,25(OH)2D3, 1alpha-25-(OH)2D2

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**Supplementary Table 3. Quality assessment of metabolomics studies included in this
systematic review by QUADOMICS**

First Year	author	Item																
		1	2	3	4a	4b	5	6	7	8	9	10	11	12	13	14	15	16
Varma 2018		Y	NA	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	NA	Y	Y
Marksteiner 2018		Y	NA	Y	Y	Y	Y	?	Y	Y	Y	Y	Y	N	Y	NA	Y	Y
Pan 2017		Y	NA	Y	Y	?	Y	?	Y	Y	Y	Y	Y	N	Y	NA	Y	N
Oresic 2017		Y	NA	Y	Y	Y	Y	?	Y	Y	Y	Y	Y	N	Y	NA	Y	N
Lau 2017		Y	NA	Y	Y	Y	Y	?	?	Y	Y	Y	Y	Y	Y	NA	Y	N
Proitsi 2015		Y	NA	Y	Y	?	Y	?	?	Y	Y	Y	Y	N	Y	NA	Y	Y
Oberacher 2017		Y	NA	Y	Y	Y	Y	?	Y	Y	Y	Y	Y	N	Y	NA	Y	Y
De Leeuw 2017		Y	NA	Y	Y	Y	Y	?	Y	Y	Y	Y	Y	N	Y	NA	Y	Y
Zhu 2016		Y	NA	Y	Y	?	Y	Y	?	Y	Y	Y	N	N	Y	NA	Y	Y
Xu 2016		N	NA	Y	Y	?	Y	Y	Y	Y	Y	Y	N	N	Y	NA	Y	N
Paglia 2016		N	NA	Y	Y	?	Y	?	?	?	Y	Y	N	Y	Y	NA	Y	N
Nasaruddin 2016		N	NA	Y	Y	?	Y	?	Y	Y	Y	Y	N	Y	Y	NA	Y	Y
Casanova 2016		Y	NA	Y	Y	?	Y	Y	Y	Y	Y	Y	Y	N	Y	NA	Y	Y
Gonzalez-Domi nguez 2016		Y	NA	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	N	Y	NA	Y	Y
Ciavardelli, D. 2016		Y	NA	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	NA	Y	N
Yoshida 2015		Y	NA	Y	Y	Y	Y	?	Y	Y	Y	Y	Y	N	Y	NA	Y	N
Vankova 2016		Y	NA	Y	Y	Y	Y	Y	Y	?	Y	Y	Y	N	Y	NA	Y	Y
Cho 2006		Y	NA	Y	Y	?	Y	?	Y	?	Y	Y	Y	N	Y	NA	Y	N
Koal 2015		Y	NA	Y	?	?	Y	?	Y	Y	Y	Y	Y	N	Y	NA	Y	Y
Klavins 2015		Y	NA	Y	Y	Y	Y	?	?	Y	Y	Y	N	N	Y	NA	Y	Y
Gonzalez-Domi nguez 2015		Y	NA	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	NA	Y	Y
Cui 2015		Y	NA	Y	Y	Y	Y	Y	Y	?	Y	Y	Y	N	Y	NA	Y	N
Ansoleaga 2015		Y	NA	Y	Y	Y	Y	?	Y	Y	Y	Y	Y	N	Y	NA	Y	N
Wisniewski 2013		Y	NA	Y	Y	Y	Y	?	?	Y	Y	Y	N	N	Y	NA	Y	N
Gonzalez-Domi nguez 2014		Y	NA	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	NA	Y	N
Gonzalez-Domi nguez 2014		Y	NA	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	NA	Y	Y
Liu 2014		Y	NA	Y	Y	Y	Y	?	Y	Y	Y	Y	Y	N	Y	NA	Y	N

Gonzalez-Dominguez 2014	Y	NA	Y	Y	Y	Y	Y	Y	?	Y	Y	Y	N	Y	NA	Y	Y
Trushina 2013	E	Y	NA	Y	Y	?	Y	?	Y	Y	Y	Y	Y	Y	NA	Y	Y
Kaddurah-Daouk 2013		Y	NA	Y	Y	Y	Y	?	Y	Y	Y	Y	N	N	Y	NA	Y
Sato 2012		?	NA	Y	Y	?	Y	?	?	Y	Y	Y	?	N	Y	NA	Y
Czech 2012		Y	NA	Y	Y	Y	Y	?	Y	Y	Y	Y	Y	Y	Y	NA	Y
Ibanez 2013		Y	NA	Y	Y	?	Y	?	?	Y	Y	Y	N	Y	Y	NA	Y
Wang 2012		Y	NA	Y	Y	Y	Y	?	Y	Y	Y	Y	Y	N	Y	NA	Y
Oresic 2011		Y	NA	Y	Y	Y	Y	?	Y	Y	Y	Y	Y	N	Y	NA	Y
Kaddurah-Daouk 2011		Y	NA	Y	Y	?	Y	?	Y	Y	Y	Y	Y	N	Y	NA	Y
Han 2011		Y	NA	Y	Y	?	Y	?	?	Y	Y	Y	N	Y	Y	NA	Y
Li 2010		Y	NA	Y	Y	Y	Y	?	Y	Y	Y	Y	Y	N	Y	NA	Y
Lee 2007		Y	NA	Y	Y	?	Y	?	?	Y	Y	Y	N	Y	Y	NA	Y
Paik 2006		Y	NA	Y	Y	Y	Y	?	Y	Y	Y	Y	Y	N	Y	NA	Y
Yoshida 2009		Y	NA	Y	Y	Y	Y	?	Y	Y	Y	Y	Y	N	Y	NA	Y
Kim 2004		Y	NA	Y	Y	?	Y	?	?	Y	Y	Y	N	N	Y	NA	Y
Fonteh 2013		?	NA	Y	Y	?	Y	?	?	Y	Y	Y	N	N	Y	NA	Y
Wang 2005		?	NA	Y	Y	?	Y	?	?	?	Y	Y	N	N	Y	NA	Y
Huang 2004		Y	NA	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	NA	Y
Gonzalez-Dominguez 2015		Y	NA	Y	Y	Y	Y	?	Y	Y	Y	Y	Y	Y	Y	NA	Y
Whiley 2014		Y	NA	Y	Y	?	Y	?	Y	Y	Y	Y	Y	N	Y	NA	Y
Popp 2013		Y	NA	Y	Y	Y	Y	?	Y	Y	Y	Y	Y	N	Y	NA	Y
Snowden 2017		Y	NA	Y	Y	?	Y	?	Y	Y	Y	Y	Y	Y	Y	NA	Y
Guiraud 2017		N	NA	Y	Y	?	Y	?	?	?	Y	Y	N	Y	Y	NA	Y
Graham 2015		Y	NA	Y	Y	?	Y	?	Y	Y	Y	Y	Y	Y	Y	NA	Y
Kim 2017		Y	NA	Y	Y	?	Y	?	?	Y	Y	Y	N	N	Y	NA	Y
Qun Liang 2015		Y	NA	Y	Y	?	Y	?	Y	Y	Y	Y	Y	Y	Y	NA	Y
Andrea Armirotti 2014		Y	NA	Y	Y	Y	Y	?	Y	Y	Y	Y	Y	Y	Y	NA	Y
Iltaf Shah 2012		Y	NA	Y	Y	Y	Y	?	?	Y	Y	Y	?	N	Y	NA	Y
Yu Cui 2014		Y	NA	Y	Y	Y	Y	?	Y	Y	Y	Y	Y	Y	Y	NA	Y
Muguruma 2018		?	NA	Y	Y	?	Y	?	?	Y	Y	Y	N	Y	Y	NA	Y
van der Lee 2008		Y	NA	Y	Y	Y	Y	?	Y	Y	Y	Y	Y	N	Y	NA	Y
Tukiainen 2008		Y	NA	Y	Y	Y	Y	?	Y	Y	Y	Y	Y	N	Y	NA	Y
Ellison 2017		Y	NA	Y	Y	?	Y	?	Y	Y	Y	Y	Y	N	Y	NA	Y

Dayon 2017	Y	NA	Y	Y	?	Y	Y	Y	Y	Y	Y	Y	N	Y	NA	Y	Y
Fiandaca 2015	Y	NA	Y	Y	Y	Y	?	Y	Y	Y	Y	Y	N	Y	NA	Y	Y
Ibanez 2012	Y	NA	Y	Y	?	Y	?	?	?	Y	Y	Y	Y	Y	NA	Y	Y
Ronnemaa 2012	Y	NA	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	NA	Y	N
Toledo 2017	Y	NA	Y	Y	Y	Y	?	Y	Y	Y	Y	Y	N	Y	NA	Y	Y
Takayama 2015	Y	NA	Y	?	?	Y	?	?	?	Y	Y	?	Y	Y	NA	Y	N
Shah 2014	Y	NA	Y	Y	Y	Y	?	?	Y	Y	Y	Y	N	Y	NA	Y	Y
Y%	88.1	0	100	97.0	56.7	100	22.4	70.2	86.6	100	100	70.2	31.3	100	0	100	44.8
N%	6.0	0	0	0	0	0	0	0	0	0	0	25.4	68.7	0	0	0	55.2
?%	6.0	0	0	3.0	43.3	0	77.6	29.9	13.4	0	0	4.5	0	0	0	0	0
NA%	0	100	0	0	0	0	0	0	0	0	0	0	0	0	100	0	0

Index: Y=criteria achieved, N=criteria not achieved, ?=Unclear, NA=not applicable.

Item 1. Were selection criteria clearly described?

2. Was the spectrum of patients' representative of patients who will receive the test in practice?

3. Was the type of sample fully described?

4. Were the procedures and timing of biological sample collection with respect to clinical factors described with enough detail?

4a. Clinical and physiological factors; 4b. Diagnostic and treatment procedures

5. Were handling and pre-analytical procedures reported in sufficient detail and similar for the whole sample? And, if differences in procedures were reported, was their effect on the results assessed?

6. Is the time period between the reference standard and the index test short enough to reasonably guarantee that the target condition did not change between the two tests?

7. Is the reference standard likely to correctly classify the target condition?

8. Did the whole sample or a random selection of the sample receive verification using a reference standard of diagnosis?

9. Did patients receive the same reference standard regardless of the result of the index test?

10. Was the execution of the index test described in sufficient detail to permit replication of the test?

11. Was the execution of the reference standard described in sufficient detail to permit its replication?

12. Were the index test results interpreted without knowledge of the results of the reference standard?

13. Were the reference standard results interpreted without knowledge of the results of the index test?

14. Were the same clinical data available when test results were interpreted as would be available when the test is used in practice?

15. Were uninterpretable/intermediate test results reported?

16. Is it likely that the presence of over-fitting was avoided?

Supplementary Table 4. Differential metabolites of Alzheimer's disease and their reported frequencies in previous studies

Number	Metabolite Name	HMDB ID	Frenquency	Number	Metabolite Name	HMDB ID	Frenquency ^a
1	L-Tryptophan	HMDB0000929	8 ^[10,8,10,27,32,46,57,66]	416	SM(d18:1/23:0)	HMDB0012105	1 ^[8]
2	L-Phenylalanine	HMDB0000159	7 ^[8,10,27,32,46,57,66]	417	LysoPC(17:0)	HMDB0012108	1 ^[1]
3	Palmitic acid	HMDB0000220	7 ^[12,21,22,28,34,46,49]	418	3-Dehydrocarnitine	HMDB0012154	1 ^[53]
4	L-Arginine	HMDB0000517	7 ^[1,8,11,28,29,32,49]	419	Imidazole acetol-phosphate	HMDB0012236	1 ^[29]
5	Ornithine	HMDB0000214	6 ^[8,10,32,46,53,57]	420	L-Aspartyl-4-phosphate	HMDB0012250	1 ^[56]
6	L-Methionine	HMDB0000696	6 ^[8,11,26,29,30,32]	421	Ubiquinol-10	HMDB0013111	1 ^[41]
7	Hypoxanthine	HMDB0000157	5 ^[10,11,29,49,53]	422	Glutaconylcarnitine	HMDB0013129	1 ^[13]
8	L-Histidine	HMDB0000177	5 ^[8,14,26,28,46]	423	PC(o-14:0/16:1(9Z))	HMDB0013402	1 ^[19]
9	L-Lactic acid	HMDB0000190	5 ^[10,29,35,46,66]	424	PC(o-16:0/20:0)	HMDB0013406	1 ^[1]
10	Oleic acid	HMDB0000207	5 ^[21,22,34,46,49]	425	PC(o-16:0/20:4(8Z, 11Z,14Z,17Z))	HMDB0013407	1 ^[1]
11	Creatinine	HMDB0000562	5 ^[10,19,26,32,33]	426	PC(o-16:0/22:6(4Z, 7Z,10Z,13Z,16Z,19Z))	HMDB0013409	1 ^[8]
12	L-Cysteine	HMDB0000574	5 ^[8,10,29,32,49]	427	PC(o-16:1(9Z)/18:0)	HMDB0013412	1 ^[8]
13	L-Valine	HMDB0000883	5 ^[10,29,35,46,66]	428	PC(o-16:1(9Z)/18:2 (9Z,12Z))	HMDB0013413	1 ^[8]
14	LysoPC(18:1(9Z))	HMDB0002815	5 ^[8,13,20,25,28]	429	PC(o-18:1(11Z)/18:2(9Z,12Z))	HMDB0013425	1 ^[1]
15	Cholesterol	HMDB0000067	4 ^[6,46,48,49]	430	PC(o-18:1(9Z)/20:1 (11Z))	HMDB0013431	1 ^[19]
16	Choline	HMDB0000097	4 ^[11,26,28,32]	431	PC(o-18:1(9Z)/22:0)	HMDB0013433	1 ^[1]
17	D-Glucose	HMDB0000122	4 ^[10,28,45,46]	432	PC(o-20:0/20:4(8Z, 11Z,14Z,17Z))	HMDB0013442	1 ^[7]
18	Glycine	HMDB0000123	4 ^[10,20,23,50]	433	PC(o-22:1(13Z)/20:4(8Z,11Z,14Z,17Z))	HMDB0013451	1 ^[13]
19	L-Glutamic acid	HMDB0000148	4 ^[4,10,11,28]	434	PC(o-22:2(13Z,16Z)/22:3(10Z,13Z,16Z))	HMDB0013456	1 ^[8]
20	L-Serine	HMDB0000187	4 ^[8,10,11,32]	435	PC(o-24:0/18:3(6Z, 9Z,12Z))	HMDB0013458	1 ^[1]
21	L-Aspartic acid	HMDB0000191	4 ^[10,11,46,49]	436	O-Desmethylnapro	HMDB0013989	1 ^[29]

				xen			
22	Taurine	HMDB0000251	4 ^[13,21,29,32]	437	Pyrimethamine	HMDB0014350	1 ^[29]
23	Uric acid	HMDB0000289	4 ^[11,29,32,46]	438	Calcium Gluceptate	HMDB0014471	1 ^[29]
24	Urea	HMDB0000294	4 ^[10,21,29,46]	439	Hydromorphone	HMDB0014472	1 ^[29]
25	L-Glutamine	HMDB0000641	4 ^[11,28,35,46]	440	Ethopropazine	HMDB0014536	1 ^[29]
26	Palmitoleic acid	HMDB0003229	4 ^[12,21,22,28]	441	Promazine	HMDB0014564	1 ^[29]
27	PC(16:0/18:2(9Z,12Z))	HMDB0007973	4 ^[14,25,28,35]	442	Doxapram	HMDB0014701	1 ^[29]
28	LysoPC(18:0)	HMDB0010384	4 ^[1,56,25,28]	443	Ethosuximide	HMDB0014731	1 ^[29]
29	2-Hydroxybutyric acid	HMDB0000008	3 ^[8,15,29]	444	Pirenzepine	HMDB0014808	1 ^[29]
30	Ascorbic acid	HMDB0000044	3 ^[10,41,49]	445	Aciclovir	HMDB0014925	1 ^[29]
31	L-Carnitine	HMDB0000062	3 ^[26,28,32]	446	Alfentanil	HMDB0014940	1 ^[29]
32	Creatine	HMDB0000064	3 ^[21,28,29]	447	Oxazepam	HMDB0014980	1 ^[29]
33	Dopamine	HMDB0000073	3 ^[21,28,32]	448	Mycophenolic acid	HMDB0015159	1 ^[29]
34	Fumaric acid	HMDB0000134	3 ^[10,29,49]	449	Vigabatrin	HMDB0015212	1 ^[29]
35	L-Tyrosine	HMDB0000158	3 ^[8,32,46]	450	Pergolide	HMDB0015317	1 ^[29]
36	L-Alanine	HMDB0000161	3 ^[11,19,21]	451	Bepidil	HMDB0015374	1 ^[29]
37	L-Proline	HMDB0000162	3 ^[8,10,11]	452	Acenocoumarol	HMDB0015487	1 ^[29]
38	L-Asparagine	HMDB0000168	3 ^[11,26,46]	453	Cilastatin	HMDB0015535	1 ^[29]
39	L-Dopa	HMDB0000181	3 ^[29,32,49]	454	Glutamylglutamine	HMDB0028817	1 ^[26]
40	L-Acetylcarnitine	HMDB0000201	3 ^[13,15,56]	455	Glycyl-Valine	HMDB0028854	1 ^[26]
41	myo-Inositol	HMDB0000211	3 ^[10,29,32]	456	SM C16:1	HMDB0029216	1 ^[1]
42	Pyruvic acid	HMDB0000243	3 ^[11,29,32]	457	Glutaral	HMDB0029599	1 ^[29]
43	Sphinganine	HMDB0000269	3 ^[27,38,56]	458	Arecoline	HMDB0030353	1 ^[29]
44	Uridine	HMDB0000296	3 ^[29,32,33]	459	Aromadendrin	HMDB0030847	1 ^[29]
45	Xanthosine	HMDB0000299	3 ^[11,23,30]	460	Acetamide	HMDB0031645	1 ^[29]
46	PC(16:0/16:0)	HMDB0000564	3 ^[14,19,25]	461	Succinic anhydride	HMDB0032523	1 ^[29]
47	Linoleic acid	HMDB0000673	3 ^[22,28,49]	462	Citropten	HMDB0032952	1 ^[29]
48	Myristic acid	HMDB0000806	3 ^[22,28,34]	463	Octadecanamide	HMDB0034146	1 ^[21]
49	Stearic acid ^b	HMDB0000827	3 ^[12,22,46]	464	Hydroxypropanedioic acid	HMDB0035227	1 ^[32]
50	Histamine	HMDB0000870	3 ^[8,32,35]	465	(R)-Citronellal	HMDB0035820	1 ^[29]
51	Citrulline	HMDB0000904	3 ^[8,13,32]	466	Coumaric acid	HMDB0041592	1 ^[49]
52	N1-Acetylspermidine	HMDB0001276	3 ^[26,29,40]	467	11,14,17-Eicosatrienoic acid	HMDB0060039	1 ^[12]
53	Alpha-Linolenic acid	HMDB0001388	3 ^[22,34,49]	468	Linoleamide	HMDB0062656	1 ^[21]
54	Docosahexaenoic acid	HMDB0002183	3 ^[28,34,49]	469	8-Amino-7-oxononanoate	METPA0126	1 ^[29]
55	PC(18:2(9Z,12Z)/20:2(11Z,14Z))	HMDB0008145	3 ^[1,13,19]	470	Benzene-1,2,4-triol	METPA0328	1 ^[29]
56	LysoPC(16:0)	HMDB0010382	3 ^[14,25,28]	471	1-Hydroxy-2-napthoate	METPA0374	1 ^[29]
57	LysoPC(20:5(5Z,8Z,1	HMDB0010397	3 ^[14,25,28]	472	epsilon-Caprolacta	METPA0843	1 ^[29]

	1Z,14Z,17Z))				m		
58	PPE(18:1/20:4)	/	3 ^[14,25,28]	473	Gibberellin A9	METPA1064	1 ^[29]
59	PPE(16:0/22:6)	/	3 ^[14,25,28]	474	Anthracene	METPA1122	1 ^[29]
60	PPE(18:1/22:6)	/	3 ^[25,28,29]	475	12-amino-dodecanoic acid	/	1 ^[29]
61	Alpha-ketoisovaleric acid	HMDB0000019	2 ^[29,35]	476	10-hydroxy-8E-Decene-2,4,6-triynoic acid	/	1 ^[29]
62	Adenine	HMDB0000034	2 ^[10,49]	477	10-hydroxy-2E,8E-Decadiene-4,6-dienoic acid	/	1 ^[29]
63	Adenosine monophosphate	HMDB0000045	2 ^[10,11]	478	10-hydroxy-11-dodecenoic acid	/	1 ^[29]
64	Beta-Alanine	HMDB0000056	2 ^[10,29]	479	10,11-epoxy-chlorovulone I	/	1 ^[29]
65	Cortisol	HMDB0000063	2 ^[17,32]	480	1,3-Glycerol dinitrate	/	1 ^[29]
66	Deoxyguanosine	HMDB0000085	2 ^[23,39]	481	1,3-DIPROPYL-8-CYCLOPENTYLXANTHINE ^[DPCPX]	/	1 ^[29]
67	Dimethylglycine	HMDB0000092	2 ^[29,49]	482	1,2-diacyl-sn-glycerophosphoserine	/	1 ^[43]
68	Citric acid	HMDB0000094	2 ^[10,11]	483	1-(2-Pyrimidyl)pipeazine	/	1 ^[29]
69	Gamma-Aminobutyric acid	HMDB0000112	2 ^[10,49]	484	1-(11E-octadecenoyl)-rac-glycerol	/	1 ^[29]
70	Glycolic acid	HMDB0000115	2 ^[8,29]	485	(SM (OH) C14:1	/	1 ^[1]
71	Guanosine	HMDB0000133	2 ^[10,11]	486	(6R)-vitamin D3 6,19-(4-phenyl-1,2,4-triazoline-3,5-dione)	/	1 ^[56]
72	Glyceric acid	HMDB0000139	2 ^[8,10]	487	(2-Chlorophenyl)diphenylmethane	/	1 ^[29]
73	L-Threonine	HMDB0000167	2 ^[10,11]	488	(24S)-1alpha,24-dihydroxy-22-oxavitamin D3 / (24S)-1alpha,24-dihydroxy-22-oxacholecalciferol	/	1 ^[29]
74	L-Lysine	HMDB0000182	2 ^[8,10]	489	(23R,25R)-1alpha,25-dihydroxyvitamin D3 26,23-lactone / (23R,25R)-1alpha,2	/	1 ^[29]

75	L-Cystine	HMDB0000192	2 ^[8,10]	490	5-dihydroxycholecalciferol (22S)-1alpha,22,25-trihydroxy-23,24-tetradehydro-24a,24b-dihomo-20-epivitamin D3 /	/	1 ^[29]
76	Inosine	HMDB0000195	2 ^[11,53]	491	(22S)-1alpha,22,25-trihydroxy-23,24-tetradehydro-24a,24b-dihomo-20-epivitamin D3 /	/	1 ^[29]
77	Indoleacetic acid	HMDB0000197	2 ^[36,49]	492	(22R)-1alpha,22,25-trihydroxy-23,24-tetradehydro-24a,24b-dihomo-20-epivitamin D3 /	/	1 ^[29]
78	Norepinephrine	HMDB0000216	2 ^[32,36]	493	(22E,24E,26E)-1alpha,26b-dihydroxy-22,23,24,25,26,26a-hexadehydro-26a,26b-dihomo-27-norvitamin D3 /	/	1 ^[29]
79	Sorbitol	HMDB0000247	2 ^[10,32]	494	(+/-)-13-HDoHE	/	1 ^[17]
80	Serotonin	HMDB0000259	2 ^[1,21]	495	16a-hydroxyprogesterone	/	1 ^[56]
81	Pyroglutamic acid	HMDB0000267	2 ^[29,46]	496	16-bromo-9-hexadecenoic acid	/	1 ^[17]
82	Xanthine	HMDB0000292	2 ^[11,29]	497	17-Hydroxypregnenolone	/	1 ^[17]
83	Uracil	HMDB0000300	2 ^[8,10]	498	17-Hydroxyprogesterone	/	1 ^[29]
84	Allantoin	HMDB0000462	2 ^[29,49]	499	1a,1b-dihomo-PGJ2	/	1 ^[56]
85	L-Arabinose	HMDB0000646	2 ^[10,32]	500	1a,25-dihydroxy-2a-(3-hydroxypropoxy) vitamin D3	/	1 ^[67]
86	Malic acid	HMDB0000744	2 ^[10,21]	501	1alpha-25-(OH)2D2	/	1 ^[29]
87	5-Hydroxyindoleacetic acid	HMDB0000763	2 ^[30,32]	502	1-heptadecanoyl-2-(9Z-heptadecenoyl)-3-eicosanoyl-sn-glycerol	/	1 ^[29]
88	Pseudouridine	HMDB0000767	2 ^[32,39]	503	1-hexadecylamine	/	1 ^[5]
89	Pregnenolone sulfate	HMDB0000774	2 ^[14,17]	504	1-phenantherol	/	1 ^[43]
					1-radyl-2-acyl- sn-glycerophosphoeth	/	

90	N-Acetyl-L-aspartic acid	HMDB0000812	2 ^[10,11]	505	anolamine 2,3-dinor-8-iso-PG F2a	/	1 ^[8]
91	S-Adenosylhomocysteine	HMDB0000939	2 ^[11,50]	506	2,4-DICHLOROPHENOXYBUTYRIC ACID, METHYLESTER	/	1 ^[29]
92	N-Acetylglutamic acid	HMDB0001138	2 ^[10,11]	507	2,4-DINITROPHENOL	/	1 ^[29]
93	S-Adenosylmethionine	HMDB0001185	2 ^[11,50]	508	2,5-Dimethoxycinnamic acid	/	1 ^[29]
94	Spermidine	HMDB0001257	2 ^[1,40]	509	20alpha-Dihydroprenolone	/	1 ^[29]
95	SM(d18:1/18:0)	HMDB0001348	2 ^[8,14]	510	24R,25(OH)2D3	/	1 ^[67]
96	Prostaglandin D2	HMDB0001403	2 ^[8,9]	511	25-hydroxy-26,27-dimethylvitamin D3 / 25-hydroxy-26,27-dimethylcholecalciferol	/	1 ^[29]
97	Putrescine	HMDB0001414	2 ^[8,40]	512	25OHD2	/	1 ^[55]
98	Vinyglycol	HMDB0001490	2 ^[32,33]	513	2-Aminoadipic	/	1 ^[8]
99	Eicosapentaenoic acid	HMDB0001999	2 ^[47,49]	514	2-Aminopropanol	/	1 ^[29]
100	Oleamide	HMDB0002117	2 ^[14,21]	515	2beta,3beta-Dihydroxy-6-oxo-5alpha-chole-7-en-24-oic Acid	/	1 ^[29]
101	Desmosterol	HMDB0002719	2 ^[24,31]	516	2-Hydroxy-3-(4-methoxyethylphenoxy)-propanoic acid	/	1 ^[29]
102	1-Methyladenosine	HMDB0003331	2 ^[29,39]	517	2-Hydroxyglutaric acid	/	1 ^[10]
103	Phytosphingosine	HMDB0004610	2 ^[27,38]	518	2-hydroxy-N-(2-hydroxyethyl)-N,N-dimethyl-1-dodecanaminium,	/	1 ^[56]
104	N2,N2-Dimethylguanidine	HMDB0004824	2 ^[29,39]	519	2-ISOPROPYL-3-METHOXYCINNAMIC ACID	/	1 ^[29]
105	Ceramide (d18:1/16:0)	HMDB0004949	2 ^[14,21]	520	2-Naphthaleneacetic acid, 6-hydroxy	/	1 ^[29]
106	N-Acetylglutamine	HMDB0006029	2 ^[28,56]	521	2-oxo-4-hydroxyhexanoic acid	/	1 ^[29]
107	PC(14:0/20:4(8Z,11Z	HMDB0007884	2 ^[19,20]	522	3-(a-Naphthoxy)lact	/	1 ^[29]

	,14Z,17Z))				tic acid		
108	PC(16:0/18:0)	HMDB0007970	2 ^[25,28]	523	3-(a-Naphthoxy)lac tic acid glucuronide	/	1 ^[29]
109	PC(16:0/18:1(11Z))	HMDB0007971	2 ^[25,28]	524	3,7,12-Trioxochola- 1,5-dien-24-oic Acid	/	1 ^[29]
110	PC(16:0/18:3(6Z,9Z, 12Z))	HMDB0007974	2 ^[25,28]	525	3alpha,12alpha,25-t rihydroxy-5beta-ch olestan-7-one	/	1 ^[29]
111	PC(16:0/20:5(5Z,8Z, 11Z,14Z,17Z))	HMDB0007984	2 ^[25,28]	526	3alpha,6alpha,12alp ha-Trihydroxy-7-ox o-5beta-cholan-24- oic Acid	/	1 ^[29]
112	PC(16:0/22:6(4Z,7Z, 10Z,13Z,16Z,19Z))	HMDB0007991	2 ^[25,28]	527	3beta-ACETOXYD EOXYANGOLENS IC ACID, METHYL ESTER	/	1 ^[29]
113	PC(16:1(9Z)/16:0)	HMDB0008001	2 ^[14,25]	528	3E,13Z-octadecadie n-1-ol	/	1 ^[29]
114	PC(18:0/20:4(5Z,8Z, 11Z,14Z))	HMDB0008048	2 ^[14,35]	529	3-hydroxykyurenin e	/	1 ^[57]
115	PC(18:0/22:6(4Z,7Z, 10Z,13Z,16Z,19Z))	HMDB0008057	2 ^[25,28]	530	3-Hydroxyphenytoi n	/	1 ^[29]
116	PC(18:1(11Z)/20:4(5 Z,8Z,11Z,14Z))	HMDB0008081	2 ^[25,28]	531	3'-Methoxy-E,E-die noestrol	/	1 ^[29]
117	PC(18:2(9Z,12Z)/18: 1(11Z))	HMDB0008136	2 ^[25,28]	532	3-oxo-4-pentenoic acid	/	1 ^[29]
118	PC(18:2(9Z,12Z)/18: 2(9Z,12Z))	HMDB0008138	2 ^[25,28]	533	4-Aminophenyl 1-thio-beta-D-glucu ronide	/	1 ^[29]
119	PC(22:5(4Z,7Z,10Z,1 3Z,16Z)/14:1(9Z))	HMDB0008657	2 ^[19,20]	534	4-hydroxy pelargonic acid	/	1 ^[29]
120	SM(d18:1/16:0)	HMDB0010169	2 ^[8,14]	535	4'-Hydroxyminoxid il	/	1 ^[29]
121	LysoPC(18:2(9Z,12Z)	HMDB0010386	2 ^[25,56]	536	4-Hydroxypyridine	/	1 ^[29]
122	LysoPC(22:6(4Z,7Z,1 0Z,13Z,16Z,19Z))	HMDB0010404	2 ^[14,25]	537	4-Hydroxytacrine	/	1 ^[29]
123	MG(18:0/0:0/0:0)	HMDB0011131	2 ^[14,29]	538	5-[2-(hydroxymethyl)-5-meth ylphenoxy]-2,2-dimethy l-Pentanoic acid (Gemfibrozil M4)	/	1 ^[29]
124	PC(O-16:0/18:2(9Z,1 2Z))	HMDB0011151	2 ^[1,8]	539	5α-Androstane-3β,1 7β-diol sulfate	/	1 ^[17]

125	Palmitic amide	HMDB0012273	2 ^[21,56]	540	5-Acetyl-4-methylthiazole	/	1 ^[29]
126	PC(o-16:0/18:0)	HMDB0013405	2 ^[1,19]	541	5 β -Androstan-3 α -ol-17-one sulfate	/	1 ^[29]
127	PPE(18:0/22:6)	/	2 ^[25,28]	542	5-hydroxycytosine	/	1 ^[44]
128	PPE(18:0/20:4)	/	2 ^[25,28]	543	5-hydroxyuracil	/	1 ^[44]
129	PPC(18:1/22:6)	/	2 ^[25,28]	544	5-iPF2a VI	/	1 ^[8]
130	PPC(16:0/22:6)	/	2 ^[25,28]	545	5-octadecylenic acid	/	1 ^[29]
131	PGE2 α dimethylamine	/	2 ^[29,56]	546	5 β -Androstane-3 α ,17 β -diol sulfate	/	1 ^[17]
132	LPC C20:4	/	2 ^[27,38]	547	6 α -Hydroxycasterone	/	1 ^[29]
133	LPC C18:2	/	2 ^[27,38]	548	7,12-Dioxo-5 β -cholestan-24-oic Acid	/	1 ^[29]
134	LPC C18:1	/	2 ^[27,38]	549	7E-decen-1-ol	/	1 ^[29]
135	LPC C18:0	/	2 ^[27,38]	550	7-hydroxy Tetranorprostaglandin	/	1 ^[29]
136	LPC C16:0	/	2 ^[27,38]	551	8,12-iPF2a IV	/	1 ^[8]
137	Epitiolcholanolone sulfate	/	2 ^[17,29]	552	8,13-dihydroxy-9,11-octadecadienoic acid	/	1 ^[29]
138	1-Methylhistidine	HMDB0000001	1 ^[8]	553	8-Amino Caprylic acid	/	1 ^[29]
139	2-Ketobutyric acid	HMDB0000005	1 ^[35]	554	9(S)-HODE-d4	/	1 ^[29]
140	Deoxycorticosterone	HMDB0000016	1 ^[32]	555	9,12-dioxo-dodecanoic acid	/	1 ^[29]
141	4-Pyridoxic acid	HMDB0000017	1 ^[29]	556	9-amino-nonanoic acid	/	1 ^[29]
142	3-Methoxytyramine	HMDB0000022	1 ^[8]	557	9-chloro-10-hydroxyhexadecanoic acid	/	1 ^[29]
143	(S)-3-Hydroxyisobutyric acid	HMDB0000023	1 ^[8]	558	9R-hydroxy-10E-oxidodecenoic acid	/	1 ^[29]
144	Biotin	HMDB0000030	1 ^[29]	559	Adriamycinone	/	1 ^[29]
145	Carnosine	HMDB0000033	1 ^[8]	560	AGELASINE	/	1 ^[29]
146	Taurocholic acid	HMDB0000036	1 ^[3]	561	Ala Phe Arg	/	1 ^[29]
147	Adenosine	HMDB0000050	1 ^[46]	562	all-cis-13,16-docosadienoic acid	/	1 ^[12]
148	Argininosuccinic acid	HMDB0000052	1 ^[56]	563	Allocortol	/	1 ^[29]
149	Androstenedione	HMDB0000053	1 ^[17]	564	Allopregnanolone sulfate	/	1 ^[17]
150	Bilirubin	HMDB0000054	1 ^[29]	565	AMBELLINE	/	1 ^[29]

151	Acetoacetic acid	HMDB0000060	1 ^[29]	566	Aminobutanal	/	1 ^[49]
152	Pipecolic acid	HMDB0000070	1 ^[46]	567	ANISOMYCIN	/	1 ^[29]
153	cis-Aconitic acid	HMDB0000072	1 ^[8]	568	Arg Cys Cys	/	1 ^[29]
154	Cytidine	HMDB0000089	1 ^[56]	569	Asp Glu	/	1 ^[29]
155	Deoxyadenosine	HMDB0000101	1 ^[29]	570	Benzaldehyde, p-amino-, thiosemicarbazone	/	1 ^[29]
156	Galactitol	HMDB0000107	1 ^[32]	571	BENZANTHRONE	/	1 ^[29]
157	Fructose 6-phosphate	HMDB0000124	1 ^[10]	572	BERGENIN	/	1 ^[29]
158	Glutathione	HMDB0000125	1 ^[30]	573	beta-D-Glucopyran osiduronic acid	/	1 ^[29]
159	Glycerol 3-phosphate	HMDB0000126	1 ^[10]	574	beta-vinyl acrylic acid	/	1 ^[29]
160	Glycerol	HMDB0000131	1 ^[10]	575	bicyclo-PGE2	/	1 ^[29]
161	Guanine	HMDB0000132	1 ^[23]	576	Bifemelane (M4)	/	1 ^[29]
162	Ethanolamine	HMDB0000149	1 ^[10]	577	Bis (2-hydroxypropyl) amine	/	1 ^[29]
163	L-Malic acid	HMDB0000156	1 ^[11]	578	Butanediol	/	1 ^[10]
164	L-Isoleucine	HMDB0000172	1 ^[8]	579	C10:0-carnitine	/	1 ^[26]
165	Inosinic acid	HMDB0000175	1 ^[11]	580	C10:1-carnitine	/	1 ^[26]
166	Isocitric acid	HMDB0000193	1 ^[46]	581	C10:2	/	1 ^[19]
167	Methylmalonic acid	HMDB0000202	1 ^[8]	582	C16-OH	/	1 ^[19]
168	Oxoglutaric acid	HMDB0000208	1 ^[46]	583	C20:2	/	1 ^[22]
169	Pantothenic acid	HMDB0000210	1 ^[11]	584	C22:6	/	1 ^[22]
170	Myo-inositol 1-phosphate	HMDB0000213	1 ^[10]	585	C3-DC-M/C5-OH	/	1 ^[19]
171	N-Acetyl-D-glucosa mine	HMDB0000215	1 ^[10]	586	C5-Carnitine	/	1 ^[26]
172	L-Palmitoylcarnitine	HMDB0000222	1 ^[14]	587	C8-carnitine	/	1 ^[26]
173	Phenol	HMDB0000228	1 ^[29]	588	CARYLOPHYLLE NE OXIDE	/	1 ^[29]
174	Pregnenolone	HMDB0000253	1 ^[17]	589	Catalpol	/	1 ^[29]
175	Succinic acid	HMDB0000254	1 ^[11]	590	CER(d18:1/16:1)	/	1 ^[21]
176	Sarcosine	HMDB0000271	1 ^[8]	591	CER(d18:1/18:0)-1 P	/	1 ^[21]
177	Vanillylmandelic acid	HMDB0000291	1 ^[30]	592	CER(d18:1/18:1)	/	1 ^[21]
178	16-a-Hydroxypregne nolone^b	HMDB0000315	1 ^[17]	593	CER(d18:1/24:1)	/	1 ^[21]
179	3-Amino-2-piperidon e	HMDB0000323	1 ^[29]	594	Cer16:0	/	1 ^[52]
180	Isohomovanillic acid	HMDB0000333	1 ^[29]	595	Cer18:0	/	1 ^[52]
181	2-Methylbutyrylglyci ne	HMDB0000339	1 ^[29]	596	Cer24:1	/	1 ^[52]

182	2-Octenedioic acid	HMDB0000341	1 ^[29]	597	cholesteryl ester 32:0	/	1 ^[6]
183	Erythrono-1,4-lactone	HMDB0000349	1 ^[29]	598	cholesteryl ester 32:4	/	1 ^[6]
184	3-Hydroxybutyric acid	HMDB0000357	1 ^[10]	599	cholesteryl ester 33:6	/	1 ^[6]
185	17a-Hydroxypregnen olone	HMDB0000363	1 ^[17]	600	cholesteryl ester 34:0	/	1 ^[6]
186	17-Hydroxyprogester one	HMDB0000374	1 ^[17]	601	cholesteryl ester 34:6	/	1 ^[6]
187	2-Hydroxy-3-methylb utyric acid	HMDB0000407	1 ^[10]	602	cholesteryl ester40:4	/	1 ^[6]
188	2-Methyl-3-ketovaler ic acid	HMDB0000408	1 ^[29]	603	clavirin I	/	1 ^[29]
189	Adipic acid	HMDB0000448	1 ^[49]	604	Clonidine Metabolite 3	/	1 ^[29]
190	5-Hydroxy-L-tryptop han	HMDB0000472	1 ^[29]	605	cLPA C18:0	/	1 ^[8]
191	3-Methylhistidine	HMDB0000479	1 ^[29]	606	cLPA C18:1	/	1 ^[8]
192	Caprylic acid	HMDB0000482	1 ^[28]	607	conjugated 5α-androstane-3β,1 7β-diol	/	1 ^[17]
193	7-Hydroxyoctanoic acid	HMDB0000486	1 ^[29]	608	conjugated 5β-androstane-3α,1 7β-diol	/	1 ^[17]
194	3-Methyl-2-oxovaleri c acid	HMDB0000491	1 ^[29]	609	Conjugated 5β-pregnane-3α,20α -diol	/	1 ^[17]
195	Aminoadipic acid	HMDB0000510	1 ^[8]	610	Conjugated pregnanolone	/	1 ^[17]
196	Capric acid	HMDB0000511	1 ^[28]	611	COTARNINE	/	1 ^[29]
197	8-Hydroxyadenine	HMDB0000542	1 ^[44]	612	Cyclopentiazide	/	1 ^[29]
198	Elaidic acid	HMDB0000573	1 ^[12]	613	Cys Cys Tyr	/	1 ^[29]
199	PC(18:1(9Z)/18:1(9Z))	HMDB0000593	1 ^[25]	614	Cys Tyr Cys	/	1 ^[29]
200	Erythronic acid	HMDB0000613	1 ^[10]	615	d18:1/16:0	/	1 ^[54]
201	D-Ribulose 5-phosphate	HMDB0000618	1 ^[11]	616	d18:1/18:0	/	1 ^[54]
202	Cholic acid	HMDB0000619	1 ^[3]	617	d18:1/24:1	/	1 ^[54]
203	Glutaconic acid	HMDB0000620	1 ^[29]	618	decenoylcarnitine	/	1 ^[15]
204	D-Leucic acid	HMDB0000624	1 ^[29]	619	Deoxyflurouridine	/	1 ^[49]
205	Gluconic acid	HMDB0000625	1 ^[49]	620	diacetyl-spermidine	/	1 ^[57]
206	Citraconic acid	HMDB0000634	1 ^[29]	621	diacetyl-spermine	/	1 ^[57]
207	Dodecanoic acid	HMDB0000638	1 ^[28]	622	Diglycolic acid	/	1 ^[29]

208	Clionasterol	HMDB0000649	1 ^[35]	623	DIHYDROFISSIN OLIDE	/	1 ^[29]
209	Decanoylcarnitine	HMDB0000651	1 ^[15]	624	dihydroxyacetone phosphate (DHAP)	/	1 ^[29]
210	D-Fructose	HMDB0000660	1 ^[10]	625	Disaccharide	/	1 ^[10]
211	L-Kynurenine	HMDB0000684	1 ^[57]	626	Docosahexanoic acid	/	1 ^[12]
212	L-Leucine	HMDB0000687	1 ^[8]	627	dodecanamide	/	1 ^[29]
213	Isovalerylcarnitine/2- Methylbutyroylcarniti ne/Valerylcarnitine	HMDB0000688 /HMDB000037 8/HMDB00131 28	1 ^[13]	628	dodecenoylcarnitine	/	1 ^[15]
214	4-Hydroxybutyric acid	HMDB0000710	1 ^[10]	629	EMODIC ACID	/	1 ^[29]
215	L-Homoserine	HMDB0000719	1 ^[8]	630	EPICATECHIN PENTAACETATE	/	1 ^[29]
216	4-Hydroxyproline	HMDB0000725	1 ^[11]	631	ethyl 3-cyano-2,3-bis (2,5,-dimethyl-3-thi enyl)-acrylate	/	1 ^[5]
217	Alpha-Hydroxyisobut yric acid	HMDB0000729	1 ^[29]	632	EUPATORIOCHR OMENE	/	1 ^[29]
218	Hydroxykynurenine	HMDB0000732	1 ^[57]	633	fapyadenine	/	1 ^[44]
219	Indoleacrylic acid	HMDB0000734	1 ^[29]	634	Fapyguanine	/	1 ^[44]
220	Isobutyryl-L-carnitin e	HMDB0000736	1 ^[56]	635	Furafylline	/	1 ^[29]
221	Indole	HMDB0000738	1 ^[29]	636	Galabiosylceramide (d18:1/12:0)	/	1 ^[29]
222	3-Hydroxyisovaleric acid	HMDB0000754	1 ^[8]	637	Galbeta1-4GlcNAc beta-Sp	/	1 ^[29]
223	Lithocholic acid	HMDB0000761	1 ^[2]	638	gamma-Hydroxyph enylbutazone glucuronide	/	1 ^[29]
224	Mannitol	HMDB0000765	1 ^[29]	639	GlcAbeta-Cer(d18: 1/18:0)	/	1 ^[29]
225	Phenyllactic acid	HMDB0000779	1 ^[53]	640	Gln	/	1 ^[19]
226	Azelaic acid	HMDB0000784	1 ^[56]	641	Gln Pro Lys	/	1 ^[29]
227	L-Octanoylcarnitine	HMDB0000791	1 ^[15]	642	Glu Ser	/	1 ^[29]
228	Monoiodothyronine	HMDB0000793	1 ^[56]	643	GPCh	/	1 ^[28]
229	Normetanephrene	HMDB0000819	1 ^[32]	644	GPEtn(13:0/15:0) ^[U]	/	1 ^[29]
230	Phenylacetyl glycine	HMDB0000821	1 ^[14]	645	GPGro(17:0/20:4(5 Z,8Z,11Z,14Z))	/	1 ^[29]
231	Propionylcarnitine	HMDB0000824	1 ^[1]	646	GPSer(16:0/18:1(11 Z))	/	1 ^[29]

232	Pentadecanoic acid	HMDB0000826	1 ^[12]	647	GPSer(18:0/20:4(5Z,8Z,11Z,14Z))	/	1 ^[29]
233	Stearoylcarnitine	HMDB0000848	1 ^[14]	648	Granisetron metabolite 1	/	1 ^[29]
234	Ribonic acid	HMDB0000867	1 ^[32]	649	Gualenate	/	1 ^[29]
235	Vitamin D3	HMDB0000876	1 ^[55]	650	Guanidobutanoate	/	1 ^[49]
236	Ergocalciferol	HMDB0000900	1 ^[55]	651	Gummiferol	/	1 ^[29]
237	DL-2-Aminooctanoic acid	HMDB0000991	1 ^[29]	652	H1	/	1 ^[1]
238	Biliverdin	HMDB0001008	1 ^[29]	653	HAEMATOXYLIN	/	1 ^[29]
239	Dehydroepiandrosterone sulfate	HMDB0001032	1 ^[18]	654	Hcy-Cys	/	1 ^[26]
240	Arachidonic acid	HMDB0001043	1 ^[49]	655	hexadecasphinganine	/	1 ^[38]
241	2'-Deoxyguanosine 5'-monophosphate	HMDB0001044	1 ^[23]	656	Hex-CER(d18:1/16:0)	/	1 ^[14]
242	Leukotriene B4	HMDB0001085	1 ^[28]	657	Hex-CER(d18:1/18:0)	/	1 ^[14]
243	2-Aminobenzoic acid	HMDB0001123	1 ^[57]	658	HYDROLYSIS PRODUCT OF BUSSEIN	/	1 ^[29]
244	Prostaglandin F2a	HMDB0001139	1 ^[42]	659	inoleyl-carnitine	/	1 ^[14]
245	Pyruvaldehyde	HMDB0001167	1 ^[29]	660	Isoquinoline N-oxide	/	1 ^[29]
246	4-Aminophenol	HMDB0001169	1 ^[29]	661	KOBUSONE	/	1 ^[29]
247	Lathosterol	HMDB0001170	1 ^[48]	662	Lac-CER(d18:1/14:0)	/	1 ^[14]
248	Adenosine diphosphate ribose	HMDB0001178	1 ^[11]	663	Lac-CER(d18:1/16:0)	/	1 ^[14]
249	N1-Acetylspermine	HMDB0001186	1 ^[40]	664	Lac-CER(d18:1/16:1)	/	1 ^[14]
250	Flavin adenine dinucleotide	HMDB0001248	1 ^[29]	665	L-Alanine n-butyl ester	/	1 ^[29]
251	N-Acetylarlyamine	HMDB0001250	1 ^[29]	666	Lecanoric acid	/	1 ^[29]
252	Lanosterin	HMDB0001251	1 ^[48]	667	Leu Pro	/	1 ^[26]
253	Spermine	HMDB0001256	1 ^[40]	668	L-gamma-Cyano-gamma-aminobutyric acid	/	1 ^[29]
254	Dehydroascorbic acid	HMDB0001264	1 ^[29]	669	L-Glutamic acid dibutyl ester	/	1 ^[29]
255	ADP	HMDB0001341	1 ^[11]	670	Linolenamide	/	1 ^[21]
256	Purine	HMDB0001366	1 ^[29]	671	LPA C14:0	/	1 ^[8]
257	Diaminopimelic acid	HMDB0001370	1 ^[29]	672	LPA C16	/	1 ^[8]
258	Vaporole	HMDB0001382	1 ^[29]	673	LPA C18	/	1 ^[8]

259	Sphinganine 1-phosphate	HMDB0001383	1 ^[53]	674	LPA C18:3	/	1 ^[8]
260	Guanosine monophosphate	HMDB0001397	1 ^[11]	675	LPA C20:1	/	1 ^[8]
261	Glucose 6-phosphate	HMDB0001401	1 ^[10]	676	LPA C22:4	/	1 ^[8]
262	24-Hydroxycholester ol	HMDB0001419	1 ^[48]	677	LPC (16:1)	/	1 ^[14]
263	Estrone sulfate	HMDB0001425	1 ^[29]	678	LPC (20:5)	/	1 ^[14]
264	Allopregnanolone	HMDB0001449	1 ^[17]	679	LPC (22:5)	/	1 ^[14]
265	Alloepipregnanolone	HMDB0001455	1 ^[17]	680	LPE (16:0)	/	1 ^[14]
266	Prostaglandin F2b	HMDB0001483	1 ^[42]	681	LPE (18:2)	/	1 ^[14]
267	Octane	HMDB0001485	1 ^[29]	682	LPPC(18:0)	/	1 ^[25]
268	Queuine	HMDB0001495	1 ^[29]	683	LPPC(18:1)	/	1 ^[25]
269	Asymmetric dimethylarginine	HMDB0001539	1 ^[26]	684	lyosPC a C16:0	/	1 ^[19]
270	D-Ribose 5-phosphate	HMDB0001548	1 ^[10]	685	MaR1	/	1 ^[9]
271	Progesterone	HMDB0001830	1 ^[27]	686	Mebeverine	/	1 ^[29]
272	Aminopterin	HMDB0001833	1 ^[56]	687	MERBROMIN	/	1 ^[29]
273	N-Acryloylglycine	HMDB0001843	1 ^[56]	688	Met Ala His	/	1 ^[29]
274	D-threo-Isocitric acid	HMDB0001874	1 ^[29]	689	Met Glu Cys	/	1 ^[29]
275	Alpha-Tocopherol	HMDB0001893	1 ^[41]	690	Met Glu Lys	/	1 ^[29]
276	Salicylic acid	HMDB0001895	1 ^[32]	691	Met His Lys	/	1 ^[29]
277	Methionine sulfoxide	HMDB0002005	1 ^[57]	692	Met Trp Gln	/	1 ^[29]
278	Ureidoisobutyric acid	HMDB0002031	1 ^[29]	693	Methoxsalen Metabolite	/	1 ^[29]
279	8-Hydroxyguanine	HMDB0002032	1 ^[44]	694	METHYL 7-DESHYDROXY PYROGALLIN-4- CARBOXYLATE	/	1 ^[29]
280	2-Pyrrolidinone	HMDB0002039	1 ^[29]	695	methyl 8-[2-(2-formyl-vinyl)-3-hydr oxy-5-oxo-cyclopentyl]-oct anoate	/	1 ^[29]
281	N-Acetylputrescine	HMDB0002064	1 ^[29]	696	Methylheptadecadi ynoic acid	/	1 ^[49]
282	27-Hydroxycholester ol	HMDB0002103	1 ^[48]	697	Methyl-phosphate	/	1 ^[10]
283	Phosphoric acid	HMDB0002142	1 ^[10]	698	Methylstearate	/	1 ^[49]
284	N8-Acetylspermidine	HMDB0002189	1 ^[40]	699	N,N-Didemethylchl orpromazine	/	1 ^[29]
285	Picolinic acid	HMDB0002243	1 ^[21]	700	N1,N4-Diacetylsulf anilamide	/	1 ^[29]
286	Dodecanoylcarnitine	HMDB0002250	1 ^[15]	701	N16:0	/	1 ^[37]

287	Heptadecanoic acid	HMDB0002259	1 ^[12]	702	N17:1	/	1 ^[37]
288	N-Acetylcadaverine	HMDB0002284	1 ^[40]	703	N18:0	/	1 ^[37]
289	Cadaverine	HMDB0002322	1 ^[40]	704	N1-acetylputrescine	/	1 ^[40]
290	Stearaldehyde	HMDB0002384	1 ^[49]	705	N1N12-diacetyl-spe rmine	/	1 ^[57]
291	Trimethyltridecanoic acid	HMDB0002396	1 ^[56]	706	N1N8-diacetyl-sper midine	/	1 ^[57]
292	Terephthalic acid	HMDB0002428	1 ^[29]	707	N20:0	/	1 ^[37]
293	Beta-Glycerophospho ric acid	HMDB0002520	1 ^[10]	708	N21:0(ceramide)	/	1 ^[37]
294	6-Hydroxynicotinic acid	HMDB0002658	1 ^[29]	709	N21:0(Sphingomye lin)	/	1 ^[37]
295	1-Methylinosine	HMDB0002721	1 ^[56]	710	N22:0	/	1 ^[37]
296	Androsterone sulfate	HMDB0002759	1 ^[17]	711	N22:1	/	1 ^[37]
297	Testosterone sulfate	HMDB0002833	1 ^[29]	712	N23:0(ceramide)	/	1 ^[37]
298	D-Xylitol	HMDB0002917	1 ^[10]	713	N23:0(Sphingomye lin)	/	1 ^[37]
299	Erythritol	HMDB0002994	1 ^[32]	714	N23:1	/	1 ^[37]
300	O-Acetylserine	HMDB0003011	1 ^[8]	715	N24:0	/	1 ^[37]
301	Isoacitretin	HMDB0003039	1 ^[29]	716	N24:1	/	1 ^[37]
302	Lactaldehyde	HMDB0003052	1 ^[29]	717	N24:2	/	1 ^[37]
303	20a-Dihydroprogester one	HMDB0003069	1 ^[17]	718	N26:0	/	1 ^[37]
304	Quinic acid	HMDB0003072	1 ^[32]	719	N28:2	/	1 ^[37]
305	Gamma-Linolenic acid	HMDB0003073	1 ^[22]	720	N-Acetyl-p-benzoq uinonimine	/	1 ^[29]
306	Sedoheptulose	HMDB0003219	1 ^[29]	721	Nalorphine	/	1 ^[29]
307	Acetoin	HMDB0003243	1 ^[29]	722	Ne-Methyl-L-lysine	/	1 ^[29]
308	8-Hydroxy-deoxygua nosine	HMDB0003333	1 ^[39]	723	N-gamma-Acetyl-N -2-formyl-5-methox ykynurenamine	/	1 ^[29]
309	Symmetric dimethylarginine	HMDB0003334	1 ^[13]	724	NO2-aLA (C18:3)	/	1 ^[8]
310	IDP	HMDB0003335	1 ^[23]	725	NO2-OA (C18:1)	/	1 ^[8]
311	Pectin	HMDB0003402	1 ^[32]	726	Norcodeine	/	1 ^[29]
312	Tryptophanol	HMDB0003447	1 ^[29]	727	O-BENZYL-l-SERI NE	/	1 ^[29]
313	4-Guanidinobutanoic acid	HMDB0003464	1 ^[29]	728	OH-N24:1	/	1 ^[37]
314	Carbamic acid	HMDB0003551	1 ^[49]	729	OH-N24:2	/	1 ^[37]
315	Dethiobiotin	HMDB0003581	1 ^[56]	730	oleylcarnitine	/	1 ^[14]
316	Resolvin D5	HMDB0004038	1 ^[9]	731	Oxoarginine	/	1 ^[49]
317	D-Threitol	HMDB0004136	1 ^[10]	732	OXOLINIC ACID	/	1 ^[29]
318	L-Urobilin	HMDB0004159	1 ^[29]	733	Palmitoleamide	/	1 ^[21]

319	3,3',4'5-Tetrahydroxy stilbene	HMDB0004215	1 ^[29]	734	PC 16:0/20:5	/	1 ^[47]
320	Pyrrole-2-carboxylic acid	HMDB0004230	1 ^[29]	735	PC aa C32:3	/	1 ^[13]
321	Imidazolone	HMDB0004363	1 ^[29]	736	PC aa C36:1	/	1 ^[19]
322	Etiocholanolone glucuronide	HMDB0004484	1 ^[56]	737	PC aa C40:5	/	1 ^[1]
323	3-Methyluridine	HMDB0004813	1 ^[39]	738	PC(18:2/20:5)	/	1 ^[25]
324	Proline betaine	HMDB0004827	1 ^[26]	739	PC(32a:0)	/	1 ^[43]
325	Ceramide (d18:1/18:0)	HMDB0004950	1 ^[21]	740	PC(34a:1)	/	1 ^[43]
326	Glucosylceramide (d18:1/20:0)	HMDB0004973	1 ^[29]	741	PC(34p:0/34e:1)	/	1 ^[43]
327	8-Isoprostaglandin F2a	HMDB0005083	1 ^[8]	742	PC(36a:0/38p:6)	/	1 ^[43]
328	TG(16:0/16:0/16:0)	HMDB0005356	1 ^[8]	743	PC(36a:1)	/	1 ^[43]
329	TG(16:0/16:0/18:0)	HMDB0005357	1 ^[8]	744	PC(38a:5)	/	1 ^[43]
330	TG(16:0/16:0/16:1(9 Z))	HMDB0005359	1 ^[8]	745	PC(38a:6)	/	1 ^[43]
331	TG(16:0/16:0/18:1(9 Z))	HMDB0005360	1 ^[8]	746	PC(O-18:0/18:2)	/	1 ^[35]
332	TG(16:0/16:0/20:1(11 Z))	HMDB0005361	1 ^[8]	747	PC(O-36:6)	/	1 ^[8]
333	TG(16:0/16:0/18:2(9 Z,12Z))	HMDB0005362	1 ^[8]	748	PC16:0/22:6	/	1 ^[47]
334	TG(16:0/16:0/20:4(5 Z,8Z,11Z,14Z))	HMDB0005363	1 ^[8]	749	PC18:0/22:6	/	1 ^[47]
335	TG(16:0/18:0/18:2(9 Z,12Z))	HMDB0005369	1 ^[8]	750	PC36:5	/	1 ^[52]
336	TG(16:0/16:1(9Z)/16:1(9Z))	HMDB0005376	1 ^[8]	751	PC38:6	/	1 ^[52]
337	TG(16:0/16:1(9Z)/18:2(9Z,12Z))	HMDB0005379	1 ^[8]	752	PC40:6	/	1 ^[52]
338	TG(16:0/16:1(9Z)/20:4(5Z,8Z,11Z,14Z))	HMDB0005380	1 ^[8]	753	PD1	/	1 ^[9]
339	TG(16:0/18:1(9Z)/18:2(9Z,12Z))	HMDB0005384	1 ^[8]	754	PE(40p:4/40e:5)	/	1 ^[43]
340	TG(16:0/18:1(9Z)/20:4(5Z,8Z,11Z,14Z))	HMDB0005385	1 ^[8]	755	PE(O-38:5)	/	1 ^[8]
341	TG(16:0/18:2(9Z,12Z)/20:4(5Z,8Z,11Z,14 Z))	HMDB0005391	1 ^[8]	756	Pentonic acid A	/	1 ^[10]
342	TG(16:0/20:4(5Z,8Z,11Z,14Z)/20:4(5Z,8Z	HMDB0005392	1 ^[8]	757	Pentonic acid B	/	1 ^[10]

	,11Z,14Z))						
343	TG(16:1(9Z)/16:1(9Z)/16:1(9Z))	HMDB0005432	1 ^[8]	758	Phe Ala Arg	/	1 ^[29]
344	TG(16:1(9Z)/16:1(9Z)/18:2(9Z,12Z))	HMDB0005435	1 ^[8]	759	Phe Phe	/	1 ^[26]
345	TG(18:1(9Z)/18:2(9Z,12Z)/20:4(5Z,8Z,11Z,14Z))	HMDB0005462	1 ^[8]	760	Phenoperidine	/	1 ^[29]
346	TG(18:1(9Z)/20:4(5Z,8Z,11Z,14Z)/20:4(5Z,8Z,11Z,14Z))	HMDB0005463	1 ^[8]	761	phosphatidylethanolamine(18:0/20:4(5Z,8Z,11Z,14Z)) ^[U]	/	1 ^[]
347	TG(18:2(9Z,12Z)/20:4(5Z,8Z,11Z,14Z)/20:4(5Z,8Z,11Z,14Z))	HMDB0005476	1 ^[8]	762	phosphatidylethanolamine(18:1(11Z)/18:1(9Z)) ^[U]	/	1 ^[29]
348	scyllo-Inositol	HMDB0006088	1 ^[32]	763	phosphatidylethanolamine(20:4(5Z,8Z,11Z,14Z)/20:4(5Z,8Z,11Z,14Z)) ^[U]	/	1 ^[29]
349	gamma-Glutamylalanine	HMDB0006248	1 ^[8]	764	phosphatidylethanolamine(O-16:0/22:5(4Z,7Z,10Z,13Z,16Z))	/	1 ^[29]
350	5a-Cholest-8-en-3b-o1	HMDB0006841	1 ^[49]	765	phosphatidylethanolamineNMe(18:1(9Z)/18:1(9Z)) ^[U]	/	1 ^[29]
351	DG(14:1(9Z)/16:0/0:0)	HMDB0007040	1 ^[21]	766	phosphatidylethanolamineNMe(18:2(9Z,12Z)/18:2(9Z,12Z)) ^[U]	/	1 ^[29]
352	DG(14:1(9Z)/22:2(13Z,16Z)/0:0)	HMDB0007059	1 ^[8]	767	Pizotyline	/	1 ^[29]
353	DG(16:0/18:1(11Z)/0:0)	HMDB0007101	1 ^[21]	768	PPC(16:0/18:2)	/	1 ^[14]
354	DG(16:0/18:3(6Z,9Z,12Z)/0:0)	HMDB0007104	1 ^[21]	769	PPC(16:0/22:5)	/	1 ^[28]
355	DG(16:0/20:4(5Z,8Z,11Z,14Z)/0:0)	HMDB0007112	1 ^[21]	770	PPC(18:0/20:4)	/	1 ^[25]
356	DG(18:2(9Z,12Z)/18:1(11Z)/0:0)	HMDB0007246	1 ^[21]	771	PPC(18:0/22:6)	/	1 ^[25]
357	DG(18:3(6Z,9Z,12Z)/18:2(9Z,12Z)/0:0)	HMDB0007277	1 ^[21]	772	PPC(18:1/20:4)	/	1 ^[25]
358	DG(18:3(6Z,9Z,12Z)/18:3(6Z,9Z,12Z)/0:0)	HMDB0007278	1 ^[21]	773	PPE(16.0/22.6)	/	1 ^[25]
359	DG(22:4(7Z,10Z,13Z	HMDB0007700	1 ^[29]	774	PPE(16:0/20:4)	/	1 ^[25]

	,16Z)/22:5(7Z,10Z,13Z,16Z,19Z)/0:0)						
360	PC(14:0/20:1(11Z))	HMDB0007879	1 ^[19]	775	PPE(16:0/20:5)	/	1 ^[25]
361	PC(14:0/20:3(8Z,11Z,14Z))	HMDB0007882	1 ^[13]	776	PPE(18:1/18:1)	/	1 ^[25]
362	PC(15:0/18:1(11Z))	HMDB0007938	1 ^[14]	777	PPE(18:1/18:2)	/	1 ^[25]
363	PC(15:0/18:2(9Z,12Z))	HMDB0007940	1 ^[14]	778	PRISTIMEROL	/	1 ^[29]
364	PC(16:0/20:3(5Z,8Z,11Z))	HMDB0007980	1 ^[14]	779	Pro Lys Pro	/	1 ^[29]
365	PC(16:0/20:3(8Z,11Z,14Z))	HMDB0007981	1 ^[13]	780	Pro Pro	/	1 ^[29]
366	PC(16:0/20:4(5Z,8Z,11Z,14Z))	HMDB0007982	1 ^[35]	781	Propanoic acid, 2-hydroxy-3-[(4-hydroxy-1-naphthalenyl)oxy]_	/	1 ^[29]
367	PC(16:0/22:5(4Z,7Z,10Z,13Z,16Z))^b	HMDB0007989	1 ^[25]	782	Propionylglycine methyl ester	/	1 ^[29]
368	PC(16:1(9Z)/16:1(9Z))	HMDB0008002	1 ^[25]	783	Prostaglandin	/	1 ^[28]
369	PC(16:1(9Z)/18:3(6Z,9Z,12Z))	HMDB0008007	1 ^[25]	784	PS(18:1/0:0)	/	1 ^[56]
370	PC(16:1(9Z)/22:6(4Z,7Z,10Z,13Z,16Z,19Z))	HMDB0008023	1 ^[14]	785	PS(34a:3)	/	1 ^[43]
371	PC(18:0/18:0)	HMDB0008036	1 ^[25]	786	PS(36a:4)	/	1 ^[43]
372	PC(18:0/18:2(9Z,12Z))	HMDB0008039	1 ^[35]	787	PYROGALLIN	/	1 ^[29]
373	PC(18:0/20:3(5Z,8Z,11Z))	HMDB0008046	1 ^[25]	788	Ritodrine glucuronide	/	1 ^[29]
374	PC(18:1(11Z)/20:3(5Z,8Z,11Z))	HMDB0008079	1 ^[25]	789	S-3-Hydroxyisobutyric acid	/	1 ^[8]
375	PC(18:1(11Z)/22:6(4Z,7Z,10Z,13Z,16Z,19Z))	HMDB0008090	1 ^[14]	790	Ser Asp Gly	/	1 ^[29]
376	PC(18:1(9Z)/22:5(4Z,7Z,10Z,13Z,16Z))	HMDB0008121	1 ^[1]	791	SM (d18:1/18:0)	/	1 ^[19]
377	PC(18:2(9Z,12Z)/18:0)	HMDB0008135	1 ^[28]	792	SM (d18:1/18:1)	/	1 ^[19]
378	PC(18:2(9Z,12Z)/20:4(5Z,8Z,11Z,14Z))	HMDB0008147	1 ^[19]	793	SM (OH) C22:1	/	1 ^[1]
379	PC(20:1(11Z)/18:4(6Z,9Z,12Z,15Z))	HMDB0008306	1 ^[19]	794	SM (OH) C22:2	/	1 ^[1]
380	PC(20:4(5Z,8Z,11Z,14Z)/20:4(5Z,8Z,11Z,	HMDB0008443	1 ^[14]	795	SM (OH) C24:1	/	1 ^[1]

	14Z))						
381	PC(20:4(5Z,8Z,11Z,14Z)/22:6(4Z,7Z,10Z,13Z,16Z,19Z))	HMDB0008452	1 ^[14]	796	SM C16:0	/	1 ^[1]
382	PC(22:0/18:4(6Z,9Z,12Z,15Z))	HMDB0008536	1 ^[1]	797	SM C18:1	/	1 ^[1]
383	PE(14:1(9Z)/24:1(15Z))	HMDB0008882	1 ^[8]	798	SM C24:1	/	1 ^[1]
384	PE(16:0/18:0)	HMDB0008925	1 ^[14]	799	SM C26:1	/	1 ^[1]
385	PE(16:0/20:5(5Z,8Z,11Z,14Z,17Z))	HMDB0008939	1 ^[25]	800	SM(d18:1/18:1)	/	1 ^[14]
386	PE(16:1(9Z)/20:5(5Z,8Z,11Z,14Z,17Z))	HMDB0008972	1 ^[25]	801	SM(d18:1/18:2)	/	1 ^[14]
387	PE(18:0/22:6(4Z,7Z,10Z,13Z,16Z,19Z))	HMDB0009012	1 ^[25]	802	SM(d18:1/20:1)	/	1 ^[8]
388	PE(18:1(11Z)/20:4(5Z,8Z,11Z,14Z))	HMDB0009036	1 ^[25]	803	SM(d18:1/20:1)	/	1 ^[8]
389	PE(18:1(11Z)/20:5(5Z,8Z,11Z,14Z,17Z))	HMDB0009038	1 ^[25]	804	SM(d18:1/24:2)	/	1 ^[8]
390	PE(18:1(11Z)/22:6(4Z,7Z,10Z,13Z,16Z,19Z))	HMDB0009045	1 ^[25]	805	SM(d18:1/24:2)	/	1 ^[8]
391	PE(18:2(9Z,12Z)/22:6(4Z,7Z,10Z,13Z,16Z,19Z))	HMDB0009111	1 ^[25]	806	SM(d18:1/25:0)	/	1 ^[8]
392	PE(22:5(4Z,7Z,10Z,13Z,16Z)/22:4(7Z,10Z,13Z,16Z))	HMDB0009636	1 ^[25]	807	SM(d18:1/25:0)	/	1 ^[8]
393	PE(22:6(4Z,7Z,10Z,13Z,16Z,19Z)/22:5(4Z,7Z,10Z,13Z,16Z))	HMDB0009703	1 ^[25]	808	SM(OH)C14:1	/	1 ^[19]
394	PI(18:0/20:4(5Z,8Z,11Z,14Z))	HMDB0009815	1 ^[35]	809	S-Methylpenicillamine	/	1 ^[29]
395	LysoPC(16:1(9Z))	HMDB0010383	1 ^[13]	810	sphingosine-1-phosphate	/	1 ^[14]
396	LysoPC(20:3(5Z,8Z,11Z))	HMDB0010393	1 ^[56]	811	stra-1,3,5(10),7-tetraene-3,17alpha-diol	/	1 ^[56]
397	LysoPC(20:4(5Z,8Z,11Z,14Z))	HMDB0010395	1 ^[8]	812	SULBACTAM	/	1 ^[29]
398	TG(16:0/14:0/16:0)	HMDB0010411	1 ^[8]	813	SULF(d18:1/18:0)	/	1 ^[14]
399	TG(16:0/14:0/16:1(9Z))	HMDB0010412	1 ^[8]	814	t8-iso-PGF2	/	1 ^[41]
400	TG(16:1(9Z)/14:0/16:1(9Z))	HMDB0010419	1 ^[8]	815	TEGASEROD	/	1 ^[29]

401	3-Oxododecanoic acid	HMDB0010727	1 ^[29]	816	tetradecadienoylcar nitine	/	1 ^[15]
402	LysoPC(O-18:0)	HMDB0011149	1 ^[14]	817	tetradecenoylcarniti ne	/	1 ^[15]
403	PC(P-16:0/14:0)	HMDB0011203	1 ^[19]	818	TG(51:1)	/	1 ^[8]
404	LysoPE(0:0/16:0)	HMDB0011473	1 ^[25]	819	TG(O-50:0)	/	1 ^[8]
405	LysoPE(0:0/18:1(11Z)	HMDB0011475	1 ^[25]	820	THIODIGLYCOL	/	1 ^[29]
406	LysoPE(0:0/18:2(9Z, 12Z))	HMDB0011477	1 ^[25]	821	Thr Gly	/	1 ^[29]
407	MG(16:0/0:0/0:0)	HMDB0011564	1 ^[14]	822	Thr Ser Gln	/	1 ^[29]
408	gamma-Glutamylglyc ine	HMDB0011667	1 ^[56]	823	thyrotropin releasing hormone	/	1 ^[29]
409	p-Cresol glucuronide	HMDB0011686	1 ^[56]	824	Tripeptide	/	1 ^[26]
410	SM(d18:1/24:0)	HMDB0011697	1 ^[35]	825	Trp Gly Phe	/	1 ^[29]
411	TG(15:0/16:0/20:2(11 Z,14Z))	HMDB0011700	1 ^[8]	826	TUBAIC ACID	/	1 ^[29]
412	TG(15:0/16:0/20:3(8 Z,11Z,14Z))	HMDB0011701	1 ^[8]	827	Tyr Tyr Thr	/	1 ^[29]
413	Methyldopa	HMDB0011754	1 ^[8]	828	Val Gly	/	1 ^[29]
414	SM(d18:1/12:0)	HMDB0012096	1 ^[14]	829	Val Ser Lys	/	1 ^[29]
415	SM(d18:1/14:0)	HMDB0012097	1 ^[14]	830	VALERYL SALYCILATE	/	1 ^[29]

^areference number are same as in Supplementary Table 2. Frequency indicates the reported frequency of the metabolite in previous studies included in this systematic review.

^baging-related metabolites

Supplementary Table 5. Differential metabolites of mild cognitive impairment and their reported frequencies in previous studies

Number	Metabolite Name	HMDB ID	Frequency	Number	Metabolite Name	HMDB ID	Frequency ^a
1	L-Tryptophan	HMDB0000929	3 ^[27,29,30]	148	10-hydroxy-8E-Decene-2,4,6-triynoic acid	/	1 ^[29]
2	5'-Methylthioadenosine	HMDB0001173	2 ^[33,51]	149	1a,1b-dihomo-PGJ2	/	1 ^[29]
3	L-Valine	HMDB0000883	2 ^[29,59]	150	VALERYL SALYCILATE	/	1 ^[29]
4	5-Hydroxyindoleacetic acid	HMDB0000763	2 ^[29,30]	151	VD 2656	/	1 ^[29]
5	L-Methionine	HMDB0000696	2 ^[29,30]	152	Visnagin	/	1 ^[29]
6	L-Arginine	HMDB0000517	2 ^[29,51]	153	1-Aminocyclohexanecarboxylic acid	/	1 ^[29]
7	5-Hydroxy-L-tryptophan	HMDB0000472	2 ^[29,30]	154	Tyr Pro	/	1 ^[29]
8	L-Phenylalanine	HMDB0000159	2 ^[27,29]	155	1-eicosanoyl-rac-glycerol	/	1 ^[29]
9	epsilon-Caprolactam	METPA0843	1 ^[29]	156	1-Hydroxyvitamin D3 3-D-glucopyranoside	/	1 ^[29]
10	Benzene-1,2,4-triol	METPA0328	1 ^[29]	157	1-Phenyl-2-(diethylamino)-1-propanol	/	1 ^[29]
11	(R)-Citronellal	HMDB0035820	1 ^[29]	158	2,5-Dimethoxycinnamic acid	/	1 ^[29]
12	Isoquinoline	HMDB0034244	1 ^[29]	159	20-oxo-heneicosanoic acid	/	1 ^[29]
13	2-Amino-4-hydroxy-6-pteridinecarboxylic acid	HMDB0033136	1 ^[29]	160	2-Amino-3-methyl-1-butanol	/	1 ^[29]
14	Citropten	HMDB0032952	1 ^[29]	161	Thr Ser Gln	/	1 ^[29]
15	Succinic anhydride	HMDB0032523	1 ^[29]	162	2-Hydroxy-3-(4-methoxyethylphenoxy)-propanoic acid	/	1 ^[29]
16	Acetamide	HMDB0031645	1 ^[29]	163	3-(a-Naphthoxy)lactic acid	/	1 ^[29]
17	4-Hydroxybenzenecetonitrile	HMDB0029757	1 ^[29]	164	3,6-octadecadiynoic acid	/	1 ^[29]
18	Glutamylglutamine	HMDB0028817	1 ^[26]	165	TEGASEROD	/	1 ^[29]
19	Dimercaprol	HMDB0015677	1 ^[29]	166	3beta,4beta-Dihydroxy-5beta-cholan-24-oic Acid	/	1 ^[29]
20	Acenocoumarol	HMDB0015487	1 ^[29]	167	3-dodecynoic acid	/	1 ^[29]
21	Bepridil	HMDB0015374	1 ^[29]	168	4-dodecynoic acid	/	1 ^[29]
22	Penicillin G	HMDB0015186	1 ^[29]	169	4-hydroxy enanthoic acid	/	1 ^[29]
23	Netilmicin	HMDB0015090	1 ^[29]	170	4'-Hydroxyminoxidil	/	1 ^[29]
24	Aciclovir	HMDB0014925	1 ^[29]	171	4-undecynoic acid	/	1 ^[29]
25	Nalidixic Acid	HMDB0014917	1 ^[29]	172	Trp Ala Ile	/	1 ^[29]
26	Azatadine	HMDB0014857	1 ^[29]	173	5,7-nonadienoic acid	/	1 ^[29]
27	Pirenzepine	HMDB0014808	1 ^[29]	174	5beta-Androstan-3alpha-ol-17-one sulfate	/	1 ^[29]

28	Ethosuximide	HMDB0014731	1 ^[29]	175	TUBAIC ACID	/	1 ^[29]
29	Ethopropazine	HMDB0014536	1 ^[29]	176	5-NITRO-2-PHENYLPROPY LAMINO BENZOIC ACID [NPPB]	/	1 ^[29]
30	Tranexamic Acid	HMDB0014447	1 ^[29]	177	5-octadecylenic acid	/	1 ^[29]
31	Lidocaine	HMDB0014426	1 ^[29]	178	5-oxo-7-decynoic acid	/	1 ^[29]
32	Pyrimethamine	HMDB0014350	1 ^[29]	179	6-hydroxy-2-hexynoic acid	/	1 ^[29]
33	Lorazepam	HMDB0014332	1 ^[29]	180	7,12-Dioxo-5beta-cholan-24-o ic Acid	/	1 ^[29]
34	N-Nonanoylglycine	HMDB0013279	1 ^[33]	181	7,8-Didehydroastaxanthin	/	1 ^[29]
35	3-Dehydroquinate	HMDB0012710	1 ^[29]	182	8R-hydroxy-9Z-octadecenoic acid	/	1 ^[29]
36	SM(d18:1/14:0)	HMDB0012097	1 ^[14]	183	9,12-dioxo-dodecanoic acid	/	1 ^[29]
37	MG(18:0/0:0/0:0)	HMDB0011131	1 ^[29]	184	9-lauroleic acid	/	1 ^[29]
38	SM(d18:1/16:0)	HMDB0010169	1 ^[14]	185	9-pentadecen-1-ol	/	1 ^[29]
39	PE(16:0/18:0)	HMDB0008925	1 ^[14]	186	Adriamycinone	/	1 ^[29]
40	PC(22:5(4Z,7Z,10Z ,13Z,16Z)/14:1(9Z))	HMDB0008657	1 ^[20]	187	Ala Ala Asp	/	1 ^[29]
41	PC(20:0/18:3(6Z,9 Z,12Z))	HMDB0008271	1 ^[20]	188	Ala Leu	/	1 ^[29]
42	PC(18:1(9Z)/22:5(4 Z,7Z,10Z,13Z,16Z))	HMDB0008121	1 ^[20]	189	Ala Met Lys	/	1 ^[29]
43	PC(16:1(9Z)/22:6(4 Z,7Z,10Z,13Z,16Z, 19Z))	HMDB0008023	1 ^[14]	190	Ala Thr Pro	/	1 ^[29]
44	PC(16:0/20:3(5Z,8 Z,11Z))	HMDB0007980	1 ^[14]	191	AMBELLINE	/	1 ^[29]
45	PC(16:0/18:2(9Z,12 Z))	HMDB0007973	1 ^[14]	192	Anandamide (20:2, n-6)	/	1 ^[29]
46	PC(14:0/20:4(8Z,11 Z,14Z,17Z))	HMDB0007884	1 ^[20]	193	Asn Gln Gln	/	1 ^[29]
47	Docosapentaenoic acid	HMDB0006528	1 ^[29]	194	Asp Asn Glu	/	1 ^[29]
48	Loratadine	HMDB0005000	1 ^[29]	195	BERGENIN	/	1 ^[29]
49	Guaifenesin	HMDB0004998	1 ^[29]	196	bicyclo-PGE2	/	1 ^[29]
50	Ceramide (d18:1/16:0)	HMDB0004949	1 ^[14]	197	Bifemelane (M4)	/	1 ^[26]
51	13,14-Dihydro-15-k eto PGF2a	HMDB0004685	1 ^[29]	198	C10:0-carnitine	/	1 ^[26]
52	Phytosphingosine	HMDB0004610	1 ^[27]	199	C8-carnitine	/	1 ^[6]
53	Imidazolone	HMDB0004363	1 ^[29]	200	cholesteryl ester 32:0	/	1 ^[6]
54	Tryptophanol	HMDB0003447	1 ^[29]	201	cholesteryl ester 32:4	/	1 ^[6]

55	Diacetyl	HMDB0003407	1 ^[29]	202	cholesteryl ester 33:6	/	1 ^[6]
56	Acetoin	HMDB0003243	1 ^[29]	203	cholesteryl ester 34:0	/	1 ^[6]
57	Isoacitrein	HMDB0003039	1 ^[29]	204	cholesteryl ester 34:6	/	1 ^[6]
58	Testosterone sulfate	HMDB0002833	1 ^[29]	205	cholesteryl ester 40:4	/	1 ^[29]
59	Desmosterol	HMDB0002719	1 ^[31]	206	cis-3-(6-Hydroxy-7-methoxy-5-benzofuranyl)acrylic acid	/	1 ^[29]
60	6-Hydroxynicotinic acid	HMDB0002658	1 ^[29]	207	clavulone I	/	1 ^[29]
61	Sumiki's acid	HMDB0002432	1 ^[29]	208	cyclohexylammonium	/	1 ^[54]
62	N-Acetylcadaverine	HMDB0002284	1 ^[29]	209	d18:1/16:0	/	1 ^[54]
63	27-Nor-5b-cholestane-3a,7a,12a,24,25-pentol	HMDB0002126	1 ^[29]	210	d18:1/24:0	/	1 ^[54]
64	Oleamide	HMDB0002117	1 ^[14]	211	d18:1/24:1	/	1 ^[29]
65	N-Acetylputrescine	HMDB0002064	1 ^[51]	212	DALBERGIONE, 4-METHOXY-4'-HYDROXY -	/	1 ^[29]
66	2-Pyrrolidinone	HMDB0002039	1 ^[29]	213	DIALLYL SULFIDE	/	1 ^[29]
67	D-threo-Isocitric acid	HMDB0001874	1 ^[29]	214	dihydro-alpha-ergocryptine	/	1 ^[29]
68	Progesterone	HMDB0001830	1 ^[27]	215	Dihydrolevobunolol	/	1 ^[29]
69	Asymmetric dimethylarginine	HMDB0001539	1 ^[29]	216	dodecanamide	/	1 ^[29]
70	Glucosamine	HMDB0001514	1 ^[29]	217	EB 1213	/	1 ^[29]
71	Queuine	HMDB0001495	1 ^[29]	218	Embelin	/	1 ^[29]
72	Pyridoxamine	HMDB0001431	1 ^[29]	219	EMODIC ACID	/	1 ^[29]
73	Putrescine	HMDB0001414	1 ^[51]	220	Estradiol valerate	/	1 ^[29]
74	p-Aminobenzoic acid	HMDB0001392	1 ^[29]	221	Furafylline	/	1 ^[29]
75	Diaminopimelic acid	HMDB0001370	1 ^[29]	222	GlcAbeta-Cer(d18:1/18:0)	/	1 ^[29]
76	Purine	HMDB0001366	1 ^[29]	223	Gln Pro Lys	/	1 ^[29]
77	SM(d18:1/18:0)	HMDB0001348	1 ^[14]	224	Glu Ser	/	1 ^[29]
78	N1-Acetylspermidine	HMDB0001276	1 ^[26]	225	GPA(21:0/22:6(4Z,7Z,10Z,13Z,16Z,19Z))	/	1 ^[29]
79	Spermidine	HMDB0001257	1 ^[51]	226	GPEtn(18:1(11Z)/18:1(9Z)) ^[U]	/	1 ^[29]
80	Spermine	HMDB0001256	1 ^[51]	227	GPEtn(20:4(5Z,8Z,11Z,14Z)/20:4(5Z,8Z,11Z,14Z)) ^[U]	/	1 ^[29]
81	N-Acetylarlyamine	HMDB0001250	1 ^[29]	228	GPEtn(O-16:0/22:5(4Z,7Z,10Z,13Z,16Z))	/	1 ^[29]
82	(S)-Succinyldihydroliipoamide	HMDB0001177	1 ^[29]	229	GPSer(16:0/18:1(11Z))	/	1 ^[29]
83	4-Aminophenol	HMDB0001169	1 ^[29]	230	Granisetron metabolite	/	1 ^[29]
84	Pyruvaldehyde	HMDB0001167	1 ^[29]	231	Gualenate	/	1 ^[29]

85	3-Aminopropionaldehyde	HMDB0001106	1 ^[29]	232	Gummiferol	/	1 ^[14]
86	4-Aminobutyraldehyde	HMDB0001080	1 ^[51]	233	Hex-CER(d18:1/16:0)	/	1 ^[14]
87	Glyceraldehyde	HMDB0001051	1 ^[29]	234	Hex-CER(d18:1/18:0)	/	1 ^[29]
88	Biliverdin	HMDB0001008	1 ^[29]	235	Ile Ser Lys	/	1 ^[14]
89	Trehalose	HMDB0000975	1 ^[29]	236	inoleyl-carnitine	/	1 ^[29]
90	Traumatic acid	HMDB0000933	1 ^[29]	237	KARANJIN	/	1 ^[14]
91	Stearoylcarnitine	HMDB0000848	1 ^[14]	238	Lac-CER(d18:1/14:0)	/	1 ^[14]
92	Phenylacetylglycine	HMDB0000821	1 ^[14]	239	Lac-CER(d18:1/16:0)	/	1 ^[14]
93	Indoleacrylic acid	HMDB0000734	1 ^[29]	240	Lac-CER(d18:1/16:1)	/	1 ^[29]
94	Hippuric acid	HMDB0000714	1 ^[29]	241	L-Alanine n-butyl ester	/	1 ^[29]
95	L-Kynurenine	HMDB0000684	1 ^[30]	242	Leu Glu Gln	/	1 ^[29]
96	Citraconic acid	HMDB0000634	1 ^[29]	243	Leu Leu Ala	/	1 ^[29]
97	Cytosine	HMDB0000630	1 ^[60]	244	L-Glutamic acid dibutyl ester	/	1 ^[29]
98	Ethylmalonic acid	HMDB0000622	1 ^[29]	245	Loroxanthin ester/ Loroxanthin dodecenoate	/	1 ^[27]
99	2-Furoic acid	HMDB0000617	1 ^[29]	246	LPC C 18:0	/	1 ^[27]
100	PC(16:0/16:0)	HMDB0000564	1 ^[14]	247	LPC C 18:1	/	1 ^[27]
101	Creatinine	HMDB0000562	1 ^[29]	248	LPC C 18:2	/	1 ^[27]
102	Caproic acid	HMDB0000535	1 ^[33]	249	LPC C 20:4	/	1 ^[20]
103	Aminoadipic acid	HMDB0000510	1 ^[29]	250	lysoPC a C18:2	/	1 ^[29]
104	3-Methylhistidine	HMDB0000479	1 ^[29]	251	Mebeverine	/	1 ^[29]
105	3,4-Dihydroxyhydrocinnamic acid	HMDB0000423	1 ^[29]	252	Met Trp Gln	/	1 ^[29]
106	3-Hydroxydodecanedioic acid	HMDB0000413	1 ^[29]	253	Methoxsalen Metabolite	/	1 ^[29]
107	2-Methyl-3-ketovaleric acid	HMDB0000408	1 ^[29]	254	METHYL 7-DESHYDROXYPYROGA LLIN-4-CARBOXYLATE	/	1 ^[33]
108	2-Hydroxy-3-methylbutyric acid	HMDB0000407	1 ^[29]	255	methyl-salsolinol	/	1 ^[51]
109	3-Hydroxybutyric acid	HMDB0000357	1 ^[59]	256	N1 or N8-acetyl-spermidine	/	1 ^[51]
110	2-Methylbutyrylglycine	HMDB0000339	1 ^[29]	257	N1,N12-diacetylspermine	/	1 ^[29]
111	Urocanic acid	HMDB0000301	1 ^[29]	258	N4-Acetylsulfapyridine	/	1 ^[29]
112	Uric acid	HMDB0000289	1 ^[30]	259	SM(OH) C14:1	/	1 ^[14]
113	Sphingosine 1-phosphate	HMDB0000277	1 ^[14]	260	N-arachidonoyl D-serine	/	1 ^[29]
114	Sphinganine	HMDB0000269	1 ^[27]	261	N-Didesethylquinagolide	/	1 ^[29]
115	Pyroglutamic acid	HMDB0000267	1 ^[29]	262	N-methyl-Gabapentin	/	1 ^[14]
116	Taurine	HMDB0000251	1 ^[29]	263	oleylcarnitine	/	1 ^[29]
117	Tetrahydrofuran	HMDB0000246	1 ^[29]	264	Ophiobolin A	/	1 ^[20]

118	Pyruvic acid	HMDB0000243	1 ^[29]	265	PC aa C40:5	/	1 ^[7]
119	Ornithine	HMDB0000214	1 ^[51]	266	PC aaC32:0	/	1 ^[7]
120	Oxoglutaric acid	HMDB0000208	1 ^[29]	267	PC aeC32:2	/	1 ^[7]
121	Indoleacetic acid	HMDB0000197	1 ^[30]	268	PC aeC34:1	/	1 ^[43]
122	L-Lactic acid	HMDB0000190	1 ^[59]	269	PC(32a:0)	/	1 ^[43]
123	L-Asparagine	HMDB0000168	1 ^[26]	270	PC(38a:5)	/	1 ^[43]
124	Hypoxanthine	HMDB0000157	1 ^[30]	271	PC(38a:6)	/	1 ^[26]
125	Fumaric acid	HMDB0000134	1 ^[29]	272	Phe Phe	/	1 ^[29]
126	D-Glucose	HMDB0000122	1 ^[59]	273	Phe Val Val	/	1 ^[14]
127	Gamma-Aminobutyric acid	HMDB0000112	1 ^[51]	274	PPC(16:0/18:2)	/	1 ^[29]
128	Choline	HMDB0000097	1 ^[26]	275	Pro Pro	/	1 ^[29]
129	Dimethylglycine	HMDB0000092	1 ^[29]	276	Propionylglycine methyl ester	/	1 ^[43]
130	Cholesterol	HMDB0000067	1 ^[6]	277	PS(38a:6)	/	1 ^[29]
131	Creatine	HMDB0000064	1 ^[51]	278	PURPUROGALLIN	/	1 ^[29]
132	L-Carnitine	HMDB0000062	1 ^[26]	279	PYROGALLIN	/	1 ^[29]
133	Acetoacetic acid	HMDB0000060	1 ^[29]	280	QUERCETIN	/	1 ^[29]
134	Bilirubin	HMDB0000054	1 ^[29]		TETRAMETHYL (5,7,3',4') ETHER		
135	Acetic acid	HMDB0000042	1 ^[59]	281	Rimiterol	/	1 ^[29]
136	Biotin	HMDB0000030	1 ^[29]	282	Ritodrine glucuronide	/	1 ^[29]
137	4-Pyridoxic acid	HMDB0000017	1 ^[29]	283	S-(p-Azidophenacyl)glutathione	/	1 ^[14]
138	(17Z)-1alpha,25-dihydroxy-26,27-dimethyl-17,20,22,22,23,23-hexadehydrovitamin D3	/	1 ^[29]	284	SM(d18:1/18:1)	/	1 ^[7]
139	(22E,24E)-1alpha,25-dihydroxy-22,23,24,24a-tetrahydro-24a-homovitamin D3	/	1 ^[29]	285	1alpha,25-dihydroxy-11beta-p henylvitamin D3 / 1alpha,25-dihydroxy-11beta-p henylcholecalciferol	/	1 ^[29]
140	(22R)-1alpha,22,25-trihydroxy-23,24-tetrahydro-24a,24b-dihomo-20-epivitamin D3	/	1 ^[29]	286	1alpha,25-dihydroxy-22-oxavitamin D3 3-hemiglutarate/ 1alpha,25-dihydroxy-22-oxac holecalciferol 3-he	/	1 ^[29]
141	(22R)-1alpha,22,25	/	1 ^[29]	287	1alpha,25-dihydroxy-3-deoxy-3-thiavitamin D3 / 1alpha,25-dihydroxy-3-deoxy-3-thiacholecalciferol	/	1 ^[29]
				288	1beta,25-dihydroxy-2beta-(3-h	/	1 ^[29]

	-trihydroxy-26,27-dimethyl-23,24-tetrahydro-24a-homo-20-epivitamin D3 / (22R)-1a				ydroxypropoxy)vitamin D3 / 1beta,25-dihydroxy-2beta-(3-hydroxypropoxy)c		
142	(22S)-1alpha,22,25-trihydroxy-23,24-tetrahydro-24a,24b-dihomo-20-epivitamin D3 / (22S)-1alpha,22,2	/	1 ^[29]	289	5-(4-hydroxy-2,5-dimethylphenoxy)-2,2-dimethyl-Pentanoic acid (Gemfibrozil M1)	/	1 ^[29]
143	(23R)-1alpha,23,25-trihydroxy-24-oxo vitamin D3 / (23R)-1alpha,23,25-trihydroxy-24-oxo cholecalciferol	/	1 ^[29]	290	5H-Oxireno ^[4,5] furo ^{[3,2-g][1]} benzopyran-5-one, 1a,8b-dihydro-3-methoxy-	/	1 ^[29]
144	(23R,25R)-1alpha,25-dihydroxyvitamin D3 26,23-lactone / (23R,25R)-1alpha,25-dihydroxycholecalciferol	/	1 ^[29]	291	3alpha,6alpha,12alpha-Trihydroxy-7-oxo-5beta-cholan-24-oic Acid	/	1 ^[29]
145	(24S)-1alpha,24-dihydroxy-22-oxa-20-epivitamin D3 / (24S)-1alpha,24-dihydroxy-22-oxa-20-epicholecalc	/	1 ^[29]	292	N'-5Z,8Z,11Z,14Z-eicosatetraenoyl-N"-diethyl-ethylenediamine	/	1 ^[29]
146	(24S)-1alpha,24-dihydroxy-22-oxavitamin D3 / (24S)-1alpha,24-dihydroxy-22-oxacholecalciferol	/	1 ^[29]	293	2H-1-Benzopyran-6-acetic acid, 7-hydroxy-8-methoxy-2-oxo-	/	1 ^[29]
147	1,3-DIPROPYL-8-CYCLOPENTYLXANTHINE ^[DPCPX]	/	1 ^[29]				

^areference number are same as in Supplementary Table 2. Frequency indicates the reported frequency of the metabolite in previous studies included in this systematic review.

Supplementary Table 6. Differential metabolites between Alzheimer's disease and mild cognitive impairment and their reported frequencies in previous studies

Number	Metabolite Name	HMDB ID	Frequency	Number	Metabolite Name	HMDB ID	Frequency ^a
1	L-Histidine	HMDB0000177	2 ^[14,26]	61	SULF(d18:1/18:0)	/	1 ^[14]
2	L-Tryptophan	HMDB0000929	2 ^[27,29]	62	1-Aminocyclohexane carboxylic acid	/	1 ^[29]
3	Creatine	HMDB0000064	1 ^[34]	63	1-Hexadecylamine	/	1 ^[29]
4	2-Hydroxybutyric acid	HMDB0000008	1 ^[15]	64	20alpha-Dihydroprednisolone	/	1 ^[29]
5	4-Pyridoxic acid	HMDB0000017	1 ^[29]	65	2-oxo-4-hydroxy-hexanoic acid	/	1 ^[29]
6	Pipecolic acid	HMDB0000070	1 ^[33]	66	3,6-octadecadiynoic acid	/	1 ^[29]
7	Choline	HMDB0000097	1 ^[63]	67	3E-undecenoic acid	/	1 ^[29]
8	Glycolic acid	HMDB0000115	1 ^[29]	68	4-Hydroxytacrine	/	1 ^[29]
9	L-Tyrosine	HMDB0000158	1 ^[29]	69	5,7-nonadienoic acid	/	1 ^[29]
10	L-Phenylalanine	HMDB0000159	1 ^[29]	70	Trp Gly Phe	/	1 ^[29]
11	L-Proline	HMDB0000162	1 ^[29]	71	5-hydroxymethylcytosine	/	1 ^[60]
12	L-Acetylcarnitine	HMDB0000201	1 ^[15]	72	5-tert-Butyl-4-hydroxymethylfuran-2-carboxylic acid	/	1 ^[29]
13	Phenol	HMDB0000228	1 ^[29]	73	Ala Leu	/	1 ^[29]
14	Taurine	HMDB0000251	1 ^[33]	74	Allocortol	/	1 ^[29]
15	Sphinganine	HMDB0000269	1 ^[27]	75	Arg Asn Gln	/	1 ^[29]
16	Urea	HMDB0000294	1 ^[29]	76	Asn Gly Ser	/	1 ^[29]
17	Uracil	HMDB0000300	1 ^[33]	77	BUFEXAMAC	/	1 ^[29]
18	2-Methylbutyrylglycine	HMDB0000339	1 ^[29]	78	C10:1-carnitine	/	1 ^[26]
19	3-Methylindole	HMDB0000466	1 ^[29]	79	Carbaryl	/	1 ^[29]
20	5-Hydroxy-L-tryptophan	HMDB0000472	1 ^[30]	80	Chloramphenicol alcohol	/	1 ^[29]
21	3-Methylhistidine	HMDB0000479	1 ^[29]	81	clavulone I	/	1 ^[29]
22	L-Arginine	HMDB0000517	1 ^[63]	82	Gly His	/	1 ^[29]
23	Cytosine	HMDB0000630	1 ^[60]	83	decenoylcarnitine	/	1 ^[15]
24	Deoxycholic acid glycine conjugate	HMDB0000631	1 ^[2]	84	Diglycolic acid	/	1 ^[29]
25	Chenodeoxycholic acid glycine conjugate	HMDB0000637	1 ^[2]	85	dodecenoylcarnitine	/	1 ^[15]
26	Decanoylcarnitine	HMDB0000651	1 ^[15]	86	dopamine-quinone	/	1 ^[33]
27	L-Methionine	HMDB0000696	1 ^[26]	87	free carnitine	/	1 ^[15]
28	Lithocholic acid	HMDB0000698	1 ^[2]	88	DALBERGIONE,	/	1 ^[29]

glycine conjugate				4-METHOXY-4'-HYDROXY- hydroxyphosphinyl-piruvate			
29	Indoleacrylic acid	HMDB0000734	1 ^[29]	89	hydroxyphosphinyl-piruvate	/	1 ^[33]
30	Pregnenolone sulfate	HMDB0000774	1 ^[14]	90	LPE (16:0)	/	1 ^[14]
31	L-Octanoylcarnitine	HMDB0000791	1 ^[15]	91	L-Glutamic acid dibutyl ester	/	1 ^[29]
32	L-Valine	HMDB0000883	1 ^[63]	92	LPC (16:1)	/	1 ^[14]
33	Traumatic acid	HMDB0000933	1 ^[29]	93	LPC (22:6)	/	1 ^[14]
34	Trehalose	HMDB0000975	1 ^[29]	94	LPC C 16:0	/	1 ^[27]
35	(S)-Succinyl dihydroliipoamide	HMDB0001177	1 ^[29]	95	LPC C 18: 0	/	1 ^[27]
36	Pyridoxamine	HMDB0001431	1 ^[29]	96	LPC C 18: 1	/	1 ^[27]
37	Asymmetric dimethylarginine	HMDB0001539	1 ^[29]	97	LPC C 18:2	/	1 ^[27]
38	Caffeine	HMDB0001847	1 ^[29]	98	LPC C 20:4	/	1 ^[27]
39	27-Nor-5b-cholestane-3a,7a,12a,24,25-pentol	HMDB0002126	1 ^[29]	99	L-gamma-Cyano-gamma-aminobutyric acid	/	1 ^[29]
40	Dodecanoylcarnitine	HMDB0002250	1 ^[15]	100	LPE (18:2)	/	1 ^[14]
41	Terephthalic acid	HMDB0002428	1 ^[29]	101	Methoxsalen Metabolite	/	1 ^[29]
42	5-Methylcytosine	HMDB0002894	1 ^[60]	102	Propionylglycine methyl ester	/	1 ^[29]
43	Isoacitretin	HMDB0003039	1 ^[29]	103	N,N-Didemethylchlorpromazine	/	1 ^[29]
44	5-Methoxyindoleacetate	HMDB0004096	1 ^[29]	104	Nε-Methyl-L-lysine	/	1 ^[29]
45	L-Urobilin	HMDB0004159	1 ^[29]	105	N-methyl-Gabapentin	/	1 ^[29]
46	Guaifenesin	HMDB0004998	1 ^[29]	106	oleylcarnitine	/	1 ^[15]
47	MG(18:0/0:0/0:0)	HMDB0011131	1 ^[14]	107	Phenyl sulfate	/	1 ^[29]
48	LysoPC(O-18:0)	HMDB0011149	1 ^[14]	108	Phenytoin-N-glucuronide	/	1 ^[29]
49	MG(16:0/0:0/0:0)	HMDB0011564	1 ^[14]	109	PPE(16:0/22:6)	/	1 ^[14]
50	Methylphenidate	HMDB0014566	1 ^[29]	110	PPE(18:1/20:4)	/	1 ^[14]
51	Isoniazid	HMDB0015086	1 ^[29]	111	Pro Lys Pro	/	1 ^[29]
52	4-Hydroxybenzeneacetoneitrile	HMDB0029757	1 ^[29]	112	SULBACTAM	/	1 ^[29]
53	Clofenotane	HMDB0032127	1 ^[29]	113	METHYL 7-DESHYDROXYPIROGALLIN-4-CA	/	1 ^[29]

54	Succinic anhydride	HMDB0032523	1 ^[29]	RBOXYLATE		
55	Tyrosyl-Serine	HMDB0029114	1 ^[33]	114	tetradecadienoylcarni tine	/ 1 ^[15]
56	Anthracene	METPA1122	1 ^[29]	115	tetradecenoylcarnitin e	/ 1 ^[15]
57	1,3-Glycerol dinitrate	/	1 ^[29]	116	tripeptide	/ 1 ^[63]
58	10-hydroxy-11-dodecenoic acid	/	1 ^[29]	117	13E,17-octadecadienoic acid	/ 1 ^[29]
59	5-[2-(hydroxymethyl)-5-methylphenoxy]-2,2-dimethyl-Pentanoic acid (Gemfibrozil M4)	/	1 ^[29]	118	Tyr Pro	/ 1 ^[29]
60	(22R)-1alpha,22,25-trihydroxy-26,27-dimethyl-23,24-tetrahydro-24a-homo-20-epivitamin D3 / (22R)-1a	/	1 ^[29]	119	1alpha,25-dihydroxy-2beta-(5-hydroxypentoxyl)vitamin D3 / 1alpha,25-dihydroxy-2beta-(5-hydroxypentoxyl) 120 1alpha,25-dihydroxy-3-deoxy-3-thiavitamin D3 / 1alpha,25-dihydroxy-3-deoxy-3-thiacholecalciferol	/ 1 ^[29]

^areference number are same as in Supplementary Table 2. Frequency indicates the reported frequency of the metabolite in previous studies included in this systematic review.

Supplementary Table 7. Metabolites related with Alzheimer's disease replicated in previous prospective studies

Metabolite Name	HMDB ID	Frequency ^a
L-Glutamine	HMDB0000641	1 ^[58]
Dihydroxyacetone	HMDB0001882	1 ^[58]
Palmitic acid	HMDB0000220	1 ^[64]
Linoleic acid	HMDB0000673	1 ^[64]
Myristic acid	HMDB0000806	1 ^[64]
Stearic acid	HMDB0000827	1 ^[64]
Oleic acid	HMDB0000207	1 ^[64]
S-HDL-free cholesterol	/	1 ^[58]
M-HDL-phospholipids	/	1 ^[58]

^areference number are same as in Supplementary Table 2. Frequency indicates the reported frequency of the metabolite in previous studies included in this systematic review.

Supplementary Table 8. Metabolites related with the conversion from mild cognitive impairment to Alzheimer's disease in previous prospective studies

Number	Metabolite Name	HMDB ID	Frequency ^a
1	Creatine	HMDB0000064	1 ^[51]
2	L-Histidine	HMDB0000177	1 ^[33]
3	L-Lactic acid	HMDB0000190	1 ^[35]
4	Pyruvic acid	HMDB0000243	1 ^[35]
5	Xanthine	HMDB0000292	1 ^[33]
6	2,4-Dihydroxybutanoic acid	HMDB0000360	1 ^[35]
7	L-Arginine	HMDB0000517	1 ^[51]
8	4-Aminobutyraldehyde	HMDB0001080	1 ^[51]
9	5'-Methylthioadenosine	HMDB0001173	1 ^[51]
10	Spermine	HMDB0001256	1 ^[51]
11	Spermidine	HMDB0001257	1 ^[51]
12	Putrescine	HMDB0001414	1 ^[51]
13	D-Ribose 5-phosphate	HMDB0001548	1 ^[35]
14	PC(o-22:0/18:3(6Z,9Z,12Z))	HMDB0013445	1 ^[65]
15	PC(o-22:0/20:4(8Z,11Z,14Z,17Z))	HMDB0013448	1 ^[65]
16	PC(o-2:1(13Z)/22:3(10Z,13Z,16Z))	HMDB0013453	1 ^[65]
17	PC(o-18:0/18:2(9Z,12Z))	HMDB0013418	1 ^[65]
18	PC(16:0/20:5(5Z,8Z,11Z,14Z,17Z))	HMDB0007984	1 ^[35]
19	lysoPC (16:0)	/	1 ^[35]
20	PC (18:0/20:4)	/	1 ^[35]
21	PC (O-18:1/16:0)	/	1 ^[35]
22	N1 or N8-acetyl-spermidine	/	1 ^[51]
23	SM (OH) C14:1	/	1 ^[65]
24	SM C16:0	/	1 ^[65]
25	SM C20:2	/	1 ^[65]
26	PC (16:0/16:0)	/	1 ^[35]

^areference number are same as in Supplementary Table 2. Frequency indicates the reported frequency of the metabolite in previous studies included in this systematic review.

Supplementary Table 9. Pathways altered in mild cognitive impairment and Alzheimer's disease identified by direct extraction and pathway enrichment analysis

Groups/Pathway Name	Biosamples	Software	Source ^a	Frequency ^b
AD VS CN				
Alanine, aspartate and glutamate metabolism	brain, CSF, serum, urine	Mummichog, ORA, MetPA	enrichment, article	3
TCA cycle	brain, CSF, serum, plasma	Mummichog, MetaCore, MetPA	enrichment, article	3
Purine metabolism	brain, CSF, serum, plasma, urine, saliva	Metaboanalyst, ORA, Mummichog	enrichment, article	3
Arginine and proline metabolism	brain, CSF, serum, saliva, plasma, urine	Mummichog, ORA	enrichment, article	2
Cysteine and methionine metabolism	brain, CSF, serum, plasma, urine	Mummichog, ORA	enrichment, article	2
Glycine, serine and threonine metabolism	brain, CSF, serum, plasma, urine	Mummichog, ORA	enrichment, article	2
Pantothenate and CoA biosynthesis	brain, CSF, serum, plasma	Mummichog, ORA	enrichment, article	2
tryptophan metabolism	plasma, serum	MetaCore, MetPA	article	2
Aminoacyl-tRNA biosynthesis	brain, CSF, serum, plasma, urine	Mummichog	enrichment	1
Nitrogen metabolism	brain, CSF, serum, plasma, urine	Mummichog	enrichment	1
Glutathione metabolism	brain, CSF, serum, plasma, urine, saliva	Mummichog	enrichment	1
beta-Alanine metabolism	brain, CSF, serum, plasma, urine	Mummichog	enrichment	1
Valine, leucine and isoleucine biosynthesis	brain, CSF, serum, plasma	Mummichog	enrichment	1
Sphingolipid metabolism	brain, CSF, serum, plasma, saliva	Mummichog	enrichment	1
Biotin metabolism	brain, CSF, plasma, urine	Mummichog	enrichment	1
Butanoate metabolism	brain, CSF, plasma	Mummichog	enrichment	1
Propanoate metabolism	brain, CSF, serum, plasma	Mummichog	enrichment	1
Cholesterol and sphingolipids transport	plasma, CSF	MetaCore	article	1
Vitamin d2 metabolism	plasma	MetaCore	article	1
Polyamine metabolism	plasma	MetaCore	article	1
Urea cycle	plasma, CSF	MetaCore	article	1
Intracellular cholesterol transport	plasma, CSF	MetaCore	article	1
(L)-Arginine metabolism	plasma, CSF	MetaCore	article	1
cortisone biosynthesis and metabolism	plasma, CSF	MetaCore	article	1
lipid metabolism	plasma	MetaCore	article	1
FXR-regulated cholesterol and bile acid	plasma	MetaCore	article	1

transport				
Lysine metabolism	plasma	MetaCore	article	1
Bile acid metabolism	plasma, CSF	MetaCore	article	1
Regulation of CFTR gating	plasma, CSF	MetaCore	article	1
Role of VDR in regulation of genes involved in osteoporosis	plasma	MetaCore	article	1
Vitamin D3 metabolic C-23 and C-24 pathways	plasma	MetaCore	article	1
Triacylglycerol biosynthesis in obesity and diabetes mellitus, type II	plasma	MetaCore	article	1
Mechanism of action of DGaT1 in obesity and diabetes mellitus, type II	plasma	MetaCore	article	1
Aminoacyl-tRNA biosynthesis in mitochondria	plasma	MetaCore	article	1
Triacylglycerol metabolism p.2	plasma	MetaCore	article	1
Muscle contraction_nNOS signaling in skeletal muscles	plasma	MetaCore	article	1
Aminoacyl-tRNA biosynthesis in cytoplasm	plasma	MetaCore	article	1
Regulation of lipid MB FXR-dependent negative-feedback regulation of bile acid concentration	plasma	MetaCore	article	1
Cortisol biosynthesis from cholesterol	plasma	MetaCore	article	1
Development_Activation of astroglia cell proliferation by ACM3	plasma	MetaCore	article	1
Fatty Acid Omega Oxidation	plasma	MetaCore	article	1
Prostaglandin 2 biosynthesis and metabolism	CSF	MetaCore	article	1
Aspartate and asparagine metabolism	CSF	MetaCore	article	1
Nicotine metabolism in liver	CSF	MetaCore	article	1
Cholesterol and sphingolipids transport/transport from Golgi	CSF	MetaCore	article	1
Glycolysis and gluconeogenesis	CSF	MetaCore	article	1
FXR-regulated cholesterol and bile acid cellular transport	CSF	MetaCore	article	1
Saturated fatty acids metabolism	CSF	MetaCore	article	1
Cortisol BS from cholesterol	CSF	MetaCore	article	1
arginineand proline metabolism	serum	MetPA	article	1
histidine metabolism	serum	MetPA	article	1
Pyruvate metabolism	serum	MetPA	article	1
phenylalanine metabolism	serum	MetPA	article	1
MCI VS CN				
lysine metabolism	plasma	MetaCore	article	2
tryptophan metabolism	plasma	MetaCore	article	2
Polyamine metabolism	plasma	MetaCore	article	2
Urea cycle	CSF, plasma	MetaCore	article	2
Arginine and proline metabolism	CSF, plasma	Mummichog	enrichment	1
Butanoate metabolism	CSF, plasma, serum	Mummichog	enrichment	1

Alanine, aspartate and glutamate metabolism	CSF, plasma, serum	Mummichog	enrichment	1
beta-Alanine metabolism	CSF, plasma	Mummichog	enrichment	1
Glycine, serine and threonine metabolism	CSF, plasma, serum	Mummichog	enrichment	1
Sphingolipid metabolism	plasma, serum	Mummichog	enrichment	1
Glutathione metabolism	CSF, plasma	Mummichog	enrichment	1
Synthesis and degradation of ketone bodies	CSF, plasma, serum	Mummichog	enrichment	1
Glycolysis or Gluconeogenesis	CSF, serum	Mummichog	enrichment	1
Phenylalanine metabolism	CSF, plasma, serum	Mummichog	enrichment	1
D-Arginine and D-ornithine metabolism	plasma	Mummichog	enrichment	1
Vitamin B6 metabolism	CSF, plasma	Mummichog	enrichment	1
Pyruvate metabolism	CSF, serum	Mummichog	enrichment	1
TCA cycle	plasma, CSF	MetaCore	article	1
saturated fatty acid metabolism	plasma	MetaCore	article	1
prostaglandin 2 biosynthesis and metabolism	plasma, CSF	MetaCore	article	1
aminoacyl-tRNA biosynthesis in cytoplasm	plasma	MetaCore	article	1
neurophysiological process_ delta-type opioid receptor in the nervous system	plasma	MetaCore	article	1
melatonin signaling	plasma	MetaCore	article	1
Nicotine MB in liver	CSF	MetaCore	article	1
Cortisone biosynthesis and metabolism	CSF	MetaCore	article	1
Role of Diethylhexyl Phthalate and Tributyltin in fat differentiation	CSF	MetaCore	article	1
Phospholipid metabolism	plasma	MetaCore	article	1
CHOL & Sphingolipid transport	plasma	MetaCore	article	1
Sat fatty acid biosynthesis	plasma	MetaCore	article	1
Regulation of lipid metabolism	plasma	MetaCore	article	1
Glycolysis & GNG p.2	plasma	MetaCore	article	1
Transport of IC CHO	plasma	MetaCore	article	1
Niacin-HDL metabolism	plasma	MetaCore	article	1
Plasmalogen biosynthesis	plasma	MetaCore	article	1
UMP biosynthesis	plasma	MetaCore	article	1
GABA biosynthesis& metabolism	plasma	MetaCore	article	1
PG 2 biosynthesis & metabolism	plasma	MetaCore	article	1
Glycolysis GNG(short map)	plasma	MetaCore	article	1
L-Arginine metabolism	plasma	MetaCore	article	1
AD VS MCI				
Nitrogen metabolism	CSF, serum, plasma	Mummichog, MetaCore	enrichment, article	2
Aminoacyl-tRNA biosynthesis	CSF, serum, plasma	Mummichog	enrichment	1
Phenylalanine, tyrosine and tryptophan biosynthesis	CSF, plasma	Mummichog	enrichment	1
Pyrimidine metabolism	CSF, plasma, DNA of brain tissue	Mummichog	enrichment	1
Lysine metabolism	plasma	MetaCore	article	1

Cholesterol metabolism	plasma	MetaCore	article	1
Arginine metabolism	plasma	MetaCore	article	1
Vitamin D3 metabolic C-23 and C-24 pathways	plasma	MetaCore	article	1
Aminoacyl-tRNA biosynthesis in cytoplasm	plasma	MetaCore	article	1
Polyamine metabolism	plasma	MetaCore	article	1
Urea cycle	plasma	MetaCore	article	1
Bile Acid Biosynthesis	plasma	MetaCore	article	1
Aminoacyl-tRNA biosynthesis in mitochondrion	plasma	MetaCore	article	1
Histidine-glutamate-glutamine metabolism	plasma	MetaCore	article	1
Neurophysiological process_GABAergic neurotransmission	plasma	MetaCore	article	1
tryptophan metabolism	plasma	MetaCore	article	1
Proline metabolism	plasma	MetaCore	article	1
Saturated fatty acid biosynthesis	plasma	MetaCore	article	1
Catecholamine metabolism	plasma	MetaCore	article	1
Muscle contraction_nNOS Signaling in Skeletal Muscle	plasma	MetaCore	article	1
Acetylcholine biosynthesis and metabolism	plasma	MetaCore	article	1
Development Activation of astroglial cells proliferation by ACM3	plasma	MetaCore	article	1
Fatty Acid Omega Oxidation	plasma	MetaCore	article	1
Nicotine signaling in GABAergic neurons	plasma	MetaCore	article	1
Neurophysiological process_ACM1 and ACM2 in neuronal...	plasma	MetaCore	article	1
Serotonin modulation of dopamine release in nicotine addiction	plasma	MetaCore	article	1
Transport ACM3 in salivary glands	plasma	MetaCore	article	1
Development_ACM2 and ACM4 activation of ERK	plasma	MetaCore	article	1
Prostaglandin 2 biosynthesis and metabolism	CSF	MetaCore	article	1
Cortisone biosynthesis and metabolism	CSF	MetaCore	article	1
Regulation of CFTR gating (nomal and CF)	CSF	MetaCore	article	1
HETE and HPETE biosynthesis and metabolism	CSF	MetaCore	article	1
Neurophysiological process_Role of CDK5 in presynaptic signaling	CSF	MetaCore	article	1
Role of Diethylhexyl Phthalate and Tributyltin in fat cell differentiation	CSF	MetaCore	article	1
Phosphatidylinositol metabolism	CSF	MetaCore	article	1
Aldosterone biosynthesis and metabolism	CSF	MetaCore	article	1
Transcription role of VDR in regulation of genes involved in osteoporosis	CSF	MetaCore	article	1
Tyrosine metabolism p.1(dopamine)	CSF	MetaCore	article	1
CN VS CN_AD				

Fatty acid biosynthesis	serum	Mummichog	enrichment	1
D-Glutamine and D-glutamate metabolism	plasma	Mummichog	enrichment	1
Linoleic acid metabolism	serum	Mummichog	enrichment	1
MCI VS MCI_AD				
Arginine and proline metabolism	plasma, serum	Mummichog	enrichment	1
beta-Alanine metabolism	Plasma, CSF	Mummichog	enrichment	1
Glutathione metabolism	plasma	Mummichog	enrichment	1
Glycolysis or Gluconeogenesis	serum	Mummichog	enrichment	1
Pentose phosphate pathway	serum	Mummichog	enrichment	1
pentose phosphate pathway	serum	MPEA	article	1
Pyruvate metabolism	serum	Mummichog	enrichment	1
Glycine, serine and threonine metabolism	plasma, serum	Mummichog	enrichment	1
Cysteine and methionine metabolism	plasma, serum	Mummichog	enrichment	1
D-Arginine and D-ornithine metabolism	plasma	Mummichog	enrichment	1
CHOL sphingolipid transport	plasma	MetaCore	article	1
Polyamine metabolism	plasma	MetaCore	article	1
Transport of IC CHOL	plasma	MetaCore	article	1
Glycolysis & GNG	plasma	MetaCore	article	1
Prostaglandin 2 biosynthesis and metabolism	plasma	MetaCore	article	1
Regulation of lipid metabolism	plasma	MetaCore	article	1
Ascorbate metabolism	plasma	MetaCore	article	1
Plasmalogen biosynthesis	plasma	MetaCore	article	1
Lysine metabolism	plasma	MetaCore	article	1
Tyrosine metabolism	plasma	MetaCore	article	1
Catecholamine metabolism	plasma	MetaCore	article	1
L-Arginine metabolism	plasma	MetaCore	article	1
NAE & PL A2 pathway	plasma	MetaCore	article	1

Abbreviations: ORA, over-representation analysis.

^aThis column gave information on how we obtain this pathway. “Enrichment” indicated that we conducted pathway enrichment analyses using differential metabolites extracted from included studies; “article” means that original articles conducted pathway enrichment analysis and we extracted these pathways’ name directly from literature.

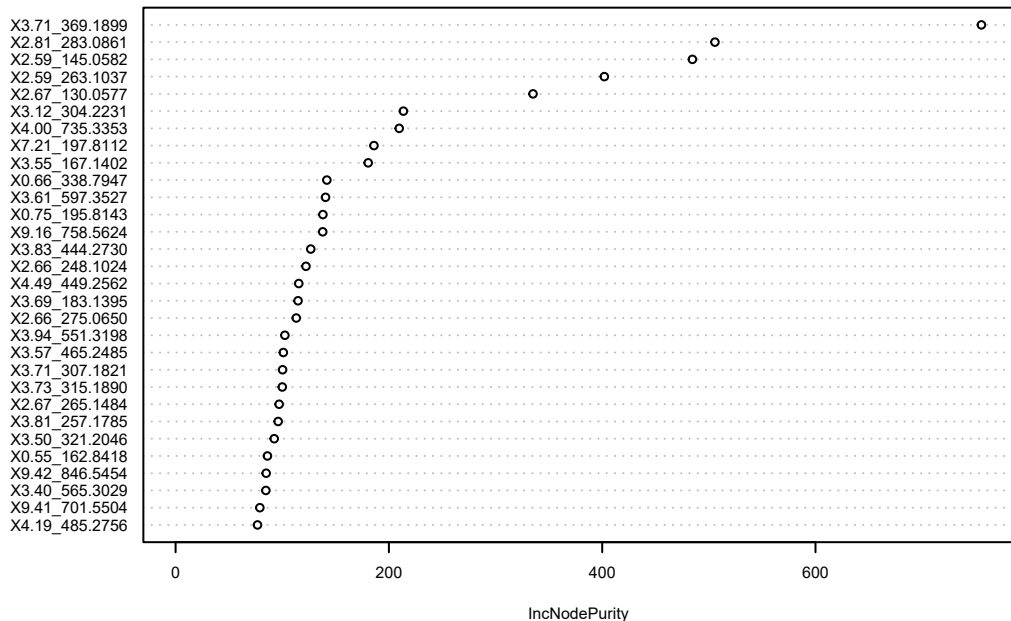
^bThis frequency of pathway includes the frequency reported in previous studies in this systematic review and the frequency of pathway enriched in our analysis based on the extracted metabolites.

Supplementary Table 10. Pathways altered in Alzheimer's disease identified in brain tissue, CSF, plasma and serum

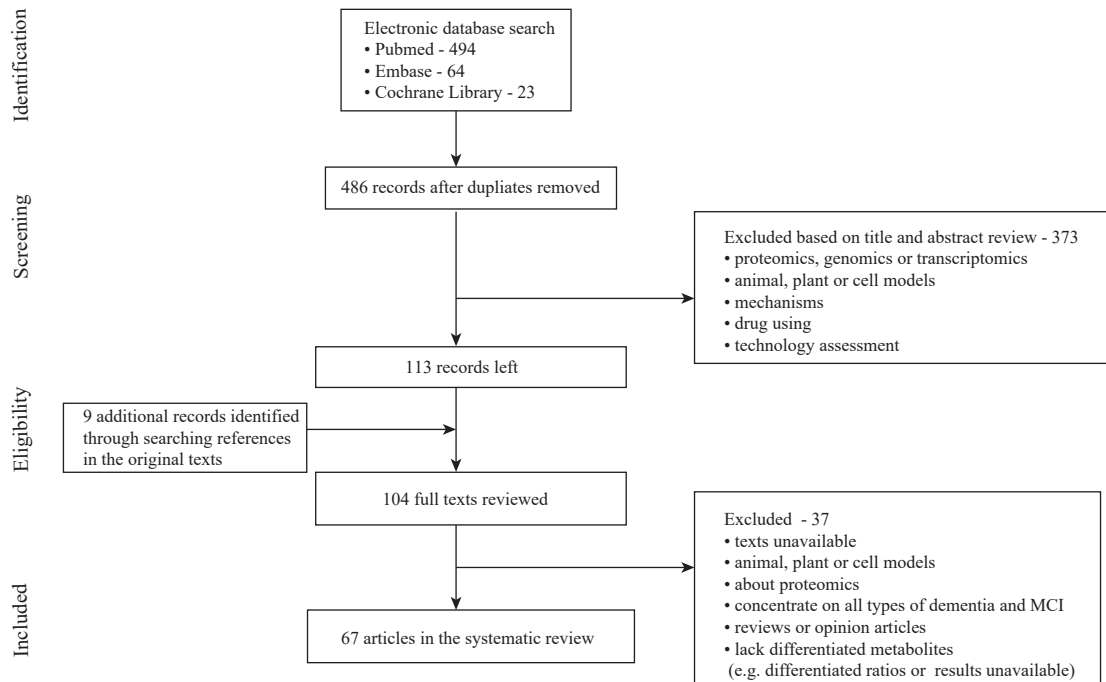
Pathway Name	Biosample type
Glycolysis or Gluconeogenesis	CSF
Aldosterone biosynthesis and metabolism	CSF
Aspartate and asparagine metabolism	CSF
Cholesterol and sphingolipids transport/transport from Golgi	CSF
Cortisol BS from cholesterol	CSF
FXR-regulated cholesterol and bile acid cellular transport	CSF
Glycolysis and gluconeogenesis	CSF
HETE and HPETE biosynthesis and metabolism	CSF
Neurophysiological process_Role of CDK5 in presynaptic signaling	CSF
Nicotine MB in liver	CSF
Nicotine metabolism in liver	CSF
Phosphatidylinositol metabolism	CSF
Prostaglandin 2 biosynthesis and metabolism	CSF
Regulation of CFTR gating (nomal and CF)	CSF
Role of Diethylhexyl Phthalate and Tributyltin in fat cell differentiation	CSF
Role of Diethylhexyl Phthalate and Tributyltin in fat differentiation	CSF
Saturated fatty acids metabolism	CSF
Transcription role of VDR in regulation of genes involved in osteoporosis	CSF
Tyrosine metabolism p.l(dopamine)	CSF
alpha-Linolenic acid metabolism	plasma
D-Arginine and D-ornithine metabolism	plasma
D-Glutamine and D-glutamate metabolism	plasma
Glycerophospholipid metabolism	plasma
Acetylcholine biosynthesis and metabolism	plasma
aminoacyl-tRNA biosynthesis in cytoplasm	plasma
Aminoacyl-tRNA biosynthesis in mitochondria	plasma
Aminoacyl-tRNA biosynthesis in mitochondrion	plasma
Arginine metabolism	plasma
Ascorbate metabolism	plasma
Bile Acid Biosynthesis	plasma
Catecholamine metabolism	plasma
CHOL & Sphingolipid transport	plasma
CHOL sphingolipid transport	plasma
Cholesterol metabolism	plasma
Cortisol biosynthesis from cholesterol	plasma
Development Activation of astroglial cells proliferation by ACM3	plasma
Development_ACM2 and ACM4 activation of ERK	plasma
Development_Activation of astroglia cell proliferation by ACM3	plasma

Fatty Acid Omega Oxidation	plasma
FXR-regulated cholesterol and bile acid transport	plasma
GABA biosynthesis& metabolism	plasma
Glycolysis & GNG	plasma
Glycolysis GNG(short map)	plasma
Histidine-glutamate-glutamine metabolism	plasma
L-Arginine metabolism	plasma
lipid metabolism	plasma
Lysine metabolism	plasma
Mechanism of action of DGaT1 in obesity and diabetes mellitus, type II	plasma
melatonin signaling	plasma
Muscle contraction_nNOS Signaling in Skeletal Muscle	plasma
NAE & PL A2 pathway	plasma
neurophysiological process_ delta-type opioid receptor in the nervous system	plasma
Neurophysiological process_ ACM1 and ACM2 in neuronal...	plasma
Neurophysiological process_ GABAergic neurotransmission	plasma
Niacin-HDL metabolism	plasma
Nicotine signaling in GABAergic neurons	plasma
PG 2 biosynthesis & metabolism	plasma
Phospholipid metabolism	plasma
Plasmalogen biosynthesis	plasma
Polyamine metabolism	plasma
Proline metabolism	plasma
prostaglandin 2 biosynthesis and metabolism	plasma
Regulation of lipid MB FXR-dependent negative-feedback regulation of bile acid concentration	plasma
Regulation of lipid metabolism	plasma
Role of VDR in regulation of genes involved in osteoporosis	plasma
Sat fatty acid biosynthesis	plasma
saturated fatty acid metabolism	plasma
Serotonin modulation of dopamine release in nicotine addiction	plasma
Transport ACM3 in salivary glands	plasma
Transport of IC CHOL	plasma
Triacylglycerol biosynthesis in obesity and diabetes mellitus, type II	plasma
Triacylglycerol metabolism	plasma
Tyrosine metabolism	plasma
UMP biosynthesis	plasma
Vitamin d2 metabolism	plasma
Vitamin D3 metabolic C-23 and C-24 pathways	plasma
Pentose phosphate pathway	serum
Fatty acid biosynthesis	serum

arginineand proline metabolism	serum
histidine metabolism	serum
pyruvatemetabolism	serum
Phenylalanine, tyrosine and tryptophan biosynthesis	CSF and plasma
Pyrimidine metabolism	CSF and plasma
Vitamin B6 metabolism	CSF and plasma
(L)-Arginine metabolism	CSF and plasma
Bile acid metabolism	CSF and plasma
Cholesterol and sphingolipids transport	CSF and plasma
cortisone biosynthesis and metabolism	CSF and plasma
Intracellular cholesterol transport	CSF and plasma
Regulation of CFTR gating	CSF and plasma
Urea cycle	CSF and plasma
Linoleic acid metabolism	serum and plasma
tryptophan metabolism	serum and plasma
Pyruvate metabolism	CSF and serum
Biotin metabolism	brain, CSF, plasma
Phenylalanine metabolism	CSF, plasma, serum
Synthesis and degradation of ketone bodies	CSF, plasma, serum
Alanine, aspartate and glutamate metabolism	brain, CSF, plasma, serum
TCA cycle	brain, CSF, plasma, serum
Purine metabolism	brain, CSF, plasma, serum
Arginine and proline metabolism	brain, CSF, plasma, serum
Cysteine and methionine metabolism	brain, CSF, plasma, serum
Glycine, serine and threonine metabolism	brain, CSF, plasma, serum
Pantothenate and CoA biosynthesis	brain, CSF, plasma, serum
Aminoacyl-tRNA biosynthesis	brain, CSF, plasma, serum
Nitrogen metabolism	brain, CSF, plasma, serum
Glutathione metabolism	brain, CSF, plasma, serum
beta-Alanine metabolism	brain, CSF, plasma, serum
Valine, leucine and isoleucine biosynthesis	brain, CSF, plasma, serum
Sphingolipid metabolism	brain, CSF, plasma, serum
Butanoate metabolism	brain, CSF, plasma, serum
Propanoate metabolism	brain, CSF, plasma, serum

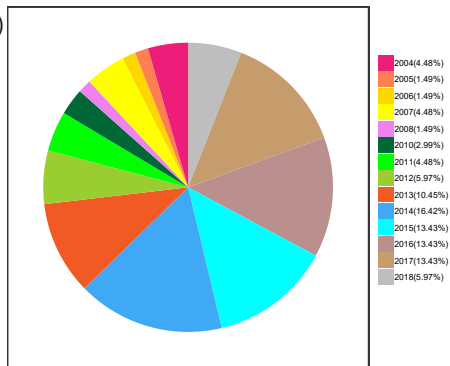


Supplementary Fig. 1

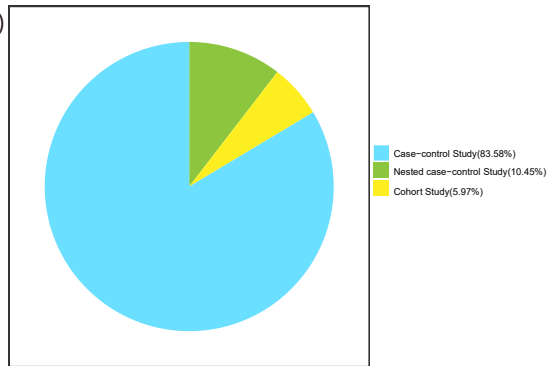


Supplementary Fig. 2

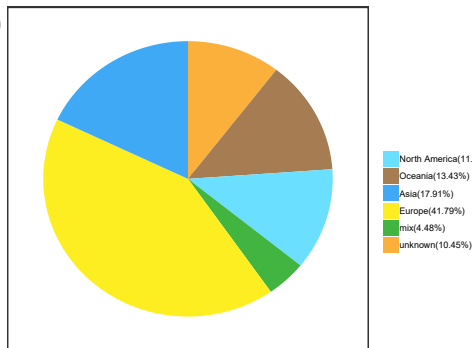
(A)



(B)



(C)



(D)

