Food and microbiota metabolites associate with cognitive decline in older subjects: A twelve-year prospective study

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Table S1. Concentrations (expressed as mean ± standard deviation, μg L^{-1}) detected within the cases and controls subjects for the metabolites identified to be associated with cognitive decline by LASSO regression in the discovery (Bordeaux) and validation (Dijon) sample sets.

Metabolites	**Bordeaux sample set**		**Dijon sample set**	
	cases	**controls**	**cases**	**controls**
Phenolic acids and derivatives				
Vanillin	21.3 ± 38.2	29.3 ± 45.8	7.2 ± 31.1	13.2 ± 47.7
3-Hydroxybenzoic acid sulfate (3-HBA-S)	8.2 ± 13.6	8.6 ± 12.1	14.5 ± 19.0	16.1 ± 18.0
2-Hydroxybenzoic acid (2-HBA)	189.2 ± 1508.2	100.5 ± 405.6	162.1 ± 1200.9	50.1 ± 185.7
3,4-Dihydroxybenzoic acid (3,4-DHBA)	40.8 ± 93.9	45.3 ± 65.2	32.4 ± 103.6	23.6 ± 26.8
3-Hydroxyphenylacetic acid sulfate (3-HPAA-S)	52358.7 ± 104446.7	52881.8 ± 121984.6	60125.6 ± 132259.5	23424.6 ± 71751.2
Dihydroferulic acid sulfate (DHFA-S)	3.0 ± 8.7	4.0 ± 8.9	2.7 ± 5.9	2.7 ± 6.1
3-Hydroxyhippuric acid (3-HHA)	49.1 ± 58.5	50.9 ± 66.4	33.8 ± 41.4	42.2 ± 50.5
Xanthine alkaloids				
3-Methylxanthine	51.0 ± 140.8	75.5 ± 168.1	80.6 ± 173.0	65.4 ± 113.3
Caffeine	1202.7 ± 1403.1	888.0 ± 1044.1	692.6 ± 943.4	687.5 ± 854.2
1,3-Dimethyluric acid	46.9 ± 34.7	40.5 ± 29.8	34.9 ± 38.2	40.7 ± 33.5
Artificial sweeteners				
Saccharin	11.5 ± 35.4	6.8 ± 26.4	5.9 ± 25.2	3.6 ± 13.8
Acesulfame K	7.6 ± 35.3	5.2 ± 24.5	2.8 ± 9.3	5.6 ±

				29.2
Other food-related metabolites				
Umbelliferone sulfate	1.7 ± 1.6	3.4 ± 13.9	1.3 ± 2.2	1.6 ± 3.7
2-Furoylglycine	9.6 ± 30.0	11.4 ± 41.4	6.8 ± 20.2	5.0 ± 9.5
Tartaric acid	111.4 ± 140.6	97.1 ± 134.4	101.5 ± 193.5	74.7 ± 142.2
Proline betaine	278.3 ± 256.5	220.2 ± 222.0	277.6 ± 292.7	315.8 ± 275.2
Enterolactone sulfate	1.1 ± 1.6	1.4 ± 1.7	0.2 ± 1.0	0.1 ± 0.5
5-(4'-Hydroxy-3'-methoxyphenyl)-γ-valerolactone sulfate (MHPV-S)	21.4 ± 55.5	34.2 ± 74.5	35.0 ± 101.3	19.0 ± 55.6
Ergothioneine	1268.3 ± 1637.0	1308.8 ± 1807.0	272.3 ± 290.7	381.7 ± 398.5
Ethyl sulfate	15.8 ± 44.6	13.8 ± 44.1	7.6 ± 19.9	4.6 ± 14.9
cis-Resveratrol 3-sulfate	6.8 ± 8.2	5.7 ± 6.4	20.6 ± 30.4	22.3 ± 34.3
Aromatic amino acid derivatives				
Indoxyl sulfate	1205.8 ± 809.7	1291.9 ± 690.6	745.1 ± 410.3	706.1 ± 388.9
4-Hydroxyphenylacetic acid glucuronide (4-HPAA-G)	82.8 ± 281.2	46.9 ± 180.5	76.0 ± 324.2	21.3 ± 114.8
3,4-Dihydroxyphenylacetic acid sulfate (DOPAC-S)	9019.7 ± 21384.7	9205.1 ± 26811.2	12516.7 ± 29668.5	5275.2 ± 11550.2
4-Hydroxyphenyllactic acid sulfate (4-HPLA-S)	452.1 ± 1055.8	440.1 ± 1239.4	499.6 ± 1305.7	212.2 ± 629.3
5-Hydroxytryptophan	93.0 ± 48.9	93.4 ± 43.4	154.2 ± 115.2	204.0 ± 181.2
4-Methylcatechol sulfate (4-MeCAT-S)	3906.2 ± 4286.8	5058.7 ± 8976.6	4963.8 ± 7482.6	3888.8 ± 4501.6
Phenylacetylglutamine	1025.6 ± 726.6	857.4 ± 536.8	1050.2 ± 611.4	951.3 ± 647.0

p-Cresol sulfate	4395.1 ± 1980.6	4224.9 ± 1894.8	3773.7 ± 1883.7	3282.5 ± 1815.3
Serotonin	77.0 ± 29.9	76.5 ± 27.0	47.0 ± 38.5	54.8 ± 41.9
Fatty acids and derivatives				
Myristic acid	17318.1 ± 11356.4	15060.6 ± 10631.2	20858.1 ± 7616.1	18396.0 ± 5991.8
Lauric acid	2989.4 ± 2704.4	2592.3 ± 2172.4	11949.8 ± 7133.1	10055.2 ± 5493.6
Linoleoyl-carnitine	89.1 ± 39.5	76.0 ± 34.1	53.8 ± 5.5	54.6 ± 10.9
Other endogenous metabolites				
Betaine	25364.7 ± 11863.7	29467.6 ± 12956.8	8044.8 ± 4121.9	8149.0 ± 3630.6
Dehydroepiandrosterone sulfate (DHEAS)	593.8 ± 502.3	666.3 ± 527.8	370.8 ± 309.1	356.1 ± 292.0
Citric acid	5608.7 ± 5315.1	6596.5 ± 6718.9	3800.3 ± 3739.1	3970.9 ± 3324.0
Thiamine	26.2 ± 37.5	26.2 ± 28.7	6.9 ± 19.5	7.7 ± 16.6

Table S2. Metabolites associated with subsequent cognitive decline in the total sample (i.e., combination of the populations from Bordeaux and Dijon) identified by least absolute shrinkage and selection operator (LASSO) penalized conditional logistic regression.

Metabolites	**Odds ratio**
Phenolic acids and derivatives	
3-Hydroxybenzoic acid sulfate (3-HBA-S)	0.87

Hippuric acid (HA)	0.98
Vanillin	0.83
Xanthine alkaloids	
3-Methylxanthine	0.86
1-Methylxanthine	0.96
Artificial sweeteners	
Saccharin	1.26
Other food-related metabolites	
Umbelliferone sulfate	0.91
Ergothioneine	0.90
Aromatic amino acid derivatives	
Phenylacetylglutamine	1.23
p-Cresol glucuronide	1.19
5-Hydroxytryptophan	0.89
5-Hydroxyindoleacetic acid	1.10
4-Hydroxyphenyllactic acid sulfate (4-HPLA-S)	1.12
Fatty acids and derivatives	
Oleic acid	1.12
Linoleic acid	1.19
Lauroyl-carnitine	1.18
Oleoyl-carnitine	1.18
Other endogenous metabolites	
Alanine	1.09
Glutamic acid	1.14
Carnosine	1.22
Creatinine	1.00
Guanosine	1.06
Riboflavin	1.02
Pantothenic acid	1.13

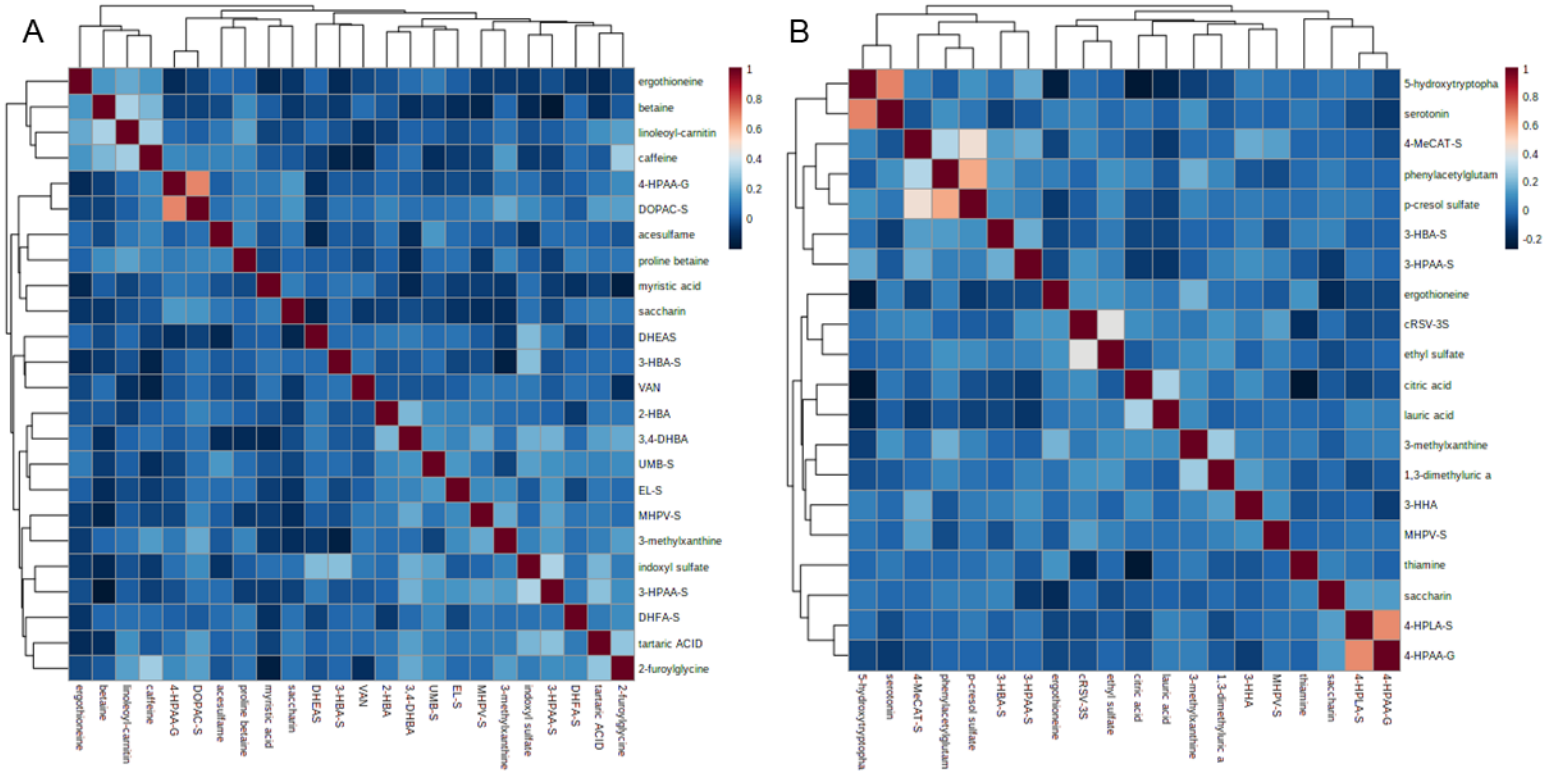

Figure S1. Pearson's correlation analysis between the metabolites that were identified by bootstrap-enhanced least absolute shrinkage and selection operator (LASSO) penalized conditional logistic regression to be associated with subsequent cognitive decline in the discovery (Bordeaux, A) and validation (Dijon, B) sample sets.

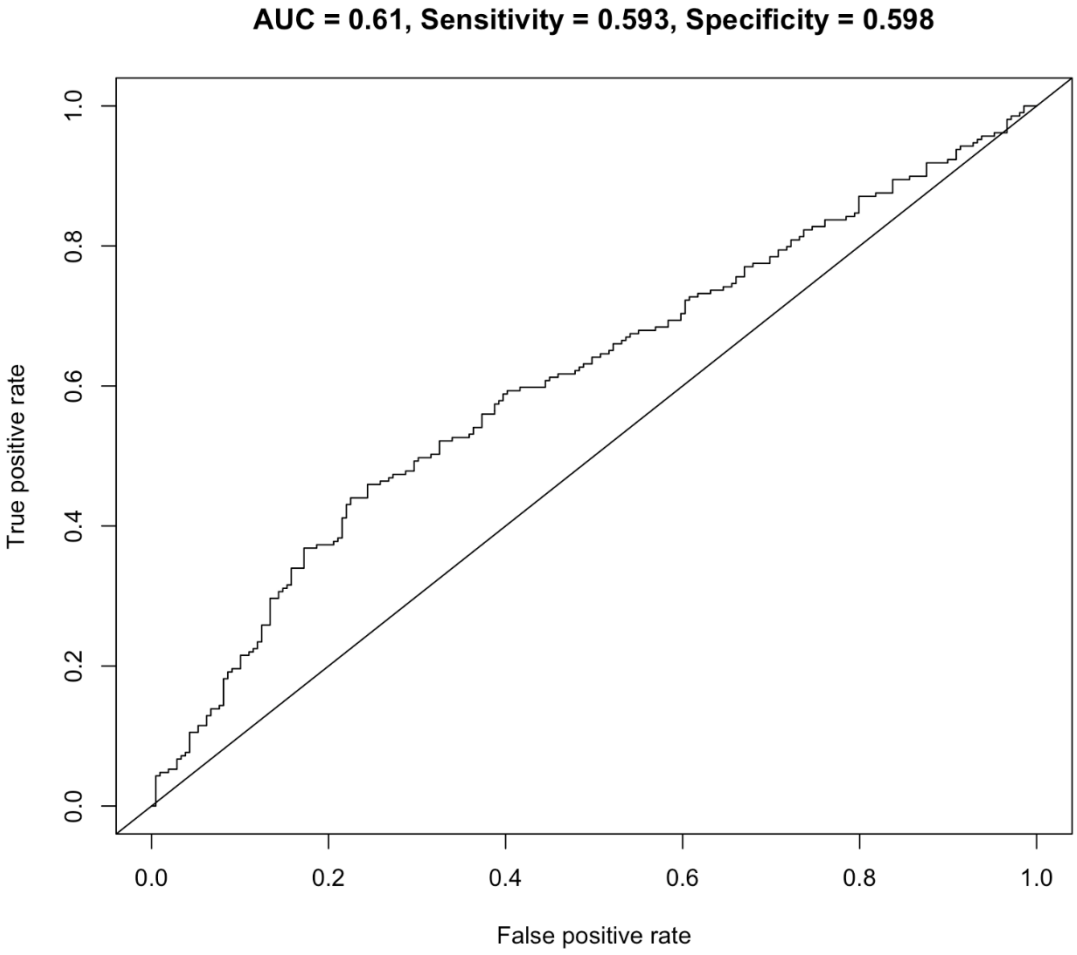

Figure S2. Receiver operating characteristic curve evaluating the performance of the 24-metabolite set identified in the discovery phase to predict the odds of CD in the external validation set.