Supporting Information

Table S1. Metabolites included in the MDMS as biomarkers of key MD food groups*

MDMS metabolite	metabolite class	food
EL*	enterolignans (microbial metabolites of lignans)	fiber-rich fruits and vegetables, grains, nuts, and legumes[1,2]
HA*	hydroxybenzoic acids (microbial metabolites of polyphenols)	fruits and vegetables, tea, coffee, cocoa, grains, nuts, legumes, olive oil, and wine[1,3–10]
proline betaine*	proline derivates	citrus fruits (mainly), Chinese artichoke, and rye and wheat bran[1,11–13]
Trigonelline*	pyridinium derivatives	coffee, legumes, and rye and wheat bran[1,12–14]
UroA-G*	urolithins (microbial metabolites of ellagitannins)	berries, wine, pomegranate, and nuts[1,15]
3,4-DHBA*	hydroxybenzoic acids (microbial metabolites of polyphenols)	fruits and vegetables, tea, coffee, cocoa, grains, nuts, legumes, olive oil, and wine[1,3–10]
3,4-DHPAA-S*	hydroxyphenylacetic acids (microbial metabolites of polyphenols)	fruits and vegetables, tea, cocoa, olives and olive oil, and wine[1,3–5,9,10]
3,4-DHPV-S*	hydroxyphenylvalerolactones (microbial metabolites of flavan-3-ols)	procyanidin-rich foods (berries, apple, tea, cocoa, wine, nuts, and legumes)[1,4,5,7,8,10,16]
DHA	n-3 PUFA	total fish and shellfish[17]
EPA	n-3 PUFA	total fish and shellfish [17]
margaric acid	LCFA	dairy products[18]
pentadecanoic acid	LCFA	dairy products[18,19]
oleic acid	LCFA	dietary MUFAs[20,21]
palmitic acid	LCFA	dietary SFAs[20]

DHA, docosahexaenoic acid. EL, enterolactone. EPA, eicosapentaenoic acid. HA, hippuric acid. LCFA, long-chain fatty acids. MDMS, Mediterranean diet metabolomic score. MD, Mediterranean diet. n-3 PUFA, n-3 polyunsaturated fatty acids. UroA-G, 3,8-dihydroxy-urolithin glucuronide. 3,4-DHBA, 3,4-dihydroxybenzoic acid. 3,4-DHPAA-S, 3′,4′-dihydroxyphenylacetic acid sulfate. 3,4-DHPV-S, 5-(3′,4′-dihydroxyphenyl)-γ-valerolactone sulfate

***METABOLITES SELECTION CRITERIA FOR THE DEVELOPMENT OF MDMS**

The metabolites for the MDMS were selected based on three criteria: a) metabolites reported as putative biomarkers of key MD food groups[17–20,22–32] and b) metabolites available in the serum metabolomic panel described previously.[1,33,34] c) metabolites with described health-related proprieties. Specifically, the metabolomic panel from D-CogPlast project consisted of 206 metabolites,[33] 35% of which were food-related metabolites and 15% were gut microbiota-derived metabolites.[33,34]

Six in eight selected putative biomarkers of the plant-based MD food group were microbiome-generated metabolites (enterolactone (EL), hippuric acid (HA), 3,8-dihydroxy-urolithin glucuronide (UroA-G), 3,4-dihydroxybenzoic acid (3,4-DHBA), 3′,4′-dihydroxyphenylacetic

acid sulfate (3,4-DHPAA-S), 5-(3′,4′-dihydroxyphenyl)-γ-valerolactone sulfate (3,4-DHPV-S)), and the remaining two were betaine derivatives.

Concretely, distinct diversity of polyphenols classes (i.e., hydroxybenzoic and hydroxyphenylacetic acids, hydroxycoumarins, hydroxyphenylvalerolactones and lignans) representative of some different metabolism phases (e.g., 3,4-DHPV-S is the degradation product of (epi)catechin, arising from the pyrogallol C-ring opening; 3,4-DHBA comes from the decarboxylation of caffeic acid or the demethylation of vanillic acid) were considered, although some of these compounds have also been described in certain foods.[35] Circulating levels of microbiome-generated metabolites last longer than those derived from the host itself and thus reflect long-term effect on health.[36] In fact, we also chose those metabolites which have showed a potential role as well on health. For instance, the microbiota-derived flavonoid metabolites (e.g., 3,4-DHBA and γ-valerolactones) not only preserve the antioxidant and anti-inflammatory activity of the native flavonoid but also have bioactive properties that promote mitochondrial health and cerebrovascular microcapillary function.[37] EL has been reported to exert antiproliferative and anti-inflammatory activities in vitro,[38] exhibits blood–brain barrier permeability, protects murine microglia against inflammation[39] and has been associated with more favorable cardiometabolic risk factors.[40] On the other hand, a study showed that UroA was the most common urolithin specie produced in nature.[41] Moreover, the production of UroA is variable and takes place in only approximately 40% of the human elderly population,[42] which restricts its positive impacts on health conditions (e.g., mitochondrial, cardiometabolic and muscle health) as well as those from its food sources (i.e., berries, wine, pomegranate, and nuts) indeed.[43–46] HA, a terminal metabolite of multiple microbial catabolites, has been suggested to exhibit in vitro myoprotective properties and may contribute to a better glycemic control and β-cell function, as well as to lessen the risk of developing age-related cognitive disorders.[47,48] 3,4-DHPAA has showed a decrease in the formation of amyloid fibrils, a protection from cytotoxicity and oxidative stress, a regulation of inflammatory pathways in vitro,[49–52] and significant reductions in high sensitivity C-reactive protein in patients with type 2 diabetes.[53] In addition, we gave priority to dihydroxylated metabolites rather than

monohydroxylated metabolites given their higher antioxidant capacity[54] and marked anti-inflammatory properties, which indicate their potential value as beneficial agents.[54]

Among all the DHBA available in out multi-metabolite platform, we selected the 3,4- isomer position, as 3,4-DHBA has showed potent inhibitory effects, as well as antioxidant, anti-inflammatory, antihyperglycemic and neuroprotective activities.[55,56] Moreover, at physiological pH, anthocyanins easily convert to 3,4-DBHA, which is also abundantly formed and absorbed in the large intestine due to microbial metabolization.[57]

With regard to non-polyphenols metabolites, trigonelline appears to have neuroprotective and antidiabetic effects[58,59] and has been suggested as a therapeutic agent for cardiovascular disorders[60] given its anti-inflammatory and antioxidant proprieties.[61] In fact, it has been associated with a lower risk of type 2 diabetes among a generally healthy population[62] and it has been associated to a urine molecular signature in the metabolic syndrome.[63] Finally, proline betaine is a well-known biomarker of citrus intake[11,64] which has been selected in this study as citrus is a fruit group highly consumed in the Southern Europe and is one of the top dietary sources of polyphenol intake in the 3C Study.[65,66] Moreover, proline betaine has been negatively correlated with glucose and insulin concentrations, blood lipid profiles, BMI and inflammation marker hsCRP[13,67] as well as inversely associated with blood pressure.[68] In fact, citrus intake has been suggested to be associated with global cognition benefits,[69] as well as with lower risk of incident dementia,[70,71] and cardiovascular risk factors.[72–75]

Table S2. Concentrations of MDMS dietary biomarkers by levels of MDMS in the 3C discovery (Bordeaux, n = 418) and validation (Dijon, n = 422) cohorts

MDMS metabolites (µg/L)	Bordeaux cohort (n = 418)				Dijon cohort (n = 422)			
	Total	Low MDMS (n = 205)	High MDMS (n = 213)	*p*	Total	Low MDMS (n = 207)	High MDMS (n = 215)	*p*
EL	6.1 (1.5)	5.7 (1.6)	6.5 (1.2)	0.009	10.0 (5.7)	8.1 (5.2)	11.8 (5.6)	0.006
HA	1985.2 (2267.5)	1477.2 (1878.4)	2474.0 (2495.7)	< 0.001	1434.0 (1492.5)	1098.2 (1030.8)	1757.3 (1773.4)	< 0.001
proline betaine	249.2 (241.3)	208.6 (224.4)	288.3 (250.9)	< 0.001	296.5 (284.4)	282.0 (297.3)	310.5 (271.5)	0.140
trigonelline	13.9 (15.4)	12.0 (16.2)	15.7 (14.4)	0.001	10.5 (11.3)	9.9 (12.6)	11.2 (9.8)	0.047
UroA-G	0.7 (2.8)	0.3 (1.5)	1.0 (3.6)	0.004	0.8 (2.6)	0.3 (1.6)	1.3 (3.2)	< 0.001
3,4-DHBA	43.0 (80.8)	27.2 (43.0)	58.3 (102.9)	< 0.001	28.1 (75.9)	23.4 (101.1)	32.5 (38.0)	< 0.001
3,4-DHPAA-S	9112.4 (24221.3)	5221.9 (15125.7)	12856.8 (30084.8)	< 0.001	8889.1 (22819.1)	8704.4 (23539.6)	9067.0 (22156.8)	< 0.001
3,4-DHPV-S	6.6 (11.2)	3.9 (5.6)	9.1 (14.2)	< 0.001	8.4 (16.3)	6.4 (14.1)	10.4 (17.9)	0.001
DHA	6490.5 (2381.6)	6167.8 (1928.9)	6801.1 (2716.3)	0.006	5379.9 (895.5)	5167.8 (794.3)	5584.1 (940.6)	< 0.001
EPA	3000.1 (795.2)	2855.6 (463.9)	3139.3 (998.5)	< 0.001	3223.9 (486.3)	3114.8 (387.4)	3329.0 (546.1)	< 0.001
margaric acid	5558.5 (2280.7)	6141.5 (2070.6)	4997.4 (2336.8)	< 0.001	4608.6 (448.7)	4684.9 (461.1)	4535.2 (424.7)	< 0.001
pentadecanoic acid	5247.3 (2129.7)	5834.0 (2207.8)	4682.6 (1891.5)	< 0.001	4212.1 (680.3)	4408.1 (664.8)	4023.4 (642.0)	< 0.001
oleic acid	68038.3 (27325.2)	66700.6 (26934.5)	69325.8 (27698.2)	0.473	76072.0 (26349.5)	75030.2 (26006.4)	77075.1 (26697.8)	0.401
palmitic acid	35210.2 (13848.5)	35458.1 (13947.0)	34971.6 (13781.7)	0.627	18559.4 (5099.8)	18492.4 (4925.1)	18624.0 (5273.2)	0.859

Values are mean (SD). DHA, docosahexaenoic acid. EL, enterolactone. EPA, eicosapentaenoic acid. HA, hippuric acid. MDMS, Mediterranean diet metabolomic score. UroA-G, 3,8-dihydroxy-urolithin glucuronide. 3C, Three-City. 3,4-DHBA, 3,4-dihydroxybenzoic acid. 3,4-DHPAA-S, 3′,4′-dihydroxyphenylacetic acid sulfate. 3,4-DHPV-S, 5-(3′,4′-dihydroxyphenyl)-γ-valerolactone sulfate

Table S3. Concentrations of MDMS dietary biomarkers (µg/L) by sex-specific medians in the 3C discovery (Bordeaux, n = 418) and validation (Dijon, n = 422) cohorts

MDMS metabolite	median (µg/L)	Bordeaux cohort (n = 418)		Dijon cohort (n = 422)	
		males (n = 142)	females (n = 276)	males (n = 156)	females (n = 266)
EL	< median	5.2 (1.2)	5.0 (1.2)	6.1 (3.0)	4.9 (2.8)
	≥ median	7.1 (0.7)	7.3 (0.8)	15.3 (3.6)	14.3 (3.7)
HA	< median	866.0 (395.6)	800.7 (381.3)	546.7 (192.6)	589.3 (249.7)
	≥ median	3229.6 (2617.6)	3105.1 (2792.0)	1912.3 (1330.5)	2518.7 (1866.2)
proline betaine	< median	66.0 (29.1)	85.8 (38.7)	94.5 (40.0)	102.0 (47.4)
	≥ median	357.1 (239.6)	451.4 (233.5)	415.9 (262.5)	539.5 (290.7)
trigonelline	< median	4.7 (2.5)	4.8 (3.0)	3.4 (2.1)	3.9 (2.2)
	≥ median	18.3 (9.3)	25.3 (19.8)	14.4 (9.8)	19.1 (13.7)
UroA-G	< median	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)
	≥ median	5.1 (3.0)	8.8 (7.6)	6.0 (3.3)	5.7 (4.7)
3,4-DHBA	< median	19.9 (17.5)	1.2 (4.1)	4.1 (6.9)	1.7 (4.0)
	≥ median	97.2 (81.8)	68.9 (109.8)	47.5 (28.8)	57.1 (125.3)
3,4-DHPAA-S	< median	0.0 (0.0)	845.3 (1116.0)	423.3 (955.3)	1408.8 (1480.3)
	≥ median	13366.9 (20301.1)	19975.7 (36555.3)	11009.7 (22301.8)	20090.8 (33765)
3,4-DHPV-S	< median	1.9 (1.3)	1.0 (0.9)	0.9 (0.8)	0.9 (0.7)
	≥ median	13.6 (14.0)	10.9 (13.8)	15.7 (15.6)	16.2 (22.7)
DHA	< median	5058.3 (802.3)	4927.0 (643.5)	4817.4 (334.8)	4668.9 (323.0)
	≥ median	7999.1 (1890.9)	8014.8 (2765.6)	6124.8 (874.9)	5983.9 (741.2)
EPA	< median	2601.1 (158.2)	2612.4 (116.2)	2949.4 (122.0)	2896.4 (128.1)
	≥ median	3449.9 (832.7)	3361.8 (1036.1)	3597.2 (665.6)	3493.6 (403.3)
margaric acid	< median	3874.4 (1014.5)	3842.2 (781.5)	4272.8 (169.3)	4248.1 (160.0)
	≥ median	6989.3 (1441.5)	7405.0 (2168.3)	4967.1 (384.1)	4955.9 (344.6)
pentadecanoic acid	< median	3243.3 (967.4)	3852.2 (845.9)	3672.6 (314.6)	3679.4 (296.5)
	≥ median	6573.1 (2101.6)	6991.3 (1529.4)	4572.2 (422.2)	4850.0 (530.9)
oleic acid	< median	45939.9 (11711.6)	47191.4 (12749.5)	56327.0 (12694.6)	54107.8 (12206.9)
	≥ median	83203.0 (16105.8)	92450.0 (22296.8)	98210.2 (15334.8)	96632.8 (20054.6)
palmitic acid	< median	25222.8 (5963.9)	24828.0 (5043.9)	14774.5 (2448.1)	14392.4 (2316.8)
	≥ median	43709.5 (8755.8)	46357.9 (13344.3)	23282.6 (2917.5)	22176.2 (4098.4)

Values are mean (SD). DHA, docosahexaenoic acid. EL, enterolactone. EPA, eicosapentaenoic acid. HA, hippuric acid. MDMS, Mediterranean diet metabolomic score. UroA-G, 3,8-dihydroxy-urolithin glucuronide. 3C, Three-City. 3,4-DHBA, 3,4-dihydroxybenzoic acid. 3,4-DHPAA-S, 3′,4′-dihydroxyphenylacetic acid sulfate. 3,4-DHPV-S, 5-(3′,4′-dihydroxyphenyl)-γ-valerolactone sulfate

Table S4. Dietary intake of MD key food groups (FFQ) and nutrients (24-HDR) in subjects from the Bordeaux cohort (n = 351)

MD key food groups	**median (p25, p75)**
Plant-based foods (serv/wk)	54.0 (46.0, 63.0)
Vegetables (serv/wk)	18.0 (14.0, 24.0)
Fruits (serv/wk)	14.0 (9.8, 17.0)
Legumes (serv/wk)	0.5 (0.3, 1.0)
Cereals (serv/wk)[a]	23.0 (18.0, 25.0)
Fish and seafood (serv/wk)	2.5 (1.5, 3.5)
Dairy products (serv/wk)	14.0 (13.0, 20.0)
Ratio of MUFAs/SFAs (g/d)[b]	0.8 (0.6, 1.0)
MUFAs (g/d)	19.4 (13.1, 27.0)
SFAs (g/d)	24.6 (16.7, 34.1)

MD, Mediterranean diet. SFAs, saturated fatty acids. g/d, grams/day. Serv/wk, servings/week. 24-HDR, 24 h dietary recall. [a] Cereals included cereals (including bread), pasta, and rice. [b] Data available from 359 subjects from the Bordeaux set.

Table S5. Correlations between intakes of MD food groups (FFQ) and nutrients (24-HDR) and serum dietary biomarkers in subjects from the Bordeaux cohort (n = 351)

MD key food group	serum metabolite	ρ coefficient[c]	*p*
Plant-based food group: vegetables, fruits, legumes, and cereals[a]	EL; HA; proline betaine; trigonelline; UroA-G; 3,4-DHBA; 3,4-DHPAA-S and 3,4-DHPV-S[22–32]	0.155	0.004
Fish and seafood	DHA and EPA[17]	0.240	< 0.001
Dairy products	margaric acid and pentadecanoic acid[18,19]	0.070	0.189
MUFAs & SFAs[b]			
MUFA intake	oleic acid[20,21]	0.110	0.037
SFA intake	palmitic acid[20]	0.168	0.001

DHA, docosahexaenoic acid. EL, enterolactone. EPA, eicosapentaenoic acid. FFQ, food frequency questionnaire. HA, hippuric acid. MD, Mediterranean diet. SFAs, saturated fatty acids. UroA-G, 3,8-dihydroxy-urolithin glucuronide. 24-HDR, 24 h dietary recall. 3,4-DHBA, 3,4-dihydroxybenzoic acid. 3,4-DHPAA-S, 3′,4′-dihydroxyphenylacetic acid sulfate. 3,4-DHPV-S, 5-(3′,4′-dihydroxyphenyl)-γ-valerolactone sulfate. [a] Cereals included cereals (including bread), pasta, and rice. [b] Data available from 359 subjects from the Bordeaux set. [c] Correlations between total intake of each MD key food group (serv/wk) and nutrients (g/d), and the sum of their selected dietary biomarkers (µg/L).

Table S6. Multivariate conditional logistic regression models for association between MDMS and CD in the 3C discovery (Bordeaux, n = 418) and validation (Dijon, n = 422) cohorts in various subgroups. OR (95% CI)

Discovery set				Validation set			
variables	**cases/controls**	**OR (95% CI)**	***p* for interaction**	**variables**	**cases/controls**	**OR (95% CI)**	***p* for interaction**
Sex			0.763	Sex			0.954
Male	71/71	0.85 (0.59–1.23)		Male	78/78	0.91 (0.64–1.28)	
Female	138/138	0.88 (0.61–1.27)		Female	133/133	0.91 (0.64–1.29)	
Age, y			0.720	Age, y			0.719
< 75.9 (median)	105/104	0.88 (0.65–1.21)		< 76.5 (median)	106/105	0.94 (0.67–1.31)	
≥ 75.9	104/105	0.89 (0.65–1.22)		≥ 76.5	105/106	0.92 (0.66–1.29)	
Educational level			0.256	Educational level			0.799
< secondary school	148/149	0.86 (0.76–0.98)		< secondary school	151/151	0.91 (0.80–1.02)	
≥ secondary school	61/60	0.99 (0.87–1.12)		≥ secondary school	60/60	0.93 (0.83–1.05)	
BMI, kg/m^2			0.214	BMI, kg/m^2			0.891
< 26.1 (median)	99/112	0.82 (0.59–1.14)		< 25.1 (median)	98/113	1.00 (0.71–1.40)	
≥ 26.1	110/97	0.87 (0.63–1.21)		≥ 25.1	113/98	0.94 (0.67–1.33)	
Polypharmacy (≥ 5)			0.097	Polypharmacy (≥ 5)			0.168
No	98/126	0.98 (0.73–1.33)		No	77/136	1.19 (0.85–1.65)	

Yes	111/83	0.93 (0.68–1.25)		Yes	134/75	0.99 (0.71–1.38)	
Diabetes			0.627	Diabetes			0.223
No	182/197	0.90 (0.81–1.01)		No	184/199	0.93 (0.84–1.04)	
Yes	27/12	0.82 (0.73–0.92)		Yes	27/12	0.76 (0.68–0.84)	
ApoE-ε4 carrier			0.138	ApoE-ε4 carrier			0.415
No	155/184	0.92 (0.82–1.03)		No	155/167	0.89 (0.79–1.00)	
Yes	54/25	0.73 (0.65–0.81)		Yes	56/44	0.99 (0.88–1.11)	
Hypertension			0.006	Hypertension			0.540
No	45/50	1.19 (0.95–1.50)		No	34/36	0.98 (0.76–1.27)	
Yes	164/159	0.83 (0.66–1.05)		Yes	177/175	0.90 (0.70–1.16)	
Smoking status			0.827	Smoking status			0.675
Never	141/136	0.90 (0.80–1.02)		Never	129/136	0.91 (0.80–1.04)	
Former or current	68/73	0.88 (0.78–0.99)		Former or current	82/75	0.90 (0.79–1.03)	
Depression			0.034	Depression			0.272
No	189/194	0.86 (0.76–0.97)		No	164/186	0.89 (0.80–1.00)	
Yes	20/15	1.31 (1.16–1.47)		Yes	47/25	1.06 (0.94–1.18)	
Alcohol intake, g/d			0.526	Alcohol intake, g/d			0.182
< 9.9 (median)	113/121	0.95 (0.69–1.30)		< 9.6 (median)	90/87	1.13 (0.80–1.60)	

≥ 9.9	96/88	0.91 (0.66–1.25)		≥ 9.6	121/124	0.99 (0.70–1.40)	
Hypercholesterolemia			0.780	Hypercholesterolemia			0.414
No	82/81	0.91 (0.78–1.06)		No	85/92	0.96 (0.82–1.12)	
Yes	127/128	0.88 (0.76–1.03)		Yes	126/119	0.88 (0.75–1.03)	

ApoE-ε4, apolipoprotein E-ε4 genotype. CI, confidence interval. OR, odds ratio. 3C, Three-City.

The cognitive decline (CD) variable was built defining the composite score of global cognition at each follow-up visit.[33,76] Individual slopes of cognitive change were then evaluated using linear mixed models, as detailed in the previous publication.[76] Cases were defined as the participants with the worst CD slopes.

P-values for interaction were calculated by adding product terms in the fully adjusted conditional logistic regression models. Each subgroup analysis was adjusted, if not stratified, for BMI, diabetes, alcohol intake, hypertension, smoking status, depression, hypercholesterolemia, ApoE-ε4, and number of medications.

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