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Original Article

Characterization of a metabolomics signature of the brain-health-promoting MIND diet in older persons

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ABSTRACT

Background: The MIND diet supports healthy cognitive aging. Yet, a challenge remains to identify individuals who do not adhere to the MIND and could be at risk for accelerated cognitive decline. A multi-metabolite biomarker panel could facilitate population screening.
Objectives: To determine and validate a blood metabolomics signature of MIND adherence in a large cohort of older adults, and to estimate its association with subsequent cognitive decline.
Design, setting and participants: Participants were older adults (≥65 years) from the population-based three-City (3C) cohort, free of dementia at study baseline and followed for up to 12 years for cognition, who were included in two case-control samples on cognitive decline nested within two centers (Bordeaux and Dijon cities, n = 838).
Exposures: 155 diet-related serum metabolites measured with a multianalyte metabolomics platform.
Main outcomes and measurements: The primary outcome was adherence to the MIND diet, assessed in a subsample of 344 participants from Bordeaux center (which underwent the dietary surveys, 24 h recall and food-frequency questionnaire). A metabolomics signature of MIND diet adherence was characterized with penalized regression and a metabolomics score ("metaboscore") reflecting the overall MIND biological fingerprint was calculated. The secondary outcome was cognitive decline status (coded as binary: accelerated, vs. null or minimal decline) over follow-up, assessed using repeated cognitive measures in the two case-control samples. The metaboscore was reconstructed and linked to the odds of cognitive decline.
Results: Eight metabolites were identified: three were associated with higher MIND adherence (3-hydroxyhippuric acid, 5-hydroxyindole-3-acetic acid, betaine - phenolic acids and amino acid related to plant foods) and

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five with lower MIND adherence (1-methylhistidine from red meat; cyclo(L-leucyl-L-prolyl) from coffee; tartaric acid from wine; myristoyl-carnitine and dehydroepiandrosterone sulfate, endogenous). The French-MIND metaboscore was linked to lower odds of cognitive decline, although replication was not statistically significant after multivariable adjustment.
Conclusion: A novel metabolomic signature of the MIND diet was characterized, which may help screen older adults at risk of poor brain nutrition and could support personalized dietary prevention strategies.

1. Introduction

Cognitive decline refers to the progressive deterioration of cognitive functions (including memory, language and reasoning) that occurs with aging. While it may represent a normal aspect of aging and then generally remains relatively mild, when accelerated, it may signal progression towards age-related disorders like Alzheimer's disease [1]. With increasing life expectancy and the global increase in aging populations worldwide, cognitive aging has become a significant public health concern. As the underlying biological mechanisms (neurodegenerative and vascular disorders, inflammation, oxidative stress, among others) evolve over years and often overlap, preventive strategies are particularly promising, especially via nutrition, which can modulate many of these pathways [2]. Diet approaches combining multiple dietary compounds are key and, in this context, the hybrid Mediterranean-DASH intervention for neurodegenerative delay (MIND) diet has been proposed and validated as an optimized diet to promote brain health with aging [3]. The MIND diet is characterized by a high intake of neuroprotective foods (olive oil, fish, whole grains, berries, green leafy and other vegetables) and contains a lower intake of foods found to be detrimental to general and brain health (red meats, pastries and sweets, cheese, butter and fried food) [3]. Higher adherence to the MIND diet has indeed been associated with a lower risk of dementia and a lower cognitive decline in several population-based cohorts [3–6].

However, evaluation of the adherence to diets like MIND depends on questionnaire-based tools, which are prone to various sources of biases, including measurement errors. There is therefore a growing interest in complementing these approaches with objective biomarker panels to assess the adherence to healthy diets, like the MIND. In this context, metabolomics offers a distinct and complementary perspective: rather than capturing declared dietary intakes, metabolomic signatures reflect the biological footprint of diet at the individual level, integrating both nutritional exposures and inter-individual variability in metabolic responses. Mass Spectrometry (MS)-based metabolomic profiles, which reflect both external exposures as well as endogenous metabolism, represent a promising tool to capture the markers of nutritional exposures, situated at the crossroad between dietary intakes and their impact on internal biology [7]. In addition, deciphering the molecular patterns associated with brain-health promoting diets such as the MIND would provide a better understanding of the biological mechanisms underlying the association between these diets and cognitive aging [8].

The few studies which have investigated metabolomic predictors of adherence to the MIND diet [9–13] used either nuclear magnetic resonance (NMR) spectroscopy-based metabolomics in blood [9,11], or liquid chromatography-mass spectrometry (LC-MS)-based metabolomics in blood [10,13] or urines [12]. While the results were promising, there was little overlap between the studies, possibly because the metabolomic platforms used were not specific, covering mainly the endogenous metabolome (especially NMR) and missing most of the food metabolome. So far, no metabolomic biomarker discovery study has been conducted that was based on a specific and comprehensive targeted food metabolomics platform.

Here, we leveraged a unique combination of nutrition, food metabolomics and repeated cognitive data from a large population-based cohort on dementia, the 3C study. Our aim was to determine a metabolomics signature of the brain health-promoting MIND diet and evaluate its prospective association with cognitive decline in a period of 12 years.

2. Methods

2.1. Population

2.1.1. 3C study design

The 3C study is a French cohort initiated in 1999 with the primary aim of studying vascular risk factors for dementia. It included 9294 non-institutionalized community dwellers aged 65 years or over, from three French cities: Bordeaux (n = 2104), Dijon (n = 4931) and Montpellier (n = 2259) [14]. The 3C study protocol was approved by the Consultative committee for the protection of Persons participating in Biomedical Research at Kremlin-Bicêtre University hospital in France and all participants provided written informed consent. At baseline, face-to-face interviews were conducted to collect socio-demographic data, lifestyle and health parameters. In addition, anthropometric and blood pressure measurements were performed, as well as fasting blood sampling for constitution of a biobank. The number of medications regularly consumed by participants was recorded. Follow-up visits were conducted at home every two to three years. At baseline and at each follow-up visit, a battery of cognitive tests was ascertained by a certified and experienced neuropsychologist [14].

In Bordeaux, a nutritional survey was performed by trained dietitians during a home interview conducted at the first follow-up in 2001–2002, including a food frequency questionnaire (FFQ) and a 24 h recall [15,16].

2.1.2. Nested case-control study on serum metabolome and cognitive decline

An ancillary study on metabolomics and trajectories of cognitive decline was initiated in 2016, exploiting the blood biobank collected at baseline (1999–2000) in two 3C study centers, Bordeaux and Dijon cities. Eligible participants had serum samples available in the biobank, no dementia diagnosis at the time of blood draw at baseline, and at least one repeated cognitive examination over the subsequent 12 years (with a maximum of five repeated examinations at visit V = 2, 4, 7, 10 and 12 years, with a median of 7 years of follow-up) [17]. The methods of this ancillary study are detailed elsewhere [17].

Two nested case-control samples were designed from Bordeaux and Dijon 3C centers, as described previously [17]. In both samples, case and control status were defined using slopes of change in global cognitive composite scores over the 12 years of follow-up (estimated by linear mixed models). Cases included the 220 participants with the strongest slopes of cognitive decline, and each case was matched to a control participant (i.e., a participant with a slope of cognitive change better than the population median) with same age (±3 years), sex and educational level (lower or higher than secondary school). In total, 209 cases in Bordeaux were successfully matched to a control, leading to a discovery sample of 418 subjects (209 cases, 209 controls). Similarly, in Dijon, 212 cases were successfully matched to a control, amongst whom two had no metabolomics measurement available and were excluded, leading to a validation sample of 420 subjects (210 cases, 210 controls).

2.1.3. Analytical study samples

The MIND metabolomics signature discovery analysis was conducted on the subsample with both metabolomics and nutrition data available, i.e., n = 344 3C Bordeaux participants (out of the 418 subjects from the original case-control sample) (**Supplementary figure 1**). Estimates

from this discovery stage were used to predict a metabolomics signature of the MIND diet among individuals without dietary data. This allowed us to study the association between the MIND metabolomics signature and cognitive decline status in the entire case control sample (Bordeaux, n = 418; Dijon, n = 420).

2.2. MIND diet adherence score

A MIND diet adherence score adapted to the French population was estimated using the methodology previously developed in the 3C cohort [4]. The components of this score were selected from the literature [3] and adapted to the dietary habits of the French population and to national recommendations [18]. The MIND diet adherence score was composed of 15 items combining the consumption of 10 foods associated with better cognitive aging in the literature (green leafy vegetables, other vegetables, nuts, berries' polyphenols, whole grains, fish, olive oil, and wine [consumed in moderation]) and 5 unhealthy foods (red meat, butter and margarine, cheese, pastries and sweets, and fried foods). Each component was assigned a score of 0, 0.5, or 1, depending on the frequency of consumption. The final adherence score was obtained by summing the scores for all components. Dietary intakes were obtained from the FFQ whenever possible and from the 24-hour recall when no information was available on the FFQ (for berries' polyphenols, whole grains, nuts and green leafy vegetables, **Supplementary Table 1**).

2.3. Metabolomics data

MS-based metabolomics analysis of serum samples was conducted using a large-scale and quantitative multi-metabolite platform for the simultaneous detection and quantification of food-related metabolites, microbiota derivatives and endogenous metabolites [19].

Serum samples were first subjected to protein precipitation with acetonitrile containing 1.5 M formic acid, as previously described [17]. Supernatants were transferred to 96-well injection plates after addition of a set of internal standards. Analyses were carried out by ultra-high performance liquid chromatography coupled to tandem mass spectrometry (UHPLC-MS/MS), using the operating conditions described elsewhere [19]. Calibration curves were prepared at 10 concentration levels in the range of 0.01–100 μg/L.

The concentration of metabolites known to be influenced by pre-analytical factors (e.g., improper handling/storage of blood samples) was checked for the absence of abnormal values ($\pm 3 \times$ IQR). The coefficients of variation for peak areas, retention times and peak widths of the internal standards were computed to evaluate the reproducibility. Endogenous metabolites with more than 20% missing data were excluded, and the other metabolites were imputed by the k-nearest neighbors (KNN) algorithm. We further removed metabolites with a high proportion of zero values (>70% of the dataset), as these may compromise accuracy in the signature discovery statistical procedure (our primary interest being relatively prevalent markers of the food metabolome). Finally, 155 metabolites (104 endogenous and 51 exogenous) were included in the analyses (**Supplementary Table 2**). Metabolites were analyzed as z-scores (subtracting the mean concentration of the metabolite and dividing by its standard deviation) to allow comparison of effect estimated across compounds.

3. Statistical analyses

3.1. Characterization of a metabolomics signature of MIND diet

We characterized a serum metabolomics signature of MIND diet adherence (dependent variable, continuous) using Least Absolute Shrinkage and Selection Operator (LASSO) penalized regression, adjusted for: age; sex; education; smoking; BMI; use of cholesterol-lowering, hypoglycemic and antihypertensive medications; regular practice of physical activity; daily caloric intake; and the date of blood draw (unpenalized covariates). LASSO allows simultaneous variable selection by adding a penalty to the regression coefficients [20]. The penalty parameter was estimated through cross-validation. As LASSO could lead to unstable results and false positives, the method was optimized with bootstrap resampling (n = 1000 bootstraps) [21]. The metabolites detected in more than 40% of the bootstrap samples were selected to be included in the MIND metabolomics signature.

3.2. Computation of a MIND metaboscore

The metabolites selected with LASSO in the discovery stage were subsequently introduced in a non-penalized linear regression of the MIND diet score (dependent variable), adjusted on the same covariates as in the LASSO, to estimate unbiased regression coefficients and compute a unique metabolomics signature score (hereafter referred to as the French-MIND metaboscore). Confidence intervals were not estimated at this step as they are known to be biased due to post-selection inference. The score was the sum of the concentration scaled to have mean zero and unit variance concentrations of the selected metabolites, weighted by the coefficient of association with the MIND adherence score. The French-MIND metaboscore can be interpreted as the overall serum metabolomics fingerprint of a MIND diet in the French population. The metaboscore was further predicted for each participant of the case-control study, in the Bordeaux and Dijon study centers.

3.3. Association study of the MIND metaboscore with the odds of cognitive decline

In each case/control sample (Bordeaux and Dijon), the association between the French-MIND metaboscore and cognitive decline status was estimated independently by a logistic regression model conditioned on matching variables (age, sex and education). The model was adjusted for smoking, alcohol consumption, BMI, physical activity, diabetes, hypercholesterolemia and hypertension.

3.4. Sensitivity analyses

We performed a sensitivity analysis excluding the participants with extreme values (defined graphically as values <-2 or >2 (**supplementary Figure 2**) for the MIND metaboscore.

All statistical analyses were conducted using R software version 4.0.3 (R Foundation for Statistical Computing, Vienna, Austria). Missing data for covariates (less than 17% for all variables) were imputed using chained equations with fully conditional specification method, whenever necessary [22].

4. Results

4.1. Characterization of the metabolomics signature and the MIND metaboscore

Participants from the discovery sample (n = 344) were on average 75.7 years old (Table 1) with a majority of women (68%). Increasing MIND adherence was associated with a higher proportion of men, of participants taking cholesterol-lowering drugs or exercising regularly. The proportion of participants taking an anti-hypertensive medication was lower as MIND adherence increased. As expected, participants with higher adherence to the MIND diet showed higher intakes in whole grains, nuts, total polyphenols, vegetables, fish, and poultry (Table 1). Conversely, they had lower intakes of red meat, cheese, sweets, fried and fast foods, butter and margarine, and they were more likely to use olive oil as their primary added fat.

Among the 155 metabolites, 8 were selected by the bootstrap-LASSO in the discovery subsample and defined as the metabolomics signature of MIND diet (Table 2). Five of those metabolites were associated with lower MIND diet (1-methylhistidine, myristoyl-carnitine, tartaric acid,

Table 1
Characteristics of the French-MIND metabolomics signature discovery sample (3C Bordeaux, n = 344).

	Total population N = 344	MIND diet adherence score[1] Mean (SD) = 7.2 (1.6)		
		Low [3.5; 6.5] N = 141	Medium [6.5; 8] N = 108	High [8; 11.5] N = 95
Sociodemographic and health characteristics				
Age (years), mean (SD)	75.7 (4.3)	76.0 (4.6)	75.0 (4.3)	76.0 (4.0)
Women	233 (68%)	107 (76%)	69 (64%)	57 (60%)
Education > high school	103 (30%)	42 (30%)	35 (32%)	26 (28%)
Smoking (pack-years), mean (SD)	8.9 (18.1)	9.3 (19.6)	7.9 (16.7)	9.4 (17.4)
Alcohol intake (g/day), mean (SD)	14.1 (16.6)	13.6 (16.5)	14.7 (16.9)	14.2 (16.5)
BMI (kg/m^2), mean (SD)	26.5 (4.2)	26.5 (4.4)	26.3 (4.0)	26.7 (4.0)
Cholesterol-lowering treatment	119 (35%)	35 (25%)	35 (32%)	49 (52%)
Antidiabetic treatment	29 (8%)	13 (9%)	9 (8%)	7 (7%)
Anti-hypertensive treatment	36 (10%)	19 (13%)	9 (8%)	8 (8%)
Number of medications, mean (SD)	4.5 (2.7)	4.6 (2.6)	4.5 (2.8)	4.2 (2.5)
Regular physical activity	100 (34%)	33 (29%)	34 (37%)	33 (38%)
Daily energy intake (Kcal), mean (SD)	1699.8 (542.3)	1697.2 (557.6)	1707.5 (545.2)	1695.1 (521.0)
Coffe intake (cups/ week), mean (SD)	5.6 (4.9)	4.9 (4.8)	5.8 (5.0)	6.3 (5.1)
MIND diet Components				
Whole grains (>0 g / day)	32 (9%)	2 (1%)	8 (7%)	22 (23%)
Nuts (>0 g / day)	14 (4%)	4 (3%)	3 (3%)	7 (7%)
Total polyphenols (>1.21 g / day)	117 (34%)	32 (23%)	42 (39%)	43 (45%)
Green leafy vegetables (>60 g / day)	118 (34%)	23 (16%)	40 (37%)	55 (58%)
Other vegetables (>14 times / week)	159 (46%)	24 (17%)	66 (61%)	69 (73%)
Beans (≥2 times / week)	19 (6%)	7 (5%)	7 (6%)	5 (5%)
Fish (≥2 times / week)	247 (72%)	78 (55%)	90 (83%)	79 (83%)
Poultry (≥2 times / week)	174 (51%)	52 (37%)	57 (53%)	65 (68%)
Red meat and products (≤4 times / week)	113 (33%)	29 (21%)	38 (35%)	46 (48%)
Cheese (<1 time / week)	22 (6%)	5 (4%)	7 (6%)	10 (11%)
Pastries and sweets (<5 times / week)	208 (60%)	51 (36%)	73 (68%)	84 (88%)
Fried and fast food (<1 time / week)	282 (82%)	103 (73%)	90 (83%)	89 (94%)
Butter and margarine (<7 times / week)	155 (45%)	48 (34%)	45 (42%)	62 (65%)
Olive oil (Primary added fat)	63 (18%)	9 (6%)	21 (19%)	33 (35%)
Wine ([7–10] glasses/ week)	55 (16%)	12 (9%)	16 (15%)	27 (28%)

Values are numbers (percentage) unless otherwise stated. Percentages are of non-missing values.
[1] Low, medium and high categories were defined at tertiles of the MIND diet score.

dehydroepiandrosterone sulfate [DHEA-S] and cyclo(L-leucyl-L-prolyl)) and three were associated with higher MIND diet adherence (5-hydroxyindole-3-acetic acid [5-HIAA], betaine and 3-hydroxyhippuric acid [3-HHA]). Out of the 8 metabolites from the signature, 3 were from endogenous metabolism (5-HIAA, myristoyl-carnitine and DHEA-S) and the remaining 5 were of external, from dietary origin (Table 2). Thus, the metabolites inversely associated with MIND were markers of red meat (1-methylhistidine), red wine (tartaric acid), cocoa/coffee (cyclo(L-leucyl-L-prolyl)) while all metabolites positively associated with MIND (5-HIAA, betaine, 3-HHA) were putative markers of plant foods.

4.2. Association between the MIND metaboscore and cognitive decline

The case-control samples used to estimate the association of the metaboscore and cognitive decline (Bordeaux and Dijon samples) were similar in terms of mean age, sex ratio, and education level (**Supplementary Table 3**). However, the Bordeaux sample included a lower proportion of participants with hypertension compared to the Dijon sample, where participants consumed less alcohol. In the two samples, cases included a higher proportion of participants smoking, practicing regular physical activity, or suffering from diabetes. The French-MIND metaboscore was equally distributed in both samples, albeit with a slightly higher number of extreme values in the Dijon sample, which did not participate in MIND metabolomic signature discovery (**Supplementary Figure 2**).

The French-MIND metaboscore was significantly associated with lower odds of subsequent cognitive decline in the Bordeaux sample (Fig. 1). For each increase of one point of the MIND metaboscore, the odds of cognitive decline decreased by 38% (OR = 0.62, 95% CI 0.43; 0.90, model 1, light green line) and by 37% after adjusting for potential confounders (OR = 0.63, 95% CI 0.42; 0.90, model 2, light green line). A similar trend was found in the external Dijon sample although the association did not reach statistical significance (OR = 0.73, 95% CI 0.49;1.10 in model 2, dark green line).

Six participants were identified as having an extreme French-MIND metaboscore (n = 1 in discovery and n = 5 in validation sample), defined graphically as values <−2 or >2 (**Supplementary Figure 2**). After removal of these participants and their matched pair member, the association between the French-MIND metaboscore and cognitive decline did not change meaningfully in the discovery sample and was slightly strengthened in the validation sample (OR = 0.61, 95%CI 0.39–0.96 in model 1 and OR = 0.63, CI 0.38–1.04 in model 2) (**Supplementary Figure 3**).

5. Discussion

Capitalizing on a unique database combining MS-based assessment of the food metabolome, dietary intake and repeated cognitive data from the large population-based 3C cohort, we characterized a serum metabolomics signature of adherence to the brain health-promoting MIND diet. The signature was composed of eight metabolites encompassing markers from the endogenous metabolism and exogenous compounds derived from diet. The three metabolites associated with better adherence to the MIND diet (3-HHA, 5-HIAA and betaine) were phenolic acids and amino acid derivatives - two ubiquitous families of the food metabolome related to plant foods, which are lead components of the MIND diet. The metabolites associated with lower MIND adherence were derived from red meat (1-methylhistidine), coffee (cyclo(L-leucyl-L-prolyl)) and wine (tartaric acid) – the two first diet components scoring negatively in MIND - or resulted from endogenous metabolism (myristoyl-carnitine and DHEA-S). When modeling this biomarker fingerprint globally in the form of a French-MIND metaboscore, the signature was associated with a lower odd of accelerated cognitive decline in the following 12 years in the Bordeaux sample, that was confirmed (albeit not statistically significantly after full covariate adjustment) in the Dijon sample. Taken together, the French-MIND metaboscore, derived from a unique combination of MS-based food metabolome assessment, dietary intake and repeated cognitive data, captured a biologically meaningful signature of MIND diet adherence in the French population that was associated with a reduced risk of

Table 2
Identification of a metabolomics signature of MIND diet adherence and definition of a French-MIND metaboscore (3C Bordeaux, n = 344).

Metabolites	% of selection across 1000 bootstrap-LASSO[1]	β coefficient (unpenalized)[2]	Primary origin (diet or endogenous)
1-methylhistidine	91	−0.24	Red meat
Myristoyl-carnitine	72	−0.25	Endogenous
5-HIAA	67	0.27	Endogenous, increase with serotonin-rich foods intake
Betaine	66	0.15	Fruits and vegetables
Tartaric acid	46	−0.17	Red wine and grapes
3-HHA	43	0.21	Fruits and vegetables
DHEA-S	42	−0.10	Endogenous
cyclo(L-leucyl-L-prolyl)	40	−0.12	Cocoa and coffee

[1] LASSO regression was applied to 1000 bootstrapped samples to identify metabolites robustly associated with the MIND diet adherence score. Metabolites selected in more than 40% of the bootstraps were selected. For each bootstrap sample, the optimal penalty was selected by cross-validation. Models were adjusted for age, sex, education, smoking status, BMI, cholesterol-lowering, antidiabetic and anti-hypertensive treatments, physical activity, daily energy intake and blood sampling date.
[2] β coefficients estimated for one SD increase in standardized metabolite concentration in a non-penalized linear regression model including all the metabolites selected by LASSO and adjusted for the same list of covariates. Abbreviations: 3-HHA: 3-hydroxyhippuric acid, 5-HIAA: 5-hydroxyindole-3-acetic acid, DHEA-S: dehydroepiandrosterone sulfate.

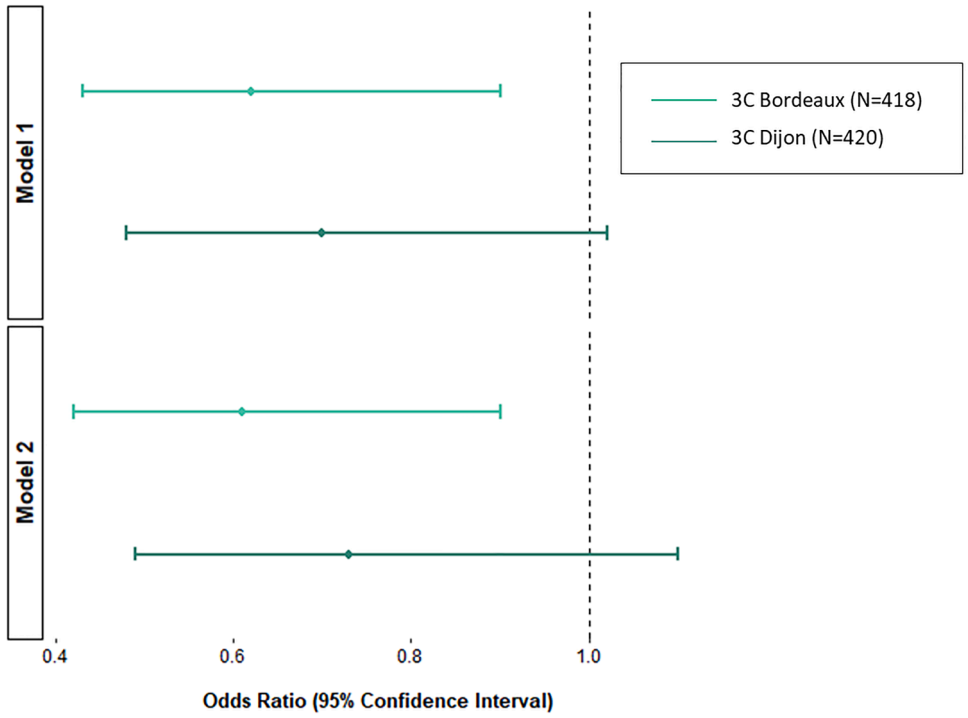

Fig. 1. Association between the French-MIND metaboscore and the case/control status for cognitive decline (3C Bordeaux, discovery, n = 418; 3C Dijon, validation, n = 420). Odds ratio were estimated for the increase of one unit of the MIND metaboscore using conditional logistic regression (with age, sex and education as matching factors). Model 1 was unadjusted and model 2 was adjusted for BMI, smoking, alcohol consumption, physical activity, diabetes, hypercholesterolemia and hypertension.

accelerated cognitive decline over 12 years.

Five previous studies have characterized a metabolomics signature of the MIND diet [9–12], and strikingly, none of them reported any metabolite in common with our signature. However, in contrast with our research, the metabolomics platform used in those studies was not specialized on the food metabolome per se that contains many small molecules, or were performed on urine samples, leading to a different set of metabolites measured. In two studies of 100 000 middle-aged individuals from the UK biobank [9,11], metabolites from the NMR-based *Nightingale* platform, measured in plasma, were linked to MIND diet adherence score and subsequently associated with frailty or cognition. The two studies found a MIND signature composed of around 40 metabolites, including HDL cholesterol, various lipids and lipoproteins, fatty acids and inflammatory markers. NMR has low sensitivity and does not detect compounds below one millimolar, allowing to capture only a few hundred compounds from the endogenous metabolism and thereby missing all small molecules from the food metabolome (that are measured in our UHPLC-MS/MS-based platform) [23]. In the US Baltimore Longitudinal Study of Aging (BLSA) cohort, a metabolomics signature of the MIND diet was searched among 806 participants from the *Biocrates* platform, a targeted LC-MS approach encompassing 249 metabolites from main biochemical classes, that does not covers the food metabolome [10]. Their signature included 218 metabolites, and mediated significantly the association between adherence to the MIND diet and frailty. A previous study conducted in the ARIC cohort among 3908 adults identified a signature of 27 metabolites associated with MIND diet adherence using the *Metabolon* platform (LC-MS approach, in serum). None of these metabolites overlapped with our signature, which is likely attributable to the limited specificity of the Metabolon panel for the food metabolome compared to our UHPLC-MS/MS-based platform [13]. Finally, a study conducted in the POLYINTAKE cohort among 218 middle-aged participants identified 15 urinary metabolites constituting

a MIND diet signature, most of which were polyphenols [12]. Although the metabolite panel was restricted to the food metabolome (i.e., plant-derived metabolites), the use of urine as the biological matrix allows only limited overlap with the metabolites measured in our study. Of course, other differences in study designs such as slight variations in the definitions of MIND diet scores or the statistical approach used for signature selection could also explain the divergent results.

One of the metabolites identified in lower concentrations associated with MIND in our signature, 1-methylhistidine, was also identified in decreased levels with Mediterranean diet adherence in previous metabolomics-based studies, including the BLSA cohort and a small sample of diabetes-free participants from the Spanish PREDIMED intervention study [24]. This metabolite is a derivative of the amino acid histidine and a biomarker of red meat consumption which has been linked to increased risk of brain aging-related outcomes in the literature [24,25]. For instance, a recent study of >100 elderly subjects found higher levels of 1-methylhistidine in the plasma and cerebrospinal fluid of patients with Alzheimer's disease compared to controls [26]. We found another endogenous metabolite potentially linked to meat intake, myristoyl-carnitine [27], related to lower MIND adherence. This metabolite belongs to the acylcarnitine family and has previously been associated with cognitive decline in our cohort [21]. Other studies have consistently reported that myristoyl-carnitine metabolism is dysregulated in metabolic syndrome and in early Alzheimer's disease [28–30].

Our signature also included betaine as a biomarker positively associated to MIND diet adherence. Betaine, an exogenous molecule derived from the amino acid glycine, has ubiquitous dietary sources, including beets, spinach, wheat bran, and seafood. Betaine has been regularly identified as a biomarker of healthy diets such as the Healthy Eating Index (HEI, based on US dietary recommendations) and the DASH diet [31,32]. This metabolite has also been associated with reduced brain aging-related markers (e.g., cognitive function) in animals and humans [33,34]. This protective relationship could be linked to a role in the conversion of homocysteine to methionine (homocysteine being an established vascular risk factor implicated in dementia) [35,36], and in the regulation of osmotic stress [37].

The two other amino acid derivatives identified in our signature of the MIND diet, 5-hydroxyindole-3-acetic acid (5-HIAA) and cyclo(L-leucyl-L-prolyl), are more novel metabolites in relation to a brain health-promoting dietary pattern. 5-HIAA is derived from serotonin, and its concentration in plasma is increased after intake of serotonin-rich foods (pineapple, banana, kiwi, and walnuts) [38,39]. It is therefore biologically relevant to identify 5-HIAA as a biomarker of MIND, a diet which emphasizes fruit and vegetable, berries and nuts consumption. Furthermore, there is preliminary evidence suggesting that 5-HIAA could prevent some cognitive aging endpoints. For instance, a small study (N = 78) showed a significantly reduced concentration of 5-HIAA in the cerebrospinal fluid of patients with advanced Lewy body dementia, compared with newly-diagnosed participants [40].

Our findings of cyclo(L-leucyl-L-prolyl) are more complex to interpret. Cyclo(L-leucyl-L-prolyl), derived from leucine and proline, is a validated biomarker of coffee consumption [17]. While this metabolite was *inversely* associated with the protective MIND diet in the present study, we previously found cyclo(L-leucyl-L-prolyl) (from non-targeted metabolomics) as *positively* associated with cognitive preservation in the 3C cohort [21]. There is biological plausibility for such protective association, as cyclo(L-leucyl-L-prolyl) increases the heat shock protein 70 (HSP70) that lowers brain accumulation of the Alzheimer's disease proteins Amyloid beta and tau [41]. Like the aforementioned coffee biomarker, tartaric acid, an organic acid present in wine, was inversely associated with adherence to the MIND diet. This finding is coherent with the inclusion of moderate wine consumption as a component of the MIND adherence score (higher wine consumptions scoring negatively in MIND). We previously linked tartaric acid to higher cognitive decline [42]. Actually, in Western dietary patterns, the consumption of wine, meat, and coffee are correlated, thus the identification of metabolites such as tartaric acid (wine), 1-methylhistidine (meat), and cyclo(L-leucyl-L-prolyl) (coffee) may reflect dietary behaviors inversely correlated to MIND diet habits [43].

Besides the coffee, wine and meat biomarkers scoring negatively in the French-MIND metaboscore, we also reported the steroid hormone dehydroepiandrosterone sulfate (DHEA-S), a potential biomarker of stress [44], inversely associated with the MIND diet. There are multiple potential pathways by which healthier diets such as MIND could decrease stress levels, and increased stress is a risk factor for cognitive decline [45].

The polyphenol metabolite 3-HHA, a benzoic acid derived from intake of various polyphenol-rich foods and found as a positive contributor to the French-MIND metaboscore, is also a novel metabolite found in relation to a neuroprotective diet. Currently, polyphenol metabolites are poorly measured in metabolomics studies, partly due to their low circulating levels, requiring sensitive analytical tools to detect them in the general population. They are, however, of strong interest in the context of brain aging. Several prospective studies found an association between higher flavonoid intake and a lower risk of dementia and cognitive decline while also preclinical studies are of interest in this respect . Their pleiotropic effects on various biological pathways could underly, at least in part, the potentially neuroprotective role of the MIND diet [46].

Our study has important strengths. The unique collection of epidemiological data offered by the 3C study, combining a dietary survey (FFQ and 24 h recall), a blood biobank and a comprehensive assessment of cognitive performances over more than a decade, provide a unique opportunity to map the food exposome from dietary intakes to their biological fingerprints within the food metabolome and finally the longitudinal assessment of brain health with aging. The use of a unique multi-metabolite metabolomics platform based on innovative MS technology coupled with ultra-high performance liquid chromatography, enabled the accurate quantification of metabolites specifically related to diet, some of which being not often measured in metabolomics studies (e.g., short-chain fatty acids and phenolic acids). The availability of samples with different geographical origins (south-west France (Bordeaux) and north-east France (Dijon)) with different dietary and lifestyle habits, is also an important strength of the study [47–51].

There are also some limitations. First, there was an average 1.9 year-lag (min = 1.0; max = 3.5) between the dietary survey and blood-draw collection, which may have caused some mis-specification of the signature in the event that participants have changed their dietary habits. However, FFQ assess habitual diet habits over the year and these habits are generally stable in longer periods, especially in older persons [52,53]. A single time point for metabolite measurement is also a limitation to develop biomarkers of dietary habits, especially when it is to capture non-daily food intakes. Nonetheless, even in the context of non-daily consumed foods such as fish, we previously found reasonably good correlations between a single measurement of long-chain omega-3 fatty acids and fish intake [54]. As another limitation, a detailed dietary survey was available in 3C Bordeaux only, thus we were not in capacity of evaluating the external validity of our MIND metabolomic signature discovery. We could only evaluate in the external sample the ability of the signature to associate with cognitive decline. Finally, the present findings were derived from a French older adult population, which may limit their generalizability to populations of different age groups, ethnicities, or dietary cultures, where the food metabolome and dietary patterns may substantially differ.

Overall, we reported here a novel metabolomics signature of a brain-health promoting diet, composed of robust serum biomarkers of plant foods typically emphasized in the MIND diet such as betaine, 3-HHA and 5-HIAA (specifically enriched in fruits, vegetables and nuts, important components of the MIND) and negatively scored with metabolites related to meat intake (myristoyl-carnitine and 1-methylhistidine), coffee (cyclo(L-Leucyl-L-Prolyl)), wine (tartaric acid), and the stress hormone DHEA-S. The global metabolomics fingerprint of MIND diet

adherence in the form of a French-MIND metaboscore was associated with lower odds of accelerated cognitive decline over 12 years in the first sample and a similar borderline significant trend was found in an external validation sample (with very different metabolomic profile and lifestyle habits). This study contributes to a broader effort to identify reproducible food metabolomics signatures of dietary patterns, which, through comparisons across studies, may ultimately lead to more robust signatures with wider applicability beyond the French population. The signature proposed here could be quantified and further refined in other cohorts by incorporating additional markers, thereby progressively improving its robustness and reliability. Once replicated in external studies, such a food metabolomics-based signature of MIND diet adherence could primarily serve as a tool to better understand the biological mechanisms linking diet to cognitive aging, and to identify older individuals at risk of suboptimal nutrition for brain health. Although on a practical point of view, dietary screeners may remain a primary tool for screening populations at risk of poor adherence, the metaboscore could provide complementary biological insight to support tailored diet counseling in primary prevention programs.

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Data statement

Data not available due to ethical restrictions.

AI use statement

During the preparation of this manuscript, the authors used *Claude (anthropic)* to improve the phrasing of a limited number of individual sentences. The tool was not used to draft, generate, or restructure any part of the manuscript's content. After using this tool, the authors reviewed and edited the affected sentences and take full responsibility for the content of the publication.

CRediT authorship contribution statement

Jeanne Neuffer: Writing – review & editing, Writing – original draft, Methodology, Investigation, Formal analysis, Conceptualization. **Raúl González-Domínguez:** Writing – review & editing, Methodology, Investigation. **Sophie Lefèvre-Arbogast:** Writing – review & editing, Methodology, Investigation, Formal analysis. **Dorrain Y Low:** Writing – review & editing, Investigation. **Alba Tor-Roca:** Writing – review & editing, Methodology, Investigation. **Catherine Helmer:** Writing – review & editing, Investigation, Funding acquisition. **Andrea Du Preez:** Writing – review & editing, Investigation, Funding acquisition. **Chiara de Lucia:** Writing – review & editing, Investigation. **Silvie R. Ruigrok:** Writing – review & editing, Investigation. **Barbara Altendorfer:** Writing – review & editing, Investigation. **Ludwig Aigner:** Writing – review & editing, Investigation, Funding acquisition. **Paul J Lucassen:** Writing – review & editing, Investigation, Funding acquisition. **Aniko Korosi:** Writing – review & editing, Investigation, Funding acquisition. **Sandrine Thuret:** Writing – review & editing, Investigation, Funding acquisition. **Claudine Manach:** Writing – review & editing, Investigation, Funding acquisition. **Mercè Pallàs:** Writing – review & editing, Investigation. **Alex Sánchez-Pla:** Writing – review & editing, Methodology, Investigation. **Cristina Andres-Lacueva:** Writing – review & editing, Methodology, Investigation, Funding acquisition. **Mireia Urpi-Sarda:** Writing – review & editing, Methodology, Investigation, Funding acquisition. **Cécilia Samieri:** Writing – review & editing, Writing – original draft, Supervision, Investigation, Funding acquisition, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.tjpad.2026.100670.

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