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A Mediterranean Diet-Based Metabolomic Score and Cognitive Decline in Older Adults: A Case–Control Analysis Nested within the Three-City Cohort Study

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Scope: Evidence on the Mediterranean diet (MD) and age-related cognitive decline (CD) is still inconclusive partly due to self-reported dietary assessment. The aim of the current study is to develop an MD- metabolomic score (MDMS) and investigate its association with CD in community-dwelling older adults.

Methods and results: This study includes participants from the Three-City Study from the Bordeaux ($n = 418$) and Dijon ($n = 422$) cohorts who are free of dementia at baseline. Repeated measures of cognition over 12 years are collected. An MDMS is designed based on serum biomarkers related to MD key food groups and using a targeted metabolomics platform. Associations with CD are investigated through conditional logistic regression (matched on age, sex, and education level) in both sample sets. The MDMS is found to be inversely associated with CD (odds ratio [OR] [95% confidence interval (CI)] = 0.90 [0.80–1.00]; $p = 0.048$) in the Bordeaux (discovery) cohort. Results are comparable in the Dijon (validation) cohort, with a trend toward significance (OR [95% CI] = 0.91 [0.83–1.01]; $p = 0.084$).

Conclusions: A greater adherence to the MD, here assessed by a serum MDMS, is associated with lower odds of CD in older adults.

1. Introduction

Dementia is a rapidly growing public health problem affecting around 50 million people worldwide. Every year, there are nearly 10 million new cases, and this figure is projected to triple by 2050 due to the global aging population and its anticipated impact and costs for society are huge.[1] Dementia is characterized by progressive cognitive decline (CD), a major cause of disability and dependency among older people.

While there is currently no treatment for dementia, certain lifestyle factors have been associated with a delay in the age-at-onset or with a slowing down of disease progression. In fact, a healthy diet is thought to have great preventive potential for CD, both directly and through its role in reducing other risk factors (such as hypertension and type

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2 diabetes).[2] Healthy dietary patterns have indeed been associated with a lower risk of dementia[3–5] and better cognitive performance.[6] Also, several observational studies have concluded that a high adherence to in particular the Mediterranean diet (MD) is associated with a decreased risk of mild cognitive impairment and Alzheimer's disease (AD),[7] and with better episodic memory and global cognition.[8] Two other related dietary patterns also associated with better cognitive performance are the Dietary Approaches to Stop Hypertension (DASH)[9] and the Mediterranean-DASH Intervention for Neurodegenerative Delay (MIND) diets.[10,11] However, evidence of the associations between dietary patterns and cognitive function is still inconclusive.[12] For instance, a meta-analysis of randomized controlled trials investigating MD effects on cognition, or on brain morphology and function, concluded that the associations were mostly non-significant, with small effect sizes.[13] Gauci et al. also found conflicting results in studies investigating the effects of the DASH and MIND diets on neurocognitive function.[14]

Some of these inconsistencies may be attributable to the fact that current epidemiological data on dietary patterns mostly rely on self-reported questionnaires, which may misreport the actual food consumption and thereby underestimate the inter- and intraindividual variability in bioavailability of bioactive food components that could arise from numerous factors (e.g., sex, age, genetic background, chronic diseases, liver function, and gut microbiota).[15]

To overcome these limitations, the use of a panel of dietary biomarkers would constitute an alternative (or complement) to provide a more specific assessment of dietary exposure and to better evaluate the association between dietary exposure and health outcomes.[16] Prior studies have indeed identified protective associations between urinary total polyphenols, individual plant-derived metabolites – including phenolic acids such as 3-hydroxyhippuric acid and 3-hydroxyphenylacetic sulfate, urinary urolithin derivatives, lutein, ergothioneine, and equol – and CD, as well as negative associations with metabolites related to generally considered unhealthy dietary components, such as saccharin and propionic acid.[17–23] Yet, studies using combinations of diverse biomarkers to monitor compliance with specific dietary patterns are scarce.

Here, we developed an MD-based metabolomic score and investigated its association with CD in two sample sets from the centers of Bordeaux and Dijon, as of the Three-City Cohort (3C Study).

2. Experimental Section

2.1. Study Design and Population

This study conducted a nested case–control study using data from the 3C Study, a population-based cohort on dementia that included older persons (≥65 years) from three French cities.[24] A detailed description was provided elsewhere.[17–19,24–29] Briefly, sociodemographic and lifestyle characteristics, medical information, neuropsychological testing, blood pressure, anthropometric measurements, and fasting blood samples were collected at baseline from 1999 to 2000, and follow-up visits were then scheduled every 2–3 years for repeated health and neuropsychological assessment.[24] The study was performed in accordance with the principles contained in the Declaration of Helsinki. The Consultative Committee for the Protection of Persons participating in Biomedical Research at Kremlin-Bicêtre University Hospital (Paris, France) approved the 3C Study protocol (IRB approval number 9928, Kremlin Bicêtre, June 10, 1999), and all participants provided written consent.

In this nested case–control study, two sample sets were built among participants from the centers of Bordeaux and Dijon of the 3C Study, with Bordeaux as the discovery set and Dijon as the set used for external validation.[17,18] From the entire Bordeaux and Dijon cohorts, eligible participants were selected for the present study if they were not diagnosed with dementia at baseline, had available serum samples, and had at least one repeated cognitive evaluation over the subsequent 12 years.

To build the case–control samples on CD, the study defined a composite score of global cognition at each follow-up visit as the average *Z*-scores of five neuropsychological tests (Mini-Mental State Examination [MMSE], Benton Visual Retention Test, Isaac's Set Test, Trail-Making Test part A, and Trail-Making Test part B).[17,18] Individual slopes of cognitive change were then estimated using linear mixed models, as previously detailed.[18] Cases were defined as the participants with the worst CD slopes. Then, it matched each case to a control (i.e., a participant with a CD slope better than the population median) based on age at baseline, sex, and education level. Overall, 209 cases were individually matched to a control in Bordeaux, leading to a discovery sample of 418 subjects. In Dijon, 211 cases were successfully matched to 211 controls, leading to a validation sample of 422 subjects.

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Table 1. Clinical and demographic characteristics of the discovery (Bordeaux, $n = 418$) and validation (Dijon, $n = 422$) case–control samples.

	Bordeaux cohort			Dijon cohort		
	Controls ($n = 209$)	Cases ($n = 209$)	$p^{a)}$	Controls ($n = 211$)	Cases ($n = 211$)	$p^{a)}$
Age [years]	75.7 (4.2)	75.9 (4.5)	–	76.2 (4.7)	76.5 (5.2)	–
Sex, female (n [%])	138 (66)	138 (66)	–	133 (63)	133 (63)	–
Educational level, ≥ secondary school (n [%])	60 (28.7)	61 (29.2)	–	60 (28.4)	60 (28.4)	–
BMI [kg m^{-2}]	25.8 [4.3]	26.4 [5.6]	0.12	24.9 [4.4]	25.4 [6]	0.099
Number of medications regularly consumed	4.1 (2.4)	4.9 (2.7)	0.003	4.0 [3.0]	5.0 [4.0]	< 0.001
MMSE (points)	28.0 [2.0]	28.0 [3.0]	< 0.001	29.0 [1.0]	26.0 [4.0]	< 0.001
Diabetes, yes (n [%])	12 (5.7)	27 (12.9)	0.017	12 (5.7)	27 (12.8)	0.017
ApoE-ϵ4, carrier (n [%])	25 (12.0)	54 (25.8)	0.001	44 (20.9)	56 (26.5)	0.187
Alcohol intake [g d^{-1}]	9.6 [19.2]	9.6 [17.8]	0.263	9.6 [16.5]	9.6 [17.8]	0.822
Current smoking, yes (n [%])	9 (4.3)	10 (4.8)	0.695	4 (1.9)	13 (6.2)	0.150
Depression, yes (n [%])	15 (7.2)	20 (9.6)	0.386	25 (11.8)	47 (22.3)	0.005
Hypercholesterolemia, yes (n [%])	128 (61.2)	127 (60.8)	0.922	119 (56.4)	126 (59.7)	0.482
Hypertension, yes (n [%])	159 (76.1)	164 (78.5)	0.564	175 (82.9)	177 (83.9)	0.789
MDS (points)$^{b)}$	4.3 (1.6)	4.3 (1.7)	0.404	–	–	–
MDMS (points)	6.7 (2.1)	6.4 (2.2)	0.168	6.8 (2.0)	6.5 (2.0)	0.067

Values are mean (SD), median [IQR], or number of subjects with the characteristic (%). ApoE-ϵ4, apolipoprotein E-ε4 genotype; IQR, interquartile range; MDMS, Mediterranean diet metabolomic score; MDS, Mediterranean diet score; MMSE, Mini-Mental State Examination; SD, standard deviation. [a)] Estimated using conditional logistic regression models; [b)] Data available from 349 subjects from the Bordeaux cohort.

2.2. Targeted Metabolomics Analysis of Serum Samples

The study conducted a targeted metabolomics analysis of serum samples using a multi-metabolite platform for the simultaneous detection and quantification of food-related metabolites, microbiota derivatives, and endogenous metabolites following the methodology detailed in previous publications.[17,30] The samples were randomly distributed for metabolomics analysis utilizing an Infinity UHPLC system (Agilent, Santa Clara, CA, USA) coupled to a QTRAP 6500 mass spectrometer equipped with an Ion Drive Turbo V ion source (Sciex, Framingham, MA, USA) using the operating conditions described elsewhere.[17]

2.3. Mediterranean Diet Metabolomic Score

In line with the Mediterranean diet score (MDS) defined by Trichopoulou et al.[31] the MD metabolomic score (MDMS) was developed de novo using a 14-point linear scale that incorporated two putative dietary metabolomic biomarkers of seven key components of the MD (vegetables, legumes, fruits, cereals, dairy, fats, and fish) (**Table 1** and Table S1, Supporting Information).[31,32]

The metabolites for the MDMS were selected based on three criteria: a) metabolites reported as putative biomarkers of key MD food groups,[33–47] b) metabolites available in the serum metabolomic panel described previously,[17,30,48] and c) metabolites with described health-related proprieties (Table S1, Supporting Information). Detailed information about the eligibility criteria of the metabolites for the MDMS is shown in Table S1 (Supporting Information). In this MDMS, the meat item from the MDS was excluded as it was not possible to establish a set of metabolites that can reliably discriminate between meat intake, products of human muscle catabolism, and other protein-rich foods (e.g., fish and seafood), as well as between different meat sources (e.g., red meat vs. poultry).[44] This study did not include an alcohol-related item either since low levels of alcohol have shown slight reductions in health-related harm (i.e., ischemic heart disease and diabetes in very specific populations) but an increased risk of other health-related conditions, including cirrhosis, infectious diseases, early dementia, and cancer.[49,50]

We thus worked with $n = 14$ serum biomarker components. We decided to group four categories of foods (vegetables, fruits, legumes, and cereals) as a plant-based food group since some of the biomarkers described could be ubiquitously present among all these food groups. Enterolactone (EL), hippuric acid (HA), proline betaine; trigonelline; 3,8-dihydroxyurolithin glucuronide (UroA-G), 3,4-dihydroxybenzoic acid (3,4-DHBA), 3′,4′-dihydroxyphenylacetic acid sulfate (3,4-DHPAA-S), and 5-(3′,4′-dihydroxyphenyl)-γ-valerolactone sulfate (3,4-DHPV-S) represented the plant-based food group. Docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA) depicted the fish group, while pentadecanoic acid and margaric acid represented the dairy products group. Finally, the dietary intake of MUFAs and saturated fatty acids (SFAs) were depicted by oleic acid and palmitic acid, respectively (Tables S1 and S2, Supporting Information).

Following the same design used by Trichopoulou et al.[31] the study assigned a value of 0 or 1 to each dietary biomarker with the use of the sex-specific median as the cutoff (Table S3, Supporting Information). For dietary biomarkers of beneficial components (vegetables, legumes, fruits, cereals, and fish), subjects whose circulating level was below the median were assigned a value of 0, and individuals whose level was at or above the median were assigned a value of 1. According to the MDS defined by Trichopoulou et al.,[31,32] dairy products were presumed to be detrimental. For this reason, the scoring for dietary biomarkers

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of dairy products was inverted.[31,32] Finally, for the relation between MUFAs and SFAs, the study assigned a value of 1 to those individuals whose oleic acid concentration was at or above the median and a value of 0 to those whose concentrations were below it. The scoring was inverted for palmitic acid concentrations. Oleic acid and palmitic acid are the most abundant dietary and plasma FAs.[47,51] Moreover, oleic acid is a biomarker of olive oil intake, the main source of MUFAs in the MD context.[31,52]

Thus, the total MDMS ranged from 0 (minimal adherence) to 14 (maximal adherence). The MDMS was secondarily categorized, using cutoff values based on the sex- and cohort-specific medians, as low (<7 points) and high (≥7 points) adherence for both sexes and cohorts.

2.4. Dietary Data

Details of dietary habits assessment were described elsewhere.[53,54] Briefly, the study used a comprehensive food frequency questionnaire (FFQ)[53] and a 24 h dietary recall (24-HDR)[54] administered in 3C Bordeaux at the first follow-up visit in the period 2001–2002 (2–3 years after baseline when blood was drawn). For foods from the FFQ, data were available for 351 Bordeaux sample subjects, and for MUFAs and SFAs intake from the 24-HDR, data were available for 359 subjects. An MDS based on the FFQ and the 24-HDR was available for 349 subjects from Bordeaux (Table S4, Supporting Information).

2.5. Statistical Analysis

Baseline characteristics of the participants were expressed as means and standard deviations (SDs) for variables with normal distribution, medians, and interquartile ranges (IQRs) for variables with asymmetric distribution, and percentages for categorical variables. Baseline characteristic comparisons were tested using conditional logistic regression models. Correlation analyses were performed to examine the relation between MDMS and MDS, and between food groups and dietary biomarkers of MD key food groups in the Bordeaux cohort.

To study the association between MDMS and CD, the study estimated odds ratios (ORs) and their 95% confidence interval (CI) using logistic regression models conditioned on matching variables (i.e., age at baseline, sex, and education level) (Model 1). For multivariable-adjusted analyses, the study considered potentially modifiable risk factors for dementia (i.e., BMI, diabetes, alcohol intake, smoking status, hypertension, depression, and hypercholesterolemia)[55,56] (Model 2) as well as genetic factors (i.e., apolipoprotein E-ε4 genotype [ApoE-ε4])[56] and the total number of medications regularly consumed[17] (Model 3). The goodness of fit of the proposed models was evaluated using the likelihood-ratio chi-square test of the full model versus the null model, where $p < 0.05$ was considered to be a good fit.

Effect modification by age at baseline, sex, education level, BMI, diabetes, alcohol intake, smoking status, hypertension, depression, hypercholesterolemia, the total number of medications regularly consumed, and ApoE-ε4 was assessed by adding product terms in the fully adjusted regression models. Bonferroni correction was utilized for multiple testing correction ($p < 0.05/12$, statistical threshold at $\alpha = 0.004$).

For covariates, missing values comprised <2% of the samples and the reference category was assigned to missing data (for categorical variables) or the median value (for continuous variables). All statistical analyses were performed using the SPSS software package (SPSS 25.0, IBM, NY) and the significance level was a two-tailed $p < 0.05$.

3. Results

3.1. Characteristics of the Study Populations

Clinical and demographic characteristics of the study populations at baseline are shown in Table 1. The participants were matched for age, sex, and education level within the two samples, and these characteristics were similar between the discovery (i.e., Bordeaux) and validation (i.e., Dijon) sample sets. As expected, we observed lower scores for MMSE tests assessed in this study among subjects with CD. Medication use was significantly higher in cases, as well as the prevalence of diabetes. In the Bordeaux cohort, the presence of ApoE-ε4 was higher among cases than among controls, although the percentage was similar in the Dijon set. Cases from the Dijon cohort also showed a significantly higher percentage of participants with depression compared to controls (Table 1). However, in the Bordeaux set, cases and controls had a similar percentage of subjects with depression (Table 1).

3.2. Mediterranean Diet Metabolomic Score

The correlations among FFQ dietary components of MD key food groups and concentrations of serum biomarkers in the Bordeaux set are presented in Table S5 (Supporting Information). Nearly all MD key food groups had a positive and significant correlation with their serum metabolites. The strongest correlation was between the intake of fish and seafood and the sum of EPA and DHA (Table S5, Supporting Information). The plant-based food group (i.e., total intake of vegetables, fruits, legumes, and cereals) and the sum of their selected biomarkers were also positively correlated (Table S5, Supporting Information). Dairy intake and serum pentadecanoic acid and margaric acid were not correlated. MDS was also positively correlated with MDMS ($r = 0.135$, $p = 0.012$) in the Bordeaux cohort ($n = 349$).

3.3. MDMS and CD

The associations between MDMS and CD are shown in **Figure 1**. In the discovery set, CD was not associated with MDMS in the basic model (Figure 1A, Model 1). This association was unchanged after further adjustment for CD risk factors (i.e., BMI, diabetes, alcohol intake, smoking status, hypertension, depression, and hypercholesterolemia) (Figure 1A, Model 2). However, after additionally adjusting for the total number of medications regularly consumed and for ApoE-ε4 genotype (Model 3), subjects with a higher MDMS were less likely to experience CD (OR [95% CI]

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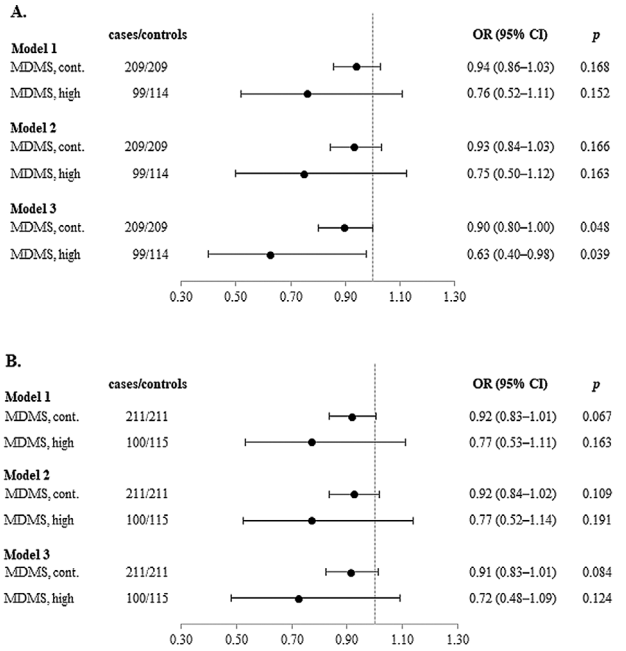

Figure 1. Multivariate conditional logistic regression models for association between MDMS (continuous and categorical) and CD in the 3C discovery (Bordeaux, $n = 418$) A) and validation (Dijon, $n = 422$) B) cohorts. OR (95% CI). Model 1 is unadjusted. Model 2 is adjusted for BMI, diabetes, alcohol intake, hypertension, smoking status, depression, and hypercholesterolemia. Model 3 is further adjusted for ApoE-ε4 and number of medications. The CD variable was built defining the composite score of global cognition at each follow-up visit.[17,18] Individual slopes of cognitive change were then evaluated using linear mixed models, as detailed in the previous publication.[18] Cases were defined as the participants with the CD worst slopes. ApoE-ε4, apolipoprotein E-ε4 genotype; 3C, Three-City; CD, cognitive decline; CI, confidence interval; MDMS, Mediterranean diet metabolomic score; OR, odds ratio.

= 0.90 (0.80–1.00); $p = 0.048$, MDMS as continuous variable) (Figure 1A, Model 3). This was consistent with the results observed in Dijon, with a trend toward significance in this validation sample (OR [95% CI] = 0.91 [0.83–1.01]; $p = 0.084$ for Model 3 and MDMS as a continuous variable) (Figure 1B, Model 3). The omnibus test suggested a significant improvement in fit of the models relative to the null (χ^2 (10) = 34.292; $p \leq 0.001$ and χ^2 (10) = 37.670; $p \leq 0.001$ in Bordeaux and Dijon, respectively, for Model 3, MDMS as continuous variable).

Stratified analyses were performed to assess the association between MDMS and the risk of CD in various subgroups (Table S6, Supporting Information). We noticed a close to significant interaction between MDMS and hypertension in the Bordeaux cohort (no hypertension, adjusted OR [95% CI] = 1.19 [0.95–1.50], compared with hypertension, adjusted OR [95% CI] = 0.83 [0.66–1.05]; p for interaction = 0.006). None of the other variables, including age at baseline, sex, education level, BMI, diabetes, alcohol intake, smoking status, hypercholesterolemia, depression, the total number of medications regularly consumed, and ApoE-ε4, significantly modified the association between MDMS and the risk of CD in the Bordeaux cohort. No interaction between MDMS and the abovementioned variables was found in the Dijon cohort (all p for interactions > 0.004 for multiple testing correction) (Table S6, Supporting Information).

4. Discussion

Leveraging targeted large-scale metabolomics data from the 3C Study, we here developed a Mediterranean diet metabolomic score (MDMS) based on serum biomarkers of MD key food groups. Our findings show that a higher MDMS is prospectively associated with a lower risk of CD in older adults free of dementia at baseline (median follow-up 12 years).

These results are in line with some prior prospective studies, where a high adherence to the MD, as assessed using dietary questionnaires, has been associated with a slower decline in global cognition in older adults.[57,58] However, despite the efforts made to reduce the heterogeneity of the scoring systems used for assessing adherence to the MD, it is still challenging to elucidate why current literature still reports mixed results for cognitive function and the MD in older adults.[57,59] For instance, in the 3C Study, Féart et al. suggested that a higher adherence to the MD, using the MDS, was associated with a slower CD, as based on MMSE score, but not with the risk of incident dementia or AD.[32] In another large-scale prospective study including 16 058 women from the Nurses' Health Study aged ≥70 years, authors found that an alternate MDS was related to moderately better cognition overall, but not to change in cognition over four repeated measures after 6 years of follow-up.[60] By contrast, in the EPIC-Spain Dementia Cohort Study, recent results showed that MD appeared to be protective and lowered the incidence of dementia.[61] Also, Scarmeas et al. reported that a higher MD adherence was associated with a reduced risk of AD.[62]

One source of these biases could be linked to the modality of assessing dietary intake, as most studies used dietary records, which lack accuracy and are prone to random bias and systematic errors. As a matter of fact and as potentially expected, the MDMS was weakly correlated with the MDS, as were most of the MD key food groups with their metabolites. The MDMS was created a priori based on the current state of the art on food intake biomarkers[63,64] and aiming at taking a step forward by surrogating traditional indicators of dietary patterns intake (i.e., FFQ and 24-HDR derived scores) and thus their inherent prone-to-subjectivity and lack of accuracy.[65–67] For instance, dairy intake and serum pentadecanoic and margaric acids were not correlated in this cohort. This may be attributable to the heterogeneity of fat content through different dairy products in the marketplace or within a specific product resulting from differences in processing (e.g., skimming, among others), as well as in the quality of the milk used as raw material (e.g., cattle breed and feeding, among others).[45] This particular case might serve as a revealing example of the need of better dietary definition, since in the MDS defined by Trichopoulou et al. the dairy products are presumed to be detrimental on account of their fat content.[31]

The weakness of correlation between the other food groups and their dietary biomarkers could be attributed to i) the variability of phytochemical or fatty acid content through a food group or a specific product resulting from differences in harvesting or between species (e.g., fatty fish have higher levels of long chain n-3 PUFA than lean fish and seafood),[68] among others; ii) the presence of the selected metabolites in other food sources not

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included in the MD key food groups (e.g., coffee, tea, and cocoa products)[69]; and iii) the presence of other metabolites that could contribute to the real content of an MD key food group (i.e., MUFA and SFA).

In a move to obtain more revealing information from dietary intake data and to overcome the above-mentioned problems, food biomarkers could be valuable in this respect as they can capture not only food composition but also their bioavailability. In this sense, several works have highlighted promising results when evaluating single food biomarkers in relation to CD. Rabassa et al. showed in their 3-year follow-up study that higher levels of urinary total polyphenols, a biomarker of fruit and vegetable intake, were associated with a lower risk of CD in older adults.[21] Interestingly, in the 3C Study, distinct associations were found between several serum food-derived metabolites and CD.[17–19] Yet, in another move aimed at obtaining more meaningful evidence, nutritional researchers have begun examining biomarkers as measures of dietary patterns rather than of single nutrients or dietary components. Unlike individual compounds, dietary patterns better reflect a person's habitual diet and provide a more integrated measure of the synergistic and accumulative effects of a combination of dietary factors.

To date, few studies have captured metabolomic signatures related to the MD through predictive and discriminant analysis, and some have studied their association with health outcomes, such as cardiovascular diseases and its risk factors.[70–75] To the best of our knowledge, our current work is the first study to have developed an a priori dietary metabolomic score based on serum biomarkers of MD food groups and to evaluate it in association with CD. Specifically, the MDMS comprises a set of serum phytochemical and fatty acid metabolites that reflect the individual bioavailability. Moreover, some of them have been recognized as exposure markers of the key MD food groups to which, in turn, the protective effects on health of the MD have been attributed to (Supporting Information).[76]

Validation is important but has rarely been carried out in previous food metabolomics studies, likely because it is challenging in research on nutrimetabolomics and cognitive impairment as there is an intrinsic and large heterogeneity across studies, and profound intervariability arising from factors like gut microbiota and/or health status,[15,77] and the complexity of outcomes based on long-term trajectories such as CD and different types of dementia. For example, despite belonging to the same cohort study, the features of our validation sample differed somewhat from the discovery sample (e.g., participants were older, showed a higher percentage of depression and ApoE-ε4 carriers, and had more cardiovascular risk factors at baseline). This could explain the weaker association we found in the Dijon (validation) sample compared to the discovery one, even though both sample sets were positively related to a greater MDMS, indicating a protective effect.

The major strengths of our study are the population-based and prospective design with repeated cognitive assessment over up to 12 years, a rigorous case-control sampling, and the application of a powerful targeted metabolomics approach to serum samples collected at baseline, i.e., at an age prior to the appearance of any dementia symptoms, which reduces the possibility of reverse causation. In addition, the use of two separate nested case–control sample sets noticeably enhances the reliability of our findings.

However, also several limitations warrant further discussion. First, serum samples for metabolomics analysis were only available at baseline, and thus we could not examine prior exposures or changes during the follow-up. An approach based on multiple sampling would have been of great interest to investigate the trajectory of CD. Moreover, although we adjusted the model by several potential confounders including ApoE-ε4, residual confounding factors cannot be dismissed. Another limitation is that the MDMS scoring system is based on sex-specific median values across metabolite concentrations of the studied populations. Therefore, the score may not be related to a healthy level of concentrations per se. Although we evaluated the reproducibility of the results in a separate nested case–control sample set, this metabolomic score deserves to be validated also in other cohorts and geographic areas, and its association with other chronic diseases should be examined.

In summary, a greater adherence to the MD assessed by a novel MDMS was associated with a lower risk of CD in older adults during a 12-year follow-up. The development of dietary metabolic scores based on dietary patterns may help further refine dietary assessment measures and will hopefully contribute to a better understanding of the biological mechanisms via which diet impacts cognitive health in the aging population.

Supporting Information

Supporting Information is available from the Wiley Online Library or from the author.

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Conflict of Interest

The authors declare no conflict of interest.

Author Contributions

Conceptualization: A.T.-R., C.M., A.K., P.J.L., L.A., S.T., C.H., C.S., C.A.-L., M.U.-S.; Data curation: R.G.-D., P.C.-E., F.C., E.V., A.S.-P.; Formal analysis: A.T.-R., M.U.-S.; Funding acquisition: C.M., A.K., P.J.L., L.A., M.P., S.T., C.H., C.S., C.A.-L.; Investigation: A.T.-R., A.S.-P., A.K., M.P., P.J.L., P.C.-E., L.A., R.G.-D., C.M., F.C., E.V., C.H., C.F.-C., S.L.-A., J.N., H.L., S.T., C.A.-L., C.S., M.U.-S.; Methodology: R.G.-D., M.P., A.S.-P., S.L.-A., C.A.-L., M.U.-S.; Supervision, C.S., C.A.-L., M.U.-S.; Writing – original draft: A.T.-R., M.U.-S.; Writing – review & editing: A.T.-R., A.S.-P., A.K., M.P., P.J.L., P.C.-E., L.A., R.G.-D., C.M., F.C., E.V., C.H., C.F.-C., S.L.-A., J.N., H.L., S.T., C.A.-L., C.S., M.U.-S. All authors have read and approved the final manuscript.

Data Availability Statement

Data used in the manuscript will be made available by the corresponding author upon request pending application and approval.

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