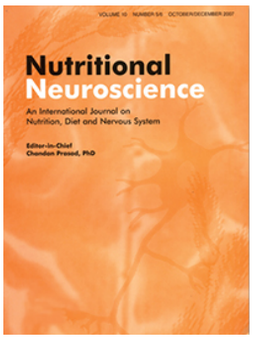

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Association between adherence to the Mediterranean-DASH Intervention for Neurodegenerative Delay (MIND) diet and cerebrospinal fluid Alzheimer's disease biomarkers in middle-life individuals without dementia: the ALBION study

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ABSTRACT

Objectives: Accumulative evidence links MIND diet with a reduced risk of Alzheimer's disease, but the connecting mechanisms remain unclear. We explored whether this dietary patterns and its components was associated with Amyloid beta (Aβ) deposition in dementia-free middle-life individuals.

Methods: 250 participants [65 (58, 73) years, 63.2% women] underwent neurological cognitive assessments and dietary assessment (through four 24-hour dietary recalls). Aβ concentrations were measured in cerebrospinal fluid samples. MIND diet adherence was examined both as a continuous variable and as a distribution-based categorical variable using quartiles (Q1–Q4), with higher quartiles reflecting higher adherence. Multivariate logistic regression analyses were conducted using MIND diet adherence (continuous or quartile-based) as the independent variable and Aβ deposition as the dependent variable.

Results: Compared to lower MIND adherence (Q1), higher adherence (Q4) was associated with less pathological Aβ concentrations (OR = 0.431, 95% CI: 0.195–0.950, $p = 0.037$). Each 1-SD increase in adherence was associated with a 26% reduction in the odds of having pathological Aβ concentrations (OR = 0.736, 95% CI: 0.563–0.962, $p = 0.025$). Among MIND diet components, only leafy vegetables intake showed a significant association with Aβ burden (OR = 0.519, 95% CI: 0.277–0.972, $p = 0.040$, q = 0.485).

Discussion: These cross-sectional findings suggest a potential mechanism that may partially explain the association between MIND diet adherence and cognitive function. However, they should be interpreted with caution, as the study sample may not be representative of community-based populations. Randomized clinical trials are needed to confirm this relationship.

KEYWORDS
MIND diet; Alzheimer's disease; amyloid beta; cerebrospinal fluid; neurodegeneration biomarkers

1. Background

Investigating dietary patterns is a widely used approach in nutrition research, as they capture diet as a multi-component exposure. Evaluating the relationship between health and dietary patterns, rather than isolating individual nutrients or food items, offers intuitive and practical insight. Free-living individuals consume combinations of foods containing diverse nutrients [1]; dietary patterns reflect total eating habits, taking into account the complex interactions between different nutrients and foods.

Healthy dietary patterns – including the Mediterranean diet and the Dietary Approaches to Stop Hypertension (DASH) diet – are increasingly recognized for their benefits in preventing chronic conditions and

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supporting cognitive health [2–5]. The Mediterranean-DASH Intervention for Neurodegenerative Delay (MIND) diet, combining features of the Mediterranean and DASH diets, uniquely targets brain health [6]. It emphasizes the consumption of plant-based foods (whole grains, vegetables, beans, and nuts), with special focus on berries and leafy green vegetables. The diet restricts consumption of red meat, as well as other foods with high total and saturated lipid content (fast and fried foods, cheese, butter and margarine, and pastries and sweets), and uses olive oil as the primary oil in the diet. It also recommends consuming fish more than once a week and poultry more than twice a week. The MIND diet has shown some potential benefits in relation to cognitive outcomes [7]. Specifically, observational data have consistently associated greater adherence to the MIND diet with lower incidence of Alzheimer's disease (AD) and slower cognitive decline [4, 8, 9]. In 2023, the first randomized clinical trial investigating the MIND diet and cognitive decline was published [10]. This three-year study randomized 604 overweight, cognitively healthy adults ($\geq$ 65 years) at risk of dementia. Participants were assigned to either the MIND diet with mild caloric restriction (–250 kcal/day) or a control diet with equivalent caloric restriction. While both groups showed minor cognitive improvements, the difference between them was not significant. Notably, pre-COVID-19 data suggested a small, statistically significant cognitive benefit for the MIND group, equivalent to being four years younger [11]. Although the findings remain inconclusive, the trial highlights the potential importance of studying diet in cognitively normal individuals and the need to include younger adults (<65 years) in future research.

Considering that different pathways may explain the effects of the MIND diet on cognitive function, the diet may prevent the induced aberrant activation of cell death through various mechanisms, including the amyloid beta (Aβ) pathway, neuroinflammation, tau hyperphosphorylation, dysregulation of calcium homeostasis, and others. Among the various mechanisms, only a few have been studied. Specifically, adherence to the MIND diet is positively associated with factors that may partly explain its link to cognition, such as preservation of brain white matter microstructure [12] and increased hippocampal volume [13].

Additionally, Aβ plaques and neurofibrillary tangles are the two key hallmarks of AD. Years before AD symptoms appear, abnormal accumulation of these biomarkers can be detected in the brain [14]. Changes in Aβ levels are typically the first biomarker abnormality observed in AD, often presenting as increased positivity in plasma and cerebrospinal fluid (CSF) in cognitively normal individuals [15]. To the best of our knowledge, the potential relationship between Aβ and adherence to the MIND diet has only been examined in postmortem brain tissues [16, 17], and there are no studies investigating the association between the MIND diet and Aβ deposition in middle-aged and older adults without dementia, a critical age group for early prevention. Therefore, the aim of this cross-sectional study was to examine the association between adherence to the MIND diet, including its component food groups, and concentrations of Aβ in CSF samples from participants of the ALBION study.

2. Methods

2.1. Study design and procedures

The data used in this study were derived from the Aiginition Longitudinal Biomarker Investigation of Neurodegeneration (ALBION), a population-based cohort study conducted at the Cognitive Disorders Clinic of Aiginition University Hospital, which is affiliated with the National and Kapodistrian University of Athens. Its primary objective is to investigate research inquiries pertaining to the preclinical and prodromal stages of AD. A detailed description of the study protocol has been published previously [18]. In brief, neurologists conducted a comprehensive interview and clinical examination. Vital signs and anthropometric measurements were meticulously recorded. Each study participant underwent a thorough assessment encompassing various parameters, including demographics (age, education, sex), medical history, social and environmental factors, clinical indicators, nutritional aspects and neuropsychological determinants. This assessment was conducted through a series of questionnaires. Participants diagnosed with dementia at baseline using specific criteria [19, 20] were excluded, as were individuals with neurological, psychiatric or medical conditions known to carry a high risk of cognitive impairment (including but not limited to Parkinson's disease, multiple sclerosis, Huntington's disease, Down syndrome, active alcohol or drug abuse or major psychiatric conditions such as major depressive disorder, schizophrenia and bipolar disorder). In addition,

participants with contraindications for lumbar puncture, such as use of anticoagulant medication, were excluded.

The ALBION protocol was approved by the Institutional Review Board of the Aiginition University Hospital of Athens. All volunteers gave written informed consent to participate in the examinations according to the Helsinki declaration.

2.2. Participants

The ALBION study comprised 290 individuals aged 40 years or older, who were either referred by other specialists or self-referred to the cognitive disorders outpatient clinic the Aiginition University Hospital of Athens, a tertiary university hospital. Patients were invited to participate in ALBION study if they met the following criteria; having a positive family history of dementia, expressing personal concerns regarding their cognitive ability, or demonstrating a sincere dedication to advancing medical science. After excluding participants with dementia or without CSF measurements ($n = 2$), and those without available dietary data at baseline ($n = 38$), the present cross-sectional analysis includes a total of 250 participants. A total of 38 participants were not included in the analyses because their dietary data were not available. Importantly, these individuals did not differ significantly ($p > 0.05$) from those included in the study with respect to key demographic characteristics, clinical diagnosis or the likelihood of having abnormal CSF $A\beta_{42}$ levels (data not shown).

2.3. Measurement of CSF indices

Lumbar puncture took place at the baseline visit. All procedures, as well as the collection, processing, and storage of the CSF, were conducted according to international guidelines [21]. CSF $A\beta_{42}$ was quantified using the Roche Elecsys electrochemiluminescence platform (cobas e platform). Samples were stored at −80 °C with no prior freeze–thaw cycles until analysis. Assays were conducted in multiple batches and internal quality control was conducted using PreciControl CSF (levels 1 and 2; Roche Diagnostics, Mannheim, Germany) to ensure between-batch consistency and analytical reliability. According to the manufacturer's precision data, repeatability (intra-assay) for the $A\beta_{42}$ assay ranges from 1.7-3.6%, while intermediate precision (intra-assay) ranges from 2.1 to 4.0%. Laboratory personnel were blinded to dietary and clinical data throughout the analytical process. Using this analysis, a value below 1,030 pg/mL of $A\beta_{42}$ was agreed upon to define amyloid positivity [22].

2.4. APOEε4 status

APOEε4 genotyping procedures have been described in detail previously [23]. Briefly, genotyping was performed on genomic DNA extracted from the blood buffy coat, using a commercial LightMix kit (TIB MOLBIOL, Berlin, Germany) on a Roche LightCycler 2 instrument (Roche Diagnostics, Mannheim, Germany), following the hybridization probe method. APOE genotyping data are available for 156 individuals. Based on the resulting genotype, participants were subsequently categorized as APOEε4 carriers (i.e. individuals with at least one ε4 allele) or non-carriers (i.e. with no ε4 alleles).

2.5. Assessment of dietary intake

Dietary intake was assessed through four 24-hour dietary recalls, using the multiple-pass method [24]. Trained registered dietitians conducted interviews with participants, requesting comprehensive reports of all foods and beverages consumed on the preceding day. The initial recall was conducted in person on the same day as the CSF collection, while the subsequent recalls were administered via telephone calls within the subsequent month. This timing ensured feasibility and participant convenience, but it also reflects dietary intake over a relatively short observational window. The telephone-administered recall demonstrated comparable effectiveness to the face-to-face method. Three of the recalls were conducted on weekdays, while one was conducted on a weekend day, aiming to enhance the accuracy of estimating habitual intake over the entire week. Prior knowledge of the recall day was not provided to the participants,

ensuring that they did not alter their dietary habits in anticipation of the interview. The recall data were subsequently analyzed for nutrient content using the dietary analysis software Nutritionist Pro™ (2007, Axxya Systems, Texas, U.S.A.). To ensure cultural and dietary relevance, food items were adapted to reflect Greek food products and their nutritional labels. Nutrient values were cross-checked and, where necessary, adjusted according to the Food Composition Tables and Greek Dishes [25]. The average dietary intake was calculated from the four recalls.

2.6. MIND diet score

For the present analysis, dietary intake was derived from four 24-hour recalls. For each participant, we first calculated the mean daily intake across all recalls and then converted into weekly servings to align with the original MIND cut-offs. Servings were defined using the same criteria as Morris et al. [6]. Specifically, as described by Morris et al. [6], the MIND diet score ranges from 0 to 15, with higher score indicating greater adherence. The score is based on 15 dietary components, including 10 brain-healthy food groups: green leafy vegetables, other vegetables, berries, nuts, beans, whole grains, fish, poultry, olive oil and wine. The remaining 5 components represent unhealthy food groups – red meats, butter and stick margarine, cheese, pastries and sweets, and fried or fast food. Olive oil consumption is scored 1 if the participant identifies it as the primary oil usually used at home, and 0 otherwise. All other diet components are assigned a score of 0, 0.5, or 1, depending on the level of adherence to dietary guidelines – where 1 indicates full adherence, 0.5 partial adherence, and 0 no adherence. The total MIND diet score was computed by summing the 15 component scores [6]. To improve transparency regarding measurement precision, we provide the distribution of component-level scores (0/0.5/1) in Table S1 in supporting information.

2.7. Statistical analyses

Continuous variables are presented as median with interquartile range (25th and 75th percentiles). Comparisons were performed using the Kruskal–Wallis H test for continuous variables. Group differences in categorical variables were assessed using the chi-squared test. Effect sizes for continuous variables were expressed as eta-squared (ε^2) derived from Kruskal–Wallis test, while effect sizes for categorical variables were reported as Cramer's V.

Multivariate logistic regression analyses were conducted using MIND diet adherence both as a standardized continuous variable (per 1-SD increase, z-score) and as a categorical variable based on quartiles (Q1–Q4), with higher quartiles reflecting greater adherence, and Aβ positivity as the dependent outcome. To explore potential non-linear associations, restricted cubic spline analyses were performed using knots at the 5th, 35th, 65th, and 95th percentiles of the MIND diet score. All spline terms were found to be non-significant ($p > 0.005$), indicating the relationship between MIND adherence and Aβ positivity is essentially linear.

Regressions were initially adjusted for sex, participants' age and years of education (Model 1). Total energy intake was then included as an additional covariate (Model 2). Finally, the models were further adjusted for clinical diagnosis (normal vs. MCI), and for cardiometabolic comorbidities (diabetes mellitus, hypertension, hyperlipidemia) (Model 3).

Adjustment for total energy intake was included in Model 2 to account for variations in overall food consumption. As highlighted by McCullough and Byrd [26], adjusting for energy intake helps reduce extraneous variation related to body size and physical activity, allowing nutrient-disease associations to be interpreted more accurately and independently of total energy intake. Sex, clinical diagnosis, and cardiometabolic comorbidities were treated as dichotomous variables; education, age and total energy intake were treated as continuous variables.

Furthermore, exploratory, hypothesis-generating analyses were conducted for components of the MIND diet. Given the large number of statistical tests in this secondary set of analyses, the Benjamini–Hochberg False Discovery Rate (FDR) method was applied to adjust *p*-values in order to control for multiple comparisons, and both raw and FDR-corrected *p*-values (q-values) are reported [27].

Statistical analyses were performed using IBM SPSS Statistics version 29. Type I probabilistic error was defined as $p \leq 0.05$.

Subsample analyses were conducted in the subset of participants of whom APOE genotyping data were available ($N = 156$), adjusting for previous covariates.

3. Results

3.1. Characteristics of participants

Of the 250 individuals without dementia at baseline, the median age was 65 (58, 73) years; they had 15 (12, 17) years of education, and the majority of them were women (63.2%) (Table 1). Overall, 38.2% of participants met the diagnostic criteria for mild cognitive impairment (MCI), and over half of study participants (52%) had pathological Aβ concentrations in the CSF. With regard to cardiometabolic health, 11% had a diagnosis of diabetes mellitus, 36.8% had hypertension, and 44.5% had hyperlipidemia. In the subsample of 156 individuals with available APOE genotyping, 28.8% were ε4 carriers. Participants had a median daily energy intake of 1728 (1400, 2104) kcal, and a median MIND score of 8.5 (7.0, 9.5). Participants across the MIND diet quartiles were generally comparable in terms of demographic characteristics and overall genetic and cardiometabolic profile. However, significant differences emerged in dietary intake, with higher adherence associated with lower total energy intake, while the percentage of energy derived from carbohydrates increased progressively across quartiles (Table 1).

3.2. Association of adherence to the MIND diet with Amyloid Beta (Aβ) deposition

Multivariate logistic regression analyses revealed that, compared to lowest adherence quartile (Q1) to the MIND diet, higher adherence (Q4) was associated with lower odds of Aβ positivity across all models.

Table 1. Characteristics of the study population.

Study Variables	Total Sample (N = 250)	MIND diet (in quartiles)				Effect size
		Q1 (n = 47)	Q2 (n = 63)	Q3 (n = 63)	Q4 (n = 77)	
Demographic factors						
Age (years)	65 (58, 73)	63 (54, 72)	66 (57, 74)	65 (58, 73)	65 (59, 71)	0.005
Sex (N / % Women)	158 / 63.2%	24 / 51.1%	39 / 61.9%	42 / 66.7%	52 / 68.4%	0.130
Education (years)	15 (12, 17)	14 (12, 16)	14 (12, 16)	16 (12, 17)	15 (12, 17)	0.004
Cognitive function						
Clinical diagnosis (N / % MCI)	95 / 38.2%	19 / 40.4%	29 / 46.0%	18 / 28.6%	29 / 38.2%	0.130
Cerebrospinal fluid Alzheimer's disease biomarker						
Amyloid beta$_{42}$ (N / % pathological)	130 / 52.0%	29 / 61.7%	37 / 58.7%	30 / 47.6%	33 / 43.4%	0.150
Genetic and Cardiometabolic factors						
APOE ε4 carrier (N / % positive)	45 / 28.8% (n = 156)	9 / 28.1% (n = 32)	11 / 30.6% (n = 36)	11 / 32.4% (n = 34)	14 / 25.9% (n = 54)	0.056
Diabetes mellitus (N / % present)	27 / 11%	4 / 8.7%	8 / 12.9%	7 / 11.5%	8 / 10.5%	0.046
Hypertension (N / % present)	91 / 36.8%	18 / 38.3%	26 / 41.9%	21 / 33.9%	26 / 34.2%	0.070
Hyperlipidemia (N / % present)	110 / 44.5%	17 / 36.2%	32 / 51.6%	26 / 41.9%	35 / 46.1%	0.107
Dietary intake						
MIND score††	8.5 (7.0, 9.5)	6.0 (5.5, 6.5)	7.0 (7.5, 8.0)	8.5 (8.5, 9.0)	10 (9.5, 10.5)	0.940
Total energy intake (kcal/day) ††	1728 (1400, 2104)	2055 (1584, 2409)	1528 (1274, 1979)	1763 (1473, 2034)	1698 (1381, 2082)	0.057
Carbohydrates (% daily energy) †	42.3 (36.3, 47.6)	38.9 (34.5, 43.6)	43.7 (36.3, 50.3)	42.3 (35.9, 47.9)	44.1 (37.6, 48.3)	0.029
Proteins (% daily energy)	14.9 (13.3, 17.6)	14.8 (13.2, 17.5)	15.7 (13.7, 18.3)	14.6 (12.9, 16.4)	15.8 (14.0, 17.8)	0.005
Lipids (% daily energy)	42.3 (37.8, 47.1)	45.2 (40.3, 48.5)	41.5 (35.9, 46.3)	41.8 (38.6, 47.1)	42.7 (37.0, 47.4)	0.012
Saturated fatty acids (% daily energy) ††	11.7 (9.7, 13.6)	14.2 (12.0, 16.2)	12.1 (10.3, 13.6)	11.2 (8.8, 13.3)	10.7 (9.1, 12.6)	0.129
Monounsaturated fatty acids (% daily energy)	20.8 (17.7, 24.1)	20.5 (18.2, 23.7)	19.3 (16.4, 22.8)	21.2 (18.4, 23.5)	21.4 (18.4, 24.8)	0.010
Polyunsaturated fatty acids (% daily energy) ††	6.7 (5.4, 7.8)	6.3 (5.3, 7.5)	6.3 (4.8, 7.1)	6.9 (5.6, 8.7)	6.9 (6.0, 8.2)	0.050

† $p < 0.02$, †† $p < 0.001$.

MCI = Mild cognitive impairment, MIND = Mediterranean-DASH Intervention for Neurodegenerative Delay.

Data are presented as median with interquartile range (25th and 75th percentiles) for continuous variables. Effect sizes for continuous variables were calculated using epsilon-squared (ε^2) (Kruskal-Wallis tests). Effect sizes for categorical variables were expressed as Cramer's V.

This association remained significant after sequential adjustment for sex, age, years of education (Model 1: OR = 0.448, 95% CI: 0.207–0.968, $p = 0.041$); additional adjustment for total energy intake (Model 2: OR = 0.439, 95% CI: 0.202–0.957, $p = 0.038$); and further adjustment for clinical diagnosis, and cardiometabolic comorbidities including diabetes mellitus, hypertension, and hyperlipidemia (Model 3: OR = 0.431, 95% CI: 0.195–0.950, $p = 0.037$). Results for all models are presented in Table 2. The fully adjusted model (Model 3) explained approximately 14.6% of the variance in Aβ positivity (Nagelkerke $R^2 = 0.146$). Additionally, for every 1-SD increase in MIND diet adherence, participants had 26% lower odds of having pathological Aβ concentrations in CSF samples, after adjusting for Model 3 confounders (OR = 0.736, 95% CI: 0.563–0.962, $p = 0.025$; Nagelkerke $R^2 = 0.102$) (Table 2).

Additionally, APOE status was included as a covariate and a subsample analysis was conducted in a subset of 156 participants. In this analysis, compared to lower adherence to the MIND diet (Q1), higher adherence (Q4) was associated with lower odds of Aβ positivity after adjusting for sex, age, years of education, total energy intake, APOE status, clinical diagnosis, and cardiometabolic confounders (hypertension, diabetes mellitus, hyperlipidemia). Specifically, when the MIND diet was treated as a categorical variable the OR was 0.374 (95% CI: 0.139–0.992, $p = 0.046$; Nagelkerke $R^2 = 0.237$). When treated as a standardized continuous variable (z-score), the OR was 0.701 (95% CI: 0.492-0.998, $p = 0.049$; Nagelkerke $R^2 = 0.204$) (Table S2 in supporting information).

3.3. Association of the components of the MIND diet with Amyloid Beta (Aβ) deposition

We further examined which of the 15 components of the MIND diet were most strongly associated with Aβ deposition. These exploratory, component-level associations were examined using logistic regression models assessing the relationship between servings of individual MIND food components and Aβ positivity, with both raw and FDR-corrected *p*-values presented (q-values). Specifically, in this analysis, participants who consumed leafy vegetables were 48% less likely to have pathological Aβ deposition (OR = 0.519, 95% CI: 0.277, 0.972, $p = 0.04$) in CSF samples, even after adjustment for confounders (Figure 1) (Table S3 in supporting information). This association did not remain significant after false discovery rate (FDR) correction for multiple comparisons ($q = 0.485$). Additionally, no significant associations were found when Aβ was treated as a continuous variable (data not shown).

4. Discussion

In this cross-sectional analysis of middle-life individuals without dementia, we found that higher adherence to the MIND diet was inversely associated with Aβ burden. Among the 15 MIND diet components the consumption of green leafy vegetables was the only component inversely associated with Aβ positivity.

To the best of our knowledge, this study provides the opportunity to examine the potential association between MIND diet adherence and Aβ deposition. Our findings add to the current evidence by suggesting an additional mechanism that may partly explain the relationship between MIND diet adherence and cognitive function. The finding of a relationship between a healthy diet and brain Aβ deposition is in general consistent with previous studies. For example, previous data from Rush Memory and Aging Project (MAP) either found no association between MIND diet adherence and Aβ load [17], or reported an association

Table 2. Cross-sectional association between MIND diet and amyloid beta deposition.

	MIND diet (in Quartiles)							
	Q2		Q3		Q4		MIND (z-score)	
	Q1 OR (95% CI)	*p*	OR (95% CI)	*p*	OR (95% CI)	*p*	OR (95% CI)	*p*
Model 1	0.831 (0.375-1.842)	0.648	0.539 (0.244-1.190)	0.126	0.448 (0.207-0.968)	**0.041**	0.746 (0.573-0.972)	**0.030**
Model 2	0.801 (0.353-1.820)	0.597	0.529 (0.238-1.177)	0.119	0.439 (0.202-0.957)	**0.038**	0.745 (0.572-0.970)	**0.029**
Model 3	0.770 (0.335-1.773)	0.540	0.498 (0.218-1.135)	0.097	0.431 (0.195-0.950)	**0.037**	0.736 (0.563-0.962)	**0.025**

Values are odds ratios with confidence intervals between brackets.

$A\beta_{42}$ = amyloid beta 42; CI = confidence interval; MIND = Mediterranean-DASH Intervention for Neurodegenerative Delay; OR = odds ratio; ref. = reference category.

Model 1: adjusted for age, sex and education in years; Model 2: additionally, adjusted for total energy intake; Model 3: additionally, adjusted for clinical diagnosis, and cardiometabolic comorbidities (diabetes mellitus, hypertension and hyperlipidemia).

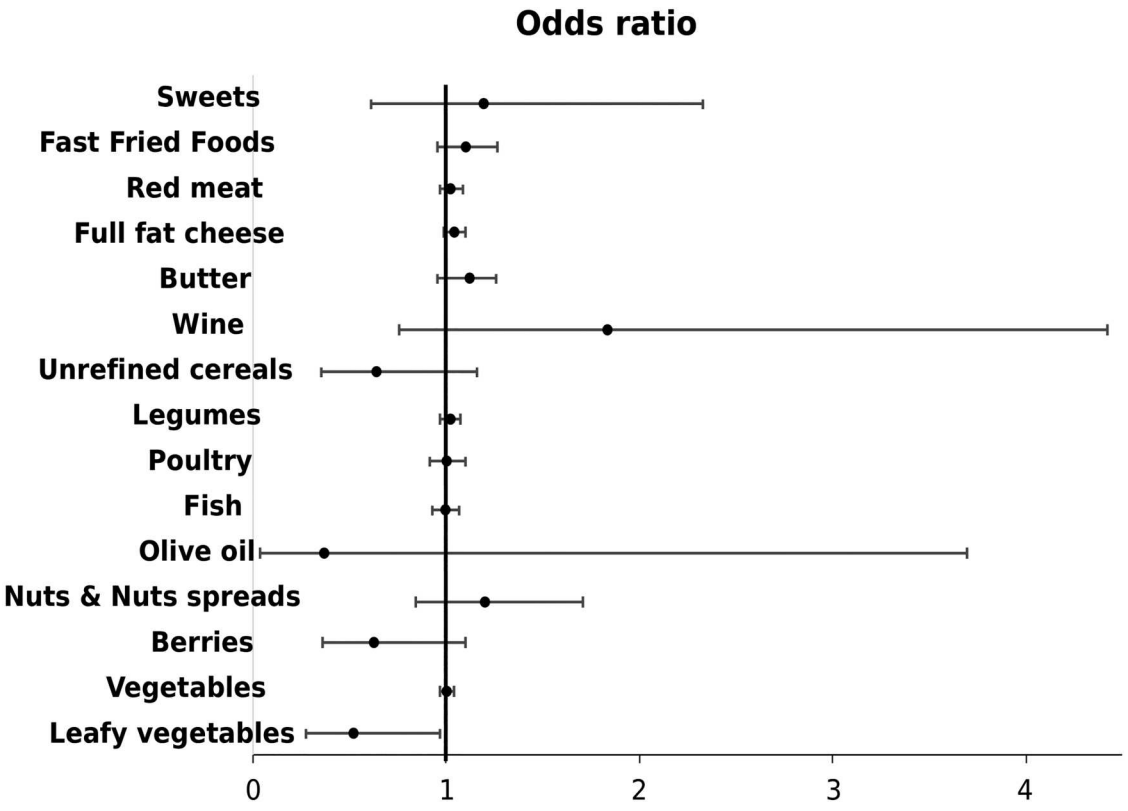

Figure 1. Forest plot of the association between MIND components and amyloid beta deposition.

with lower Aβ load [16] in postmortem brain tissues. In addition, Mediterranean diet was shown to be associated with slower Aβ accumulation [28, 29] or a lower likelihood of having pathological Aβ concentrations [30, 31], as measured by positron emission tomography imaging. Overall, current evidence suggests a role of healthy diet in preventing or slowing down accumulation of Aβ but more longitudinal studies are warranted.

Furthermore, the mechanistic link between diet and AD neuropathology in humans is not fully known and merits further investigation. The MIND diet is a plant-based diet rich in various essential nutrients and bioactive compounds with antioxidant and anti-inflammatory properties, which are associated with reduce low-grade inflammation [32, 33] and oxidative stress [34]. A 4-week randomized controlled trial comparing a high-fat/high-glycemic index diet and a low–saturated fat/low–glycemic index diet suggested that diet modulates AD risk through its effects on lipoproteins, oxidative stress, insulin and central nervous system concentrations of $A\beta_{42}$ [35].

In terms of green leafy vegetable consumption, the MAP study found that participants in the highest tertile of green leafy vegetable intake had lower global AD pathology, as measured by neurofibrillary tangles and neuritic and diffuse plaques in postmortem brain tissues [16]. Additionally, regarding leafy vegetable consumption and cognitive function, previous observational studies have found that, compared to lower leafy vegetable intake, participants with higher intake had lower odds of cognitive decline in late life [36–39]. Specifically, in a study of 27,842 U.S. male health professionals, higher consumption of green leafy vegetables was significantly associated with lower odds of cognitive decline in late life [36]. Similarly, in 15,080 U.S. female participants in the Nurses' Health Study, higher green leafy vegetable intake was also related to slower cognitive decline [37]. Furthermore, in 960 older U.S. participants in the MAP study, consumption of green leafy vegetables was linearly associated with slower cognitive decline [38]. In a Chinese population, a cross-sectional study revealed that participants who consumed green vegetables every day had significantly lower odds of mild cognitive impairment compared to those who consumed less [39]. These findings align with our results, which showed that higher leafy vegetable consumption was associated with lower Aβ positivity in a sample of middle-aged and older adults without dementia. However, this association did not remain significant after FDR correction for multiple comparisons.

Regarding the nutrients for which green leafy vegetables are a rich or primary source, higher dietary intakes of folate, phylloquinone, and lutein have each linearly associated with slower cognitive decline [38]. Several potential mechanisms have been proposed through which green leafy vegetable intake may affect cognitive function. Green leafy vegetables are rich in (i) carotenoids, vitamin C, vitamin E, and (n-3) polyunsaturated fatty acids, which can inhibit oxidative stress and inflammation [40]; (ii) folate, as adequate folate status protects against hyperhomocysteinemia, a condition that increases the risk of cognitive dysfunction [41]; and (iii) polyphenols, which may promote neuroprotection by inhibiting the activity of caspase-3 and apoptosis-inducing factor – key elements in the pathway through which Aβ peptides trigger apoptotic cell death [42, 43].

Bearing in mind that the association between leafy vegetable intake and Aβ deposition did not remain significant after FDR correction for multiple comparisons, we hypothesized that the potential link with Aβ burden reflects the overall dietary pattern and the complex interactions between different nutrients and foods rather than a single food group. As leafy green vegetables are one of the core components of the MIND diet, the lack of a strong association in our sample may be due both to their frequent consumption in this population and to their biologically plausible protective effects, highlighting the need for more longitudinal studies in different populations to elucidate causal relationships between leafy green vegetable consumption and Aβ deposition.

We acknowledge that the cross-sectional design precludes our ability to make causal inferences. Additionally, although we have adjusted for known confounders, potential residual confounding cannot be ruled out. However, this study allows us to generate hypotheses for future studies. We also recognize that the moderate sample size ($n = 250$) may have limited the statistical power and restricted the generalizability of our results. Moreover, participants in this study were self-referred or clinic-referred due to memory concerns or a family history of dementia, resulting in a higher-than-expected prevalence of Aβ positivity. Another limitation relates to CSF biomarkers: $A\beta_{40}$ concentrations were not available and thus the $A\beta_{42}$ /$A\beta_{40}$ ratio could not be calculated. Future studies incorporating both $A\beta_{40}$ and $A\beta_{42}$ would allow more refined quantification of amyloid pathology. Finally, although the nutritional analysis was performed using software originally developed based on U.S. food composition data, data entries were adapted to Greek dietary habits and verified using the Food Composition Tables and Greek Dishes [25]; however, minor discrepancies may still exist.

This study has several important strengths. First, dietary intake was assessed using 24-h diet recalls, which allowed us to obtain detailed information on daily dietary habits and accurately calculate both MIND diet adherence, and total energy intake. Moreover, using four dietary recalls (three weekdays and one weekend day) minimized the effect of random error (day-to-day variability in dietary intake) and ensured a more accurate reflection of usual dietary intake. Furthermore, because the recalls were collected within a short time window relative to CSF collection, they may better reflect current or recent eating patterns. In addition, this analysis introduces several food groups in the context of CSF AD biomarkers research. While our primary analyses focused on the overall to the MIND dietary pattern, future studies could consider multivariable, data-driven approaches, such as principal component analysis (PCA) or penalized regression, to further identify which individual food groups might be most strongly related to CSF biomarkers. The utilization of automated methods for assessing CSF biomarkers, which appear to align well with amyloid PET scan imaging compared to previously employed assays [44]. Clinical evaluation was carried out by clinicians with subspecialty training and considerable experience in the cognitive disorders field. Another strength of the study is that participants were self-referred due to memory concerns or a positive family history of late-onset AD dementia. As a result, participants were evaluated in middle age, providing an opportunity to examine preclinical Aβ deposition years before the onset of clinical symptoms.

The study documented an inverse association between adherence to the MIND diet and Aβ positivity. Additionally, higher intake of leafy vegetables was associated with lower Aβ positivity. None of the other MIND diet components were associated with Aβ burden. Considering that nutritional factors are modifiable across the lifespan, our findings may have significant implications for aging and nutritional neuroscience, highlighting how specific dietary patterns may influence neurodegenerative biomarkers. Future research, including prospective and randomized clinical trials, is needed to elucidate causal relationships between MIND diet adherence and Aβ deposition, to quantify alternative biomarkers, and to investigate potential mechanisms.

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Disclosure statement

No potential conflict of interest was reported by the author(s).

Data availability statement

The datasets used and analyzed during the current study are available from the corresponding author upon reasonable request.

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References

[1] Kant AK. Dietary patterns and health outcomes. J Am Diet Assoc. 2004;**104**(4):615–35.
[2] Yannakoulia M, Scarmeas N. Diets. N Engl J Med. 2024;**390**(22):2098–106.
[3] Charisis S, Yannakoulia M, Scarmeas N. Diets to promote healthy brain ageing. Nat Rev Neurol. 2025;**21**(1):5–16.

[4] van Soest AP, et al. The mediterranean-dietary approaches to stop hypertension intervention for neurodegenerative delay (MIND) diet for the aging brain: a systematic review. Adv Nutr. 2024;**15**(3):100184.
[5] Dominguez LJ, et al. Impact of mediterranean diet on chronic non-communicable diseases and longevity. Nutrients. 2021;**13**:2028.
[6] Morris MC, et al. MIND diet slows cognitive decline with aging. Alzheimers Dement. 2015;**11**(9):1015–22.
[7] Scarmeas N, Anastasiou CA, Yannakoulia M. Nutrition and prevention of cognitive impairment. Lancet Neurol. 2018;**17**(11):1006–15.
[8] Huang L, et al. Mediterranean-dietary approaches to stop hypertension intervention for neurodegenerative delay (MIND) diet and cognitive function and its decline: a prospective study and meta-analysis of cohort studies. Am J Clin Nutr. 2023;**118**(1):174–82.
[9] Kheirouri S, Alizadeh M. MIND diet and cognitive performance in older adults: a systematic review. Crit Rev Food Sci Nutr. 2022;**62**(29):8059–77.
[10] Barnes LL, et al. Trial of the MIND diet for prevention of cognitive decline in older persons. N Engl J Med. 2023;**389**(7):602–11.
[11] Barnes LL, et al. Primary prevention of cognitive decline in older individuals with the MIND diet. Alzheimer's Dement. 2023;**19**:e078519.
[12] Thomas A, et al. Association of a MIND diet with brain structure and dementia in a French population. J Prev Alzheimers Dis. 2022;**9**(4):655–64.
[13] Arjmand G, Abbas-Zadeh M, Eftekhari MH. Effect of MIND diet intervention on cognitive performance and brain structure in healthy obese women: a randomized controlled trial. Sci Rep. 2022;**12**(1):2871.
[14] Insel PS, et al. Determining clinically meaningful decline in preclinical Alzheimer disease. Neurology. 2019;**93**(4): e322–e333.
[15] Murphy MP, LeVine H. Alzheimer's disease and the amyloid-beta peptide. J Alzheimers Dis. 2010;**19**(1):311–23.
[16] Agarwal P, et al. Association of Mediterranean-DASH intervention for neurodegenerative delay and Mediterranean diets with Alzheimer disease pathology. Neurology. 2023;**100**(22):e2259–e2268.
[17] Dhana K, et al. MIND diet, common brain pathologies, and cognition in community-dwelling older adults. J Alzheimers Dis. 2021;**83**(2):683–92.
[18] Kalligerou F, et al. Aginition longitudinal biomarker investigation of neurodegeneration (ALBION): study design, cohort description, and preliminary data. Postgrad Med. 2019;**131**(7):501–8.
[19] McKhann GM, et al. The diagnosis of dementia due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. Alzheimers Dement. 2011;**7**(3):263–9.
[20] McKhann G, et al. Clinical diagnosis of Alzheimer's disease: report of the NINCDS-ADRDA work group under the auspices of department of health and human services task force on Alzheimer's disease. Neurology. 1984;**34**(7):939–44.
[21] Teunissen CE, et al. Biobanking of CSF: international standardization to optimize biomarker development. Clin Biochem. 2014;**47**(4-5):288–92.
[22] Blennow K, et al. Second-generation Elecsys cerebrospinal fluid immunoassays aid diagnosis of early Alzheimer's disease. Clin Chem Lab Med. 2023;**61**(2):234–44.
[23] Sampatakakis SN, et al. Objective physical function in the Alzheimer's disease continuum: association with Cerebrospinal Fluid Biomarkers in the ALBION study. Int J Mol Sci. 2023;**24**:14079.
[24] Conway JM, et al. Effectiveness of the US Department of Agriculture 5-step multiple-pass method in assessing food intake in obese and nonobese women. Am J Clin Nutr. 2003;**77**(5):1171–8.
[25] Trichopoulou A. Food composition tables and Greek dishes [in Greek]. 3 ed. Athens: Parisianos; 2004.
[26] McCullough LE, Byrd DA. Total energy intake: implications for epidemiologic analyses. Am J Epidemiol. 2023;**192**(11):1801–5.
[27] Benjamini Y, Hochberg Y. Controlling the false discovery rate: a practical and powerful approach to multiple testing. J Royal Statist Soc Series B. 1995;**57**(1):289–300.
[28] Rainey-Smith SR, et al. Mediterranean diet adherence and rate of cerebral Abeta-amyloid accumulation: data from the Australian imaging, biomarkers and lifestyle study of ageing. Transl Psychiatry. 2018;**8**(1):238.
[29] Berti V, et al. Mediterranean diet and 3-year Alzheimer brain biomarker changes in middle-aged adults. Neurology. 2018;**90**(20):e1789–e1798.
[30] Vassilaki M, et al. Mediterranean diet, its components, and amyloid imaging biomarkers. J Alzheimers Dis. 2018;**64**(1):281–90.
[31] Matthews DC, et al. Physical activity, Mediterranean diet and biomarkers-assessed risk of Alzheimer's: a multimodality brain imaging study. Adv J Mol Imaging. 2014;**4**(4):43–57.
[32] Fung TT, et al. Diet-quality scores and plasma concentrations of markers of inflammation and endothelial dysfunction. Am J Clin Nutr. 2005;**82**(1):163–73.
[33] van Zonneveld SM, et al. An anti-inflammatory diet and its potential benefit for individuals with mental disorders and neurodegenerative diseases-a narrative review. Nutrients. 2024;**16**:16.
[34] Avila-Escalante ML, et al. The effect of diet on oxidative stress and metabolic diseases-clinically controlled trials. J Food Biochem. 2020;**44**(5):e13191.

[35] Bayer-Carter JL, et al. Diet intervention and cerebrospinal fluid biomarkers in amnestic mild cognitive impairment. Arch Neurol. 2011;**68**(6):743–52.
[36] Yuan C, et al. Long-term intake of vegetables and fruits and subjective cognitive function in US men. Neurology. 2019;**92**(1):e63–e75.
[37] Kang JH, Ascherio A, Grodstein F. Fruit and vegetable consumption and cognitive decline in aging women. Ann Neurol. 2005;**57**(5):713–20.
[38] Morris MC, et al. Nutrients and bioactives in green leafy vegetables and cognitive decline: Prospective study. Neurology. 2018;**90**(3):e214–e222.
[39] Li W, et al. The association between eating green vegetables every day and mild cognitive impairment: a community-based cross-sectional study in Shanghai. Neuropsychiatr Dis Treat. 2019;**15**:3213–8.
[40] Kesse-Guyot E, et al. Carotenoid-rich dietary patterns during midlife and subsequent cognitive function. Br J Nutr. 2014;**111**(5):915–23.
[41] Wang Z, et al. B vitamins and prevention of cognitive decline and incident dementia: a systematic review and meta-analysis. Nutr Rev. 2022;**80**(4):931–49.
[42] Bastianetto S, et al. Possible involvement of programmed cell death pathways in the neuroprotective action of polyphenols. Curr Alzheimer Res. 2011;**8**(5):445–51.
[43] Caruso G, et al. Phenolic acids and prevention of cognitive decline: polyphenols with a neuroprotective role in cognitive disorders and Alzheimer's disease. Nutrients. 2022;**14**:819.
[44] Doecke JD, et al. Elecsys CSF biomarker immunoassays demonstrate concordance with amyloid-PET imaging. Alzheimers Res Ther. 2020;**12**(1):36.