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# Association of Mediterranean-DASH Intervention for Neurodegenerative Delay and Mediterranean Diets With Alzheimer Disease Pathology

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## ABSTRACT

**Objective:** Diet may reduce Alzheimer's dementia risk and slow cognitive decline, but the understanding of the relevant neuropathologic mechanisms remains limited. The association of dietary patterns with Alzheimer's disease (AD) pathology has been suggested using neuroimaging biomarkers. This study examined the association of MIND and Mediterranean dietary patterns with beta-amyloid load, phosphorylated tau tangles, and global AD pathology in postmortem brain tissue of older adults.

**Methods:** Autopsied participants of the Rush Memory and Aging Project) with complete dietary information (collected through a validated food frequency questionnaire) and AD pathology data (beta-amyloid load, phosphorylated tau tangles, and global AD pathology [summarized neurofibrillary tangles, neuritic and diffuse plaques]) were included in this study. Linear regression models controlled for age at death, sex, education, APO-ε4 status, and total calories were used to investigate the dietary patterns (MIND and Mediterranean diet) and dietary components associated with AD pathology. Further effect modification was tested for APO-ε4 status and sex.

**Results:** Among our study participants (N=581, age at death: 91.0 ± 6.3 years; mean age at first dietary assessment: 84.2 ±5.8; 73% female; 6.8 ± 3.9 years of follow-up) dietary patterns were associated with lower global AD pathology (MIND: β= -0.022, p=0.034, standardized β=-2.0; Mediterranean: β=-0.007, p=0.039, standardized β=-2.3) and specifically less beta-amyloid load (MIND: β=-0.068, p=0.050, standardized β=-2.0; Mediterranean: β=-0.040, p=0.004, standardized β=-2.9). The findings persisted when further adjusted for physical activity, smoking, and vascular disease burden. The associations were also retained when participants with mild cognitive impairment or dementia at the baseline dietary assessment were excluded. Those in the highest tertile of green leafy vegetables intake had less global AD pathology when compared to those in the lowest tertile (Tertile-3 vs. Tertile-1: β= -0.115, p=0.0038).

**Conclusion:** The MIND and Mediterranean diets are associated with less postmortem AD pathology, primarily beta-amyloid load. Among dietary components, green leafy vegetables inversely correlate with AD pathology.

**Keywords:** healthy dietary pattern, diet, food groups, beta-amyloid, tangles

## 1. Introduction

Healthy dietary patterns, including Mediterranean-DASH Intervention for Neurodegenerative Delay (MIND), the Mediterranean, and the DASH diet, are associated with slower cognitive decline[1-3] reduced Alzheimer's dementia risk,[4] better cognition independent of Alzheimer's disease (AD) pathology,[5] and less functional disability[6]. By contrast, high-fat, high-sugar diets, such as the Western diet, are associated with poor cognition.[7, 8] Diets such as the MIND, Mediterranean, and DASH diets are primarily plant-based diets that are rich in nutrients and bioactive compounds essential for brain health as well as having antioxidant properties. Some researchers have reported that the MIND and Mediterranean diets are positively associated with factors that may partly explain their associations with cognition, such as total brain volume,[9, 10] cortical thickness,[11, 12] and white matter hyperintensity.[13]

Amyloid and neurofibrillary tangles are the two important hallmarks of AD. A Mediterranean diet was reported to be associated with biomarkers of cerebral Aβ-amyloid (assessed by Pittsburgh compound B positron emission tomography [PiB-PET])[14] and cerebrospinal fluid (Aβ42/40 ratio, pTau181)[15] but we are unaware of any studies on the association of healthy dietary patterns with AD pathology in the postmortem human brain. The present study examined the association of MIND and Mediterranean diet scores (two of the most widely studied diet scores for their association with cognition in older adults in different populations[16]) and various food groups with beta-amyloid load, phosphorylated tau tangles, and global AD pathology among autopsied participants of the Rush Memory and Aging Project (MAP).

## 2. Subjects and Method

### 2.1. Study participants

The MAP participants included in this study were those with autopsies. MAP is an ongoing longitudinal cohort of older adults without known dementia at the time of enrollment[17]. At baseline, MAP participants sign an informed consent for annual assessments and an Anatomic Gift Act for brain donation at the time of death. MAP was initiated in 1997, and as of June 2021, 2,198 participants had enrolled and completed baseline assessments. Of those, 2,042 were alive and active when a food frequency questionnaire (FFQ) sub-study began in 2004, although 161 were not available for FFQs (9 withdrew from MAP, 83 died, and 70 were Spanish speakers, had

dementia, or declined to enroll in dietary sub study). Excluding those with unprocessed dietary data (n = 565), 1,471 MAP participants had complete dietary data, and, of those, 786 were deceased. Those without autopsy (n = 112), neuropathological data (n = 10), or checked nutrient data (n = 68) or with missing covariate data (n = 4) were excluded, leaving an analytical sample of 581 participants. The institutional review board of Rush University approved the study.

### 2.2. Dietary assessment

The study participants underwent annual dietary assessments during the years of follow-up before death. We used previously validated 144-item FFQ for older adults to record what they ate over the past year.[18, 19] For each food item in the FFQ, total calories and nutrient levels were computed as previously defined.[1] For this analysis, we considered the mean dietary intake using multiple dietary assessments during the follow-up years before death.

*MIND diet score*: The MIND diet score, as previously described, is the sum of 15 dietary components (range: 0–15; a higher score indicates higher concordance; details in e-Methods).[1] Includes 10 brain-healthy food groups (green leafy vegetables, other vegetables, nuts, berries, beans, whole grains, fish, poultry, olive oil, and wine) and 5 unhealthy food groups (red meats, butter and stick margarine, cheese, pastries and sweets, and fried/fast food) that were reverse coded i.e. "0" if consumed more and "1" if consumed less[1].

*Mediterranean diet score*: The Mediterranean diet score as described by Panagiotakos and colleagues was also computed [20]. Includes 11 dietary components and uses serving quantities of the traditional Greek Mediterranean diet as the comparison metric. Each component is scored 0 to 5, and all are summed for a total score ranging from 0 to 55 (highest dietary concordance)[4].

*Food groups/dietary components*: Fourteen food groups (servings/week) were also assessed for their associations with AD pathology, including green, leafy vegetables; total vegetables; total fruits; beans and legumes; nuts; fish and seafood; poultry; whole grains; wine; red and processed meat; butter and margarine; cheese; pastries and sweets; and fried/fast foods. Details on all the foods in each food group are presented in eTable 1.

### 2.3. Alzheimer's disease neuropathology

The brain autopsy and pathological evaluation methods for the study are same as described in detail earlier[21]. Amyloid-beta as previously described was assessed using immunohistochemistry at multiple brain regions (eight regions-entorhinal, mid frontal, inferior temporal, angular gyrus, calcarine, anterior cingulate, superior frontal cortices and hippocampus)[22]. For quantitative analysis of amyloid-beta deposition in each cortical area, video images of amyloid-β stained sections were captured using systematic sampling. Finally, a composite continuous summary measure of the total beta-amyloid load was generated using the mean percent area of each region occupied by beta- amyloid [23].

The antibody specific for phosphorylated tau (AT8, Innogenetics, San Ramon, CA, 1:1000) was used to quantify phosphorylated tau-tangles density as mean tangle density per $mm^2$ with a stereological method[23]. A composite summary measure of phosphorylated tau-tangles was generated by averaging the values for all eight regions as previously reported [23].

We stained 6µm sections of five brain regions including frontal, temporal, parietal, and entorhinal cortices, and hippocampus using modified Bielschowsky silver-staining to identify Alzheimer's disease pathology markers (diffuse and neuritic amyloid plaques and neurofibrillary tangles). A global AD pathology burden was computed by averaging the mean standardized raw scores of plaques and tangles (the highest number in the 1 $mm^2$ area) of each region[24]. We also used the National Institute on Aging (NIA)-Reagan criteria to determine the pathologic diagnosis of AD[25]. The criteria rely on both neurofibrillary tangles and neuritic plaques where a score is assigned for no AD, low, intermediate or high likelihood of AD. Those with intermediate and high likelihood indicate a pathologic diagnosis of AD and low or no pathology indicate no AD.

### 2.4. Other covariates

To compute age at death in years, dates of birth and death was used. At the time of enrollment in the study sex, education (in years), and smoking status (never smoked, former or current smoker)[26] were self-reported. Polymorphic DNA Technologies performed the apolipoprotein (APOE-ε) genotyping.[27] Total calories and alcohol intake were computed from the FFQ as

previously described[1]. Physical activity was captured using an adapted National Health Interview Survey (5 items: waking, gardening, exercise, biking, swimming))[28]. Vascular disease burden was computed using self-reported questions on claudication, heart conditions, stroke, and congestive heart failure. Body mass index (BMI) was calculated using weight in kilograms and height in meters squared and used as a categorical measure (underweight, normal, overweight, obese). The variable for time between last FFQ and death was computed from the date of last dietary assessment and date of death.

### 2.5. Diagnostic criteria

Based on the criteria of the joint working group of the Neurological and Communicative Disorders and Stroke and AD and Related Disorders Association (NINCDS-ADRDA), clinical Alzheimer's dementia diagnosis was defined.[29]

### 2.6. Statistical analysis

The correlations between diet scores (MIND, Mediterranean diet) and various food groups were assessed using Spearman's rank correlation coefficient. In separate models, both the diet scores were assessed as continuous and then modeled in tertiles, with the lowest tertile as the referent category. The outcomes of global AD pathology, amyloid-β load, and phosphorylated tau tangle density were square-root transformed, and linear regression models were applied. The basic model was adjusted for age at death, sex, education, APO-ε4 status, and total calorie intake. We further adjusted our basic model for the time between last dietary assessment and death. As secondary analyses, these models were further adjusted for (i) lifestyle factors-physical activity, and smoking, as well as vascular disease burden and (ii) BMI, that could either be mediator or confounder in the model given it is a clinical sequalae of Alzheimer's dementia and is related to diet. We also investigated the association of diet scores with the NIA-Reagan score. The linear trend of the association in each model was assessed by assigning the median tertile intake level to all those in each tertile and modeling the dietary intake as a single variable. Standardized betas (β/ SE) were also calculated for MIND and Mediterranean diet from the primary models. Additionally, to provide clinical context, we estimated the age difference in years providing the same change difference in amyloid load as one unit increase in the MIND diet score, by computing the ratio of the beta coefficients [β (MIND score) / β (age)] from the basic-adjusted models. In separate sensitivity analyses, we excluded (i) dietary observations that were collected

during the last year of life and ii) people with dementia (n = 52) or mild cognitive impairment (MCI) (n = 149) at the first FFQ assessment and repeated the models.[30] Finally, we also explored the role of APO-ε4 and sex in exploratory analyses, given evidence from animal and human studies that demonstrate APO-ε4 is involved in lipid metabolism, associates with amyloid burden and gliosis, and interacts with diet-induced metabolic impairments in female animal models[29-31.] Thus, we proposed to explore the interaction by APO-ε4 status and sex by including a multiplicative term between the diet scores/ food groups and the effect modifier of interest. Further, considering significant interaction terms ($p \leq .05$), we ran models with dummy variables for the presence (or absence) of APOE ε4 and for male (or female) sex, with the specific parametrization of dummy variables chosen to clearly describe the group differences for various associations. For ease of interpretation, we show the stratified analysis for basic models in the supplementary files. All the analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC).

Data availability: MAP data can be requested at https://www.radc.rush.edu.

## 3. Results

Table 1 presents the baseline characteristics of the analytic sample of 581 autopsied participants (overall and according to tertile of the MIND diet, characteristics of participants as per the tertile of Mediterranean diet score are presented in eTable 2). The mean follow-up time from the first dietary assessment at the mean age of 84.2 ± 5.8 years until death was 6.8 (± 3.9 years). The characteristics were similar to those of all deceased participants from MAP (n = 1,158; age at death = 89.9 [± 6.4] years; female = 69%; education = 14.6 [± 3.1] years; APO-ε4 allele = 21%) as well as to those of the overall MAP cohort participants (n = 2,198; female = 73%; education = 14.9 [± 3.3] years; APO-ε4 allele = 20%). The MIND and Mediterranean diet scores are correlated[4] and in this sample had a $\rho = 0.69$ ($p = < .0001$). The mean intake of alcohol was 3.4 ±7.1 grams/day i.e., less than 1/3$^{rd}$ of a drink per day. Proximate to death, 38.5% of the participants (n = 224) had a diagnosis of clinical dementia, and 383 participants (66%) had a pathologic diagnosis of Alzheimer's disease (modified NIA-Reagan diagnosis) at time of death. Over the years of follow-up, 50% completed three or more diet assessments. The first and last MIND diet scores were moderately correlated ($\rho = 0.70$, $p = <.0001$).

### 3.1. Diet scores and AD pathology

Overall, both the MIND diet scores (β[SE] = -0.022 [0.011], p = 0.035; standardized beta = -2.0) and Mediterranean diet scores (β[SE] = -0.007[.003], p = 0.039; standardized beta = -2.3) were significantly associated with lower global AD pathology (Figures 1A and 1B). The MIND and Mediterranean diets were associated with less beta-amyloid (MIND standardized beta = -2.0, Mediterranean standardized beta = -2.9, Figure 1C.and 1D). For clinical context, we calculated the ratio of the coefficients (MIND (beta coefficient)/ age (beta coefficient): 4.25= -0.068/0.016) and found that a MIND diet score one point higher corresponded to typical plaque deposition of participants who are 4.25 years younger in age, with other characteristics being the same. Tertile comparisons and models further adjusted for the time between the last dietary assessment and death indicated similar findings (Table 2). However, none of the diet scores had an association with phosphorylated tau tangles (Table 2). When models were further adjusted for physical activity, smoking, and vascular disease burden, both MIND ((β[SE] = -0.022 [0.011], p = 0.047; standardized beta = -2.0) and Mediterranean diet (β[SE] = -0.008 [0.004], p = 0.027; standardized beta = -2.0) associations with global AD pathology were retained. Whereas for beta-amyloid only the Mediterranean diet (β[SE] = -0.031 [0.011], p = 0.007) but not the MIND diet (β[SE] = -0.057 [0.036], p = 0.115) was significant. In secondary analysis, controlled for BMI, the association of MIND diet with global AD pathology (β[SE] = -0.023 [0.011], p = 0.037) was retained but that with beta-amyloid (β[SE] = -0.071 [0.037], p = 0.055) weakened. IN contrast, the Mediterranean diet association with global AD pathology was weakened (β[SE] = -0.007 [0.004], p = 0.058; but remained for beta-amyloid ((β[SE] = -0.035 [0.012], p = 0.005).

In sensitivity analyses we excluded dietary assessments during the last year of life, considering various end-of-life events may alter diet, and found similar results, i.e., overall MIND diet and Mediterranean diet was negatively associated with global AD pathology and beta-amyloid load (Table 3). Additionally, in another sensitivity analysis when we excluded those with dementia or MCI at the first FFQ, the significant associations persisted for global AD pathology and amyloid load (Table 3). The highest tertiles of the MIND (OR [95% confidence interval] = 0.62 [0.39, 0.99]) and Mediterranean diets (OR [95% confidence interval] = 0.60 [0.37, 0.96]) when compared to the lowest, had almost 40% lower odds of having an NIA-Reagan diagnosis of AD.

The association of diet with AD pathology was further tested for effect modification by APO-ε4 status and sex. For AD pathology, the interaction terms were not significant for the MIND diet with APO-ε4 status (global AD pathology: p = 0.94; beta-amyloid: p = 0.64; phosphorylated tau: p = 0.58) or sex (global AD pathology: p = 0.30; beta-amyloid: p = 0.91; phosphorylated tau: p = 0.18). The second tertile Mediterranean diet score showed an interaction with APO-ε4 status (p = 0.036) for phosphorylated tau tangles (eTable 3: Comparing those with and without APO-ε4 status in the same model).. Since the second tertile results were unexpected, we examined two groups separately and found no significant association between the Mediterranean diet and phosphorylated tau tangles in either group (eTable 4). . There was also no significant difference between men and women with varying Mediterranean diet adherence for association with global AD pathology (data not shown).

### 3.2. Dietary components: Food groups and AD pathology

We further explored the associations of selected food groups with AD pathology outcomes. Those in the highest tertile of green leafy vegetable intake had lower global AD pathology (β[SE] = -0.115 (0.040), p=0.0038) when compared with those in the lowest tertile. Participants with a higher intake of fried and fast food had more phosphorylated tau tangles (T3 vs. T1: (β[SE] = 0.284[0.142], p = 0.046; p trend= 0.044). Similarly, higher sugar and pastries intake was suggestive of more global AD pathology (T3 vs. T1: (β[SE] = .081[.042], p = .053). When compared to those consuming no wine or more than two glasses per day, those consuming one glass of wine per day had less overall AD pathology (β[SE] = -0.067[0.034], p = 0.046) and lower amyloid load (β[SE] = -0.239[0.110], p = 0.031). Effect estimates for some food groups (fish and seafood, beans, nuts, and poultry) suggested associations (0.05 < p <0.1) while others (total vegetables, fruits, whole grains, butter, cheese, and red meat) had no association with AD pathology (eTable 5). Applying the multiple comparison threshold (p values < 0.0036 (0.05/14), for 14 dietary components tested) none of the food groups met the strict Bonferroni correction, however the green leafy intake and the global AD pathology model has a p value =0.0038. We further adjusted these models of individual food groups by adding a modified MIND diet score as the main exposure (i.e., the diet score minus a food group of interest) and found that most of the associations did not retain significance once adjusted for other recommended food groups (results not shown).

Interactions of various food groups with APO-ε4 status were also investigated. Wine intake showed an interaction with APO-ε4 status for the association with amyloid load (p = 0.012, eTable 6). In exploratory stratified analysis, green leafy vegetable and bean intake was inversely associated with phosphorylated tau tangles among APO-ε4 non-carriers and not among APO-ε4 carriers whereas fried food and sweets/pastries consumption was positively associated with phosphorylated tau tangles and global AD pathology, respectively (eTable 6). However, none of these associations met the strict Bonferroni correction. .

Interaction models for various food groups and sex indicated a significant effect modification of fish and seafood intake with sex for its association with amyloid load (p = 0.035). Similarly, nuts and pastries/sweets intake had a significant interaction with sex for phosphorylated tau tangles (p = 0.049) and beta-amyloid load (p = 0.038), respectively. The interaction was further tested comparing men and women in the same model (eTable 7). In an exploratory stratified analysis presented in eTable 8, higher fish and seafood intake was associated with less global AD pathology and amyloid load among men but not among women. Surprisingly, nuts intake was associated with higher phosphorylated tau tangles in men while no association was observed among women, however this association was no longer significant after applying the multiple comparison p-value (eTable 8).

## 4. Discussion

In this study of deceased from a community-based cohort of older adults, we found those adhering to the MIND and Mediterranean diet patterns for almost a decade of follow-up before death had less global AD pathology, primarily less beta-amyloid load. Comparing to participants whose MIND diet score was one unit higher, the difference in the amyloid load was similar to being about four years younger. Even when controlled for other lifestyle factors, and vascular disease burden the findings for both diet scores and global AD pathology were retained with similar effect estimates. However, the inverse association with beta-amyloid load was stronger for the Mediterranean diet than for the MIND diet. Thus, we speculate that the MIND diet which recommends berries and green leafy vegetables intake, and other important nutrients for brain health may have its relationship with Alzheimer's disease via unknown mechanisms in addition to beta-amyloid load and needs further investigation. Among the various dietary components, a higher intake of green leafy vegetables and a recommended intake of wine were associated with

less AD pathology while greater fried/fast food and pastries/sweets intake was associated with more AD pathology. However, considering the multiple comparisons threshold only the green leafy vegetable intake association with global AD pathology approached significance. These findings suggest that the potential benefit of these dietary components relies on their consumption in combination as an overall healthy dietary pattern rather than the effect of a single food or food group that may directly impact AD pathology in human brains.

The MIND and Mediterranean diets have been associated with reduced Alzheimer's dementia risk in various population-based cohorts.[31] To the best of our knowledge, this study is the first to report the association of the MIND and Mediterranean diets with postmortem AD pathology in a community-based sample of older adults with multiple dietary assessments during a long follow-up period before death. The use of molecular PET imaging has enabled previous studies of the association of diet with pathology during life. The Mediterranean diet association with less PiB-PET amyloid load in older adults [14, 32] and middle-aged participants [33,34] have been reported, but one study shows null findings.[35] Our data also support studies using PiB-PET in AD regions that have shown that a diet rich in omega-3 fatty acids, vitamin B12, and vitamin D (which correlates with a higher intake of vegetables, fruit, whole grains, fish, and legumes) and a lower intake of high-fat dairy, meat, and sweets is associated with lower amyloid load.[36] We previously reported an association of the MIND diet with cognition independent of AD and other brain pathologies.[5] In the current study, we complement these findings by demonstrating the MIND diet's association with lower AD pathology. In the previous study, however, the relationship between the MIND diet and global AD pathology or amyloid load did not reach significance, although the beta estimates were comparable between the studies.[34] The differences in the analyses (i.e., the p-value) could be attributed to the smaller sample size, fewer data points for FFQs, and short follow-up in our previous study.

In the food group analysis, we found green, leafy vegetable intake was associated with less AD pathology, which supports the previous literature relating green, leafy vegetables to slower cognitive decline.[37] The relationship of sugary and fried foods with greater AD pathology without multiple comparison threshold, support previous research on Western diet (i.e., diet rich in sugar, fats, refined grains, and meat) association with poorer cognitive function[7] and on how the Western diet may attenuate the relationship of a healthy diet with cognitive decline.[2] Some

food groups—such as fish/seafood[38-40] and other vegetables,[41] for which we report a lower AD risk—indicated only group-specific associations with AD pathology. Thus, we speculate that the effect of these foods in reducing AD risk could be due to other underlying mechanisms, including vascular pathologies, neuronal loss, gliosis, neuroinflammation, gut health, etc. In exploratory analyses, only APO-ε4 non-carriers showed greater benefit with higher green leafy vegetable and beans intake and reduced intake of fried/fast foods and pastries/sweets. We speculate that there may be various reasons for such associations, including but not limited to the role of APO-ε in lipid metabolism, immune regulation, and oxidative stress. In addition, the APO-ε4 group is smaller and thus has less statistical power. Sex differences in dietary effects were also evident which may indicate variable metabolic responses to different foods. Women with higher green, leafy vegetable, lower red and processed meat, and recommended wine intake had less AD pathology. By contrast, men with higher fish intake and moderate poultry intake had less AD pathology. Unexpectedly, men with a recommended wine and higher nut intake had more phosphorylated tau tangles. Although these exploratory analyses could not survive multiple comparison threshold, the individual-level factors and other mechanisms warrant further investigation to understand the role of precision nutrition and the underlying biological pathways in AD.

The mechanistic link between diet and AD neuropathology in humans is not fully known and merits further investigation. Both the MIND and Mediterranean are plant-based diets rich in various essential nutrients and bioactive compounds with antioxidant and anti-inflammatory properties that are associated with reduce low grade inflammation[42, 43] and oxidative stress.[44] A four-week randomized controlled trial of a high-fat/high-glycemic index diet and a low–saturated fat/low–glycemic index diet suggested that diet modulates AD risk via its effects on lipoproteins, oxidative stress, insulin, and central nervous system concentrations of amyloid-beta-42.[45] In APP/PS1 transgenic mice, a pro-oxidant diet (a normal chow diet without any enriched vitamin and mineral premixes) resulted in enhanced β/γ secretase–mediated amyloid precursor protein processing.[46] Furthermore, the MIND and Mediterranean diets recommend limiting processed meats, refined grains, high-fat foods, and high-sugar foods. Animal studies have shown that long-term exposure to a high-fat diet increases beta-amyloid deposition[47] and neurofibrillary tangle formation while decreasing synaptic plasticity, effects that are accompanied by

inflammatory and stress response in whole brain lysate[48] and overall enhanced astrogliosis and microglia activation.[49]

This study has many strengths, including the large autopsy sample size, multiple dietary assessments administered annually using a comprehensive and validated FFQ for older adults, other structured clinical assessments, standardized neuropathological measures, and a study design in which the community-based sample of dementia-free (at baseline) older adults were observed until death. This minimizes measurement error and selection bias resulting from loss to follow-up. The high autopsy rates also increase generalizability to the living cohort. Finally, employing multiple diet assessments during follow-up, we used the average of repeated measures, which reduced measurement error due to within-person variability. However, we do have some limitations. The observational study design examining the association of diet during life with pathology at the time of death, limits our ability to establish causal relationships. Cognitive decline may alter dietary patterns, but we performed sensitivity analyses that excluded those with MCI and dementia at FFQ baseline. The participants were mostly white, non-Hispanic older individuals, thus we cannot generalize these results to younger adults or to more diverse populations.

Older adults adhering to MIND or Mediterranean diets may have less AD pathology, and this may provide one mechanism by which healthy diets protect cognition. Future diet studies should investigate other potential mechanisms for protective effects on the brain, including the direct effects of diet on AD pathology, and should examine potential mechanisms and pathways via vascular and other pathologies as well as the role of inflammation. Studies should also investigate person-specific factors and capitalize on emerging in-vivo biomarkers and human brain tissue when available.



http://links.lww.com/WNL/C661

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Table 1: Characteristics of 581 deceased participants of the Memory and Aging Project

| | **Overall** | **Tertile of MIND diet score** | | |
|---|---|---|---|---|
| | N=581 | T1 (n=194) | T2 (n=199) | T3 (n=188) |
| **MIND diet score*** | 7.5 ± 1.5 | 5.9 ± 0.7 | 7.4 ± 0.4 | 9.1 ± 0.8 |
| **Age at death, years** | 91.3 ± 6.1 | 91.1 ± 6.5 | 91.0 ± 6.3 | 91.9 ± 5.5 |
| **Age at first FFQ, years** | 84.2 ± 5.8 | 84.6 ± 6.5 | 83.9 ± 6.0 | 84.1 ± 4.8 |
| **Education, years** | 14.8 ± 2.8 | 14.0 ± 2.9 | 15.1 ± 2.8 | 15.3 ± 2.5 |
| **Female, (n) %** | (418) 72 % | (165) 70 % | (162) 68 % | (138) 78 % |
| **APO-ε status, (n) % present** | (123) 21 % | (58) 21 % | (55) 19 % | (55) 24 % |
| **Total calories* kcal/day** | 1810 ± 534 | 1746 ± 593 | 1846 ± 506 | 1838 ± 492 |
| **Smoking, (n) % Former/ current smoker** | 223 (38%) | 73 (38%) | 68 (34%) | 82 (44%) |
| **Vasculart disease burden score (range 0-4)[a]** | 0.70 ± 0.91 | 0.74 ± 0.95 | 0.71 ± 0.93 | 0.64 ± 0.86 |
| **BMI[a]** | 26.1 ± 4.9 | 26.3 ± 5.4 | 26.0 ± 5.0 | 26.1 ± 4.7 |
| **Physical activity, hours/week** | 2.60 ± 3.13 | 1.95 ± 2.23 | 2.42 ± 3.41 | 3.45 ± 3.42 |

*Mean intake during the years of follow-up, BMI: Body Mass Index; [a]At last dietary assesment

**Table 2: Association of MIND and Mediterranean diet scores with Alzheimer's disease pathology in 581 deceased participants of the Memory and Aging Project**

| | Median | Global AD pathology * | Beta-Amyloid load * | Phosphorylated Tau-tangle* |
|---|---|---|---|---|
| | | β (SE, p-value) | β (SE, p-value) | β (SE, p-value) |
| **MIND Diet scores (score range 0-15)** | | | | |
| **Model 1** | | | | |
| **continuous score** | 7.0 | -0.022 (0.011, 0.035) | -0.068 (0.034, 0.050) | 0.012 (0.038, 0.761) |
| **T1 (n=194)** | 6.0 | Ref | Ref | Ref |
| **T2 (n=199)** | 7.5 | -0.024 (0.037, 0.516) | -0.115 (0.119, 0.335) | -0.102 (0.133, 0.443) |
| **T3 (n=188)** | 9.0 | -0.071 (0.038, 0.063) | -0.274 (0.123, 0.027) | 0.042 (0.137, 0.757) |
| **P trend** | | 0.062 | 0.027 | 0.751 |
| **Model 2** | | | | |
| **continuous score** | 7.0 | -0.024 (0.011, 0.025) | -0.062 (0.034, 0.071) | -0.024 (0.037, 0.528) |
| **T1 (n=194)** | 6.0 | Ref | Ref | Ref |
| **T2 (n=199)** | 7.5 | -0.027 (0.037, 0.461) | -0.099 (0.118, 0.402) | -0.139 (0.130, 0.285) |
| **T3 (n=188)** | 9.0 | -0.077 (0.038, 0.044) | -0.246 (0.123, 0.047) | -0.108 (0.134, 0.422) |
| **P trend** | | 0.044 | 0.047 | 0.420 |
| **Mediterranean Diet scores (score range 0-55)** | | | | |
| **Model 1** | | | | |
| **continuous score** | 30 | -0.007 (0.003, 0.039) | -0.032 (0.011, 0.004) | 0.004 (0.012, 0.768) |

| | | | | |
|---|---|---|---|---|
| **T1 (n=220)** | 26 | Ref | Ref | Ref |
| **T2 (n=192)** | 30 | -0.066 (0.037, 0.070) | -0.116 (0.120, 0.333) | 0.035 (0.134, 0.795) |
| **T3 (n=187)** | 35 | -0.105 (0.039, 0.007) | -0.404 (0.126, 0.001) | 0.008 (0.141, 0.956) |
| **P trend** | | 0.007 | 0.001 | 0.958 |
| **Model 2** | | | | |
| **continuous score** | 30 | -0.008 (0.003, 0.028) | -0.030 (0.011, 0.008) | -0.002 (0.012, 0.878) |
| **T1 (n=220)** | 26 | Ref | Ref | Ref |
| **T2 (n=192)** | 30 | -0.070 (0.037, 0.058) | -0.097 (0.119, 0.417) | -0.020 (0.131, 0.876) |
| **T3 (n=187)** | 35 | -0.110 (0.039, 0.005) | -0.387 (0.126, 0.002) | -0.041 (0.138, 0.766) |
| **P trend** | | 0.005 | 0.002 | 0.776 |

Linear regression models: Model 1 controlled for age at death, sex, education, Apo-ε4 status, and total calories. Model 2 controlled for model1 + time between last dietary assessment and death.

*Square root transformation

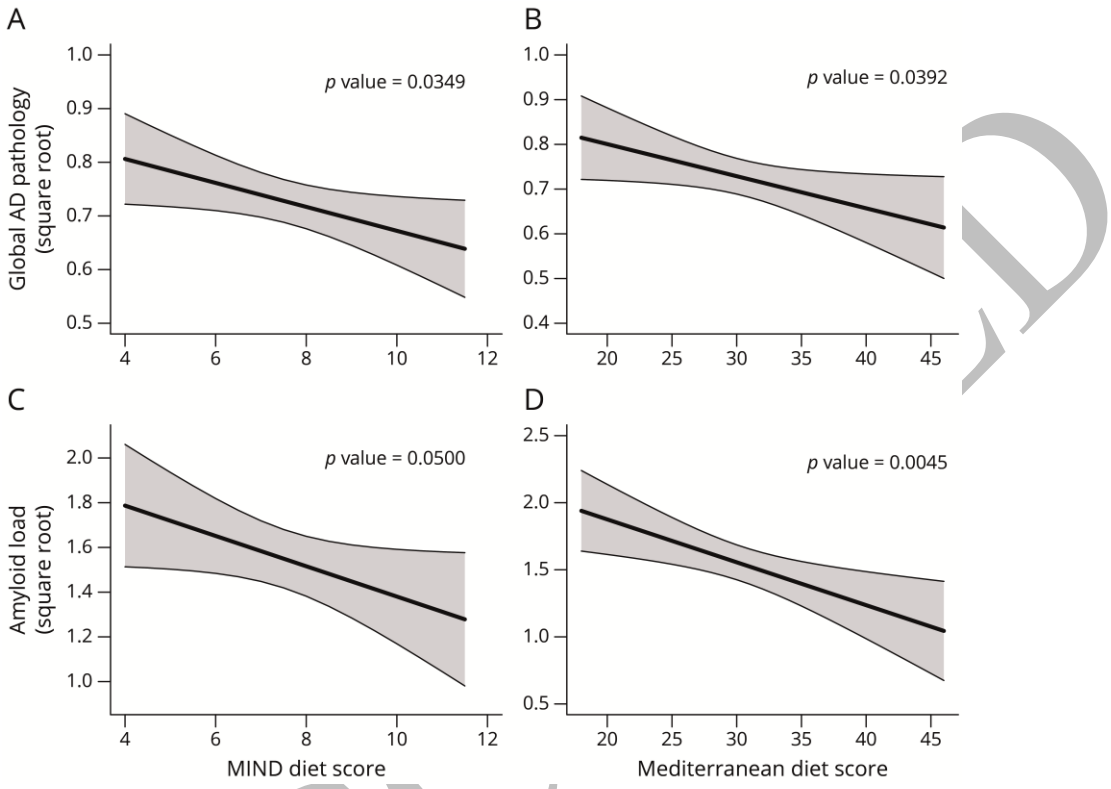
**Table 3: Association of MIND and Mediterranean diet scores with Alzheimer's disease pathology excluding dementia and MCI at first dietary assessment (N=379)**

| | Global AD pathology * β (SE, p-value) | Beta-Amyloid load * β (SE, p-value) | Phosphorylated Tau-tangle* β (SE, p-value) |
|---|---|---|---|
| **Excluding dietary assessments in the last year before death (N=560)** | | | |
| **MIND Diet scores (score range 0-15)** | | | |
| **continuous score** | -0.022 (0.010, 0.033) | -0.069 (0.034, 0.045) | -0.013 (0.039, 0.744) |
| **Standardized beta (β/SE)** | -2.20 | -2.03 | -0.33 |
| **Mediterranean Diet scores (score range 0-55)** | | | |
| **continuous score** | -0.007 (.004, 0.050) | -0.022 (0.012, 0.005) | 0.002 (0.013, 0.901) |
| **Standardized beta (β/SE)** | -1.75 | -1.83 | -0.15 |
| **Excluding dementia and MCI at first dietary assessment (N=379)** | | | |
| **MIND Diet scores (score range 0-15)** | | | |
| **continuous score** | -0.032 (0.013, 0.015) | -0.090 (0.044, 0.040) | -0.037 (0.044, 0.401) |
| **Standardized beta (β/SE)** | -2.46 | -2.04 | -0.84 |
| **Mediterranean Diet scores (score range 0-55)** | | | |
| **continuous score** | -0.010 (0.004, 0.016) | -0.043 (0.014, 0.002) | 0.002 (0.0143, 0.893) |
| **Standardized beta (β/SE)** | -2.50 | -3.07 | -0.13 |

Linear regression models controlled for age at death, sex, education, Apo-ε4 status, and total calories. *Square root transformation

**Figure 1: Association between A) MIND diet and Global AD pathology B) Mediterranean diet and Global AD pathology C) MIND diet and Amyloid load D) Mediterranean diet and Amyloid load**

Linear regression models controlled for age at death, sex, Apo-ε4 status, education, and total calories.



# Association of Mediterranean-DASH Intervention for Neurodegenerative Delay and Mediterranean Diets With Alzheimer Disease Pathology

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