

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

Puja Agarwal, PhD, Sue E. Leurgans, PhD, Sonal Agrawal, PhD, Neelum T. Aggarwal, MD, Laurel J. Cherian, MD, Bryan D. James, PhD, Klodian Dhana, MD, PhD, Lisa L. Barnes, PhD, David A. Bennett, MD, and Julie A. Schneider, MD

## Correspondence

Dr. Agarwal  
puja\_agarwal@rush.edu

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## Abstract

### Background and Objectives

Diet may reduce Alzheimer dementia risk and slow cognitive decline, but the understanding of the relevant neuropathologic mechanisms remains limited. The association of dietary patterns with Alzheimer disease (AD) pathology has been suggested using neuroimaging biomarkers. This study examined the association of Mediterranean-DASH Intervention for Neurodegenerative Delay (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 and neuritic and diffuse plaques]) were included in this study. Linear regression models controlled for age at death, sex, education, *APOE- $\epsilon$ 4* status, and total calories were used to investigate the dietary patterns (MIND and Mediterranean diets) and dietary components associated with AD pathology. Further effect modification was tested for *APOE- $\epsilon$ 4* status and sex.

### Results

Among our study participants ( $N = 581$ , age at death:  $91.0 \pm 6.3$  years; mean age at first dietary assessment:  $84.2 \pm 5.8$  years; 73% female;  $6.8 \pm 3.9$  years of follow-up), dietary patterns were associated with lower global AD pathology (MIND:  $\beta = -0.022$ ,  $p = 0.034$ , standardized  $\beta = -2.0$ ; Mediterranean:  $\beta = -0.007$ ,  $p = 0.039$ , standardized  $\beta = -2.3$ ) and specifically less  $\beta$ -amyloid load (MIND:  $\beta = -0.068$ ,  $p = 0.050$ , standardized  $\beta = -2.0$ ; Mediterranean:  $\beta = -0.040$ ,  $p = 0.004$ , standardized  $\beta = -2.9$ ). 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 with those in the lowest tertile (tertile 3 vs tertile 1:  $\beta = -0.115$ ,  $p = 0.0038$ ).

### Discussion

The MIND and Mediterranean diets are associated with less postmortem AD pathology, primarily  $\beta$ -amyloid load. Among dietary components, higher green leafy vegetable intake was associated with less AD pathology.

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From the Rush Alzheimer's Disease Center (P.A., S.E.L., N.A., B.D.J., L.L.B., D.A.B., J.A.S.), Departments of Internal Medicine (P.A., B.D.J., K.D.), Clinical Nutrition (P.A.), Neurological Sciences (S.E.L., N.T.A., L.J.C., L.L.B., D.A.B., J.A.S.) and Pathology (S.A., J.A.S.); and Rush Institute of Healthy Aging (K.D.), Rush University Medical Center, Chicago, IL.

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## Glossary

AD = Alzheimer disease; FFQ = food frequency questionnaire; MAP = Memory and Aging Project; MCI = mild cognitive impairment; MIND = Mediterranean-DASH Intervention for Neurodegenerative Delay; PiB-PET = Pittsburgh compound B positron emission tomography.

Healthy dietary patterns, including the Mediterranean-DASH Intervention for Neurodegenerative Delay (MIND), Mediterranean, and DASH diets, are associated with slower cognitive decline,<sup>1-3</sup> reduced Alzheimer dementia risk,<sup>4</sup> better cognition independent of Alzheimer disease (AD) pathology,<sup>5</sup> and less functional disability.<sup>6</sup> By contrast, high-fat, high-sugar diets, such as the Western diet, are associated with poor cognition.<sup>7,8</sup> 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 and 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,<sup>9,10</sup> cortical thickness,<sup>11,12</sup> and white matter hyperintensity.<sup>13</sup>

Amyloid and neurofibrillary tangles are the 2 important hallmarks of AD. A Mediterranean diet was reported to be associated with biomarkers of cerebral A $\beta$ -amyloid (assessed by Pittsburgh compound B positron emission tomography [PiB-PET])<sup>14</sup> and the CSF (A $\beta$ 42/40 ratio, pTau181),<sup>15</sup> but we are unaware of any studies on the association of healthy dietary patterns with AD pathology in the postmortem human brain. This study examined the association of MIND and Mediterranean diet scores (2 of the most widely studied diet scores for their association with cognition in older adults in different populations<sup>16</sup>) 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).

## Methods

### Study Participants

The MAP participants included in this study were those with autopsies. The MAP is an ongoing longitudinal cohort of older adults without known dementia during enrollment.<sup>17</sup> At baseline, MAP participants sign an informed consent for annual assessments and an Anatomic Gift Act for brain donation during death. The MAP was initiated in 1997, and as of June 2021, 2,198 participants had enrolled and completed baseline assessments. Of them, 2,042 were alive and active when a food frequency questionnaire (FFQ) substudy 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 substudy). Excluding those with unprocessed dietary data (n = 565), 1,471 MAP participants had complete dietary data, and, of them, 786 were deceased. Those without autopsy (n = 112), neuropathologic

data (n = 10), 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.

### 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.<sup>18,19</sup> For each food item in the FFQ, total calories and nutrient levels were computed as previously defined.<sup>1</sup> 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).<sup>1</sup> It includes 10 brain-healthy food groups and a score of “1” is given if consumed as or more than recommended (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, that is, “0” if consumed more and “1” if consumed less.<sup>1</sup>

#### Mediterranean Diet Score

The Mediterranean diet score, as described by Panagiotakos et al.,<sup>20</sup> was also computed. It 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).<sup>4</sup>

#### 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 summarized in eTable 1 ([links.lww.com/WNL/C661](https://links.lww.com/WNL/C661)).

### Alzheimer Disease Neuropathology

The brain autopsy and pathologic evaluation methods for the study are the same as described in detail earlier.<sup>21</sup>  $\beta$ -Amyloid, as previously described, was assessed using immunohistochemistry at multiple brain regions (8 regions: entorhinal, mid-frontal, inferior temporal, angular gyrus, calcarine, anterior cingulate, superior frontal cortices, and hippocampus).<sup>22</sup>

For quantitative analysis of  $\beta$ -amyloid deposition in each cortical area, video images of  $\beta$ -amyloid-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.<sup>23</sup>

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  $\text{mm}^2$  with a stereological method.<sup>23</sup> A composite summary measure of phosphorylated tau tangles was generated by averaging the values for all 8 regions, as previously reported.<sup>23</sup>

We stained 6  $\mu\text{m}$  sections of 5 brain regions including frontal, temporal, parietal, and entorhinal cortices and hippocampus using modified Bielschowsky silver staining to identify Alzheimer 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  $\text{mm}^2$  area) of each region.<sup>24</sup> We also used the National Institute on Aging (NIA)–Reagan criteria to determine the pathologic diagnosis of AD.<sup>25</sup> 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.

### Other Covariates

To compute age at death in years, dates of birth and death were used. During enrollment in the study, sex, education (in years), and smoking status (never smoked, former smoker, or current smoker)<sup>26</sup> were self-reported. Polymorphic DNA Technologies performed the apolipoprotein (*APOE- $\epsilon$ 4*) genotyping.<sup>27</sup> Total calories and alcohol intake were computed from the FFQ, as previously described.<sup>1</sup> Physical activity was captured using an adapted National Health Interview Survey (5 items: waking, gardening, exercise, biking, and swimming).<sup>28</sup> 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, and obese). The variable for time between last FFQ and death was computed from the date of last dietary assessment and date of death.

### Diagnostic Criteria

Based on the criteria of the joint working group of the Neurologic and Communicative Disorders and Stroke and AD and Related Disorders Association, clinical Alzheimer dementia diagnosis was defined.<sup>29</sup>

### Statistical Analysis

The correlations between diet scores (the MIND and Mediterranean diets) and various food groups were assessed using

the Spearman 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,  $\beta$ -amyloid 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, *APOE- $\epsilon$ 4* 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 (1) lifestyle factors: physical activity, smoking, and vascular disease burden and (2) BMI, which could either be mediator or confounder in the model, given it is a clinical sequela of Alzheimer 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 ( $\beta$ /SE) were also calculated for the MIND and Mediterranean diets from the primary models. In addition, to provide clinical context, we estimated the age difference in years providing the same change difference in amyloid load as 1 unit increase in the MIND diet score, by computing the ratio of the beta coefficients [ $\beta$  (MIND score)/ $\beta$  (age)] from the basic adjusted models. In separate sensitivity analyses, we excluded (1) dietary observations that were collected during the last year of life and (2) people with dementia ( $n = 52$ ) or mild cognitive impairment (MCI) ( $n = 149$ ) at the first FFQ assessment and repeated the models.<sup>30</sup> Finally, we also explored the role of *APOE- $\epsilon$ 4* and sex in exploratory analyses, given evidence from animal and human studies that demonstrate *APOE- $\epsilon$ 4* is involved in lipid metabolism, associates with amyloid burden and gliosis, and interacts with diet-induced metabolic impairments in female animal models.<sup>29-31</sup> Thus, we proposed to explore the interaction by *APOE- $\epsilon$ 4* status and sex by including a multiplicative term between the diet scores/food groups and the effect modifier of interest. Furthermore, considering significant interaction terms ( $p \leq 0.05$ ), we ran models with dummy variables for the presence (or absence) of *APOE- $\epsilon$ 4* and for male (or female) sex, with the specific parametrization of dummy variables chosen to clearly describe the group differences for various associations. For the ease of interpretation, we have shown the stratified analysis for basic models in the supplementary files. All analyses were performed using SAS software, version 9.4 (SAS Institute, Cary, NC).

### Data Availability

MAP data can be requested at [www.radc.rush.edu](http://www.radc.rush.edu).

## Results

Table 1 summarizes the baseline characteristics of the analytic sample of 581 autopsied participants (overall and according to tertiles of the MIND diet; characteristics of participants as per the tertiles of the Mediterranean diet score are summarized in eTable 2, [links.lww.com/WNL/C661](https://links.lww.com/WNL/C661)). The mean follow-up

**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 <sup>a</sup>	7.5 ± 1.5	5.9 ± 0.7	7.4 ± 0.4	9.1 ± 0.8
Age at death, y	91.3 ± 6.1	91.1 ± 6.5	91.0 ± 6.3	91.9 ± 5.5
Age at first FFQ, y	84.2 ± 5.8	84.6 ± 6.5	83.9 ± 6.0	84.1 ± 4.8
Education, y	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%
APOE-ε4 status, (n) % present	(123) 21%	(58) 21%	(55) 19%	(55) 24%
Total calories <sup>a</sup> kcal/d	1810 ± 534	1746 ± 593	1846 ± 506	1838 ± 492
Smoking, (n) % former/current smoker	223 (38%)	73 (38%)	68 (34%)	82 (44%)
Vascular disease burden score (range 0–4) <sup>b</sup>	0.70 ± 0.91	0.74 ± 0.95	0.71 ± 0.93	0.64 ± 0.86
BMI	26.1 ± 4.9	26.3 ± 5.4	26.0 ± 5.0	26.1 ± 4.7
Physical activity, h/wk <sup>b</sup>	2.60 ± 3.13	1.95 ± 2.23	2.42 ± 3.41	3.45 ± 3.42

Abbreviations: BMI = body mass index; FFQ = food frequency questionnaire; MIND = Mediterranean-DASH Intervention for Neurodegenerative Delay.

<sup>a</sup> Mean intake during the years of follow-up.

<sup>b</sup> At last dietary assessment.

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 the MAP (n = 1,158; age at death = 89.9 [±6.4] years; female = 69%; education = 14.6 [±3.1] years; APOE-ε4 allele = 21%) and to those of the overall MAP cohort participants (n = 2,198; female = 73%; education = 14.9 [±3.3] years; APOE-ε4 allele = 20%). The MIND and Mediterranean diet scores are correlated<sup>4</sup> and in this sample had a  $\rho = 0.69$  ( $p < 0.0001$ ). The mean intake of alcohol was 3.4 ± 7.1 g/d, that is, less than one-third 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 AD (modified NIA-Reagan diagnosis) during death. Over the years of follow-up, 50% completed 3 or more diet assessments. The first and last MIND diet scores were moderately correlated ( $\rho = 0.70$ ,  $p < 0.0001$ ).

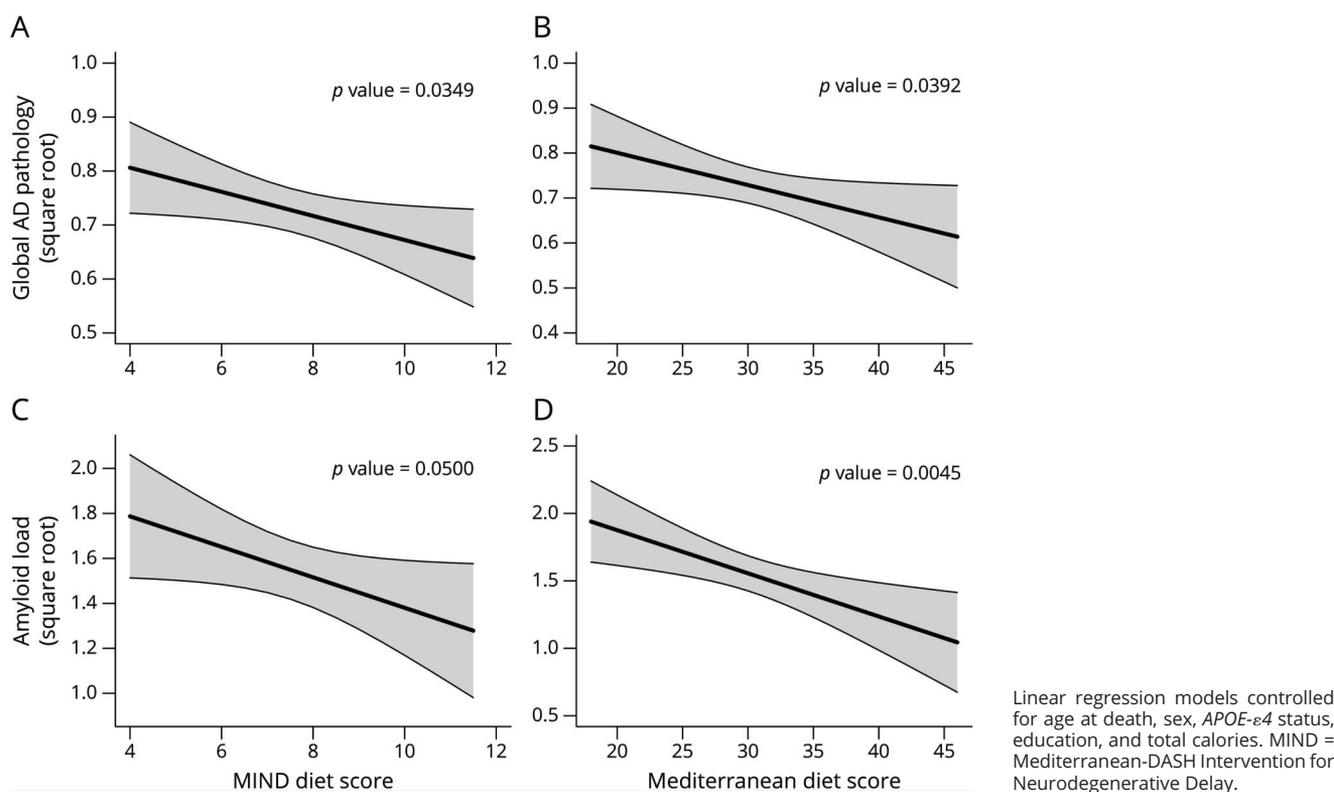
### Diet Scores and AD Pathology

Overall, both the MIND diet scores ( $\beta$ [SE] = -0.022 [0.011],  $p = 0.035$ ; standardized  $\beta = -2.0$ ) and Mediterranean diet scores ( $\beta$ [SE] = -0.007 [0.003],  $p = 0.039$ ; standardized  $\beta = -2.3$ ) were significantly associated with lower global AD pathology (Figure 1, A and B). The MIND and Mediterranean diets were associated with less beta-amyloid (MIND standardized beta = -2.0, Mediterranean standardized beta = -2.9, Figure 1, C and D). 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 1 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 ( $\beta$ [SE] = -0.022 [0.011],  $p = 0.047$ ; standardized beta = -2.0) and Mediterranean diet ( $\beta$ [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 ( $\beta$ [SE] = -0.031 [0.011],  $p = 0.007$ ) but not the MIND diet ( $\beta$ [SE] = -0.057 [0.036],  $p = 0.115$ ) was significant. In secondary analysis, controlled for BMI, the association of the MIND diet with global AD pathology ( $\beta$ [SE] = -0.023 [0.011],  $p = 0.037$ ) was retained but that with beta-amyloid ( $\beta$ [SE] = -0.071 [0.037],  $p = 0.055$ ) weakened. By contrast, the Mediterranean diet association with global AD pathology was weakened ( $\beta$ [SE] = -0.007 [0.004],  $p = 0.058$ ) but remained for beta-amyloid ( $\beta$ [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, that is, overall MIND diet and the Mediterranean diet were negatively associated with global AD pathology and beta-amyloid load (Table 3). In addition, 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% CI] = 0.62 [0.39, 0.99]) and Mediterranean diets (OR [95% CI] = 0.60 [0.37, 0.96]) when compared with the lowest had almost 40% lower odds of having an NIA-Reagan diagnosis of AD.

**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



The association of diet with AD pathology was further tested for effect modification by *APOE-ε4* status and sex. For AD pathology, the interaction terms were not significant for the MIND diet with *APOE-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 *APOE-ε4* status ( $p = 0.036$ ) for phosphorylated tau tangles (eTable 3, links.lww.com/WNL/C661: comparing those with and without *APOE-ε4* status in the same model). Because the second tertile results were unexpected, we examined 2 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).

### 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 ( $\beta$ [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: ( $\beta$ [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: ( $\beta$ [SE] =  $0.081$ [0.042],  $p = 0.053$ ). When compared with those consuming no wine or more than 2 glasses per day, those consuming 1 glass of wine per day had less overall AD pathology ( $\beta$ [SE] =  $-0.067$  [0.034],  $p = 0.046$ ) and lower amyloid load ( $\beta$ [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, links.lww.com/WNL/C661). 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 *APOE-ε4* status were also investigated. Wine intake showed an interaction with *APOE-ε4* status for the association with amyloid load ( $p = 0.012$ , eTable 6, links.lww.com/WNL/C661). In an exploratory stratified analysis, green leafy vegetable and bean intake

**Table 2** Association of MIND and Mediterranean Diet Scores With Alzheimer Disease Pathology in 581 Deceased Participants of the Memory and Aging Project

	Median	Global AD pathology <sup>a</sup> β (SE, <i>p</i> value)	Beta-amyloid load <sup>a</sup> β (SE, <i>p</i> value)	Phosphorylated Tau tangle <sup>a</sup> β (SE, <i>p</i> value)
<b>MIND diet scores (score range 0–15)</b>				
<b>Model 1</b>				
<b>Continuous score</b>	7.0	−0.022 (0.011, 0.035)	−0.068 (0.034, 0.050)	0.012 (0.038, 0.761)
<b>T1 (n = 194)</b>	6.0	Ref	Ref	Ref
<b>T2 (n = 199)</b>	7.5	−0.024 (0.037, 0.516)	−0.115 (0.119, 0.335)	−0.102 (0.133, 0.443)
<b>T3 (n = 188)</b>	9.0	−0.071 (0.038, 0.063)	−0.274 (0.123, 0.027)	0.042 (0.137, 0.757)
<b><i>p</i> trend</b>		0.062	0.027	0.751
<b>Model 2</b>				
<b>Continuous score</b>	7.0	−0.024 (0.011, 0.025)	−0.062 (0.034, 0.071)	−0.024 (0.037, 0.528)
<b>T1 (n = 194)</b>	6.0	Ref	Ref	Ref
<b>T2 (n = 199)</b>	7.5	−0.027 (0.037, 0.461)	−0.099 (0.118, 0.402)	−0.139 (0.130, 0.285)
<b>T3 (n = 188)</b>	9.0	−0.077 (0.038, 0.044)	−0.246 (0.123, 0.047)	−0.108 (0.134, 0.422)
<b><i>p</i> trend</b>		0.044	0.047	0.420
<b>Mediterranean diet scores (score range 0–55)</b>				
<b>Model 1</b>				
<b>Continuous score</b>	30	−0.007 (0.003, 0.039)	−0.032 (0.011, 0.004)	0.004 (0.012, 0.768)
<b>T1 (n = 220)</b>	26	Ref	Ref	Ref
<b>T2 (n = 192)</b>	30	−0.066 (0.037, 0.070)	−0.116 (0.120, 0.333)	0.035 (0.134, 0.795)
<b>T3 (n = 187)</b>	35	−0.105 (0.039, 0.007)	−0.404 (0.126, 0.001)	0.008 (0.141, 0.956)
<b><i>p</i> trend</b>		0.007	0.001	0.958
<b>Model 2</b>				
<b>Continuous score</b>	30	−0.008 (0.003, 0.028)	−0.030 (0.011, 0.008)	−0.002 (0.012, 0.878)
<b>T1 (n = 220)</b>	26	Ref	Ref	Ref
<b>T2 (n = 192)</b>	30	−0.070 (0.037, 0.058)	−0.097 (0.119, 0.417)	−0.020 (0.131, 0.876)
<b>T3 (n = 187)</b>	35	−0.110 (0.039, 0.005)	−0.387 (0.126, 0.002)	−0.041 (0.138, 0.766)
<b><i>p</i> trend</b>		0.005	0.002	0.776

Abbreviation: MIND = Mediterranean-DASH Intervention for Neurodegenerative Delay.

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

<sup>a</sup>Square root transformation.

was inversely associated with phosphorylated tau tangles among *APOE-ε4* noncarriers and not among *APOE-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,

intake of nuts and pastries/sweets 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, [links.lww.com/WNL/C661](https://links.lww.com/WNL/C661)). In an exploratory stratified analysis summarized 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, whereas no association was observed among

**Table 3** Association of MIND and Mediterranean Diet Scores With Alzheimer Disease Pathology Excluding Dementia and MCI at First Dietary Assessment (N = 379)

	Global AD pathology <sup>a</sup> β (SE, <i>p</i> value)	Beta-amyloid load <sup>a</sup> β (SE, <i>p</i> value)	Phosphorylated Tau-tangle <sup>a</sup> β (SE, <i>p</i> value)
<b>Excluding dietary assessments in the last year before death (N = 560)</b>			
<b>MIND Diet scores (score range 0–15)</b>			
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
<b>Mediterranean diet scores (score range 0–55)</b>			
Continuous score	−0.007 (0.004, 0.050)	−0.022 (0.012, 0.005)	0.002 (0.013, 0.901)
Standardized beta (β/SE)	−1.75	−1.83	−0.15
<b>Excluding dementia and MCI at first dietary assessment (N = 379)</b>			
<b>MIND diet scores (score range 0–15)</b>			
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
<b>Mediterranean diet scores (score range 0–55)</b>			
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

Abbreviation: MIND = Mediterranean-DASH Intervention for Neurodegenerative Delay.  
Linear regression models controlled for age at death, sex, education, *APOE-ε4* status, and total calories.  
<sup>a</sup> Square root transformation.

women; however, this association was no longer significant after applying the multiple comparison *p* value (eTable 8).

## 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 with participants whose MIND diet score was 1 unit higher, the difference in the amyloid load was similar to being about 4 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 vegetable intake and other important nutrients for brain health, may have its relationship with AD through 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 intake of pastries/sweets 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 affect AD pathology in human brains.

The MIND and Mediterranean diets have been associated with reduced Alzheimer dementia risk in various population-based cohorts.<sup>31</sup> 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<sup>14,32</sup> and middle-aged participants<sup>33,34</sup> have been reported, but 1 study shows null findings.<sup>35</sup> Our data also support studies using PiB-PET in AD regions that have shown that a diet rich in omega-3 fatty acids, vitamin B<sub>12</sub>, 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.<sup>36</sup> We previously reported

an association of the MIND diet with cognition independent of AD and other brain pathologies.<sup>5</sup> In this study, we complement these findings by demonstrating the association of the MIND diet 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.<sup>34</sup> The differences in the analyses (i.e., the *p* value) could be attributed to the smaller sample size, fewer data points for FFQs, and a 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.<sup>37</sup> 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<sup>7</sup> and on how the Western diet may attenuate the relationship of a healthy diet with cognitive decline.<sup>2</sup> Some food groups—such as fish/seafood<sup>38–40</sup> and other vegetables,<sup>41</sup> 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 *APOE-ε4* noncarriers 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 *APOE-ε* in lipid metabolism, immune regulation, and oxidative stress. In addition, the *APOE-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<sup>42,43</sup> and oxidative stress.<sup>44</sup> A 4-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 through its effects on lipoproteins, oxidative stress, insulin,

and central nervous system concentrations of amyloid-beta-42.<sup>45</sup> In APP/PS1 transgenic mice, a pro-oxidant diet (a normal chow diet without any enriched vitamin and mineral premixes) resulted in enhanced  $\beta/\gamma$  secretase-mediated amyloid precursor protein processing.<sup>46</sup> 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<sup>47</sup> and neurofibrillary tangle formation while decreasing synaptic plasticity, effects that are accompanied by inflammatory and stress response in whole brain lysate<sup>48</sup> and overall enhanced astroglial and microglia activation.<sup>49</sup>

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 neuropathologic 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, using 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 during 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 1 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 through vascular and other pathologies and the role of inflammation. Studies should also investigate person-specific factors and capitalize on emerging in vivo biomarkers and human brain tissue when available.

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## Appendix Authors

Name	Location	Contribution
<b>Puja Agarwal, PhD</b>	Rush Alzheimer's Disease Center; Departments of Internal Medicine and Clinical Nutrition, Rush University Medical Center, Chicago, IL	Drafting/revision of the article for content, including medical writing for content; major role in the acquisition of data; study concept or design; and analysis or interpretation of data
<b>Sue E. Leurgans, PhD</b>	Rush Alzheimer's Disease Center; Department of Neurological Sciences, Rush University Medical Center, Chicago, IL	Drafting/revision of the article for content, including medical writing for content; major role in the acquisition of data; analysis or interpretation of data
<b>Sonal Agrawal, PhD</b>	Rush Alzheimer's Disease Center; Department of Pathology, Rush University Medical Center, Chicago, IL	Drafting/revision of the article for content, including medical writing for content; major role in the acquisition of data; analysis or interpretation of data
<b>Neelum T. Aggarwal, MD</b>	Rush Alzheimer's Disease Center; Department of Neurological Sciences, Rush University Medical Center, Chicago, IL	Drafting/revision of the article for content, including medical writing for content; analysis or interpretation of data
<b>Laurel J. Cherian, MD</b>	Department of Neurological Sciences, Rush University Medical Center, Chicago, IL	Drafting/revision of the article for content, including medical writing for content; analysis or interpretation of data
<b>Bryan D. James, PhD</b>	Rush Alzheimer's Disease Center; Department of Internal Medicine, Rush University Medical Center, Chicago, IL	Drafting/revision of the article for content, including medical writing for content; analysis or interpretation of data
<b>Klodian Dhana, MD, PhD</b>	Department of Internal Medicine; Rush Institute of Healthy Aging, Rush University Medical Center, Chicago, IL	Drafting/revision of the article for content, including medical writing for content; analysis or interpretation of data
<b>Lisa L. Barnes, PhD</b>	Rush Alzheimer's Disease Center; Department of Neurological Sciences, Rush University Medical Center, Chicago, IL	Drafting/revision of the article for content, including medical writing for content; analysis or interpretation of data
<b>David A. Bennett, MD</b>	Rush Alzheimer's Disease Center; Department of Neurological Sciences, Rush University Medical Center, Chicago, IL	Drafting/revision of the article for content, including medical writing for content; major role in the acquisition of data; study concept or design

## Appendix (continued)

Name	Location	Contribution
<b>Julie A. Schneider, MD</b>	Rush Alzheimer's Disease Center; Departments and Pathology, Rush University Medical Center, Chicago, IL	Drafting/revision of the article for content, including medical writing for content; major role in the acquisition of data; study concept or design; and analysis or interpretation of data

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

Puja Agarwal, Sue E. Leurgans, Sonal Agrawal, et al.

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