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MIND diet, common brain pathologies, and cognition in community-dwelling older adults

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Abstract

Background—MIND diet – a hybrid of the Mediterranean diet and the Dietary Approaches to Stop Hypertension diet – is associated with a slower cognitive decline and lower risk of Alzheimer's dementia in older adults.

Objective—We aim to examine whether the association of the MIND diet with cognition is independent of common brain pathologies.

Methods—Utilizing data from the Rush Memory and Aging Project (MAP), a longitudinal clinical-pathologic study, we studied 569 decedents with valid dietary data, cognitive testing proximate to death, and complete autopsy data at the time of these analyses. A series of regression analyses were used to examine associations of the MIND diet, dementia-related brain pathologies, and global cognition proximate to death adjusting for age, sex, education, APOE $\epsilon 4$, late-life cognitive activities, and total energy intake.

Results—A higher MIND diet score was associated with better global cognitive functioning proximate to death (β=0.119, SE=0.040, *P*-value=0.003), and neither the strength nor the significance of association changed substantially when Alzheimer's disease (AD) pathology and other brain pathologies were included in the model. The β-estimate after controlling for global AD pathology was 0.111 (SE=0.037, p=0.003). The MIND diet-cognition relationship remained significant when we restricted our analysis to individuals without mild cognitive impairment at the baseline (β=0.121, SE=0.042, *P*-value=0.005) or in people diagnosed with postmortem diagnosis of AD based on NIA-Reagan consensus recommendations (β=0.114, SE=0.050, *P*-value=0.023).

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Conflict of Interest/Disclosure Statement

The authors have no conflict of interest to report

Conclusion—MIND diet is associated with better cognitive functioning independently of common brain pathology, suggesting that the MIND diet may contribute to cognitive resilience in the elderly.

Keywords

MIND diet; amyloid-β; brain pathology; cognition

Introduction

The hallmark of Alzheimer's disease is the deposition of amyloid plaques and neurofibrillary tangles in the brain [1]. Elevated levels of brain-pathologies, including amyloid-β and neurofibrillary tangles, initiate a series of molecular events leading to neuronal damage and, ultimately, to cognitive impairment [2–6]. However, not all individuals with pathologies in the brain experience cognitive dysfunction – some have the ability to maintain function despite damage from the accumulation of brain pathologies [7,8]. This phenomenon, known as cognitive resilience (defined as performing better than expected given burden of neuropathology[9]), has been proposed as a moderator between brain pathology and clinical outcomes and has recently become an active area of research [10–14]. For example, we previously have shown that late-life cognitive activities and physical activity are associated with a better cognitive score independently of brain pathologies [13,14]. Identifying modifiable lifestyle factors that act independently of brain pathologies is critical in Alzheimer's research, in part, because pharmacological interventions that focus on brain pathology have failed to reduce or slow cognitive decline [15], despite some evidence of clearance of amyloid plaque from the brain [16].

Among modifiable lifestyle factors [17], diet has been associated with cognitive decline and Alzheimer's dementia [18]. We have shown that the MIND diet, a hybrid of the Mediterranean diet with the Dietary Approaches to Stop Hypertension (DASH) diet, slows cognitive decline in older adults, and reduce the risk of Alzheimer's dementia [19,20]. The MIND diet is a modifiable lifestyle factor, tailored for brain health, and rich in nutrients (e.g., folate, vitamin E, lutein-zeaxanthin, flavonoids) that are known for their anti-inflammatory, antioxidant, and pro-cognition properties [21–23]. Therefore, it is essential to assess whether the MIND diet is associated with cognition independently of brain pathologies in older adults.

In this study, we examined the associations of the MIND diet score, brain pathologies, and cognitive functioning in older adults of the Rush Memory and Aging Project.

Methods

Study Sample

The Rush Memory and Aging Project (MAP) is a longitudinal clinical-pathologic study of aging and Alzheimer's disease composed of older adults aged 65 years and older living in retirement communities in the Chicagoland area [24]. Details of the study design and methodology are provided elsewhere [24]. In short, MAP began in 1997 with an annual

assessment of risk factors, blood donation, and a detailed clinical evaluation. In particular, for the MAP study, participants agree to the donation of the brain at the time of death.[24] In 2004, the self-administered food frequency questionnaire was provided to study participants and every year afterward. For the current study, we included 569 decedents with valid dietary data, cognitive testing proximate to death, and complete autopsy data at the time of these analyses. The study was approved by an Institutional Review Board of Rush University Medical Center (IRB 16012503-IRB02). All participants signed an Informed Consent and Anatomic Gift Act for organ donation.

Assessment of the MIND diet score

The MIND diet score was computed based on the responses to a semi-quantitative food frequency questionnaire (FFQ), a modified version of the Harvard FFQ that was validated for use in Chicago community residents [25]. MAP participants reported the usual frequency of consumption of 144 food items over the previous 12 months. The MIND diet score has 15 dietary components, including 10 brain-healthy food groups (green leafy vegetables, other vegetables, nuts, berries, beans/legumes, whole grains, fish, poultry, olive oil, and wine) and 5 unhealthy food groups (red meat, fried and fast foods, pastry and sweets, butter, and cheese) [19]. Based on the frequency of intake reported for the healthy and unhealthy food groups, the MIND diet score was computed for each participant summing all 15 of the component scores. A cumulative average of MIND diet score across follow-up was used in analyses to limit measurement error [26]. The average of dietary assessments in the MAP cohort study was 3.5.

Assessment of [postmortem] brain pathology

A standardized protocol was used for brain removal, sectioning and preserving of tissue, and quantifying Alzheimer's disease pathology and cerebral infarctions, as described in detail previously [27]. Briefly, staff blinded to any clinical data removed and weighed brains, and placed each hemisphere in a Plexiglas jig and cut coronally into 1 cm slabs. After slabs from one hemisphere were fixed in 4% paraformaldehyde for 3–21 days, they were dissected into blocks that were embedded in paraffin and cut into 6-μm sections.

Alzheimer disease (AD) pathology

Bielschowsky silver stain was used to visualize neuritic plaques, diffuse plaques, and neurofibrillary tangles in five cortical regions (frontal, temporal, parietal, the entorhinal cortex, hippocampus). Number of neuritic, diffuse plaques, and neurofibrillary tangles identified in a $1mm^2$ area of highest density in 5 cortical regions were counted and used to develop a composite measure of global AD pathology as previously described [4]. In addition, to the global AD measure we also obtained molecularly specific and more quantitative estimates of the 2 major pathologic proteins. amyloid-β protein was identified by molecularly-specific immunohistochemistry and quantified by image analysis in each region [27,28]. A summary measure for amyloid-β burden across all regions was calculated. Neuronal neurofibrillary tangles are identified by molecularly specific immunohistochemistry (antibodies to abnormally phosphorylated Tau protein, AT8).

Computer-assisted sampling was used to quantify the cortical density (per mm2) of tau immunoreactive tangles, and mean tangle density for all regions was used in these analyses.

Lewy body disease pathology

Lewy bodies were assessed in 6 regions, including substantia nigra, anterior cingulate cortex, entorhinal cortex, midfrontal cortex, superior or middle temporal cortex, inferior parietal cortex using a monoclonal phosphorylated antibody to α-synuclein (1:20,000; Wako Chemical, Rich- mond, VA) with alkaline phosphatase as the chromogen. Details for the diagnosis of Lewy body we have previously described [29]. In short, Lewy bodies in the cortex were identified as round intracytoplasmic structures, which often lack any halo and an eccentric nucleus, whereas Nigral Lewy bodies were identified as round, intracytoplasmic structures with a darker halo.

TAR DNA-binding protein 43 (TDP-43)

TDP-43 immunohistochemistry was performed on 8 brain regions using phosphorylated monoclonal TAR5P-1D3 (pS409/410; 1:100, Ascenion, Munich, Germany) TDP-43 antibody. Since 2015, this antibody has been obtained from MilliporeSigma, Burlington, MA [30].

Hippocampal sclerosis—Hippocampal sclerosis was evaluated unilaterally in a coronal section of the midhippocampus at the level of the lateral geniculate body, and graded as absent or present based on severe neuronal loss and gliosis in CA1 and/or subiculum as described previously [31].

Macroscopic cerebral infarcts—A gross examination of the slabs assessed examination of infarcts by age, size, and location (side and region). All suspected macroscopic infarcts were confirmed histologically. In the analysis, chronic macroinfarcts were coded as present or absent [32].

Cerebral atherosclerosis—Atherosclerosis was evaluated by visual inspection of the vertebral, basilar, posterior cerebral, middle cerebral, and anterior cerebral arteries and their proximal branches and was rated using a semiquantitative scale with 7 levels from no atherosclerosis to severe involvement of most vessels or more than 75% occlusion of one or more vessels [33].

Microscopic cerebral infarcts—The presence of microinfarcts was defined as any infarct seen by microscopic examination but not identified by gross inspection. Microscopic infarcts ranged from cavitated to puckered to incomplete in appearance. The regions examined for microinfarcts include middle frontal cortex, middle temporal cortex, anterior cingulate cortex, inferior parietal cortex, entorhinal cortex, hippocampus, anterior basal ganglia, anterior thalamus, and hemisection of the midbrain, including the substantia nigra [34].

Arteriolosclerosis—Arteriolosclerosis refers to the histological changes in the small vessels of the brain that are responsible for narrowing the vascular lumen. Vessels of the

anterior basal ganglia were evaluated with a semiquantitative scaling system from 0 (none) to 7 (occluded) [35].

Cerebral amyloid angiopathy—Cerebral amyloid angiopathy (CAA) pathology was assessed in 4 neocortical regions, the midfrontal, midtemporal, parietal, and calcarine cortices. For each region, meningeal and parenchymal vessels were assessed for amyloid deposition and scored from 0 (no deposition) to 4 (circumferential deposition over 75% of the entire region) [36]. The maximum of the meningeal and parenchymal scores was then averaged across the 4 regions.

Assessment of cognition

All subjects underwent a uniform structured clinical evaluation with emphasis on neurologic function, and neuropsychological testing. Nineteen neuropsychological tests were used to create a composite measure of global cognitive function and five specific cognitive domains, including episodic memory, semantic memory, working memory, perceptual speed, and visuospatial ability. The raw scores of individual tests were standardized and averaged to z-scores, using the mean and standard deviation from the baseline evaluation of the entire study. Detailed information on the individual tests and the derivation of these scores has been described previously [37].

Assessment of covariates

Covariates included age at death, sex, years of education, APOE $\epsilon-4$, cognitive activities, and total energy intake. APOE genotype was determined for each participant by the Broad Institute for Population Genetics using the Polymorphic DNA Technologies [38,39]. Participants were classified as APOE $\epsilon-4$ carriers (>1 allele) or noncarriers. Participation in cognitively stimulating activities was assessed with a structured questionnaire that assessed usual time spent in the past year on seven activities, including reading, writing letters, visiting a library, and playing games such as chess or checkers [40]. Each of these seven activities was scored and then averaged to yield a composite measure of the frequency of participation in cognitively stimulating activities.

Statistical analysis

Characteristics of the study population are presented as mean and SD, median and interquartile, or as number and percentages of participants. Pearson correlations were used to assess the correlation between the MIND diet and covariates. Linear and logistic regression models were used to investigate the association between the MIND diet, brain pathology, and cognitive functioning proximate to death. Models were adjusted for age at death, sex, education, APOE $\epsilon4$, late-life cognitive activities, and total energy intake.

Our primary question was to determine whether the association of MIND diet with cognition varied with the level of brain pathologies. We conducted three analyses: First, we investigated the association of MIND diet score with cognitive functioning proximate to death and determined whether an additional adjustment for global AD pathology and other brain pathologies attenuated the association. Second, we evaluated the interaction of the MIND diet with brain pathology indices and determined whether brain pathology modified

the relationship between MIND diet score and cognition. Third, we estimated the direct association of the MIND diet with AD brain pathologies, including indices of brain vascular pathology.

To tests the robustness of our primary findings we conducted seven sensitivity analyses. First, we excluded participants with mild cognitive impairment at the baseline and examined whether the association between MIND diet and cognition is due to cognitive influences on dietary behaviors or reporting accuracy. Second, we examined the association of MIND diet score from just the baseline assessment with cognitive functioning in the model controlled for global AD pathology and confounders. Third, we investigated the impact of dietary changes over time on the association between MIND diet score and cognition by excluding individuals whose MIND diet scores increased (e.g., improved) or decreased by more than 20% over the study period. Fourth, we accounted for the effect of physical activity on the relationship between MIND diet and cognition by adding a term for physical activity in the multivariable-adjusted model. Fifth, to determine whether the MIND diet score is associated with cognition in people with significant brain pathology, we repeated our analysis considering only participants meeting NIA-Reagan consensus criteria for the postmortem diagnosis of Alzheimer's disease. Sixth, we investigated whether the participant's age modifies the relationship between MIND diet score and cognition at death. In this analysis, we evaluated the significance of the interaction between MIND diet and age in a multivariable-adjusted model. Lastly, we used linear mixed-effects models to examine the association of MIND diet with cognitive decline during the follow-up and determine whether brain pathology influences the relationship between the MIND diet and cognitive decline.

All the analyses were performed with R software, CRAN version 4.0.0, and its packages (R Foundation for Statistical Computing, Vienna, Austria).

Results

Characteristics of study sample

The average age at death was 91 years, the mean level of education was about 15 years, and approximately 70% were women (Table 1). The average MIND diet score was 7.35 (men: 7.20; women: 7.41; p=0.11) with a standard deviation of 1.42. The MIND diet score was positively correlated with education (r=0.18, p<0.01) and late-life cognitive activities (r=0.18, p<0.01), but not with age at death (r=0.03, p=0.45). According to NIA-Reagan criteria, two-thirds of the participants had a postmortem diagnosis of Alzheimer's disease, but only one-third were diagnosed with clinical Alzheimer's dementia proximate to death.

MIND diet, brain pathology, and cognition

A higher MIND diet score was associated with better cognition. One standard deviation increase of the MIND diet score was associated with 0.119 units higher in the cognitive score (β=0.119, SE=0.040, *P*-value=0.003; Table 2 A). As expected, a higher measure of global AD pathology was associated with a worse cognitive score (β=−0.609, SE=0.066, p<0.001; Table 2 B–D). When both MIND diet and AD pathology were included in the

same model, the MIND diet score remained independently associated with cognition, and estimates did not change substantially (β=0.111, SE=0.037, *P*-value=0.003; Table 3 A). Similar findings were noted for the association of the MIND diet with cognition when amyloid-β load and tangles were added individually in the multivariable-adjusted model (Table 3 B–C). There was no evidence that AD pathology modified the relationship of MIND diet with cognition, as evidenced by the non-significant interaction terms of the MIND diet with Alzheimer's disease pathology (*P*-value=0.667), amyloid-β (*P*-value=0.871), and tangles (*P*-value=0.930).

Because other common neuropathologies in aging contribute to cognitive impairment, we developed separate linear regression models to examine whether the association of the MIND diet score with cognitive performance is independent of the associations of the other brain pathologies with cognition. In each of these models, the β-estimates of the association between MIND diet score and cognition were essentially unchanged when other common neuropathologies were included in separate analyses (Table 4 A–I). The greatest attenuation, albeit small, of the MIND diet estimates across all the pathologies considered, was seen in the model that included hippocampal sclerosis (β=0.103 versus β=0.119). There were no significant interactions between the MIND diet and any of the other common neuropathologies of aging (p>0.341 for each interaction term).

As a reflection of the overall burden of brain pathologies, all common neuropathologies of aging, together with AD pathology, were included in a single model, along with the MIND diet (Table 5 A-B). A higher MIND diet score was associated with a better cognition independently of the overall burden of brain pathologies (β=0.103, SE=0.037, *P*-value=0.005; Table 5 B).

MIND diet was not associated with brain pathology (AD pathology, amyloid-β and tangles), including indices of vascular pathology such as macroinfarcts, microinfarcts, cerebral atherosclerosis, and arteriolosclerosis (Table 6).

Sensitivity analysis

Results of sensitivity analysis are presented in the Table 7 A-F. Excluding participants (n=178) with mild cognitive impairment at the baseline to investigate the cognitive influences on dietary behaviors and reporting accuracy did not change the strength or the significance of the association between MIND diet with cognition and its independence to AD pathology (β=0.121, SE=0.042, *P*-value=0.005). MIND diet score at the baseline was significantly associated with cognition in a multivariable-adjusted model, including AD pathology, but the effect estimates were marginally attenuated compared to primary analysis (β=0.098 vs. β=0.111). Restricting analysis on participants (n=363) whose MIND diet scores were relatively constant during the study period (e.g., consecutive change less than 20%) showed similar results to the primary analysis (β=0.120, SE=0.044, *P*-value=0.007). Further adjustment for physical activity in the multivariable model adjusted for confounders and global AD pathology burden did not change the strength or significance between MIND diet score and cognition (β=0.108, SE=0.037, *P*-value=0.004). The MIND diet was associated with a better cognitive function proximate to death in participants (n=374) who

had significant brain pathology and met NIA-Reagan consensus criteria for the postmortem diagnosis of Alzheimer's disease (β=0.114, SE=0.050, *P*-value=0.023). We also investigated potential modifications in the estimated effect of the MIND diet score on cognitive function by age. We found no evidence that the diet effect on cognition differed by age (*P*-value for interaction 0.5). MIND diet score was associated with a slower cognitive decline, and the relationship was independent of AD pathology. One standard deviation increase in the MIND diet score was associated with a slower cognitive decline by 0.012 units per year (β=0.012, SE=0.005, P=0.022).

Discussion

In this study of autopsy findings from 569 well-characterized community-dwelling older adults, a higher MIND diet score was associated with better cognitive function and slower cognitive decline independently of AD pathology and other common age-related brain pathologies. The independence from AD pathology and other age-related brain pathologies suggests that adherence to the MIND diet may protect from some of the cognitive loss associated with brain pathology and that ultimately may contribute to building cognitive resilience in older adults. In the absence of effective pharmacological interventions to prevent or slow the progression of Alzheimer's dementia [15], it is of great scientific interest to identify modifiable lifestyle factors that lower the risk of faster cognitive decline independent of AD pathology and other common brain pathologies.

In recent years, data from autopsy studies have shown that a substantial number of people without a clinical diagnosis of dementia have significant brain pathology at death that meets the NIA-Reagan criteria for the postmortem diagnosis of Alzheimer's disease [4,27,41]. For instance, we reported in an early study that 35.8% of individuals without cognitive impairment before death met NIA-Reagan criteria for the intermediate likelihood [27]. Similarly, data from the Baltimore Longitudinal Study of Aging reports that subjects with asymptomatic Alzheimer's disease represent approximately 50% of individuals older than 75 years of age [41]. From the perspective of primary prevention of Alzheimer's dementia, all these data suggest that other factors exist, and should be identified, to counter the burden of brain pathology on cognitive functioning. Previous studies have identified modifiable risk factors such as late-life cognitive activities[13] and physical activity[14] associated with better cognitive functioning independently of common neuropathologic conditions, supporting the cognitive resilience hypothesis. In this study, we provide evidence that the MIND diet could also contribute to cognitive resilience.

While we showed that the association between the MIND diet and cognition was independent of brain pathology, there was no evidence that the MIND diet score modified the associations of brain pathologies with cognition. Together, these findings suggest that the mechanism by which the MIND diet supports cognitive resilience is not related to the levels of pathology in the brain, and other neurobiological mechanisms remain to be identified. Such mechanisms may provide novel therapeutic targets to slow cognitive decline in older adults with significant pathology in the brain. These findings also have public health implications because, many older individuals exhibit neuropathology that contributes

to cognitive impairment, and this large group may benefit from the adherence to the MIND diet.

The MIND diet may contribute to brain health through its food components that have antioxidative, anti-inflammatory, and neuroprotective activities [21–23]. For example, the MIND diet encourages the consumption of green leafy vegetables and berries. Green leafy vegetables are rich in nutrients such as vitamin E, folate, β-carotene, lutein-zeaxanthin, and flavonoids that contribute to better cognitive functioning [42]. Vitamin E, an antioxidant found in green leafy vegetables and nuts protects neurons from damage related to oxidative stress caused by free radicals [43]. Similarly, in animal models, berries consumption has been shown to increase neurogenesis, insulin-like growth factor-1 signaling, and reverse neuronal aging by reducing oxidative stress [44]. In older adults, oxidative stress is a significant contributor to neurodegeneration independently of brain pathology [21]. Deficiency in folate has been associated with neurotoxicity in mouse models. In humans, low levels of folate cause homocysteine elevations, which has been related to the risk of developing Alzheimer's dementia [45]. Neuroimaging studies have shown that dietary choices can lead to changes in brain structure; a cross-sectional study demonstrated that lower adherence to the Mediterranean diet was associated with increased atrophy on the specific brain regions for Alzheimer's disease [46]. It is not known whether similar mechanisms contribute to enhanced cognitive resilience in individuals with higher adherence to the MIND diet.

Strengths and limitations of this study should be noted. The reliance on a self-reported diet is a limitation of the study because of cognitive impairment could interfere with inaccurate reporting. We explored this concern by excluding from analysis participants whose first global cognitive evaluation was in the lowest 25% of the sample. We also calculated the cumulative average of the MIND diet score across follow-up to limit measurement error [26]. Another limitation is that the study sample is composed of mostly white volunteers who agreed to annual evaluations and post-mortem organ donation, thus limiting generalizability. This study's strengths are the prospective design with a yearly assessment of cognitive function using a standardized battery of tests and collection of the dietary information using validated questionnaires; the neuropathologic evaluations were performed by examiners blinded to clinical data.

In conclusion, MIND diet is associated with better cognitive functioning independently of brain pathology, suggesting that the MIND diet may contribute to cognitive resilience in older adults.

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Table 1.

Demographic, clinical, and postmortem characteristics of study sample

Characteristics	N=569
Demographic and clinical measures	
Age at death, years	90.8 (6.1)
Sex, males (%)	168 (29.5 %)
Education, years	14.8 (2.9)
APOE4 allele carrier (%)	123 (21.6 %)
Late-life cognitive activity, score	2.59 (0.91)
MIND diet, score	7.35 (1.42)
Physical activity, moderate/vigorous-intensity exercise, hours/week	50 (0-180)
Total energy intake, kcal	1831 (534)
Postmortem measures	
NIA-Reagan AD (%)	374 (65.7 %)
Global AD pathology	0.72 (0.58)
β-amyloid load	1.70 (1.17)
Tangle density	7.35 (8.19)
Lewy Bodies (%)	136 (24.6 %)
Microinfarcts (%)	211 (37.1 %)
Microinfarcts (%)	178 (31.3 %)
Cerebral atherosclerosis, moderate–severe (%)	135 (23.7 %)
Arteriolosclerosis, moderate–severe (%)	159 (27.9 %)
Cerebral amyloid angiopathy (%)	452 (79.6 %)
TDP-43 pathology in amygdala and beyond (%)	310 (54.7 %)
Hippocampal sclerosis (%)	54 (9.5 %)
Postmortem interval autopsy, hours	9.43 (8.96)

Data is shown as mean (standard deviation), median (interquartile), or number (%)

Table 2.

Association of MIND diet score and AD pathology with global cognition proximate to death

Model	Predictor	β-estimate (SE)	*P*-value	Adjusted R^2, %
A	MIND diet score	0.119 (0.040)	0.003	24.5
B	AD pathology	−0.609 (0.066)	<0.001	33.3
C	β-amyloid	−0.184 (0.034)	<0.001	27.1
D	Tangle density	−0.057 (0.004)	<0.001	40.5

Each model (A-D) is a separate linear regression model adjusted for the predictor (as shown in table) and age at death, sex, APOE4, education, total energy intake, and late-life cognitive activities (not shown). β-estimate for MIND diet score is for 1 standard deviation (SD=1.42) increase.

Table 3.

Association of MIND diet score with global cognition proximate to death when controlling for AD pathology

Model	Predictors	β-estimate (SE)	*P*-value	Adjusted R^2, %
A	MIND diet score	0.111 (0.037)	0.003	34.2
	AD pathology	−0.604 (0.066)	<0.001	
B	MIND diet score	0.114 (0.039)	0.003	28.0
	β-amyloid	−0.181 (0.034)	<0.001	
C	MIND diet score	0.123 (0.035)	<0.001	41.7
	Tangle density	−0.057 (0.004)	<0.001	

Each model (A-C) is a separate linear regression model adjusted for the predictors (as shown in table) and age at death, sex, APOE4, education, total energy intake, and late-life cognitive activities (not shown). β-estimate for MIND diet score is for 1 standard deviation (SD=1.42) increase.

Table 4.

Association of MIND diet score with global cognition proximate to death when controlling for common brain pathologies

Model	Predictors	β-estimate (SE)	*P*-value	Adjusted R^2, %
A	MIND diet score	0.122 (0.04)	0.002	24.8
	Arteriolosclerosis, moderate–severe	−0.16 (0.086)	0.065	
B	MIND diet score	0.116 (0.039)	0.003	25.4
	Cerebral amyloid angiopathy	−0.269 (0.097)	0.006	
C	MIND diet score	0.12 (0.04)	0.003	24.7
	Macroinfarcts	−0.13 (0.08)	0.105	
D	MIND diet score	0.122 (0.04)	0.002	24.5
	Microinfarcts	−0.093 (0.083)	0.266	
E	MIND diet score	0.12 (0.04)	0.003	24.4
	Cerebral atherosclerosis, moderate–severe	−0.067 (0.091)	0.465	
F	MIND diet score	0.12 (0.04)	0.003	26.5
	Lewy Bodies	−0.306 (0.09)	0.001	
G	MIND diet score	0.103 (0.039)	0.008	28.1
	Hippocampal sclerosis	−0.708 (0.13)	0.000	
H	MIND diet score	0.123 (0.038)	0.001	29.7
	NIA-Reagan AD	−0.533 (0.082)	0.000	
I	MIND diet score	0.116 (0.04)	0.003	24.9
	TDP-43 pathology in amygdala and beyond	−0.195 (0.079)	0.014	

Each model (A-I) is a separate linear regression model adjusted for the predictors (as shown in table) and age at death, sex, APOE4, education, total energy intake, and late-life cognitive activities (not shown). β-estimate for MIND diet score is for 1 standard deviation (SD=1.42) increase.

Table 5.

Associations of AD pathology and common age-related brain pathologies and global cognition with and without MIND diet score

Model	Predictors	β-estimate (SE)	*P*-value	Adjusted R^2, %
A	AD pathology	−0.595 (0.067)	<0.001	39.3
	Arteriolosclerosis, moderate–severe	−0.131 (0.082)	0.110	
	Cerebral amyloid angiopathy	−0.121 (0.09)	0.180	
	Macroinfarcts	−0.118 (0.076)	0.122	
	Microinfarcts	−0.073 (0.078)	0.346	
	Cerebral atherosclerosis, moderate–severe	−0.044 (0.086)	0.608	
	Lewy Bodies	−0.266 (0.083)	0.001	
	Hippocampal sclerosis	−0.735 (0.128)	<0.001	
	TDP-43 pathology in amygdala and beyond	−0.045 (0.075)	0.552	
B	MIND diet score	0.103 (0.037)	0.005	40.1
	AD pathology	−0.594 0.066	<0.001	
	Arteriolosclerosis, moderate–severe	−0.141 (0.082)	0.084	
	Cerebral amyloid angiopathy	−0.108 (0.09)	0.229	
	Macroinfarcts	−0.119 (0.076)	0.116	
	Microinfarcts	−0.086 (0.077)	0.268	
	Cerebral atherosclerosis, moderate–severe	−0.042 0.086	0.621	
	Lewy Bodies	−0.264 (0.082)	0.001	
	Hippocampal sclerosis	−0.704 (0.128)	<0.001	
	TDP-43 pathology in amygdala and beyond	−0.044 (0.074)	0.557	

Each model (A-B) is a separate linear regression model adjusted for the predictors (as shown in table) and age at death, sex, APOE4, education, total energy intake, and late-life cognitive activities (not shown). β-estimate for MIND diet score is for 1 standard deviation (SD=1.42) increase.

Table 6.

Association of MIND diet score with brain pathology

Model	Outcome	Predictor	β-estimate (SE)	*P*-value
A	AD pathology	MIND diet score	−0.013 (0.024)	0.578
B	β-amyloid	MIND diet score	−0.03 (0.049)	0.395
C	Tangles	MIND diet score	0.058 (0.332)	0.862
D	Macroinfarcts	MIND diet score	0.038 (0.091)	0.680
E	Microinfarcts	MIND diet score	0.132 (0.095)	0.163
F	Arteriolosclerosis, moderate–severe	MIND diet score	0.087 (0.098)	0.378
G	Cerebral atherosclerosis, moderate–severe	MIND diet score	0.033 (0.104)	0.754

Models A to C are separate linear regression models and models D to G are separate logistic regression models. Each model (A-G) is adjusted for the age at death, sex, APOE4, education, total energy intake, and late-life cognitive activities (not shown).

β-estimate for MIND diet score is for 1 standard deviation (SD=1.42) increase.

Table 7.

Association of MIND diet score with global cognition proximate to death and cognitive decline

Model	N	β-estimate (SE)	*P*-value
A	391	0.121 (0.042)	0.005
B	569	0.098 (0.037)	0.008
C	363	0.120 (0.044)	0.007
D	569	0.108 (0.037)	0.004
E	374	0.114 (0.050)	0.023
F	569	0.012 (0.005)	0.022

Each model (A-E) is a separate linear regression model adjusted for age at death, sex, APOE4, education, total energy intake, and late-life cognitive activities and global AD pathology (not shown). Model F is a linear mixed-effect model adjusted for age at death, sex, APOE4, education, total energy intake, and late-life cognitive activities (not shown), and their interactions with time (years before death).

Estimates are reported for the interaction of predictor with time. β-estimate for MIND diet score is for 1 standard deviation (SD=1.42) increase.

Model A excludes individuals with mild cognitive impairment or other conditions contributing to cognitive impairment at the baseline.

Model B MIND diet score is based on dietary information collected at the baseline.

Model C restrict analysis on participants whose MIND diet scores were relatively constant (e.g., consecutive change less than 20%) during the study period.

Model D is further adjusted for physical activity

Model E includes cases diagnosed with postmortem diagnosis of Alzheimer's disease based on NIA-Reagan consensus recommendations.

Model F evaluates the rates of cognitive decline. β-estimate indicates rate of change in cognitive decline per year.