Mediterranean diet and brain structure in a multiethnic elderly cohort

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ABSTRACT

Objective: To determine whether higher adherence to a Mediterranean-type diet (MeDi) is related with larger MRI-measured brain volume or cortical thickness.

Methods: In this cross-sectional study, high-resolution structural MRI was collected on 674 elderly (mean age 80.1 years) adults without dementia who participated in a community-based, multiethnic cohort. Dietary information was collected via a food frequency questionnaire. Total brain volume (TBV), total gray matter volume (TGMV), total white matter volume (TWMV), mean cortical thickness (mCT), and regional volume or CT were derived from MRI scans using FreeSurfer program. We examined the association of MeDi (scored as 0–9) and individual food groups with brain volume and thickness using regression models adjusted for age, sex, ethnicity, education, body mass index, diabetes, and cognition.

Results: Compared to lower MeDi adherence (0–4), higher adherence (5–9) was associated with 13.11 ($p = 0.007$), 5.00 ($p = 0.05$), and 6.41 ($p = 0.05$) milliliter larger TBV, TGMV, and TWMV, respectively. Higher fish ($b = 7.06$, $p = 0.006$) and lower meat ($b = 8.42$, $p = 0.002$) intakes were associated with larger TGMV. Lower meat intake was also associated with larger TBV ($b = 12.20$, $p = 0.02$). Higher fish intake was associated with 0.019 mm ($p = 0.03$) larger mCT. Volumes of cingulate cortex, parietal lobe, temporal lobe, and hippocampus and CT of the superior-frontal region were associated with the dietary factors.

Conclusions: Among older adults, MeDi adherence was associated with less brain atrophy, with an effect similar to 5 years of aging. Higher fish and lower meat intake might be the 2 key food elements that contribute to the benefits of MeDi on brain structure. *Neurology*® 2015;85:1744-1751

GLOSSARY

AD = Alzheimer disease; **AGE** = advanced glycation end products; **BMI** = body mass index; **CDR** = Clinical Dementia Rating; **DSM-III-R** = *Diagnostic and Statistical Manual of Mental Disorders, 3rd edition, revised*; **FFQ** = food frequency questionnaire; **GLM** = generalized linear model; **GM** = gray matter; **ICV** = intracranial volume; **MANOVA** = multivariate analysis of variance; **MCI** = mild cognitive impairment; **mCT** = mean cortical thickness; **MeDi** = Mediterranean diet; **PUFA** = polyunsaturated fatty acids; **ROI** = region of interest; **SFA** = saturated fats; **TBV** = total brain volume; **TGMV** = total gray matter volume; **TWMV** = total white matter volume; **WHICAP** = Washington Heights/Hamilton Heights Inwood Columbia Aging Project; **WM** = white matter.

The Mediterranean diet (MeDi) has been recognized from epidemiologic studies over several different populations worldwide as one of the healthiest diets.[1] We have previously showed that adherence to the MeDi was associated with reduced risk of Alzheimer disease (AD)[1] and our results have been confirmed in a few populations,[2–5] although not in others.[6] While population differences in absolute levels of foods/nutrients intake, cultural and socioeconomic aspects, or comorbidity burdens may contribute to the inconsistencies of the findings, subjectivity and heterogeneity in procedures of clinical diagnosis may also play a role. Neuroimaging markers are sensitive measurements of structural changes in the aging brain, allowing us to examine associations between diet and aging-related brain changes that might not be detectable using clinical assessments.[7] Thus, it would be interesting to examine the relationship between MeDi and structural

neuroimaging markers such as brain atrophy and cortical thickness.[8] To our knowledge, only 2 studies have examined this relationship,[9,10] which were relatively small, and had little demographic diversity, potentially limiting the extrapolation of their findings.

In the current study, we examined the association between MeDi adherence and structural MRI-assessed brain volume and cortical thickness among elderly participants of a community-based, multiethnic cohort, the Washington Heights/Hamilton Heights Inwood Columbia Aging Project (WHICAP).

METHODS **Study design.** We performed a cross-sectional study to examine the association between MeDi and structural brain measures.

Study participants. The current study included participants from an ongoing prospective study of aging and dementia (WHICAP) who were identified from a probability sample of elderly Medicare beneficiaries (≥65 years) residing in northern Manhattan.[11] The original sample for this study included 2,776 participants. At baseline, a physician obtained each participant's medical and neurologic history, conducted a standardized physical and neurologic examination, and assessed their health and function. Cognitive status was assessed using a neuropsychological battery.[12] Participants were followed every 18 months, repeating the baseline examinations. The diagnosis of dementia was based on standard research criteria *DSM-III-R*,[13] using all available information at a consensus conference. The type of dementia was subsequently determined using the criteria of the National Institute of Neurological and Communicative Disorders and Stroke–Alzheimer's Disease and Related Disorders Association for the diagnosis of probable or possible AD,[14] and using Petersen[15] criteria for the diagnosis of MCI, as described elsewhere.[16] Severity of dementia was rated with the Clinical Dementia Rating (CDR) scale.

The imaging substudy was started in 2004 among active dementia-free WHICAP participants.[17] Overall, 769 WHICAP participants received MRI scans, and they were slightly younger, and more likely to be African American or male compared to those who were eligible but did not undergo MRI.[17] Among them, T1 images were not available for 45 participants. We further excluded 10 participants without diet data and 40 participants who met diagnostic criteria for dementia at the neuroimaging visit. Therefore, in the current analysis we included a total of 674 (88% of 769) participants without dementia.

Standard protocol approvals, registrations, and patient consents. The Columbia University Institutional Review Board has reviewed and approved this project. All individuals provided written informed consent.

MRI protocol. Scans were acquired on a 1.5T Philips (Best, the Netherlands) Intera scanner at Columbia University. All the T1 images were analyzed using Freesurfer (V.5.1) (http://surfer.nmr.mgh.harvard.edu/). Freesurfer output underwent visual quality control and manual correction whenever necessary, and then Freesurfer steps were repeated. Regional cortical thicknesses and volumetric measures were obtained in 34 regions of interest (ROI) in each hemisphere through a series of steps including removal of nonbrain tissue using a hybrid watershed/surface deformation procedure,[18] followed by automated

Talairach transformation, segmentation of the subcortical white matter (WM) and deep gray matter (GM) volumetric structures,[19] intensity normalization,[20] tessellation of the GM-WM boundary, automated topology correction,[21] and surface deformation following intensity gradients to optimally place the gray/white and gray/CSF borders at the location where the greatest shift in intensity defines the transition to the other tissue class.[22,23]

Volume measures. We first explored global brain measures such as total brain volume (TBV), total GM volume (TGMV), and total WM volume (TWMV). Individual Desikan-Killiany ROIs were combined into 5 regions (left and right hemispheres summed) for regional cortical volume analysis (https://surfer.nmr.mgh.harvard.edu/fswiki/CorticalParcellation), including frontal (sum of superior frontal; rostral and caudal middle frontal; pars opercularis, pars triangularis, and pars orbitalis; lateral and medial orbitofrontal; precentral; paracentral; frontal pole), parietal (superior parietal; inferior parietal; supramarginal; postcentral; precuneus), temporal (superior, middle, and inferior temporal; banks of the superior temporal sulcus; fusiform; transverse temporal; entorhinal; temporal pole; parahippocampal), occipital (lateral occipital; lingual; cuneus; pericalcarine), and cingulate (rostral anterior; caudal anterior; posterior; isthmus). In addition, 5 regions in the depths of the brain were also analyzed, including hippocampus, caudate, putamen, thalamus, and amygdala.

To adjust for differences in head size across participants, regression models were run with intracranial volume (ICV) as the independent variable and brain volume as the outcome variable, and the regression residuals were then used in the analyses.

Cortical thickness. We calculated mean cortical thickness (mCT) across all ROIs within each participant. We also selected 12 FreeSurfer CT ROIs (mean of left and right hemispheres) to represent 9 regions that have been shown to reflect AD-associated neurodegeneration,[24] including (1) entorhinal cortex and parahippocampus (rostral medial temporal lobe), (2) inferior temporal lobe, (3) temporal pole, (4) inferior parietal lobe (angular gyrus), (5) superior frontal lobe, (6) superior parietal lobe, (7) supramarginal gyrus, (8) precuneus, and (9) pars opercularis, pars orbitalis, and pars triangularis (inferior frontal lobe).[25] CT was not adjusted for ICV.

Dietary information. Information about average diet over the prior year was collected using Willett's semi-quantitative food frequency questionnaire (FFQ) (Channing Laboratory, Cambridge, MA), administered by trained interviewers in English or Spanish. We have previously reported good validity and reliability of various components of the FFQ in WHICAP.[26,27]

We calculated the MeDi score as described in our previous reports.[1] Individuals were assigned a value of 1 for each beneficial food component (including vegetables, legumes, cereals, fish, fruits/nuts, and a ratio of monounsaturated fats to saturated fats [SFA]) if his or her caloric-adjusted consumption of the food was equal to or greater than the sex-specific population median, for each detrimental component (meat and dairy products) if the caloric-adjusted consumption was below the median, and for mild to moderate alcohol consumption (>0 to <30 g/day). The MeDi score (ranging 0–9) was calculated for each participant by summing the scores in the 9 food components, with higher MeDi score indicating closer adherence to the MeDi. The diet data were obtained on average 0.6 (SD = 1.8) years before the MRI scan.

Other information. We considered continuous variables including age (years), education (years), caloric intake, and body mass index (BMI; kg/m²). Ethnicity, including African American (black non-Hispanic), Hispanic, white (non-Hispanic), or other, based on self-report using the format of the 2000 US census, was used as a

dummy variable, with non-Hispanic white as the reference. Sex (female vs male) and *APOE* genotype (presence of either 1 or 2 vs absence of ε4 alleles) were used as dichotomous variables. Stroke information was self-reported by participants or relatives as well as neurologic examination or medical records review. Presence or absence of heart disease, diabetes mellitus, and hypertension were based on self-report or use of medications. These 4 vascular comorbidities were used as dichotomous variables with absence of the condition used as the reference. Cognition was determined using a neuropsychological battery[12] and exploratory factor

analysis was used to derive 4 composite scores (memory, language, executive/speed, and visuospatial) based on selected neuropsychological tests scores.[12]

Statistical analyses. Characteristics of participants by MeDi adherence and by tertiles of TBV or mCT were compared using *t* test for continuous variables and χ^2 test for categorical variables.

Generalized linear models (GLMs) were used to assess the association between MeDi and brain MRI markers, initially unadjusted (model 1), then adjusted for age at time of scan only

Table 1	Characteristics of the study population			
	Total	Lower MeDi (0-4)	Higher MeDi (5-9)	p^a
No. of participants	674	370	304	
Demographics and clinical factors				
Age, y, mean (SD)	80.1 (5.6)	80.1 (5.8)	80.1 (5.3)	0.96
Education, y, mean (SD)	10.7 (4.8)	10.7 (4.7)	10.7 (4.9)	0.92
Energy intake, calories, mean (SD)	1,399.6 (533)	1,417.2 (543)	1,378.3 (518)	0.35
Female, n (%)	454 (67)	247 (67)	207 (68)	0.71
APOE ε4+, n (%)	163 (25)	91 (25)	72 (24)	0.82
Ethnicity, n (%)				
White	187 (28)	102 (28)	85 (28)	0.27
Black	235 (35)	140 (38)	95 (31)	
Hispanic	239 (36)	122 (33)	117 (39)	
Others	13 (1.9)	6 (1.6)	7 (2.3)	
Stroke, n (%)	70 (10.5)	41 (11)	29 (9.7)	0.53
Diabetes, n (%)	139 (21)	77 (21)	62 (21)	0.85
Hypertension, n (%)	491 (74)	263 (72)	228 (76)	0.28
Heart disease, n (%)	139 (21)	84 (23)	55 (18)	0.13
BMI, kg/m², mean (SD)	27.8 (5.6)	28.0 (6.1)	27.7 (4.9)	0.49
Cognitive z scores				
Language, mean (SD)	0.32 (0.63)	0.29 (0.64)	0.35 (0.63)	0.20
Memory, mean (SD)	0.14 (0.73)	0.10 (0.74)	0.19 (0.71)	0.11
Speed, mean (SD)	0.21 (1)	0.26 (0.96)	0.14 (1.05)	0.15
Visuospatial, mean (SD)	0.29 (0.58)	0.27 (0.57)	0.31 (0.59)	0.43
Mean cognition, mean (SD)	0.23 (0.59)	0.21 (0.59)	0.24 (0.59)	0.48
CDR 0.5, n (%)	221 (33)	132 (36)	89 (29)	0.08
Brain structural measures				
mCT, mm, mean (SD)	2.46 (0.12)	2.45 (0.11)	2.46 (0.12)	0.44
ICV, mL, mean (SD)	1,304 (1,557)	1,306 (151)	1,302 (160)	0.74
Brain volume, mL, mean (SD)				
TBV	871 (101)	865 (99)	878 (103)	0.11
TGMV	519 (52)	517 (51)	522 (52)	0.16
TWMV	375 (55)	372 (55)	379 (55)	0.10
ICV-adjusted residuals, mL, mean (SD)				
TBV	0 (63)	−6.5 (63)	7.9 (61)	0.003
TGMV	0 (35)	−2.9 (35)	3.6 (35)	0.017
TWMV	0 (43)	−3.6 (42)	4.4 (43)	0.016

Abbreviations: BMI = body mass index; CDR = Clinical Dementia Rating; ICV = intracranial volume; mCT = mean cortical thickness; MeDi = Mediterranean diet; TBV = total brain volume; TGMV = total gray matter volume; TWMV = total white matter volume.
^{a} *p* Values from analysis of variance for continuous variables and χ^2 for categorical variables.

(model 2), and then adjusted for age at time of scan, sex, ethnicity, education, BMI, diabetes, and mean cognitive *z* score (model 3). The variables were selected into model 3 based on their associations with MeDi and brain measures. MeDi score was examined as a continuous variable as well as a dichotomized variable by population median level (i.e., high 5–9 vs low 0–4).

We performed a few supplementary analyses. First, we examined which of the 9 food components (dichotomized) of MeDi might drive the relationship between MeDi and brain measures. Second, we additionally adjusted for *APOE* genotype, caloric intake, hypertension, heart disease, and stroke in model 3. Third, we examined whether sex, *APOE*, or ethnicity modified the relationship between MeDi and brain measures. Fourth, we excluded participants with MCI and repeated the analyses on global brain measures among cognitively normal participants only. Finally, we explored regional brain measures in relation to diet using multivariate analysis of variance (MANOVA) to see whether the linear combination of the 10 regional volumes (as described previously) maximally distinguishes the diet groups; in other words, is associated with dietary variables. We then examined univariate *F* tests for individual ROIs. Any ROI found to be significantly associated with the dietary variables was further examined in adjusted GLMs to estimate its association with diet. A similar analysis was conducted for 12 thickness ROIs. Because individual ROI analyses were guided by the MANOVA results, and were essentially exploratory, no correction for multiple comparisons has been performed.

Statistical analyses were performed using PASW Statistics program (IBM, Chicago, IL). All *p* values were based on 2-sided tests with the significance level set at 0.05.

RESULTS **Characteristics of the study population.** Participants with lower and higher MeDi adherence were comparable in terms of their demographic and cognitive profiles (table 1). Compared to lower MeDi adherence participants, those with higher adherence had similar mCT, but larger TBV, TGMV, and TWMV (table 1).

Individuals who had larger TBV tended to be younger, to have higher education, to be male, to be less likely to have diabetes, to have lower BMI, to be less likely to have mild dementia (CDR = 0.5), and to have better cognition in each of the 4 domains. Similar patterns were found for TGMV and TWMV (data not shown), and mCT, except that those with larger mCT were more likely to be female and had higher percentage of Hispanic but lower percentage of black participants (table e-1 on the *Neurology*® Web site at Neurology.org).

MeDi adherence with global brain MRI markers. Higher MeDi score was associated with larger TBV, TGMV, and TWMV after adjusting for multiple covariates (table 2 and figure). In the model with dichotomous MeDi and age, 1 year increase in age was associated with 2.62 mL less TBV ($p < 0.0001$), indicating that the average difference in TBV between the higher and the lower MeDi score (14.43 mL) was about the same magnitude of effect corresponding to the change in TBV during half-decade of aging.

Supplementary analyses. Among the 9 food components of MeDi, higher fish intake, lower meat intake, and moderate alcohol intake were associated with larger brain volumes when adjusted for age. The associations remained significant for fish and meat in multivariable-adjusted models. Higher intake of fish was associated with thicker mCT (table e-2 and figure).

| Table 2	Cross-sectional association between Mediterranean diet and global brain measures							
	TBV, mL		TGMV, mL		TWMV, mL		mCT, mm	
	B	p	B	p	B	p	B	p
Model 1: Unadjusted								
MeDi, per unit	4.13[a]	0.01[a]	2.47[a]	0.007[a]	1.93	0.09	0.003	0.35
MeDi, high vs low	16.95[a]	0.003[a]	7.97[a]	0.01[a]	8.76[a]	0.03[a]	0.01	0.53
Model 2: Adjusted for age only								
MeDi, per unit	3.37[a]	0.01[a]	1.79[a]	0.02[a]	1.77[a]	0.05[a]	0.002	0.44
MeDi, high vs low	14.43[a]	0.002[a]	6.48[a]	0.01[a]	7.9[a]	0.01[a]	0.007	0.44
Model 3: Adjusted for age, sex, education, ethnicity, BMI, diabetes, and mean cognition								
MeDi, per unit	3.07[a]	0.03[a]	1.31	0.08	1.55	0.10	0.001	0.63
MeDi, high vs low	13.11[a]	0.007[a]	5.00[a]	0.05[a]	6.41[a]	0.05[a]	0.004	0.66
Model 3: Excluding MCI participants,[b] adjusted for age, sex, education, ethnicity, BMI, diabetes, and mean cognition								
MeDi, per unit	4.02[a]	0.01[a]	2.32[a]	0.006[a]	1.85	0.08	0.002	0.46
MeDi, high vs low	14.87[a]	0.007[a]	6.79[a]	0.02[a]	6.87	0.07	0.005	0.63

Abbreviations: BMI = body mass index; MCI = mild cognitive impairment; mCT = mean cortical thickness; MeDi = Mediterranean diet; TBV = total brain volume; TGMV = total gray matter volume; TWMV = total white matter volume.
[a] Significant ($p < 0.05$).
[b] Excluding 159 MCI participants, 23 participants whose cognitive data were insufficient for MCI diagnosis, and 24 participants missing 1 or 2 covariates. Model based on 468 remaining participants.

Association of Mediterranean diet, fish, and meat with brain volume and cortical thickness
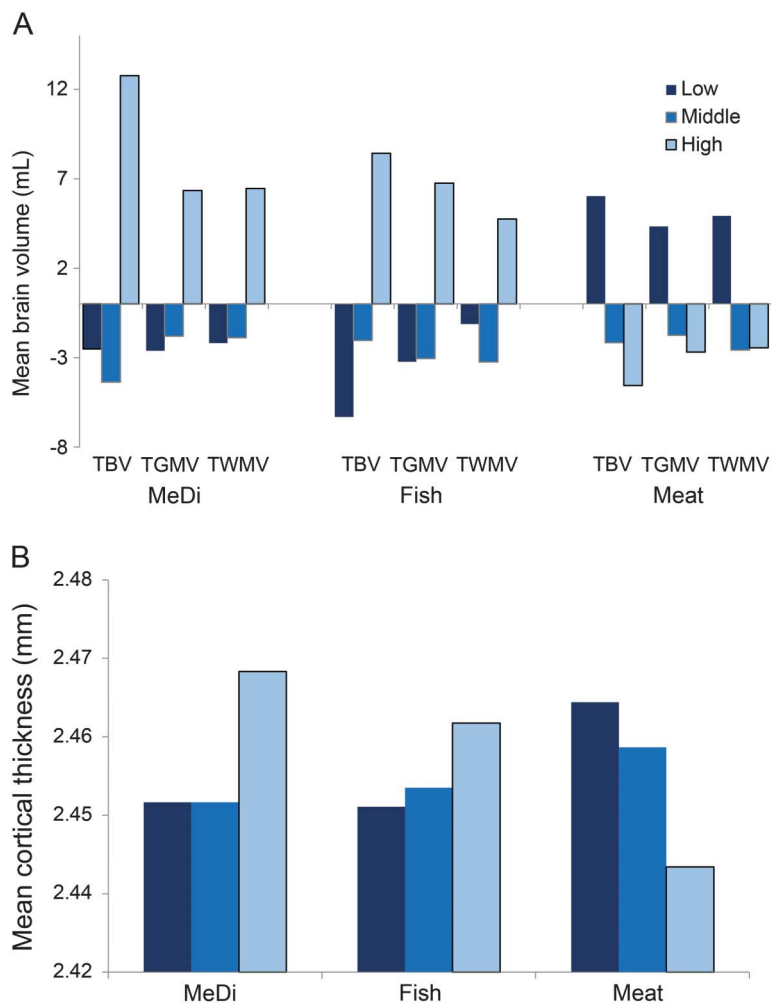
(A) Mean levels (intracranial-adjusted residuals) of total brain volume (TBV), total gray matter volume (TGMV), and total white matter volume (TWMV) among participants with low (score 0–2), middle (score 3–5), and high (score 6–9) levels of adherence to the Mediterranean diet (MeDi), among tertiles of fish consumption (caloric intake adjusted residuals), and among tertiles of meat consumption (caloric intake adjusted residuals). (B) Mean cortical thickness by levels of MeDi, fish, and meat consumption.

Including additional covariates (see Statistical analyses) did not change the results much (data not shown).

The relationships of MeDi with brain MRI measures were not significantly modified by sex, ethnicity, or *APOE* ε4 status (data not shown).

MeDi or its components remained associated with brain measures among 478 cognitively normal participants (table 2 and table e-2).

Multivariate analysis indicated marginally significant differences between MeDi groups on a linear combination of the volumes in 10 regions (Wilks λ = 0.97, $p = 0.06$), and on a linear combination of the 12 ROIs CT (Wilks λ = 0.97, $p = 0.05$). The volumes of the cingulate, parietal, temporal, and hippocampus regions (univariate p values < 0.05) contributed most to distinguish the low and high MeDi adherence. The CT in

the superior-frontal region ($p = 0.03$) contributed most to distinguish between low and high MeDi adherence. Adjusted GLM analyses confirmed these associations (table 3). Higher fish and lower meat intakes tended to be associated with these regions, except for hippocampus (table e-3, model 3). Fruit intake was associated with lower temporal and hippocampus volumes. Lower meat intake was associated with larger CT of the superior-frontal region (table e-3, model 3).

DISCUSSION In this cross-sectional study of an elderly population without dementia, we found that participants who adhered more to a MeDi had larger brain volumes, both in GM and WM. The association was driven most likely by high fish and low meat consumption. MeDi was associated with volume in cingulate cortex, parietal lobe, temporal lobe, and hippocampus, and CT of the superior-frontal region. The absolute effect of MeDi on brain measures were relatively small. However, the magnitude of the effect of consuming at least 5 recommended MeDi food components on TBV is comparable to that of 5 years of increasing age. Similarly, having fish intake of 3–5 oz at least weekly, or keeping meat intake 100 g daily or less, may also provide a considerable protection against brain atrophy that is equivalent to about 3–4 years of aging. Thus, a modifiable factor such as diet is of interest from the prevention point of view.

To our knowledge, only 2 studies have examined the relationship between MeDi and brain atrophy. In contrast to our findings, a Swedish study found no association between the MeDi score and brain volumes.[9] The Swedish population might have different dietary habits (for example, lower intake of legumes) compared to our US population. In addition, our study population is more diverse in terms of ethnicity (white, black, and Hispanic participants) and of lower education level. Nevertheless, similar to our study, the Swedish study also found a negative association between meat intake and TBV,[9] and a positive association between dietary intakes of omega-3 polyunsaturated fatty acids (ω-3 PUFA) from marine or fish sources and TGMV.[28] We found MeDi, more fish, and less meat intakes were related with larger brain volume in cingulate cortex, parietal lobe, temporal lobe, and hippocampus, partially echoing a previous study that found regular fish consumption was associated with larger GMV in the hippocampus, posterior cingulate, precuneus, and orbital frontal cortex.[29] However, null association with brain atrophy has also been reported for fish[30] or ω-3 PUFA dietary pattern.[31] Taken together, although data regarding the relationship of MeDi or its components and markers of brain atrophy are scarce and mixed, the findings from our study and some others suggested a potential beneficial role of MeDi or fish intake, and a detrimental role of meat intake.

Table 3   Cross-sectional association between Mediterranean diet and regional gray matter volume or thickness

	Cingsulate		Parietal		Temporal		Hippocampus		Superior-frontal CT	
	B	p	B	p	B	p	B	p	B	p
Model 1: Unadjusted										
MeDi per unit	0.12[a]	0.01[a]	0.43[a]	0.01[a]	0.02[a]	0.06[a]	0.03[a]	0.08[a]	0.01[a]	0.06[a]
MeDi high vs low	0.41[a]	0.01[a]	1.76[a]	0.004[a]	0.08[a]	0.04[a]	0.14[a]	0.03[a]	0.03[a]	0.01[a]
Model 2: Adjusted for age only										
MeDi per unit	0.12[a]	0.01[a]	0.45[a]	0.01[a]	0.02[a]	0.03[a]	0.04[a]	0.03[a]	0.01[a]	0.05[a]
MeDi high vs low	0.41[a]	0.01[a]	1.75[a]	0.003[a]	0.08[a]	0.03[a]	0.14[a]	0.02[a]	0.03[a]	0.01[a]
Model 3: Adjusted for age, sex, education, ethnicity, BMI, diabetes, and mean cognition										
MeDi per unit	0.10[a]	0.04[a]	0.37[a]	0.03[a]	0.02[a]	0.07[a]	0.03[a]	0.10[a]	0.01[a]	0.13[a]
MeDi high vs low	0.37[a]	0.02[a]	1.40[a]	0.02[a]	0.07[a]	0.05[a]	0.11[a]	0.08[a]	0.03[a]	0.02[a]

Abbreviations: BMI = body mass index; MeDi = Mediterranean diet.
[a] Significant ($p < 0.05$).

Only one previous study[10] examined the relationship between MeDi and cortical thickness. In this small study of 52 cognitively normal middle-aged participants, higher MeDi adherence was associated with greater thickness of 3 ROIs (orbital frontal cortex, entorhinal cortex, posterior cingulate cortex of the left hemisphere).[10] Combined with our findings, it seems that at least some of the AD-vulnerable cortical regions, especially the frontal region, are related with MeDi.

Accumulating evidence has shown that a closer adherence to the MeDi was associated with a reduced risk of developing MCI or AD.[1–5] While the mechanisms for the beneficial role of MeDi on cognitive health remain largely unknown, the current study suggests a potential pathway involving the brain structure maintenance or delaying aging-related atrophy, especially as brain atrophy has been related to cognitive decline.[32] MeDi may be related to accumulation of amyloid β[33] or phosphorylation and aggregation of tau,[34] which in turn contributes to the brain atrophy.[35] Fish contains several beneficial nutrients including ω-3 PUFA, vitamin D, and B vitamins. The beneficial effects of ω-3 PUFA on brain include increasing neurite outgrowth and synaptogenesis, neurogenesis, and anti-inflammation.[36] Vitamin D can protect against biological processes associated with AD and cognition, including amyloid-β deposition, inflammation, and calcium homeostasis,[37] and vitamin D depletion has been linked with brain atrophy.[38] Studies have shown that B vitamins, including B_6, B_{12}, and niacin, play important roles in slowing brain atrophy.[39] Meats are high in SFA and protein and are prone to advanced glycation end products (AGE) formation through high-temperature cooking. A large body of research shows that diets high in AGE may promote AD amyloid-β generation, increased tau phosphorylation, insulin resistance, and inflammation.[40]

A few limitations of the present study need to be noted. Our study is cross-sectional so we cannot exclude the possibility of reverse causality, i.e., that changes in brain structure result in behavioral changes including alterations in dietary habits. Longitudinal studies are needed to examine whether baseline MeDi adherence is associated with less brain atrophy over time. We cannot completely rule out the possibility of residual confounding. Finally, despite a relatively large overall sample size, our study might be underpowered to examine interactions and for stratified analyses in subgroups.

Our study has many strengths. Few studies exist examining the relationship between MeDi and brain structures. Our study added new evidence to this line of research by including a large sample of study participants and by examining different brain regions. Our study examined the relationship among multiple ethnic groups, including not only white but also African American and Hispanic participants, and is thus likely to be more generalizable to the increasingly diverse US population.[17] We used comprehensive cognitive assessments with full neuropsychological testing and physician evaluations administered to all participants. The final diagnoses of dementia and MCI were based on consensus diagnosis according to standard research criteria.[13–15] We excluded participants with dementia and MCI, thus reducing potential recall bias on dietary intake due to memory deficits. Several potential confounding factors have been adjusted for in the analyses. We analyzed multiple types and levels of brain measures, including volume and cortical thickness, GM and WM volumes, cortical and deep GM volumes, and finally, selected ROIs.

Overall, our study suggests that closer adherence to MeDi might be associated with larger brain volumes in elderly people, an association conceivably driven by higher fish and lower meat intake. Cingulate, parietal, and potentially temporal regions might be more relevant in terms of the association with MeDi adherence, while higher intake of fish and lower intake of meat seem to nonspecifically protect against atrophy across cortical regions.

AUTHOR CONTRIBUTIONS

Yian Gu: drafting/revising the manuscript, study concept or design, analysis or interpretation of data, accepts responsibility for conduct of research and final approval, statistical analysis, obtaining funding. Adam M. Brickman: drafting/revising the manuscript, analysis or interpretation of data, accepts responsibility for conduct of research and final approval, acquisition of data, obtaining funding. Yaakov Stern: drafting/revising the manuscript, study concept or design, analysis or interpretation of data, accepts responsibility for conduct of research and final approval, study supervision. Christian Habeck: analysis or interpretation of data, accepts responsibility for conduct of research and final approval, statistical analysis. Qolamreza Razlighi: analysis or interpretation of data, accepts responsibility for conduct of research and final approval, statistical analysis. Jose A. Luchsinger: drafting/revising the manuscript, study concept or design, accepts responsibility for conduct of research and final approval, acquisition of data, obtaining funding. Jennifer J. Manly: analysis or interpretation of data, accepts responsibility for conduct of research and final approval, acquisition of data, study supervision, obtaining funding. Nicole Schupf: drafting/revising the manuscript, accepts responsibility for conduct of research and final approval, acquisition of data, study supervision, obtaining funding. Richard Mayeux: study concept or design, accepts responsibility for conduct of research and final approval, acquisition of data, study supervision, obtaining funding. Nikolaos Scarmeas: drafting/revising the manuscript, study concept or design, analysis or interpretation of data, accepts responsibility for conduct of research and final approval, study supervision.

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