Associations of the Mediterranean diet with cognitive and neuroimaging phenotypes of dementia in healthy older adults

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ABSTRACT

Background: Accumulating evidence suggests that higher Mediterranean diet (MedDiet) adherence is associated with higher global cognitive performance and brain structural integrity as well as decreased risk of Alzheimer disease (AD) and vascular dementia (VaD).

Objectives: We directly examined cross-sectional associations between the MedDiet and cognitive and neuroimaging phenotypes associated with AD and VaD (separately) in a cohort of nondemented, nondepressed older adults.

Methods: Community-dwelling older adults ($n = 82$; aged ~68.8 y; 50% female, 50% minority) underwent dietary (Block Food Frequency Questionnaire 2005) and neuropsychological assessments and neuroimaging. MedDiet scores were quantified with the use of published criteria, and participants were divided into High and Low (median split) adherence groups. We focused our neuropsychological investigation on cognitive phenotypes primarily associated with AD [i.e., learning and memory (L&M)] and VaD (i.e., information processing and executive functioning). AD neuroimaging phenotypes consisted of hippocampal and dentate gyrus volumes quantified using T1-weighted images and the FreeSurfer 6.0 segmentation pipeline (http://surfer.nmr.mgh.harvard.edu). The VaD neuroimaging phenotype consisted of total white matter hyperintensity (WMH) volumes quantified using combined T1-weighted and T2-fluid-attenuated inversion recovery images. Neuroimaging metrics were adjusted for total intracranial volume. Separate multivariable linear regression models controlling for age, sex, education, body mass index, and caloric intake examined the associations between MedDiet groups (High compared with Low) and cognitive and neuroimaging outcomes.

Results: When compared with the Low MedDiet group, the High MedDiet group was associated with better L&M performance and larger dentate gyri. MedDiet adherence was not associated with information processing, executive functioning, or WMH.

Conclusion: Results highlight the association between increasing MedDiet adherence and specific cognitive and neuroimaging phenotypes that, when altered, are associated with AD. *Am J Clin Nutr* 2019;109:361–368.

Keywords: Mediterranean diet, cognition, aging, learning, memory, dentate gyrus, hippocampus, Alzheimer disease

Introduction

A decade of testing pharmacologic treatments for Alzheimer disease (AD) resulted in 413 failed clinical trials of 224 drugs (1). Thus, targeting modifiable risk factors for dementia prevention is increasingly important. Diet is one modifiable factor shown to improve cardiovascular and brain health in older adults potentially through improved metabolic and vascular functioning (2, 3). The Mediterranean diet (MedDiet), a diet composed of fruits, vegetables, whole grains, olive oil, fish, nuts, and legumes; limited consumption of red meat; and moderate alcohol consumption (4) has been associated with lower rates of cognitive decline and risk of dementia including AD (2). Metabolic and vascular dysfunction may contribute to the cascade of neuroanatomic events and neuropsychological sequelae of AD [e.g., relatively greater neurodegeneration involving the hippocampal complex leading to memory impairment (5, 6)] and

Supported by the following grants from the NIH: K01 AG040192 (to ML), R21 AG048176 (to ML), and 1S10RR028898 (to XJZ). AJK was additionally supported by a grant from the National Heart, Lung, and Blood Institute of the NIH (grant R01 HL129153).

Supplemental Figure 1 and Supplemental Table 1 are available from the "Supplementary data" link in the online posting of the article and from the same link in the online table of contents at https://academic.oup.com/ajcn/.

Abbreviations used: AD, Alzheimer disease; FFQ, food-frequency questionnaire; L&M, learning and memory; MCI, mild cognitive impairment; MedDiet, Mediterranean diet; mFSRP, modified Framingham Stroke Risk Profile; UIC, University of Illinois at Chicago; VaD, vascular dementia; WMH, white matter hyperintensity.

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Received April 27, 2018. Accepted for publication September 13, 2018.

First published online January 24, 2019; doi: https://doi.org/10.1093/ajcn/nqy275.

vascular dementia (VaD) [relatively greater subcortical ischemic and white matter damage contributing to slowed information processing and executive dysfunction (5, 7)].

Some but not all empirical studies of self-reported MedDiet adherence have found associations of MedDiet adherence with memory (8–11) and/or executive functioning (11, 12). Although previous empirical investigations have found greater MedDiet adherence associated with larger volumes of hippocampi (13) and associated regions (14) as well as smaller white matter hyperintensity (WMH) volumes (15), very few studies [e.g., (16)] have examined the mediating effect of neuroimaging markers on associations between the MedDiet and cognition. Furthermore, a recent systematic review (17) found evidence lacking for a significant beneficial effect of randomized controlled trials (18) of a MedDiet on brain or behavior, with the exception of one study involving older adults at high risk of cardiovascular disease and cognitive impairment living in a Mediterranean country (19). Investigating how specific brain-behavior phenotypes—for example, those generally more related to AD [learning and memory (L&M) and hippocampal and dentate gyrus volumes (5, 6, 20, 21)] and VaD [information processing, executive functioning, and WMHs (5, 7)]—associate with MedDiet adherence in healthy older adults may provide alternative avenues for targeted recruitment to improve future randomized controlled trials.

The current study examines cross-sectional associations of self-reported MedDiet adherence with cognitive and neuroimaging phenotypes relatively more reflective of early AD or VaD in a cohort of nondemented, nondepressed older adults. We hypothesized that higher MedDiet adherence would be associated with better L&M performance and larger hippocampal and dentate gyrus volumes. We further hypothesized that higher MedDiet adherence would be associated with better information processing and executive functioning performance and smaller WMH volumes. Where indicated, we investigated the mediating effects of brain structural integrity on associations between MedDiet adherence and cognition.

Methods

Participants

Participants included 121 adults aged >60 y recruited through community outreach (e.g., advertisements and fliers) and word of mouth for a larger study focused on healthy brain aging and cardiovascular disease risk factors at the Department of Psychiatry, University of Illinois at Chicago (UIC). The study was approved by the UIC Institutional Review Board as well as the Rush University Medical Center Institutional Review Board and conducted in accordance with the Declaration of Helsinki of 1975, as revised in 1983, with written informed consent obtained on all participants.

All potential participants underwent a preliminary telephone screen in their language of choice (i.e., English or Spanish). Exclusion criteria consisted of current or past history of an axis I or axis II disorder (e.g., depression or bipolar disorder), current or past history of substance (i.e., alcohol or drug) abuse or dependence, current or past history of neurological disorders [e.g., stroke, dementia including AD and/or VaD, mild cognitive impairment (MCI), seizure, etc.], a history of head injury with or without loss of consciousness, MRI contraindications (e.g., cardiac pacemaker/defibrillator, MRI-incompatible metallic implants, and claustrophobia), and/or current psychotropic medication use including antidepressants or cognition-enhancing medications. Individuals were not eligible to participate in this study if they had received cognitive testing within the past year or if they were currently involved in a study with cognitive testing. A self-reported history of stable (e.g., diabetes) or remitted (e.g., cancer) medical illness was not an exclusionary factor.

After passing the telephone screen, participants were scheduled for a more detailed in-person evaluation including cognitive and affective screens for final inclusion and exclusion determination. Participants were excluded if they scored ≤24 on the Mini-Mental State Examination (22), reported subjective memory impairments, or met the threshold for psychiatric disorders including depression as measured by the Structured Clinical Interview for the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition*, *Text Revision* (23) and/or the 17-item Hamilton Depression Rating Scale (score ≥8) (24). Screening measures were administered by a trained research assistant fluent in either English or Spanish followed by an evaluation by a board-eligible psychiatrist who administered the Hamilton Depression Rating Scale; all evaluators were blinded to telephone screen information. **Supplemental Figure 1** includes a descriptive participant flowchart of inclusion and exclusion criteria.

Age, sex, and education were documented. To assess stroke risk, a modified Framingham Stroke Risk Profile (mFSRP; age not included) was calculated using information obtained by trained staff in the Center for Clinical and Translational Science's Clinical Research Center at UIC including systolic blood pressure, hypertension medication, diabetes mellitus, current cigarette smoking, and cardiovascular disease, as well as electrocardiogram-determined atrial fibrillation and left ventricular hypertrophy (25). During a physical examination conducted by staff at the Clinical Research Center, weight and height were measured to calculate BMI and all medications including over-the-counter medications were reviewed and documented. In addition to calculating mFSRP, we determined current hypertension status (i.e., whether systolic blood pressure ≥140 mm Hg or diastolic blood pressure ≥90 mm Hg and/or antihypertensive medication use were present at the study visit) and current diabetes (i.e., whether fasting glucose ≥100 mg/dL or glycated hemoglobin ≥5.7% and/or medication use for diabetes were present at the study visit).

Dietary assessment

The Block 2005 Food Frequency Questionnaire (FFQ) was administered by trained research assistants in either Spanish or English in person or over the phone to evaluate dietary intake of ∼110 food items over the past year (26). The Block Dietary Data Systems portion guide was used to provide images of 0.25-, 0.5-, 1-, and 2-cup serving sizes. For each food item, participants were asked to estimate the frequency with which they consumed each item and the average portion size. The Block FFQ was validated against repeated 4-d diet records collected over 1 y, and the reliability of food items and nutrients ranged from 0.5 to 0.9 (27, 28).

Of the 121 participants enrolled in the original study, 89 participants completed the FFQ (all but one in English) due, in

TABLE 1 Mediterranean diet component score criteria according to frequency of self-reported consumption[1]

	Component score criteria					
Components	0 points	1 point	2 points	3 points	4 points	5 points
Nonrefined grains	0	1–6	7–12	13–18	19–31	>32
Potatoes	0	1–4	5–8	9–12	13–18	>18
Fruit	0	1–4	5–8	9–15	16–21	>22
Vegetables	0	1–6	7–12	13–20	21–32	>33
Legumes and nuts	0	<1	1–2	3–4	5–6	>6
Fish	0	<1	1–2	3–4	5–6	>6
Red meat and processed meat	>10	8–10	6–7	4–5	2–3	≤1
Poultry	>10	9–10	7–8	5–6	4–5	≤3
Full-fat dairy products	>30	29–30	21–28	16–20	11–15	≤10
Olive oil[2]	Never	Rarely	<1	1–3	3–5	≥6
Alcohol, g/d	0 or ≥84	72–83	60–71	48–59	36–47	1–35

[1]With the exception of alcohol, all consumption score criteria denote the number of servings per week. Scoring criteria were adapted from criteria used by Tangney et al. (31) and originally developed by Panagiotakos et al. (32).

[2]Olive oil is reported in number of times used in cooking per week.

part, to the late introduction of the FFQ into our study. Of the 89 participants, 4 were excluded from all analyses due to implausibly low or high daily caloric intakes (<500 or >4000 kcal for men and <400 or >3800 kcal for women) shown to suggest invalid responding and provide inaccurate and/or skewed estimates of adherence (29). Among the remaining 85 participants, none was missing FFQ data and estimated kilocalories were in the appropriate range; thus, all 85 participants' FFQs were deemed valid (30). In direct comparisons, those with ($n = 85$) and those without ($n = 36$) FFQ data did not differ on any key variable of this study including demographic characteristics and cognitive performance (data not shown).

On the basis of participants' estimated frequency of consumption, a MedDiet score was calculated using adapted criteria (31) originally developed by Panagiotakos et al. (32). Self-reported weekly-portion consumption of the 7 components indicative of the MedDiet (i.e., nonrefined grains, fruits, vegetables, potatoes, fish, legumes, and nuts) was scored using the following scale: 0 = never, 1 = rare, 2 = frequent, 3 = very frequent, 4 = weekly, and 5 = daily consumption. This scale was reversed (e.g., 5 = never, 4 = rare, etc.) for consumption of the 3 components that were counterindicative of the MedDiet (i.e., red and processed meat, poultry, full-fat dairy). Alcohol consumption was scored separately, with higher scores given for more moderate daily alcohol consumption. The total MedDiet score ranged from 0 to 55, with higher scores representing greater MedDiet adherence. **Table 1** provides component score criteria per estimated frequency of consumption; **Supplemental Table 1** provides more detailed information on the Block 2005 FFQ variables used to calculate the MedDiet adherence score.

Neuropsychological assessment of specific cognitive phenotypes

A comprehensive neuropsychological protocol was administered once by trained research assistants fluent in English or Spanish and supervised by a licensed clinical neuropsychologist (ML). Given our targeted focus on specific brain-behavior phenotypes (i.e., those related to AD and VaD), only neuropsychological tests germane to the current project were used to construct theoretically derived composites representing the following—L&M: the California Verbal Learning Test–Second Edition (33) Trials 1–5 (learning) and long-delay free recall (Cronbach's α for L&M composite = 0.92); information processing: Trail Making Tests Part A time to completion (34) and Wechsler Adult Intelligence Scale-IV (35) Digit Symbol Coding (Cronbach's $\alpha = 0.67$); executive functioning: Trail Making Test Part B time to completion minus Trail Making Test Part A time to completion (34) and the Wechsler Adult Intelligence Scale-IV Letter Number Sequencing subtest (35) total number correct (Cronbach's $\alpha = 0.74$). Scores were standardized and inverted as appropriate so that higher values indicate better cognitive performance; an average composite score for each domain (as outlined above) was created for this study. The Wechsler Test of Adult Reading (36) was also administered. Of the 85 participants with valid FFQ data, one participant completed cognitive testing in Spanish and was subsequently excluded from all cognitive analyses.

Neuroimaging protocol

Data acquisition.

Whole-brain MRI scans were acquired on a GE 3.0T whole-body scanner (MR 750 Discovery; General Electric Health Care) using an 8-channel head coil. Participants were positioned comfortably on the scanner table and fitted with soft earplugs; foam pads were used to stabilize the head and minimize movement. Participants were instructed to remain still throughout the scan, and any movement was monitored in real time through an in-bore infrared camera. For this study, we utilized data from T1- and T2-weighted images. A high-resolution 3-dimensional T1-weighted image was acquired using a Brain Volume (BRAVO) imaging sequence (field of view: 22 cm; voxel size = 0.42 × 0.42 × 1.5 mm^3; 120 contiguous axial slices; TR/TE = 1200 ms/5.3 ms; flip angle = 13°) to measure gray matter volumes. A set of 2-dimensional T2-weighted FLAIR (fluid-attenuated inversion recovery) images was acquired to quantify WMHs (field of view: 22 cm; voxel size = 0.35 × 0.35 × 3.0 mm^3; 40 contiguous axial slices; TR/TI/TE = 9500/2500/93.3 ms; flip angle = 142.35°).

The acquisition of these images was part of a larger protocol. Of the 85 participants enrolled with FFQ data, 78 participants completed the MRI protocol.

Image processing.

Visual inspection of all image data was conducted to ensure good quality and to examine incidental findings; relevant images and/or participants were excluded from all analyses ($n = 2$), leaving a total of 76 participants for MRI analyses and 82 for cognitive analyses. T1-weighted images were used to generate label maps using FreeSurfer 6.0 (http://surfer.nmr.mgh.harvard.edu/) for cortical thickness and subcortical structure volumetric segmentation. Processing included motion correction, removal of nonbrain tissue, transformation into Talairach space, registration of image to an atlas and parcellation of the cerebral cortex into 87 region of interest units based on gyral and sulcal structures and total gray matter and total white matter volumes (37–39). Furthermore, hippocampal subfield volumes were segmented automatically from the T1-weighted images using an approach based on Bayesian inference and a probabilistic atlas of the hippocampal formation ex vivo MRI data (40) and were then adjusted for FreeSurfer-generated total intracranial volume. We chose the hippocampus and the dentate gyrus (right + left) given that atrophy of these structures is associated with AD (6, 20, 21). When statistically indicated, additional analyses by hemisphere were conducted.

Described in detail elsewhere (41), WMHs for each participant were quantified by co-registering T1-weighted BRAVO to T2-weighted FLAIR data using affine registration (FLIRT, FMRIB's Linear Image Registration Tool; University of Oxford) (42). First, brain images were extracted from the combined T1- and T2-weighted image volumes (FMRIB's Brain Extraction Tool; University of Oxford) (43) followed by automated WMH segmentation using a support vector machine classifier (White Matter Lesion Segmentation, Section for Biomedical Image Analysis; University of Pennsylvania) (44). WMH volumes were adjusted for FreeSurfer-generated intracranial volume and then log transformed. We also measured whole white matter volume regardless of WMH.

Statistical approach

Given the limited variance in the overall sample's MedDiet scores (mean ± SD: 68.81 ± 6.85), we created High and Low self-reported MedDiet adherence groups based on the median split [dummy-coded high (1) and low (0)]. Differences in participant characteristics between these MedDiet groups were examined using SPSS (version 22) ANOVA for continuous variables and chi-square for categorical variables. Outcome scores that were ±3 SDs from the IQR range were winsorized (i.e., outliers were replaced with the most extreme value within the 3-SD range) to maintain our sample size while removing the potential influence of outliers. Multivariable linear regression models adjusting for age, sex, education, BMI, and estimated daily calorie intake (kilocalories) examined the association between MedDiet groups and all cognitive and neuroimaging outcomes separately. SAS University Edition was used for multivariable linear regressions, and mediation models were tested using the PROCESS macro for SAS developed by Hayes (45) using a bootstrap estimate (5000 samples) of the indirect effect of the MedDiet on cognition via brain structure variables. Data missing at random (<5%) were dropped from relevant analyses. Significance was set at $P < 0.05$, and effect sizes were calculated using the standardized mean-difference effect size (d) for standardized regression coefficients.

Results

Sample characteristics

Demographic characteristics and MedDiet and dietary component scores in the total sample ($n = 82$) as well as by group, including differences between the Low (score range: 25–33) and High (score range: 34–43) MedDiet groups, are reported in **Table 2**. Despite equal proportions of men and women in the overall sample, there was a tendency for a greater proportion of women (62%) in the High MedDiet group and a greater proportion of men (59%) in the Low MedDiet group [$\chi^2(1, n = 82) = 3.86$; $P = 0.05$, NS]. All other characteristics did not differ between groups, including stroke risk and individual cardiovascular disease risk factors (all $P \geq 0.10$).

On the basis of individual MedDiet component scores, our sample reported, on average, very frequent legume and nut intake (mean = 3.55), frequent red and processed meat intake (mean = 3.58; scale reversed), and rare intake of full-fat dairy products (mean = 4.93; scale reversed). As expected, the High MedDiet group reported greater consumption of nonrefined grains, fruits, vegetables, legumes and nuts, and olive oil than did the Low MedDiet group (all $P < 0.05$). The Low MedDiet group had a tendency to report greater red meat and processed meat consumption ($P < 0.10$). MedDiet groups did not differ in self-reported poultry, full-fat dairy product, or alcohol consumption.

Associations between self-reported MedDiet adherence groups and cognitive and neuroimaging phenotypes

Fully adjusted linear regression models controlling for age, sex, education, BMI, and estimated kilocalories found that the High MedDiet group had significantly better L&M composite scores when compared with the Low MedDiet group [$\beta = 0.52$, SE = 0.21, $t(74) = 2.53$, $P = 0.01$, $d = 1.23$]. There was no significant effect of MedDiet group on information processing [$\beta = 0.02$, SE = 0.19, $t(69) = 0.09$, $P = 0.93$, $d = 0.04$, NS] or executive functioning [$\beta = -0.02$, SE = 0.22, $t(73) = -0.09$, $P = 0.92$, $d = 0.04$, NS].

In similar adjusted linear regression models, the High MedDiet group had significantly larger dentate gyrus volumes [$\beta = 0.24$, SE = 4.74, $t(70) = 2.24$, $P = 0.03$, $d = 0.50$] when compared with the Low MedDiet group. There was a tendency toward larger hippocampal volumes in the High compared with the Low MedDiet group; however, results were not significant [$\beta = 0.18$, SE = 8.67, $t(70) = 1.82$, $P = 0.07$, $d = 0.37$, NS]. There was no significant effect of MedDiet group on log-transformed WMH volumes [$\beta = -0.04$, SE = 0.01, $t(69) = -0.39$, $P = 0.70$, $d = 0.08$, NS] or total white matter volume [$\beta = 0.01$, SE = 644.25, $t(70) = 0.12$, $P = 0.90$, $d = 0.02$, NS].

TABLE 2 Participant characteristics in the total sample and High and Low MedDiet adherence groups[1]

	Total sample ($n = 82$)	MedDiet adherence group	
		Low ($n = 39$)	High ($n = 43$)
Demographic variables			
Age, y	68.8 ± 6.88[2]	68.3 ± 7.73	69.2 ± 6.06
Female, *n* (%)	42 (50)	16 (41)†	26 (60.5)†
Black:white:Latino, *n*	39:41:2	21:16:2	18:25:0
Education (degree year)	15.4 ± 2.63	15.0 ± 2.66	15.8 ± 2.58
WTAR	106.9 ± 12.5	105.3 ± 12.0	108.3 ± 12.8
MMSE	28.6 ± 1.43	28.4 ± 1.57	28.8 ± 1.26
Beck Depression Inventory	3.09 ± 3.30	2.87 ± 3.06	3.28 ± 3.51
Beck Anxiety Inventory	2.64 ± 2.91	2.44 ± 2.68	2.83 ± 3.13
BMI, kg/m^2	28.7 ± 6.40	28.3 ± 6.79	29.2 ± 6.05
mFSRP	5.67 ± 2.94	5.82 ± 2.93	5.53 ± 2.98
Previous CVD, *n* (%)	3 (3.6)	2 (5.1)	1 (2.3)
Current smoking, *n* (%)	6 (7.3)	4 (10.3)	2 (4.7)
Current diabetes, *n* (%)	46 (56.1)	21 (53.8)	25 (58.1)
Current hypertension, *n* (%)	56 (68.3)	30 (76.9)	26 (60.5)
MedDiet and components scores			
MedDiet total score	33.31 ± 4.42	29.54 ± 2.61**	36.72 ± 2.52**
Nonrefined grains	1.81 ± 1.04	1.50 ± 0.91**	2.09 ± 1.06**
Potatoes	0.81 ± 0.71	0.67 ± 0.66†	0.93 ± 0.74†
Fruit	2.40 ± 1.25	1.79 ± 1.03**	2.95 ± 1.17**
Vegetables	2.57 ± 1.16	1.85 ± 0.87**	3.23 ± 0.97**
Legumes and nuts	3.55 ± 1.49	2.90 ± 1.49**	4.16 ± 1.21**
Fish	1.87 ± 0.83	1.69 ± 0.83†	2.02 ± 0.80†
Red meat and processed meat	3.62 ± 1.32	3.36 ± 1.51†	3.86 ± 1.08†
Poultry	4.74 ± 0.84	4.67 ± 0.93	4.81 ± 0.76
Full-fat dairy products	4.93 ± 0.38	4.87 ± 0.52	4.98 ± 0.15
Olive oil	2.07 ± 1.73	1.41 ± 1.74**	2.67 ± 1.49**
Alcohol	4.94 ± 0.36	4.87 ± 0.52	5.00 ± 0.00

[1]MedDiet scores range from 0 to 55 and component scores range from 0 to 5. One participant did not complete the Beck Anxiety Inventory. ANOVA examined differences between groups in age, education, WTAR, MMSE, Beck Depression and Anxiety Inventories, as well as BMI, mFSRP, and MedDiet total and component scores. Chi-square examined differences between groups by sex, race, previous CVD, current smoking, current hypertension, and current diabetes status. **,*,†Difference between Low and High adherence groups: $^{**}P < 0.01$, $^{*}P < 0.05$, $^{\dagger}P < 0.10$. CVD, cardiovascular disease (self-reported including history of myocardial infarction, angina pectoris, coronary insufficiency, intermittent claudication, or congestive heart failure as defined by the mFSRP); MedDiet, Mediterranean diet; mFSRP, modified Framingham Stroke Risk Profile Score (excluding age); MMSE, Mini-Mental State Examination; WTAR, Wechsler Test of Adult Reading (with scores representing estimated verbal IQ).

[2]Mean ± SD (all such values).

Potential mediating effects of brain structure on MedDiet adherence and cognitive associations

Bootstrap-estimated mediation models adjusting for age, sex, education, BMI, and estimated kilocalories showed a significant effect of MedDiet group (High compared with Low) on L&M [$\beta = 0.61$, SE = 0.22, $t(69) = 2.78$, $P = 0.007$] and a significant effect of MedDiet group on the volume of the dentate gyrus [$\beta = 10.62$, SE = 4.82, $t(69) = 2.20$, $P = 0.03$] but no significant indirect effects of MedDiet group on L&M via this same bilateral dentate gyrus volume [b = 0.004, SE = 0.06, 95% CI: −0.11, 0.15]. Because our L&M tasks were verbally mediated, we examined the left dentate gyrus in isolation; however, left lateralized analyses did not show significant indirect effects (data not shown).

Discussion

In this cross-sectional study in cognitively healthy, nondepressed older adults, we found that individuals with higher self-reported MedDiet adherence scores exhibited better L&M and larger bilateral dentate gyrus volumes after adjusting for age, sex, education, BMI, and estimated kilocalorie intake. Specifically, using a median split to define High compared with Low self-reported adherence groups, results showed medium to large effect sizes for differences in verbal list L&M as well as volumes of the dentate gyrus. This profile of associations involves brain-behavior phenotypes that, when altered, are some of the earliest indicators of AD (5, 6, 20, 21). This study did not, however, support a mediating effect of the dentate gyrus on the relation between MedDiet adherence and L&M.

Furthermore, we did not find any associations between MedDiet adherence and our targeted VaD phenotypes. Taken within the context of the larger literature, our findings confirm some (8–12, 46–48), but not all (12, 16, 18, 49, 50), previous studies suggesting an association between higher MedDiet adherence and better cognitive performance and/or brain structural integrity for markers generally more associated with early AD. They also suggest that these cognitive and neuroimaging phenotypes may be independently associated with MedDiet adherence in healthy older adults.

Underlying mechanisms to explain these associations, although beyond the scope of this cross-sectional study, may be found in the literature. It has been proposed that the MedDiet contributes to cognitive and brain health secondary to anti-inflammatory and antioxidative properties in the diet (51) that improve metabolic and vascular functioning (2, 3). In fact, previous investigations of the MedDiet show that certain foods and/or nutrients that reflect these properties may confer differential benefits on brain health (13, 19, 52, 53). For example, Gu et al. (13) found that fish intake was associated with AD-related gray matter volumes in a multiethnic cohort of older adults. Despite this, more work is needed to understand the underlying mechanisms for the synergism of dietary components and nutrients present in the MedDiet as a whole diet pattern related to brain/behavior associates reported in this and other studies of healthy aging.

Although our study may provide cross-sectional support for targeted dietary interventions to prevent Alzheimer-type dementia as opposed to other forms of dementia, associations of the MedDiet with higher information processing, executive functioning, and white matter integrity cannot be ruled out given the prevalence of mixed neuropathology in decedents with dementia (54). Despite previous null findings for these cognitive domains (8, 9, 18, 50), Pelletier et al. (16) found that MedDiet adherence was prospectively associated with preserved white matter integrity in their cohort of French older adults. Cardiovascular health (mFSRP), a major dose-dependent contributor to risk of dementia in older adults (55), did not vary between the High and Low MedDiet adherence groups. Comparable levels of relatively good heart health between these groups may intimate overall levels of good brain health (i.e., a relative lack of gross white matter tissue damage as measured by WMHs). Future work using more sensitive markers of white matter integrity such as diffusion tensor imaging may be more suitable to detect significant associations in an otherwise healthy cohort as evidenced by recent associations between higher MedDiet adherence and better diffusion tensor imaging–derived metrics of white matter integrity (16).

Mediation models showed that there was no significant indirect effect of MedDiet adherence (High compared with Low) on L&M via the dentate gyrus. This may suggest that the MedDiet's relation with L&M compared with subcortical structures underlying L&M may rely on separate mechanisms of association. Several additional reasons may exist for this lack of mediation. For example, the dentate gyrus has shown specialization for visual memory (56), an aspect of cognition not assessed in this study. In fact, neither bilateral nor left dentate gyrus volumes were associated with L&M in the current study. In addition, cross-sectional studies suggest sex differences in the associations between L&M and the hippocampal complex (57–59). Although we adjusted for sex, differences between women (represented in the High MedDiet group with greater tendency) and men (represented in the Low MedDiet group with greater tendency) may have washed out possible mediation effects in this study. Larger-scale studies are needed to investigate the possible role of sex differences in the potential mediating effects of brain structure on associations between MedDiet adherence and L&M.

This study has several strengths. We investigated the relation between self-reported MedDiet adherence and cognitive and neuroimaging phenotypes of AD as well as VaD including mediation effects in the same study. We also used stringent inclusion and exclusion criteria to ensure a nondemented, nondepressed cohort of older adults and an absence of various other potential confounders (e.g., MCI, psychotropic medication use). The cross-sectional nature of the current study, however, limits our ability to infer causality. As such, more longitudinal studies are needed to determine whether higher MedDiet adherence truly buffers against alterations in early markers of AD secondary to its association with higher integrity of cognitive (i.e., L&M) and neuroimaging (i.e., dentate gyrus volumes) phenotypes.

Despite our use of a validated FFQ administered to participants by trained research assistants, our ability to detect associations is limited. For example, reliability of the FFQ generally ranges from ∼0.60 to 0.70 in older adults (60); our study resulted in a smaller final sample size secondary to our rigorous inclusion and exclusion criteria, a smaller range in MedDiet scores (i.e., 25–43 compared with 12–45 in a comparably scored sample) (31), and a lack of sex-specific consumption cutoffs. Although our attempts to use sex-specific scoring systems led to data overly influenced by estimated energy intake, any of these issues may have contributed to an underestimation of the effect of the MedDiet. A possible limitation in our ability to detect associations between MedDiet adherence and neuroimaging outcomes may have been a lack of power given the relatively small effect size shown for the trending effect of High compared with Low MedDiet adherence on total hippocampal volume. Although we excluded individuals with MCI or dementia, there is the potential that worse memory influences one's ability to accurately self-report one's diet, and self-report, regardless of memory problems, has its own inherent biases; however, the average composite *z* score for the majority of individuals in this study fell within 1 SD of the mean, suggesting memory within the normal range. As with all studies, measuring all possible confounders [e.g., apolipoprotein E (*APOE*) genotype] was not possible. Last, although this study was focused on the cognitive phenotypes primarily associated with AD (i.e., L&M) and VaD (i.e., information processing and executive functioning), consideration of other cognitive domains (e.g., visuospatial ability) would have broadened the scope of this work.

In sum, this study contributes to the literature on MedDiet and cognitive and neuroimaging phenotypes negatively associated with AD in otherwise healthy older adults. The MedDiet is rich in nutrients with antioxidative and anti-inflammatory properties that may increase metabolic and/or vascular functioning (2, 3, 51) and ultimately protect against neurodegenerative processes associated with AD (6). Together with other studies in healthy older adults, this work provides support for increased intervention efforts to bolster cognitive reserve in older adults with specific L&M problems using dietary interventions as well as through

public health efforts including national food policies and guidelines or food subsidy programs.

The authors' responsibilities were as follows—AJK, JC, CD, and ML: contributed to data collection; AJK, LZ, NR, XJZ, and ML: contributed to data processing; LZ, NR, XJZ, and ML: were involved in programming; AJK, LT-H, and ML: designed the proposed study; AJK and ML: wrote the manuscript. LT-H: provided critical revisions; AK and ML: were responsible for final content; and all authors: read and approved the final manuscript. The authors had no conflicts of interest to disclose.

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