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Measures of MRI Brain Biomarkers in Middle Age According to Average Modified Mediterranean Diet Scores Throughout Young and Middle Adulthood

Zeinah Al-darsani[a], David R. Jacobs, Jr.[b], R. Nick Bryan[c], Lenore J. Launer[d], Lyn M. Steffen[b], Kristine Yaffe[e], James M. Shikany[f] and Andrew O. Odegaard[a,*]

[a]*Department of Epidemiology and Biostatistics, University of California, Irvine, Irvine, CA, USA*
[b]*Division of Epidemiology and Community Health, University of Minnesota School of Public Health, Minneapolis, MN, USA*
[c]*Department of Radiology, University of Pennsylvania, Philadelphia, PA, USA*
[d]*Laboratory of Epidemiology and Population Sciences, National Institute on Aging, Baltimore, MD, USA*
[e]*Department of Psychiatry, Neurology, and Epidemiology and Biostatistics, University of California, San Francisco, USA*
[f]*Division of Preventive Medicine, School of Medicine, University of Alabama at Birmingham, Birmingham, AL, USA*

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Abstract.
BACKGROUND: The Mediterranean diet (MedDiet) has been linked with better cognitive function and brain integrity.
OBJECTIVE: To examine the association of modified Mediterranean diet (mMedDiet) scores from early through middle adulthood in relation to volumetric and microstructural midlife MRI brain measures. Assess the association of mMedDiet and brain measures with four cognitive domains. If variables are correlated, determine if brain measures mediate the relationship between mMedDiet and cognition.
METHODS: 618 participants (mean age 25.4 ± 3.5 at year 0) of the Coronary Artery Risk Development in Young Adults (CARDIA) study were included. Cumulative average mMedDiet scores were calculated by averaging scores from years 0, 7, and 20. MRI scans were obtained at years 25 and 30. General linear models were used to examine the association between mMedDiet and brain measures.
RESULTS: Higher cumulative average mMedDiet scores were associated with better microstructural white matter (WM) integrity measured by fractional anisotropy (FA) at years 25 and 30 (all $p_{trend} < 0.05$). Higher mMedDiet scores at year 7 were associated with higher WM FA at year 25 ($\beta = 0.003$, $p_{trend} = 0.03$). Higher mMedDiet scores at year 20 associated with higher WM FA at years 25 ($\beta = 0.0005$, $p_{trend} = 0.002$) and 30 ($\beta = 0.0003$, $p_{trend} = 0.02$). mMedDiet scores were not associated with brain volumes. Higher mMedDiet scores and WM FA were both correlated with better executive function, processing speed, and global cognition (all $p_{trend} < 0.05$). WM FA did not mediate the association between mMedDiet scores and cognition.
CONCLUSIONS: mMedDiet scores may be associated with microstructural WM integrity at midlife.

Keywords: Mediterranean diet, MRI, biomarkers, cognition, midlife, life course

*Corresponding author: Dr. Andrew O. Odegaard, Department of Epidemiology and Biostatistics, University of California, Irvine, Irvine CA 92617-3957, USA. E-mail: aodegaar@hs.uci.edu.

1. Introduction

Given that available pharmacological treatments are ineffective in halting the progression of cognitive impairment [1], targeting modifiable risk factors remains the most effective means for preserving cognitive function. Procuring an understanding of how modifiable risk factors relate to underlying brain pathologies through neuroimaging studies is critical in order to pave the way for novel preventive measures. Furthermore, it is important to investigate life-course trajectories of risk factors in relation to biomarkers of cognitive impairment in order to identify the optimal time point for prevention [2]. Brain changes that underlie cognitive impairment begin decades before manifestation of symptoms [3]. In fact, evidence suggests that structural brain deficits can manifest as soon as early adulthood [4].

The extant literature supports the hypothesis that the Mediterranean diet (MedDiet), which is characterized by consumption of fish, unsaturated fats, whole grains, fruits and vegetables, nuts and legumes [5], and the key component being olive oil, may have neuroprotective properties [6–8]. Magnetic resonance imaging (MRI) studies have elucidated several brain measures that may be associated with the MedDiet. Several MRI studies done in older adults have found that higher MedDiet scores were associated with preserved volumetric brain measures including white matter volume [9], lower white matter hyperintensities [10], larger medial temporal gray matter volume [11], and larger cortical thickness [12]. One study concluded that the MedDiet was solely associated with white matter structural connectivity, not volumes [13] Additionally, another study conducted on older adults found no correlation between MedDiet scores and brain volumes [14]. Since brain structural changes occur well before old age, investigations of MedDiet in relation to brain MRI measures in midlife are important for identifying critical exposure and outcome windows. The few studies that have investigated the relationship between the MedDiet and brain measures in midlife have produced conflicting results. Two studies reported no association between the MedDiet and midlife brain structures [15, 16], whereas two other studies demonstrated links between higher MedDiet scores and larger midlife gray matter volumes in AD brain regions [17] and cortical thickness [18]. However, these studies only included diet scores from one time point, and therefore did not capture long-term dietary patterns. Furthermore, previous midlife brain MRI studies have not included dietary intake from early adulthood. This warrants further investigation in light of studies that have demonstrated detrimental effects of vascular risk factors during early adulthood on future brain pathologies [19, 20].

To that end, the present study aims to investigate the association between the cumulative average of a modified MedDiet (mMedDiet) pattern score from early through middle adulthood and MRI-based measures of brain volume and microstructural white matter integrity indexed by fractional anisotropy obtained at 25 and 30 years of follow up in participants of the Coronary Artery Risk Development in Young Adults (CARDIA) brain MRI sub study. This study also aims to explore the association between mMedDiet scores at individual timepoints and brain measures at years 25 and 30. A prior CARDIA investigation [21] along with other previous studies have shown associations between higher MedDiet scores and better cognitive function [22–26]. Therefore, this study's third aim is to assess statistical mediation of brain measures on the relationship between cumulative average mMedDiet scores and cognition. We hypothesize that higher mMedDiet scores are associated with preserved brain volumes and microstructural white matter integrity, and that brain measures mediate the association between mMedDiet scores and cognition.

2. Materials and methods

2.1. Study design

The CARDIA study is a prospective cohort study of cardiovascular health in 5,115 Black and White adults from four US metropolitan areas: Birmingham, Alabama; Chicago, Illinois; Minneapolis, Minnesota, and Oakland, California. Participants were healthy young adults aged 18 to 30 years old at year 0 in 1985–1986 [27]. Participants were followed up at eight time points over the course of 30 years: 1987 to 1988 (year 2), 1990 to 1991 (year 5), 1992 to 1993 (year 7), 1995 to 1996 (year 10), 2000 to 2001 (year 15), 2005 to 2006 (year 20), 2010 to 2011 (year 25), and 2015 to 2016 (year 30) [26]. A subset of participants partook in the brain MRI sub study at year 25, year 30, or both [28].

2.2. Standard protocol approvals, registrations, and participant consents

The study was approved by institutional review boards for the protection of human participants for the CARDIA study sites, and written informed consent was obtained from all participants at each examination.

2.3. Dietary assessment and dietary pattern scores

Dietary intake was assessed at years 0, 7, and 20 through an interviewer-administered, structured 100-question diet history [29]. Participants were asked open-ended questions about specific foods and beverages consumed in each of the 100 food categories and beverage questions [29]. Food and beverages were categorized into 166 subgroups according to the food grouping system in the Nutrition Data System for Research (NDSR) developed by the University of Minnesota Nutrition Coordinating Center (NCC) [29]. Reported servings for each item were converted to standard serving in accordance with the US Department of Agriculture recommendations. Individual food group intake was calculated as the total number of standard servings reported per day of each food within a given food group [29].

The modified Mediterranean Diet (mMedDiet) score (range 0–55) was calculated from 11 food items as previously done [21, 30]. Non-refined grains, fruits, vegetables, potatoes, legumes, fish, alcohol, and the ratio of monounsaturated to saturated fatty acids were scored on a scale from 0–5, with a higher score indicating higher adherence to the Mediterranean diet. Red meat, poultry, and full-fat dairy were scored on a reverse scale. Consumption of non-refined grains, fruits, vegetables, legumes, fish, poultry, red meat, and full fat dairy was categorized into sextiles using PROC Rank in SAS. A ratio ≥ 2 of monounsaturated to saturated fatty acids was assigned a score of 5. Alcohol was scored as 0 for non-consumption or for consumption greater 50 grams for men and 25 grams for women [31]. A score of 5 was assigned for alcohol consumption of 10–50 grams for men and 5–25 grams for women [31].

2.4. Brain MRI methods

Brain MRI was obtained from 893 participants, of which 231 had data from year 25 only, 174 at year 30 only, and 488 at both time points [28]. Exclusion criteria for sample selection included contraindication to MRI, possible pregnancy, or a body size that was too large for the MRI tube bore. Participants of the MRI sub study were more likely to be White, older, and more educated; less likely to be current smokers, have hypertension, and have a history of cardiovascular disease; and had lower BMIs and higher mMedDiet scores (See Supplemental Table 1).

MRI acquisition and processing have been described in detail previously [32, 33]. Brain MRI were acquired on 3-T MR scanners located proximal to each CARDIA clinic site (UCB: Siemens 3T Tim Trio/VB 15 platform; UMN: Siemens 3T Tim Trio/VB 15 platform and UAB: Philips 3T Achieva/2.6.3.6 platform). The MRI Reading Center (RC), located at the University of Pennsylvania, worked in collaboration with the MRI field centers to train technologists to standardized protocols, and transfer MRI data to a central archive located at the MRI RC. To evaluate scanner stability and image distortion prior to site acceptance and quarterly thereafter, each MRI field center followed standard quality assurance protocols developed for the Functional Bioinformatics Research Network (FBIRN), and the Alzheimer's disease Neuroimaging Initiative (ADNI). The following established quality assurance acceptance thresholds were used: FBIRN—Siemens scanners SFNR > 220, RDC > 3.1, Philips scanners SFNR > 220, RDC > 2.4; ADNI—SNR>300, Maximum Distortion > 2.0. Performance across the scanners was acceptable for all sequences of interest.

Image processing was performed by the Section of Biomedical Image Analysis, Department of Radiology, University of Pennsylvania. Before starting the processing pipeline, an initial QC protocol identified any motion artifacts or any other quality issues; images that failed this QC test were flagged for inspection. After this QC procedure, the scans were processed through an automated pipeline. Quality checks were performed on intermediate and final processing steps by visual inspection and by identifying outliers of calculated variable or parameter distributions.

Parameters of interest were estimated as follows: From the sagittal 3D T1 sequence, we estimated total intracranial volume (TICV), (a measure of head size) as the sum of grey matter (GM), white matter (WM), and cerebral spinal fluid (CSF) volumes, and total brain tissue volume (TBV) as the sum of GM and WM volumes). We estimated abnormal white matter (AWM) tissue from the sagittal 3D FLAIR sequences.

Structural MRI, processed using previously described methods [34–37], were based on an automated multispectral computer algorithm that classifies all supratentorial brain tissue into GM, WM, and CSF. GM and WM were further characterized as normal and abnormal and then into specific regions of interest (98 in the normal tissue and 94 in the abnormal tissue). Abnormal WM includes tissue damage due to ischemia, demyelination and inflammation, as well as the damaged penumbra tissue surrounding focal infarcts. Since the amount of abnormal GM was very low (average: 0.17–0.35 cc., median: 0.1 cc.), we do not report these data separately. The following volumetric-based brain measures were studied: total brain, total GM, WM, AWM, entorhinal area, amygdala, hippocampus, posterior cingulate gyrus, and precuneus volumes. These brain regions have been linked with cognitive function in the literature [30, 31]. In the current study, brain volumes were expressed as the percent of TICV. AWM was log transformed to normalize skewness.

Brain microstructural tissue integrity was estimated from axial Diffusion Tensor Images (DTI). DTI is a MRI technique that provides information about the diffusion of water molecules in brain tissue. In DTI, magnetic field gradients are applied to the tissue, causing water molecules to diffuse along the direction of the gradient. By measuring the magnitude and direction of this diffusion, DTI can provide information about the orientation and integrity of white matter tracts in the brain [38, 39]. Fractional anisotropy (FA) is a metric derived from DTI that provides information about the directionality or anisotropy of water diffusion in tissues. Here we report on total white matter FA, which estimates the degree or uniformity to which water diffuses along the direction of myelinated tracks in the white matter [40]. FA scores range from 0 (indicating isotropic diffusion, where water diffuses equally in all directions) to 1 ((indicating highly anisotropic diffusion, where water diffuses predominantly along a single direction) with lower scores indicating worse white matter integrity. Higher WM FA values indicate greater directionality and organization of axonal fibers [41]. Studies have shown that (WM FA) decreases with age [42, 43].

2.5. Cognitive measures

Cognitive function was assessed at year 30 using four cognitive tests. (1) Rey Auditory Verbal Learning Test (RAVLT) assessed verbal learning and memory; the number of words correctly recalled after a 10-minute delay was used in the current analyses (range 0–15), with higher scores indicating better performance [44]. (2) Digit Symbol Substitution Test (DSST) assessed processing speed and executive function (range 0–133), with higher scores for digits correctly substituted indicating better performance [45]. (3) The Stroop Test evaluated executive function by assessing the ability to view complex visual stimuli and to respond to one dimension while suppressing the response to another dimension [46]. The test was scored by the time to correctly state ink color (e.g., yellow) of color words (e.g., the word blue) plus number of errors; thus, a higher score (seconds plus errors) indicated worse performance [47]. (4) The Montreal Cognitive Assessment (MoCA) assessed global cognitive function with components of attention, executive function, memory, language, visuospatial skills, calculations, and orientation [46]. Scores range from 0 to 30, with higher scores indicating better global cognitive function.

2.6. Covariates

Demographic variables, including age, race (Black or White), sex (male or female), education attainment (high school or less and greater than high school), caloric intake (Kcal), and CARDIA center, were obtained by self and interview administered questionnaires. Lifestyle factors included physical activity intensity and smoking status (current, former, never). Physical activity intensity, expressed in exercise units, was derived from 13 moderate and vigorous intensity exercises reported as part of the CARDIA physical activity questionnaire [48]. The algorithm used to calculate physical activity intensity was described previously [49]. Smoking status was self-reported. Vascular and metabolic comorbidities included body mass index (kg/m^2), binary classifications of diabetes, hypertension, and cardiovascular disease history. BMI was derived from weight and height measured in the clinic during visits. Diabetes diagnosis was defined as fasting glucose concentration $\geq$ 126, mg/dL which was assessed from blood samples, or self-reported intake of antidiabetic medication [50]. Hypertension was defined as systolic blood pressure $\geq$ 130 mm Hg or diastolic pressure $\geq$ 80 mm Hg, in accordance with AHA/ACC guidelines [51]. Three blood pressure measurements were obtained by a trained technician using a standard automated BP measurement monitor (model

HEM907XL; Omron, Bannockburn, Illinois) after a 5-minute seated rest; the averages of the last two measurements were used in analyses [40]. CVD was ascertained by interviews and included fatal or non-fatal coronary heart disease (myocardial infarction or non–myocardial infarction acute coronary syndrome), congestive heart failure, and stroke [52].

2.7. Analytic sample

The final analytic sample consisted of 618 participants of the CARDIA MRI sub study (see Supplemental Figure 1). Participants were excluded from the current analysis due to the following reasons: poor imaging quality ($N = 26$), missing dietary intake at year 20 ($N = 170$), implausible energy intake at year 0, 7, and 20 (<800 and > 8,000 kcal/day for men and < 600 and > 6,000 kcal/day for women; $N = 75$), and missing hypertension diagnosis at year 25 ($N = 4$). Out of the 618 participants included in the current analysis, 497 had MRI data from year 25, and 469 had MRI data from year 30, of which 348 had MRI data from both time points. The 618 participants included in the final analytic sample had mMedDiet scores from all three time points.

2.8. Statistical analysis

Cumulative average mMedDiet scores were calculated by taking the mean of scores from year 0, year 7, and year 20. Differences between cumulative average mMedDiet tertiles were assessed by ANOVA for continuous variables and chi-square tests for categorical variables. mMedDiet scores were analyzed as tertiles in relation to brain measures in order to assess a dose response relationship and were presented as least square means and standard errors. General linear models were used to examine the association between mMedDiet scores and brain measures. Models were adjusted for age, sex, race, education, energy intake (Kcal/day), field center, physical activity intensity, smoking status, CVD history, diabetes, BMI, and hypertension. Age, race, sex, and field center were used from year 0. The last non-missing values across years 0, 7, and 20 were used for education attainment and smoking status. BMI, physical activity intensity, and caloric intake were averaged from years 0, 7, and 20. Diabetes, hypertension, and CVD history were obtained from year 25.

mMedDiet scores from individual timepoints were analyzed separately in relation to brain measures using general linear models. The goal of this analysis was to determine if the association between mMedDiet and brain measures differed depending on the time of exposure. This analysis was restricted to individuals with complete covariate information from years 0, 7, and 20. The following covariates were used from the timepoint corresponding with mMEDdiet scores: age, education, energy intake, smoking status, physical activity, and BMI. For example, the aforementioned covariates were taken from year 7 when examining mMEDdiet scores from year 7 in relation to brain measures.

Pearson correlations were used to test the associations of cumulative average mMedDiet scores and year 25 brain measures with cognitive test scores at year 30. Statistical mediation was assessed if i) mMedDiet scores were associated with year 30 cognitive test scores, ii) mMedDiet scores were associated with year 25 brain measures in the main analysis using general linear models, and iii) year 25 brain measures were associated with year 30 cognitive test scores. Mediation analyses were conducted using the CAUSALMED procedure in SAS.

All statistical analyses were performed using SAS software version 9.4 for Windows (SAS Institute Inc., Cary, NC)

3. Results

3.1. Participants characteristics

The study consisted of 618 individuals, with a mean (±standard deviation) age of 25.4 ± 3.5 years at year 0 (see Table 1). Of the 618 participants, 56.8% of were female, 61.8 % White, 17.6 % current smokers, and 68.0% had completed education beyond high school. The prevalence of hypertension at year 25 was 23.9%, 1.6 % for CVD, and 10.7% for diabetes. For the entire sample, the mean (SD) mMedDiet score was 28.3 (4.67), while the mean (SD) mMedDiet scores for the low, mid, and high mMedDiet tertiles were 23.1 (2.58), 28.2 (1.03), and 33.1 (2.52), respectively.

As shown in Table 1, participants in the highest cumulative average mMedDiet tertile were more likely to be older, White, physically active, and have completed more than high school degree (all p_{trend} >0.05). Participants in the highest cumulative average mMedDiet tertile were also less likely to be current smokers, have hypertension, and had lower BMIs (all p_{trend} >0.05).

Table 1
Cohort characteristics by tertile of cumulative average mMedDiet scores ($N = 618$)

Characteristics	Low ($N = 201$)	Mid ($N = 193$)	High ($N = 223$)	Total ($N = 618$)	*P* value
Demographic Characteristics					
Age at Year 0					
Mean (SD)	24.5 (3.57)	25.5 (3.72)	26.3 (3.01)	25.4 (3.51)	<0.001
Sex					
Male, N (%)	90 (44.6)	78 (40.4)	99 (44.4)	267 (43.2)	0.64
Female, *N* (%)	112 (55.5)	115 (59.6)	124 (55.6)	351 (56.8)	
Race					
Black, *N* (%)	115 (56.9)	072 (37.3)	049 (22.0)	236 (38.2)	<0.001
White, *N* (%)	087 (43.1)	121 (62.7)	174 (78.0)	382 (61.8)	
MRI					
Year 25 Only, *N* (%)	58 (28.7)	46 (23.8)	45 (20.2)	149 (24.1)	0.10
Year 30 Only, *N* (%)	45 (22.3)	37 (19.2)	39 (17.5)	121 (19.6)	
Years 25 and 30, *N* (%)	99 (49.0)	110 (57.0)	139 (62.3)	348 (56.3)	
Education (Cumulative)					
High School≥, *N* (%)	97 (48.0)	61 (31.61)	40 (17.9)	198 (32.0)	<0.001
>High School, *N* (%)	105 (52.0)	132 (68.4)	183 (82.1)	420 (68.0)	
Clinical Measures					
Hypertension (Year 25)					
Yes, *N* (%)	61 (30.2)	52 (26.9)	35 (15.7)	148 (23.9)	<0.001
Cardiovascular Disease (Year 25)					
Yes, *N* (%)	4 (2.00)	2 (1.00)	4 (1.79)	10 (1.62)	0.79
Diabetes (Year 25)					
Yes, *N* (%)	31 (15.4)	18 (9.33)	17 (7.62)	66 (10.7)	0.028
BMI (Cumulative)					
Mean (SD)	27.0 (4.90)	26.1 (4.52)	25.0 (4.31)	26.0 (4.64)	<0.001
Behavior					
Physical Activity Intensity (Cumulative)					
Mean (SD)	299 (208)	350 (208)	442 (226)	367 (223)	<0.001
Smoking Status (Cumulative)					
Never, *N* (%)	121 (59.9)	127 (65.8)	133 (59.6)	381 (61.7)	<0.001
Past, *N* (%)	028 (13.9)	039 (20.2)	061 (27.4)	128 (20.7)	
Current, *N* (%)	053 (26.2)	027 (14.0)	029 (13.0)	109 (17.6)	
Total mMedDiet Score					
Mean (SD)	23.1 (2.58)	28.2 (1.03)	33.1 (2.52)	28.3 (4.67)	<0.001

As Supplemental Table 2 shows, fish, fruit, legume, monounsaturated fat to saturated fat ratio, potato, vegetable, and whole grain consumption increased linearly across mMedDiet tertiles (all $p_{trend} > 0.05$). Dairy and red meat consumption decreased linearly across mMedDiet tertiles (all $p_{trend} > 0.05$). Alcohol consumption was also most optimal in participants in the highest mMedDiet tertile (all $p_{trend} > 0.05$). Poultry consumption and energy intake did not differ across mMedDiet tertiles.

3.2. Cumulative average mMedDiet scores and brain measures in midlife

The analysis of cumulative average mMedDiet scores and brain measures included a total of 618 participants. For the year 25 analyses, 497 participants were included, except for AWM ($N = 492$) and WM FA ($N = 463$). For the year 30 analysis, 469 participants were included, except for AWM ($N = 474$) and WM FA ($N = 344$). Cumulative average mMedDiet scores were not associated with brain volumes at either year 25 or 30 (see Table 2). Higher cumulative average mMedDiet scores were associated with higher values of WM FA at years 25 ($p_{trend} = 0.01$) and 30 ($p_{trend} = 0.04$).

3.3. mMedDiet scores at different time points and brain measures in midlife

577 participants had mMedDiet scores and complete covariate information from years 0, 7, and

Table 2
Association (Least Square Means (SE)) of cumulative average MedDiet scores with brain volumes (MRI) at Year 25 and Year 30 ($N = 618$)

Brain volumes	Low mMedDiet	Mid mMedDiet	High mMedDiet	*P*-value
Year 25 ($N = 497$)	($N = 157$)	($N = 156$)	($N = 184$)	–
TBV	84.9 (0.22)	85.2 (0.21)	85.4 (0.21)	0.44
GM	46.6 (0.18)	46.8 (0.16)	47.1 (0.16)	0.27
WM	38.3 (0.14)	38.3 (0.13)	38.3 (0.13)	0.99
AWM[a]	0.02 (0.001)	0.02 (0.001)	0.02 (0.001)	0.33
Amygdala	0.17 (0.001)	0.16 (0.001)	0.16 (0.001)	0.70
Entorhinal Area	0.33 (0.003)	0.33 (0.003)	0.33 (0.003)	0.62
Hippocampus	0.56 (0.004)	0.56 (0.004)	0.56 (0.004)	0.84
Posterior Cingulate Gyrus	0.56 (0.004)	0.55 (0.004)	0.56 (0.004)	0.79
Precuneus	1.53 (0.01)	1.53 (0.01)	1.54 (0.01)	0.81
WM FA[b]	0.31 (0.002)	0.31 (0.001)	0.32 (0.002)	**0.01**
Year 30 ($N = 469$)	($N = 144$)	($N = 147$)	($N = 178$)	–
TBV	83.6 (0.24)	83.6 (0.22)	84.0 (0.22)	0.45
GM	45.6 (0.20)	45.7 (0.18)	46.0 (0.18)	0.37
WM	38.1 (0.14)	37.9 (0.13)	38.0 (0.13)	0.81
AWM[c]	0.05 (0.01)	0.06 (0.01)	0.05 (0.01)	0.64
Amygdala	0.16 (0.001)	0.16 (0.001)	0.16 (0.001)	0.33
Entorhinal Area	0.34 (0.003)	0.33 (0.003)	0.34 (0.003)	0.18
Hippocampus	0.55 (0.004)	0.55 (0.004)	0.55 (0.004)	0.79
Posterior Cingulate Gyrus	0.54 (0.004)	0.54 (0.004)	0.54 (0.004)	0.87
Precuneus	1.48 (0.01)	1.50 (0.01)	1.51 (0.01)	0.25
WM FA[d]	0.29 (0.002)	0.29 (0.002)	0.30 (0.001)	**0.04**

Adjusted for: Age, sex, race, education, energy intake, field center, physical activity intensity, smoking status, BMI, diabetes, hypertension, and CVD. Bold *P*-value indicates statistical significance. [a]$N = 492$, [b]$N = 463$, [c]$N = 474$, [d]$N = 334$.

20. For the year 25 analyses, 465 participants were included, except for AWM ($N = 460$) and WM FA ($N = 442$). For the year 30 analyses, 443 participants were included, except for AWM ($N = 437$) and WM FA ($N = 316$). Higher mMedDiet scores at year 0 were associated with smaller hippocampal volume ($\beta = -0.001$, $p_{trend} = 0.04$) at year 25 and larger posterior cingulate gyrus at year 30 ($\beta = 0.001$, $p_{trend} = 0.01$) volumes. Higher mMedDiet scores at year 7 were associated with higher WM FA at year 25 ($\beta = 0.003$, $p_{trend} = 0.03$). Higher mMedDiet scores at year 20 associated with higher WM FA at year 25 ($\beta = 0.0005$, $p_{trend} = 0.002$) and 30 ($\beta = 0.0003$, $p_{trend} = 0.02$). These results are summarized in Table 3.

3.4. Correlations of MedDiet and Brain Measures with Cognition and Mediation Analysis

A total of 435 participants who had mMedDiet data and MRI data from year 25 had completed all four cognitive tests at Year 30. Bivariate correlation analyses were conducted for 435 participants, with the exception of AWM ($N = 430$) and WM FA ($N = 413$).Bivariate correlation analyses demonstrated that higher cumulative average mMedDiet scores were correlated with better performance on all four cognitive tests (all $p_{trend} > 0.001$; see Table 4). Larger total brain ($r = 0.123$, $p_{trend} = 0.01$) and GM volumes ($r = 0.104$, $p_{trend} = 0.03$) were correlated with better performance on the DSST exam. Higher WM FA was correlated with better performance the DSST ($r = 0.128$, $p_{trend} = 0.01$), MOCA ($r = 0.097$, $p_{trend} = 0.05$), and Stroop ($r = -0.115$, $p_{trend} = 0.02$). WM FA was the only brain measure associated with both the mMedDiet scores and cognitive tests; therefore, mediation analyses were carried out for DSST, MOCA, and Stroop exams for 413 participants. WM FA did not statistically mediate the relationship between cumulative average mMedDiet scores and cognitive test performance (see Table 5).

4. Discussion

This study investigated mMedDiet scores from early through middle adulthood in relation to midlife structural brain MRI measures obtained at the 25th and 30th years of follow up. Higher cumulative average mMedDiet scores were associated with microstructural white matter integrity, assessed by

Table 3
Association (β (SE)) of mMedDiet scores at individual time points with brain volumes (MRI) at Year 25 and Year 30 ($N = 577$)

Brain volumes	Year 0	Year 7	Year 20
Year 25 ($N = 465$)			
TBV	–0.02 (0.02)	–0.02 (0.02)	0.02 (0.02)
GM	–0.02 (0.02)	–0.01 (0.02)	0.03 (0.02)$^{+}$
WM	0.001 (0.01)	–0.01 (0.01)	–0.01 (0.01)
AWM[a]	–0.0001 (0.0001)	–0.0001 (0.0001)	–0.0001 (0.0001)
Amygdala	–0.0002 (0.0001)$^{+}$	–0.0001 (0.0001)	0.00002 (0.0001)
Entorhinal Area	–0.0001 (0.0003)	–0.0002 (0.0003)	0.0001 (0.0003)
Hippocampus	–0.001 (0.0004)*	–0.001 (0.0004)$^{+}$	–0.0002 (0.0004)
Posterior Cingulate Gyrus	0.0003 (0.0004)	–0.001 (0.0004)	–0.0003 (0.0004)
Precuneus	–0.002 (0.001)$^{+}$	–0.002 (0.001)	0.001 (0.001)
WM FA[b]	0.0003 (0.0002)$^{+}$	0.0003 (0.0002)*	0.0005 (0.0002)**
Year 30 ($N = 443$)			
TBV	0.02 (0.02)	–0.001 (0.02)	0.004 (0.02)
GM	0.02 (0.02)	–0.0001 (0.02)	0.02 (0.02)
WM	–0.001 (0.01)	–0.001 (0.01)	–0.02 (0.01)
AWM[c]	0.001 (0.001)	–0.001 (0.001)$^{+}$	–0.001 (0.001)
Amygdala	0.0001 (0.0001)	–0.00001 (0.0001)	–0.00002 (0.0001)
Entorhinal Area	0.001 (0.0003)	0.0001 (0.0003)	–0.0002 (0.0003)
Hippocampus	–0.00004 (0.0004)	–0.0002 (0.0004)	–0.0005 (0.0004)
Posterior Cingulate Gyrus	0.001 (0.0005)*	–0.0001 (0.0005)	–0.0004 (0.0005)
Precuneus	0.002 (0.001)	0.0001 (0.001)	0.001 (0.001)
WM FA[d]	0.0002 (0.0002)	0.0003 (0.0001)$^{+}$	0.0003 (0.0001)*

Adjusted for: Age, sex, race, education, energy intake, field center, physical activity intensity, smoking status, BMI, diabetes, hypertension, and CVD. [a]$N = 460$, [b]$N = 442$, [c]$N = 437$, [d]$N = 316$. $+P$ values less than 0.10. $*P$ value less than 0.05. $**P$ value less than 0.01. $***P$ value less than 0.001.

Table 4
Bivariate Correlations of Cumulative Average mMedDiet Score and Year 25 Brain Measures with Year 30 Cognitive Test Scores ($N = 435$)

Brain Measures	DSST	MoCA	RAVLT	Stroop
Cumulative Average mMedDiet	0.205***	0.226***	0.190***	–0.246***
TBV	0.132*	0.035	–0.007	–0.030
GM	0.105*	0.017	0.009	0.004
WM	0.083^{+}	0.036	–0.025	–0.056
AWM[a]	0.038	–0.074	–0.033	0.048
Amygdala	–0.0003	–0.008	–0.038	–0.057
Entorhinal Area	0.012	0.065	0.037	–0.054
Hippocampus	0.083	0.001	0.007	0.053
Posterior Cingulate Gyrus	–0.018	–0.049	–0.044	0.017
Precuneus	0.085^{+}	0.102*	0.028	–0.056
WM FA[b]	0.128*	0.097*	0.067	–0.115*

[a]$N = 430$, [b]$N = 413$. ^{+}P values less than 0.10. $*P$ value less than 0.05. $**P$ value less than 0.01. $***P$ value less than 0.001.

FA, from years 25 and 30. Higher mMedDiet scores at years 7 and 20, but not year 0, were also associated with higher midlife WM FA. WM FA from year 25 did not mediate the association between cumulative average mMedDiet scores and cognition at year 30 even though WM FA and mMedDiet were associated with cognition. No associations were found between mMedDiet scores and volume-based MRI measures.

To our knowledge, the current study is the first to explore microstructural white matter integrity as a function of the MedDiet in middle age. Nevertheless, our results confirm previous findings from epidemiological studies supporting associations between the MedDiet and preserved microstructural white matter integrity indicated by FA in older adults [13, 53, 54]. The biological underpinnings of the pathway from MedDiet adherence to preserved microstructural white matter integrity are not clearly understood. Vascular risk factors such as obesity, hypertension, and diabetes have been linked with microstructural white

Table 5
Mediation of Year 25 WM Fractional Anisotropy on the Association Between Cumulative Average mMedDiet Score and Year 30 Cognitive Test Scores ($N = 413$)

Cognitive tests	WM fractional anisotropy	
	% Mediated	*P*-value
DSST	7.11	0.12
MoCA	3.93	0.22
Stroop	4.43	0.15

matter integrity, and thus may underlie the association between MedDiet and preserved microstructural white matter integrity [55]. For instance, a previous CARDIA investigation found that increasing blood pressure trajectories throughout early adulthood is associated with an increased risk of diffuse small vessel disease in midlife [28]. However, our results remained significant when controlling for vascular factors. Therefore, other underlying mechanisms may explain these associations. Neuroinflammation has been linked to reduced white matter microstructural integrity [56, 57], and the MedDiet has been shown to have anti-inflammatory properties due to its high content of anti-inflammatory compounds, such as polyphenols, and omega-3 fatty acids [58]. Furthermore, the MedDiet is abundant in antioxidants that can counteract the harmful effects of free radicals and mitigate oxidative stress [59], which has been linked to impaired white matter microstructural integrity [60].

This study's findings in regard to volumetric brain measures are not in line with the majority of cross-sectional [9, 10–12, 61] and longitudinal [62] studies exploring late life MEDdiet scores and brain volumes done in elderly populations, which have reported that the MedDiet may confer protection against brain atrophy. A possible explanation for this discrepancy is that the association between the MedDiet and volume-based MRI brain measures may not be apparent during middle age [15], which would be in line with evidence suggesting that brain atrophy accelerates increasingly after the age of 60 [63]. Microstructural changes in the brain may precede changes in tissue volume, thereby explaining the association between mMedDiet scores and WM FA observed in the present study. Fractional anisotropy reportedly peaks at around 30 years of age, whereas WM volumes peak at the age of 50 [64]. In support of this view, systolic blood pressure was associated with FA in a cohort of young adults (mean age 39.2 ± 8.4), whereas there was no association with white matter hyperintensities [65]. Longitudinal studies with multiple MRI assessments across middle and late adulthood are required to determine how diet quality relates to microstructural and volumetric brain measures over the life course.

The few studies that have examined the association between the MedDiet and MRI-based brain volumetric measures in midlife have provided inconclusive evidence. Some of these studies have demonstrated positive associations between the MedDiet and brain volumes, whereas some have reported no association. The few studies that have investigated this exposure-outcome relationship in middle-aged adults are not entirely comparable with our results since they investigated MedDiet scores strictly in midlife. A brain imaging study (mean age 50 ± 8 at baseline) done at NYU and Cornell with a three year follow up found no significant cross-sectional or longitudinal association between midlife MedDiet scores and midlife volumetric brain MRI measures [15], consistent with our findings. The UK Biobank study reported no association between a cross-sectional analysis of midlife (mean age 53.8 ± 6.9) MedDiet scores and MRI brain measures [16]. Contrastingly, a cross-sectional study of middle-aged adults (mean age 54 ± 11) reported an association between higher MedDiet scores and larger gray matter volumes in AD brain regions [17]. Similarly, another cross-sectional study of middle-aged adults (mean age 50 ± 6) found that higher MedDiet scores were associated with increased cortical thickness [18]. The differences in the findings of some of these studies and the present study may be attributed to the methods used to score MedDiet. Furthermore, those studies' positive results may reflect reverse causation due to the cross-sectional design. It is possible that participants had adopted healthier eating habits to manage or reverse negative health outcomes that may be associated with brain health near the time of the MRI scans.

The results generated from the analysis examining mMedDiet scores at individual time points indicate that diet scores from midlife were more strongly associated with microstructural white matter integrity. This is evidenced from the increase in statistical significance across mMedDiet scores years 0, 7, and 20 in relationship WM FA at years 25 and 30. The observed increase in statistical significance closer to the time of MRI could be due to participants changing their diet to manage health conditions that are more common in middle age. However, more studies exploring MedDiet and MRI brain measures over the life course are needed in order to elucidate the matter.

This study's findings that mMedDiet scores at year 0 were associated with lower hippocampal volume at year 25 and higher posterior cingulate gyrus volume at year 30 likely due to chance given the number of statistical tests done.

This study's results do not support statistical mediation of microstructural white matter integrity on the association between mMedDiet and cognitive test scores. Higher WM FA was associated with both higher cumulative average mMedDiet scores and better performance on the DSST, MOCA, and Stroop tests. The literature on the mediating effect of microstructural white matter integrity on the relationship between diet and cognition is limited. One study found that microstructural white matter integrity assessed by FA mediated the association between a dietary pattern characterized by polyunsaturated fat and Vitamin E consumption and cognitive function in sample of older adults (mean age 84.1 ± 5.1) [66]. Dietary patterns may be associated with cognition independently from brain integrity in middle age.

The current study has several strengths. First, this study included detailed repeated measures of dietary intake from early and middle adulthood over the course of 20 years. Second, bias due to reverse causality is less likely since dietary information was collected before the MRI visit. Reverse causation would occur in the event that participants change their diets close to the time of MRI due to health conditions that could affect brain pathology. Third, this study is among few to explore a wide range of brain measures related to cognitive impairment in the context of the MedDiet in a biracial sample. However, this study has limitations. Voluntary participation into the MRI sub study resulted in selection bias, given that those who participated in the MRI sub study differed in demographics and health as previously discussed. Additionally, diet history may have been misreported due to social-desirability bias during the interviews. Furthermore, we did not adjust for multiple comparisons given the exploratory nature of our study and the conflicting viewpoints in the literature regarding the need for such adjustments [67].

5. Conclusion

Higher mMedDiet scores from early through middle adulthood were associated with better microstructural white matter integrity at midlife indicated by higher WM FA. However, the current study does not support associations between dietary patterns characterized by the mMedDiet from early through middle adulthood and midlife brain volumes. Additionally, microstructural white matter integrity did not statistically mediate the association between the mMedDiet and cognition. Additional studies with repeat MRI and diet measures spanning early and late adulthood are necessary in order to better understand longitudinal trajectories of brain structural integrity as a function of MedDiet.

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Conflict of interest

The authors have no conflict of interest to report.

Supplementary material

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