

White Matter Integrity as a Mediator in the Relationship between Dietary Nutrients and Cognition in the Elderly

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Objective: We examined the association of nutrient intake with microstructural white matter integrity, and the role of white matter integrity in the association between nutrient consumption and cognition.

Methods: This cross-sectional analysis included 239 elderly (age ≥ 65 years) participants of a multiethnic cohort. White matter integrity was measured with fractional anisotropy (FA) from diffusion tensor magnetic resonance imaging. Nutrient patterns were derived from principal component analysis based on energy-adjusted intake of 24 selected nutrients. Generalized linear models were used to assess the association between nutrient patterns and mean FA of 26 white matter tracts. Mediation analysis was used to determine whether FA mediates the nutrient–cognition relationship. All models were adjusted for age at time of scan, gender, ethnicity, education, caloric intake, and apolipoprotein genotype.

Results: Among the identified 6 nutrient patterns, 1 (nutrient pattern 6, characterized by high intakes of Ω -3 and Ω -6 polyunsaturated fatty acids and vitamin E) was positively associated with FA. Those with the highest tertile of nutrient pattern 6 score had a mean of 0.01 ($p = 0.01$) higher FA value than those with the lowest tertile, similar to the effect of a 10-year decrease in age (b for age = -0.001 , $p = 0.01$). FA mediated the relationship between nutrient pattern 6 and memory, language, visuospatial and speed/executive function, and mean cognitive scores.

Interpretation: Our study suggests that older adults consuming more polyunsaturated fatty acids and vitamin E rich foods had better white matter integrity, and that maintaining white matter microstructural integrity might be a mechanism for the beneficial role of diet on cognition.

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Mounting evidence suggests that dietary factors are associated with risk for Alzheimer disease and cognitive decline among the elderly.¹ Dietary factors have also been implicated in maintaining brain macrostructures, such as brain volumes assessed by magnetic resonance imaging (MRI).^{2–7} However, little is known about the association of dietary patterns with microstructural brain imaging markers such as white matter integrity.

Diffusion tensor imaging (DTI) is a sensitive MRI-based neuroimaging technique that assesses the integrity of white matter microstructure in the brain by measuring

diffusion properties of water.⁸ Fractional anisotropy (FA), the most widely used metric derived from DTI, ranges from 0 to 1, with higher values indicating greater directionality of diffusion and preserved microstructure. Low FA is associated with subtle white matter abnormalities in prodromal and frank Alzheimer disease,⁹ and is associated with cognitive function and decline.¹⁰ Studies also showed that DTI metrics predicted cognitive decline better than measures of cerebrospinal fluid tau and $A\beta$,¹¹ distinguished prodromal Alzheimer disease from healthy controls better than gray matter volume,¹² and correlated

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more reliably with memory performance in healthy elderly than hippocampal volumes.¹³ Overall, DTI is a promising technique for research in prodromal Alzheimer disease.¹⁴

Given that there is no effective treatment for dementia to date, an earlier intervention at the prodromal or earlier stage is important to delay disease onset. Thus, it is essential to investigate modifiable factors that can contribute to the maintenance of white matter integrity. It is particularly important to examine the role of diet on white matter because certain nutrients such as polyunsaturated fatty acids (PUFAs) are key components of the glial, myelin sheath, and neuronal membrane phospholipid¹⁵ factors that comprise the brain's white matter, thus insufficient consumption of these nutrients may interfere with membrane fluidity and function. Finally, elucidating the relationship between diet and the integrity of white matter tracts may also provide a foundation for further investigation of whether early disruption or preservation of white matter microstructure explain the diet–cognition relationship. However, to date only few studies have addressed these issues. In animal experiments, thiamine-deprived rats had lower FA values,¹⁶ whereas calorie restriction in rhesus macaques had increased FA.¹⁷ Studies in humans are also rare, with limited evidence suggesting that vitamin B12 supplementation,¹⁸ higher serum level of 25-hydroxyvitamin D,¹⁹ plasma PUFA concentration,²⁰ and supplementation of Ω -3 PUFA⁴ or fish oil²¹ might be associated with favorable DTI metrics like higher FA values. However, except for one study showing adherence to the Mediterranean diet²² was associated with higher FA values, whether and which nutritional or dietary factors directly from foods are related to white matter integrity is largely unknown. In addition, to our knowledge, whether white matter integrity may mediate the relationship between diet and cognition has never been examined.

In the current study, we investigated the association between dietary nutrient intake and white matter integrity among participants of a community-based, multiethnic cohort. We also evaluated the extent to which the association between nutrient intake and cognition is due to the variability in white matter microstructure.

Subjects and Methods

Study Participants

The study participants were from the Washington Heights/Hamilton Heights Inwood Columbia Aging Project (WHICAP), and were identified (via ethnicity and age stratification processes) from a probability sample of Medicare beneficiaries aged 65 years or older, residing in northern Manhattan.²³ The initial sample for this study included 2,776 participants of the

ongoing WHICAP II cohort, with the majority of the participants from a cohort recruited between 1999 and 2001 ($n = 2,174$), and a smaller percentage from continuing members of the WHICAP I cohort originally recruited in 1992 ($n = 602$). Briefly, at entry, a physician elicited each participant's medical and neurological history, and conducted a standardized physical and neurological examination. Each participant received an assessment of health and function and a neuropsychological battery.²⁴ The diagnosis of any type of dementia or its absence,²⁵ Alzheimer disease,²⁶ and mild cognitive impairment²⁷ was based on standard research criteria, using all available information at a consensus conference. Participants were followed every 18 months, repeating the baseline examination and consensus diagnosis. Institutional review boards at Columbia University approved this project. All individuals provided written informed consent.

The imaging substudy was started in 2004 among ongoing dementia-free WHICAP II participants.²⁸ In total, 769 WHICAP participants received MRI scans, and they were slightly younger and more likely to be African Americans or male compared with those who were eligible but did not undergo MRI.²⁸ Approximately 4 years later, we invited the participants to come back for a follow-up MRI scan. A total of 337 subjects received second structural MRI scans, among whom 255 subjects also received DTI. We additionally excluded 16 subjects who had no diet assessments. Therefore, a total of 239 (71% of 337) subjects were included in the current analysis. Twenty-eight subjects met diagnostic criteria for dementia at neuroimaging visit and were further excluded in sensitivity analysis.

MRI Protocol

Scan acquisition was performed on a 1.5T Philips (Best, the Netherlands) Intera scanner at Columbia University Medical Center.²⁹ T1-weighted images (repetition time [RT] = 20 milliseconds, echo time [TE] = 2.1 milliseconds, field of view = 240°, matrix = 256 × 160, slice thickness = 1.3mm) were acquired and analyzed with FreeSurfer v5.1 (<http://surfer.nmr.mgh.harvard.edu/>) for cortical thickness and regional and total volume. Whole brain diffusion imaging (matrix field of view = 224 × 224, contiguous slices, slice thickness = 2mm, TR = 10,586 milliseconds, TE = 70 milliseconds) were acquired along 15 directions with a maximum b-factor of 800 s/mm², complemented by 2 scans with b = 0 s/mm². FA maps were constructed for each participant with software implemented in MATLAB (R2013b; FMRIB Software Library [FSL] and MathWorks, Natick, MA). Regions of interest (ROIs) were derived with the JHU-ICBM-DTI-81 white matter labels atlas.³⁰ Each subject's FA map was first registered to the FA atlas template with the nonlinear transformation tool (FNIRT) in FSL using a linear initialization (default FSL parameters) and the predefined configuration file for FA registration provided by FSL. By applying the inverse nonlinear registration transformation to the atlas, the atlas was warped, allowing for ROI analysis in subject space. Twenty-six ROIs in left and right hemispheres, and midline structures, were considered for analysis. A mean

FA value of the 26 tract-specific FAs, measuring global white matter microstructure, was used as the main outcome variable.

Dietary Information

Information about average diet over the prior year was obtained using the 61-item version of Willett's semiquantitative food frequency questionnaire (Channing Laboratory, Cambridge, MA), administered by trained interviewers in English or Spanish. The validity (using two 7-day food records) and reliability (using two 3-month frequency assessments) of various components of the food frequency questionnaire in WHICAP were good and have been previously reported.³¹ The database used for the nutrient content analysis was a specifically designed program,³² primarily using United States Department of Agriculture Nutrient Database for Standard Reference, as well as information from McCance and Widdowson's *The Composition of Foods*, published data, and manufacturers. The daily intake of nutrients was computed by multiplying the consumption frequency of each food item by the nutrient content of the specified portion of the food item, which was from this specifically designed nutritional database. The diet information was collected on average 5.1 (standard deviations [SD] = 2.2) years before the MRI scan.

Cognitive Evaluation

Cognition was assessed with a neuropsychological battery,²⁴ which was administered either in English or Spanish at baseline and each follow-up visit. Selected neuropsychological tests scores were combined into 4 composite scores (memory, language, executive-speed, and visuospatial) based on an exploratory factor analysis using principal axis factoring and oblique rotation.²⁴ Memory was assessed with the Selective Reminding Test, including total recall, delayed recall, and delayed recognition, and with recognition from the Benton Visual Retention Test. The language domain was assessed by measuring naming, letter fluency, category fluency, verbal abstract reasoning, and repetition and comprehension. Executive-speed was assessed with the Color Trails Test 1 and 2. Visuospatial function was assessed with the Rosen Drawing Test, the Benton Visual Retention Test–Matching, and the Identities and Oddities subtest of the Mattis Dementia Rating Scale.

Means and SD were calculated from baseline scores for nondemented WHICAP subjects controlling for age, race/ethnicity, and years of education. *Z* scores for each of the cognitive tests were calculated and then averaged to create a composite *Z* score for each of the 4 domains.³³ These 4 factor domain scores were subsequently averaged to produce a composite “mean cognition” *Z* score. A higher *Z* score indicates better cognitive performance.

Other Information

Age (years), education (years), caloric intake (calories), and body mass index (BMI; weight in kilograms divided by height in square meters [kg/m^2]) were used as continuous variables. Participants were assigned to 1 of 4 groups: African American (black non-Hispanic), Hispanic, white (non-Hispanic), or other

based on self-report using the format of the 2000 US Census. Ethnicity was used as a dummy variable with non-Hispanic white as the reference. Sex was used as a dichotomous variable with male as the reference. Apolipoprotein (APOE) genotype was used dichotomously: absence (as reference) versus presence of either 1 or 2 $\epsilon 4$ alleles. The diagnosis of clinical stroke was based on questioning of the participant or relatives and supplemented by a neurological examination or review of medical records. Heart disease, diabetes mellitus, and hypertension were defined by collective information on measured blood pressure, self-report, and use of disease-specific medications. These 4 vascular comorbidities were used as dichotomous variables with absence of the condition as the reference. Standard FreeSurfer outputs of brain measures including total brain volume, total white matter volume, or total gray matter volume, all adjusted for intracranial volume using the residual method, were also included in the analysis as a covariate.

Statistical Analyses

PRINCIPAL COMPONENT ANALYSIS. To identify underlying latent dietary constructs (dietary patterns) in the population, we used exploratory principal component analysis (PCA) performed on the correlation matrix of 24 nutrients. The following 24 nutrients were considered in the analysis: protein, carbohydrate, fatty acids (saturated, cholesterol, monounsaturated, Ω -3 and Ω -6 PUFA), B vitamins (B1, B2, B3, B5, B6, B12, folate), A vitamins (lycopene, lutein and zeaxanthin, vitamin A), antioxidants (vitamin C, vitamin E, β -carotenes, β -cryptoxanthin), vitamin D, calcium, and iron, selected based on their biological functions and their relationship with cognition and neurodegenerative conditions reported in the literature.^{6,34} Nutrient intake was adjusted for total caloric intake using the regression models, and their residuals were used in the analysis.

The number of nutrient patterns to be retained was determined by eigenvalues > 1.0 , scree plot, parallel analysis, and interpretability of the factors. We considered nutrients with an absolute factor loading value ≥ 0.50 on a nutrient pattern as dominant nutrients contributing to that particular nutrient pattern. Each subject received a factor score (ie, a linear combination of nutrients weighted by factor loadings) for each identified nutrient pattern, with higher score indicating relatively higher adherence to that nutrient pattern.

DESCRIPTIVE ANALYSIS AND ASSOCIATION ANALYSIS BETWEEN NUTRIENT PATTERNS AND WHITE MATTER INTEGRITY. Characteristics of participants by tertiles of nutrient pattern adherence or mean FA were compared using analysis of variance for continuous variables and chi-square test for categorical variables. Generalized linear models were used to assess the association between nutrient patterns and mean FA, initially adjusted for age at time of scan only (Model 1), and then followed by adjustment of age at time of scan, gender, ethnicity, education, caloric intake, and APOE genotype (Model 2). We also additionally included total brain volume, 4 vascular conditions, and BMI as covariates (Model 3). For Model 3, we

replaced total brain volume with either total gray matter or white matter volume.

MEDIATION ANALYSIS. We performed mediation analysis to examine the potential mediating role of white matter integrity on the relationship between nutrient intake and cognition. Age, sex, education, race/ethnicity, caloric intake, and APOE status were included as covariates in the models.

SUPPLEMENTARY ANALYSES. We explored the potential effect modification by sex, APOE genotype, or ethnicity on the relationship between nutrient patterns and mean FA. We also examined the association between the individual dominant nutrients of the nutrient pattern that was associated with FA. We excluded participants with dementia and repeated the analyses. To evaluate the robustness of the identified dietary patterns, we performed PCA on an exhaustive set of 34 nutrients that included 10 additional nutrients (zinc, copper, phosphorous, potassium, magnesium, manganese, sodium, alcohol, caffeine, and fiber). We then examined whether these alternative nutrient patterns retained from this PCA were associated with FA. We also additionally adjusted for the supplements intake (including vitamins A, C, E, and B6, and calcium, all as binary variables indicating yes or no for supplementation) in Model 3. Similar to the PCA method we used for deriving nutrient patterns, we used PCA on the 26 tract-specific FAs as an alternative way to summarize the overall FA value rather than using the mean FA value, and examined the relationship between nutrient patterns and the derived white matter tract FA pattern scores. Finally, we examined whether FA had a mediating role in the associations of all nutrient patterns (not just the ones associated with FA) and cognitive functions.

All analyses were conducted using PASW Statistics (IBM, Armonk, NY). All probability values were based on 2-sided tests. The significance level was set at 0.05 for all tests.

Results

Nutrient Patterns

We retained 6 major nutrient patterns that had eigenvalues ≥ 1 . Parallel analysis suggested the same number of patterns to be retained. The 6 nutrient patterns in total explained about 80% of total variance in nutrients (Table 1). Table 1 shows the factor loading matrix for the nutrient patterns. Based on the loading coefficients, the first nutrient pattern (nutrient pattern 1) was characterized by high intake of antioxidants and A vitamins; nutrient pattern 2 by high intake of B vitamins and iron; nutrient pattern 3 by high intake of vitamin D, calcium, and vitamin B2; nutrient pattern 4 by high intakes of saturated fatty acids, monounsaturated fatty acids, cholesterol, and low intake of carbohydrates; nutrient pattern 5 by high intake of protein, cholesterol, vitamin B3, and vitamin B6; and nutrient pattern 6 by high intake of Ω -3 PUFA, Ω -6 PUFA, and vitamin E. Preliminary regression analysis adjusted for age, sex, education, and

race/ethnicity showed that nutrient pattern 6 was the only nutrient pattern significantly associated with higher values of FA. Therefore, we focused on nutrient pattern 6 and its relationship with FA in the subsequent analyses.

Characteristics of the Study Population

Participants had different language performance, prevalence of diabetes, and mean FA across tertiles of nutrient pattern 6 (Table 2). Post hoc analyses showed that participants with high tertile nutrient pattern 6 had higher FA than those with low ($p = 0.04$) or middle ($p = 0.04$) tertile, and had higher language Z scores than those with low nutrient pattern 6 ($p = 0.01$). Participants with middle tertile of nutrient pattern 6 scores had lower total caloric intake than those with low ($p = 0.02$) or high ($p = 0.05$) tertile.

Compared with those having the lowest tertile of FA, subjects with the higher tertiles of FA were younger, and had better cognition, lower BMI, larger gray matter volume, and larger white matter volume (Table 3).

Nutrient Pattern 6 and White Matter Integrity

Regression analyses showed that higher nutrient pattern 6 score was associated with higher mean FA (Table 4, all models). In the model adjusted for age, sex, education, ethnicity, APOE, and caloric intake (see Table 4, Model 2), subjects who had the highest tertile had a mean of 0.01 ($p = 0.01$) higher FA value compared to those with the lowest tertile of nutrient pattern 6 score. Of note, in the same model (Model 2), the only other variable associated with FA was age, with 1-year increase in scan age associated with 0.001 lower FA ($b = -0.001$, $p = 0.01$). Thus, the estimated effect for FA comparing the highest to the lowest tertile of nutrient pattern 6 was about the same magnitude as a 10-year increase in age.

Additional adjustment for total brain volume, BMI, hypertension, stroke, diabetes, and heart disease did not change the results (see Table 4, Model 3). Replacing total brain volume with either total gray matter volume or total white matter volume did not change the results (data not shown).

Mediating Effect of White Matter Integrity for the Association between Nutrient Pattern 6 and Cognitive Functions

Mediation analysis adjusted for age, sex, education, ethnicity, APOE, and caloric intake showed that mean FA was positively associated with cognitive functions in all domains (positive β_b in Table 5). In addition, there was a significant mediation effect ($\beta_a \cdot \beta_b$ in Table 5) of nutrient pattern 6 on cognition through FA, for all cognitive scores, suggesting a path linking diet (nutrient pattern 6) and cognition (cognitive scores) via white matter

TABLE 1. Factor Loading Matrix and Explained Variances for the 6 Major Dietary Patterns Identified by Principal Component Analysis

Factor	Components ^a						Communalities
	1	2	3	4	5	6	
Total protein, g					0.762 ^b		0.682
Total carbohydrates, g	0.504 ^b			-0.646 ^b	-0.399		0.921
Saturated fatty acids, g	-0.471			0.707 ^b			0.838
Cholesterol, mg				0.571 ^b	0.593 ^b		0.730
Monounsaturated fatty acids, g	-0.437			0.719 ^b			0.881
Ω-3 PUFA, g						0.892 ^b	0.853
Ω-6 PUFA, g			-0.331			0.703 ^b	0.710
Thiamin (vitamin B1), mg		0.876 ^b					0.910
Riboflavin (vitamin B2), mg		0.532 ^b	0.658 ^b		0.313		0.872
Niacin (vitamin B3), mg		0.739 ^b			0.514 ^b		0.883
Vitamin B5 (pantothenic acid), mg		0.757 ^b	0.450				0.844
Vitamin B6, mg	0.334	0.798 ^b					0.820
Vitamin B12, μg					0.646 ^b		0.482
Total folate, μg	0.308	0.754 ^b		-0.350			0.802
Vitamin C, mg	0.784 ^b				-0.319		0.832
Vitamin E, mg		0.742 ^b				0.413	0.856
β-Carotene, μg	0.903 ^b						0.887
β-Cryptoxanthin, μg	0.802 ^b						0.792
Lycopene, μg	0.729 ^b						0.582
Lutein, μg	0.715 ^b			-0.342			0.670
Vitamin A, IU	0.919 ^b						0.910
Vitamin D, IU			0.826 ^b				0.763
Calcium, mg			0.878 ^b				0.859
Iron, mg		0.844 ^b					0.786
Proportion of variance explained, %	34.218	19.608	9.608	6.170	5.868	4.386	
Cumulative proportion of variance explained, %	34.218	53.826	63.434	69.604	75.471	79.857	
Association with FA, β (p) ^c	0.0001 (0.99)	0.002 (0.21)	0.001 (0.39)	-0.003 (0.11)	0.001 (0.57)	0.004 (0.006)	

^aPrincipal component analysis with varimax rotation was used to extract all the components (ie, nutrient patterns). Only loadings with an absolute value ≥ 0.3 are shown in the table, and those < 0.30 are suppressed. Each nutrient pattern score is a linear weighted (by loadings) combination of the nutrients. Hence, nutrients with highest absolute loadings (≥ 0.5) are considered as dominant nutrients contributing to the particular nutrient pattern.

^bNutrients with highest absolute loadings, ≥ 0.5 .

^cBeta coefficient (β) and probability value for the association with FA was estimated from a regression model with mean FA as the outcome variable, and all 6 nutrient patterns as independent variables, adjusted for age, sex, education, and ethnicity.

FA = fractional anisotropy; PUFA = polyunsaturated fatty acid.

microstructure (mean FA). Taking memory score as an example (see Table 5 and Fig), the total effect of nutrient pattern 6 on memory score was significant ($\beta_c = 0.10$,

$p = 0.05$), but after taking into consideration the significant path via white matter integrity (the mediation effects $\beta_a^* \beta_b = 0.024$, 95% confidence interval =

TABLE 2. Demographic and Cognitive Characteristics of the Study Subjects by Tertiles of Nutrient Pattern 6 Score

Characteristic	Nutrient Pattern 6 Tertiles			Total	<i>p</i>
	Low	Middle	High		
No.	81	82	76	239	
Age, yr, mean \pm SD	83.7 \pm 4.78	84.6 \pm 5.3	84.1 \pm 5.1	84.1 \pm 5.1	0.56
Education, yr, mean \pm SD	10.4 \pm 4.9	10.7 \pm 4.5	12.0 \pm 5.1	11.1 \pm 4.9	0.08
Female, No. (%)	56 (71)	57 (71)	54 (68)	167 (70)	0.85
Race/ethnicity, No. (%)					0.16
White	24 (30)	25 (31)	21 (26)	70 (29)	
African American	26 (33)	21 (26)	37 (46)	84 (35)	
Hispanic	28 (35)	34 (43)	21 (26)	83 (35)	
Other	1 (1)	0 (0)	1 (1)	2 (1)	
APOE ϵ 4, No. (%)	21 (27)	22 (28)	19 (24)	62 (26)	0.85
Caloric intake, cal, mean \pm SD	1,472 \pm 731	1,260 \pm 408	1,432 \pm 480	1,388 \pm 562	0.04 ^a
Cognitive status					
Language, mean \pm SD	0.12 \pm 0.66	0.30 \pm 0.66	0.40 \pm 0.62	0.27 \pm 0.66	0.03 ^a
Memory, mean \pm SD	-0.04 \pm 0.79	0.10 \pm 0.8	0.09 \pm 0.83	0.05 \pm 0.81	0.46
Speed, mean \pm SD	0.10 \pm 1.04	0.10 \pm 0.93	0.30 \pm 1.02	0.17 \pm 0.99	0.45
Visuospatial, mean \pm SD	0.25 \pm 0.65	0.29 \pm 0.58	0.37 \pm 0.56	0.30 \pm 0.60	0.46
Cognition, mean \pm SD	0.27 \pm 0.6	0.26 \pm 0.65	0.36 \pm 0.59	0.30 \pm 0.61	0.56
Dementia, No. (%)	10 (13)	8 (10)	10 (13)	28 (12)	0.84
Vascular risk/comorbidities					
BMI, kg/m ² , mean \pm SD	28.4 \pm 5.9	27.7 \pm 4.5	28.0 \pm 5.8	28.0 \pm 5.4	0.73
Diabetes, No. (%)	22 (28)	28 (35)	13 (16)	63 (26)	0.03 ^a
Hypertension, No. (%)	64 (81)	67 (84)	68 (85)	199 (83)	0.79
Heart disease, No. (%)	18 (23)	27 (34)	24 (30)	69 (29)	0.30
Stroke, No. (%)	6 (8)	9 (11)	8 (10)	23 (10)	0.73
Total brain volume, ml, mean \pm SD	868 \pm 109	862 \pm 90	884 \pm 106	871 \pm 102	0.38
Total gray matter volume, ml, mean \pm SD	514 \pm 53	511 \pm 47	523 \pm 53	509 \pm 51	0.34
Total white matter volume, ml, mean \pm SD	375 \pm 56	370 \pm 48	386 \pm 50	377 \pm 52	0.16
FA, mean \pm SD	0.4460 \pm 0.0251	0.4460 \pm 0.0227	0.4541 \pm 0.0248	0.4487 \pm 0.0244	0.05 ^a

Probability values were from analysis of variance for continuous variables and chi-square for categorical variables.
^aStatistically significant.
 APOE = apolipoprotein; BMI = body mass index; FA = fractional anisotropy; SD = standard deviation.

0.002–0.064), the remaining direct effect of nutrient pattern 6 on memory score was reduced and no longer significant ($\beta c' = 0.077$, $p = 0.157$). When we

additionally adjusted for BMI, hypertension, stroke, diabetes, and heart disease in the mediation models, we found the results were similar (data not shown).

TABLE 3. Demographic and Cognitive Characteristics of the Study Subjects by Tertiles of FA Value

Characteristic	Low FA	Middle FA	High FA	Total	<i>p</i>
No.	79	81	79	239	
FA, mean \pm SD (range)	0.4210 \pm 0.0135 (0.38–0.44)	0.4505 \pm 0.0057 (0.44–0.46)	0.4746 \pm 0.0122 (0.46–0.51)	0.4487 \pm 0.0244 (0.38–0.51)	<0.0001 ^a
Age, yr, mean \pm SD	84.84 \pm 5.38	84.54 \pm 5.03	82.98 \pm 4.69	84.12 \pm 5.09	0.046 ^a
Education, yr, mean \pm SD	10.89 \pm 4.73	10.74 \pm 5.13	11.53 \pm 4.77	11.05 \pm 4.88	0.563
Female, No. (%)	54 (68)	55 (68)	58 (73)	167 (70)	0.702
Race/ethnicity, No. (%)					0.053
White	21 (27)	24 (30)	25 (32)	70 (29)	
African American	37 (47)	22 (27)	25 (32)	84 (35)	
Hispanic	21 (27)	35 (43)	27 (34)	83 (35)	
Other	0	0	2 (2)	2 (1)	
APOE ϵ 4, No. (%)	23 (29)	20 (25)	19 (24)	62 (26)	0.731
Caloric intake, cal, mean \pm SD	1,389 \pm 569	1,390 \pm 662	1,383 \pm 435	1,387 \pm 562	0.990
Cognitive status					
Cognition, mean \pm SD	0.14 \pm 0.65	0.27 \pm 0.6	0.49 \pm 0.53	0.3 \pm 0.61	0.001 ^a
Memory, mean \pm SD	–0.18 \pm 0.80	0.05 \pm 0.78	0.26 \pm 0.79	0.05 \pm 0.81	0.004 ^a
Language, mean \pm SD	0.10 \pm 0.68	0.28 \pm 0.67	0.42 \pm 0.58	0.27 \pm 0.66	0.010 ^a
Speed, mean \pm SD	–0.17 \pm 1	0.12 \pm 1.04	0.49 \pm 0.84	0.17 \pm 0.99	0.001 ^a
Visuospatial, mean \pm SD	0.13 \pm 0.65	0.30 \pm 0.63	0.47 \pm 0.45	0.30 \pm 0.60	0.002 ^a
Dementia, No. (%)	18 (23)	5 (6.2)	5 (6.3)	28 (12)	0.001 ^a
Vascular risk/comorbidities					
BMI, kg/m ² , mean \pm SD	29.3 \pm 6.3	27.0 \pm 4.6	27.8 \pm 5.1	28.0 \pm 5.4	0.034 ^a
Diabetes, No. (%)	24 (30)	22 (27)	17 (22)	63 (26)	0.441
Heart disease, No. (%)	23 (29)	22 (27)	24 (30)	69 (29)	0.902
Hypertension, No. (%)	67 (85)	69 (85)	63 (70)	199 (83)	0.591
Stroke, No. (%)	12 (15)	4 (5)	7 (9)	23 (10)	0.086
Total brain volume, ml, mean \pm SD	857 \pm 102	885 \pm 110	872 \pm 93	871 \pm 102	0.230
Total gray matter volume, ml, mean \pm SD	501 \pm 46	520 \pm 55	526 \pm 48	516 \pm 51	0.007 ^a
Total white matter volume, ml, mean \pm SD	355 \pm 50	389 \pm 50	387 \pm 49	377 \pm 52	<0.0001 ^a
intracranial volume, ml, mean \pm SD	1,449 \pm 170	1,462 \pm 217	1,405 \pm 187	1,439 \pm 193	0.156

Probability values were from analysis of variance for continuous variables and chi-square for categorical variables.

^aStatistically significant.

APOE = apolipoprotein; BMI = body mass index; FA = fractional anisotropy; SD = standard deviation.

TABLE 4. Associations between Nutrient Pattern 6 and White Matter Integrity

Model	Continuous Nutrient Pattern 6		Tertiles of Nutrient Pattern 6		
	b	p	Tertile	b	p
1	0.0040	0.02 ^a	Middle	0.001	0.87
			High	0.008	0.03 ^a
			p-Trend		0.03 ^a
2	0.0043	0.007 ^a	Middle	0.001	0.80
			High	0.010	0.01 ^a
			p-Trend		0.01 ^a
3	0.0045	0.006 ^a	Middle	0.002	0.70
			High	0.010	0.01 ^a
			p-Trend		0.02 ^a

Results are from generalized linear models. Model 1: adjusted for age only. Model 2: adjusted for age, sex, education, ethnicity, apolipoprotein (APOE), and caloric intake. Model 3: adjusted for age, sex, education, ethnicity, APOE, caloric intake, total brain volume, body mass index, hypertension, stroke, diabetes, and heart disease.

^aStatistically significant.

Supplementary Analyses

Interaction analyses indicated that the relationships of nutrient pattern 6 with FA was not modified by gender (p for interaction = 0.52), education (p = 0.44), ethnicity (p = 0.99 for whites and blacks, p = 0.35 for Hispanics and whites), or APOE $\epsilon 4$ status (p = 0.66). Post hoc stratified analysis showed similar results in whites and African Americans (b = 0.008, p = 0.005, and b = 0.007, p = 0.025, respectively), whereas no association was observed in Hispanics (b = -0.00005, p = 0.84) with Model 3 covariates except for race/ethnicity.

Among the 3 dominant nutrients contributing to nutrient pattern 6, we found subjects with high and middle tertile of Ω -3 PUFA both had higher FA than those with low tertile (b = 0.009, p = 0.02, and b = 0.011, p = 0.005, respectively; p -trend = 0.005), and those with high tertile of vitamin E had higher FA (b = 0.009, p = 0.02) than those with low vitamin E tertile (p -trend = 0.02), whereas Ω -6 PUFA by itself was not associated with FA. When all individual 24 nutrients were included in the model simultaneously, Ω -3 PUFA remained independently associated with FA (b = 0.018 for 1-SD increase, p = 0.04).

When the analysis was limited to 211 nondemented subjects, nutrient pattern 6 and Ω -3 PUFA (both as continuous variables) remained associated with FA, with b = 0.006, p = 0.001 and b = 0.018, p = 0.001 in Model 3, respectively.

When we included 10 additional nutrients, we retained 8 alternative nutrient patterns. Among them, alternative nutrient pattern 6 was the only one significantly associated with FA (b = 0.004, p = 0.009, Model

3), and the nutrients with highest loadings for this alternative nutrient pattern 6 were again Ω -3 PUFA, Ω -6 PUFA, and vitamin E (loadings = 0.88, 0.74, and 0.45, respectively). Interestingly, the original and alternative nutrient patterns 6 had a correlation coefficient of 0.94 (p < 0.0001), suggesting the robustness of extracting the unobservable pattern in this population using PCA.

When additionally adjusted for the supplements intake in the Model 3, the results did not change much; compared to the low tertile of nutrient pattern 6, those with middle and high tertiles had 0.001 (p = 0.073) and 0.01 (p = 0.006) higher FA values, respectively.

We used PCA to derive 5 white matter tract FA pattern scores that had eigenvalues > 1. As the first FA pattern score explained a large proportion of variance (41%), and all 26 tract FAs had positive loadings > 0.3, we focused on the first pattern score as an alternative summary of the global white matter integrity. We found nutrient pattern 6 was the only pattern significantly associated with this FA pattern (b = 0.20, p = 0.005).

Mean FA did not mediate the relationship between other derived nutrient patterns (ie, nutrient patterns 1–5 in Table 1) and cognitive functions (data not shown).

Discussion

We identified a “PUFAs and vitamin E” nutrient pattern that was associated with better microstructural white matter integrity indicated by higher FA. The strength of the association was about the same magnitude as a 10-year increase in age, which is a well-established factor contributing to white matter integrity deterioration.³⁵ In addition, white matter integrity was associated with

TABLE 5. Mediation Effect of White Matter Integrity on the Association between Nutrient Pattern and Cognitive Functions

	Mean Cognition		Memory		Language		Speed		Visuospatial	
	β	<i>p</i> or 95% CI	β	<i>p</i> or 95% CI	β	<i>p</i> or 95% CI	β	<i>p</i> or 95% CI	β	<i>p</i> or 95% CI
Number of subjects	233		218		224		187		219	
R^2 (mediation model)	0.51		0.18		0.49		0.23		0.45	
Total effect β_c (nutrient pattern 6 on cognition)	-0.009	0.760	0.101	0.050 ^a	0.057	0.090	0.099	0.150	0.002	0.940
β_a (nutrient pattern 6 on FA)	0.004	0.016 ^a	0.005	0.002 ^a	0.005	0.003 ^a	0.004	0.020 ^a	0.004	0.044 ^a
β_b (FA on cognition, given nutrient pattern 6)	3.854	0.002 ^a	4.717	0.030 ^a	3.595	0.039 ^a	11.150	<0.0001 ^a	5.078	0.001 ^a
Mediation effect $\beta_a^*\beta_b$ (nutrient pattern 6 on cognition via FA)	0.017	0.003–0.041 ^a	0.024	0.002–0.064 ^a	0.019	0.003–0.046 ^a	0.049	0.012–0.109 ^a	0.019	0.003–0.046 ^a
Direct effect β_c' (nutrient pattern 6 on cognition)	-0.026	0.410	0.077	0.157	0.038	0.277	0.049	0.548	-0.017	0.644

Mediation analysis was used to examine the potential indirect relationship between nutrient intake (independent variable) and cognition (dependent variable) through white matter integrity (mediator), in other words, the mediation role of white matter integrity on the relationship between nutrient and cognition.

All models were based on a subsample that was limited to subjects with all variables, and thus the sample sizes as well as β 's were slightly different due to missing values on each cognitive score. FA from diffusion tensor imaging assessment was used as an indicator of white matter integrity, with higher FA value indicating better integrity.

β_a indicates the association between nutrient pattern 6 and FA: beta coefficient for nutrient pattern 6 on FA from an adjusted model with age, sex, education, race/ethnicity, apolipoprotein (APOE), caloric intake, and nutrient pattern 6 as predicting variables, and FA as outcome variable.

β_b indicates the association between FA and cognition: beta coefficient for FA on cognition from a mediation model with age, sex, education, race/ethnicity, APOE, caloric intake, nutrient pattern 6, and FA as predicting variables, and cognitive Z score as outcome variable.

β_c indicates the total effect of nutrient pattern 6 on cognition: beta coefficient for nutrient pattern 6 on cognition from an adjusted model with age, sex, education, race/ethnicity, APOE, caloric intake, and nutrient pattern 6 as predicting variables, and cognitive Z score as outcome variable.

$\beta_a^*\beta_b$ indicates the indirect effect of nutrient pattern 6 on cognition via FA. Bias-corrected bootstrap 95% CIs were estimated from 10,000 bootstrap samples using the PROCESS SPSS macro of Preacher and Hayes.⁴⁹ A 95% CI that does not include 0 is considered statistically significant, suggesting a significant mediating role of FA on the relationship between nutrient pattern 6 and cognition.

β_c' indicates the remaining direct effect of nutrient pattern 6 on cognition after controlling for the mediating factor as well as other covariates; thus, it is approximately equivalent to $\beta_c - \beta_a^*\beta_b$. It is the beta coefficient for nutrient pattern 6 from a mediation model with age, sex, education, race/ethnicity, APOE, caloric intake, nutrient pattern 6, and FA as predicting variables, and cognitive Z score as outcome variable.

^aSignificant at $p < 0.05$ (2-tailed), or a 95% CI for the indirect effect that does not include 0.

CI = confidence interval; FA = fractional anisotropy.

cognitive function, and it mediated the relationship between this “PUFAs and vitamin E” nutrient pattern and cognitive function.

Few prior epidemiological studies have examined the role of diet in microstructural white matter integrity. In young male adults with psychosis, plasma total PUFA concentration was positively correlated with FA.²⁰ In a

double-blind randomized interventional study, Ω -3 PUFA supplementation led to significant increases in FA during the 26-week follow-up.⁴ A recent study on 146 nondemented elderly people found that higher adherence to a Mediterranean diet was associated with preserved white matter microstructure in extensive brain areas.²² Interestingly, the main food sources for Ω -3 PUFA, Ω -6

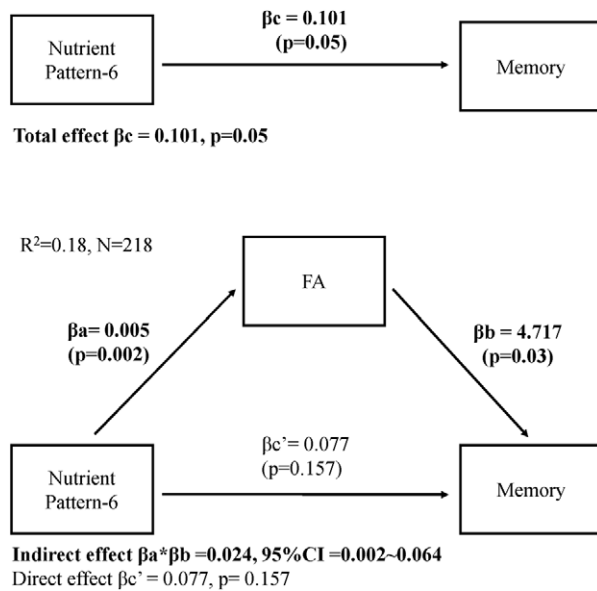


FIGURE 1: Mediation model for composite memory score. Models were analyzed using Preacher and Hayes's (Preacher and Hayes 2008) PROCESS SPSS macro. β indicate standardized beta weights and were estimated from models adjusted for age, sex, education, ethnicity, APOE, and caloric intake. The 95%CI indicates the 10000 sample bootstrapped 95% confidence intervals for the indirect effects. A 95%CI not including 0 indicates statistic significance. R^2 indicates the fit of the mediation model. Acronyms: fractional anisotropy (FA); confidence interval (CI).

PUFA, and vitamin E are fish, nuts, cereals, and vegetables, all of which are considered as the beneficial food components in the Mediterranean diet. Thus, our study is in line with the previous reports in supporting beneficial roles of PUFAs and other healthy elements of diet on brain white matter. In addition, our study used a data-driven method to find dietary patterns naturally existing in this multiethnic study population, who might not consume a typical Mediterranean diet. Rather than giving equal weights to the food components in a Mediterranean diet, the PCA-derived nutrient pattern identified the most relevant nutrients, allowing different weights for the nutrients in the pattern.

The nutrient pattern 6 only explains a small percentage of total variation of nutrients intake in this study population. However, this nutrient pattern can be viewed as similar to those risk factors that are rare but strongly associated with certain diseases. In addition to their strong association with white matter integrity, there is also strong evidence supporting the potential biological feasibility for PUFAs and vitamin E playing a role in maintaining white matter microstructural integrity. PUFAs and vitamin E are well documented to have beneficial effects on vascular factors.³⁶ Therefore, it is possible that following a diet diverging from nutrient pattern 6 may lead to accumulated vascular risk factors such as

hypertension and diabetes, which in turn have been linked with damaged white matter integrity.³⁷ However, as adjusting vascular factors did not change the association between nutrient pattern 6 and FA in our study, other mechanisms might be involved. For example, PUFAs may be related to white matter integrity through inflammation or oxidative stress, both of which have been implicated in the pathochemistry of myelin membrane disruptions.^{38,39} In the cuprizone mouse model of multiple sclerosis, Ω -3 PUFAs in the brain inhibited inflammation by reducing the release of nitric oxide and tumor necrosis factor- α from primary microglia while at the same time enhancing beneficial immune responses such as microglial phagocytosis.⁴⁰ Furthermore, the mechanisms underlying the association between nutrient pattern 6 and FA can be explained by the biophysiological roles of the PUFAs and vitamin E on pathways directly involving axonal loss or demyelization.⁴¹ An in vivo study showed that a Ω -3 PUFA injection in the rat brain increased myelinogenesis.⁴² Another mouse study also demonstrated that Ω -3 PUFAs prevented the loss of myelin basic protein, preserved the integrity of the myelin sheath, maintained nerve fiber conductivity, and protected oligodendrocytes from excitotoxicity and death.⁴³ Similarly, in vivo and in vitro studies suggest that vitamin E deficiency induces axonal degeneration and loss of myelination,⁴⁴ whereas vitamin E treatment attenuates demyelination and promotes remyelination.⁴⁵

Our study revealed that microstructural white matter integrity was positively associated with cognitive performance. Consistent with our results, several longitudinal studies showed that deficits in white matter microstructure predicted cognitive decline.¹¹ Combined with the observation that DTI can detect diffuse abnormalities in white matter that appears to be normal on conventional MRI images,⁴⁶ DTI-derived white matter indices may be a sensitive method to detect the underpinnings of subtle cognitive changes. It is therefore not surprising to find that beneficial dietary factors might be related with better cognition via maintaining better white matter integrity. To our knowledge, there are very few studies that have examined whether brain structural abnormalities mediated the effect of dietary factors on cognition.^{47,48} These studies found that white matter hyperintensity volume⁴⁸ or gray matter volume⁴⁷ might explain the relationship between Ω -3 PUFAs and executive function. In our study, we expanded the findings to several cognitive domains, and to nutrient patterns, and for the first time established a mediating role of white matter integrity in the relationship between a "PUFAs and vitamin E" dietary pattern and cognition.

Our study has many strengths. The study included a relatively large sample of a multiethnic community-dwelling elderly population with extensive data on demographic, clinical, and lifestyle factors including nutritional data. In sensitivity analysis, we excluded participants with dementia, thus limiting our analysis to a preclinical stage, and the results remained the same. In addition, we used mediation analysis to estimate whether there was a potential mediating role of white matter integrity in the relationship of diet and cognition, and the results shed light on our understanding of the mechanisms for dietary factors to be related with cognition.

Our study has some limitations that need to note. It is a cross-sectional study, and therefore no causal relationship between diet and DTI, or relationship between DTI and cognition, can be established. However, dietary assessment was performed a few years before MRI scan, which helped to reduce the possibility of reverse causality to some extent. Although the food frequency questionnaire has been validated for some nutrients (including vitamins A, C, and E),³¹ the accuracy for the measurement of other selected nutrients was unknown, and there is a possibility of information bias. There might be a concern for selection bias, as our MRI study required subjects to be dementia-free. It is possible that the proportion of subjects who had developed dementia and were excluded from the MRI study might be higher among those with worse diet than among those with healthier diet, leaving people with healthier brain overselected among people with worse diet (such as those with low nutrient pattern 6 scores). However, such a selection process might have biased the results toward null. Although we adjusted for many potential confounders, we cannot completely rule out residual confounding. For example, despite that we have used as much information as possible, including self-report of the diseases, actual measure of blood pressure, and medication use, to best judge whether a subject had a vascular comorbidity, we could not rule out the residual confounding from unmeasured vascular factors. Another limitation of our study is that we only used nutrient intake from food in the analysis, due to the less detailed and reliable information we collected on supplements intakes. However, foods contain a variety of nutrients that may work synergistically to provide the best biological benefits. In addition, the Dietary Guidelines for Americans (<http://health.gov/dietaryguidelines/2015/guidelines/>) recommend that nutritional needs should be met primarily from foods. Thus, our results may help to provide scientific evidence on the benefits of food sources of nutrients for such guidelines.

Overall, the current study found that a diet high in PUFAs and vitamin E was associated with less white matter damage in elderly people. Our study also found that white matter integrity was associated with cognitive performances and it might explain, at least partially, certain dietary factors' association with cognition. Future studies, especially longitudinal ones, are warranted to confirm our findings and to test causality in these observed relationships.

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Author Contributions

Y.Gu contributed to study concept and design. All authors contributed to data acquisition and analysis. Y.Gu and A.M.B. contributed to drafting the manuscript and figures.

Potential Conflicts of Interest

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