ORIGINAL CONTRIBUTION

Mediterranean Diet and White Matter Hyperintensity Volume in the Northern Manhattan Study

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Objective: To examine the association between a Mediterranean-style diet (MeDi) and brain magnetic resonance imaging white matter hyperintensity volume (WMHV).

Design: A cross-sectional analysis within a longitudinal population-based cohort study. A semiquantitative food frequency questionnaire was administered, and a score (range, 0-9) was calculated to reflect increasing similarity to the MeDi pattern.

Setting: The Northern Manhattan Study.

Participants: A total of 1091 participants, of whom 966 had dietary information (mean age, 72 years; 59.3% women, 64.6% Hispanic, 15.6% white, and 17.5% black).

Main Outcome Measures: The WMHV was measured by quantitative brain magnetic resonance imaging. Linear regression models were constructed to examine the association between the MeDi score and the log-transformed WMHV as a proportion of total cranial volume, controlling for sociodemographic and vascular risk factors.

Results: On the MeDi scale, 11.6% scored 0 to 2, 15.8% scored 3, 23.0% scored 4, 23.5% scored 5, and 26.1% scored 6 to 9. Each 1-point increase in MeDi score was associated with a lower log WMHV ($\beta = -.04$, $P = .01$). The only MeDi score component that was an independent predictor of WMHV was the ratio of monounsaturated to saturated fat ($\beta = -.20$, $P = .001$).

Conclusions: A MeDi was associated with a lower WMHV burden, a marker of small vessel damage in the brain. However, white matter hyperintensities are etiologically heterogenous and can include neurodegeneration. Replication by other population-based studies is needed.

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WHITE MATTER HYPERintensities (WMHs) visible on T2-weighted magnetic resonance imaging (MRI) are markers of chronic small vessel damage. Although they are often seen in people who are aging normally, WMHs are associated with vascular risk factors, including smoking, diabetes mellitus, high blood pressure, and dyslipidemia; correlate with small vessel damage in other organs, such as the eye and kidney; and can predict an increased risk of stroke and dementia (when a heavy burden is present).[1-4]

Although diet may be an important predictor of vascular disease, little is known about the possible association between dietary habits and WMHs. The Mediterranean-style diet (MeDi), representing the typical dietary habits of the populations bordering the Mediterranean Sea, includes a relatively high intake of fruits, vegetables, monounsaturated fat, fish, whole grains, legumes, and nuts; moderate alcohol consumption; and a low intake of red meat, saturated fat, and refined grains.

Studies have suggested that consumption of a MeDi is associated with a reduced risk of the metabolic syndrome,[5] coronary heart disease,[6] stroke,[6] and cognitive disorders,[7-9] but no studies to date, to our knowledge, have examined the association between a MeDi and WMH volume (WMHV). A greater understanding of modifiable risk factors for small vessel damage may facilitate the prevention of both stroke and cognitive decline. The previously observed associations between the MeDi and vascular risk factors and vascular outcomes–in addition to studies showing that 2 components of a MeDi, moderate alcohol use and fish consumption, are inversely associated with white matter abnormalities[10-12] –suggest the importance of examining the potential association between a MeDi and WMHV. Therefore, the goals of the current study are to examine the association between consumption of a MeDi and brain WMHV in a large, multiethnic, population-based cohort and to examine the potential moderating effects of known vascular risk factors, including age, blood pressure, diabetes, and lipid profiles.

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METHODS

STUDY POPULATION

The Northern Manhattan Study (NOMAS) is a prospective cohort study designed to determine stroke incidence, risk factors, and prognosis in a multiethnic urban population. Northern Manhattan is a well-defined area of New York City with a race/ethnicity distribution of 63% Hispanics, 20% non-Hispanic blacks, and 15% non-Hispanic whites. Details of the study have been published previously.[13-15]

Study participants were eligible if they (1) had never been diagnosed as having a stroke, (2) were aged 40 years and older, and (3) resided in Northern Manhattan for 3 months or longer in a household with a telephone. Study participants were identified by random-digit dialing, and interviews were conducted by trained bilingual research assistants. The telephone response rate was 91% (9% refused to be screened). Participants were recruited from the telephone sample to have an in-person baseline interview and assessment. The enrollment response rate was 75%, the overall participation rate was 69%, and a total of 3298 participants were enrolled. The study was approved by the institutional review boards of Columbia University and the University of Miami, and all participants provided informed consent.

MRI SUBSTUDY

Participants remaining clinically free of stroke were recruited sequentially during annual follow-up of the sample using the following criteria: (1) age older than 55 years, (2) no contraindications to MRI, and (3) signed institutional review board–approved informed consent. Of 3298 NOMAS participants, 2636 were alive and free of stroke in 2003 when the MRI subcohort was recruited. Of those, 488 had a stroke or died during enrollment, 1057 were not able to participate (133 were ineligible for MRI due to contraindications, 36 were unable to complete the MRI, 80 had severe cognitive impairment and were unable to provide consent, 150 had moved away from the study region, 80 were too ill or disabled to participate, and 578 refused), and 1091 were enrolled.

Imaging was performed on a 1.5-T MRI system (Philips Medical Systems) at the Hatch Research Center. The processing of MRI scans to extract WMHVs has been previously described.[16] Briefly, semiautomated measurements of pixel distributions using mathematical modeling of pixel-intensity histograms for cerebrospinal fluid and brain white and gray matter were used to identify the optimal pixel-intensity threshold to distinguish cerebral spinal fluid from brain matter, using a custom-designed image analysis package (QUANTA 6.2 using a Sun Microsystems Ultra 5 workstation). The WMHV was expressed as a proportion of total cranial volume (WMHV divided by total cranial volume multiplied by 100) to correct for head size and log-transformed to create a normal distribution. All analyses were performed with the investigator masked to the participant-identifying information. Interrater reliabilities for the MRI measures of intracranial volume (0.97), brain volume (0.97), and WMHV (0.99) from images of this study were high.[16]

BASELINE EVALUATION

Data were collected through interviews with trained bilingual research assistants in English or Spanish, depending on the language spoken by the participant at home. Physical and neurologic examinations were conducted by study physicians. Race/ethnicity was based on self-identification through a series of questions modeled after the US Census and conforming to standard definitions outlined by Directive 15.[17] Standardized questions were adapted from the Behavioral Risk Factor Surveillance System by the Centers for Disease Control and Prevention regarding hypertension, diabetes, cigarette smoking, and cardiac conditions.[14] Smoking was categorized as current (within the past year), former, or never smoker of cigarettes, cigars, or pipes. Blood pressure was obtained from the right brachial artery after a 10-minute rest in a supine position (Dinamap Pro100; Critikon Inc). Blood pressure was measured twice, before and after each examination, and averaged. Fasting blood specimens were analyzed at the Core Laboratory of the Irving Center for Clinical Research to determine glucose and lipid profiles as described previously.[18] Briefly, blood samples were drawn after an overnight fast. Plasma levels of high-density lipoprotein cholesterol (HDL-C) and low-density lipoprotein cholesterol (LDL-C) were measured using standardized enzymatic procedures with a Hitachi 705 automated spectrophotometer (Boehringer Mannheim). Use of antihypertensive medication, cholesterol-lowering medication, and insulin or diabetes medication were also recorded. Diabetes mellitus was defined by the patient's self-report of such a history, use of insulin or oral antidiabetic medication, or fasting glucose level of 126 mg/dL or higher (to convert to millimoles per liter, multiply by 0.0555). Physical activity was defined as the frequency and duration of 14 different recreational activities during the 2-week period before the interview, as described previously.[15]

DIET

At baseline, trained research assistants administered a modified Block National Cancer Institute food frequency questionnaire in English or Spanish.[19] This food frequency questionnaire assesses dietary patterns during the previous year. Food responses were modified to include specific Hispanic dietary items. We followed previously described methods for the construction of the MeDi score.[8,20] Briefly, we first regressed caloric intake (in kilocalories) and calculated the derived residuals of daily gram intake for each of the following 7 categories as delineated previously: dairy, meat, fruits, vegetables, legumes, cereals, and fish.[20] Individuals were assigned a value of 1 for each beneficial component (fruits, vegetables, legumes, cereals, and fish) whose consumption was at or above the sex-specific median, for each detrimental component (meat and dairy products) whose consumption was below the median, for a ratio of monounsaturated fats to saturated fats above the median, and for mild to moderate alcohol consumption (>0 drinks per week but ≤ 2 drinks per day in the previous year).[14] The MeDi score was the sum of the scores in the food categories (range, 0-9), with a greater score indicating greater similarity to a MeDi pattern. The MeDi score was analyzed as categories (scores of 0-2, 3, 4, 5, and 6-9) to facilitate comparison with other studies of the MeDi score and as a continuous variable.

STATISTICAL ANALYSIS

The univariate association between MeDi score categories and sociodemographic variables and vascular risk factors was examined using analysis of variance for continuous variables and χ^2 tests for categorical variables. To examine the association between a MeDi and WMHV, linear regression models were constructed with log-transformed WMHV as the dependent variable. The MeDi was analyzed as a continuous variable on a 9-point scale and as a categorical variable, with the lowest category (score, 0-2) as the reference category.

The following sequence of models were constructed: (1) adjusted for age at MRI only; (2) adjusted for age at MRI, sex, race/ethnicity, completion of high school, smoking (current, former, or never), moderate to heavy physical activity, and kilocalories consumed per day; (3) adjusted for the covariates in

Table 1. Mediterranean Dietary Patterns in the NOMAS Cohort and the Current MRI Study Subcohort[a]

Mediterranean Diet Component	NOMAS Cohort (n=2964)		MRI Subcohort (n=966)	
	Grams per Day, Mean (SD) [Median]	Servings per Day, Mean (SD) [Median]	Grams per Day, Mean (SD) [Median]	Servings per Day, Mean (SD) [Median]
Alcohol	1.15 (2.76) [0]	NA	1.37 (3.00) [0]	NA
Fish	12 (11) [10]	0.13 (0.12) [0.10]	12 (12) [10]	0.13 (0.13) [0.12]
Legumes	16 (18) [9]	0.14 (0.14) [0.12]	17 (18) [11]	0.15 (0.14) [0.12]
Vegetables	77 (54) [67]	0.83 (0.56) [0.73]	79 (57) [68]	0.86 (0.60) [0.75]
Fruit	149 (102) [131]	1.12 (0.76) [0.96]	147 (100) [126]	1.10 (0.74) [0.92]
Cereal	68 (40) [61]	0.80 (0.46) [0.72]	68 (38) [62]	0.77 (0.44) [0.70]
Meat	40 (29) [33]	0.36 (0.26) [0.32]	40 (28) [35]	0.35 (0.24) [0.32]
Dairy	104 (83) [92]	0.77 (0.54) [0.72]	107 (86) [97]	0.77 (0.56) [0.68]

Abbreviations: MRI, magnetic resonance imaging; NA, not applicable; NOMAS, Northern Manhattan Study.
[a]The mean (SD) ratio of monounsaturated to saturated fatty acids was 1.20 (0.34) (median, 1.13) in the NOMAS cohort and 1.23 (0.35) (median, 1.16) in the MRI subcohort.

model 2 and vascular risk factors that were potential confounders, as well as mediators including LDL-C, HDL-C, systolic blood pressure, diastolic blood pressure, the interaction between diastolic blood pressure and antihypertensive medication use, diabetes, and cardiac disease history; and (4) adjusted for the covariates in model 3 and body mass index (BMI; calculated as weight in kilograms divided by height in meters squared). In addition, we tested for possible interactions between the following covariates and a MeDi by adding interactions terms to model 4: age at MRI, race/ethnicity, LDL-C, HDL-C, systolic blood pressure, diastolic blood pressure, diabetes, and cardiac disease history.

In a supplementary analysis, we entered the 9 MeDi score components simultaneously into model 2 to examine which components were independently associated with WMHV.

RESULTS

The mean daily consumption of each component of the MeDi among the full NOMAS cohort at baseline in which the score was created and in the current MRI study subcohort is given in **Table 1**. The mean (SD) lapse in time from the baseline diet assessment to MRI was 7.2 (2.4) years (range, 2.0-14.0 years). Of the 1091 participants in the MRI subcohort, 966 had diet data available and were included in the current analyses. We modeled a MeDi score as a predictor of missing MRI data, controlling for covariates, to test for selection bias. However, no association was found between MeDi score (continuous or categorical) and availability of MRI WMHV data (ie, participation in our MRI subcohort), suggesting that selection of participants for the MRI substudy was not an important source of bias in the current study (multivariate-adjusted odds ratio for missing MRI data with each 1-point increase in MeDi score = 0.97; 95% CI, 0.92-1.02). The mean (SD) WMHV before log transformation, expressed as a percentage of total cranial volume, was 0.69% (0.82%) (minimum, 0.003%; first quartile, 0.22%; median, 0.38%; third quartile, 0.80%; and maximum, 5.70%).

Women had lower MeDi scores than the men ($P = .01$), and participants who reported moderate to heavy physical activity were more likely to report greater consumption of a MeDi ($P = .03$) (**Table 2**). Those with MeDi scores of 6 or higher also had lower BMI. There was a marginally significant difference in WMHV across MeDi categories in the univariate analysis ($P = .07$), with a trend toward higher WMHV among those with lower MeDi scores.

Each 1-point increase in MeDi score was associated with a significantly lower log WMHV (**Table 3**). The association persisted across all 4 models, and the parameter estimates remained stable as more covariates were added. Although the linear trend test *P* value was statistically significant, examination of the parameter estimates across the MeDi categories did not suggest a monotonic trend. We did not find evidence of effect modification between the MeDi score and any of the covariates in relation to log WMHV (data not shown). After simultaneous adjustment, the only component of the MeDi score that was an independent predictor of WMHV was the ratio of monounsaturated to saturated fat (**Table 4**).

The other covariates that were significantly associated with WMHV in multivariate-adjusted model 4 were age at MRI ($\beta = .047$, $P < .001$), black race (vs white; $\beta = .355$, $P < .001$), Hispanic ethnicity (vs white race; $\beta = .208$, $P = .02$), diastolic blood pressure ($\beta = .010$, $P = .01$), interaction between diastolic blood pressure and antihypertensive medication use ($\beta = .002$, $P = .02$), and BMI ($\beta = -.014$, $P = .01$).

COMMENT

The results of this study suggest a lower burden of WMHV among those with greater consumption of a MeDi. The association between a MeDi and WMHV was independent of sociodemographic and vascular risk factors, including physical activity, smoking, blood lipid levels, hypertension, diabetes, history of cardiac disease, and BMI. In particular, the data suggest that the most important component of the MeDi in predicting WMHV may be the ratio of monounsaturated to saturated fat. These findings indicate a potential role of dietary factors in small vessel disease.

To our knowledge, this is the first study to examine the association between the MeDi and brain WMHV. In fact, we found no previous studies examining the potential association between overall dietary patterns and WMHV. Previous studies[10-12] have shown a protective effect of moderate fish intake and moderate alcohol consumption on MRI white matter abnormalities. However, these components of the MeDi score were not significant independent

Table 2. Covariates Stratified by Mediterranean Diet Score

Variable	NOMAS MRI Subcohort (n=966)	Mediterranean Diet Score				
		0-2 (112 [11.6%])	3 (153 [15.8%])	4 (222 [23.0%])	5 (227 [23.5%])	6-9 (252 [26.1%])
WMHV, mean (SD)[a,b]	0.69 (0.82)	0.87 (0.83)	0.73 (0.95)	0.71 (0.83)	0.62 (0.80)	0.63 (0.74)
Sex, No. (%)[a]						
Male	393 (40.7)	33 (29.5)	63 (41.2)	92 (41.4)	82 (36.1)	123 (48.8)
Female	573 (59.3)	79 (70.5)	90 (58.8)	130 (58.6)	145 (63.9)	129 (51.2)
Race/ethnicity, No. (%)						
White	151 (15.6)	22 (19.6)	25 (16.3)	31 (14.0)	38 (16.7)	35 (13.9)
Black	169 (17.5)	21 (18.8)	30 (19.6)	36 (16.2)	40 (17.6)	42 (16.7)
Hispanic	624 (64.6)	67 (59.8)	95 (62.1)	147 (66.2)	147 (64.8)	168 (66.7)
Other	22 (2.3)	2 (1.8)	3 (2.0)	8 (3.6)	2 (0.9)	7 (2.8)
High school completion, No. (%)						
Yes	439 (45.4)	49 (43.8)	81 (52.9)	97 (43.7)	99 (43.6)	113 (44.8)
No	527 (54.6)	63 (56.2)	72 (47.1)	125 (56.3)	128 (56.4)	139 (55.2)
Cigarette smoking, No. (%)						
Current smoker	152 (15.7)	17 (15.2)	27 (17.6)	38 (17.1)	32 (14.1)	38 (15.1)
Former smoker	361 (37.4)	39 (34.8)	49 (32.0)	89 (40.1)	94 (41.4)	90 (35.7)
Never smoker	453 (46.9)	56 (50.0)	77 (50.3)	95 (42.8)	101 (44.5)	124 (49.2)
Physical activity, No. (%)[a]						
None-light	859 (89.3)	107 (96.4)	135 (90.0)	194 (87.4)	207 (91.2)	216 (85.7)
Moderate-heavy	103 (10.7)	4 (3.6)	15 (10.0)	28 (12.6)	20 (8.8)	36 (14.3)
Diabetes mellitus, No. (%)						
Yes	184 (19.0)	24 (21.4)	28 (18.3)	42 (18.9)	45 (19.8)	45 (17.9)
No	782 (81.0)	88 (78.6)	125 (81.7)	180 (81.1)	182 (80.2)	207 (82.1)
History of cardiac disease, No. (%)						
Yes	168 (17.4)	19 (17.0)	29 (19.0)	41 (18.5)	38 (16.7)	41 (16.3)
No	798 (82.6)	93 (83.0)	124 (81.0)	181 (81.5)	189 (83.3)	211 (83.7)
Age at MRI, mean (SD), y	71.6 (8.3)	73.2 (7.8)	71.2 (8.8)	71.3 (8.4)	71.7 (8.1)	71.3 (8.4)
Caloric intake, mean (SD), kcal	1606.2 (720.8)	1569.0 (736.3)	1668.4 (774.8)	1607.9 (744.1)	1620.4 (755.6)	1570.5 (623.1)
LDL-C, mean (SD), mg/dL	128.2 (34.7)	134.0 (35.1)	130.7 (35.8)	124.0 (33.7)	127.4 (37.2)	128.7 (32.2)
HDL-C, mean (SD), mg/dL	46.6 (14.5)	46.2 (14.8)	46.9 (15.3)	46.8 (15.0)	45.5 (14.0)	47.4 (14.0)
Systolic BP, mean (SD), mm Hg	140.7 (19.9)	143.7 (19.4)	140.0 (21.2)	139.9 (21.5)	140.6 (19.4)	140.7 (18.2)
Diastolic BP, mean (SD), mm Hg	83.7 (10.5)	83.1 (10.1)	83.8 (10.2)	83.4 (11.0)	84.1 (10.3)	83.9 (10.6)
BMI, mean (SD)[a]	28 (5)	29 (5)	29 (6)	28 (5)	29 (5)	28 (5)

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; MRI, magnetic resonance imaging; NOMAS, Northern Manhattan Study; WMHV, white matter hyperintensity volume.
SI conversion factors: To convert LDL-C and HDL-C to millimoles per liter, multiply by 0.0259.
[a] Difference across Mediterranean diet categories, $P<.05$.
[b] White matter hyperintensity volume as a percentage of total cranial volume.

Table 3. Association Between Mediterranean Diet and White Matter Hyperintensity Volume

Mediterranean Diet Score	β (*P* Value) for White Matter Hyperintensity Volume			
	Model 1[a]	Model 2[b]	Model 3[c]	Model 4[d]
3 vs 0-2	−.221 (.04)	−.228 (.03)	−.241 (.03)	−.235 (.03)
4 vs 0-2	−.156 (.11)	−.146 (.14)	−.149 (.14)	−.157 (.12)
5 vs 0-2	−.358 (<.001)	−.356 (<.001)	−.363 (<.001)	−.366 (<.001)
6-9 vs 0-2	−.248 (.01)	−.232 (.02)	−.248 (.01)	−.256 (.01)
Trend *P* value	.01	.01	.01	.01
Continuous: 1-point increase in score	−.040 (.02)	−.039 (.03)	−.041 (.02)	−.043 (.01)

[a] Controlling for age at magnetic resonance imaging.
[b] Controlling for age at magnetic resonance imaging, sex, race/ethnicity, high school education completion, moderate to heavy physical activity, smoking, and caloric intake.
[c] Controlling for age at magnetic resonance imaging, sex, race/ethnicity, high school education completion, moderate to heavy physical activity, caloric intake, smoking, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, systolic blood pressure, diastolic blood pressure, the interaction between diastolic blood pressure and antihypertensive medication use, diabetes mellitus, and cardiac disease history.
[d] Controlling for age at magnetic resonance imaging, sex, race/ethnicity, high school education completion, moderate to heavy physical activity, caloric intake, smoking, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, systolic blood pressure, diastolic blood pressure, the interaction between diastolic blood pressure and antihypertensive medication use, diabetes, cardiac disease history, and body mass index.

predictors of WMHV in the current study. Vitamin D deficiency and low serum folate levels have also been associated with increased WMHV in previous studies.[21,22]

Our finding of a lower WMH burden among those with greater consumption of a MeDi are consistent with previous studies that have shown inverse associations be-

tween adherence to the MeDi and several subclinical markers of vascular disease risk. The MeDi has been associated with improved endothelial function,[23] adiposity,[24] and lower levels of inflammatory markers, including C-reactive protein[25] and interleukin 6,[26] and these may be mechanisms underlying the observed association between the MeDi and WMHV.

The results of the current study link a MeDi with a lower burden of WMHV (a marker of small vessel damage in the brain) and suggest a possible mechanism to explain studies showing that a MeDi is protective against overall mortality and death due to cardiovascular disease.[6] Furthermore, consumption of a MeDi has been associated with a lower risk of mild cognitive impairment, Alzheimer disease, and dementia, and there is great interest in small vessel damage in these processes as well.[7-9] Although replication of these findings in other cohorts, as well as prospective imaging studies, are needed, our findings add to a growing body of literature indicating that a MeDi may be protective against subclinical vascular damage.

Roughly half of the NOMAS participants self-identified as Hispanic, and most immigrated to the United States from the Dominican Republic in the Caribbean. Several studies[27-30] have demonstrated beneficial health effects of a MeDi in non-Mediterranean populations, supporting the importance of examining the association between a MeDi and subclinical vascular disease in our non-Mediterranean and multiethnic population in Northern Manhattan. As a whole, the dietary habits of the NOMAS cohort at baseline were less consistent with a MeDi pattern compared with other European (Greek[31] and Spanish[32]) and US[6,30] cohort studies in which the MeDi has been examined. In particular, the consumption of fruits, vegetables, legumes, fish, and cereals was less in our cohort than in others.[6,30-32] Therefore, the diet patterns of the NOMAS cohort may not accurately reflect a true MeDi (ie, similar to that followed by populations in the Mediterranean region). For example, consumption of monounsaturated fatty acids, mostly deriving from olive oil, is considerably lower in our population compared with Mediterranean ones. In this context, the results of the current study imply that even a modest adherence to a MeDi (compared with those whose dietary habits are even farther away from the MeDi principles) may protect against vascular outcomes. Similarly, the fact that the ratio of monounsaturated fatty acids to saturated fatty acids was significantly associated with WMHV, despite the low level of olive oil use, only underscores its importance because it implies that even low consumption of olive oil has the potential to be etiologically relevant.

Strengths of our study include the large, ethnically diverse, population-based cohort of both middle-aged and elderly adults and the comprehensive data on other established vascular risk factors. However, our study has several limitations. We only measured food frequency at baseline, which was on average 7 years before the time of MRI WMH assessment (range, 2-14 years), and thus participants could have changed their diet before the MRI was performed. However, dietary patterns appear to be stable in other population-based studies.[33] In addition, despite the use of a valid and reliable food frequency questionnaire[19,34,35] to calculate MeDi scores, a potential for both random and systematic misclassification of dietary habits persists, although any misclassification is most likely to be random and thus tending to minimize an association between a MeDi and WMHV. Most studies depend on similar methods, and they are a practical approach, albeit subjective in nature. In addition, we used the traditional MeDi score method to quantify adherence, but this too has limitations because the score is based on the cohort- and sex-specific median values across 9 food categories, which does not readily allow for an examination of dose-dependent associations. However, most population-based studies have used this approach. Although the potential for confounding always exists, the persistence of associations after adjustment for many potential confounders suggests that this form of bias does not account for the associations observed. The MRI study population represents a subcohort of the overall NOMAS cohort and was younger and generally healthier than the full cohort. However, as mentioned previously, we did not observe diet differences between those who were included and excluded, again suggesting that selection into the study cohort did not bias our results. Last, MRIs to measure WMHV were only conducted once, so we are unable to infer the temporal association between the MeDi and development of WMHs.

Table 4. Association Between Each Component of the Mediterranean Diet Score and White Matter Hyperintensity Volume

Dichotomous Mediterranean Diet Score Component	β (*P* Value) for White Matter Hyperintensity Volume[a]
Alcohol	−.049 (.43)
Fish	.022 (.69)
Legumes	−.048 (.40)
Vegetables	−.020 (.73)
Fruit	−.079 (.17)
Cereal	.057 (.32)
Meat	−.014 (.81)
Dairy	.016 (.79)
Monounsaturated: saturated fat	−.201 (.001)

[a] Controlling for all Mediterranean diet score components, age at magnetic resonance imaging, sex, race/ethnicity, high school education completion, moderate to heavy physical activity, smoking, and caloric intake.

In summary, the current study suggests a possible protective association between increased consumption of a MeDi and small vessel disease. The MeDi emphasizes a high consumption of olive oil, plant proteins, whole grain, and fish; a moderate consumption of alcohol; and a low consumption of red meat, refined grains, and sweets. The associations with WMHV may be driven by the favorable ratio of monounsaturated fat consumption over saturated fat. However, the results of the analysis of the individual MeDi scale components suggest that the overall dietary pattern, rather than any of the individual components, may be more etiologically relevant in relation to WMHV. Future studies are necessary to replicate and further explore the nature of the association between a MeDi and WMHV.

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