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A Mediterranean-Style Diet and White Matter Hyperintensity Volume: the Northern Manhattan Study

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Abstract

Objective—To examine the association between a Mediterranean-style diet (MeDi) and brain MRI white matter hyperintensities (WMH). The MeDi has previously been associated with a reduced risk of cardiovascular morbidity, possibly including stroke. A greater understanding of modifiable risk factors for small vessel damage may facilitate the prevention of stroke and cognitive decline.

Design—A cross-sectional analysis within a longitudinal population-based cohort study. A semi-quantitative 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—1,091 participants, of which 966 had dietary information (mean age 72, 59% women, 65% Hispanic, 16% White, 17% Black).

Main outcome measures—WMH volume was measured by quantitative brain MRI. Linear regression models were constructed to examine the relation between the MeDi score and the log-

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transformed WMH volume as a proportion of total cranial volume, controlling for sociodemographic and vascular risk factors.

Results—On the MeDi scale, 12% scored 0-2, 16 scored 3, 23% scored 4, 23% scored 5, 26% scored 6-9. Each 1-point increase in MeDi score was associated with a lower log WMH volume (β=-0.04, p=0.02). The only MeDi score component that was an independent predictor of WMH volume was the ratio of monounsaturated to saturated fat (β=-0.20, p=0.001).

Conclusions—A Mediterranean-style diet was associated with a lower WMH 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.

Introduction

White matter hyperintensities (WMH) visible on T2 weighted MRI are markers of chronic small vessel damage. Although they are often seen in people who are aging normally, WMH are associated with vascular risk factors including smoking, diabetes, high blood pressure and dyslipidemia, correlate with small vessel damage in other organs such as the eye and kidney, and a heavy burden predicts an increased risk of stroke and dementia [1-4].

Although diet may be an important predictor of vascular disease, little is known about the possible association between dietary habits and WMH. The Mediterranean 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 Mediterranean-style diet 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 have examined the relationship between MeDi and WMH. A greater understanding of modifiable risk factors for small vessel damage may facilitate the prevention of both stroke and cognitive decline. The goal of the current study is to examine the relationship between consumption of a Mediterranean dietary pattern and brain WMH volume in a large multi-ethnic population-based cohort, and to examine the potential moderating effects of known vascular risk factors including age, blood pressure, diabetes, and lipid profiles.

Methods

Study population

The Northern Manhattan Study is a prospective cohort study designed to determine stroke incidence, risk factors, and prognosis in a multi-ethnic urban population. Northern Manhattan is a well-defined area of New York City with a race/ethnic distribution of 63% Hispanics, 20% Non-Hispanic black, and 15% non-Hispanic white residents. Details of the study have been published previously[10-12].

Subjects were eligible if they: a) had never been diagnosed with a stroke; b) were >40 years old; and c) resided in Northern Manhattan for ≥ 3 months, in a household with a telephone. Subjects 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). Subjects were recruited from the telephone sample to have an in-person baseline interview and assessment. The enrollment response rate was 75% and the overall participation rate was 69% and a total of 3,298 subjects were enrolled. The study was approved by the IRBs of Columbia University and the University of Miami and all subjects provided informed consent.

MRI sub-study—Participants remaining clinically stroke-free were recruited sequentially during annual follow-up of the sample using the following criteria: (1) age >55; (2) no contraindications to MRI; and (3) signed IRB-approved informed consent. Out 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 1.5T MRI system (Philips Medical Systems, Best, the Netherlands) at the Hatch Research Center. The processing of MRI scans to extract WMH volumes (WMHV) has been described[13]. Briefly, semi-automated measurements of pixel distributions using mathematical modeling of pixel-intensity histograms for CSF 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 (WMH/TCV*100) to correct for head size, and log-transformed to create a normal distribution. All analyses were performed blind to participant identifying information. Interraterreliabilities for the MRI measures of intracranial volume (0.97), brain volume (0.97), and WMHV (0.99) from images of this study were high.

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 neurological examinations were conducted by study physicians. Race-ethnicity was based upon self-identification through a series of questions modeled after the US census and conforming to standard definitions outlined by Directive 15[14]. Standardized questions were adapted from the Behavioral Risk Factor Surveillance System by the Centers for Disease Control regarding hypertension, diabetes, cigarette smoking, and cardiac conditions[11]. 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[15]. Briefly, blood samples were drawn after an overnight fast. Plasma levels of high density lipoprotein (HDL) and low density lipoprotein (LDL) cholesterol were measured using standardized enzymatic procedures with a Hitachi 705 automated spectrophotometer (Boehringer Mannheim, Mannheim, Germany). Use of anti-hypertensive medication, cholesterol-lowering medication and insulin/diabetes medication were also recorded. Diabetes mellitus was defined by the patient's self-report of such a history, use of insulin or oral anti-diabetic medication, or fasting glucose ≥126 mg/dl. 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[12].

Diet—At baseline participants were administered a modified Block National Cancer Institute food frequency questionnaire by trained research assistants, in English or Spanish[16]. This food frequency questionnaire assesses dietary patterns over 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[8,17]. Briefly, we first regressed caloric intake (in kilocalories) and calculated the derived residuals of daily gram intake for each of the following seven categories as delineated previously: dairy, meat, fruits, vegetables, legumes, cereals, and fish[17]. 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 over the previous year)[11]. The diet score was the sum of the scores in the food categories (range, 0-9) with a greater score indicating greater similarity to a Mediterranean dietary pattern. The diet score was analyzed as categories (scores of 0-2, 3, 4, 5, 6-9) to facilitate comparison with other studies of the Mediterranean diet score, and as a continuous variable.

Statistical analyses—The univariate association between MeDiscore categories and sociodemographic variables and vascular risk factors was examined using analysis of variance for continuous variables and chi-square tests for categorical variables. To examine the association between MeDi and WMH, linear regression models were constructed with log-transformed WMHV as the dependent variable. 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 referent 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 highschool, smoking (current, former versus never), moderate to heavy physical activity, and kilocalories consumed per day. A third model was also constructed that included the covariates in model 2 as well as vascular risk factors that were potential confounders as well as mediators: LDL, HDL, systolic blood pressure, diastolic blood pressure, the interaction between diastolic blood pressure and antihypertensive medication use, diabetes, and cardiac disease history. In addition, we tested for possible interactions between the following covariates and MeDi by adding interactions terms to model 3: age at MRI, race/ethnicity, LDL, HDL, systolic blood pressure, diastolic blood pressure, diabetes, and cardiac disease history.

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

Results

The average daily consumption of each component of the Mediterranean diet among the full NOMAS baseline cohort in which the score was created is shown in Table 1. The mean 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 MeDi score as a predictor of missing MRI data, controlling for covariates, to test for selection bias. However, there was no association between MeDi score (continuous or categorical) and availability of MRI WMH data (i.e. 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 OR for missing MRI data with each 1-point increase in MeDi score=0.97, 95% CI 0.92-1.02). The mean volume of white matter hyperintensities prior to log transformation, expressed as a percentage of total cranial volume, was 0.69% ± 0.82 (range 0.003-5.70).

Women had lower MeDi scores than the men, and participants who reported moderate to heavy physical activity were more likely to report greater consumption of a Mediterranean-style diet ($p<0.05$) (Table 2). There was a marginally significant difference in WMHV across MeDi categories in the univariate analysis ($p=0.07$), with a trend towards 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 3 models, as 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. In a sensitivity analysis in which BMI was added as a covariate to model 3, the parameter estimates and p-values remained essentially unchanged (data not shown). We did not find evidence of effect modification between 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).

Discussion

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

To the best of our knowledge this is the first study to examine the association between Mediterranean diet and brain WMH. In fact, we found no previous studies examining the potential relationship between overall dietary patterns and WMH. Previous studies have shown a protective effect of moderate fish intake and moderate alcohol consumption on MRI white matter abnormalities[18-20]. However, these components of the MeDi score were not significant independent predictors of WMHV in the current study. Vitamin D deficiency and low serum folate levels have also been associated with increased white matter hyperintensities in previous studies [21, 22].

Our finding of a lower WMH burden among those with greater consumption of a Mediterranean-style diet are consistent with previous studies that have shown inverse associations between adherence to the Mediterranean diet and several subclinical markers of vascular disease risk. The Mediterranean diet 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 Mediterranean dietary pattern and white matter hyperintensities.

The results of the current study link a Mediterranean diet with a lower burden of WMH – a marker of small vessel damage in the brain – and suggest a possible mechanism to explain studies showing that a Mediterranean style diet is protective against overall mortality and death due to cardiovascular disease[6]. Further, consumption of a Mediterranean-style diet 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]. While small vessel damage is pathologically linked to WMH, these lesions are also heterogeneous in etiology and thus the association between MeDi and WMH may represent other underlying processes such as neurodegeneration as well. 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 Mediterranean-style diet may be protective against subclinical vascular damage.

Roughly half of NOMAS participants self-identified as Hispanic, and most immigrated to the United States from the Dominican Republic in the Caribbean. As a whole the dietary habits of the NOMAS cohort at baseline were less consistent with a Mediterranean-style pattern as compared to other European and American cohort studies in which the Mediterranean diet has been examined [6, 27, 28]. In particular, the consumption of fruits, vegetables, legumes, fish and cereals was less in our cohort than in others[6, 27, 28]. Therefore, the diet patterns of the NOMAS cohort may not accurately reflect a 'truly' Mediterranean diet (i.e. similar to that followed by populations in the Mediterranean region). For example, consumption of MUFA, mostly deriving from olive oil, is considerably lower in our population compared to Mediterranean ones. In this context, the results of the current study imply that even a modest adherence to a Mediterranean-style diet (compared to subjects whose dietary habits are even further away from the MeDi principles) may protect against vascular outcomes.

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. First, 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 occurred. However, dietary patterns appear to be stable in other population-based studies[29]. In addition, despite the use of a valid and reliable food frequency questionnaire [16, 30, 31] 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 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 as the score is based on the cohort- and sex-specific median values across nine 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. Lastly, MRIs to measure WMH volume were only conducted once, so we are unable to infer the temporal association between MeDi and development of WMH.

In summary, the current study suggests a possible protective association between increased consumption of a Mediterranean-style dietary pattern and small vessel disease. The Mediterranean diet 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 WMH may be driven by the favorable ratio of monounsaturated fat consumption over saturated fat. Future studies are necessary to replicate and further explore the nature of the relationship between a Mediterranean diet and WMH.

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Table 1
Mediterranean dietary patterns in the NOMAS cohort (N=2964)

Mediterranean diet component	Grams/day: Mean ± SD, Median	Servings/day: Mean ± SD, Median
Alcohol	1.15±2.76, 0	N/A
Fish	12±11, 10	0.13±0.12, 0.10
Legumes	16±18, 9	0.14±0.14, 0.12
Vegetables	77±54, 67	0.83±0.56, 0.73
Fruit	149±102, 131	1.12±0.76, 0.96
Cereal	68±40, 61	0.80±0.46, 0.72
Meat	40±29, 33	0.36±0.26, 0.32
Dairy	104±83, 92	0.77±0.54, 0.72
Monounsaturated:saturated fat	Ratio: 1.20±0.34, 1.13	

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Table 2

Covariates stratified by Mediterranean diet score

Variable	Overall NOMAS MRI Cohort N=966	Mediterranean diet score				
		0-2 N=112, 12%	**3** N=153, 16%	**4** N=222, 23%	**5** N=227, 23%	**6-9** N=252, 26%
WMH[*†]						
mean (SD)	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 n (%)[*]						
Male	393 (41)	33 (29)	63 (41)	92 (41)	82 (36)	123 (49)
Female	573 (59)	79 (71)	90 (59)	130 (59)	145 (64)	129 (51)
Race/ethnicity n (%)						
White	151 (16)	22 (20)	25 (16)	31 (14)	38 (17)	35 (14)
Black	169 (17)	21 (19)	30 (20)	36 (16)	40 (18)	42 (17)
Hispanic	624 (65)	67 (60)	95 (62)	147 (66)	147 (65)	168 (67)
Other race	22 (2)	2 (2)	3 (2)	8 (4)	2 (1)	7 (3)
High school completion n (%)						
Yes	439 (45)	49 (44)	81 (53)	97 (44)	99 (44)	113 (45)
No	527 (55)	63 (56)	72 (47)	125 (56)	128 (56)	139 (55)
Cigarette smoking n (%)						
Current smoker	152 (16)	17 (15)	27 (18)	38 (17)	32 (14)	38 (15)
Former smoker	361 (37)	39 (35)	49 (32)	89 (40)	94 (41)	90 (36)
Never smoker	453 (47)	56 (50)	77 (50)	95 (43)	101 (45)	124 (49)
Physical activity[*] **n (%)**						
None-light	859 (89)	107 (96)	135 (90)	194 (87)	207 (91)	216 (86)
Moderate-Heavy	103 (11)	4 (4)	15 (10)	28 (13)	20 (9)	36 (14)
Diabetes n (%)						
Yes	184 (19)	24 (21)	28 (18)	42 (19)	45 (20)	45 (18)
No	782 (81)	88 (79)	125 (82)	180 (81)	182 (80)	207 (82)
History of cardiac disease n (%)						
Yes	168 (17)	19 (17)	29 (19)	41 (18)	38 (17)	41 (16)
No	798 (83)	93 (83)	124 (81)	181 (82)	189 (83)	211 (84)
Age at MRI						

Variable	Overall NOMAS MRI Cohort N=966	Mediterranean diet score				
		0-2 N=112, 12%	3 N=153, 16%	4 N=222, 23%	5 N=227, 23%	6-9 N=252, 26%
mean (SD)	71.6 (8.3)	73.2 (7.8)	71.2 (8.8)	71.3 (8.4)	71.7 (8.1)	71.3 (8.4)
Kcal mean (SD)	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						
mean (SD)	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						
mean (SD)	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)	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)	83.7 (10.5)	83.1 (10.1)	83.8 (10.2)	83.4 (11.0)	84.1 (10.3)	83.9 (10.6)

*Difference across MeDi categories $p<0.05$

†White matter hyperintensity volume as a percentage of total cranial volume

Table 3
Association between Mediterranean diet and white matter hyperintensity volume (N=966)

Mediterranean Diet Score	**β (p-value) for WMHV**		
	Model 1*	**Model 2†**	**Model 3‡**
3 vs. 0-2	-0.221 (0.04)	-0.228 (0.03)	-0.241 (0.03)
4 vs. 0-2	-0.156 (0.11)	-0.146 (0.14)	-0.149 (0.14)
5 vs. 0-2	-0.358 (0.0003)	-0.356 (0.0003)	-0.363 (0.0003)
6-9 vs. 0-2	-0.248 (0.01)	-0.232 (0.02)	-0.248 (0.01)
Trend p-value	0.01	0.01	0.01
Continuous: 1-point increase in score	-0.040 (0.02)	-0.039 (0.03)	-0.041 (0.02)

*Controlling for age at MRI

†Controlling for age at MRI, sex, race/ethnicity, high school education completion, moderate to heavy physical activity, Kcal

‡Controlling for age at MRI, sex, race/ethnicity, high school education completion, moderate to heavy physical activity, Kcal, smoking, LDL, HDL, systolic blood pressure, diastolic blood pressure, the interaction between diastolic blood pressure and antihypertensive medication use, diabetes, and cardiac disease history

Table 4

Association between each component of the Mediterranean diet score and white matter hyperintensity volume (N=966)

Dichotomous Mediterranean Diet Score Component	β (p-value) for WMHV *
Alcohol	-0.049 (0.43)
Fish	0.022 (0.69)
Legumes	-0.048 (0.40)
Vegetables	-0.020 (0.73)
Fruit	-0.079 (0.17)
Cereal	0.057 (0.32)
Meat	-0.014 (0.81)
Dairy	0.016 (0.79)
Monounsaturated: saturated fat	-0.201 (0.001)

* Controlling for all MeDi score components, age at MRI, sex, race/ethnicity, high school education completion, moderate to heavy physical activity, Kcal