

Mediterranean-style diet and risk of ischemic stroke, myocardial infarction, and vascular death: the Northern Manhattan Study^{1–4}

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ABSTRACT

Background: A dietary pattern common in regions near the Mediterranean appears to reduce risk of all-cause mortality and ischemic heart disease. Data on blacks and Hispanics in the United States are lacking, and to our knowledge only one study has examined a Mediterranean-style diet (MeDi) in relation to stroke.

Objective: In this study, we examined an MeDi in relation to vascular events.

Design: The Northern Manhattan Study is a population-based cohort to determine stroke incidence and risk factors (mean \pm SD age of participants: 69 \pm 10 y; 64% women; 55% Hispanic, 21% white, and 24% black). Diet was assessed at baseline by using a food-frequency questionnaire in 2568 participants. A higher score on a 0–9 scale represented increased adherence to an MeDi. The relation between the MeDi score and risk of ischemic stroke, myocardial infarction (MI), and vascular death was assessed with Cox models, with control for sociodemographic and vascular risk factors.

Results: The MeDi-score distribution was as follows: 0–2 (14%), 3 (17%), 4 (22%), 5 (22%), and 6–9 (25%). Over a mean follow-up of 9 y, 518 vascular events accrued (171 ischemic strokes, 133 MIs, and 314 vascular deaths). The MeDi score was inversely associated with risk of the composite outcome of ischemic stroke, MI, or vascular death (P -trend = 0.04) and with vascular death specifically (P -trend = 0.02). Moderate and high MeDi scores were marginally associated with decreased risk of MI. There was no association with ischemic stroke.

Conclusions: Higher consumption of an MeDi was associated with decreased risk of vascular events. Results support the role of a diet rich in fruit, vegetables, whole grains, fish, and olive oil in the promotion of ideal cardiovascular health. *Am J Clin Nutr* 2011;94:1458–64.

INTRODUCTION

The AHA⁵ recently launched a national campaign to define goals for achieving ideal cardiovascular health that includes dietary recommendations (1) and issued a scientific advisory stating that an MeDi had impressive effects on cardiovascular disease (2, 3). An MeDi, which represents the typical dietary habits of populations that border the Mediterranean Sea, includes a relatively high intake of fruit, vegetables, mono-unsaturated fat, fish, whole grains, legumes, and nuts; moderate alcohol consumption; and a low intake of red meat, saturated fat, and refined grains. Therefore, adherence to an MeDi is consistent with the AHA dietary guidelines. An MeDi has been widely

publicized for its many health benefits. Studies have suggested that consumption of an MeDi is a strong protective factor against all-cause mortality, as well as several cancers, IHD, diabetes, hypertension, obesity, Alzheimer disease, and dyslipidemia (4–14). However, to our knowledge, only one previous study has examined the relation between MeDi and stroke risk. An MeDi was inversely associated with risk of stroke and IHD in a large cohort of primarily white, female nurses (15).

Data on health consequences of an MeDi in US residents, particularly in Hispanics and blacks, are limited. Because of increased risk of vascular disease, particularly stroke, among blacks and Hispanics (16), studies that examine modifiable vascular risk factors in racially and ethnically diverse US populations are important. The goal of this study was to examine the relation between MeDi and risk of ischemic stroke, MI, and vascular death in a population-based prospective cohort that included men and women and blacks, whites, and Hispanics living in the same community.

SUBJECTS AND METHODS

Study population

The NOMAS is a prospective cohort study designed to determine stroke incidence, risk factors, and prognosis in a multi-

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⁵ Abbreviations used: AHA, American Heart Association; IHD, ischemic heart disease; MeDi, Mediterranean-style diet; MI, myocardial infarction; NOMAS, Northern Manhattan Study.

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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 (17).

Eligible subjects were those who 1) had never been diagnosed with ischemic stroke, 2) were >40 y old, and 3) resided in Northern Manhattan for ≥ 3 mo 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%. Subjects 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 subjects were enrolled with an average annual contact rate of 95%. Participants with a MI before baseline ($n = 237$) were excluded. The study was approved by the Columbia University and University of Miami institutional review boards, and all subjects provided informed consent.

Baseline evaluation

Data were collected through interviews with trained bilingual research assistants in English or Spanish. Physical and neurologic examinations were conducted by study neurologists. Race-ethnicity was based on self-identification through a series of questions modeled after the US Census and that conformed to standard definitions outlined by directive 15 (18). Standardized questions were adapted from the Behavioral Risk Factor Surveillance System by the CDC regarding hypertension, diabetes, smoking, and cardiac conditions (19). Blood pressure was measured with mercury sphygmomanometers and appropriately sized cuffs. Hypertension was defined as a blood pressure $\geq 140/90$ mm Hg (on the basis of an average of 2 measurements during one sitting) or the patient's self-reported hypertension or anti-hypertensive medication use. Diabetes was defined by the patient's self-reported diabetes, use of insulin or oral antidiabetic medication, or fasting glucose ≥ 126 mg/dL. Fasting lipid profile was measured at enrollment. Hypercholesterolemia was defined as having a total cholesterol >200 mg/dL, statin use, or a self-reported history of hypercholesterolemia. Physical activity was defined as the frequency and duration of 14 different recreational activities during the 2-wk period before the interview, as previously described (20).

Diet

At baseline, participants were administered a modified Block National Cancer Institute food-frequency questionnaire in English or Spanish by trained research assistants (21). 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 (12, 22). We first regressed kilocalorie intake and calculated the derived residuals of daily gram intakes for each of the following categories: dairy, meat, fruit, vegetables (excluding potatoes), legumes, cereals (all cereals including refined and whole grain), and fish (22). Individuals were assigned a value of one for each beneficial component (fruit, vegetables, legumes, cereals, and fish), the consumption of which was at or above the sex-specific median, for each detrimental component (meat and dairy products), the

consumption of which 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/wk but ≤ 2 drinks/d over the previous year) (19). The diet score was the sum of scores in food categories (range: 0–9), and a greater score indicated greater similarity to an MeDi pattern. The score was analyzed as quintiles (scores 0–2, 3, 4, 5, and 6–9) and as a continuous variable. Food-frequency data that were sufficient to calculate an MeDi score were available for 84% of NOMAS participants.

Prospective follow-up

Subjects were screened annually by telephone to determine changes in vital status, detect neurologic events, document interval hospitalizations, and review risk-factor status, medication changes, and changes in functional status. Persons who screened positive were scheduled for an in-person assessment, which included a chart review and examination by study neurologists. Ongoing hospital surveillance of admission and discharge data, including the screening of *International Classification of Diseases, Ninth Revision*, codes, was reviewed to detect outcome events.

Definition of outcomes

Primary outcomes were 1) incident vascular event (incident ischemic stroke, MI, or vascular death) as well as 2) incident ischemic stroke, 3) incident MI, and 4) vascular death. Follow-up procedures and outcome classifications were detailed previously (23, 24). Medical records of all hospitalizations were reviewed to verify the details of suspected events. Outcome events were reviewed by a specially trained research assistant, and when available, medical records were reviewed for all outcome events (91% for stroke and 99% for MI). Two neurologists classified the strokes independently after review of the data, and one of the principal investigators (RLS or MSVE) adjudicated disagreements.

Statistical analysis

The distribution of covariates of interest across MeDi-score categories was examined by using chi-square tests for categorical variables and ANOVA for continuous variables. Cox proportional hazard models were constructed to estimate HRs and 95% CIs for predictors of each outcome by using the time from baseline to the event as the time-dependent variable. Participants who did not have an outcome event were censored at the time of their last follow-up. To examine potential bias in our analyses, we created a binary variable to represent missing diet data ($n = 730$) and modeled this as a predictor of outcomes.

We used 2 models to assess the association between MeDi scores and vascular outcomes by 1) adjusting for age, sex, race-ethnicity, education, moderate-to-heavy physical activity, average total daily kilocalorie consumption, and smoking (never, past, and current) and 2) adjusting for potential mediators as well as confounders, including the covariates in model 1 as well as diabetes, hypertension, hypercholesterolemia, and history of self-reported cardiac disease. In a supplementary analysis, we simultaneously entered MeDi-score components into a model as predictors of our vascular outcomes. Because a self-report of



<500 or >4000 kcal might have indicated inaccurate reporting of dietary information, we conducted sensitivity analyses that excluded these participants.

RESULTS

A total of 2568 NOMAS participants were included in the study (mean \pm SD age: 68.6 \pm 10.3 y; 64% women; 55% Hispanic, 24% black, and 21% white). The average daily consumption of each MeDi-score component in the full NOMAS cohort in which the score was created is shown in **Table 1**. The availability of diet data was not a significant predictor of outcome events, even after the covariates were controlled for (HR for combined vascular events: 1.12; 95% CI: 0.92, 1.36; $P = 0.28$). During a mean follow-up of 9.0 \pm 3.5 y, there were 518 incident vascular events, including 171 ischemic strokes, 133 MIs, and 314 vascular deaths.

Characteristics of the study population stratified by MeDi scores are shown in **Table 2**. The following characteristics were associated with increased consumption of an MeDi pattern: moderate alcohol consumption, male sex, Hispanic ethnicity, and moderate-to-heavy physical activity.

Modeled as a continuous variable, the MeDi score was inversely associated with risk of the combined outcome of ischemic stroke, MI, and vascular death after adjustment for sociodemographics, physical activity, kilocalories, and smoking (**Table 3**). When the MeDi score was categorically modeled in quintiles, with the lowest quintile (scores 0–2) as the referent, a trend test suggested a significant inverse dose-response relation (**Table 3**), although an examination of effect estimates and CIs for each quintile suggested a possible threshold effect beyond the third quintile (score ≥ 4). As expected, the trend was attenuated and no longer significant after adjustment for potential mediating variables on the causal pathway between diet and vascular outcomes, including hypertension, diabetes, hypercholesterolemia, and cardiac disease history. However, individuals in the third and fourth quintiles (ie, scores 4 and 5), still had significantly decreased risk of combined vascular events compared with participants in the lowest quintile. In a sensitivity analysis in which BMI was added as a covariate to model 2, results remained essentially unchanged (data not shown). There was no significant interaction between race-ethnicity and MeDi scores in relation to the vascular events.

There was no significant association between MeDi scores and risk of ischemic stroke (**Table 4**). Although point estimates were stronger for MI than for combined vascular events, decreased risk was only significant for those in the second compared with first quintiles and were suggestive of a possible protective effect in individuals in the top 3 quintiles ($P < 0.10$) after adjustment for sociodemographic characteristics, physical activity, individuals, and smoking. Estimates were slightly attenuated after adjustment for potential mediating variables (**Table 4**). Although there was a suggestive decreased risk of MI in individuals with moderate and high consumption of an MeDi (quintiles 2–5 compared with quintile 1), no dose-response relation was evident. Again, in sensitivity analyses in which BMI was added to model 2, results remained essentially unchanged (data not shown).

There was an inverse association between the MeDi score and risk of vascular death in a dose-response pattern (**Table 4**). After adjustment for sociodemographic characteristics, physical activity, individuals, and smoking, there was a 9% decrease in risk of vascular death with each one-point increase in the MeDi score. Subjects in the highest MeDi-score quintile (scores 6–9) had a 33% lower risk of vascular death than did subjects in the lowest quintile (scores 0–2). As expected, this association was slightly attenuated in model 2 (**Table 4**). When BMI was added as a covariate to model 2, effect estimates were also only slightly attenuated. MeDi score components that were independently associated with a decreased risk of vascular death were moderate alcohol consumption ($P = 0.004$), high fish consumption ($P = 0.03$), and high consumption of legumes ($P = 0.06$) (**Table 5**). The results remained consistent in sensitivity analyses in which 74 participants with a reported total daily kilocalorie consumption <500 or >4000 were excluded (not shown).

DISCUSSION

In this multiethnic, population-based, prospective cohort study we showed that a dietary pattern that was more consistent with that observed near the Mediterranean was protective against the combined outcome of ischemic stroke, MI, and vascular death after adjustment for sociodemographic and vascular risk factors. The association was significant for vascular death and appeared to be dose-dependent. The components of an MeDi that appeared to drive the inverse association with vascular death were the

TABLE 1
Mediterranean dietary patterns in the Northern Manhattan Study cohort ($n = 2964$)

Mediterranean diet component	Values in g/d		Values in servings/d	
	Mean \pm SD	Median	Mean \pm SD	Median
Alcohol	1.15 \pm 2.76	0	Not applicable	Not applicable
Fish	12 \pm 11	10	0.13 \pm 0.12	0.10
Legumes	16 \pm 18	9	0.14 \pm 0.14	0.12
Vegetables	77 \pm 54	67	0.83 \pm 0.56	0.73
Fruit	149 \pm 102	131	1.12 \pm 0.76	0.96
Cereal	68 \pm 40	61	0.80 \pm 0.46	0.72
Meat	40 \pm 29	33	0.36 \pm 0.26	0.32
Dairy	104 \pm 83	92	0.77 \pm 0.54	0.72
Monounsaturated:saturated fat	1.20 \pm 0.34	1.13	—	—

TABLE 2

Covariates stratified by Mediterranean diet score

Variable	NOMAS ¹ cohort (n = 2568)	Mediterranean diet score				
		0–2 (n = 348; 14%)	3 (n = 437; 17%)	4 (n = 576; 22%)	5 (n = 572; 22%)	6–9 (n = 635; 25%)
Moderate alcohol consumption [n (%)] ²						
Yes	868 (34)	81 (23)	128 (29)	180 (31)	206 (36)	273 (43)
No	1697 (66)	266 (77)	309 (71)	396 (69)	365 (64)	361 (57)
Sex [n (%)] ²						
M	931 (36)	98 (28)	164 (38)	212 (37)	194 (34)	263 (41)
F	1637 (64)	250 (72)	273 (62)	364 (63)	378 (66)	372 (59)
Race-ethnicity [n (%)] ²						
White	542 (21)	91 (26)	105 (24)	130 (23)	113 (20)	103 (16)
Black	609 (24)	96 (28)	117 (27)	139 (24)	127 (22)	130 (21)
Hispanic	1417 (55)	161 (46)	215 (49)	307 (53)	332 (58)	402 (63)
High school completion [n (%)]						
Yes	1156 (45)	165 (47)	215 (49)	261 (45)	245 (43)	270 (43)
No	1412 (55)	183 (53)	222 (51)	315 (55)	327 (57)	365 (57)
Cigarette smoking [n (%)] ²						
Never	1202 (47)	164 (47)	196 (45)	252 (44)	270 (47)	315 (50)
Former	970 (38)	109 (31)	163 (37)	232 (40)	221 (39)	245 (39)
Current	396 (15)	74 (21)	75 (17)	92 (16)	81 (14)	74 (12)
Physical activity [n (%)] ²						
None to light	2343 (91)	328 (95)	401 (92)	525 (91)	526 (92)	563 (89)
Moderate to heavy	220 (9)	19 (5)	33 (8)	51 (9)	46 (8)	71 (11)
Hypertension [n (%)]						
Yes	1876 (73)	267 (77)	314 (72)	409 (71)	417 (73)	469 (74)
No	692 (27)	81 (23)	123 (28)	167 (29)	155 (27)	166 (26)
Diabetes [n (%)]						
Yes	529 (21)	73 (21)	90 (21)	124 (22)	119 (21)	123 (19)
No	2039 (79)	275 (79)	347 (79)	452 (78)	453 (79)	512 (81)
Hypercholesterolemia [n (%)]						
Yes	1108 (43)	194 (56)	243 (56)	323 (56)	322 (56)	378 (60)
No	1460 (57)	154 (44)	194 (44)	253 (44)	250 (44)	257 (40)
Previous cardiac disease [n (%)]						
Yes	463 (18)	62 (18)	87 (20)	114 (20)	99 (17)	101 (16)
No	2105 (82)	286 (82)	350 (80)	462 (80)	473 (83)	534 (84)
Age (y)	69 ± 10 ³	69 ± 10	69 ± 11	69 ± 11	68 ± 10	68 ± 10
Kilocalories	1581 ± 746	1537 ± 819	1620 ± 817	1584 ± 750	1581 ± 735	1575 ± 652

¹ NOMAS, Northern Manhattan Study.² Chi-square $P < 0.05$.³ Mean ± SD (all such values).

consumption of alcohol, fish, and legumes. There was no apparent dose-response relation between an MeDi and MI. However, the data were suggestive of a possible protective association for MI in individuals with even a moderate consumption of an MeDi (everyone in the top 4 MeDi-score quintiles), although the association was not significant after adjustment for all covariates. Point estimates were stronger for MI than for vascular death or combined vascular events, but with only 133 MIs accrued, the power to detect significant associations for this outcome was low. In contrast, an MeDi was not associated with risk of ischemic stroke.

Several studies have shown associations between the consumption of an MeDi and a lower risk of overall mortality, death because of IHD, cardiovascular disease in general, and Alzheimer disease (12–14, 22, 25). However, few studies have been conducted in the United States, and to our knowledge, our study was the first to examine the association between MeDi and MI and stroke in a multiethnic urban sample.

To our knowledge, only one other study has examined MeDi in relation to stroke risk (15). In the all-women, and primarily white, Nurses' Health Study, the greater consumption of an MeDi pattern was associated with a modest decreased risk of stroke. Compared with our study, the Nurses' Health Study sample was 30 times larger, and the number of incident strokes was 10 times as many, which resulted in greater power to detect associations. When stroke cases in the Nurses' Health Study were divided into ischemic and hemorrhagic, there was no significant association observed for ischemic strokes, and the magnitude of estimates was similar to ours. We focused on ischemic strokes, but the inclusion of hemorrhagic strokes did not alter our results (data not shown). In addition, the authors (15) reported a stronger association between an MeDi and fatal, and therefore presumably more severe, cases of IHD and stroke than nonfatal cases. This finding was consistent with our observation of a significant dose-response association between MeDi score and vascular death.

TABLE 3

Association between Mediterranean-style diet and ischemic stroke, myocardial infarction, and vascular death combined ($n = 518$)¹

Mediterranean diet score	Model 1	Model 2
0–2 ($n = 348$)	1.00 (reference)	1.00 (reference)
3 ($n = 437$)	0.85 (0.63, 1.13)	0.85 (0.63, 1.13)
4 ($n = 576$)	0.72 (0.54, 0.96) ²	0.72 (0.54, 0.96) ²
5 ($n = 572$)	0.72 (0.53, 0.96) ²	0.72 (0.54, 0.96) ²
6–9 ($n = 635$)	0.75 (0.56, 0.99) ²	0.80 (0.60, 1.06)
<i>P</i> -trend	0.04	0.10
Continuous: 1-point increase in score	0.94 (0.89, 1.00) ²	0.95 (0.90, 1.01) ³

¹ All values are HRs for combined vascular events; 95% CIs in parentheses. Calculated by using Cox proportional hazards models. Model 1 controlled for age at baseline, sex, race-ethnicity, completion of high school education, moderate-to-heavy physical activity, kilocalories, and cigarette smoking. Model 2 controlled for age at baseline, sex, race-ethnicity, completion of high school education, moderate-to-heavy physical activity, kilocalories, cigarette smoking, hypertension, diabetes, hypercholesterolemia, and history of cardiac disease.

² $P < 0.05$.

³ $0.05 < P < 0.10$.

The fact that ischemic stroke is heterogeneous and involves both small- and large-vessel disease may have contributed to the lack of association observed with the MeDi score in our study, whereas we saw a suggested marginally significant association with MI, which was more homogeneous and primarily atherosclerotic. To determine whether there was an effect of an MeDi primarily on large vessel disease, future large studies are needed to examine the effect of an MeDi across stroke subtypes.

Our finding that the increased consumption of an MeDi was associated with a lower risk of cardiovascular events was consistent with previous studies that have shown inverse associations between MeDi adherence and subclinical markers of vascular disease risk. An MeDi has been associated with better blood lipid profiles (26), improved endothelial function (27), lower systolic and diastolic blood pressures (10), adiposity (8), insulin resistance (28), and lower concentrations of inflammatory markers including C-reactive protein (29) and IL-6 (30).

One of the components of the MeDi score that may have the greatest effect on vascular disease is alcohol. We previously

showed that a moderate alcohol intake was protective against ischemic stroke as well as stroke, MI, and vascular death in NOMAS (19, 31). Moderate alcohol, fish, and legume consumption were the MeDi-score components associated with vascular death in this sample. Many studies have shown protective effects of fish consumption on cardiovascular disease mortality, which has been attributed to the rich source of omega-3 fatty acids in fish (32). Legumes are also a rich source of omega-3 fatty acids as well as protein, fiber, and folic acid, and a legume-rich diet has been shown to reduce cholesterol concentrations (33).

We hypothesized that diabetes, hypertension, and hypercholesterolemia are potential intermediates of an association between MeDi and vascular outcomes because this dietary pattern has the potential to modify these risk factors. The consumption of an MeDi has been shown to affect risk of these conditions, but a diagnosis of any of these conditions may also affect one's diet. Because our baseline data on diet and risk factors were collected at the same time, the temporal relations between these vascular risk factors and the dietary habits of our participants are not known, and conclusions regarding the association between an MeDi and risk of vascular events from models that included these risk factors should be made cautiously. However, our finding of some attenuation of associations when these risk factors were adjusted for supported the possibility of mediation.

We did not find an interaction between MeDi and race-ethnicity in relation to vascular outcomes. However, Hispanics were more likely to consume an MeDi. Roughly half of NOMAS participants self-identified as Hispanic, and most immigrated to the United States from the Dominican Republic. As a whole, the dietary habits of the NOMAS cohort at baseline were less consistent with a Mediterranean-style pattern than with other European and American cohort studies in which the Mediterranean diet has been examined (15, 34, 35). In particular, the consumption of fruit, vegetables, legumes, fish, and cereals was less in our cohort than in other cohorts (15, 34, 35). Therefore, the diet patterns of the NOMAS cohort may not accurately reflect a truly Mediterranean diet (ie, similar to that followed by populations in the Mediterranean region). For example, the consumption of MUFAs, mostly derived from olive oil, was

TABLE 4

Association between Mediterranean-style diet and ischemic stroke, MI, and vascular death¹

Mediterranean diet score	Ischemic stroke ($n = 171$)		MI ($n = 133$)		Vascular death ($n = 314$)	
	Model 1	Model 2	Model 1	Model 2	Model 1	Model 2
0–2 ($n = 348$)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
3 ($n = 437$)	1.17 (0.69, 2.00)	1.18 (0.69, 2.01)	0.55 (0.31, 1.00) ²	0.57 (0.32, 1.03) ³	0.90 (0.62, 1.29)	0.87 (0.60, 1.26)
4 ($n = 576$)	0.90 (0.53, 1.54)	0.91 (0.53, 1.55)	0.62 (0.36, 1.06) ³	0.62 (0.37, 1.06) ³	0.76 (0.53, 1.09)	0.74 (0.52, 1.06) ³
5 ($n = 572$)	0.93 (0.55, 1.60)	0.96 (0.56, 1.63)	0.59 (0.34, 1.03) ³	0.60 (0.34, 1.04) ³	0.70 (0.48, 1.02) ³	0.69 (0.47, 1.00) ²
6–9 ($n = 635$)	0.98 (0.58, 1.65)	1.03 (0.61, 1.73)	0.61 (0.35, 1.04) ³	0.65 (0.38, 1.12)	0.67 (0.46, 0.98) ²	0.71 (0.49, 1.04) ³
<i>P</i> -trend	0.62	0.78	0.19	0.27	0.02	0.04
Continuous: 1-point increase	0.98 (0.89, 1.08)	1.00 (0.90, 1.10)	0.93 (0.83, 1.04)	0.94 (0.84, 1.05)	0.91 (0.84, 0.97) ²	0.91 (0.85, 0.98) ²

¹ All values are HRs for combined vascular events; 95% CIs in parentheses. Calculated by using Cox proportional hazards models. Model 1 controlled for age at baseline, sex, race-ethnicity, completion of high school education, moderate-to-heavy physical activity, kilocalories, and cigarette smoking. Model 2 controlled for age at baseline, sex, race-ethnicity, completion of high school education, moderate-to-heavy physical activity, kilocalories, cigarette smoking, hypertension, diabetes, hypercholesterolemia, and history of cardiac disease. MI, myocardial infarction.

² $P < 0.05$.

³ $0.05 < P < 0.10$.

TABLE 5Association between each component of the Mediterranean-style diet score and vascular death¹

Mediterranean diet component	Vascular death (<i>n</i> = 314)
Alcohol	0.69 (0.54, 0.89)
Fish	0.79 (0.63, 0.98)
Legumes	0.80 (0.63, 1.01)
Vegetables	0.89 (0.71, 1.12)
Fruit	1.13 (0.90, 1.41)
Cereal	0.98 (0.79, 1.23)
Meat	1.01 (0.81, 1.26)
Dairy	1.02 (0.81, 1.28)
Monounsaturated:saturated fat	0.87 (0.70, 1.10)

¹ All values are HRs for combined vascular events; 95% CIs in parentheses. Calculated by using Cox proportional hazards models and controlled for all Mediterranean-style diet score components, age at baseline, sex, race-ethnicity, completion of high school education, moderate-to-heavy physical activity, kilocalories, and cigarette smoking.

considerably lower in our population than in Mediterranean populations. In this context, the results of our study implied that even a modest adherence to an MeDi in individuals (compared with subjects whose dietary habits are even further away from MeDi principles) may protect against vascular outcomes. However, our findings also suggested that the dose of the MeDi consumed in the NOMAS cohort, even in subjects in the top quintile, may not have been sufficiently high or broadly distributed to detect a strong protective association with vascular events in the fully adjusted models, particularly when coupled with the limited number of event-specific endpoints.

In addition to the ethnically diverse population, study strengths included the high follow-up rate and comprehensive data on other established vascular disease risk factors. However, our study had several limitations. First, the number of incident ischemic strokes and MIs that accrued in our population was relatively small, which limit the power to detect significant relations with the MeDi score. We only measured food frequency at baseline, and thus, participants could have changed their diets before measured outcomes occurred. However, dietary patterns appear to be stable in other population-based studies (13). In addition, despite the use of a valid and reliable food-frequency questionnaire (21, 36, 37) to calculate MeDi scores, the possibility of a random misclassification of dietary habits and recall bias remained. However, most large studies depended on similar methods. We used an MeDi-score calculation method that has been extensively used in the previous literature, but this also had limitations because the score is based on cohort- and sex-specific median values across 9 food categories, which does not readily allow for a more complete examination of dose-dependent associations. Although the potential for residual confounding by measured and unmeasured variables always exists, the persistence of associations after adjustment for many potential confounders suggests that this form of bias likely does not account for the associations observed. Last, we examined the potential for selection bias because of missing diet information and showed that missing diet data were not related to risk of outcome events, which suggests that selection bias did not influence the conclusions of our study.

In conclusion, we showed an association between greater consumption of an MeDi and a lower risk of vascular events,

specifically vascular death. We did not find evidence to support an association between an MeDi and risk of ischemic stroke. To our knowledge, this is the first study in the United States to include both men and women and a multiethnic population living in the same community. Our results support the new 2020 AHA goals for achieving ideal cardiovascular health, because the Mediterranean dietary pattern is similar in several ways to the AHA's dietary recommendations. Additional studies in larger populations are needed to elucidate the association between an MeDi and risk of vascular events, particularly stroke. The relative association with fatal and nonfatal events deserves further examination.

The authors' responsibilities were as follows—HG: designed research, analyzed data, wrote the manuscript, and had primary responsibility for the final content of the manuscript; CBW: designed and conducted research, analyzed data, wrote the manuscript, and had primary responsibility for final content of the manuscript; YG and RTD: analyzed data and provided essential materials; BB-A: conducted research; MSVE and RLS: designed and conducted research and analyzed data; NS: designed and conducted research, analyzed data, provided essential materials, and wrote the manuscript; and all authors: read and approved the final manuscript. None of the authors had a conflict of interest.

REFERENCES

- Lloyd-Jones DM, Hong Y, Labarthe D, Mozaffarian D, Appel LJ, Van Horn L, Greenlund K, Daniels S, Nichol G, Tomaselli GF, et al. Defining and setting national goals for cardiovascular health promotion and disease reduction: the American Heart Association's strategic Impact Goal through 2020 and beyond. *Circulation* 2010;121:586–613.
- Kris-Etherton P, Eckel RH, Howard BV, St Jeor S, Bazzarre TL. AHA Science Advisory: Lyon Diet Heart Study. Benefits of a Mediterranean-style, National Cholesterol Education Program/American Heart Association step I dietary pattern on cardiovascular disease. *Circulation* 2001;103:1823–5.
- Kris-Etherton P, Daniels SR, Eckel RH, Engler M, Howard BV, Krauss RM, Lichtenstein AH, Sacks F, St Jeor S, Stampfer M, et al. Summary of the scientific conference on dietary fatty acids and cardiovascular health: conference summary from the nutrition committee of the American Heart Association. *Circulation* 2001;103:1034–9.
- Sofi F, Cesari F, Abbate R, Gensini GF, Casini A. Adherence to Mediterranean diet and health status: meta-analysis. *BMJ* 2008;337:a1344.
- La Vecchia C. Mediterranean diet and cancer. *Public Health Nutr* 2004;7:965–8.
- Pelucchi C, Bosetti C, Rossi M, Negri E, La Vecchia C. Selected aspects of Mediterranean diet and cancer risk. *Nutr Cancer* 2009;61:756–66.
- Buckland G, Gonzalez CA, Agudo A, Vilarde M, Berenquer A, Amiano P, Ardanaz E, Arriola L, Barricarte A, Basterretxea M, et al. Adherence to the Mediterranean diet and risk of coronary heart disease in the Spanish EPIC Cohort Study. *Am J Epidemiol* 2009;170:1518–29.
- Babio N, Bullo M, Salas-Salvado J. Mediterranean diet and metabolic syndrome: the evidence. *Public Health Nutr* 2009;12:1607–17.
- Martinez-Gonzalez MA, de la Fuente-Arrillaga C, Nunez-Cordoba JM, Basterra-Gortari FJ, Beunza JJ, Vazquez Z, Benito S, Tortosa A, Bes-Rastrollo M. Adherence to Mediterranean diet and risk of developing diabetes: prospective cohort study. *BMJ* 2008;336:1348–51.
- Psaltopoulou T, Naska A, Orfanos P, Trichopoulos D, Moutokalakis T, Trichopoulou A. Olive oil, the Mediterranean diet, and arterial blood pressure: the Greek European Prospective Investigation into Cancer and Nutrition (EPIC) study. *Am J Clin Nutr* 2004;80:1012–8.
- Panagiotakos DB, Pitsavos C, Arvaniti F, Stefanadis C. Adherence to the Mediterranean food pattern predicts the prevalence of hypertension, hypercholesterolemia, diabetes and obesity, among healthy adults; the accuracy of the MedDietScore. *Prev Med* 2007;44:335–40.
- Scarmeas N, Stern Y, Tang MX, Mayeux R, Luchsinger JA. Mediterranean diet and risk for Alzheimer's disease. *Ann Neurol* 2006;59:912–21.
- Scarmeas N, Luchsinger JA, Schupf N, Brickman AM, Cosentino S, Tang MX, Stern Y. Physical activity, diet, and risk of Alzheimer disease. *JAMA* 2009;302:627–37.

14. Mitrou PN, Kipnis V, Thiébaud AC, Reedy J, Subar AF, Wirfält E, Flood A, Mouw T, Hollenbeck AR, Leitzmann MF, et al. Mediterranean dietary pattern and prediction of all-cause mortality in a US population: results from the NIH-AARP Diet and Health Study. *Arch Intern Med* 2007;167:2461–8.
15. Fung TT, Rexrode KM, Mantzoros CS, Manson JE, Willett WC, Hu FB. Mediterranean diet and incidence of and mortality from coronary heart disease and stroke in women. *Circulation* 2009;119:1093–100.
16. White H, Boden-Albala B, Wang C, Elkind MS, Rundek T, Wright CB, Sacco RL. Ischemic stroke subtype incidence among whites, blacks, and Hispanics: the Northern Manhattan Study. *Circulation* 2005;111:1327–31.
17. Sacco RL, Boden-Albala B, Abel G, Lin IF, Elkind M, Hauser WA, Paik MC, Shea S. Race-ethnic disparities in the impact of stroke risk factors: the northern Manhattan stroke study. *Stroke* 2001;32:1725–31.
18. Wallman KK, Hodgdon J. Race and ethnic standards for Federal statistics and administrative reporting. *Stat Report* 1977;77-110:450–4.
19. Sacco RL, Elkind M, Boden-Albala B, Lin IF, Kargman DE, Hauser WA, Shea S, Paik MC. The protective effect of moderate alcohol consumption on ischemic stroke. *JAMA* 1999;281:53–60.
20. Sacco RL, Gan R, Boden-Albala B, Kargman DE, Hauser WA, Shea S, Paik MC. Leisure-time physical activity and ischemic stroke risk: the Northern Manhattan Stroke Study. *Stroke* 1998;29:380–7.
21. Block G, Hartman AM, Dresser CM, Carroll MD, Gannon J, Gardner L. A data-based approach to diet questionnaire design and testing. *Am J Epidemiol* 1986;124:453–69.
22. Trichopoulou A, Costacou T, Bamia C, Trichopoulos D. Adherence to a Mediterranean diet and survival in a Greek population. *N Engl J Med* 2003;348:2599–608.
23. Boden-Albala B, Sacco RL, Lee HS, Grahame-Clarke C, Rundek T, Elkind MV, Wright C, Giardina EG, DiTullio MR, Homma S, et al. Metabolic syndrome and ischemic stroke risk: Northern Manhattan Study. *Stroke* 2008;39:30–5.
24. Boden-Albala B, Cammack S, Chong J, Wang C, Wright C, Rundek T, Elkind MS, Paik MC, Sacco RL. Diabetes, fasting glucose levels, and risk of ischemic stroke and vascular events: findings from the Northern Manhattan Study (NOMAS). *Diabetes Care* 2008;31:1132–7.
25. Knuops KT, de Groot LC, Kromhout D, Perrin AE, Moreiras-Varela O, Menotti A, van Staveren WA. Mediterranean diet, lifestyle factors, and 10-year mortality in elderly European men and women: the HALE project. *JAMA* 2004;292:1433–9.
26. Tzima N, Pitsavos C, Panagiotakos DB, Skoumas J, Zampelas A, Chrysohooou C, Stefanadis C. Mediterranean diet and insulin sensitivity, lipid profile and blood pressure levels, in overweight and obese people; the Attica study. *Lipids Health Dis* 2007;6:22.
27. Rallidis LS, Lekakis J, Kolomvotsou A, Zampelas A, Vamvakou G, Efstathiou S, Dimitriadis G, Raptis SA, Kremastinos DT. Close adherence to a Mediterranean diet improves endothelial function in subjects with abdominal obesity. *Am J Clin Nutr* 2009;90:263–8.
28. Rumawas ME, Meigs JB, Dwyer JT, McKeown NM, Jacques PF. Mediterranean-style dietary pattern, reduced risk of metabolic syndrome traits, and incidence in the Framingham Offspring Cohort. *Am J Clin Nutr* 2009;90:1608–14.
29. Fung TT, McCullough ML, Newby PK, Manson JE, Meigs JB, Rifai N, Willett WC, Hu FB. Diet-quality scores and plasma concentrations of markers of inflammation and endothelial dysfunction. *Am J Clin Nutr* 2005;82:163–73.
30. Dai J, Miller AH, Bremner JD, Goldberg J, Jones L, Shallenberger L, Buckham R, Murrah NV, Veledar E, Wilson PW, et al. Adherence to the mediterranean diet is inversely associated with circulating interleukin-6 among middle-aged men: a twin study. *Circulation* 2008;117:169–75.
31. Elkind MS, Sciacca R, Boden-Albala B, Rundek T, Paik MC, Sacco RL. Moderate alcohol consumption reduces risk of ischemic stroke: the Northern Manhattan Study. *Stroke* 2006;37:13–9.
32. Mozaffarian D. Fish, mercury, selenium and cardiovascular risk: current evidence and unanswered questions. *Int J Environ Res Public Health* 2009;6:1894–916.
33. Bazzano LA, Thompson AM, Tees MT, Nguyen CH, Winham DM. Non-soy legume consumption lowers cholesterol levels: a meta-analysis of randomized controlled trials. *Nutr Metab Cardiovasc Dis* 2011;21:94–103.
34. Benetou V, Trichopoulou A, Orfanos P, Naska A, Lagiou P, Boffetta P, Trichopoulos D. Conformity to traditional Mediterranean diet and cancer incidence: the Greek EPIC cohort. *Br J Cancer* 2008;99:191–5.
35. Nunez-Cordoba JM, Valencia-Serrano F, Toledo E, Alonso A, Martinez-Gonzalez MA. The Mediterranean diet and incidence of hypertension: the Seguimiento Universidad de Navarra (SUN) Study. *Am J Epidemiol* 2009;169:339–46.
36. Coates RJ, Eley JW, Block G, Gunter EW, Sowell AL, Grossman C, Greenberg RS. An evaluation of a food frequency questionnaire for assessing dietary intake of specific carotenoids and vitamin E among low-income black women. *Am J Epidemiol* 1991;134:658–71.
37. Harlan LC, Block G. Use of adjustment factors with a brief food frequency questionnaire to obtain nutrient values. *Epidemiology* 1990;1:224–31.

