Published in final edited form as:

Atherosclerosis. 2014 June ; 234(2): 303–310. doi:10.1016/j.atherosclerosis.2014.03.011.

Mediterranean diet and carotid atherosclerosis in the Northern Manhattan Study

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Abstract

Objective—Adherence to a Mediterranean-style diet (MeDi) may protect against clinical vascular events by reducing atherosclerosis, but data is limited. This is the first observational study of the association between MeDi adherence and carotid plaque thickness and area.

Methods—The study included 1374 participants of the population-based Northern Manhattan Study with diet assessed and carotid intima-media thickness (cIMT) and plaque measured using B-mode ultrasound (mean age 66 ± 9 years, 60% female, 60% Hispanic, 18% White, 19% Black). A MeDi adherence score (range = 0–9, 9 representing maximal adherence) was examined continuously and in quintiles (3/4/5/6 –9 vs. 0–2).

Results—Mean cIMT = 0.9 ± 0.1 mm and 57% had plaque (median plaque thickness = 1.5 mm, 75th percentile = 2.2; median plaque area = 4.2 mm^2, 75th percentile = 15.8). There was no association between MeDi and cIMT or plaque presence. MeDi adherence was inversely associated with the 75th percentile of plaque thickness and median of plaque area in quantile regression analyses. These associations persisted after controlling for demographics, smoking, physical activity, and total energy consumption (effect of a 1-point increase in MeDi score on the 75th percentile of plaque thickness = −0.049 mm, $p = 0.03$; median of plaque area = −0.371 mm^2, $p = 0.03$), and when additionally controlling for vascular disease biomarkers, medication use, BMI, and previous cardiac disease. The protective associations appeared strongest for those with a

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MeDi score of 5 (4th quintile) vs. 0–2 (bottom quintile). Differential effects of a MeDi on plaque thickness and area across race/ethnic groups was suggested.

Conclusions—Moderate and strict adherence to a MeDi may protect against a higher burden of carotid atherosclerotic plaque, which may mediate the protection against clinical vascular events. Efforts to improve adherence to a MeDi are critical to reducing the burden of atherosclerotic disease.

Keywords

Mediterranean diet; Carotid atherosclerosis; Plaque; Intima-media thickness

1. Introduction

The American Heart Association (AHA) has stressed the importance of a healthy diet in the prevention of cardiovascular disease (CVD) and stroke [1]. Over the past decade the focus of nutritional epidemiology has shifted from specific nutrients and foods to overall dietary patterns. One specific dietary pattern supported by the AHA and previously associated with a reduced risk of clinical vascular events in our study cohort, as well as others, is the Mediterranean-style diet (MeDi) [2,3]. A MeDi, representing the typical dietary habits of the populations bordering the Mediterranean Sea, includes a 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. The association between a MeDi and risk of vascular events may be mediated, at least in part, by large artery atherosclerosis. Healthy dietary patterns have been inversely associated with risk factors for atherosclerosis, including markers of inflammation and endothelial function [4–8]. However, data on the direct relationship between a MeDi and carotid atherosclerosis, particularly atherosclerotic plaque, is lacking. Therefore, the goal of our study was to examine the relationship between a MeDi and multiple markers of carotid atherosclerosis in the Northern Manhattan Study (NOMAS).

The importance of examining the relationship between novel risk factors, including a MeDi, and markers of subclinical vascular disease is underscored by (1) the etiologic heterogeneity of stroke and CVD, which impedes the identification of risk factors, (2) the need to identify the pathways through which diet may impact the risk of clinical vascular events, and (3) the potential ability to identify subclinical markers of vascular disease risk associated with diet that could be used as surrogate endpoints in clinical trials. Two small randomized trials have investigated the relationship between a MeDi and carotid intima-media thickness (cIMT) [9,10], a marker for subclinical atherosclerosis. Neither study demonstrated an association between a MeDi and progression of cIMT over a short duration of follow-up, though one study suggested the possibility of protective effects among those with elevated baseline cIMT [10]. To the best of our knowledge, our study represents the first large observational epidemiologic study of the relationship between adherence to a MeDi and atherosclerotic plaque.

Both studies mentioned above examined cIMT as a marker of atherosclerosis, rather than carotid plaques. Carotid plaque burden, a specific marker of subclinical atherosclerosis, is a

strong predictor for future ischemic stroke due to stenosis and plaque rupture [11–15]. Carotid atherosclerotic plaque burden, defined as the two-dimensional total plaque area (TPA), may be a powerful new non-invasive tool for vascular risk estimation. Data on risk factors, including dietary ones, for plaque area are limited. The examination of a MeDi in relation to both cIMT and multiple carotid plaque phenotypes, including TPA, in a race/ethnically diverse population-based US cohort makes the current study particularly novel, and an important contribution to the literature on the potential heart and brain benefits of a MeDi.

2. Methods

2.1. Study 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. Study participants were eligible if they: a) had never been diagnosed with 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 screening). Subjects were recruited from the telephone sample to have an in-person baseline interview and assessment between 1993 and 2001. The enrollment response rate was 75%, the overall participation rate was 69%, and 3298 subjects were enrolled. This study was approved by the Institutional Review Boards at the University of Miami and Columbia University, and all participants provided written informed consent.

2.2. Baseline assessment

We have collected baseline data on demographics, psychosocial and socioeconomic factors, medical history and medication use, vascular risk factors, family history and other health-related information. Physical and neurological examinations were conducted by study neurologists. All assessments were conducted in English or Spanish depending on the participant's primary language. Data were obtained directly from study subjects with standardized questions adapted from the Behavioral Risk Factor Surveillance System developed by the CDC regarding hypertension, diabetes, peripheral vascular disease, hypercholesterolemia, smoking, and cardiac conditions as described previously [16,17]. Standard questionnaires were used to assess physical activity [18–21], and alcohol use [22]. Physical activity was examined according to the frequency and duration of 14 different recreational activities during the 2-week period before the interview, and was categorized as moderate-heavy physical activity vs. none-light using methods described previously [23]. Information was collected regarding medication use, including anti-hypertensive medications, cholesterol-lowering medications, and diabetes medications. In addition, participants were asked whether diet was prescribed for the treatment of diabetes and hypercholesterolemia.

Subjects had blood collected and stored at baseline. Fasting plasma levels of total and HDL cholesterol and triglycerides were measured as were blood glucose levels. Systolic and

diastolic blood pressure were recorded and values are based on the mean of two readings after 10 min rest. Body mass index (BMI) was recorded as kg/m^2.

2.3. Diet

At baseline, NOMAS participants completed a comprehensive in-person diet assessment using a modified Block National Cancer Institute food frequency questionnaire (FFQ) administered by trained research assistants in English or Spanish [24]. This food frequency questionnaire listed 207 foods and was intended to represent typical food consumption over the previous year. Participants were asked to record how often each food was eaten. Food responses were modified to include specific dietary items frequently consumed by Hispanic populations.

Construction of the MeDi score is consistent with previously described methods using the approach of Trichopoulou and colleagues [25,26]. We regressed energy intake (kilocalories) and calculated the derived residuals of daily gram intake for each of the following categories: dairy (milk, cheese, yogurt, cream), meat (processed and unprocessed, including poultry), fruits and nuts (fruits, fruit juices, peanuts and peanut butter), vegetables (all vegetables excluding potatoes), legumes (peas and beans), cereals and grains, and fish [26]. Individuals were assigned a value of 1 for each beneficial component (fruits and nuts, vegetables, legumes, cereals and grains, fish) whose consumption was at or above the sex-specific median, for each detrimental component (meat, dairy) 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/week but ≤2 drinks/day over the previous year) [27]. The diet score was the sum of the scores in these nine food categories (range 0–9) with a higher score indicating greater adherence.

2.4. Carotid ultrasound

High-resolution B-mode ultrasounds (GE LogIQ 700, 9- to 13-MHz linear-array transducer) were performed by trained and certified sonographers as described previously [28–30]. For 40% of participants the carotid ultrasounds were conducted at baseline when the diet data was collected. For the rest of participants the carotid ultrasounds were conducted after baseline, with a mean time span of 3 years. Presence of plaque is defined as a focal wall thickening or protrusion in the lumen >50% greater than the surrounding thickness. Carotid plaque area (mm [2]) and thickness (mm) were measured using an automated computerized edge tracking software M'Ath (Paris, France) [31]. TPA was defined as the sum of all plaque areas measured in any of the carotid artery segments within an individual. IMT in all carotid segments was measured in areas without plaque. IMT was calculated as a composite measure combining near and far walls of the CCA IMT, bifurcation IMT and ICA IMT of both sides of the neck, and examined continuously as a mean of the maximum measurements of the 12 carotid sites.

2.5. Statistical analysis

The MeDi score, the primary exposure of interest, was analyzed by dividing the distribution roughly into quintiles (scores 0–2 as the reference vs. score 3, 4, 5, 6–9) and as a continuous variable (per 1-point increase). The distribution of covariates of interest across MeDi score

categories was examined using chi-square tests for categorical variables and analysis of variance for continuous variables.

For the analyses of cIMT, linear regression models were constructed with cIMT as the dependent variable, and for analyses of plaque presence as the dependent variable logistic regression models were used. Due to the non-normal distribution of plaque thickness and area, with a large percentage of the study population having no plaque, we used quantile regression to examine these plaque phenotypes as continuous outcomes. For individuals without plaque, a value of 0 was assigned for each of these plaque phenotypes. For both plaque thickness and area we chose the median (50th percentile) and 75th percentile as our cut points of interest. We used a sequence of three models to assess the association between MeDi score and markers of atherosclerosis: 1) adjusted for age, sex, and race-ethnicity; 2) adjusted for the variables in model 1 and education, moderate to heavy physical activity, average total daily kilocalorie consumption, and smoking (never/past/current); 3) adjusting for potential mediators as well as confounders, including the covariates in model 2 as well as blood sugar, diabetes medication use, systolic and diastolic blood pressure, anti-hypertensive medication use, LDL, HDL, triglycerides, cholesterol-lowering medication use, prescribed diet, BMI, and history of self-reported cardiac disease. In a supplementary analysis we simultaneously entered the MeDi score components into model 2 as predictors of our atherosclerosis markers with suggested association with the overall MeDi score. Lastly, we examined the potential for effect modification by age, sex, and race/ethnicity by including interaction terms with the continuous MeDi score in model 2 for each of the atherosclerosis dependent variables of interest.

3. Results

A total of 2568 NOMAS participants had diet data available, and of those a total of 1415 had carotid ultrasounds. Because self-reported kcal <500 or >4000 might indicate inaccurate reporting of dietary information, we excluded 41 participants who consumed these calorie amounts, leaving a sample size of 1374 (mean age 66 ± 9 years, 60% women, 60% Hispanic, 19% non-Hispanic black, 18% non-Hispanic white, and 2% other race). The mean cIMT was 0.9 ± 0.1 mm and 57% had plaque (median plaque thickness = 1.5 mm, 75th percentile = 2.2 mm; median plaque area = 4.2mm^2, 75th percentile = 15.8). Characteristics of the study population stratified by MeDi score are shown in Table 1. In unadjusted analyses, male sex, Hispanic ethnicity, and moderate to heavy physical activity were associated with greater consumption of a MeDi pattern, while elevated BMI and cholesterol-lowering medication use were associated with lower consumption of a MeDi ($p < 0.05$).

Table 2 shows the association between the MeDi score, both continuously and in quintiles, and cIMT, plaque presence, plaque thickness, and TPA in the sequence of three models. The MeDi score was not associated with cIMT or plaque presence. Greater adherence to MeDi was inversely associated with the 75th percentile of plaque thickness and the 50th percentile of plaque area. In models 2 and 3, the 75th percentile of plaque thickness was decreased among those in the top two quintiles of the MeDi scale (scores 5 and 6–9 respectively) vs. the bottom quintile (score 0–2).

In model 2, the top 3 quintiles had significantly lower values for the median plaque area vs. the bottom quintile. Though the linear trend *p*-value was significant, the protective effect estimate was strongest in relation to score 5. Likewise, in model 2 a decreased 75th percentile of plaque area was also seen among those with MeDi score 5. The effect estimates for each quintile in relation to the median of plaque area were attenuated in model 3 adjusting for vascular risk factors, biomarkers, and medication use. However, the linear trend *p*-value remained significant and the effect estimates were consistent with a possible dose–response relationship.

In model 2 there was no significant interaction between MeDi score and age or sex in relation to any of the atherosclerosis variables. However, there was a suggestion of effect modification by race/ethnicity in relation to both plaque area and thickness ($p < 0.05$). Specifically, tests of interaction suggested that for the median of plaque area, the protective effect across greater MeDi scores was stronger for whites than blacks or Hispanics, and for the 75th percentile of plaque thickness the protective effect of a MeDi was stronger for whites and Hispanics as compared to blacks. Table 3 shows the association between the continuous MeDi score and plaque thickness and area in multivariable-adjusted model 2 stratified by race/ethnicity. The stratified analyses were underpowered, especially for non-Hispanic whites and blacks. However, among Hispanics a significant inverse association for the MeDi score was found for the 75th percentile of plaque thickness.

The only MeDi score component that was independently associated with plaque phenotypes was vegetable consumption and this was inversely associated with the 75th percentile of plaque thickness (Table 4). The 75th percentile of plaque thickness was 0.2 mm lower among those with vegetable consumption about the median.

4. Discussion

The results of this study suggest that greater adherence to a MeDi may be modestly associated with a decreased burden of carotid atherosclerotic plaque, as measured by plaque thickness and area. A MeDi was not associated with cIMT, a presumed marker of carotid atherosclerosis. Carotid plaque and cIMT are physiologically distinct atherosclerotic phenotypes with evidence of heterogeneous etiologies. The development of plaques is largely the result of a complex cascade of inflammatory processes from lipid deposition and inclusion of immunological cells to plaque calcification. In contrast, cIMT is more influenced by hypertension, which causes hypertrophy of the media layer of the vessel wall, but is also associated with inflammation and invasion of immune cells. Because of the pathological distinctions between these atherosclerotic phenotypes, it is important to study both in relation to novel risk factors for atherosclerosis, like diet, that may be on a causal pathway for clinical disease risk.

In the NOMAS cohort we have previously shown an inverse association between adherence to a MeDi and risk for clinical vascular events overall [2]. Although we saw no association specifically with clinical stroke in that study, other studies with more power have demonstrated an association of a MeDi with clinical stroke [32], and associations of a MeDi with imaging biomarkers of cerebrovascular damage have been clearly shown [33,34].

Because carotid plaque burden has been previously shown to be a potent risk factor for clinical events, it is likely that carotid atherosclerotic plaque may be on a causal pathway linking MeDi adherence and risk of clinical events. In fact, the top quartile of carotid plaque area (vs. the lowest quartile) has been associated with a 3–4-fold increased risk of stroke, MI or death [35,36]. Plaque area may be a better measure of atherosclerosis than plaque thickness [35–38] because plaque progresses along the carotid artery 2–3 times faster than it thickens [39]. Despite the relationship between carotid plaque burden and risk of clinical events, few studies have examined the role of vascular risk factors in relation to this novel and important marker of disease risk. This is particularly true in race/ethnically diverse populations, such as Northern Manhattan. Because Hispanics are the fastest growing minority population in the US, and they are at an elevated risk of stroke [40,41], a greater understanding of the role of vascular risk factors in a primarily Hispanic population is imperative, and is the overarching goal of NOMAS.

Whether the association between a MeDi and carotid plaque burden is consistent with a dose–response relationship or a threshold effect requires further study. In our study of a MeDi in relation to clinical vascular outcomes we also noted the strongest relationships for the 4th quintile, rather than the top quintile. The dietary habits among those in the top quintile, those whose diets most strictly conform to a MeDi diet, may reflect recent dietary modifications as a result of efforts to reduce vascular disease risk. Twenty-three percent of those in the top MeDi group reported having received dietary recommendations due to hypercholesterolemia or diabetes. Therefore, their current diet may not represent long-term dietary behaviors, which in turn may be more etiologically relevant for atherosclerosis development. Unfortunately we lack detailed information on dietary changes over time.

Adherence to a MeDi is advocated by the AHA, and has been hypothesized to inhibit the progression of atherosclerosis, although empirical evidence remains limited and inconclusive. If adoption of a MeDi is to be advocated by public health professionals, and by physicians, for patients at risk for vascular disease, then examination of the relationship between a MeDi and carotid atherosclerosis in large population-based studies like ours is crucial. As mentioned, two randomized controlled trials have examined the relationship between a MeDi and carotid atherosclerosis. These studies only offered limited support for an association between a MeDi and carotid atherosclerosis and had several limitations, including small sample sizes ($N < 200$) and limited length of follow-up. In the PREDIMED-Navarra trial, 187 symptom-free patients at high risk for CVD were randomized to receive quarterly nutritional counseling consistent with one of the following three interventions: MeDi with supplemental nuts, MeDi with supplemental virgin olive oil, and a control diet [9]. Carotid IMT was measured twice - at baseline and after 1 year. At the one-year follow-up there were no differences in cIMT across the three groups, but differential effects by the baseline cIMT levels were evident. Among participants with elevated baseline cIMT those in both of the MeDi intervention groups had less progression of cIMT over follow-up as compared to the control group. While a MeDi may be associated with regression in cIMT during a one-year period among those with pre-existing elevated cIMT levels, the authors were unable to support similar benefits among those with lower initial cIMT levels. The Dietary Intervention Randomized Controlled Trial–Carotid is another small trial that

included 140 participants (mean age of 51) who were randomized to a low-fat, MeDi, or low-carbohydrate diet to induce weight loss [10]. A MeDi specifically was not associated with any benefits in relation to cIMT or vessel wall volume over the course of a two-year follow-up in that study.

While direct evidence for a relationship between a MeDi and carotid atherosclerosis is limited, healthy dietary patterns in general have been inversely associated with risk factors for atherosclerosis, and some studies have suggested an inverse relationship between healthy dietary patterns similar to a MeDi and carotid atherosclerosis. However, the results have been inconsistent, and the use of well-established diet quality indices are lacking. Additionally, most studies relating diet to atherosclerosis have measured cIMT rather than plaques, and cIMT may not be a potent marker of atherosclerosis [42].

Limited evidence for an inverse association between an overall healthy dietary pattern and cIMT was observed in the Multi-ethnic Study of Atherosclerosis using their Comprehensive Healthy Dietary Pattern [43]. This *a priori*-defined healthy dietary pattern was inversely associated with cIMT in the common carotid artery, but not with cIMT in the internal carotid artery, carotid plaque, or coronary artery calcification. Other studies have examined dietary patterns across participants based on principal components analysis (PCA) or similar techniques. The prospective and Cardiovascular Risk in Young Finns Study, which included markedly younger participants, reported effect modification by sex for the relationship between a traditional dietary pattern (high consumption of rye, potatoes, butter, sausages, milk, and coffee) with cIMT, as the positive association was evident in males only [44]. A prospective cohort study of middle-aged adults in France involved the analysis of repeated 24-h dietary records using PCA, and reported no association between their four distinct dietary patterns identified and cIMT in the common carotid artery or carotid plaque [45].

The belief that overall dietary patterns, rather than individual nutrients or food groups, play a larger etiologic role in disease risk prediction, has shifted epidemiologic focus away from narrowly-defined food group analyses in recent years. Foods are highly correlated and consumed together, which impedes our ability to identify individual diet components that are independently associated with disease risk. However, some of the individual components of a MeDi have been examined in relation to atherosclerosis risk and provide some evidence to support the hypothesis that adherence to a MeDi may be atheroprotective. The MeDi components that have been inversely associated with subclinical markers of atherosclerosis include fruit [46], fish [47–49], whole grains [50,51], olive oil [52], and moderate amounts of alcohol [53,54], particularly wine [55], while meat consumption has been positively associated with such markers [56]. In the current study, the only MeDi component that was independently associated with plaque thickness or area was vegetable consumption, showing an inverse association with plaque thickness. In contrast, in our previous study of MeDi in relation to clinical vascular events in NOMAS we found that moderate alcohol use, high fish consumption, and high consumption of legumes were the components that were independently associated with a decreased risk of vascular death [2].

One unique aspect to the current study is the use of a racially and ethnically diverse population-based cohort. Results of this study were consistent with previous analyses of a

MeDi in NOMAS suggesting that adherence to a MeDi differs across race/ethnic groups. In particular, Hispanics appeared to have diets that were more consistent with a MeDi than non-Hispanic blacks and whites. In our previous publication we observed no effect modification by race/ethnicity for the association with clinical vascular outcomes, but the current results do suggest potential differential effects of a MeDi on plaque thickness and area by race/ethnicity. No association for a MeDi with plaque thickness and area was suggested for blacks. For Hispanics an inverse association was suggested between MeDi adherence and plaque thickness. Reasons underlying the potential effect modification by race/ethnicity are not known, but could relate to subtle differences in the types of foods consumed across race/ethnic groups or related health behaviors. The effects of a MeDi on carotid plaque presence and progression should therefore be examined in future multi-ethnic cohorts to see if our race/ethnic differences can be confirmed.

Adoption of a dietary pattern consistent with that commonly seen in the Mediterranean region, including high consumption of fruits, vegetables, monounsaturated fat, fish, whole grains, legumes, and nuts, moderate alcohol intake, and minimal consumption of red meat, saturated fat, and refined grains, may decrease the development of carotid atherosclerotic plaque. Our results suggest that even modest adherence to a MeDi may be associated with a reduced atherosclerotic plaque burden, as the association may not be dose-dependent, and because we have previously shown that our cohort adheres less to a traditional Mediterranean-style diet than other cohorts [2]. Our findings were independent of several important related risk factors for carotid atherosclerosis including advanced age, race/ethnicity, smoking, and lack of physical activity. The results were also suggested after accounting for other markers of vascular disease risk that may be both confounders and effect mediators, including blood sugar, blood pressure, lipid levels, BMI, and previous cardiac disease. In most analyses, the results were attenuated as expected after controlling for these variables as they may be on a casual pathway linking diet quality with atherosclerosis. Therefore, the findings for the final models should be interpreted with caution as they may be over-adjusted. The persistence of a significant association in some of these model 3 analyses is noteworthy and does not preclude the possibility that blood sugar, blood pressure, lipid levels and obesity may be mediating factors in the relationship between adherence to a MeDi and carotid plaque burden. In fact, protective factors for atherosclerosis that have been previously associated with a MeDi and are likely biological mechanisms underlying the proposed atheroprotective effect of a MeDi include better blood lipid levels [57], lower blood pressure [58], adiposity [59], improved insulin resistance [60], and decreased levels of inflammatory markers including C-reactive protein [61] and interleukin-6 [62].

Strengths of this study include (1) the population-based multiethnic cohort, (2) the comprehensive data on other vascular risk factors, and (3) the examination of an important new marker of atherosclerotic burden, plaque area. Our analysis is partially cross-sectional and did not include serial carotid measurements, preventing assumptions regarding temporality and causality of the associations observed. The FFQ refers to dietary behavior over the previous year, and is therefore designed to measure long-term dietary patterns. Data from a similar study among adults in Northern Manhattan suggested dietary habits are stable over time [63]. An additional limitation is the potential misclassification of dietary habits.

However, the Block NCI FFQ has demonstrated strong validity and reliability [24,64,65]. The observed data on total energy consumption in our study suggests the validity of the diet data as the mean and median total energy intakes that we observed were consistent with those expected in an elderly, sedentary, and predominantly female cohort [66]. We reduced the possibility of diet misclassification by excluding participants with improbably low or high self-reported total daily energy. The use of median cutoffs in the creation of the MeDi score also serves to limit the influence of outlying diet data. Lastly, the potential for residual confounding by unmeasured variables always exists and could account for deviations from a clear dose–response association.

In conclusion, our study is the first large observational population-based epidemiologic study to examine the relationship between adherence to a MeDi and markers of atherosclerosis. Our results suggest that dietary habits consistent with a MeDi may be associated with a reduced burden of carotid atherosclerotic plaque, an important risk factor for stroke. A protection against carotid plaque burden may therefore be one potential mechanism underlying our previously observed inverse association between adherence to a MeDi and risk of clinical vascular events in NOMAS [2], but future studies relating a MeDi to carotid plaque thickness and area in relation to vascular outcomes are needed to know if carotid plaque burden is a good surrogate intermediate marker of vascular disease risk for interventional trials relating to a MeDi. In particular, investigations using prospective study designs are needed to examine how adherence to a MeDi may impact the trajectories of markers of atherosclerosis, including cIMT and TPA, over time. Continued research on the role of a MeDi in vascular disease risk should be a public health priority because diet is a modifiable behavioral risk factor.

Acknowledgment

This work is supported by a grant from the National Institute of Neurological Disorders and Stroke (R37 NS 29993).

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Table 1

Covariates stratified by Mediterranean diet score.

Variable	NOMAS cohort *N* = 1374	Mediterranean diet score				
		0–2	3	4	5	6–9
		N = 171	*N* = 222	*N* = 301	*N* = 308	*N* = 372
Sex n (%)[a]						
Male	555 (40)	57 (33)	94 (42)	117 (39)	109 (35)	178 (48)
Female	819 (60)	114 (67)	128 (58)	184 (61)	199 (65)	194 (52)
Race/ethnicity n (%)[a]						
White	254 (18)	42 (25)	40 (18)	55 (18)	65 (21)	52 (14)
Black	260 (19)	40 (23)	47 (21)	55 (18)	55 (18)	63 (17)
Hispanic	831 (60)	85 (50)	130 (59)	183 (61)	186 (60)	247 (66)
Other	29 (2)	4 (2)	5 (2)	8 (3)	2 (1)	10 (3)
High school completion *n* (%)						
Yes	641 (47)	81 (47)	118 (53)	137 (46)	143 (46)	162 (44)
No	733 (53)	90 (53)	104 (47)	164 (54)	165 (54)	210 (56)
Smoking *n* (%)[a]						
Never	653 (48)	77 (45)	106 (48)	134 (45)	151 (49)	185 (50)
Former	502 (36)	58 (34)	67 (30)	122 (41)	114 (37)	141 (38)
Current	219 (16)	36 (21)	49 (22)	45 (15)	43 (14)	46 (12)
Physical activity *n* (%)[a]						
None-light	1228 (90)	163 (96)	201 (92)	270 (90)	278 (90)	316 (85)
Moderate–Heavy	142 (10)	7 (4)	18 (8)	31 (10)	30 (10)	56 (15)
Anti-hypertensive medication *n* (%)						
Yes	611 (45)	85 (50)	99 (45)	135 (45)	140 (45)	152 (41)
No	762 (55)	86 (50)	123 (55)	165 (55)	168 (55)	220 (59)
Diabetes medication *n* (%)						
Yes	162 (12)	29 (17)	30 (14)	28 (9)	28 (9)	47 (13)
No	1210 (818)	142 (83)	191 (86)	273 (91)	280 (91)	324 (87)
Cholesterol-lowering medication *n* (%)[a]						

Variable	NOMAS cohort *N* = 1374	Mediterranean diet score				
		0–2	3	4	5	6–9
		N = 171	*N* = 222	*N* = 301	*N* = 308	*N* = 372
Yes	204 (15)	35 (20)	31 (14)	33 (11)	41 (13)	64 (17)
No	1170 (85)	136 (80)	191 (86)	268 (89)	267 (87)	308 (83)
Prescribed diet *n* (%)						
Yes	260 (19)	24 (14)	33 (15)	57 (19)	61 (20)	85 (23)
No	1114 (81)	147 (86)	189 (85)	244 (81)	247 (80)	287 (77)
Previous cardiac disease *n* (%)						
Yes	251 (18)	35 (20)	42 (19)	62 (21)	50 (16)	62 (17)
No	1123 (82)	136 (80)	180 (81)	239 (79)	258 (84)	310 (83)
Age mean (SD)	66 (9)	69 (8)	66 (9)	65 (9)	66 (9)	65 (9)
Kcal mean (SD)	1593 (656)	1617 (713)	1603 (669)	1553 (601)	1607 (704)	1569 (625)
Body mass index mean (SD)[a]	28 (5)	29 (6)	28 (5)	28 (5)	28 (5)	28 (5)
LDL mean (SD)	130 (34)	132 (36)	129 (36)	129 (34)	128 (36)	132 (31)
HDL mean (SD)	46 (14)	45 (14)	45 (15)	46 (14)	45 (13)	46 (14)
Triglycerides mean (SD)	135 (79)	146 (79)	140 (89)	131 (76)	133 (76)	135 (79)
SBP mean (SD)	142 (21)	145 (22)	142 (21)	142 (22)	142 (19)	142 (19)
DBP mean (SD)	84 (11)	82 (11)	84 (10)	83 (11)	84 (10)	84 (11)
Blood sugar mean (SD)	103 (45)	108 (52)	108 (51)	100 (42)	101 (43)	101 (41)

[a] Chi-square or ANOVA $P < 0.05$.

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Table 2

MeDi and atherosclerosis in NOMAS (N = 1369 for IMT and N = 1374 for plaque).

	IMT: beta, *p*-value	**Plaque presence: OR (95% CI)**	**Plaque thickness median: Change in mm, *p*-value**	**Plaque thickness 75th percentile: Change in mm, *p*-value**	**Plaque area median: Change in mm^2, *p*-value**	**Plaque area 75th percentile: Change in mm^2, *p*-value**
MeDi score continuous (per 1-point increase)						
Model 1	−0.000112, 0.93	0.97 (0.90–1.03)	−0.0754, 0.02	−0.0424, 0.09	−0.3915, 0.01	−0.7855, 0.05
Model 2	−0.000209, 0.88	0.98 (0.91–1.05)	−0.0534, 0.12	−0.0490, 0.03	−0.3712, 0.03	−0.6582, 0.14
Model 3	−0.000357, 0.80	0.90 (0.92–1.06)	−0.0430, 0.16	−0.0622, 0.003	−0.4607, 0.01	−0.5330, 0.12
MeDi score categorical						
Model 1						
3 vs. 0–2	−0.00697, 0.40	0.73 (0.47–1.11)	−0.2043, 0.36	−0.2001, 0.12	−2.1259, 0.14	−3.7674, 0.12
4 vs. 0–2	−0.00785, 0.31	0.78 (0.52–1.17)	−0.3087, 0.11	−0.2001, 0.08	−3.3390, 0.003	−4.7640, 0.06
5 vs. 0–2	−0.00602, 0.44	0.71 (0.47–1.05)	−0.5043, 0.01	−0.4161, 0.001	−3.990, 0.0004	−7.4333, 0.002
6–9 vs 0–2	−0.00243, 0.75	0.76 (0.52–1.13)	−0.2782, 0.11	−0.3147, 0.01	−3.3454, 0.001	−5.5622, 0.03
Linear trend *P*	0.95	0.31	0.10	0.04	0.01	0.01
Model 2						
3 vs. 0–2	−0.00594, 0.48	0.72 (0.47–1.11)	−0.1956, 0.36	−0.1369, 0.23	−1.6455, 0.27	−1.7061, 0.51
4 vs. 0–2	−0.00842. 0.28	0.80 (0.53–1.20)	−0.2635, 0.16	−0.1229, 0.23	−2.5781, 0.04	−3.5801, 0.10
5 vs. 0–2	−0.00609, 0.43	0.73 (0.49–1.10)	−0.4779, 0.01	−0.2822, 0.002	−3.3306, 0.003	−5.4215, 0.03
6–9 vs. 0–2	−0.00261, 0.73	0.81 (0.54–1.21)	−0.3107, 0.09	−0.2138, 0.05	−3.1518, 0.01	−3.3993, 0.17
Linear trend P	0.98	0.53	0.06	0.01	0.003	0.10
Model 3						
3 vs. 0–2	−0.00272, 0.75	0.82 (0.52–1.31)	0.0350, 0.87	−0.0985, 0.37	0.5380, 0.69	−1.3734, 0.51
4 vs. 0–2	−0.00681, 0.39	0.93 (0.61–1.44)	−0.0247, 0.89	−0.0632, 0.59	−0.8739, 0.39	−1.4831, 0.49
5 vs. 0–2	−0.00362, 0.64	0.86 (0.56–1.31)	−0.1611, 0.39	−0.3248, 0.01	−1.4892, 0.13	−4.2119, 0.06
6–9 vs. 0–2	−0.00254, 0.74	0.90 (0.59–1.36)	−0.1215, 0.32	−0.2687, 0.01	−1.7279, 0.08	−3.2738, 0.13
Linear trend *P*	0.88	0.77	0.14	0.01	0.004	0.06

Model 1: controlling for age, sex, race/ethnicity.

Model 2: model 2 + education, smoking, physical activity, total daily calories.

Model 3: model 3 + blood sugar, systolic blood pressure, diastolic blood pressure, LDL, HDL, BMI, cardiac medications, anti-hypertensive medications, diabetes medications, cholesterol-lowering medications, prescribed diet, previous cardiac disease.

Table 3

MeDi and plaque thickness and area stratified by race/ethnicity.

MeDi continuous (per 1-point increase)	White (*N* = 254)	Black (*N* = 260)	Hispanic (*N* = 831)
Plaque thickness median: change in mm (95% CI)	−0.0340 (−0.1496, 0.0817)	0.0379 (−0.0911, 0.1669)	−0.0672 (−0.1456, 0.0112)[a]
Plaque thickness 75th percentile: change in mm (95% CI)	−0.0773 (−0.1718, 0.0172)	0.0355 (−0.0677, 0.1387)	−0.0906 (−0.1541, −0.0271)[b]
Plaque area median: change in mm^2 (95% CI)	−0.9332 (−2.4092, 0.5428)	0.2209 (−1.0158, 1.4576)	−0.2554 (−0.5567, 0.0459)[a]
Plaque area 75th percentile: change in mm^2 (95% CI)	−0.8713 (−3.2217, 1.4790)	1.0004 (−1.3440, 3.3448)	−0.9035 (−1.8422, 0.0352)[a]

Controlling for age, sex, education, smoking, physical activity, total daily calories.

[a] $0.05 < p < 0.10$.

[b] $p < 0.05$.

Table 4

Association between each component of the MeDi score and plaque thickness and area.[a]

Mediterranean diet component	Plaque thickness 75th percentile: change in mm (95% CI)	Plaque area 75th percentile: change in mm^2 (95% CI)
Alcohol	−0.0777 (−0.2132, 0.0577)	−0.4097 (−2.8737, 2.0543)
Fish	−0.0337 (−0.1737, 0.1063)	−1.1068 (−3.3915, 1.1778)
Legumes	−0.0086 (−0.1457, 0.1295)	−0.2340 (−2.9228, 2.4549)
Vegetables	−0.1574 (−0.3034, −0.0115)	−1.6022 (−4.0946, 0.8901)
Fruit and nuts	−0.0043 (−0.1332, 0.1247)	0.8991 (−1.2165, 3.0147)
Cereal and grains	−0.0848 (−0.2266, 0.0571)	−1.7629 (−4.3878, 0.8620)
Meat	0.0050 (−0.1215, 0.1316)	0.8309 (−1.6618, 3.3235)
Dairy	−0.0178 (−0.1513, 0.1157)	−2.1091 (−4.6409, 0.4226)
Monounsaturated: saturated fat	0.0105 (−0.1203, 0.1412)	−0.1633 (−2.8795, 2.5529)

[a]Calculated using Cox proportional hazards models controlling for all Medi score components, age, sex, race/ethnicity, education, smoking, physical activity, total daily calories.