



## 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  $66 \pm 9$  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 =  $0.9 \pm 0.1$  mm and 57% had plaque (median plaque thickness = 1.5 mm, 75th percentile = 2.2; median plaque area =  $4.2 \text{ mm}^2$ , 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 =  $-0.371 \text{ mm}^2$ ,  $p = 0.03$ ), and when additionally controlling for vascular disease biomarkers, medication use, BMI, and previous cardiac disease. The protective associations appeared strongest for those with a 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.

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### 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, mono-unsaturated 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

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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  $\geq 3$  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  $\text{kg}/\text{m}^2$ .

### 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 mono-unsaturated fats to saturated fats above the median, and for mild to moderate alcohol consumption ( $>0$  drinks/week but  $\leq 2$  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

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