Mediterranean Diet and Incidence of and Mortality From Coronary Heart Disease and Stroke in Women

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Background—Several studies have documented an inverse association between adherence to the Mediterranean diet and risk of coronary heart disease (CHD), but few data are available on the relationship between Mediterranean diet and risk of stroke.

Methods and Results—For the present study, 74 886 women 38 to 63 years of age in the Nurses' Health Study, a cohort study of female nurses, without a history of cardiovascular disease and diabetes were followed up from 1984 to 2004. We computed an Alternate Mediterranean Diet Score from self-reported dietary data collected through validated food frequency questionnaires administered 6 times between 1984 and 2002. Relative risks for incident CHD, stroke, and combined fatal cardiovascular disease were estimated with Cox proportional-hazards models adjusted for cardiovascular risk factors. During 20 years of follow-up, 2391 incident cases of CHD, 1763 incident cases of stroke, and 1077 cardiovascular disease deaths (fatal CHD and strokes combined) were ascertained. Women in the top Alternate Mediterranean Diet Score quintile were at lower risk for both CHD and stroke compared with those in the bottom quintile (relative risk [RR], 0.71; 95% CI, 0.62 to 0.82; P for trend$<$0.0001 for CHD; RR, 0.87; 95% CI, 0.73 to 1.02; P for trend$=$0.03 for stroke). Cardiovascular disease mortality was significantly lower among women in the top quintile of the Alternate Mediterranean Diet Score (RR, 0.61; 95% CI, 0.49 to 0.76; P for trend$<$0.0001).

Conclusion—A greater adherence to the Mediterranean diet, as reflected by a higher Alternate Mediterranean Diet Score, was associated with a lower risk of incident CHD and stroke in women. (***Circulation*. 2009;119:1093-1100.**)

Key Words: coronary disease ■ diet ■ nutrition ■ stroke

The traditional Mediterranean diet is characterized by a high intake of monounsaturated fat, plant proteins, whole grains, and fish; moderate intake of alcohol; and low consumption of red meat, refined grains, and sweets.[1] An intervention trial has recently shown that the Mediterranean diet is more effective in promoting weight loss and lowering the ratio of total to high-density lipoprotein cholesterol in obese individuals than a low-fat diet.[2] Previously, the Lyon Heart Study showed that the Mediterranean diet was more effective than a low-fat diet in the secondary prevention of cardiac events.[3,4] Since then, the Mediterranean diet pattern has been shown in several prospective studies from around the world to be inversely associated with total and cardiovascular (CVD) mortality.[5,6] However, data are limited for its relationship with nonfatal cardiovascular events. To the best of our knowledge, no studies have specifically focused on the incidence of stroke or stroke mortality. In addition, in investigating the association between diet and disease with a slow progression such as coronary heart disease (CHD) and stroke, the availability of multiple dietary measurements over time provides a better estimate of overall diet over the follow-up period.

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We have previously constructed a Mediterranean diet adherence score for the Nurses' Health Study (NHS)[7] based on a prior scoring system developed for Greek populations.[8] This Alternate Mediterranean Diet Score (aMed) focuses on higher consumption of plant foods, including plant proteins, monounsaturated fat, and fish and lower consumption of animal products and saturated fat. In the present analysis, we used data from multiple dietary assessments to prospectively examine the association between the aMed and risk of incident CHD and stroke, as well as CVD mortality, in women. We also combined nonfatal and fatal CHD and stroke incidence to assess the association of aMed with major CVD events.

Methods

Study Population

The NHS is a cohort study of 121 700 female nurses 30 to 55 years of age living in 11 US states at the time of inception (1976). The first questionnaire regarding medical, lifestyle, and other health-related information was sent at that time.[9] Since then, questionnaires have been sent biennially to update this information. Follow-up was

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Table 1. Participant Characteristics and Median (Interquartile Range) Intake of aMed Components for the Years in Which FFQ Was Administered

	1984	1986	1990	1994	1998	2002
Mean aMed score	3.9	4.0	4.0	4.5	4.4	4.3
Alcohol, g/d	2.0 (0–9.5)	1.8 (0–7.8)	1.1 (0–6.0)	1.1 (0–6.1)	1.0 (0–6.3)	1.2 (0–7.8)
Red/processed meat	0.9 (0.6–1.3)	0.8 (0.5–1.1)	0.6 (0.4–1.0)	0.6 (0.4–0.9)	0.6 (0.3–0.9)	0.5 (0.2–0.9)
Fish	0.2 (0.1–0.4)	0.3 (0.1–0.4)	0.3 (0.1–0.5)	0.2 (0.1–0.4)	0.2 (0.1–0.3)	0.2 (0.1–0.3)
Whole grains	0.6 (0.2–1.1)	1.1 (0.6–1.8)	1.1 (0.5–1.8)	1.0 (0.5–1.7)	1.0 (0.5–1.6)	1.0 (0.4–1.7)
Legumes	0.3 (0.2–0.6)	0.3 (0.2–0.6)	0.3 (0.2–0.6)	0.3 (0.2–0.6)	0.3 (0.2–0.5)	0.3 (0.1–0.5)
Nuts	0.1 (0–0.4)	0.2 (0.1–0.4)	0.1 (0–0.4)	0.1 (0–0.4)	0.1 (0–0.4)	0.2 (0.1–0.6)
Fruits	1.9 (1.2–2.8)	2.3 (1.4–3.3)	2.1 (1.3–3.1)	2.2 (1.4–3.1)	2.2 (1.4–3.2)	1.9 (1.1–2.9)
Vegetables*	2.6 (1.8–3.8)	3.1 (2.1–4.4)	2.7 (1.8–3.8)	2.9 (2.0–4.1)	2.7 (1.8–3.9)	2.5 (1.5–3.7)
Monounsaturated to saturated fat ratio	1.0 (0.9–1.1)	1.0 (0.9–1.1)	1.1 (1.0–1.2)	1.1 (1.0–1.3)	1.1 (1.0–1.3)	1.1 (1.0–1.3)

Values are expressed as servings per day unless stated otherwise.
*Potatoes and French fries were not included.

complete for >95% of the potential person-time up to 2004. In 1980, the participants completed a 61-item food frequency questionnaire (FFQ). In 1984, the FFQ was expanded to 116 items. Similar FFQs were sent in 1986, 1990, 1994, 1998, and 2002.

For this analysis, we included women who completed the 1984 FFQ with <70 missing items and total energy intake (as calculated from the FFQ) between 500 and 3500 kcal/d.[10] At baseline, we excluded those with a history of CHD, stroke, or diabetes because diagnoses of these conditions may lead to changes in diet. Thus, 76 522 women with follow-up from 1984 through 2004 were included in the analyses. This study was approved by the Institutional Review Board of the Brigham and Women's Hospital, Boston, Mass.

Dietary Assessment

Self-reported FFQs were designed to assess average food intake over the preceding year. A standard portion size and 9 possible frequency of consumption responses, ranging from "never or less than once per month" to "≥6 times per day" were given for each food. Total energy and nutrient intake was calculated by summing energy or nutrients from all foods. Previous validation studies in this cohort revealed good correlations between nutrients assessed by the FFQ and multiple weeks of food records completed over the preceding year.[10] For example, correlation coefficients between the 1986 FFQ and 4 weeks of diet records obtained in 1986 were 0.68 for saturated fat and 0.78 for crude fiber. The mean correlation coefficient between frequencies of intake of 55 foods assessed by 2 FFQ 12 months apart was 0.57.[10,11]

The aMed score was adapted from the Mediterranean diet scale by Trichopoulou et al.[8] Our components include vegetables (excluding potatoes), fruits, nuts, whole grains, legumes, fish, ratio of monounsaturated to saturated fat, red and processed meats, and alcohol. Participants with intake above the median intake received 1 point for these categories; otherwise, they received 0 points. Red and processed meat consumption below the median received 1 point. We assigned 1 point for alcohol intake between 5 and 15 g/d. This represents approximately one 12-oz can of regular beer, 5 oz of wine, or 1.5 oz of liquor. The possible score range for aMed was 0 to 9, with a higher score representing closer resemblance to the Mediterranean diet. Table 1 shows the intake of aMed components during the follow-up periods. Consumption of each food group was stable across time except for a trend toward a decrease in alcohol and red/processed meat intake.

End-Point Ascertainment

For these analyses, we ascertained incident cases of CHD (nonfatal myocardial infarct [MI] or fatal CHD) and stroke that occurred after the return of the 1984 questionnaire but before June 1, 2004. We requested permission to review medical records from women who reported having a nonfatal MI or stroke on each biennial questionnaire. Physicians unaware of the self-reported risk factor status reviewed the records. For each case, the year and month of diagnosis were recorded as the diagnosis date. For MI, we noted whether it was fatal or nonfatal. MI was classified as confirmed if the criteria of the World Health Organization were met, specifically, symptoms and either echocardiogram changes or elevated cardiac enzyme levels.[12] If medical records were not available, the case was considered probable. We included confirmed and probable cases for the analyses. Fatal CHD events were confirmed by hospital records, by autopsy, or by CHD listed as the cause of death on the death certificate, if it was listed as an underlying and the most plausible cause of death, and if evidence of previous CHD was available.

Strokes were confirmed by medical record review using National Survey of Stroke criteria,[13] which require a constellation of neurological deficits, sudden or rapid in onset with a duration of at least 24 hours or until death. We classified strokes as ischemic (embolic or thrombotic), hemorrhagic (subarachnoid or intracerebral), or undetermined according to medical record evidence and computed tomography, magnetic resonance imaging, or autopsy findings. Deaths were identified from state vital statistics records and the National Death Index or reported by the families and the postal system. Strokes for which medical records were not available were considered probable. In our cohort, ≈17% of all strokes and 24% of MIs were classified as probable. Confirmed and probable cases were combined in our analyses.

Assessment of Covariates

Body mass index (BMI) was calculated from weight reported on each biennial questionnaire and height reported in 1976. In each biennial questionnaire, we also assessed smoking status (including number of cigarettes), frequency and number of aspirin tablets used, multivitamin intake, and menopausal status and use of postmenopausal hormone. Leisure-time physical activity was measured biennially beginning in 1986 with a validated questionnaire asking about average time spent on 10 common activities. The information was then summed and calculated as metabolic equivalent hours.[14]

Statistical Analysis

We used Cox proportional-hazard modeling to assess the association between the aMed score and risk of CHD and stroke, including separate models for fatal and nonfatal CHD and ischemic and hemorrhagic stroke because the cause of subtypes may differ. We combined all CHD and stroke cases as total major CVDs and fatal CHD and fatal stroke as fatal major CVDs. For individuals with confirmed diagnoses of stroke and CHD on the same year and month, we included both end points in the CHD or stroke analyses. However, these individuals contributed to only 1 end point in the total major CVD analysis.

Table 2. Age Standardized Baseline Characteristics According to Quintiles of 1984 aMed Scores

	aMed				
	Q1	Q2	Q3	Q4	Q5
Participant characteristics					
BMI	24.9	24.9	24.9	24.9	24.6
Current smokers, %	30	26	23	20	16
Leisure time physical activity, MET/wk	11	12	14	16	19
History of hypertension, %	7	8	7	8	8
History of hypercholesterolemia, %	2	3	3	3	4
Family history of CHD	19	19	18	19	20
Dietary intake*					
Energy, kcal	1546	1644	1738	1849	1986
Glycemic load	98	99	99	99	102
Carbohydrates, g	179	183	185	187	194
Protein, g	68	70	72	73	75
Monounsaturated fat, g	24	23	23	22	21
Saturated fat, g	25	23	22	21	19
Trans fat, g	4	4	3	3	3
Long chain omega-3 fatty acids, g	0.13	0.17	0.21	0.24	0.30
Dietary fiber, g	13	15	16	18	20
Components of aMed score†					
Alcohol, g	6.8	6.9	7.1	7.0	7.2
Monounsaturated to saturated fat ratio	0.97	1.02	1.03	1.04	1.08
Fish	0.2	0.2	0.3	0.4	0.5
Red/processed meat	1.0	1.0	0.9	0.9	0.8
Whole grains	0.4	0.7	0.9	1.1	1.6
Legumes	0.2	0.3	0.4	0.5	0.6
Fruit	1.3	1.7	2.1	2.6	3.2
Vegetables	1.8	2.4	3.0	3.6	4.4
Nuts	0.1	0.3	0.3	0.4	0.5

*All values energy-adjusted except for energy.
†Servings per day unless otherwise stated.

To reduce random within-person variation and to best represent long-term dietary intake, we calculated cumulative averages of the aMed score from our repeated FFQs.[15] For example, the aMed score in 1984 was used to predict CHD and stroke occurrence from 1984 to 1986, and the average score from 1984 and 1986 was used to predict CHD and stroke risk from 1986 to 1990, and so forth. An overall risk ratio for the entire follow-up period was then computed with the Cox proportional-hazards model. We adjusted for the following potential confounders, which were updated at each 2-year cycle: age (continuous), smoking (never, past, or current with cigarette use of 1 to 14, 15 to 24, ≥25 per day or missing), BMI (<22, 22.1 to 23.0, 23.1 to 24.9, 25.0 to 29.9, ≥30 kg/m^2), menopausal status and postmenopausal hormone use (premenopausal, never, past, current hormone use), energy intake (quintiles), multivitamin intake (yes/no), alcohol intake (0, up to 5, 5 to 15, >15 g/d), family history (yes/no), physical activity (quintiles), and aspirin use (<1, 1 to 2, 3 to 6, 7 to 14, ≥15 per week). Statistical analysis was conducted with SAS version 9 (SAS Institute, Inc, Cary, NC).

In secondary analyses, we additionally adjusted for use of cholesterol-lowering and antihypertensive medications, history of hypertension, hypercholesterolemia, and diabetes diagnosed during follow-up. We also stratified by major risk factors at baseline to evaluate potential interactions between these factors and the aMed in relation to CHD and stroke risk. In addition, we assessed the association between changes in aMed score between 1984 and 1990 and risk of CHD and stroke from 1990 to 2004.

The authors had full access to and take responsibility for the integrity of the data. All authors have read and agree to the manuscript as written.

Results

During up to 20 years of follow-up, we ascertained 2391 cases of CHD, of which 1597 were nonfatal and 794 were fatal. We also ascertained 1763 cases of stroke, of which 959 cases were ischemic, 329 cases were hemorrhagic, and 475 cases could not be clearly classified. Of all strokes, 1480 cases were nonfatal and 283 cases were fatal. At baseline, women with higher aMed score tended to exercise more and were less likely to be smokers (Table 2). They also consumed more calories and fiber but less saturated fat.

After adjusting for potential confounders, we observed a significant inverse association between aMed and risk of CHD. Women in the top quintile of aMed score had a relative risk (RR) of 0.71 (95% CI, 0.62 to 0.82; *P* for trend<0.0001) compared with those in the bottom quintile (Table 3). The association appears somewhat stronger for fatal CHD, with an

Table 3. Relative Risks of CHD by Quintiles of aMED Score

	Q1	Q2	Q3	Q4	Q5	*P* Trend
Average mean score (range)	1.8 (0–2.5)	3.1 (2.5–3.4)	4.0 (3.5–4.4)	4.9 (4.5–5.4)	6.3 (5.5–9.0)	
Total CHD						
Cases	528	518	466	474	405	
Person-years	271 209	285 181	276 345	274 812	293 382	
Age and energy adjusted	1	0.81 (0.72–0.92)	0.71 (0.63–0.81)	0.66 (0.58–0.75)	0.50 (0.43–0.57)	<0.0001
Multivariate adjusted*	1	0.92 (0.82–1.04)	0.87 (0.77–0.99)	0.87 (0.76–0.99)	0.71 (0.62–0.82)	<0.0001
Nonfatal CHD						
Cases	335	333	317	318	294	
Age and energy adjusted	1	0.83 (0.71–0.97)	0.78 (0.67–0.91)	0.72 (0.61–0.84)	0.59 (0.50–0.70)	<0.0001
Multivariate adjusted*	1	0.91 (0.78–1.07)	0.90 (0.77–1.06)	0.88 (0.75–1.04)	0.78 (0.66–0.93)	0.0008
Fatal CHD						
Cases	193	185	149	156	111	
Age and energy adjusted	1	0.78 (0.64–0.96)	0.60 (0.48–0.75)	0.57 (0.46–0.71)	0.35 (0.27–0.45)	<0.0001
Multivariate adjusted*	1	0.94 (0.77–1.15)	0.81 (0.65–1.00)	0.85 (0.68–1.07)	0.58 (0.45–0.75)	<0.0001

*Adjusted for age (continuous), smoking (never, past, current with cigarette use of 1–14 per day, 15–24 per day, ≥25 per day, and missing), BMI (<22, 22.1–23.0, 23.1–24.9, 25.0–29.9, and ≥30), menopausal status and postmenopausal hormone use (premenopausal, never, past, and current hormone use), energy intake (quintiles), multivitamin intake (yes/no), alcohol intake (0g per day, up to 5 g per day, 5—15 g per day, >15g per day), family history (yes/no), physical activity (quintiles), and aspirin use (<1 time per week, 1–2 times per week, 3–6 times per week, 7–14 times per week, ≥15 times per week).

RR of 0.58 (95% CI, 0.45 to 0.75; *P* for trend<0.0001) comparing the extreme quintiles.

For stroke, a significant inverse association also was observed when the top and bottom quintiles were compared, with an RR of 0.87 (95% CI, 0.73 to 1.02; *P* for trend=0.03; Table 4). A similar magnitude of risk reduction was noted for ischemic and hemorrhagic strokes, although statistical significance was not reached, likely because of the reduced power in the subtype analysis. The association with aMed appeared to be stronger for fatal strokes (RR for extreme quintiles, 0.69; 95% CI, 0.44 to 1.07; *P* for trend=0.10) and nonfatal strokes (RR, 0.90; 95% CI, 0.75 to 1.08; *P* for trend=0.12). Results remained essentially

Table 4. Relative Risks of Stroke by Quintiles of aMED

	Q1	Q2	Q3	Q4	Q5	*P* Trend
Total stroke						
Cases	341	380	370	341	331	
Person-years	271 209	285 181	276 345	274 812	293 382	
Age and energy adjusted	1	0.91 (0.79–1.06)	0.88 (0.76–1.03)	0.75 (0.64–0.88)	0.65 (0.55–0.77)	<0.0001
Multivariate adjusted*	1	1.00 (0.86–1.16)	1.03 (0.89–1.20)	0.92 (0.79–1.08)	0.87 (0.73–1.02)	0.03
Ischemic†						
Cases	163	210	209	188	189	
Age and energy adjusted	1	1.04 (0.85–1.28)	1.01 (0.82–1.25)	0.84 (0.67–1.04)	0.74 (0.59–0.92)	0.0004
Multivariate adjusted*	1	1.12 (0.91–1.40)	1.13 (0.91–1.40)	0.98 (0.79–1.23)	0.94 (0.74–1.18)	0.24
Hemorrhagic†						
Cases	71	74	71	56	57	
Age and energy adjusted	1	0.89 (0.64–1.24)	0.87 (0.62–1.22)	0.64 (0.45–0.92)	0.60 (0.41–0.87)	0.002
Multivariate adjusted*	1	0.99 (0.71–1.37)	1.01 (0.72–1.42)	0.77 (0.55–1.15)	0.79 (0.54–1.16)	0.17
Nonfatal						
Cases	283	317	305	282	293	
Age and energy adjusted	1	0.92 (0.78–1.08)	0.88 (0.74–1.03)	0.75 (0.63–0.89)	0.69 (0.58–0.82)	<0.0001
Multivariate adjusted*	1	1.00 (0.85–1.17)	1.00 (0.85–1.19)	0.90 (0.75–1.07)	0.90 (0.75–1.08)	0.12
Fatal						
Cases	58	63	65	59	38	
Age and energy adjusted	1	0.88 (0.62–1.27)	0.91 (0.64–1.31)	0.77 (0.53–1.12)	0.46 (0.30–0.71)	0.0001
Multivariate adjusted*	1	1.04 (0.72–1.49)	1.17 (0.81–1.68)	1.07 (0.73–1.58)	0.69 (0.44–1.07)	0.10

*Adjusted for the same variables as in Table 2.

†Strokes that could not be clearly classified as ischemic or hemorrhagic were included in the analysis of total stroke but not in ischemic or hemorrhagic strokes.

Table 5. Multivariate RR (95% CI) of Total CHD by Quintiles of aMED Stratified by Selected Cardiovascular Risk Factors

	Q1	Q2	Q3	Q4	Q5	*P* Trend	*P* Interaction
BMI <25 (n=1054)	1	0.89 (0.73–1.06)	0.73 (0.60–0.89)	0.74 (0.61–0.90)	0.57 (0.46–0.71)	<0.0001	
BMI ≥25 (n=1338)	1	0.96 (0.81–1.14)	0.99 (0.84–1.18)	0.99 (0.83–1.19)	0.84 (0.69–1.02)	0.08	0.005
Physical activity >median (n=880)	1	0.97 (0.77–1.23)	0.86 (0.67–1.09)	0.92 (0.73–1.16)	0.77 (0.60–0.98)	0.006	
Physical activity ≤median (n=1511)	1	0.90 (0.78–1.05)	0.88 (0.76–1.03)	0.83 (0.70–0.97)	0.66 (0.55–0.80)	<0.0001	0.56
Nonsmokers (n=1921)	1	0.88 (0.76–1.01)	0.81 (0.70–0.94)	0.80 (0.69–0.93)	0.66 (0.56–0.77)	<0.0001	
Current smokers (n=470)	1	0.99 (0.76–1.28)	0.97 (0.73–1.29)	1.05 (0.78–1.42)	0.81 (0.56–1.17)	0.37	0.16
No history of hypertension (n=2011)	1	0.91 (0.80–1.04)	0.84 (0.73–0.96)	0.85 (0.74–0.98)	0.70 (0.60–0.81)	<0.0001	
History of hypertension (n=380)	1	0.91 (0.64–1.29)	0.95 (0.66–1.35)	0.95 (0.66–1.35)	0.83 (0.57–1.22)	0.63	0.14
No history of hypercholesterolemia (n=2235)	1	0.95 (0.84–1.08)	0.87 (0.76–0.99)	0.87 (0.76–1.00)	0.70 (0.60–0.81)	<0.0001	
History of hypercholesterolemia (n=156)	1	0.41 (0.21–0.80)	0.67 (0.37–1.21)	0.52 (0.28–1.97)	0.58 (0.31–1.06)	0.33	0.60
Family history of CHD (n=1695)	1	0.92 (0.80–1.07)	0.89 (0.77–1.04)	0.86 (0.73–1.00)	0.71 (0.60–0.84)	<0.0001	
No family history of CHD (n=696)	1	0.98 (0.77–1.24)	0.84 (0.65–1.07)	0.94 (0.73–1.20)	0.76 (0.58–0.99)	0.03	0.89

*Adjusted for the same variables as in Table 2, except for the variable of stratification.

unchanged after additional adjustment for use of cholesterol-lowering and antihypertensive medications and history of hypercholesterolemia, hypertension, and diabetes that occurred during follow-up for both CHD and stroke.

In stratified analyses, we observed consistent results according to all covariates except for BMI (Tables 5 and 6). The inverse association between aMed and CHD was stronger among women with BMI <25 kg/m^2 (RR, 0.57; 95% CI, 0.46 to 0.71; *P* for trend<0.0001) than those with BMI ≥25 kg/m^2 (RR, 0.84; 95% CI, 0.69 to 1.02; *P* for trend=0.08; *P* for interaction=0.005). However, such an interaction was not found for stroke.

Women who remained in the highest quintiles (fourth or fifth quintile; 294 CHD cases) between 1984 and 1990 had an RR of 0.72 (95% CI, 0.61 to 0.84; *P*<0.0001) for developing CHD during follow-up from 1990 to 2004 compared with those who remained in the lowest quintiles (first or second quintile; 410 cases). Risk for CHD for women who changed from low to high score (126 cases) or from high to low score (118 cases) was not significantly different from those who remained low.

When we evaluated total CVD (combined CHD and stroke incidence), we noted a 22% risk reduction comparing extreme quintiles of aMed score (*P* for trend<0.0001) after multivariate adjustment (Figure, A). Fatal CVD (fatal CHD and fatal stroke combined) risk also was lower among women in the top quintile of the aMed score (RR, 0.61; 95% CI, 0.49 to 0.76; *P* for trend<0.0001) compared with those in the lowest quintile (Figure, B).

Discussion

In the present large cohort of women with 20 years of follow-up, greater adherence to a Mediterranean dietary pattern, as measured by a higher aMed score, was significantly associated with lower risk of incident CHD and stroke. We also observed lower CVD mortality with higher aMed score.

Previous studies generally support an inverse association between adherence to the Mediterranean dietary pattern and risk of CHD. Among middle-aged American, a high aMed score (≥6) was associated with a 22% reduction in cardiovascular mortality in men and a 19% reduction in mortality in women compared with those with a low score (≤3).[6] Elderly Europeans with no history of cardiovascular disease who adhered to the Mediterranean diet more closely had a lower risk of CHD mortality.[8] However, we are unaware of any

Table 6. Multivariate RR of Total Stroke by Quintiles of aMED Stratified by Selected Cardiovascular Risk Factors

	Q1	Q2	Q3	Q4	Q5	*P* Trend	*P* Interaction
BMI <25 (n=838)	1	1.06 (0.84–1.33)	1.18 (0.94–1.48)	0.97 (0.76–1.23)	0.99 (0.77–1.26)	0.48	
BMI ≥25 (n=925)	1	0.94 (0.77–1.15)	0.91 (0.74–1.12)	0.87 (0.70–1.87)	0.75 (0.60–0.95)	0.02	0.12
Physical activity >median (n=660)	1	0.96 (0.72–1.27)	1.14 (0.87–1.49)	0.82 (0.61–1.08)	0.80 (0.60–1.03)	0.06	
Physical activity ≤median (n=1103)	1	0.98 (0.82–1.17)	0.92 (0.76–1.11)	0.95 (0.78–1.15)	0.86 (0.70–1.06)	0.06	0.44
Non mokers (n=1503)	1	0.95 (0.80–1.12)	0.98 (0.83–1.16)	0.88 (0.74–1.04)	0.85 (0.71–1.02)	0.04	
Current smokers (n=260)	1	1.10 (0.78–1.57)	1.09 (0.74–1.59)	1.06 (0.70–1.61)	0.63 (0.36–1.11)	0.17	0.96
No history of hypertension (n=1509)	1	0.98 (0.84–1.15)	1.03 (0.87–1.21)	0.92 (0.77–1.09)	0.86 (0.72–1.03)	0.05	
History of hypertension (n=254)	1	1.16 (0.77–1.74)	0.98 (0.64–1.50)	0.95 (0.61–1.48)	0.79 (0.50–1.26)	0.21	0.55
No history of hypercholesterolemia (n=1672)	1	1.00 (0.86–1.16)	1.03 (0.88–1.20)	0.94 (0.80–1.11)	0.86 (0.73–1.02)	0.04	
History of hypercholesterolemia (n=91)	1	0.99 (0.43–2.24)	0.73 (0.31–1.70)	0.66 (0.27–1.62)	0.71 (0.30–1.68)	0.31	0.63
No family history of CHD (n=1356)	1	1.04 (0.88–1.23)	1.06 (0.89–1.26)	0.93 (0.78–1.12)	0.87 (0.20–1.05)	0.05	
Family history of CHD (n=407)	1	0.91 (0.66–1.25)	0.97 (0.70–1.34)	0.94 (0.67–1.31)	0.86 (0.61–1.21)	0.44	0.70

*Adjusted for the same variables as in Table 2, except for the variable of stratification.

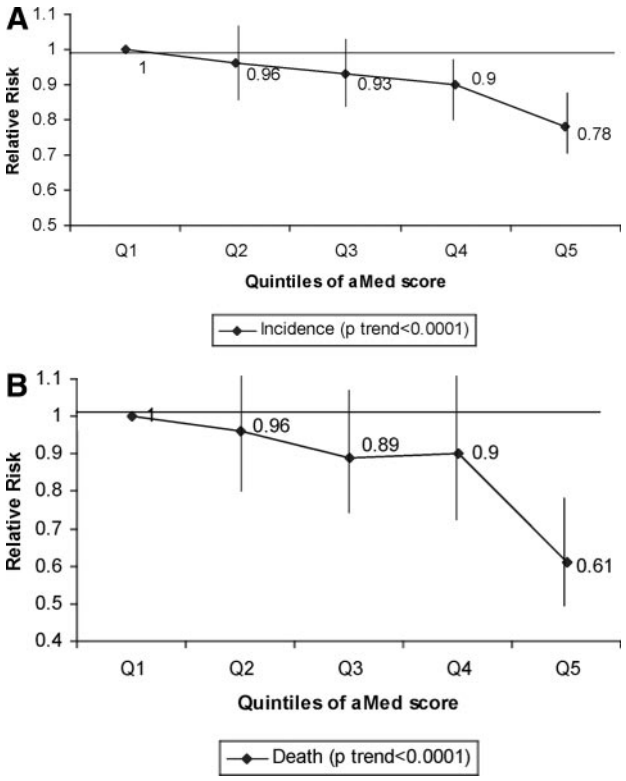

Figure. A, Multivariate (adjusted for the same variables as in Table 2) RR of CVD (combined CHD and stroke) by quintiles of aMed. ♦ Indicates incidence of CVD (*P* for trend<0.0001). B, Multivariate (adjusted for the same variables as in Table 2) RR of fatal CVD (combined CHD and stroke mortality) by quintiles of aMed. ♦ Indicates incidence of fatal CVD (*P* for trend<0.0001).

prior reports that specifically examined the association between Mediterranean diet and stroke incidence.

A Mediterranean dietary pattern shares components with several other healthy eating patterns that have previously been shown to reduce cardiovascular disease risk. The Alternate Healthy Eating Index, emphasizing plant foods and unsaturated oils, was shown to reduce CVD mortality in both men and women.[16] In addition, the Dietary Approaches to Stop Hypertension diet pattern, which also emphasizes high intake of plant foods, low intake of animal protein, and low intake of sweets,[17] was associated with lower risk of CHD and stroke in this cohort.[18]

The Mediterranean diet has been linked to beneficial effects on inflammatory markers, lipids, and blood pressure. In cross-sectional analyses, adherence to the Mediterranean diet as measured by various indexes was associated with lower levels of C-reactive protein[19] and interleukin-6[20] and markers of endothelial function.[19,21] A 2-year randomized trial with a Mediterranean-style diet was effective in reducing C-reactive protein and interleukin-6 in individuals with metabolic syndrome.[22] A higher Mediterranean diet score was associated with more favorable levels of adiponectin,[23] an adipocytokine linked to CHD risk.[24] In a Greek population without hypertension, a higher Mediterranean diet score was associated with lower systolic and diastolic blood pressures.[25] In another 3-month randomized trial, the traditional Mediterranean diet was more effective in reducing oxidized low-density lipoprotein levels[26] and blood pressure than a low-fat diet.[27] In a 2-year randomized trial, the Mediterranean diet has resulted in significant weight loss and a more favorable ratio of total to high-density lipoprotein cholesterol and was more effective than a low-fat diet.[2]

The association between Mediterranean dietary pattern appeared even stronger for fatal than nonfatal CHD. Fatal CHD events are generally characterized by either more severe disease or arrhythmia. This may reflect that higher fish intake, an important component of the aMed, has been strongly associated with lower risk of CHD deaths.[28,29] A stronger association with fatal CVD events is consistent with the idea that the Mediterranean dietary pattern not only is beneficial for prevention of nonfatal CVD events but also can improve survival among patients with existing CVD.[3,4]

The aMed is based on the literature and our a priori hypotheses. A score always involves some level of arbitrary decision in the type and number of foods to be included and assignment of points to different levels of intake. Although our score is largely similar to those reported in the literature in the choice of food groups, there are some differences. The score used by Pitsavos et al[30] and that developed by Trichopoulou et al[8] awarded points for potato intake, but ours did not. The Trichopoulou et al score included a dairy component; the aMed did not. In addition, several dietary factors that have been demonstrated to be important for CHD risk such as *trans* fat,[31] n-6 polyunsaturated fatty acids,[32] and glycemic load[33,34] were not included in any of the Mediterranean diet scores. However, the omitted dietary components are likely to be associated with foods that are included in the score; thus, the score does account for them to a certain extent. For example, in our cohort, women with high aMed score appeared to have lower *trans* fat intake.

Another difference between scoring systems is the assignment of points. The score used by Pitsavos et al[30] classified adherence by assigning 0 to 5 points for each food component, whereas the scoring by Trichopoulou et al[8] and aMed used dichotomous points. However, results from different studies generally showed more favorable health outcomes in individuals with a higher Mediterranean diet score regardless of the scoring criteria. The aMed score assignment depends on intake relative to the level in the population. Therefore, when the scoring algorithm is applied to different populations, individuals from these populations may have the same score, but actual intake of each component could vary substantially.

The major sources of monounsaturated fat differ between the United States and other countries, especially Mediterranean countries, and by time period. In the first half of the follow-up period, the major sources (>30%) of monounsaturated fat in our cohort were beef and other meats. In the second half of follow-up, the contribution of beef and other meats dropped to ≈18%. At the same time, olive oil consumption increased considerably, but it still contributed only ≈10% of all monounsaturated fat intake. In contrast, in traditional Mediterranean diets of the 1960s, olive oil, along with other plant foods, is the primary source of monounsaturated fat intake.[1]

The long follow-up period in this study allowed us to assess long-term associations between the aMed score and CVD. The prospective assessment of diet and lifestyle information in this

analysis reduces the probability of recall bias. A high rate of follow-up reduced potential selection bias caused by systematic loss to follow-up. We used repeated measurements of diet to obtain a better assessment of long-term overall diet and to reduce measurement error, and CVD ascertainment was not influenced by risk factor or dietary intake of the cases. Confounding is always a concern in observational studies, and some level of residual confounding is unavoidable. Given our detailed and updated adjustment for potential confounders, it is unlikely that this would account for the observed results. Because this analysis is conducted in women and because it is the first report on the effects of Mediterranean diet on stroke, our results need to be replicated in other populations, especially men.

Conclusion

A greater adherence to the Mediterranean diet, as reflected by a higher aMed score, was associated with a lower risk of incident CHD and stroke in women.

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Disclosures

None.

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CLINICAL PERSPECTIVE

The present study examined the association between the Alternate Mediterranean Diet Score (aMed) and risk of CHD and stroke in the Nurses' Health Study. A higher score represents higher intake of vegetables (excluding potatoes), fruits, nuts, whole grains, legumes, fish, and ratio of monounsaturated to saturated fat; lower intake of red and processed meats; and alcohol intake between 5 and 15 g/d. Although a number of studies on various scores have measured adherence to the Mediterranean diet, most of them focused on total or CHD mortality, and none examined stroke as a separate outcome. This study differs by examining the incidence of CHD and stroke, which includes both fatal and nonfatal events. After adjustment for known risk factors for cardiovascular disease and energy intake, women in the highest 20% of the Alternate Mediterranean Diet Score had a lower risk for both CHD and stroke. Therefore, greater adherence to the Mediterranean diet, as reflected by a higher Alternate Mediterranean Diet Score, was associated with a lower risk of incident CHD and stroke in women.

Mediterranean Diet and Incidence of and Mortality From Coronary Heart Disease and Stroke in Women

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Correction

In the version of the article, "Mediterranean Diet and Incidence and Mortality of Coronary Heart Disease and Stroke in Women" by Fung et al that published ahead of print on February 16, 2009 (http://circ.ahajournals.org/cgi/content/short/CIRCULATIONAHA.108.816736v1), CHD was incorrectly defined as congestive heart disease in the introduction and the clinical perspectives. This has been corrected to read coronary heart disease in the current online and print versions of the article (*Circulation*. 2009;119:1093–1100).

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