The Mediterranean-style dietary pattern and mortality among men and women with cardiovascular disease[1–3]

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ABSTRACT

Background: The role of the Mediterranean diet among individuals with previous cardiovascular disease (CVD) is uncertain.

Objective: The aim of this study was to assess the association between the Alternate Mediterranean Diet (aMED) score and all-cause, cardiovascular, and cancer mortality in men and women with CVD from the Health Professionals Follow-Up Study and the Nurses' Health Study.

Design: This study included 6137 men and 11,278 women with myocardial infarction, stroke, angina pectoris, coronary bypass, and coronary angioplasty. Diet was first assessed in 1986 for men and in 1980 for women with a food-frequency questionnaire (FFQ) and then repeatedly every 2–4 y. Cumulative consumption was calculated with all available FFQs from the diagnosis of CVD to the end of the follow-up in 2008.

Results: During a median follow-up of 7.7 y (IQR: 4.2–11.8) for men and 5.8 y (IQR: 3.8–8.0) for women, we documented 1982 deaths (1142 from CVD and 344 from cancer) among men and 1468 deaths (666 from CVD and 197 from cancer) among women. In multivariable Cox regression models, the pooled RR of all-cause mortality from a comparison of the top with the bottom quintiles of the aMED score was 0.81 (95% CI: 0.72, 0.91; P-trend < 0.001). The corresponding pooled RR for CVD mortality was 0.85 (95% CI: 0.67, 1.09; P-trend = 0.30), for cancer mortality was 0.85 (95% CI: 0.65, 1.11; P-trend = 0.10), and for other causes was 0.79 (95% CI: 0.65, 0.97; P-trend = 0.01). A 2-point increase in adherence to the aMED score was associated with a 7% (95% CI: 3%, 11%) reduction in the risk of total mortality.

Conclusion: Adherence to a Mediterranean-style dietary pattern was associated with lower all-cause mortality in individuals with CVD. *Am J Clin Nutr* 2014;99:172–80.

INTRODUCTION

The Mediterranean dietary pattern refers to the traditional diet of populations living around the Mediterranean Sea. Although the diet of each population presents specific characteristics, they all share a high consumption of fruit and vegetables, a substantial intake of proteins from plant sources (legumes and nuts), and a high fat intake, mostly from MUFAs (1, 2). There is also a moderate to relatively high fish consumption and, in contrast, a low consumption of meat and meat products. Alcohol intake is moderate, usually as red wine consumed with meals. In addition, olive oil is the predominant fat for cooking and dressing salads, and sautéing and stir frying are the cooking techniques characteristic of this diet (3). Finally, because this is a palatable dietary pattern, adherence to a Mediterranean-style diet can be easily achieved by the general population in and outside the Mediterranean basin (4, 5).

There is substantial evidence of the long-term beneficial effects of the Mediterranean diet on health. In prospective cohort studies, several versions of Mediterranean diet scores have been associated with reduced total mortality (6–10) and lower risk of cardiovascular disease (CVD)[4] (11–13), cancer (14, 15), and neurodegenerative diseases (16) in apparently healthy populations. Mechanisms that may explain these associations include a reduction in blood pressure and insulin resistance, an improvement of the lipid profile, and antiinflammatory effects (17).

However, the effect of the Mediterranean diet among individuals with previous CVD is not well established. In the Lyon Diet Heart Study, a clinical trial among patients who had suffered a first myocardial infarction, a Mediterranean-style diet was associated with a reduced risk of a second cardiovascular event over 4 y (18, 19). However, this study had some methodologic limitations, including a relatively small sample size and a short-duration of follow-up (20). In addition, in the European Prospective Investigation into Cancer and Nutrition study, adherence to a Mediterranean diet score among people with a nonfatal CVD event was associated with a reduction in total mortality in the following 7 y (21, 22). However, diet was measured only at

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[4] Abbreviations used: aMED, Alternate Mediterranean Diet; CVD, cardiovascular disease; FFQ, food frequency questionnaire; ICD-8, International Classification of Diseases, 8th Revision; IHD, ischemic heart disease.

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baseline, well in advance of the occurrence of the first CVD event.

Thus, the objective of this study was to assess the long-term association between a Mediterranean-style diet score and all-cause, cardiovascular, and cancer mortality during up to 28 y of follow-up in men and women with CVD from the Health Professionals Follow-Up Study and the Nurses' Health Study. In these large cohorts, we collected dietary information after the first CVD event, which allowed us to test the hypothesis that adherence to a Mediterranean-style diet was associated with lower mortality among patients with a history of CVD.

SUBJECTS AND METHODS

Study population and design

The Health Professionals Follow-Up Study was a prospective cohort study of 51,529 male health professionals aged 40–75 y initiated in 1986 (23). The Nurses' Health Study was established in 1976 (24) with the enrollment of 121,700 female nurses aged 30–55 y at study entry. Participants in both cohorts completed baseline and follow-up questionnaires, reporting medical history, health-related behaviors, and dietary intake. For our analyses we included men and women with a nonfatal CVD event (described below) diagnosed from the beginning of the follow-up through 2006, the last year for which diet information was available at least once after the CVD event. Then, we examined the relation between the habitual diet after the CVD event and mortality up to 2008. The Harvard School of Public Health and Brigham and Women's Hospital Human Subjects Committee Review Board approved the protocol of each study.

Ascertainment of CVD

Nonfatal CVD was self-reported in the biennial questionnaire, and permission to review medical records was sought to confirm the diagnosis. The CVD events considered were myocardial infarction, stroke, angina pectoris, coronary bypass, and coronary angioplasty. Myocardial infarction was classified as confirmed if the following criteria were met: symptoms plus either electrocardiographic changes or elevated cardiac enzyme concentrations (25). Stroke was classified according to criteria of the National Survey of Stroke (26), which required evidence of a neurologic deficit with sudden or rapid onset that persisted for >24 h. Cerebrovascular pathology due to infection, trauma, or malignancy was excluded, as were "silent" strokes discovered only by radiological imaging. For each type of stroke, the diagnosis was classified as confirmed when a computed tomography scan, MRI, angiography, or surgery had confirmed the lesion. Computed tomography or MRI reports were available for 89% of those with medical records. Cases in which medical record release was refused or when medical records were unavailable were classified as probable ischemic heart disease (IHD) or probable stroke of undetermined type. For these analyses, we included both confirmed and probable cases of IHD and stroke. Finally, information on history of angina pectoris, coronary bypass, and coronary angioplasty was self-reported. We included 6137 men who experienced a nonfatal CVD event (57.1% had a myocardial infarction, 13.7% had a stroke, and 29.2% had angina pectoris and/or underwent coronary bypass or coronary angioplasty), and 11,278 women with a nonfatal CVD event (14.5% had a myocardial infarction, 14.2% had a stroke, and 71.3% had angina pectoris and/or underwent coronary bypass or coronary angioplasty).

Dietary assessment

Dietary questionnaires were sent to the participants in 1980, 1984, 1986, 1990, 1994, 1998, 2002, and 2006 (in men since 1986). In each questionnaire, participants were asked how often on average during the previous year they had consumed each food (with the specification of standard portion sizes). The participants could choose from several responses, depending on the type of food. Using the USDA National Nutrient Database for Standard Reference (versions 10–23) corresponding to the year the dietary questionnaire was administered, we estimated total energy and nutrient intakes derived from the foods reported. These nutrients were energy-adjusted by using the residual method (27). Previous validation studies showed good correlations between energy-adjusted nutrients or food assessed by the food-frequency questionnaire (FFQ) and multiple weeks of food records completed over the preceding year in both the Health Professionals Follow-Up Study and the Nurses' Health Study (28, 29).

How the Alternate Mediterranean Diet (aMED) score was calculated was described elsewhere (14). The score rewards 1 point if intake is above the cohort-specific median for vegetables, legumes, fruit, nuts, whole-grain cereals, fish, and MUFAs:SFAs and 1 point for intake below the cohort-specific median for red and processed meats. In addition, alcohol intake of 5 to 15 g/d for women and 10 to 15 g/d for men received 1 point. Thus, a higher score represents a higher adherence to the Mediterranean diet, with a score range between 0 and 9 (*see* Supplemental Table 1 under "Supplemental data" in the online issue).

Ascertainment of mortality

Deaths were reported by the next of kin or the postal authorities or were ascertained through the National Death Index. We estimated that death ascertainment was >98% complete (30). For all deaths, we sought death certificates and, when appropriate, requested permission from the next of kin to review medical records. The underlying cause of death was assigned according to the International Classification of Diseases, 8th Revision (ICD-8). The primary endpoint in this analysis was death from any causes. We also conducted separate analyses for CVD mortality (ICD-8 codes 390.0 through 458.9 and 795.0–795.9) and cancer mortality (ICD-8 codes 140.0 through 207.9).

Medical history, anthropometric data, and lifestyle factors

On the baseline questionnaire, we requested information on age, weight, height, smoking status, parental history of myocardial infarction before age 65 y, menopausal status and use of hormone therapy (among women), and medication use. This information, with the exception of height and parental history, has been updated in the biennial follow-up questionnaires. BMI was calculated as weight in kilograms divided by the square of height in meters. Leisure-time physical activity was assessed every 2–4 y and reported as the average time spent per week during the preceding year in specific activities (eg, walking outdoors, jogging, and bicycling). The time spent in each activity was multiplied by its typical energy expenditure, expressed as metabolic equivalent

tasks and then summed over all activities. Standard portion sizes for alcoholic drinks were specified as a can/bottle or glass for beer, a 120-mL (4-oz) glass for wine, and one drink or shot for liquor. Detailed information on the validity and reproducibility of self-reported weight, physical activity, and alcohol consumption was published elsewhere (31–34).

Statistical analysis

We calculated person-years of exposure from the return date of the first dietary questionnaire after the diagnosis of CVD to the date of death or 1 June 2008, whichever came first. To represent long-term or habitual intake, and to account for changes in food consumption, we used the cumulative average of the aMED score from all available dietary questionnaires from the diagnosis of CVD through the end of follow-up (35).

Participants were classified into 5 groups according to quintiles of the aMED score. We conducted analyses separately for each cohort with the use of Cox proportional hazards models to investigate the association between the score and death from all causes and from CVD, cancer and other causes. Multivariable models were adjusted for age, BMI, smoking status, physical activity, parental history of myocardial infarction before age 65 y, menopausal status and use of hormone therapy in women, multivitamin use, and medication use (specifically aspirin, diuretics, β-blockers, calcium channel blockers, angiotensin-converting enzyme inhibitors, other antihypertensive medication, statins and other cholesterol lowering drugs, insulin, and oral antidiabetic medication). To test for a linear dose-response relation, we considered the score as a continuous variable. In addition, we calculated the mortality risk associated with a 2-point increase in the aMED score (corresponding to a 1-SD difference).

We conducted stratified analyses by parental history of myocardial infarction, BMI, leisure-time physical activity, and smoking status to assess the robustness of the results. Then, we examined the interactions between the aMED score (as a dichotomous variable, by using the sex-specific median as the cutoff) and the categories of the stratification variables with total mortality by using likelihood-ratio tests by comparing the nested models with and without cross-product interaction terms. Finally, the RRs from the multivariable-adjusted models in each cohort were pooled to obtain a summary RR estimate, by using inverse variance weights and a random-effects model (36), which allowed for between-study heterogeneity. The main analyses were not adjusted for alcohol consumption because this was one of the components of the aMED score. To assess the magnitude of the association that was attributable to alcohol intake, we performed a sensitivity analysis by additionally adjusting for alcohol intake (never, 0.1–4.9, 5.0–14.9, or $\geq$15.0 g/d). Likewise, we assessed the effect of olive oil by adjusting our analyses for its consumption (never or $<$1 time/mo, 1–3 times/mo, 1 time/wk, or $\geq$2 times/wk).

Analyses were performed with the SAS software, version 9.2 (SAS Institute Inc). This manuscript followed the Strengthening the Reporting of Observational Studies in Epidemiology recommendations (37).

RESULTS

Adherence to the Mediterranean dietary pattern was fairly stable over time in the study cohorts. The aMED mean ($\pm$SD) score across the years of follow-up dropped slightly from 4.52 $\pm$ 1.94 to 4.35 $\pm$ 1.99 between 1986 and 2006 in men, whereas in women it dropped from 3.91 $\pm$ 1.68 to 3.80 $\pm$ 1.92 between 1980 and 2006. In **Tables 1** and **2**, we observed that men and women in the lowest quintile of the aMED score were more likely to be smokers, to be less physically active, and to have reported lower alcohol consumption than individuals in the highest quintile. No appreciable differences were observed in the use of medications, although women with a higher score tended to use aspirin and statins more frequently than those with a lower aMED score. We also observed that a higher adherence to the aMED diet was associated with a healthier dietary pattern (higher in PUFAs and n$-$3 fatty acids and in vegetable protein and lower in SFAs and *trans* fats). MUFA intake was similar in all categories of the score. The main source of the intake for this type of fat in this population was from animal foods (meats and dairy products).

During a median follow-up of 7.7 y (IQR: 4.2–11.8 y) for men and 5.8 y (IQR: 3.8–8.0 y) for women, we documented 1982 deaths in men and 1468 deaths in women; of them, 1142 in men and 666 in women were from CVD, and 344 in men and 197 in women were from cancer. The aMED score was inversely associated with risk of all-cause death in men and women (**Table 3**). For individual components of the score, among men, the ratio of MUFA to SFA intake had a statistically significant inverse association with mortality, whereas the consumption of red and processed meat had a direct association (*see* Supplemental Table 2 under "Supplemental data" in the online issue). In women, whole-grain intake, the MUFA-SFA ratio, and moderate alcohol intake showed an inverse association.

All *P* values for heterogeneity between studies in men and women were $>$0.05 (*P* value for the total, CVD, cancer, and other-cause mortality random-effects models: 0.35, 0.16, 0.67, and 0.51). Therefore, we calculated pooled estimates. The adjusted RRs (95% CI) for total mortality across quintiles of the aMED score were 1.0, 0.98 (95% CI: 0.89, 1.08), 0.90 (95% CI: 0.81, 1.00), 0.94 (95% CI: 0.81, 1.08), and 0.81 (95% CI: 0.72, 0.91); *P*-trend $<$ 0.001. In addition, a 2-point increase in the aMED score was associated with a 7% decrease in the risk of total mortality (pooled adjusted RR: 0.93; 95% CI: 0.89, 0.97).

An inverse association between the aMED score and CVD mortality in men is shown in Table 3; the adjusted RRs and 95% CIs across quintiles of the aMED score were as follows: 1.0, 0.89 (95% CI: 0.75, 1.07), 0.88 (95% CI: 0.73, 1.05), 0.95 (95% CI: 0.79, 1.14), and 0.77 (95% CI: 0.63, 0.93); *P*-trend = 0.05). This association was not seen for women (*P*-trend = 0.87). Attenuation of the association was mostly a result of adjustment for physical activity, which was more noticeable in women because of the lower number of CVD deaths compared with men. No significant association was seen for cancer mortality in either sex. With regard to death from causes other than CVD and cancer (including chronic obstructive pulmonary disease, diabetes, Alzheimer disease, Parkinson disease, pneumonia, cirrhosis, and other chronic liver disease), no significant association was found in men, whereas an inverse association was evident in women; the adjusted RRs (95% CIs) across quintiles of the aMED score were as follows: 1.0, 0.97 (95% CI: 0.77, 1.22), 0.70 (95% CI: 0.54, 0.91), 0.85 (95% CI: 0.67, 1.09), and 0.75 (95% CI: 0.56, 0.98).

Stratified analyses did not show differences in the association between the score and all-cause mortality by categories of parental history of myocardial infarction (pooled *P*-interaction = 0.45),

TABLE 1
Baseline characteristics of men with cardiovascular disease according to quintiles of the Alternate Mediterranean Diet score in the Health Professionals Follow-Up Study (n = 6137)[1]

	Q1 (n = 1586)	Q2 (n = 1239)	Q3 (n = 1032)	Q4 (n = 938)	Q5 (n = 1342)
Age (y)	68 ± 9[2]	69 ± 9	68 ± 8	69 ± 9	69 ± 8
Score	2.19 ± 0.83	3.77 ± 0.39	4.85 ± 0.33	5.70 ± 0.43	7.05 ± 0.79
Current smoker (%)	9	5	4	4	2
BMI (kg/m^2)	26.5 ± 3.8	26.3 ± 3.6	26.0 ± 3.5	26.1 ± 3.6	25.7 ± 3.5
Leisure-time physical activity (MET-h/wk)	23.7 ± 33.8	28.9 ± 32.1	31.8 ± 31.4	35.8 ± 37.0	40.9 ± 38.1
Parental history of MI before age 65 y (%)	31	35	34	31	33
Multivitamin use (%)	35	28	38	33	36
Medication use (y)[3]					
Aspirin	55	46	60	52	50
Diuretics	12	11	11	8	6
β-Blockers	22	19	21	19	19
Calcium channel blockers	21	18	22	19	16
Other blood pressure medication	11	9	10	7	8
Statins and other cholesterol-lowering drugs	24	23	29	23	25
Foods in the score					
Vegetables (servings/d)	1.9 ± 1.1	2.5 ± 1.5	3.1 ± 1.6	3.8 ± 2.1	4.5 ± 2.1
Legumes (servings/d)	0.3 ± 0.3	0.4 ± 0.3	0.5 ± 0.4	0.6 ± 0.5	0.7 ± 0.6
Fruit (servings/d)	1.8 ± 1.1	2.4 ± 1.6	2.8 ± 1.6	3.1 ± 1.7	3.8 ± 1.8
Nuts (servings/d)	0.2 ± 0.3	0.4 ± 0.5	0.5 ± 0.6	0.5 ± 0.7	0.7 ± 0.8
Whole grain (servings/d)	0.9 ± 1.0	1.4 ± 1.2	1.7 ± 1.4	1.9 ± 1.4	2.3 ± 1.5
Fish (servings/d)	0.2 ± 0.2	0.3 ± 0.2	0.4 ± 0.4	0.4 ± 0.3	0.5 ± 0.3
MUFA:SFA	1.1 ± 0.2	1.2 ± 0.2	1.3 ± 0.3	1.3 ± 0.3	1.5 ± 0.3
Red and processed meats (servings/d)	0.9 ± 0.7	0.8 ± 0.7	0.7 ± 0.7	0.68 ± 0.7	0.5 ± 0.5
Alcohol intake (g/d)	9.0 ± 15.7	9.9 ± 15.3	9.5 ± 14.3	10.4 ± 13.5	11.0 ± 11.6
Nutrients (% of energy)					
PUFA	5.4 ± 1.7	5.6 ± 1.7	5.6 ± 1.7	5.7 ± 1.7	5.8 ± 1.7
SFA	10.3 ± 2.9	9.0 ± 2.7	8.1 ± 2.6	8.0 ± 2.6	7.0 ± 2.0
Long-chain n−3 fats, EPA+DHA	0.14 ± 0.03	0.17 ± 0.19	0.18 ± 0.22	0.21 ± 0.23	0.25 ± 0.26
MUFA	11.6 ± 3.3	11.1 ± 3.2	10.5 ± 3.3	10.6 ± 3.3	10.4 ± 3.2
trans Fat	1.7 ± 0.7	1.5 ± 0.7	1.3 ± 0.6	1.3 ± 0.6	1.2 ± 0.5
Vegetable protein	5.0 ± 1.1	5.6 ± 1.2	6.0 ± 1.3	6.2 ± 1.4	6.7 ± 1.4

[1] The data correspond to different periods based on the diagnosis of cardiovascular disease during follow-up (1986–2008). All data, except age, were directly standardized to the age distribution of the entire cohort. MET, metabolic equivalent task; MI, myocardial infarction; Q, quintile.

[2] Mean ± SD (all such values).

[3] One or more times per week.

BMI (pooled P = 0.87), leisure-time physical activity level (pooled P = 0.86), and smoking status (pooled P = 0.11) (**Table 4**). In addition, we performed several sensitivity analyses. We replicated the analyses in Table 3, including only participants with confirmed nonfatal IHD and stroke, and the results were similar to those shown in the tables with confirmed and probable cases. In addition, to control for the possible effect of diet consumed before the CVD event, we adjusted the models for the aMED score obtained from the closest FFQ before the CVD event, and the results did not materially change.

We tried to understand the contribution of alcohol consumption to the results. First, we adjusted the analyses for alcohol intake, and the association between the aMED score and mortality was somewhat attenuated (pooled adjusted RR for all-cause and cardiovascular mortality for a 2-point increase in the aMED score: 0.95 (95% CI: 0.90, 1.00) and 0.99 (95% CI: 0.89, 1.10), respectively. In addition, we created a new aMED score without alcohol and we adjusted the Cox models for categories of alcohol consumption and still found an inverse association between the new score and total mortality in men; the RRs were as follows: 1.0, 1.02 (95% CI: 9.89, 1.17), 0.91 (95% CI: 0.78, 1.05), 0.84 (95% CI: 0.72, 0.97), and 0.84 (95% CI: 0.72, 0.98); P-trend = 0.01). In women, the results lost statistical significance: 1.0, 1.03 (95% CI: 0.91, 1.15), 1.03 (95% CI: 0.91, 1.17), 1.03 (95% CI: 0.91, 1.16), and 0.91 (95% CI: 0.79, 1.04); P-trend = 0.14.

Finally, adjustment for olive oil consumption did not materially change the results; the pooled adjusted RRs for all-cause and cardiovascular mortality for a 2-point increase in the aMED score were as follows: 0.93 (95% CI: 0.89, 0.98) and 0.97 (95% CI: 0.89, 1.06). No significant association between olive oil consumption and total or CVD mortality was found (data not shown), but only 14.3% of men and 10.3% of women reported consuming olive oil ≥2 times/wk.

DISCUSSION

In this study, we found an inverse association between the aMED score and all-cause mortality in men and women with a history of CVD. We observed a 7% reduction in total mortality with each 2-point increase in the aMED score. In men, this inverse association was mainly explained by a lower cardiovascular mortality, whereas in women it was partly because of a reduction in mortality for causes other than CVD or cancer. These results are of interest because they show that a healthy diet can still be beneficial at an advanced stage of the atherosclerotic process and that following a Mediterranean-style dietary pattern may be of benefit for populations outside the Mediterranean area (11).

TABLE 2
Baseline characteristics of women with cardiovascular disease according to quintiles of the Alternate Mediterranean Diet score in the Nurses' Health Study (n = 11,278)[1]

	Q1 (n = 2274)	Q2 (n = 1970)	Q3 (n = 2103)	Q4 (n = 1978)	Q5 (n = 2953)
Age (y)	68 ± 9	67 ± 9	67 ± 8	67 ± 8	67 ± 8
Score	1.59 ± 0.64[2]	3.03 ± 0.13	4.01 ± 0.08	5.00 ± 0.09	6.63 ± 0.78
Current smoker (%)	16	14	12	8	7
BMI (kg/m^2)	26.9 ± 6.6	26.7 ± 6.5	26.5 ± 6.3	26.6 ± 6.1	26.2 ± 5.7
Leisure-time physical activity (MET-h/wk)	9.4 ± 14.4	11.0 ± 18.8	13.4 ± 16.8	14.1 ± 16.9	18.8 ± 22.4
Parental history of MI before age 65 y (%)	26	29	30	28	30
Postmenopausal hormone use (%)	33	31	31	29	26
Multivitamin use (%)	32	36	39	40	44
Medication use (%)[3]					
Aspirin	65	68	67	71	72
Diuretics	14	14	17	15	15
β-Blockers	24	26	26	26	26
Calcium channel blockers	17	19	21	21	21
ACE inhibitors	11	12	12	13	12
Other blood pressure medication	10	8	10	9	9
Statins	23	26	26	26	29
Other cholesterol-lowering drugs	4	3	4	3	4
Insulin	5	5	5	5	3
Oral antidiabetic drugs	6	7	6	6	5
Foods in the score					
Vegetables (servings/d)	1.6 ± 0.9	2.1 ± 1.4	2.6 ± 1.5	3.1 ± 1.7	4.2 ± 1.9
Legumes (servings/d)	1.9 ± 3.3	1.9 ± 3.1	2.0 ± 3.2	2.1 ± 3.2	2.2 ± 3.2
Fruit (servings/d)	1.4 ± 1.0	1.9 ± 1.4	2.3 ± 1.4	2.6 ± 1.5	3.3 ± 1.6
Nuts (servings/d)	0.1 ± 0.3	0.2 ± 0.4	0.3 ± 0.5	0.4 ± 0.5	0.5 ± 0.6
Whole grain (servings/d)	0.7 ± 1.0	1.0 ± 1.3	1.3 ± 1.4	1.5 ± 1.5	2.1 ± 1.7
Fish (servings/d)	0.1 ± 0.1	0.2 ± 0.2	0.2 ± 0.2	0.3 ± 0.3	0.4 ± 0.3
MUFA:SFA	1.0 ± 0.2	1.1 ± 0.3	1.2 ± 0.3	1.2 ± 0.3	1.4 ± 0.4
Red and processed meats (servings/d)	0.9 ± 0.8	0.8 ± 0.7	0.8 ± 0.8	0.7 ± 0.6	0.6 ± 0.6
Alcohol intake (g/d)	3.6 ± 9.9	4.3 ± 9.9	4.3 ± 9.4	4.0 ± 8.1	4.9 ± 8.0
Nutrients (% of energy)					
PUFA	5.4 ± 1.7	5.6 ± 1.8	5.6 ± 1.8	5.7 ± 1.8	6.0 ± 1.8
SFA	11.5 ± 3.2	10.3 ± 3.2	9.7 ± 3.1	9.0 ± 2.9	8.0 ± 2.4
Long-chain n−3 fats, EPA+DHA	0.09 ± 0.12	0.11 ± 0.15	0.12 ± 0.13	0.15 ± 0.15	0.18 ± 0.17
MUFA	11.8 ± 3.3	11.5 ± 3.8	11.4 ± 3.9	11.1 ± 3.6	11.0 ± 3.5
trans Fat	1.9 ± 0.7	1.7 ± 0.7	1.6 ± 0.7	1.5 ± 0.6	1.3 ± 0.6
Vegetable protein	4.8 ± 1.2	5.3 ± 1.4	5.6 ± 1.3	5.9 ± 1.4	6.4 ± 1.5

[1] Data correspond to different periods based on the diagnosis of cardiovascular disease during follow-up (1980–2008). All data, except age, were directly standardized to the age distribution of the entire cohort. ACE, angiotensin-converting enzyme; MET, metabolic equivalent task; MI, myocardial infarction; Q, quintile.
[2] Mean ± SD (all such values).
[3] One or more times per week.

The Lyon Diet Heart Study (18) was designed to assess whether a dietary intervention with a Mediterranean-style diet was able to reduce the risk of a second CVD event in survivors of a myocardial infarction. The intervention diet was designed to supply <35% of energy from fat, including <10% from SFAs, <4% from omega-6 (n−6) fatty acids, and >0.6% from omega-3 (n−3) fatty acids by providing the participants in the intervention group with a margarine rich in canola oil. Despite the small sample size, the authors found a protective effect of the Mediterranean dietary pattern. However, no other clinical trials have been performed to examine this effect.

A previous prospective study has also assessed the effect of the Mediterranean diet on mortality among individuals with CVD. With the use of data from the European Prospective Investigation into Cancer and Nutrition study, Trichopoulou et al (21, 22) found that, in 2 subsamples of CVD patients from the original cohort, those with high adherence to a Mediterranean dietary pattern had a substantial reduction in mortality. However, diet and lifestyle characteristics were measured only at the beginning of the 7 y of follow-up. Thus, it was not possible to account for possible changes in diet after the first nonfatal CVD event. Our findings, together with those of previous studies with different designs, strongly support a benefit of a Mediterranean-type dietary pattern among patients with CVD. In addition, our findings are consistent with recent evidence about the protective effects on health of a high-quality diet in patients with CVD (38).

Several mechanisms may explain a beneficial effect of the Mediterranean diet on all-cause and CVD mortality. This dietary pattern has been associated with lower concentrations of inflammatory markers and endothelial dysfunction in healthy individuals (39, 40), high-risk patients (41), and those with a history of coronary events (42). In addition, adherence to this dietary pattern has been linked to weight loss (43), lower blood pressure (17), a more favorable ratio of total to HDL cholesterol (43),

TABLE 3
RRs (95% CIs) for mortality according to quintiles of the aMED among men and women with cardiovascular disease in the Health Professionals Follow-Up Study and the Nurses' Health Study[1]

	Q1	Q2	Q3	Q4	Q5	*P*-trend	RR (95% CI) for a 2-point increase in the aMED score
Men							
Death from all causes							
Person-year	10,389	9920	9430	9248	9873		
Deaths (*n*)	460	437	367	380	338		
Age- and smoking-adjusted RR	1.0	0.88 (0.77, 1.00)	0.77 (0.67, 0.89)	0.80 (0.70, 0.92)	0.68 (0.59, 0.78)	<0.001	0.86 (0.82, 0.91)
Multivariable-adjusted RR	1.0	0.94 (0.82, 1.07)	0.85 (0.74, 0.98)	0.86 (0.75, 0.99)	0.79 (0.68, 0.91)	0.003	0.92 (0.86, 0.97)
Death from cardiovascular disease							
Deaths (*n*)	268	240	213	235	186		
Age- and smoking-adjusted RR	1.0	0.84 (0.71, 1.01)	0.80 (0.66, 0.96)	0.88 (0.73, 1.05)	0.66 (0.54, 0.79)	<0.001	0.87 (0.81, 0.94)
Multivariable-adjusted RR	1.0	0.89 (0.75, 1.07)	0.88 (0.73, 1.05)	0.95 (0.79, 1.14)	0.77 (0.63, 0.93)	0.05	0.93 (0.86, 1.00)
Death from cancer							
Deaths (*n*)	90	81	55	47	71		
Age- and smoking-adjusted RR	1.0	0.85 (0.63, 1.16)	0.61 (0.43, 0.86)	0.54 (0.38, 0.77)	0.78 (0.57, 1.07)	0.03	0.86 (0.75, 0.98)
Multivariable-adjusted RR	1.0	0.91 (0.67, 1.24)	0.67 (0.47, 0.95)	0.58 (0.40, 0.83)	0.88 (0.63, 1.21)	0.14	0.90 (0.79, 1.03)
Death from other causes							
Deaths (*n*)	102	5116	99	98	81		
Age- and smoking-adjusted RR	1.0	1.03 (0.79, 1.35)	0.90 (0.68, 1.20)	0.90 (0.68, 1.19)	0.72 (0.53, 0.97)	0.02	0.87 (0.78, 0.98)
Multivariable-adjusted RR	1.0	1.11 (0.85, 1.46)	1.02 (0.77, 1.36)	0.98 (0.74, 1.30)	0.85 (0.63, 1.16)	0.27	0.94 (0.83, 1.05)
Women							
Death from all causes							
Person-year	15,494	16,160	16,055	15,769	16,279		
Deaths (*n*)	346	345	288	287	202		
Age- and smoking-adjusted RR	1.0	0.95 (0.82, 1.10)	0.82 (0.70, 0.96)	0.81 (0.69, 0.95)	0.60 (0.50, 0.71)	<0.001	0.82 (0.76, 0.87)
Multivariable-adjusted RR	1.0	1.03 (0.89, 1.20)	0.95 (0.81, 1.11)	1.01 (0.86, 1.19)	0.85 (0.71, 1.02)	0.11	0.95 (0.88, 1.01)
Death from cardiovascular disease							
Deaths (*n*)	141	158	141	131	95		
Age- and smoking-adjusted RR	1.0	1.05 (0.83, 1.32)	0.97 (0.77, 1.23)	0.90 (0.71, 1.14)	0.68 (0.52, 0.88)	0.002	0.86 (0.78, 0.94)
Multivariable-adjusted RR	1.0	1.15 (0.91, 1.45)	1.13 (0.89, 1.44)	1.15 (0.90, 1.46)	0.99 (0.75, 1.29)	0.87	1.01 (0.91, 1.11)
Death from cancer							
Deaths (*n*)	43	39	47	42	26		
Age- and smoking-adjusted RR	1.0	0.85 (0.55, 1.31)	1.12 (0.74, 1.70)	1.00 (0.65, 1.54)	0.67 (0.41, 1.10)	0.14	0.87 (0.73, 1.04)
Multivariable-adjusted RR	1.0	0.87 (0.56, 1.36)	1.20 (0.79, 1.84)	1.12 (0.72, 1.74)	0.80 (0.48, 1.33)	0.48	0.94 (0.78, 1.13)
Death from other causes							
Deaths (*n*)	16	148	100	114	81		
Age- and smoking-adjusted RR	1.0	0.89 (0.71, 1.12)	0.61 (0.48, 0.79)	0.69 (0.54, 0.88)	0.52 (0.39, 0.68)	<0.001	0.76 (0.68, 0.84)
Multivariable-adjusted RR	1.0	0.97 (0.77, 1.22)	0.70 (0.54, 0.91)	0.85 (0.67, 1.09)	0.75 (0.56, 0.98)	0.02	0.88 (0.79, 0.97)
Pooled results[2]							
Death from all causes	1	0.98 (0.89, 1.08)	0.90 (0.81, 1.00)	0.94 (0.81, 1.08)	0.81 (0.72, 0.91)	<0.001	0.93 (0.89, 0.97)
Death from cardiovascular disease	1	1.00 (0.79, 1.27)	0.99 (0.78, 1.25)	1.02 (0.87, 1.21)	0.85 (0.67, 1.09)	0.30	0.96 (0.89, 1.04)
Death from cancer	1	0.89 (0.69, 1.15)	0.88 (0.50, 1.55)	0.80 (0.42, 1.54)	0.85 (0.65, 1.11)	0.10	0.91 (0.82, 1.02)
Death from other causes	1	1.03 (0.86, 1.22)	0.84 (0.59, 1.22)	0.91 (0.75, 1.09)	0.79 (0.65, 0.97)	0.01	0.91 (0.84, 0.98)

[1] Adjusted for age (1-y increment), smoking status (never, past, or current 1–14, 15–24, or ≥25 cigarettes/d), BMI (in kg/m^2; <23.0, 23.0–24.9, 25.0–27.9, 28.0–29.9, or ≥30.0), leisure-time physical activity (<1.5, 1.5–5.9, 6.0–11.9, 12.0–20.9, or ≥21.0 MET-h/wk), parental history of myocardial infarction before age 65 y, menopausal status and use of HT in women (premenopausal women, postmenopausal without HT, postmenopausal with past HT, or postmenopausal with current HT), multivitamin use, and medication use (aspirin, diuretics, β-blockers, calcium channel blockers, other blood pressure medication, or statins and other cholesterol-lowering drugs). aMED, Alternate Mediterranean Diet; HT, hormone therapy; MET, metabolic equivalent task; Q, quintile.

[2] Results from the multivariable-adjusted models were combined by using a random-effects model.

TABLE 4
RRs (95% CIs) for all-cause mortality according to the Alternate Mediterranean Diet score among men and women with cardiovascular disease, stratified by parental history of myocardial infarction, BMI, physical activity, and smoking status in the Health Professionals Follow-Up Study and the Nurses' Health Study[1]

Pooled results[2]	Q1	Q2	Q3	Q4	Q5	*P*-trend	*P*-interaction
Parental history of MI							0.45
No	1.0	0.99 (0.84, 1.17)	0.92 (0.75, 1.13)	0.88 (0.74, 1.05)	0.70 (0.58, 0.85)	<0.001	
Yes	1.0	0.92 (0.72, 1.18)	0.89 (0.78, 1.02)	0.96 (0.79, 1.16)	0.87 (0.75, 1.00)	0.21	
BMI							0.87
<30 kg/m^2	1.0	0.98 (0.85, 1.12)	0.83 (0.70, 0.99)	0.94 (0.81, 1.09)	0.86 (0.73, 1.01)	0.03	
≥30 kg/m^2	1.0	1.06 (0.76, 1.49)	1.35 (0.97, 1.88)	1.31 (0.93, 1.85)	0.72 (0.37, 1.41)	0.77	
Leisure-time physical activity							0.86
Less active[3]	1.0	0.96 (0.87, 1.07)	0.88 (0.78, 0.98)	0.88 (0.79, 0.99)	0.77 (0.68, 0.87)	<0.001	
More active	1.0	0.88 (0.64, 1.20)	0.81 (0.59, 1.11)	0.91 (0.67, 1.24)	0.74 (0.54, 1.01)	0.10	
Smoking status							0.11
Never and past	1.0	1.01 (0.87, 1.19)	0.75 (0.46, 1.22)	0.96 (0.82, 1.14)	0.85 (0.71, 1.01)	0.04	
Current[4]	1.0	0.95 (0.77, 1.17)	0.96 (0.77, 1.20)	1.04 (0.70, 1.56)	0.81 (0.63, 1.06)	0.67	

[1] MI, myocardial infarction; Q, quintile.
[2] Results from the multivariable-adjusted models were combined by using a random-effects model. Models were adjusted for the same covariates as in the multivariable model (*see* Table 3), except for the stratification variable.
[3] Defined as those with leisure-time physical activity levels below the median.
[4] Additional adjustment for the number of cigarettes smoked per day.

lower oxidized LDL concentrations (44), and lower carotid intima-media thickness in patients with high atherosclerotic burden (45). Moreover, a Mediterranean diet intervention over 4 y has been effective in preventing diabetes in patients at high CVD risk (46).

Individual foods in this diet have also shown beneficial effects on health. In a recent meta-analysis, light to moderate alcohol consumption was associated with a lower risk of CVD (47). Also, the beneficial effect of moderate alcohol consumption has been observed in patients with clinical manifestations of vascular disease (48–50). In our analyses, the magnitude of the association between the Mediterranean dietary pattern and all-cause mortality was somewhat attenuated after adjustment for alcohol intake, which suggests that it could be partly explained by moderate alcohol consumption. Another potentially beneficial component of the Mediterranean pattern is olive oil. This vegetable oil is a good source of MUFAs, which may increase HDL cholesterol (51). Olive oil also contains considerable amounts of phenolic compounds with important antioxidant activity (52) that might reduce LDL oxidation—one of the key steps in the initiation of atherosclerosis. However, sensitivity analyses suggested that olive oil consumption did not contribute greatly to the lower mortality observed in this study, probably because its consumption was low in this population. Fish is another important component in the Mediterranean diet and a major food source of long-chain omega-3 fatty acids. In a recent review of the literature, omega-3 fatty acids, especially the long-chain ones, were found to improve vascular and cardiac hemodynamics, endothelial function, inflammation, thrombosis, and arrhythmia (53). Thus, omega-3 fatty acids may reduce the risk of cardiac death. Finally, a higher consumption of food sources of fiber—including whole grains, fruit, vegetables, legumes, and nuts—has been consistently associated with a lower CVD risk, through mechanisms including lipid reduction, body weight regulation, improved glucose metabolism, blood pressure control, and reduction of chronic inflammation (54). In our secondary analyses, no single component of the aMED score drove the association, which suggests potential synergistic effects of multiple components.

Our analyses were adjusted for medication use, which was updated repeatedly during the follow-up. In addition, strong clinical evidence on the beneficial effects of angiotensin-converting enzyme inhibitors date from 1991 (55), and on the effects of statins from 1994 (56), which implies that current standard CVD treatments were set after the start of the cohort follow-up. Thus, medication use at baseline for those participants included in the follow-up from 1980 to 1995 was much lower than medication use for those included in the follow-up starting at 1995.

The strength of this study included its long follow-up; the use of updated information on diet, medication, and other CVD risk factors after the CVD event; and the large number of total and CVD deaths. However, some measurement error in the assessment of food consumption was inevitable because diet was self-reported. Also, the quantification of nutrients from the foods reported in the FFQ involved a certain degree of error. In addition, we did not have information on the severity of the nonfatal CVD event. Although we controlled for a wide range of potential confounders, we could not rule out some residual confounding. In particular, leisure-time physical activity did not capture the total amount of physical activity. Finally, because the study was conducted among professionals with access to health care, extrapolation of results to the general population should be made with caution.

In conclusion, a Mediterranean-style dietary pattern was associated with a reduced risk of mortality in men and women with CVD. More research is needed to understand the causes of this association. However, these results support the adoption of a Mediterranean-style diet in patients with CVD to prevent premature death.

The authors' responsibilities were as follows—EL-G, FR-A, TYL, TTF, SL, WCW, EBR, and FBH: study concept and design, analysis and interpretation of the data, and critical revision of the manuscript for important intellectual content; FBH: acquisition of data; EL-G: drafting of the manuscript; EL-G and TYL: statistical expertise; EL-G and FBH: procurement of funding; FR-A and FBH: administrative, technical, or material support; and FBH: study supervision. All authors had full access to the data and take responsibility for its integrity. All authors read and agreed with the manuscript as written. None of the authors had a conflict of interest.

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