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Primary Prevention of Cardiovascular Disease with a Mediterranean Diet

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ABSTRACT

BACKGROUND

Observational cohort studies and a secondary prevention trial have shown an inverse association between adherence to the Mediterranean diet and cardiovascular risk. We conducted a randomized trial of this diet pattern for the primary prevention of cardiovascular events.

METHODS

In a multicenter trial in Spain, we randomly assigned participants who were at high cardiovascular risk, but with no cardiovascular disease at enrollment, to one of three diets: a Mediterranean diet supplemented with extra-virgin olive oil, a Mediterranean diet supplemented with mixed nuts, or a control diet (advice to reduce dietary fat). Participants received quarterly individual and group educational sessions and, depending on group assignment, free provision of extra-virgin olive oil, mixed nuts, or small nonfood gifts. The primary end point was the rate of major cardiovascular events (myocardial infarction, stroke, or death from cardiovascular causes). On the basis of the results of an interim analysis, the trial was stopped after a median follow-up of 4.8 years.

RESULTS

A total of 7447 persons were enrolled (age range, 55 to 80 years); 57% were women. The two Mediterranean-diet groups had good adherence to the intervention, according to self-reported intake and biomarker analyses. A primary end-point event occurred in 288 participants. The multivariable-adjusted hazard ratios were 0.70 (95% confidence interval [CI], 0.54 to 0.92) and 0.72 (95% CI, 0.54 to 0.96) for the group assigned to a Mediterranean diet with extra-virgin olive oil (96 events) and the group assigned to a Mediterranean diet with nuts (83 events), respectively, versus the control group (109 events). No diet-related adverse effects were reported.

CONCLUSIONS

Among persons at high cardiovascular risk, a Mediterranean diet supplemented with extra-virgin olive oil or nuts reduced the incidence of major cardiovascular events. (Funded by the Spanish government's Instituto de Salud Carlos III and others; Controlled-Trials.com number, ISRCTN35739639.)

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*The PREDIMED (Prevención con Dieta Mediterránea) study investigators are listed in the Supplementary Appendix, available at NEJM.org.

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THE TRADITIONAL MEDITERRANEAN DIET is characterized by a high intake of olive oil, fruit, nuts, vegetables, and cereals; a moderate intake of fish and poultry; a low intake of dairy products, red meat, processed meats, and sweets; and wine in moderation, consumed with meals.[1] In observational cohort studies[2,3] and a secondary prevention trial (the Lyon Diet Heart Study),[4] increasing adherence to the Mediterranean diet has been consistently beneficial with respect to cardiovascular risk.[2-4] A systematic review ranked the Mediterranean diet as the most likely dietary model to provide protection against coronary heart disease.[5] Small clinical trials have uncovered plausible biologic mechanisms to explain the salutary effects of this food pattern.[6-9] We designed a randomized trial to test the efficacy of two Mediterranean diets (one supplemented with extra-virgin olive oil and another with nuts), as compared with a control diet (advice on a low-fat diet), on primary cardiovascular prevention.

METHODS

STUDY DESIGN

The PREDIMED trial (Prevención con Dieta Mediterránea) was a parallel-group, multicenter, randomized trial. Details of the trial design are provided elsewhere.[10-12] The trial was designed and conducted by the authors, and the protocol was approved by the institutional review boards at all study locations. The authors vouch for the accuracy and completeness of the data and all analyses and for the fidelity of this report to the protocol, which is available with the full text of this article at NEJM.org.

Supplemental foods were donated, including extra-virgin olive oil (by Hojiblanca and Patrimonio Comunal Olivarero, both in Spain), walnuts (by the California Walnut Commission), almonds (by Borges, in Spain), and hazelnuts (by La Morella Nuts, in Spain). None of the sponsors had any role in the trial design, data analysis, or reporting of the results.

PARTICIPANT SELECTION AND RANDOMIZATION

Eligible participants were men (55 to 80 years of age) and women (60 to 80 years of age) with no cardiovascular disease at enrollment, who had either type 2 diabetes mellitus or at least three of the following major risk factors: smoking, hypertension, elevated low-density lipoprotein cholesterol levels, low high-density lipoprotein cholesterol levels, overweight or obesity, or a family history of premature coronary heart disease. Detailed enrollment criteria are provided in the Supplementary Appendix, available at NEJM.org. All participants provided written informed consent.

Beginning on October 1, 2003, participants were randomly assigned, in a 1:1:1 ratio, to one of three dietary intervention groups: a Mediterranean diet supplemented with extra-virgin olive oil, a Mediterranean diet supplemented with nuts, or a control diet. Randomization was performed centrally by means of a computer-generated random-number sequence.

INTERVENTIONS AND MEASUREMENTS

The dietary intervention[8,10-13] is detailed in the Supplementary Appendix. The specific recommended diets are summarized in Table 1. Participants in the two Mediterranean-diet groups received either extra-virgin olive oil (approximately 1 liter per week) or 30 g of mixed nuts per day (15 g of walnuts, 7.5 g of hazelnuts, and 7.5 g of almonds) at no cost, and those in the control group received small nonfood gifts. No total calorie restriction was advised, nor was physical activity promoted.

For participants in the two Mediterranean-diet groups, dietitians ran individual and group dietary-training sessions at the baseline visit and quarterly thereafter. In each session, a 14-item dietary screener was used to assess adherence to the Mediterranean diet[8,14] (Table S1 in the Supplementary Appendix) so that personalized advice could be provided to the study participants in these groups.

Participants in the control group also received dietary training at the baseline visit and completed the 14-item dietary screener used to assess baseline adherence to the Mediterranean diet. Thereafter, during the first 3 years of the trial, they received a leaflet explaining the low-fat diet (Table S2 in the Supplementary Appendix) on a yearly basis. However, the realization that the more infrequent visit schedule and less intense support for the control group might be limitations of the trial prompted us to amend the protocol in October 2006. Thereafter, participants assigned to the control diet received personalized advice and were invited to group sessions with the same frequency and intensity as those in the Mediterranean-diet groups, with

the use of a separate 9-item dietary screener (Table S3 in the Supplementary Appendix).

A general medical questionnaire, a 137-item validated food-frequency questionnaire,[15] and the Minnesota Leisure-Time Physical Activity Questionnaire were administered on a yearly basis.[10] Information from the food-frequency questionnaire was used to calculate intake of energy and nutrients. Weight, height, and waist circumference were directly measured.[16] Biomarkers of compliance, including urinary hydroxytyrosol levels (to confirm compliance in the group receiving extra-virgin olive oil) and plasma alpha-linolenic acid levels (to confirm compliance in the group receiving mixed nuts), were measured in random subsamples of participants at 1, 3, and 5 years (see the Supplementary Appendix).

END POINTS

The primary end point was a composite of myocardial infarction, stroke, and death from cardiovascular causes. Secondary end points were stroke, myocardial infarction, death from cardiovascular causes, and death from any cause. We used four sources of information to identify end points: repeated contacts with participants, contacts with family physicians, a yearly review of medical records, and consultation of the National Death Index. All medical records related to end points were examined by the end-point adjudication committee, whose members were unaware of the study-group assignments. Only end points that were confirmed by the adjudication committee and that occurred between October 1, 2003, and December 1, 2010, were included in the analyses. The criteria for adjudicating primary and secondary end points are detailed in the Supplementary Appendix.

STATISTICAL ANALYSIS

We initially estimated that a sample of 9000 participants would be required to provide statistical power of 80% to detect a relative risk reduction of 20% in each Mediterranean-diet group versus the control-diet group during a 4-year follow-up period, assuming an event rate of 12% in the control group.[10,17] In April 2008, on the advice of the data and safety monitoring board and on the basis of lower-than-expected rates of end-point events, the sample size was recalculated as 7400 participants, with the assumption of a 6-year follow-up period and underlying event rates of

Table 1. Summary of Dietary Recommendations to Participants in the Mediterranean-Diet Groups and the Control-Diet Group.

Food	Goal
Mediterranean diet	
Recommended	
Olive oil*	≥4 tbsp/day
Tree nuts and peanuts†	≥3 servings/wk
Fresh fruits	≥3 servings/day
Vegetables	≥2 servings/day
Fish (especially fatty fish), seafood	≥3 servings/wk
Legumes	≥3 servings/wk
Sofrito‡	≥2 servings/wk
White meat	Instead of red meat
Wine with meals (optionally, only for habitual drinkers)	≥7 glasses/wk
Discouraged	
Soda drinks	<1 drink/day
Commercial bakery goods, sweets, and pastries§	<3 servings/wk
Spread fats	<1 serving/day
Red and processed meats	<1 serving/day
Low-fat diet (control)	
Recommended	
Low-fat dairy products	≥3 servings/day
Bread, potatoes, pasta, rice	≥3 servings/day
Fresh fruits	≥3 servings/day
Vegetables	≥2 servings/day
Lean fish and seafood	≥3 servings/wk
Discouraged	
Vegetable oils (including olive oil)	≤2 tbsp/day
Commercial bakery goods, sweets, and pastries§	≤1 serving/wk
Nuts and fried snacks	≤1 serving /wk
Red and processed fatty meats	≤1 serving/wk
Visible fat in meats and soups¶	Always remove
Fatty fish, seafood canned in oil	≤1 serving/wk
Spread fats	≤1 serving/wk
Sofrito‡	≤2 servings/wk

* The amount of olive oil includes oil used for cooking and salads and oil consumed in meals eaten outside the home. In the group assigned to the Mediterranean diet with extra-virgin olive oil, the goal was to consume 50 g (approximately 4 tbsp) or more per day of the polyphenol-rich olive oil supplied, instead of the ordinary refined variety, which is low in polyphenols.

† For participants assigned to the Mediterranean diet with nuts, the recommended consumption was one daily serving (30 g, composed of 15 g of walnuts, 7.5 g of almonds, and 7.5 g of hazelnuts).

‡ Sofrito is a sauce made with tomato and onion, often including garlic and aromatic herbs, and slowly simmered with olive oil.

§ Commercial bakery goods, sweets, and pastries (not homemade) included cakes, cookies, biscuits, and custard.

¶ Participants were advised to remove the visible fat (or the skin) of chicken, duck, pork, lamb, or veal before cooking and the fat of soups, broths, and cooked meat dishes before consumption.

8.8% and 6.6% in the control and intervention groups, respectively. Power curves under several assumptions can be found in Figure S1 in the Supplementary Appendix.

Yearly interim analyses began after a median of 2 years of follow-up. With the use of O'Brien–Fleming stopping boundaries, the P values for stopping the trial at each yearly interim analysis were 5×10^{-6}, 0.001, 0.009, and 0.02 for benefit and 9×10^{-5}, 0.005, 0.02, and 0.05 for adverse effects.[18] The stopping boundary for the benefit of the Mediterranean diets with respect to the primary end point was crossed at the fourth interim evaluation; on July 22, 2011, the data and safety monitoring board recommended stopping the trial on the basis of end points documented through December 1, 2010.

All primary analyses were performed on an intention-to-treat basis by two independent analysts. Time-to-event data were analyzed with the use of Cox models with two dummy variables (one for the Mediterranean diet with extra-virgin olive oil and another for the Mediterranean diet with nuts) to obtain two hazard ratios for the comparison with the control group. To account for small imbalances in risk factors at baseline among the groups, Cox regression models were used to adjust for sex, age, and baseline risk factors. We tested the proportionality of hazards with the use of time-varying covariates. All analyses were stratified according to center. Prespecified subgroup analyses were conducted according to sex, age, body-mass index (BMI), cardiovascular-risk-factor status, and baseline adherence to the Mediterranean diet. Sensitivity analyses were conducted under several assumptions, including imputation of data for missing values and participants who dropped out (see the Supplementary Appendix).

RESULTS

BASELINE CHARACTERISTICS OF THE STUDY PARTICIPANTS

From October 2003 through June 2009, a total of 8713 candidates were screened for eligibility, and

Table 2. Baseline Characteristics of the Participants According to Study Group.*

Characteristic	Mediterranean Diet with EVOO (N=2543)	Mediterranean Diet with Nuts (N=2454)	Control Diet (N=2450)
Female sex — no. (%)†	1493 (58.7)	1326 (54.0)	1463 (59.7)
Age — yr†	67.0±6.2	66.7±6.1	67.3±6.3
Race or ethnic group — no. (%)			
White, from Europe	2470 (97.1)	2390 (97.4)	2375 (96.9)
Hispanic, from Central or South America	35 (1.4)	29 (1.2)	38 (1.6)
Other	38 (1.5)	35 (1.4)	37 (1.5)
Smoking status — no. (%)			
Never smoked	1572 (61.8)	1465 (59.7)	1527 (62.3)
Former smoker	618 (24.3)	634 (25.8)	584 (23.8)
Current smoker	353 (13.9)	355 (14.5)	339 (13.8)
Body-mass index†‡			
Mean	29.9±3.7	29.7±3.8	30.2±4.0
<25 — no. (%)	195 (7.7)	204 (8.3)	164 (6.7)
25–30 — no. (%)	1153 (45.3)	1163 (47.4)	1085 (44.3)
>30 — no. (%)	1195 (47.0)	1087 (44.3)	1201 (49.0)
Waist circumference — cm	100±10	100±11	101±11
Waist-to-height ratio†§	0.63±0.06	0.63±0.06	0.63±0.07
Hypertension — no. (%)¶	2088 (82.1)	2024 (82.5)	2050 (83.7)
Type 2 diabetes — no. (%)†‖	1282 (50.4)	1143 (46.6)	1189 (48.5)
Dyslipidemia — no. (%)**	1821 (71.6)	1799 (73.3)	1763 (72.0)
Family history of premature CHD — no. (%)††	576 (22.7)	532 (21.7)	560 (22.9)

Table 2. (Continued.)

Characteristic	Mediterranean Diet with EVOO (N=2543)	Mediterranean Diet with Nuts (N=2454)	Control Diet (N=2450)
Medication use — no. (%)			
ACE inhibitors	1236 (48.6)	1223 (49.8)	1216 (49.6)
Diuretics†	534 (21.0)	477 (19.4)	562 (22.9)
Other antihypertensive agents	725 (28.5)	710 (28.9)	758 (30.9)
Statins	1039 (40.9)	964 (39.3)	983 (40.1)
Other lipid-lowering agents	121 (4.8)	145 (5.9)	126 (5.1)
Insulin	124 (4.9)	126 (5.1)	134 (5.5)
Oral hypoglycemic agents†	768 (30.2)	680 (27.7)	757 (30.9)
Antiplatelet therapy	475 (18.7)	490 (20.0)	513 (20.9)
Hormone-replacement therapy‡‡	42 (2.8)	35 (2.6)	39 (2.7)
Score for adherence to Med diet§§	8.7±2.0	8.7±2.0	8.4±2.1

* Plus–minus values are means ±SD. ACE denotes angiotensin-converting enzyme, and EVOO extra-virgin olive oil.
† P<0.05 for comparisons between groups.
‡ The body-mass index is the weight in kilograms divided by the square of the height in meters.
§ The waist-to-height ratio (an index of central obesity) is the waist circumference divided by height.
¶ Hypertension was defined as a systolic blood pressure of 140 mm Hg or higher, a diastolic blood pressure of 90 mm Hg or higher, or the use of antihypertensive therapy.
‖ Diabetes was defined as a fasting blood glucose level of 126 mg per deciliter (7.0 mmol per liter) or higher on two occasions, a 2-hour plasma glucose level of 200 mg per deciliter (11 mmol per liter) or higher during a 75-g oral glucose-tolerance test, or the use of antidiabetic medication.
** Dyslipidemia was defined as a low-density lipoprotein cholesterol level higher than 160 mg per deciliter (4.1 mmol per liter), a high-density lipoprotein cholesterol level of 40 mg per deciliter (1.0 mmol per liter) or lower in men or 50 mg per deciliter (1.3 mmol per liter) or lower in women, or the use of lipid-lowering therapy.
†† A family history of premature coronary heart disease (CHD) was defined as a diagnosis of the disease in a male first-degree relative younger than 55 years of age or in a female first-degree relative younger than 65 years of age.
‡‡ The values for hormone-replacement therapy are for women only.
§§ The score for adherence to the Mediterranean diet is based on the 14-item dietary screener shown in Table S1 in the Supplementary Appendix (a score of 0 indicates minimum adherence, and a score of 14 indicates maximum adherence).

7447 were randomly assigned to one of the three study groups (Fig. S2 in the Supplementary Appendix). Their baseline characteristics according to study group are shown in Table 2. Drug-treatment regimens were similar for participants in the three groups, and they continued to be balanced during the follow-up period (Table S4 in the Supplementary Appendix).

Participants were followed for a median of 4.8 years (interquartile range, 2.8 to 5.8). After the initial assessment, 209 participants (2.8%) chose not to attend subsequent visits, and their follow-up was based on reviews of medical records. By December 2010, a total of 523 participants (7.0%) had been lost to follow-up for 2 or more years. Dropout rates were higher in the control group (11.3%) than in the Mediterranean-diet groups (4.9%) (Fig. S2 in the Supplementary Appendix). As compared with participants who remained in the trial, those who dropped out were younger (by 1.4 years), had a higher BMI (the weight in kilograms divided by the square of the height in meters; by 0.4), a higher waist-to-height ratio (by 0.01), and a lower score for adherence to the Mediterranean diet (by 1.0 points on the 14-item dietary screener) (P<0.05 for all comparisons).

COMPLIANCE WITH THE DIETARY INTERVENTION

Participants in the three groups reported similar adherence to the Mediterranean diet at baseline (Table 2, and Fig. S3 in the Supplementary Appendix) and similar food and nutrient intakes. During follow-up, scores on the 14-item Mediterranean-diet screener increased for the participants in the two Mediterranean-diet groups (Fig. S3 in the Supplementary Appendix). There were significant differences between these groups and the control group in 12 of the 14 items at 3 years (Table S5 in the Supplementary Appen-

dix). Changes in objective biomarkers also indicated good compliance with the dietary assignments (Fig. S4 and S5 in the Supplementary Appendix).

Participants in the two Mediterranean-diet groups significantly increased weekly servings of fish (by 0.3 servings) and legumes (by 0.4 servings) in comparison with those in the control group (Table S6 in the Supplementary Appendix). In addition, participants assigned to a Mediterranean diet with extra-virgin olive oil and those assigned to a Mediterranean diet with nuts significantly increased their consumption of extra-virgin olive oil (to 50 and 32 g per day, respectively) and nuts (to 0.9 and 6 servings per week, respectively). The main nutrient changes in the Mediterranean-diet groups reflected the fat content and composition of the supplemental foods (Tables S7 and S8 in the Supplementary Appendix). No relevant diet-related adverse effects were reported (see the Supplementary Appendix). We did not find any significant difference in changes in physical activity among the three groups.

Table 3. Outcomes According to Study Group.*

End Point	Mediterranean Diet with EVOO (N=2543)	Mediterranean Diet with Nuts (N=2454)	Control Diet (N=2450)	P Value†	
				Mediterranean Diet with EVOO vs. Control Diet	Mediterranean Diet with Nuts vs. Control Diet
Person-yr of follow-up	11,852	10,365	9763		
Primary end point‡					
No. of events	96	83	109		
Crude rate/1000 person-yr (95% CI)	8.1 (6.6–9.9)	8.0 (6.4–9.9)	11.2 (9.2–13.5)	0.009	0.02
Secondary end points					
Stroke					
No. of events	49	32	58		
Crude rate/1000 person-yr (95% CI)	4.1 (3.1–5.5)	3.1 (2.1–4.4)	5.9 (4.5–7.7)	0.03	0.003
Myocardial infarction					
No. of events	37	31	38		
Crude rate/1000 person-yr (95% CI)	3.1 (2.2–4.3)	3.0 (2.0–4.2)	3.9 (2.8–5.3)	0.31	0.25
Death from cardiovascular causes					
No. of events	26	31	30		
Crude rate/1000 person-yr (95% CI)	2.2 (1.4–3.2)	3.0 (2.0–4.2)	3.1 (2.1–4.4)	0.15	0.85
Death from any cause					
No. of events	118	116	114		
Crude rate/1000 person-yr (95% CI)	10.0 (8.2–11.9)	11.2 (9.3–13.4)	11.7 (9.6–14.0)	0.11	0.68
Hazard ratio for each Mediterranean diet vs. control (95% CI)					
Primary end point					
Unadjusted	0.70 (0.53–0.91)	0.70 (0.53–0.94)	1.00 (ref)	0.009	0.02
Multivariable-adjusted 1§	0.69 (0.53–0.91)	0.72 (0.54–0.97)	1.00 (ref)	0.008	0.03
Multivariable-adjusted 2¶	0.70 (0.54–0.92)	0.72 (0.54–0.96)	1.00 (ref)	0.01	0.03
Secondary end points‖					
Stroke	0.67 (0.46–0.98)	0.54 (0.35–0.84)	1.00 (ref)	0.04	0.006
Myocardial infarction	0.80 (0.51–1.26)	0.74 (0.46–1.19)	1.00 (ref)	0.34	0.22
Death from cardiovascular causes	0.69 (0.41–1.16)	1.01 (0.61–1.66)	1.00 (ref)	0.17	0.98
Death from any cause	0.82 (0.64–1.07)	0.97 (0.74–1.26)	1.00 (ref)	0.15	0.82

Table 3. (Continued.)

End Point	Mediterranean Diet with EVOO (N=2543)	Mediterranean Diet with Nuts (N=2454)	Control Diet (N=2450)	P Value*†	
				Mediterranean Diet with EVOO vs. Control Diet	Mediterranean Diet with Nuts vs. Control Diet
Hazard ratio for Mediterranean diets combined vs. control (95% CI)					
Primary end point					
Unadjusted	0.70 (0.55–0.89)		1 (ref)	0.003	
Multivariable-adjusted 1§	0.71 (0.56–0.90)		1 (ref)	0.004	
Multivariable-adjusted 2¶	0.71 (0.56–0.90)		1 (ref)	0.005	
Secondary end points‖					
Stroke	0.61 (0.44–0.86)		1 (ref)	0.005	
Myocardial infarction	0.77 (0.52–1.15)		1 (ref)	0.20	
Death from cardiovascular causes	0.83 (0.54–1.29)		1 (ref)	0.41	
Death from any cause	0.89 (0.71–1.12)		1 (ref)	0.32	

* CI denotes confidence interval, and ref reference.
† All P values were calculated with the use of Cox proportional-hazards models with robust variance estimators and stratification according to recruiting center.
‡ The primary end point was a composite of myocardial infarction, stroke, and death from cardiovascular causes.
§ The primary end point was stratified according to recruiting center and adjusted for sex, age (continuous variable), family history of premature coronary heart disease (yes or no), and smoking status (never smoked, former smoker, or current smoker).
¶ The primary end point was additionally adjusted for body-mass index (continuous variable), waist-to-height ratio (continuous variable), hypertension at baseline (yes or no), dyslipidemia at baseline (yes or no), and diabetes at baseline (yes or no).
‖ The secondary end points were stratified according to recruiting center and adjusted for sex, age (continuous variable), family history of premature coronary heart disease (yes or no), smoking status (never smoked, former smoker, or current smoker), body-mass index (continuous variable), waist-to-height ratio (continuous variable), hypertension at baseline (yes or no), dyslipidemia at baseline (yes or no), and diabetes at baseline (yes or no).

END POINTS

The median follow-up period was 4.8 years. A total of 288 primary-outcome events occurred: 96 in the group assigned to a Mediterranean diet with extra-virgin olive oil (3.8%), 83 in the group assigned to a Mediterranean diet with nuts (3.4%), and 109 in the control group (4.4%). Taking into account the small differences in the accrual of person-years among the three groups, the respective rates of the primary end point were 8.1, 8.0, and 11.2 per 1000 person-years (Table 3). The unadjusted hazard ratios were 0.70 (95% confidence interval [CI], 0.53 to 0.91) for a Mediterranean diet with extra-virgin olive oil and 0.70 (95% CI, 0.53 to 0.94) for a Mediterranean diet with nuts (Fig. 1) as compared with the control diet (P=0.015, by the likelihood ratio test, for the overall effect of the intervention).

The results of multivariate analyses showed a similar protective effect of the two Mediterranean diets versus the control diet with respect to the primary end point (Table 3). Regarding components of the primary end point, only the comparisons of stroke risk reached statistical significance (Table 3, and Fig. S6 in the Supplementary Appendix). The Kaplan–Meier curves for the primary end point diverged soon after the trial started, but no effect on all-cause mortality was apparent (Fig. 1). The results of several sensitivity analyses were also consistent with the findings of the primary analysis (Table S9 in the Supplementary Appendix).

SUBGROUP ANALYSES

Reductions in disease risk in the two Mediterranean-diet groups as compared with the control group were similar across the prespecified subgroups (Fig. 2, and Table S10 in the Supplementary Appendix). In addition, to account for the protocol change in October 2006 whereby the intensity of dietary intervention in the control group was increased, we compared hazard ratios

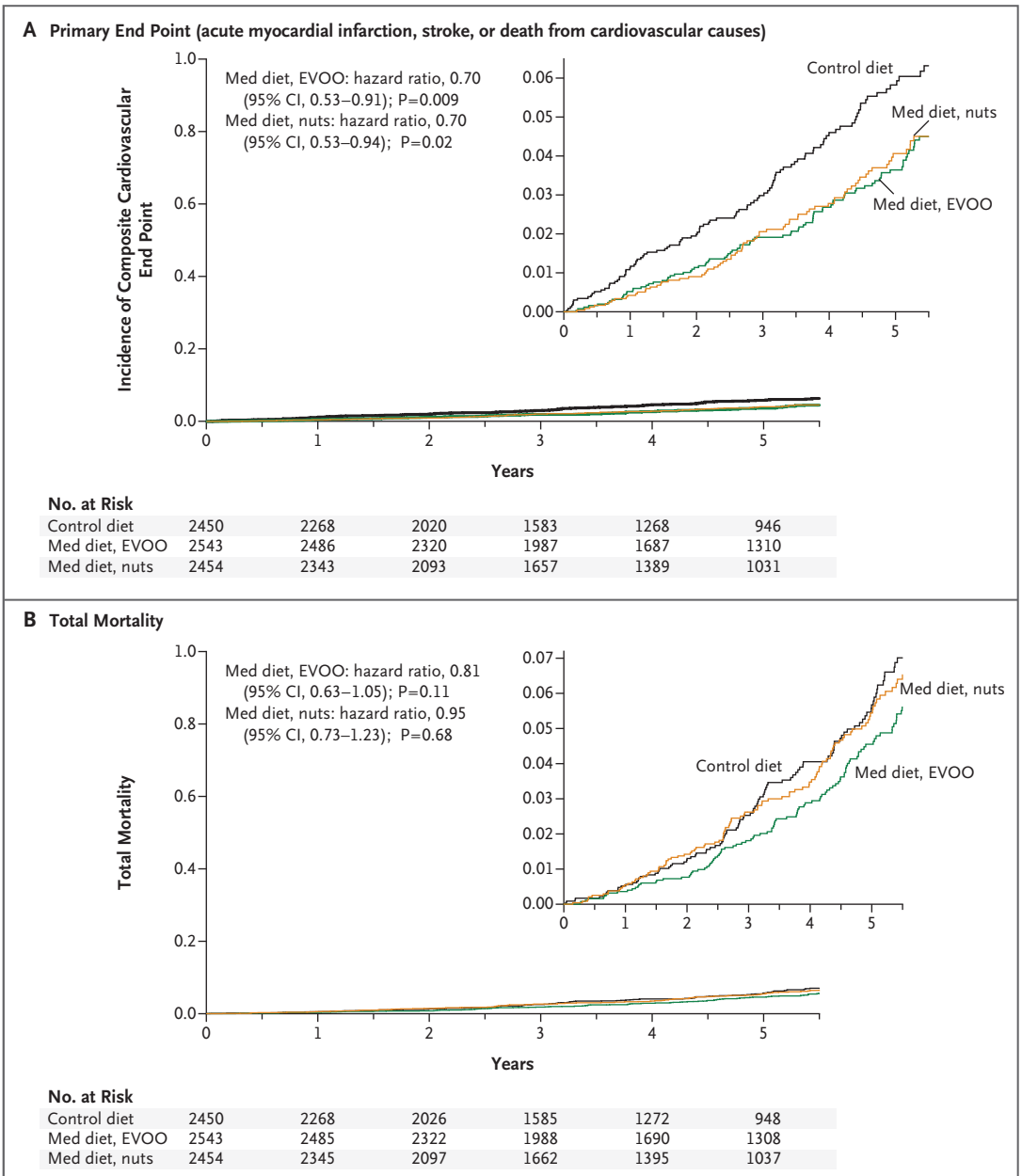

Figure 1. Kaplan–Meier Estimates of the Incidence of Outcome Events in the Total Study Population.
Panel A shows the incidence of the primary end point (a composite of acute myocardial infarction, stroke, and death from cardiovascular causes), and Panel B shows total mortality. Hazard ratios were stratified according to center (Cox model with robust variance estimators). CI denotes confidence interval, EVOO extra-virgin olive oil, and Med Mediterranean.

for the Mediterranean-diet groups (both groups merged vs. the control group) before and after this date. Adjusted hazard ratios were 0.77 (95% CI, 0.59 to 1.00) for participants recruited before October 2006 and 0.49 (95% CI, 0.26 to 0.92) for those recruited thereafter (P=0.21 for interaction).

DISCUSSION

In this trial, an energy-unrestricted Mediterranean diet supplemented with either extra-virgin olive oil or nuts resulted in an absolute risk reduction of approximately 3 major cardiovascular

Subgroup	Combined Mediterranean Diets	Control Diet	Hazard Ratio (95% CI)	P Value for Interaction
	no. of participants with primary end-point event/total no. of participants			
Sex				0.62
Male	107/2178	64/987	0.69 (0.51–0.94)	
Female	72/2819	45/1463	0.73 (0.50–1.07)	
Age				0.84
<70 yr	86/3272	47/1504	0.73 (0.52–1.05)	
≥70 yr	93/1725	62/946	0.71 (0.51–0.98)	
Diabetes				0.63
No	58/2572	40/1261	0.67 (0.45–1.01)	
Yes	121/2425	69/1189	0.71 (0.53–0.96)	
Hypertension				0.06
No	40/885	11/400	1.25 (0.64–2.45)	
Yes	139/4112	98/2050	0.65 (0.50–0.84)	
Dyslipidemia				0.06
No	77/1377	36/687	0.95 (0.64–1.42)	
Yes	102/3620	73/1763	0.60 (0.44–0.80)	
Smoking				0.75
Never	80/3037	54/1527	0.67 (0.47–0.94)	
Ever	99/1960	55/923	0.75 (0.54–1.03)	
Family history of premature CHD				0.97
No	144/3889	87/1890	0.72 (0.55–0.94)	
Yes	35/1108	22/560	0.75 (0.43–1.29)	
BMI				0.05
<25	18/399	7/164	0.69 (0.29–1.67)	
25–30	88/2316	37/1085	1.04 (0.71–1.54)	
>30	73/2282	65/1201	0.51 (0.37–0.71)	
Waist				0.72
<Median	87/2561	48/1177	0.76 (0.53–1.08)	
≥Median	92/2436	61/1273	0.67 (0.48–0.93)	
Waist-to-height ratio				0.82
<Median	81/2549	47/1182	0.74 (0.52–1.06)	
≥Median	98/2448	62/1268	0.68 (0.50–0.94)	
Baseline score for adherence to Mediterranean diet				0.44
<9 (low)	93/2178	61/1256	0.81 (0.58–1.12)	
≥9 (high)	86/2819	48/1194	0.64 (0.45–0.92)	
End-point components				
Stroke	81/4997	58/2450	0.61 (0.44–0.86)	
Myocardial infarction	68/4997	38/2450	0.77 (0.52–1.15)	
Death from cardiovascular causes	57/4997	30/2450	0.83 (0.54–1.29)	

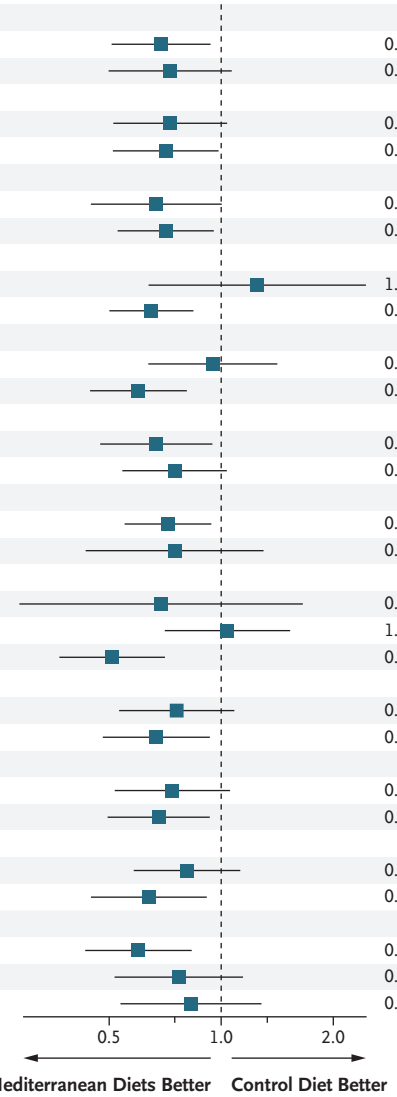

Figure 2. Results of Subgroup Analyses.

Shown are adjusted hazard ratios for the primary end point within specific subgroups. Squares denote hazard ratios; horizontal lines represent 95% confidence intervals. Hazard ratios indicate the relative risk in both intervention groups merged together (vs. the control group) within each stratum. Hazard ratios were stratified according to recruiting center and were adjusted for sex, age (continuous variable), family history of premature coronary heart disease (CHD) (yes or no), smoking (never smoked, former smoker, or current smoker), body-mass index (BMI) (continuous variable), waist-to-height ratio (continuous variable), hypertension at baseline (yes or no), dyslipidemia at baseline (yes or no), and diabetes at baseline (yes or no). Scores for adherence to the Mediterranean diet range from 0 to 14, with higher scores indicating greater adherence.

events per 1000 person-years, for a relative risk reduction of approximately 30%, among high-risk persons who were initially free of cardiovascular disease. These results support the benefits of the Mediterranean diet for cardiovascular risk reduction. They are particularly relevant given the challenges of achieving and maintaining weight loss. The secondary prevention Lyon Diet Heart Study also showed a large reduction in rates of coronary heart disease events with a modified

Mediterranean diet enriched with alpha-linolenic acid (a key constituent of walnuts). That result, however, was based on only a few major events.[4,19,20]

There were small between-group differences in some baseline characteristics in our trial, which were not clinically meaningful but were statistically significant, and we therefore adjusted for these variables. In fully adjusted analyses, we found significant results for the combined cardiovascular end point and for stroke, but not for myocardial infarction alone. This could be due to stronger effects on specific risk factors for stroke but also to a lower statistical power to identify effects on myocardial infarction. Our findings are consistent with those of prior observational studies of the cardiovascular protective effects of the Mediterranean diet,[2,5] olive oil,[21-23] and nuts[24,25]; smaller trials assessing effects on traditional cardiovascular risk factors[6-9] and novel risk factors, such as markers of oxidation, inflammation, and endothelial dysfunction[6,8,26-28]; and studies of conditions associated with high cardiovascular risk — namely, the metabolic syndrome[6,16,29] and diabetes.[30-32] Thus, a causal role of the Mediterranean diet in cardiovascular prevention has high biologic plausibility. The results of our trial might explain, in part, the lower cardiovascular mortality in Mediterranean countries than in northern European countries or the United States.[33]

The risk of stroke was reduced significantly in the two Mediterranean-diet groups. This is consistent with epidemiologic studies that showed an inverse association between the Mediterranean diet[2,34] or olive-oil consumption[22] and incident stroke.

Our results compare favorably with those of the Women's Health Initiative Dietary Modification Trial, wherein a low-fat dietary approach resulted in no cardiovascular benefit.[35] Salient components of the Mediterranean diet reportedly associated with better survival include moderate consumption of ethanol (mostly from wine), low consumption of meat and meat products, and high consumption of vegetables, fruits, nuts, legumes, fish, and olive oil.[36,37] Perhaps there is a synergy among the nutrient-rich foods included in the Mediterranean diet that fosters favorable changes in intermediate pathways of cardiometabolic risk, such as blood lipids, insulin sensitivity, resistance to oxidation, inflammation, and vasoreactivity.[38]

Our study has several limitations. First, the protocol for the control group was changed halfway through the trial. The lower intensity of dietary intervention for the control group during the first few years might have caused a bias toward a benefit in the two Mediterranean-diet groups, since the participants in these two groups received a more intensive intervention during that time. However, we found no significant interaction between the period of trial enrollment (before vs. after the protocol change) and the benefit in the Mediterranean-diet groups. Second, we had losses to follow-up, predominantly in the control group, but the participants who dropped out had a worse cardiovascular risk profile at baseline than those who remained in the study, suggesting a bias toward a benefit in the control group. Third, the generalizability of our findings is limited because all the study participants lived in a Mediterranean country and were at high cardiovascular risk; whether the results can be generalized to persons at lower risk or to other settings requires further research.

As with many clinical trials, the observed rates of cardiovascular events were lower than anticipated, with reduced statistical power to separately assess components of the primary end point. However, favorable trends were seen for both stroke and myocardial infarction. We acknowledge that, even though participants in the control group received advice to reduce fat intake, changes in total fat were small and the largest differences at the end of the trial were in the distribution of fat subtypes. The interventions were intended to improve the overall dietary pattern, but the major between-group differences involved the supplemental items. Thus, extra-virgin olive oil and nuts were probably responsible for most of the observed benefits of the Mediterranean diets. Differences were also observed for fish and legumes but not for other food groups. The small between-group differences in the diets during the trial are probably due to the facts that for most trial participants the baseline diet was similar to the trial Mediterranean diet and that the control group was given recommendations for a healthy diet, suggesting a potentially greater benefit of the Mediterranean diet as compared with Western diets.

In conclusion, in this primary prevention trial, we observed that an energy-unrestricted Mediterranean diet, supplemented with extra-virgin

olive oil or nuts, resulted in a substantial reduction in the risk of major cardiovascular events among high-risk persons. The results support the benefits of the Mediterranean diet for the primary prevention of cardiovascular disease.

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APPENDIX

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