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Effects of a Mediterranean-Style Diet on Cardiovascular Risk Factors

A Randomized Trial

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Background: The Mediterranean diet has been shown to have beneficial effects on cardiovascular risk factors.

Objective: To compare the short-term effects of 2 Mediterranean diets versus those of a low-fat diet on intermediate markers of cardiovascular risk.

Design: Substudy of a multicenter, randomized, primary prevention trial of cardiovascular disease (Prevención con Dieta Mediterránea [PREDIMED] Study).

Setting: Primary care centers affiliated with 10 teaching hospitals.

Participants: 772 asymptomatic persons 55 to 80 years of age at high cardiovascular risk who were recruited from October 2003 to March 2004.

Interventions: Participants were assigned to a low-fat diet (n = 257) or to 1 of 2 Mediterranean diets. Those allocated to Mediterranean diets received nutritional education and either free virgin olive oil, 1 liter per week (n = 257), or free nuts, 30 g/d (n = 258). The authors evaluated outcome changes at 3 months.

Measurements: Body weight, blood pressure, lipid profile, glucose levels, and inflammatory molecules.

Results: The completion rate was 99.6%. Compared with the low-fat diet, the 2 Mediterranean diets produced beneficial changes in most outcomes. Compared with the low-fat diet, the mean changes in the Mediterranean diet with olive oil group and the Mediterranean diet with nuts group were −0.39 mmol/L (95% CI, −0.70 to − 0.07 mmol/L) and − 0.30 mmol/L (CI, −0.58 to − 0.01 mmol/L), respectively, for plasma glucose levels; −5.9 mm Hg (CI, −8.7 to −3.1 mm Hg) and − 7.1 mm Hg (CI, −10.0 to −4.1 mm Hg), respectively, for systolic blood pressure; and −0.38 (CI, −0.55 to − 0.22) and − 0.26 (CI, −0.42 to −0.10), respectively, for the cholesterol–high-density lipoprotein cholesterol ratio. The Mediterranean diet with olive oil reduced C-reactive protein levels by 0.54 mg/L (CI, 1.04 to 0.03 mg/L) compared with the low-fat diet.

Limitations: This short-term study did not focus on clinical outcomes. Nutritional education about low-fat diet was less intense than education about Mediterranean diets.

Conclusion: Compared with a low-fat diet, Mediterranean diets supplemented with olive oil or nuts have beneficial effects on cardiovascular risk factors.

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*For a list of additional PREDIMED Study Investigators, see the Appendix, available at www.annals.org.

Cardiovascular disease is the main cause of death in industrialized countries, but incidence rates have marked geographic differences. The low incidence of coronary heart disease (CHD) in Mediterranean countries has been partly ascribed to dietary habits (1–3). Recent findings from large European cohort studies (4–6) suggest that a high degree of adherence to the Mediterranean diet is associated with a reduction in mortality. In small clinical studies, the Mediterranean diet or some of its components have reduced blood pressure (7) and have improved lipid profiles (8, 9) and endothelial function (10). Moreover, a recent cross-sectional study (11) and a 2-year feeding trial (12) have shown that adherence to the Mediterranean diet is associated with reduced markers of vascular inflammation. These beneficial effects on surrogate markers of cardiovascular risk add biological plausibility to the epidemiologic evidence that supports a protective effect of the Mediterranean diet.

Olive oil, a rich source of monounsaturated fatty acids, is a main component of the Mediterranean diet. Virgin olive oil retains all the lipophilic components of the fruit, α-tocopherol, and phenolic compounds with strong antioxidant and anti-inflammatory properties (13, 14). Tree nuts, which are also typical in the Mediterranean diet, have a favorable fatty acid profile and are a rich source of nutrients and other bioactive compounds that may beneficially influence the risk for CHD, such as fiber, phytosterols, folic acid, and antioxidants (15). Frequent nut intake has been associated with decreased CHD rates in prospective studies (15). Walnuts differ from all other nuts through their high content of polyunsaturated fatty acids, particularly α-linolenic acid, a plant n-3 fatty acid (16), which may confer additional antiatherogenic properties (17). Therefore, we designed a large-scale feeding trial in high-

See also:

Print
Editors' Notes 2
Summary for Patients I-11

Web-Only
Appendix
Appendix Tables
Conversion of figures and tables into slides

Context

Some experts attribute a low incidence of heart disease in Mediterranean countries to dietary habits.

Contribution

In this multicenter, 3-group trial, investigators randomly assigned 772 adults at high risk for cardiovascular disease to a low-fat diet or to a Mediterranean diet supplemented with either virgin olive oil (1 L per week) or nuts (30 g per day). After 3 months, the Mediterranean diet groups had lower mean plasma glucose level, systolic blood pressure, and total cholesterol–high-density lipoprotein cholesterol ratio than the low-fat diet group.

Cautions

The Mediterranean diet groups received more nutritional education than the low-fat diet group.

Implications

Mediterranean diets supplemented with olive oil or nuts may improve cardiovascular risk factors.

—The Editors

risk participants to assess the effects of 2 Mediterranean diets, one supplemented with virgin olive oil and the other supplemented with mixed nuts, compared with a low-fat diet on cardiovascular outcomes. We report the results of a 3-month intervention on intermediate markers of cardiovascular risk in the first 772 participants who were recruited into the trial.

METHODS

Study Design

The Prevención con Dieta Mediterránea (PREDIMED) Study is a large, parallel-group, multicenter, randomized, controlled, 4-year clinical trial that aims to assess the effects of the Mediterranean diet on the primary prevention of cardiovascular disease (www.predimed.org). An estimated 9000 high-risk participants (>5000 participants are already recruited) will be assigned to 3 interventions: Mediterranean diet with virgin olive oil, Mediterranean diet with mixed nuts, or low-fat diet. The main outcome is an aggregate of cardiovascular events (cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke). The anticipated completion date of the trial is December 2010.

We designed our present study to assess the 3-month effects of the dietary interventions on surrogate markers of cardiovascular risk in participants entering the study during the first 6 months of recruitment. The institutional review boards of the 10 participating centers approved the study protocol.

Participants and Recruitment

From October 2003 to March 2004, we selected 930 potential participants in primary care centers affiliated with 10 teaching hospitals across Spain. Eligible participants were community-dwelling men, 55 to 80 years of age, and women, 60 to 80 years of age, who fulfilled at least 1 of 2 criteria: type 2 diabetes or 3 or more CHD risk factors (current smoking, hypertension [blood pressure >140/90 mm Hg or treatment with antihypertensive drugs], low-density lipoprotein [LDL] cholesterol level ≥4.14 mmol/L [≥160 mg/dL] [or treatment with hypolipidemic drugs], high-density lipoprotein [HDL] cholesterol level ≤1.04 mmol/L [≤40 mg/dL], body mass index [BMI] ≥25 kg/m^2, or a family history of premature CHD). Exclusion criteria were history of cardiovascular disease, any severe chronic illness, drug or alcohol addiction, history of allergy or intolerance to olive oil or nuts, or low predicted likelihood of changing dietary habits according to the stages-of-change model (18).

The primary care physicians based participants' eligibility on review of clinical records and a screening visit. They obtained a list of candidates from computer-based records of patients who attended each participating center and reviewed their clinical records to exclude those who did not meet eligibility criteria. They then invited suitable candidates by telephone to attend a screening visit. The visit included an interview with administration of a 26-item questionnaire to inquire about medical conditions and risk factors related to eligibility. Of the eligible candidates who met entry requirements, 95% agreed to participate and provided informed consent.

Randomization and Intervention

After the screening visit, each center randomly assigned eligible participants to 1 of 3 diet groups by using a computer-generated random-number sequence. The coordinating center constructed the randomization table, and participants were randomly assigned into blocks of 50 participants balanced by center, sex, and age group (<70 years and ≥70 years). We concealed allocation into the intervention groups by using closed envelopes with correlative numbers by prespecified subgroups of sex and age.

The baseline examination included the administration of a 14-item questionnaire, an extension of a previously validated questionnaire (19), that assessed the degree of adherence to the traditional Mediterranean diet. We assigned values of 0 or 1 to each item (**Appendix Table 1**, available at www.annals.org). We also administered a 137-item validated food frequency questionnaire (20); the validated Spanish version (21) of the Minnesota Leisure Time Physical Activity Questionnaire; and a 47-item questionnaire about education, lifestyle, history of illnesses, and medication use. We performed anthropometric and blood pressure measurements and obtained samples of fasting blood and spot urine. We repeated all examinations at 3 months.

The same dietitian delivered the interventions to the 3 randomized groups in each center. On the basis of the assessment of individual Mediterranean diet scores, the di-

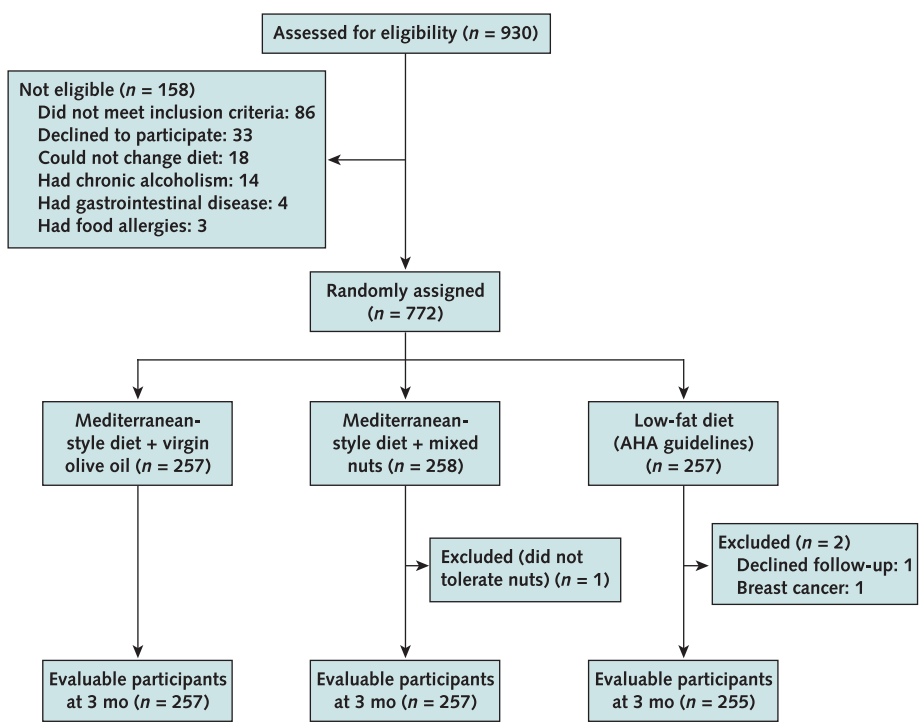
etitian gave personalized dietary advice during a 30-minute session to each participant, with recommendations on the desired frequency of intake of specific foods. We advised participants who were allocated to the low-fat diet to reduce intake of all types of fat, and we gave them a leaflet with written recommendations according to the American Heart Association guidelines (22). For total fat intake, these recommendations were opposite to those given to participants in the 2 Mediterranean diet groups, who received instructions intended to increase the 14-item Mediterranean diet score, including increased consumption of vegetable fats and oils. We did not suggest any energy restriction.

While the participants who were allocated to the low-fat diet did not receive further intervention, those assigned the 2 Mediterranean diet groups had access to more intense intervention in 2 ways. First, they were given a free provision of typical Mediterranean fatty foods (olive oil or nuts). Depending on group assignment, participants were given either free virgin olive oil (15 L [1 L/wk] for 3 months) or free sachets of walnuts, hazelnuts, and almonds (1350 g of walnuts [15 g/d], 675 g of hazelnuts [7.5 g/d], and 675 g of almonds [7.5 g/d] for 3 months). To improve adherence and account for family needs, participants in the corresponding Mediterranean diet groups were given excess olive oil or additional 1000-g packets of nuts. We analyzed the nutrient composition of the olive oil and nuts used in the study by standard methods in a reference laboratory (**Appendix Table 2**, available at www.annals.org). Second, 1 week after inclusion, the dietitian delivered a 1-hour group session with up to 20 participants, with separate sessions for each Mediterranean diet group. Each group session consisted of informative talks and provision of written materials with elaborate descriptions of typical Mediterranean foods and seasonal shopping lists, meal plans, and cooking recipes. Throughout the study, all participants had free and continuous access to their center dietitian for advice and consultation.

Measurements

Trained personnel measured weight and height by using calibrated scales and a wall-mounted stadiometer, respectively; waist circumference midway between the lowest rib and the iliac crest by using an anthropometric tape; and blood pressure in triplicate with a validated semiautomatic oscillometer (Omron HEM-705CP, Hoofddorp, the Netherlands). We calculated energy and nutrient intake from Spanish food composition tables (23). At the 3-month visit and when consulted by participants, dietitians assessed any adverse effects from the interventions by administering a checklist of symptoms and gave advice on how to remedy them. The checklist included mouth symptoms; bloating, fullness, or indigestion; altered bowel habit; and any other diet-related symptom.

Figure 1. **Study flow diagram.**



AHA = American Heart Association.

Table 1. **Baseline Characteristics***

Characteristic	Mediterranean Diet with Virgin Olive Oil (*n* = 257)	Mediterranean Diet with Mixed Nuts (*n* = 258)	Recommended Low-Fat Diet (*n* = 257)
Mean (SD) age, *y*	68.6 (6.9)	68.5 (6.2)	69.5 (6.1)
Men, *n (%)*	102 (40)	128 (50)	109 (42)
Family history of CHD, *n (%)*	63 (24)	55 (21)	60 (23)
Current smokers, *n (%)*	37 (14)	50 (19)	40 (15)
Mean (SD) BMI, kg/m^2†	29.7 (4.1)	29.4 (4.1)	30.2 (4.3)
Overweight or obese (BMI ≥25 kg/m^2), *n (%)*	232 (90)	233 (90)	231 (90)
Type 2 diabetes mellitus, *n (%)*	143 (56)	129 (50)	149 (58)
Hypertension, *n (%)*	199 (77)	193 (75)	213 (83)
Dyslipidemia, *n (%)*	165 (64)	171 (66)	179 (70)
Medications, *n (%)*			
ACE inhibitors	108 (42)	118 (46)	114 (44)
Diuretics	93 (36)	85 (33)	93 (36)
Other antihypertensive agents	60 (23)	43 (16)	57 (22)
Statins	104 (41)	115 (45)	107 (42)
Other lipid-lowering agents	18 (7)	19 (7)	14 (5)
Insulin	16 (6)	24 (9)	21 (8)
Oral hypoglycemic drugs	89 (35)	93 (36)	100 (39)
Aspirin or other antiplatelet drugs	44 (17)	49 (19)	45 (18)
Occupation, *n (%)*			
Unskilled	59 (23)	59 (23)	61 (24)
Skilled, manual	99 (39)	99 (38)	90 (35)
Skilled, nonmanual	59 (23)	54 (21)	59 (23)
Directive and professional	40 (15)	46 (18)	47 (18)
Education level, *n (%)*			
Primary school	189 (74)	180 (70)	185 (72)
First-degree high school	39 (15)	44 (17)	43 (17)
High school or university	28 (11)	34 (13)	29 (11)

* ACE = angiotensin-converting enzyme; BMI = body mass index; CHD = coronary heart disease.
† Calculated as weight in kg divided by height in m^2.

Samples of serum, EDTA plasma, and urine were coded, were shipped to central laboratories, and were stored at −80 °C until assay. The clinical investigators and laboratory technicians were blinded to the interventions. Analytes determined for each participant in frozen samples of whole serum or plasma as appropriate were blood glucose level by the glucose–oxidase method; serum insulin level by radioimmunoassay; cholesterol and triglyceride levels by enzymatic procedures; HDL cholesterol level after precipitation with phosphotungstic acid and magnesium chloride; apolipoproteins A1 and B levels by using turbidimetry; soluble intercellular adhesion molecule-1 (ICAM-1), vascular cell adhesion molecule-1 (VCAM-1), and interleukin-6 levels by standard enzyme-linked immunosorbent assays; and high-sensitivity C-reactive protein (CRP) level by particle-enhanced immunonephelometry. We performed all analyses in duplicate. Intra- and interassay variation coefficients for insulin, CRP, ICAM-1, VCAM-1, and interleukin-6 ranged from 1.8% to 5.4% and from 0.9% to 9.9%, respectively.

In participants without diabetes, we calculated insulin resistance by using the homeostasis model assessment method (24): insulin resistance = fasting insulin (μU/mL) × fasting glucose (mmol/L)/22.5. In a random sample of 273 participants (35%), we measured urinary tyrosol and hydroxytyrosol levels by gas chromatography–mass spectrometry as markers of adherence to virgin olive oil intake (25) and the α-linolenic acid plasma content by gas chromatography as a measure of adherence to nut (walnut) intake (8).

Statistical Analyses

For a parallel design, statistical power calculations indicated that 227 participants per group would be needed to detect mean differences of 0.13 mmol/L (SD, 0.49) (5 mg/dL [SD, 19]) in LDL cholesterol level (8) (α = 0.05; power = 0.8). Although we used LDL cholesterol level to set sample size, we were equally interested in changes in all end points in our exploratory and nonconfirmatory study. We based the analysis on the intention-to-treat principle. We used descriptive statistics with means and SDs for the baseline characteristics of the participants. For analysis of laboratory variables, we used the average of 2 baseline measures as the baseline value and the average of the 2 measures taken after the 3-month intervention as the final variable. We transformed values with a skewed distribution (CRP, VCAM-1, ICAM-1, and interleukin-6) to their natural logarithm for analyses. We examined 3-month changes in clinical, dietary, and laboratory variables, including center, as a stratification factor in the multivariable model. We controlled potential confounding by age, sex, and baseline body weight, entering these variables also into the multivariable model. We excluded participants whose energy intake, as derived from the food frequency ques-

tionnaires, was outside prespecified ranges (500 kcal/d to 3500 kcal/d for women and 800 kcal/d to 4000 kcal/d for men) (26) from the calculations of food, energy, and nutrient intake. In addition, we excluded participants with plasma CRP levels greater than 10 mg/L at any measurement, indicating an inflammatory process, from statistical analyses of inflammatory biomarkers. Within- and between-group differences are expressed as means and 95% CIs. All statistical tests were 2-tailed, and the significance level was 0.05. We performed analyses by using SPSS, version 11.0 (SPSS Inc., Chicago, Illinois).

Role of the Funding Sources

This study was supported by a grant from the Spanish Ministry of Health (Red G03/140). Fundación Patrimonio Comunal Olivarero and Hojiblanca SA, the California Walnut Commission, Borges SA, and Morella Nuts SA generously donated the olive oil, walnuts, almonds, and hazelnuts, respectively, used in the study. The funding sources had no role in the design, collection, analysis, or interpretation of the data or in the decision to submit the manuscript for publication.

RESULTS

We excluded 158 of 930 eligible participants before randomization for various reasons (**Figure 1**). **Table 1** shows the baseline characteristics of the 772 participants who entered the study. Of these participants, 697 were Europeans of Spanish descent and 75 were Hispanic immigrants from Central and South America. Although the trial is an ongoing, large multicenter trial with large block sizes, the groups were balanced in ethnic origin, demographic characteristics, adiposity, and risk factors. Three participants withdrew before study completion; their baseline characteristics were similar to those of the overall group.

Adverse Effects

Thirty-four (13%) participants in the Mediterranean diet with nuts group had difficulty chewing whole nuts or reported that small fragments of nuts were lodged between their teeth. This problem was solved satisfactorily by the advice to consume the nuts crushed and mixed with low-fat yogurt, except for 1 participant who withdrew from the study. Participants who were allocated to the Mediterranean diet with olive oil group or to the low-fat diet group reported no adverse effects.

Food, Energy, and Nutrient Intake

We excluded the following participants from food, energy, and nutrient calculations because they reported unrealistic energy intakes: 21 in the Mediterranean diet plus olive oil group, 19 in the Mediterranean diet plus nuts group, and 8 in the low-fat diet group (26). The main dietary changes were the large increases in consumption of virgin olive oil and nuts in the corresponding Mediterranean diet groups that were provided with these foods. Reciprocal decreases in the consumption of common olive oil indicated that participants replaced this oil by the virgin variety supplied. Both olive oil and nut intake decreased nonsignificantly in the low-fat group. Participants in the 3 groups increased the intake of vegetables, legumes, fruit, and fish and decreased the intake of meat, sweets, and dairy

Table 2. **Changes in the Consumption of Key Food Items and 14-Point Mediterranean Diet Score***

Food Consumed	Mean Changes from Baseline at 3 mo (95% CI), *g/d*			Mediterranean Diet with Olive Oil vs. Low-Fat Diet		Mediterranean Diet with Nuts vs. Low-Fat Diet	
	Mediterranean Diet with Virgin Olive Oil (*n* = 257)	Mediterranean Diet with Mixed Nuts (*n* = 257)	Low-Fat Diet (*n* = 256)	Mean (95% CI) Between-Group Difference, *g/d*†	*P* Value	Mean (95% CI) Between-Group Difference, *g/d*†	*P* Value
Virgin olive oil	32 (27 to 37)	1.2 (0.1 to 2.5)	−0.1 (−3.0 to 2.8)	33 (27 to 39)	<0.001	0.8 (−3.4 to 4.9)	0.72
Refined–mixed olive oil	−25 (−30 to −21)	−0.6 (−5.5 to 4.3)	−1.6 (−5.8 to 1.6)	−24 (−28 to −21)	<0.001	1.4 (−5.9 to 3.0)	0.52
Total nuts	1.7 (0.5 to 2.9)	40 (33 to 47)	−0.7 (−3.3 to 1.9)	0.8 (−5.5 to 7.2)	0.80	38 (32 to 45)	<0.001
Vegetables	13 (−6.2 to 39)	18.0 (−1.4 to 36.0)	8.1 (−13.0 to 29.0)	5.2 (−28.0 to 39.0)	0.76	11 (−24 to 45)	0.54
Legumes	8.5 (3.5 to 13.0)	10 (5.8 to 14)	3.5 (0.2 to 6.8)	4.6 (−1.4 to 10.0)	0.137	3.3 (−2.8 to 9.4)	0.29
Fruits	5.5 (−34.0 to 44.0)	15 (−11 to 41)	25 (1 to 50)	−12 (−56 to 32)	0.58	−10 (22 to −42)	0.53
Fish or seafood	1.8 (−6.0 to 9.7)	2.4 (−7.8 to 13.0)	11.0 (−4.5 to 28.0)	−12.0 (−29.0 to 3.5)	0.124	−7.4 (−24.0 to 10.0)	0.39
Meat or meat products	−23 (−34 to −12)	−29 (−45 to −13)	−7.8 (−16.0 to 1.0)	−17.0 (−31.0 to −3.1)	0.017	−17.0 (−31.0 to −2.3)	0.023
Pastries, cakes, or sweets	−2.1 (−3.7 to −0.5)	−3.0 (−4.6 to −1.4)	−1.8 (−3.6 to 0.2)	−2.5 (−2.7 to 2.2)	0.84	−1.5 (−4.0 to 1.0)	0.23
Dairy products	−17.0 (−38.0 to 4.1)	−45 (−70 to −19)	−22.0 (−50.0 to 4.6)	4.6 (−32.0 to 40.0)	0.31	−16 (−58 to 25)	0.45
Alcohol	−0.5 (−1.9 to 0.9)	−1.3 (−2.7 to 0.1)	0.1 (−1.6 to 1.8)	−0.7 (−2.9 to 1.5)	0.53	−1.5 (−3.7 to 0.8)	0.20
14-unit Mediterranean diet score	2.2 (1.9 to 2.4)	2.8 (2.6 to 3.1)	−0.1 (−0.3 to 0.2)	2.3 (2.0 to 2.7)	<0.001	2.7 (2.4 to 3.1)	<0.001

* Of participants in the Mediterranean diet with olive oil, Mediterranean diet with nuts, and low-fat diet groups, 21, 20, and 8 participants, respectively, were excluded from calculations of food intake because reported energy was outside of prespecified ranges.
† Adjusted for center, age, sex, and baseline body weight.

products (**Table 2**). The Mediterranean diet score increased in the 2 Mediterranean diet groups and remained unchanged in the low-fat group. The results did not change when we included the participants whose energy consumption was out of range in the calculations.

Estimated energy expenditure from physical activity was similar in the 3 groups at baseline and after 3 months (data not shown). We observed a reduction from baseline in reported energy intake in the groups allocated to the Mediterranean diet plus olive oil and low-fat diets (**Table 3**). The 3 groups decreased saturated fatty acid intake from baseline; the 2 Mediterranean diet groups reduced cholesterol intake; and the Mediterranean diet with nuts group decreased the intake of total carbohydrate and increased the intake of fiber, total fat, monounsaturated fatty acids, and polyunsaturated fatty acids.

Biochemical measurements in plasma and urine samples from a random group of 273 (35%) participants in the study showed good adherence to supplemental foods in the Mediterranean diet groups. Compared with the low-fat diet group, participants assigned to the Mediterranean diet with olive oil group showed an increase from baseline in urinary tyrosol levels of 19 ng/mL (95% CI, 5 to 35 ng/mL) and in hydroxytyrosol levels of 84 ng/mL (CI, 34 to 135 ng/mL); those allocated to the Mediterranean diet with nuts group showed an increase in plasma α-linolenic acid level of 0.15 mol% (CI, 0.09 to 0.21 mol%).

Cardiovascular Risk Factors

Table 4 shows the changes in cardiovascular risk factors. Body weight and adiposity measures were slightly reduced in the 3 groups, with no between-group differences and statistically significant within-group changes only for BMI in the low-fat group. Compared with participants assigned to the low-fat diet group, those in the 2 Mediterranean diet groups had decreased systolic and diastolic blood pressure, blood glucose levels, and cholesterol–HDL cholesterol ratio and increased HDL cholesterol levels. Fasting insulin levels and homeostasis model assessment scores were also lower in participants without diabetes in the 2 Mediterranean diet groups. Total cholesterol and triglyceride levels decreased only in the Mediterranean diet with nuts group.

Inflammatory Markers

We excluded from calculations 8 participants in the Mediterranean diet plus olive oil group, 2 participants in the Mediterranean diet plus nuts group, and 4 participants in the low-fat diet group who had plasma CRP levels greater than 10 mg/L in at least 1 measurement. **Figure 2** shows the changes from baseline values in CRP, interleukin-6, ICAM-1, and VCAM-1 concentrations in the 3 groups. The CRP concentration decreased only in participants who were allocated to the Mediterranean diet plus olive oil group. Compared with participants in the low-fat diet group, adjusted between-group changes in CRP levels were −0.54 mg/L (CI, −1.04 to −0.03 mg/L) for those in the Mediterranean diet with olive oil group and 0.33 mg/L (CI, −0.19 to 0.84 mg/L) for those in the Mediterranean diet with nuts group. Circulating interleukin-6, ICAM-1, and VCAM-1 concentrations decreased in both Mediterranean diet groups and increased in the low-fat diet group. Compared with the low-fat diet group, the between-group changes in interleukin-6 level were −1.6 ng/L (CI, −2.5 to −0.6 ng/L) for the Mediterranean diet with olive oil group and −1.3 ng/L (CI, −2.3 to −0.4 ng/L) for the Mediterranean diet with nuts group. The between-group changes in ICAM-1 level were −104 ng/mL (CI, −135 to −72 ng/mL) and −97 ng/mL (CI, −128 to −65 ng/mL), respectively; the between-group changes in VCAM-1 level were −178 ng/mL (CI, −277 to −79 ng/mL) and −167 ng/mL (CI, −267 to −68 ng/mL), respectively. Be-

Table 3. **Changes in Energy and Nutrient Intake***

Nutrients	Mean Changes from Baseline at 3 mo (95% CI)			Mediterranean Diet with Olive Oil vs. Low-Fat Diet		Mediterranean Diet with Nuts vs. Low-Fat Diet	
	Mediterranean Diet with Virgin Olive Oil (n = 257)	Mediterranean Diet with Mixed Nuts (n = 257)	Low-Fat Diet (n = 256)	Mean (95% CI) Between-Group Difference†	P Value	Mean (95% CI) Between-Group Difference†	P Value
Energy, *kcal*	–180 (–271 to –89)	–34 (–140 to 67)	–197 (–300 to –95)	4.5 (–139.0 to 148.0)	0.95	161 (12 to 310)	0.034
Energy from total protein, %	0.36 (–0.06 to 0.78)	–0.28 (–0.69 to 0.11)	0.83 (0.38 to 1.27)	–0.47 (–1.07 to 0.13)	0.122	–1.00 (–1.60 to –0.38)	0.002
Energy from total carbohydrate, %	0.33 (–0.59 to 1.26)	–2.9 (–4.0 to –1.9)	–0.36 (–1.50 to 0.80)	0.22 (–1.30 to 1.70)	0.84	–3.6 (–5.2 to –2.1)	<0.001
Fiber, *g/d*	0.98 (–0.74 to 2.70)	3.8 (1.8 to 5.7)	0.60 (–0.94 to 2.20)	0.49 (–1.90 to 2.90)	0.69	2.00 (–0.54 to 4.50)	0.124
Energy from total fat, %	–0.75 (–1.60 to 0.08)	3.4 (2.4 to 4.5)	–1.40 (–2.50 to –0.21)	0.45 (–1.00 to 1.90)	0.55	5.0 (3.5 to 6.5)	<0.001
SFA, %	–0.77 (–1.00 to –0.49)	–1.00 (–1.40 to –0.72)	–0.74 (–1.20 to –0.31)	–0.09 (–0.55 to 0.36)	0.69	0.07 (–0.40 to 0.54)	0.78
MUFA, %	0.15 (–0.39 to 0.70)	1.38 (0.81 to 2.00)	–0.52 (–1.20 to 0.22)	0.58 (–0.30 to 1.45)	0.198	1.9 (1.0 to 2.8)	<0.001
PUFA, %	–0.11 (–0.38 to 0.17)	3.0 (2.5 to 3.6)	0.14 (–0.46 to 0.17)	0.03 (–0.53 to 0.58)	0.93	3.0 (2.4 to 3.5)	<0.001
Linoleic acid, *g/d*	–2.1 (–2.8 to –1.1)	7.6 (5.8 to 9.3)	–0.68 (–1.80 to 0.44)	–0.27 (–0.85 to 0.31)	0.76	1.4 (1.1 to 1.7)	<0.001
α-linolenic acid, *g/d*	0.06 (–0.17 to 0.04)	1.20 (0.92 to 1.40)	–0.10 (–0.27 to 0.08)	0.03 (–0.32 to 0.25)	0.82	1.20 (0.86 to 1.50)	<0.001
Marine n-3 fatty acids, *g/d*	0.02 (–0.05 to 0.08)	0.11 (0.01 to 0.21)	0.13 (–0.02 to 0.28)	0.11 (–0.26 to 0.04)	0.143	–0.04 (–0.20 to 0.12)	0.60
Energy from olive oil, %	2.05 (1.20 to 2.90)	0.46 (–0.41 to 1.30)	0.06 (–1.00 to 1.20)	1.9 (0.55 to 3.20)	0.006	0.17 (–1.20 to 1.50)	0.81
Energy from nuts, %	0.40 (0.01 to 0.79)	10.2 (8.7 to 12.0)	–0.07 (–0.57 to 0.42)	0.03 (–1.30 to 1.40)	0.97	9.1 (7.7 to 10.0)	<0.001
Cholesterol, *mg/d*	–53 (–75 to –31)	–54 (–74 to –34)	–13 (–47 to 21)	–38 (–152 to 76)	0.27	–42 (–165 to 80)	0.152

* Forty-nine participants were excluded from calculations of energy and nutrient intake because reported energy was unrealistic (see Table 2). MUFA = monounsaturated fatty acid; PUFA = polyunsaturated fatty acid; SFA = saturated fatty acid.
† Adjusted for center, age, sex, and baseline body weight.

Table 4. **Changes in Adiposity, Blood Pressure, and Cardiovascular Risk Factors***

Variable	Mean Changes from Baseline at 3 mo (95% CI)			Mediterranean Diet with Olive Oil vs. Low-Fat Diet		Mediterranean Diet with Nuts vs. Low-Fat Diet	
	Mediterranean Diet with Virgin Olive Oil (n = 257)	Mediterranean Diet with Mixed Nuts (n = 257)	Low-Fat Diet (n = 256)	Mean (95% CI) Between-Group Difference†	P Value	Mean (95% CI) Between-Group Difference†	P Value
Weight, *kg*	−0.19 (−0.46 to 0.07)	−0.26 (−0.59 to 0.08)	−0.24 (−0.48 to 0.01)	0.01 (−0.39 to 0.42)	0.96	0.01 (−0.40 to 0.43)	0.95
BMI, *kg/m²*	−0.12 (−0.24 to 0.06)	−0.09 (−0.24 to 0.05)	−0.21 (−0.38 to −0.05)	0.09 (−0.12 to 0.29)	0.40	0.15 (−0.06 to 0.35)	0.165
Waist, *cm*	−0.82 (−1.80 to 0.14)	−0.29 (−0.95 to 0.37)	−0.37 (−1.20 to 0.44)	−0.52 (−1.60 to 0.61)	0.37	0.12 (−1.00 to 1.30)	0.84
Systolic BP, *mm Hg*	−4.8 (−6.7 to −2.7)	−6.5 (−8.7 to −4.3)	0.64 (−1.30 to 2.30)	−5.9 (−8.7 to −3.1)	<0.001	−7.1 (−10.0 to −4.1)	<0.001
Diastolic BP, *mm Hg*	−2.5 (−3.5 to −1.5)	−3.6 (−4.7 to −2.5)	−0.85 (−1.79 to 0.09)	−1.60 (−3.00 to −0.01)	0.048	−2.6 (−4.2 to 1.0)	0.001
Fasting glucose level					0.017		0.039
mmol/L	−0.21 (−0.41 to −0.01)	−0.14 (−0.31 to 0.03)	0.19 (−0.06 to 0.04)	−0.39 (−0.72 to −0.07)		−0.30 (−0.58 to −0.01)	
mg/dL	−3.8 (−7.4 to −0.2)	−2.5 (−5.5 to 0.5)	3.5 (−1.0 to 8.0)	−7.0 (−13.0 to −1.3)		−5.4 (−10.5 to −0.2)	
Fasting insulin level, *pmol/L*‡	−9.7 (−15.3 to −3.8)	−9.7 (−15.9 to −3.5)	6.5 (−3.8 to 16.7)	−16.7 (−27.1 to −0.4)	0.001	−20.4 (−31.9 to −9.7)	<0.001
HOMA index‡	−0.53 (−0.83 to −0.23)	−0.54 (−0.82 to −0.26)	0.32 (−0.15 to 0.79)	−0.91 (−1.40 to −0.46)	<0.001	−1.1 (−1.6 to −0.55)	<0.001
Total cholesterol level					0.26		0.040
mmol/L	−0.10 (−0.21 to 0.01)	−0.13 (−0.22 to −0.04)	0.02 (−0.10 to 0.14)	−0.09 (−0.25 to 0.07)		−0.16 (−0.31 to −0.01)	
mg/dL	−3.90 (−8.10 to 0.35)	−5.0 (−8.6 to −1.4)	0.74 (−3.80 to 5.30)	−3.5 (−9.5 to 2.6)		−6.20 (−12.00 to −0.28)	
LDL cholesterol level					0.177		0.119
mmol/L	−0.15 (−0.25 to −0.05)	−0.10 (−0.19 to −0.01)	−0.15 (−0.12 to 0.09)	−0.10 (−0.25 to 0.04)		−0.09 (−0.23 to 0.05)	
mg/dL	−5.8 (−9.8 to −1.8)	−3.80 (−7.30 to −0.39)	−0.56 (−4.60 to 3.50)	−3.9 (−9.5 to 1.7)		−3.4 (−8.9 to 2.1)	
HDL cholesterol level					<0.001		0.006
mmol/L	0.62 (0.08 to 0.04)	0.020 (0.002 to 0.050)	−0.01 (−0.03 to 0.01)	0.08 (0.04 to 0.10)		0.04 (0.01 to 0.07)	
mg/dL	2.4 (3.1 to 1.6)	0.94 (0.10 to 1.80)	−0.37 (−1.20 to 0.40)	2.9 (1.7 to 4.0)		1.60 (0.45 to 2.70)	
Triglyceride level					0.21		0.022
mmol/L	−0.03 (−0.13 to 0.07)	−0.09 (−0.16 to −0.01)	0.03 (−0.05 to 0.10)	−0.08 (−0.20 to 0.04)		−0.15 (−0.26 to −0.02)	
mg/dL	−3.0 (−11.8 to 5.9)	−7.6 (−14.0 to −1.1)	2.4 (−4.4 to 9.2)	−7.1 (−18.0 to 3.9)		−13.0 (−23.0 to −1.9)	
Cholesterol–HDL cholesterol ratio	−0.32 (−0.45 to −0.18)	−0.17 (−0.27 to −0.02)	0.06 (−0.05 to 0.16)	−0.38 (−0.55 to −0.22)	<0.001	−0.26 (−0.42 to −0.10)	0.002

* BMI = body mass index; BP = blood pressure; HDL = high-density lipoprotein; HOMA = homeostasis model assessment (a measure of insulin resistance); LDL = low-density lipoprotein.
† Adjusted for center, age, sex, and baseline body weight.
‡ Determined only for 305 participants without diabetes (95 in the Mediterranean diet with olive oil group, 110 in the Mediterranean diet with nuts group, and 100 in the low-fat diet group).

tween-diet differences in CRP levels were magnified, but statistical significance was unchanged when we included participants with CRP levels greater than 10 mg/L in the calculations. This did not affect the results of the other inflammatory molecules.

Subgroup Analyses

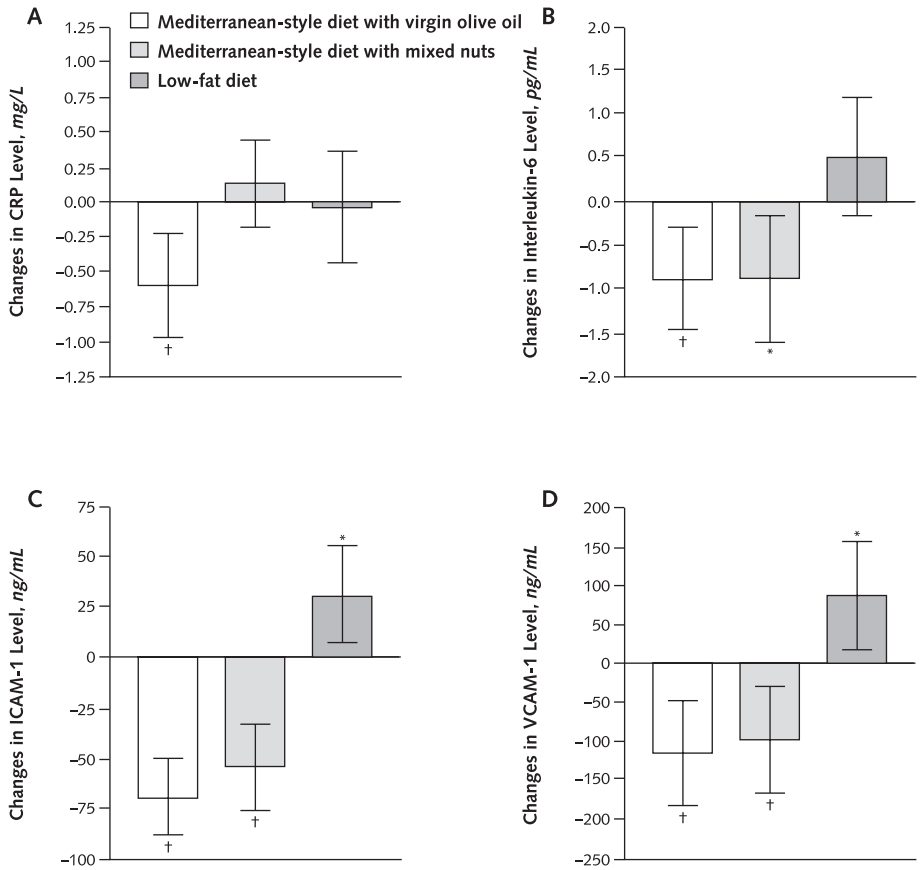
We observed no differences in outcomes for any study group in subgroups defined by center, ethnic origin, sex, age, baseline weight, or physical activity. However, participants with hypertension showed statistically significantly higher reductions from baseline in systolic blood pressure when given each of the 2 Mediterranean diets, with mean changes of −6.2 mm Hg (CI, −8.4 to −4.0 mm Hg) for olive oil and −7.4 mm Hg (CI, −9.9 to −5.0 mm Hg) for nuts. Participants with hypertension in the low-fat diet group showed a mean change in systolic blood pressure of 1.2 mm Hg (CI, −1.0 to 3.4 mm Hg). Participants with normal blood pressure in the low-fat diet, Mediterranean diet with olive oil, and Mediterranean diet with nuts groups showed mean changes in systolic blood pressure of −1.8 mm Hg (CI, −6.7 to 3.0 mm Hg), 0.5 mm Hg (CI, −1.4 to 2.5 mm Hg), and −2.2 mm Hg (CI, −4.5 to 0.1 mm Hg), respectively. Changes in diastolic blood pressure according to blood pressure status followed a similar pattern (data not shown).

Discussion

If the Mediterranean diet was useful in primary cardiovascular prevention, one would expect that persons who adhere to the diet show a reduction in risk factors for atherosclerosis. In our study, high-risk participants who improved their baseline Mediterranean diet after nutritional education and supplementation with virgin olive oil or mixed nuts showed lower blood pressure, improved lipid profiles, decreased insulin resistance, and reduced concentrations of inflammatory molecules compared with those allocated to a low-fat diet.

The Mediterranean diet is high-fat because large amounts of monounsaturated fatty acid–rich olive oil are used in Mediterranean cultures (27, 28). Scientific evidence has documented the beneficial effect of diets with a relatively high monounsaturated fatty acid content on cardiovascular risk factors, obesity, and diabetes (1, 28–31) (**Appendix Table 3**, available at www.annals.org). However, when nutritional advice is given to people with increased adiposity, clinicians are still reluctant to recommend high-fat, high–monounsaturated fatty acid diets as an alternative to the traditional (and less palatable) low-fat diets because of the belief that fat provides excess energy, thus promoting obesity. Because many participants in our study were obese or had diabetes, our results are reassuring

Figure 2. **Changes from baseline in plasma concentrations of the inflammatory biomarkers in the 3 intervention groups.**



A. Mean changes from baseline of C-reactive protein (*CRP*). **B.** Mean changes from baseline of interleukin-6. **C.** Mean changes from baseline of intercellular adhesion molecule-1 (*ICAM-1*). **D.** Mean changes from baseline of vascular cell adhesion molecule-1 (*VCAM-1*). The low-fat diet followed the guidelines of the American Heart Association. Error bars are 95% CIs. *$P < 0.018$ for difference from baseline by 2-tailed *t*-test. †$P < 0.003$ for difference from baseline by 2-tailed *t*-test.

in the lack of weight gain when supplementing ad libitum diets with sizable amounts of unsaturated fats, such as those contained in olive oil or nuts. Our results also add to the increasing evidence that diets enriched with nuts do not induce weight gain (32–34).

Healthy diet and lifestyle are critical for preventing and treating hypertension (35). In our study, both Mediterranean diets were associated with statistically significant reductions in blood pressure in participants with hypertension who were already receiving antihypertensive medication. Observational studies (36, 37) and small feeding trials (38, 39) have suggested that increased olive oil consumption helps lower blood pressure (40). Recently, the OmniHeart study (41) also reported that diets rich in monounsaturated fatty acids from various sources exerted an antihypertensive effect. No effects on blood pressure have been reported for diets enriched with nuts in small trials (15). However, walnuts seem to have favorable effects on vasomotor activity (42). Furthermore, the intake of α-linolenic acid, the plant n-3 fatty acid that is abundant in walnuts, was inversely related to blood pressure in a large cross-sectional study (43). Participants following the Mediterranean diet with nuts increased α-linolenic acid intake by an average of 1 g/d; thus, walnut consumption may have helped lower blood pressure. Another explanation for the blood pressure reduction observed with the 2 Mediterranean diet groups is the change in the overall food pattern, which was similar to that advocated in the Dietary Approaches to Stop Hypertension (DASH) trial (44), with the exception of the high content of olive oil. Salt intake was not restricted in our study. The blood pressure–lowering effect of the Mediterranean diets was similar to that of the unrestricted-sodium DASH diets (44) and was less than that of the low-sodium DASH diet (45). The effect was greater, however, than that obtained by partial substitution of carbohydrates with monounsaturated fatty acids in the OmniHeart study (41).

The 2 Mediterranean diets were associated with lower fasting glucose levels in all participants and lower fasting insulin levels and insulin resistance in those without diabe-

tes, thus extending previous observations of the favorable effects of Mediterranean diets on insulin sensitivity in patients with the metabolic syndrome (12). Insulin resistance and diabetes are linked to excess energy intake, particularly in the form of saturated fatty acids and simple sugars, and to increased adiposity (46). Low-fat, high-carbohydrate diets have traditionally been advised for patients with diabetes. However, such diets may worsen metabolic control, an untoward effect that is not observed with high-fat diets based on monounsaturated fatty acid–rich oils or nuts (31). Frequent nut consumption has been inversely associated with diabetes risk (47). In addition, decreased intake of meat and dairy products and increased fiber intake, as observed in the 2 Mediterranean diet groups, have been shown to reduce the incidence of diabetes in conjunction with lifestyle interventions (48, 49). Our results further support a beneficial effect of healthy diets on insulin resistance.

Replacing carbohydrate with dietary fat lowers triglyceride levels and increases HDL cholesterol levels, while substituting monounsaturated fatty acids for saturated fatty acids lowers LDL cholesterol levels (50, 51). Total fat intake was high both at baseline and after 3 months, and we observed a similar reduction in saturated fatty acid intake of approximately 1% of energy in the 3 groups. However, the lipid profile did not change in the low-fat diet group, while HDL cholesterol levels increased in the 2 Mediterranean diet groups, especially when olive oil was supplemented. While diets enriched with various nuts have an established hypocholesterolemic effect (8, 15, 42), why substituting virgin olive oil for refined olive oil has such beneficial lipid effects is unknown. Minor olive oil constituents contained in virgin olive oils (13, 14) might explain these effects and merit further study. Since low-fat diets usually lower both LDL cholesterol and HDL cholesterol concentrations (52–54), a fat-rich Mediterranean diet may be a better nutritional option for high-risk individuals.

Nut consumption in small trials has not resulted in lower serum triglyceride levels (15). The triglyceride-lowering effect observed in participants in the Mediterranean diet with nuts group might be related to the increased intake of α-linolenic acid from walnuts, since α-linolenic acid consumption was inversely related to triglyceride concentrations in a cross-sectional study (55).

Atherosclerosis is widely viewed as an inflammatory disease (56). Epidemiologic, clinical, and experimental studies have shown that the Mediterranean diet (10–12) or the frequent consumption of several main components of this dietary pattern, such as olive oil (14, 57), nuts (34, 42), or red wine (57, 58), is associated with a lower inflammatory status and improved endothelial function. Similar findings have been reported recently for other healthy dietary patterns (59). We observed reduced concentrations of cell adhesion molecules in participants assigned to the 2 Mediterranean diet groups, supporting the anti-inflammatory effects of this dietary pattern.

Our study has some limitations. Ensuring adherence to dietary instructions is difficult in a feeding trial. However, adherence to recommended dietary patterns and supplemental foods was good, as judged by self-report and objective measurements. On the other hand, our design has the strength of reproducing real-life conditions with home-prepared foods, reflecting usual practice. A second limitation is that nutritional education about low-fat diet was less intense than education about Mediterranean diets. In fact, fat intake was only marginally reduced in the group assigned to the low-fat diet. This was partly because of the study design but also because participants belonged to a Mediterranean culture, where people prefer using olive oil. Because the low-fat diet was not the usual diet, participants in this group also changed food habits in a healthy way. Therefore, the differences in outcomes observed between the Mediterranean diet groups and the low-fat diet group might be attributed to the supplemental foods provided. The duration of follow-up of only 3 months cannot be considered a major limitation because effects of dietary interventions on risk factors do not need a long induction period (44, 45, 53) and seem to persist as long as adherence is maintained (12, 48, 49).

In conclusion, our results suggest that the healthy effects of the Mediterranean diet observed in epidemiologic studies are exerted partly through plausible mechanisms: improved lipid profiles and reductions in blood pressure, insulin resistance, and systemic markers of inflammation. Our study duration was far too short to deal with clinical outcomes. Longer follow-up of the whole PREDIMED trial will eventually provide stronger evidence. In the meantime, an increasing body of knowledge supports the Mediterranean diet as a useful tool in managing individuals who are at high risk for CHD.

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Appendix Table 1. Quantitative Score of Adherence to the Mediterranean Diet

Foods and Frequency of Consumption	Criteria for 1 Point*
1. Do you use olive oil as main culinary fat?	Yes
2. How much olive oil do you consume in a given day (including oil used for frying, salads, out-of-house meals, etc.)?	≥4 tbsp
3. How many vegetable servings do you consume per day? (1 serving = 200 g [consider side dishes as half a serving])	≥2 (≥1 portion raw or as salad)
4. How many fruit units (including natural fruit juices) do you consume per day?	≥3
5. How many servings of red meat, hamburger, or meat products (ham, sausage, etc.) do you consume per day? (1 serving = 100–150 g)	<1
6. How many servings of butter, margarine, or cream do you consume per day? (1 serving = 12 g)	<1
7. How many sweet or carbonated beverages do you drink per day?	<1
8. How much wine do you drink per week?	≥3 glasses
9. How many servings of legumes do you consume per week? (1 serving = 150 g)	≥3
10. How many servings of fish or shellfish do you consume per week? (1 serving = 100–150 g of fish or 4–5 units or 200 g of shellfish)	≥3
11. How many times per week do you consume commercial sweets or pastries (not homemade), such as cakes, cookies, biscuits, or custard?	<3
12. How many servings of nuts (including peanuts) do you consume per week? (1 serving = 30 g)	≥1
13. Do you preferentially consume chicken, turkey, or rabbit meat instead of veal, pork, hamburger, or sausage?	Yes
14. How many times per week do you consume vegetables, pasta, rice, or other dishes seasoned with *sofrito* (sauce made with tomato and onion, leek, or garlic and simmered with olive oil)?	≥2

* 0 points if these criteria are not met.

Appendix Table 2. Fatty Acid, Tocopherol, and Sterol Composition of Virgin Olive Oil and Nuts Used in the Trial*

Constituents	Olive Oil	Walnuts	Almonds	Hazelnuts
Total fat, %	100	62.9 (0.3)	50.2 (0.2)	53.2 (0.3)
Palmitic acid	8.2 (0.2)	6.3 (0.0)	7.4 (0.1)	7.4 (0.1)
Stearic acid	3.2 (0.1)	2.6 (0.0)	1.8 (0.0)	1.9 (0.1)
Oleic acid	75.0 (0.8)	14.0 (0.3)	61.2 (0.4)	72.1 (0.2)
Linoleic acid	6.8 (0.2)	61.3 (0.4)	26.7 (0.2)	13.3 (0.2)
α-Linolenic acid	0.4 (0.0)	14.3 (0.1)	0.1 (0.0)	0.8 (0.0)
α-Tocopherol, *mg/100 g*	14.7 (0.0)	4.9 (0.1)	48.4 (0.9)	38.8 (1.5)
β-Tocopherol, *mg/100 g*	4.3 (0.0)	2.0 (0.1)	5.4 (0.9)	8.8 (1.5)
γ-Tocopherol, *mg/100 g*	0.4 (0.0)	50.2 (1.3)	6.0 (0.2)	20.7 (0.4)
Total sterols, *mg/100 g*	155.8 (0.0)	198.5 (7.8)	224.2 (25.4)	174.6 (8.6)
β-Sitosterol, %	95.5 (0.1)	84.0 (0.8)	79.1 (0.5)	82.8 (1.1)
Campesterol, %	3.2 (0.0)	5.3 (0.0)	3.3 (0.0)	5.2 (0.1)
Δ-5-Avenasterol, %	<0.1	7.6 (0.9)	6.3 (1.2)	11.1 (0.2)

* Values are means (SD) of 6 measurements of random samples from different lots.

Appendix Table 3. Randomized Feeding Trials Comparing a Mediterranean Diet with Other Healthy Diets for Intermediate Cardiovascular Outcomes*

Author, Year (Reference)	Country	Study Sample	Study Design	Duration	Main Outcomes	Results†
Michalsen et al., 2006 (60)	Germany	101 patients with CHD	Parallel group: Mediterranean diet vs. low-fat diet	1 y	Lipid profile, insulin, CRP, fibrinogen, homocysteine	No differences in changes of risk factors or inflammatory markers
Stachowska et al., 2005 (61)	Poland	37 kidney graft recipients	Parallel group: Mediterranean diet vs. low-fat diet	6 mo	Oxidative status in plasma and red blood cells	Decreased oxidative status
Vincent-Baudry et al., 2005 (62)	France	212 men and women with ≥1 risk factor	Parallel group: Mediterranean diet vs. low-fat diet	3 mo	BMI, lipids, glucose, insulin, homocysteine	No differences in changes of risk factors
Bravo-Herrera et al., 2004 (63)	Spain	41 healthy participants	Crossover: Mediterranean diet vs. low-fat diet vs. high-fat, high-saturated fat diet	3 mo	Lipids, tissue factor expression by circulating monocytes	Improvement in all outcomes except lower HDL cholesterol levels vs. high-fat diet; no differences vs. low-fat diet
Esposito et al., 2004 (12)	Italy	180 participants with the metabolic syndrome	Parallel group: Mediterranean diet vs. prudent western diet	24 mo	BMI, BP, insulin resistance, lipid profile, endothelial function, inflammatory markers	Improvement in all outcomes
Rodríguez-Villar et al., 2004 (64)	Spain	21 patients with type 2 diabetes mellitus	Crossover: Mediterranean diet vs. low-fat diet	6 wk	Glycemic control, lipids, LDL oxidizability	Reduced VLDL lipid levels; no effect on other outcomes
Ros et al., 2004 (42)	Spain	21 participants with hypercholesterolemia	Crossover: Mediterranean diet vs. a similar diet where walnuts replaced 32% of energy from MUFAs	4 wk	Endothelial function in the brachial artery, adhesion molecules, CRP, lipid profile, homocysteine, oxidation biomarkers	Reduced endothelium-dependent vasodilatation; increased levels of VCAM-1, total cholesterol, and LDL cholesterol
Søndergaard et al., 2003 (65)	Denmark	131 patients with CHD and hypercholesterolemia	Parallel group: Mediterranean diet vs. usual diet; both groups received fluvastatin, 40 mg	12 mo	Endothelial function in the brachial artery	Improved outcome
Toobert et al., 2003 (66)	United States	279 postmenopausal women with type 2 diabetes mellitus	Parallel group: Mediterranean diet nutrition education vs. usual diet	6 mo	BMI, BP, glycemic control, lipids, quality of life	Improvements in BMI, glycemic control, and quality of life
Singh et al., 2002 (67)	United Kingdom	54 healthy participants	Parallel group: Mediterranean diet vs. vitamin C, 1 g/d, vs. placebo	6 wk	Forearm blood flow by venous occlusion plethysmography	Improved outcome
Fuentes et al., 2001 (10)	Spain	22 men with hypercholesterolemia	Crossover: Mediterranean diet vs. low-fat diet after baseline high-fat, high–saturated-fat diet	4 wk	Lipids, endothelial function in the brachial artery, inflammatory markers	Improvement of all outcomes vs. baseline; marginal improvement of endothelium-dependent vasodilatation vs. low-fat diet
Mezzano et al., 2001 (68)	Chile	42 healthy participants	Parallel group: Mediterranean diet vs. high-fat diet; wine was added after the second month	90 d	Prothrombotic and profibrinolytic factors	Improved outcomes; improvement enhanced by addition of wine
Pérez-Jiménez et al., 2001 (69)	Spain	59 healthy participants	Crossover: Mediterranean diet vs. low-fat diet after baseline high-fat, high–saturated-fat diet	4 wk	Lipids, free fatty acids, insulin sensitivity, glucose uptake by isolated monocytes	Improvement of all outcomes except reduced HDL cholesterol levels vs. baseline; no differences vs. low-fat diet
Zambón et al., 2000 (8)	Spain	49 patients with hypercholesterolemia	Crossover trial: Mediterranean diet vs. a similar diet where walnuts replaced 35% of energy from MUFAs	6 wk	Lipid profile, LDL resistance to in vitro oxidative stress	Higher total and LDL cholesterol levels, other outcomes similar
Ferro-Luzzi et al., 1984 (70)	Italy	48 healthy participants	Sequential: Mediterranean diet vs. high-fat western diet	6 wk	Lipid profile	Lower total and LDL cholesterol levels
Strazzullo et al., 1986 (38)	Italy	57 healthy participants	Sequential: Mediterranean diet vs. high-fat western diet	6 wk	BP	Lower systolic BP

* With the exception of 2 widely cited Italian papers from the 1980s (38, 70), which were not randomized, we included only randomized feeding trials with intermediate outcomes in which 1 diet was a Mediterranean diet containing at least 15% energy as MUFA derived in part from olive oil. BMI = body mass index; BP = blood pressure; CHD = coronary heart disease; CRP = C-reactive protein; HDL = high-density lipoprotein; LDL = low-density lipoprotein; MUFA = monounsaturated fatty acid; VCAM-1 = vascular cell adhesion molecule-1; VLDL = very-low-density lipoprotein.
† Mediterranean diet vs. comparator diet(s).