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A Large Randomized Individual and Group Intervention Conducted by Registered Dietitians Increased Adherence to Mediterranean-Type Diets: The PREDIMED Study

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ABSTRACT

Objective To assess the effectiveness of an intervention aimed to increase adherence to a Mediterranean diet.

Design A 12-month assessment of a randomized primary prevention trial.

Subjects/settings One thousand five hundred fifty-one asymptomatic persons aged 55 to 80 years, with diabetes or ≥3 cardiovascular risk factors.

Intervention Participants were randomly assigned to a control group or two Mediterranean diet groups. Those allocated to the two Mediterranean diet groups received individual motivational interviews every 3 months to negotiate nutrition goals, and group educational sessions on a quarterly basis. One Mediterranean diet group received free virgin olive oil (1 L/week), the other received free mixed nuts (30 g/day). Participants in the control group received verbal instructions and a leaflet recommending the National Cholesterol Education Program Adult Treatment Panel III dietary guidelines.

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Main outcome measures Changes in food and nutrient intake after 12 months.
Statistical analyses Paired *t* tests (for within-group changes) and analysis of variance (for between-group changes) were conducted.
Results Participants allocated to both Mediterranean diets increased their intake of virgin olive oil, nuts, vegetables, legumes, and fruits ($P<0.05$ for all within- and between-group differences). Participants in all three groups decreased their intake of meat and pastries, cakes, and sweets ($P<0.05$ for all). Fiber, monounsaturated fatty acid, and polyunsaturated fatty acid intake increased in the Mediterranean diet groups ($P<0.005$ for all). Favorable, although nonsignificant, changes in intake of other nutrients occurred only in the Mediterranean diet groups.
Conclusions A 12-month behavioral intervention promoting the Mediterranean diet can favorably modify an individual's overall food pattern. The individual motivational interventions together with the group sessions and the free provision of high-fat and palatable key foods customary to the Mediterranean diet were effective in improving the dietary habits of participants in this trial.
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Many observational studies have reported inverse associations of Mediterranean-type diets with coronary heart diseases (CHD), mortality, and/or all-cause mortality (1-5). However, in the single randomized trial available, the Lyon Study (6), the fat composition in the experimental group was 30.5% of energy intake as total fat, with 12.9% of monounsaturated fatty acid (MUFA) intake. This value was far from the 15% to 20% MUFA content in the traditional Mediterranean diet. Moreover, no special consideration was given to olive oil, which is the major source of dietary fat in Mediterranean diets (7). On the other hand, the American Heart Association has outlined that Mediterranean-type diets are potentially useful for the prevention of CHD, but a cautious recommendation has been issued and the need for more studies has been highlighted (8).

The strategies followed to change dietary behavior in the most important dietary intervention trials have included the provision of written information, self-monitoring, goal setting, individual contacts, and group sessions. Several studies have found that intensive dietary counseling in groups has brought about changes in dietary habits more effectively than a leaflet without additional reinforcement (9,10). Previous studies have suggested that frequent contact during intensive intervention is important for maximizing the intervention effect (11-13), and that self-monitoring is a very powerful strategy in behavior change (14). Besides, the effectiveness is increased when food and nutrition professionals administer a brief questionnaire and are able to provide quick personal feedback informing the participants about their personal level of goal-achievement, and when they are also able to translate these results into individualized messages (15). Moreover, easily understandable messages expressed as the number of servings per day or per week of the food groups that the intervention is targeting may be very effective in achieving changes in dietary behaviors. In studies in which seasonal shopping lists, meal plans, or cooking recipes were provided, the compliance with the diet was enhanced (16).

Some studies have suggested that free provision of key food items is a very effective strategy to increase compliance with the intended interventions (10,16,17).

For all these reasons, we hypothesized that group sessions of nutrition advice combined with individual and negotiated goals, that are worked out as a specific number of servings/day or servings/week of food groups, together with free provision of key foods, may be very effective in increasing the adherence to a Mediterranean-type diet among free-living elderly subjects at high cardiovascular risk.

No large clinical trial has assessed the effect of a nutrition intervention on adherence to the Mediterranean-style diet and the effect of this food pattern on primary cardiovascular prevention. The Prevención con Dieta Mediterránea (PREDIMED) study is the first large trial to randomize high-risk individuals to follow either one of two Mediterranean diets or a control diet for primary cardiovascular prevention. PREDIMED stands for PREvention with MEDiterranean DIet and was designed to overcome the previous limitations of observational non-randomized studies and of the single randomized trial currently available (6) and to provide results with the best quality of evidence (randomized primary prevention trial) to support a causal association between adherence to Mediterranean-type diets and cardiovascular risk. We aimed to evaluate the effectiveness of the dietary and nutrition education intervention for 12-month in producing changes in the consumption of key foods and nutrients that are most relevant for the definition of a Mediterranean-style diet, in the first 1,511 participants who entered the PREDIMED trial.

METHODS

Overview of the PREDIMED Study

The PREDIMED study is a multicenter, randomized, controlled, single-blinded 4-year clinical trial that aims to assess the effects of a Mediterranean-type diet on the risk of major cardiovascular events. Two individual motivational interviews every 3 months to negotiate nutrition goals, and group educational sessions on a quarterly basis, focused to adapt the customary diet to a traditional Mediterranean diet, were compared with a control group, which received verbal instructions and a leaflet recommending the National Cholesterol Education Program Adult Treatment Panel III dietary guidelines (www.predimed.org). The trial protocol has been described elsewhere (18,19).

An estimated 9,000 high-risk participants (>6,000 participants have already been recruited) will be assigned to one of three intervention groups: Mediterranean diet with virgin olive oil, Mediterranean diet with mixed nuts, or control group. The main outcome is an aggregate of cardiovascular events (eg, cardiovascular death, nonfatal myocardial infarction, and/or nonfatal stroke).

Participants and Recruitment

Eligible participants are community-dwelling men aged 55 to 80 years, and women aged 60 to 80 years, who are

free of CHD at baseline and fulfill at least one of the two following criteria: type 2 diabetes or three or more CHD risk factors (eg, current smoker, hypertension [blood pressure >140/90 mm Hg or treatment with antihypertensive drugs], low-density lipoprotein cholesterol level ≥160 mg/dL [4.14 mmol/L] or treatment with hypolipidemic drugs, high-density lipoprotein cholesterol ≤40 mg/dL [1.04 mmol/L], body mass index ≥25, or family history of premature CHD [before age 55 years in men or age 60 years in women]. If high-density lipoprotein cholesterol level is ≥60 mg/dL (1.55 mmol/L), one risk factor is subtracted.

Exclusion criteria are history of CHD or other cardiovascular diseases, any severe chronic illness, drug or alcohol addiction, history of allergy or intolerance to olive oil or nuts, and low predicted likelihood of changing dietary habits according to the Prochaska stages of change model (20). The following three questions are included in the eligibility questionnaire: Are you able to change or to follow the diet the doctors of the trial will advise you to follow? Do you habitually avoid eating a lot of animal fat (eg, butter, fat, and cakes)? If this is not the case, would you be willing to try to do it? and Do you customarily follow a fiber-rich diet, that is to say with abundant fruits, vegetables, and legumes? If this is not the case, would you be willing to try to do it? We use the answers to these questions to classify the participants according to their willingness of adopting the intended dietary changes.

Randomization

All participants were recruited in primary care centers affiliated to 10 teaching hospitals in eight Spanish cities and were randomized to three equal-sized groups. After the screening visit, each center randomly assigned eligible participants to one of three diet groups by using a computer-generated random-number sequence. The coordinating center constructed the stratified randomization table, which assigned each participant into blocks of 50 participants balanced by center, sex, and age group (<70 years and ≥70 years). We concealed allocation to the intervention groups by using sealed envelopes with correlative numbers by prespecified subgroups of sex and age.

Dietary Intervention

The PREDIMED food and nutrition professionals were directly responsible for the dietary and nutrition education intervention. Each was a registered dietitian (RD) trained and certified to deliver the PREDIMED intervention protocol. Participants randomized to the control group had an interview with a PREDIMED RD that included a simplified 14-item assessment questionnaire on adherence to a Mediterranean diet (15), a leaflet with the written recommendations according to American Heart Association guidelines (21), and brief personal recommendations about how to follow this type of diet. Total fat intake recommendations were opposite to those given to participants in the two Mediterranean diet groups. No further visits were scheduled for this group until the 12-month follow-up evaluation.

The intervention in the Mediterranean diet groups was based on individual and group nutrition education. An individual motivational interview was administered quarterly and included both the 14-item questionnaire on adherence to a Mediterranean diet and positive recommendations to follow this food pattern. An RD personalized the message by adapting it to the participant's clinical condition, preferences, and beliefs. The general guidelines to the Mediterranean diet groups were for abundant use of virgin olive oil for cooking and dressing of dishes; consumption of two or more servings (125 g/serving) per day of vegetables (at least one of them as salad), not counting garnish; three or more servings (125 g/serving) per day of fresh fruits (including natural juices); three or more servings (40 g/serving) per week of legumes; three or more servings (150 g/serving) per week of fish or seafood (at least one serving of fatty fish); three or more servings (25 g/serving) per week of nuts or seeds; selected white meats (ie, poultry without skin or rabbit) instead of red meats or processed meats (ie, burgers and sausages); seven or more glasses each week of wine if the participant is a wine consumer; and regularly cooking (ie, at least twice a week) with salsa made with minced tomato, garlic, and onion simmered in olive oil, adding other aromatic herbs or not, for dressing different dishes. Negative recommendations were also given to eliminate or limit the consumption of cream, butter, margarine, cold meats, pate, duck, carbonated and/or sugared beverages, pastries, commercial bakery products (eg, sweet desserts, cakes, cookies, puddings, and custard), french fries or potato chips, and out-of-home precooked meals.

The quarterly group sessions with the Mediterranean diet groups were run by the PREDIMED RDs with up to 20 participants per session and separate sessions for each group. Each session consisted of informative talks and provision of written material with elaborate descriptions of typical Mediterranean-diet foods and seasonal shopping lists, meal plans, and cooking recipes. The participants also received free provision of typical Mediterranean diet fatty foods (ie, virgin olive oil or mixed nuts). Depending on group assignment, participants were given 3-month quantities of either virgin olive oil (1 L/week) or mixed nuts (30 g/day, distributed as 15 g walnuts, 7.5 g almonds, and 7.5 g hazelnuts). Throughout the study, all participants had free and continuous access to their center's RD for advice and consultation. At the 12-month visit and when consulted by participants, RDs assessed any adverse effects from the dietary intervention by administering a checklist of symptoms, and gave advice on how to remedy them.

Study Sample

Out of the first 1,766 randomized participants who completed a food-frequency questionnaire (FFQ) at baseline, 1,551 also completed the 12-month postrandomization FFQ and were included in our analysis. The recruitment of these participants took place between October 2003 and October 2004. All participants provided informed consent to a protocol approved by the local review boards.

Dietary Assessment

The initial and final examination were performed by a trained RD in a face-to-face interview and included two

different questionnaires: a 14-item questionnaire, an extension of a previously validated one (15), which assessed the degree of adherence to the typical Mediterranean dietary pattern; and a 137-item FFQ that assessed dietary habits that has been validated in Spain (22). Participants were asked about the frequency of consumption of each food item during the past year, specifying the usual portion size (semiquantitative assessment). Nine possibilities of frequency were offered, from never or less than once per month to six or more times per day. If a FFQ was not fully completed, certified dietary assessment staff directly contacted the participants to obtain the missing data. We calculated energy and nutrient intake from Spanish food composition tables (23).

The main outcome measurements were changes in food and nutrient intake and the overall dietary pattern. Changes in food consumption were assessed for 12 food groups: virgin olive oil; refined-mixed olive oil; total nuts; vegetables; cereals; legumes; fruits; fish or seafood; meat or meat products; pastries, cakes or sweets; dairy products; and alcohol.

Serum and Anthropometric Measurements

Trained personnel measured weight and height by using calibrated scales (TBF-300A Body Composition Analyzer/Scale, Tanita, Tokyo, Japan) and a wall-mounted stadiometer (Seca 242, HealthCheck Systems, Brooklyn, NY), respectively. The measurements of height and weight were taken once at baseline and once again at follow-up. Blood pressure was measured in triplicate with a validated semiautomatic oscillometer (Omrom HEM-705CP, Hoofddorp, The Netherlands). Analytes determined for each participant in frozen samples of whole serum or plasma as appropriate were cholesterol and triglyceride levels by enzymatic procedures and high-density lipoprotein cholesterol level after precipitation with phosphotungstic acid and magnesium chloride. We performed all analyses in duplicate (18).

Biomarkers of Compliance

Urinary (first morning void) tyrosol and hydroxytyrosol, as markers of virgin olive oil intake (24) and the proportion of oleic acid (C18:1) and α-linolenic acid (C18:3) (a marker of walnut intake) in whole plasma (extracted after 12-hour fast) were determined at baseline and the 12-month assessments in random subsamples of participants in each intervention group. Tyrosol and hydroxytyrosol were measured by gas chromatography-mass spectrometry (24). All chemicals and organic solvents used were of analytical grade. Intra- and interassay coefficients of variation were 2.9% and 3.8% for tyrosol, and 5.7% and 6.2% for hydroxytyrosol, respectively. Plasma fatty acid analyses were performed on a Shimadzu GC-2010 Gas Chromatograph (Shimadzu, Kyoto, Japan) equipped with a flame ionization detector as described (25). Intra- and interassay CVs were 1.0% and 1.8% for oleic acid, and 3.2% and 3.9% for α-linolenic acid, respectively.

Statistical Methods

Data were entered using optically scannable forms completed by the RDs during their interviews with the participants. The completed forms were sent to the coordinating center and there they were first visibly examined to observe if they were properly completed; improper completion sporadically required returning the form to the corresponding center and rewriting a form, although usually forms were overmarked with a correction pencil to amend minor defects. We used descriptive statistics with means and standard deviations for participants' characteristics at baseline and 12 months after intervention. Participants whose baseline energy intake as estimated from the FFQs was outside prespecified ranges (ie, $<$500 kcal/day or $>$3,500 kcal/day for women and $<$800 kcal/day or $>$4,000 kcal/day for men) were excluded from the calculations (26). Within- and between-group differences are expressed as means and 95% confidence intervals. Within- and between-group changes were assessed with paired t tests and analysis of variance, respectively, followed by the Dunnett post hoc test. All P values presented are two-tailed; $P<0.05$ was considered statistically significant, unless otherwise specified. All analyses were perfomed using the Statistical Package for the Social Sciences (version 13.0, 2004, SPSS Inc, Chicago, IL).

RESULTS

The initial sample consisted initially of 1,766 participants (643, 558, and 565 in the Mediterranean diet plus olive oil, Mediterranean diet plus mixed nuts, and control group, respectively). Their mean age was 67.4 years (53.4% were women). The number of contacted and eligible subjects was 2,507 and 2,065, respectively. Among 299 noneligible subjects, 148 did not meet inclusion criteria, 63 declined to participate, 38 could not change their diet, 35 had chronic alcoholism, nine had gastrointestinal disease, and six had food allergies.

After excluding participants with baseline total energy intake outside the prespecified range and also those who did not complete the 12-month follow-up FFQ, we were able to assess the 12-month dietary habits in 1,551 of them (533, 533, and 485, in the Mediterranean diet plus olive oil, Mediterranean diet plus mixed nuts, and control groups, respectively). Table 1 displays the baseline characteristics of the participants available at 12-months. The three groups were balanced with respect to demographic characteristics, cardiovascular risk factors, occupational status, and educational level. The characteristics of participants in the three groups who were excluded from calculations because of unrealistic energy intakes or missed the 12-month appointment did not differ from those of the initial cohort.

Food Intake

We excluded some participants because their baseline values for total energy intake were outside the pre-specified limits: nine in the Mediterranean diet plus virgin olive oil group, nine in the Mediterranean diet plus mixed nuts group, and five in the control group (26). The results did not materially change when we also included the participants whose energy consumption was out of range in the calculations.

In our study, participants had a baseline dietary pattern characterized by a high consumption of vegetables

Table 1. Baseline characteristics of participants in the three randomized groups studied to determine the effectiveness of an intervention aimed to increase adherence to a Mediterranean diet by elderly Spanish adults

Characteristic	Mediterranean diet with virgin olive oil (n=533)	Mediterranean diet with mixed nuts (n=533)	Control group (n=485)
	mean±standard deviation		
Age (y)	67.2±6.2	67.0±5.6	68.0±6.1
Body mass index	29.3±3.5	29.4±3.4	29.5±3.6
Total cholesterol level (mg/dL)[a]	219.7±39.1	214.4±36.9	217.2±37.1
High-density lipoprotein cholesterol level (mg/dL)[a]	54.8±14.2	54.8±13.9	54.8±12.7
Low-density lipoprotein cholesterol level (mg/dL)[a]	136.8±35.3	132.3±33.3	134.3±33.4
Triglyceride level (mg/dL)[b]	141.3±76.2	137.8±74.4	141.7±68.0
Systolic blood pressure (mm Hg)	155.1±20.9	156.3±21.4	155.9±21.4
Diastolic blood pressure (mm Hg)	85.7±10.5	87.1±11.1	86.6±11.1
	n (%)		
Men	246 (46.2)	272 (51.0)	205 (42.3)
Family history of coronary heart disease	90 (16.9)	80 (15.0)	91 (18.8)
Overweight or obese[c]	486 (91.2)	488 (91.6)	438 (90.3)
Type 2 diabetes mellitus	272 (51.0)	253 (47.5)	232 (47.8)
Hypertension	420 (78.8)	407 (76.4)	390 (80.4)
Dyslipidemia	222 (41.7)	226 (42.4)	231 (47.6)
Current smokers	104 (19.5)	101 (19.0)	82 (16.9)
Occupation			
Worker	58 (10.9)	58 (10.9)	47 (9.7)
Housewife	165 (31.0)	160 (30.0)	160 (33.0)
Retired	302 (56.7)	309 (58.0)	269 (55.5)
Unemployed or unfit	8 (1.6)	6 (1.2)	9 (1.8)
Education level			
None	6 (1.1)	3 (0.6)	7 (1.4)
Primary school	405 (76.0)	387 (72.6)	368 (75.9)
Secondary school	80 (15.0)	90 (16.9)	65 (13.4)
University	42 (7.9)	53 (9.9)	45 (9.3)

[a]To convert mg/dL cholesterol to mmol/L, multiply mg/dL by 0.026. To convert mmol/L cholesterol to mg/dL, multiply mmol/L by 38.6. Cholesterol of 193 mg/dL=5.00 mmol/L.
[b]To convert mg/dL triglyceride to mmol/L, multiply mg/dL by 0.0113. To convert mmol/L triglyceride to mg/dL, multiply mmol/L by 88.6. Triglyceride of 159 mg/dL=1.80 mmol/L.
[c]Defined as body mass index ≥25.

(>2.4 servings/day), cereals and fruits (>3.8 and 2.8 servings/day, respectively), meat (nearly 7 servings/week) and sweets (>0.4 servings/day); moderate consumption of legumes (>3 servings/week), fish (>5.3 servings/week), and dairy products (>1.8 servings/day); moderate to low consumption of nuts (>2.6 servings/week); and a high intake of olive oil (>3.9 servings/day). Besides, the baseline consumption of virgin olive oil was very similar to that of refined-mixed olive oil (Table 2), which has a fatty acid composition close to that of virgin olive oil, but lower antioxidant capacity because it is refined not only physically but also by chemical procedures that deprive it of almost all its polyphenolic components (27).

After the 12-month intervention period, an increase of 3.25 servings/day virgin olive oil was observed in the group that was provided with this food (Table 2). Reciprocal decreases were observed in the consumption of refined-mixed olive oil, indicating that participants replaced this oil by the virgin variety supplied. An increase of approximately one serving/day (0.92) was observed for the consumption of mixed nuts in the corresponding Mediterranean diet group. In this group, the consumption of virgin olive oil also increased. The consumption of mixed nuts and refined-mixed olive oil, but not that of virgin olive oil, decreased in the control group.

Statistically significant, though small, increases were observed in the consumption of vegetables (>0.18 servings/day) and legumes (0.11 servings/day) in the two groups assigned to Mediterranean-type diet. Participants in the three groups increased to a small extent the intake of fruits (>0.25 servings/day) and similarly decreased the intake of cereals, meat, pastries and sweets, and alcohol. As intended, the Mediterranean diet score (from the 14-item questionnaire on adherence to a Mediterranean diet) increased significantly in the participants included in the two Mediterranean diet groups, whereas the change was almost negligible in the control group.

Significant between-group differences in the expected direction were observed for increased consumption of virgin olive oil, nuts, vegetables, legumes, fruits and the 14-unit Mediterranean diet score for both Mediterranean diet groups vs the control group, and for decreased con-

Table 2. Mean baseline values and changes after 12 months in the consumption of key food items and in the 14-point Mediterranean diet score in the three randomized groups of elderly Spanish adults[a]. Within-group (95% confidence interval [CI]) changes and between-group changes are presented for the two groups receiving the Mediterranean diet intervention (vs the control group)

Food item	Baseline			Within-Group Changes after 12 Months			Between-Group Changes (Differences vs Control)			
	Mediterranean diet with virgin olive oil (n=533)	Mediterranean diet with mixed nuts (n=533)	Control group (n=485)	Mediterranean diet with virgin olive oil (n =533)	Mediterranean diet with mixed nuts (n=533)	Control group (n=485)	Mediterranean diet with virgin olive oil vs control group		Mediterranean diet with mixed nuts vs control group	
	← mean±standard deviation →			← mean (95% CI) →			mean (95% CI)	P value	P mean (95% CI)	P value
Virgin olive oil (10 g) (servings/d)	1.87±2.20	2.25±2.34	1.82±2.27	3.25 (3.02, 3.48)	0.54 (0.32, 0.75)	0.10 (−0.09, −0.30)	3.14 (2.78, 3.51)	<0.001	0.43 (0.08, 0.79)	0.01
Refined-mixed olive oil (10 g) (servings/d)	2.24±2.12	1.95±2.15	2.07±1.99	−2.10 (−2.29, −1.91)	0.04 (−0.16, 0.25)	−0.28 (−0.47, −0.01)	−1.82 (−2.15, −1.49)	<0.001	0.32 (−0.03, 0.66)	0.08
Total nuts (25 g) (servings/d)	0.40±0.52	0.50±0.60	0.38±0.50	0.16 (0.10, 0.20)	0.92 (0.84, 1.00)	−0.06 (−0.10, 0.00)	0.20 (0.12, 0.30)	<0.001	0.98 (0.86, 1.08)	<0.001
Vegetables (125 g) (servings/d)	2.46±1.04	2.48±0.98	2.44±1.10	0.26 (0.18, 0.36)	0.18 (0.08, 0.26)	0.006 (−0.08, 0.10)	0.26 (0.10, 0.42)	<0.001	0.16 (0.00, 0.32)	0.04
Cereals (60 g) (servings/d)	4.06±1.78	4.06±1.66	3.86±1.66	−0.28 (−0.41, −0.13)	−0.31 (−0.46, −0.16)	−0.13 (−0.28, 0.02)	−0.15 (−0.40, 0.11)	0.43	−0.18 (−0.44, 0.08)	0.28
Legumes (40 g) (servings/d)	0.45±0.22	0.45±0.21	0.47±0.26	0.11 (0.09, 0.14)	0.11 (0.08, 0.12)	−0.006 (−0.03, 0.02)	0.12 (0.06, 0.15)	<0.001	0.11 (0.06, 0.14)	<0.001
Fruits (125 g) (servings/d)	2.89±1.44	2.89±1.44	2.90±1.69	0.56 (0.42, 0.70)	0.50 (0.37, 0.64)	0.25 (0.11, 0.40)	0.30 (0.06, 0.55)	0.01	0.25 (0.00, 0.49)	0.04
Fish or seafood (125) (servings/d)	0.79±0.36	0.79±0.32	0.77±0.35	0.01 (−0.02, 0.04)	0.01 (−0.01, 0.04)	−0.02 (−0.06, 0.01)	0.04 (−0.02, 0.08)	0.38	0.04 (−0.01, 0.08)	0.26
Meat or meat products (150 g) (servings/d)	0.94±0.35	0.97±0.37	0.92±0.35	−0.07 (−0.10, −0.04)	−0.13 (−0.16, −0.09)	−0.08 (−0.11, −0.05)	0.01 (−0.04, 0.07)	0.86	−0.44 (−0.10, 0.01)	0.17
Pastries, cakes or sweets (50 g) (servings/d)	0.47±0.53	0.40±0.60	0.45±0.56	−0.14 (−0.18, −0.10)	−0.10 (−0.15, −0.06)	−0.07 (−0.11, −0.02)	−0.07 (−0.14, 0.00)	0.08	−0.03 (−0.11, 0.05)	0.71
Dairy products (200 g) (servings/d)	1.92±1.09	1.89±1.09	1.90±1.15	0.03 (−0.06, 0.12)	−0.03 (−0.12, 0.06)	−0.06 (−0.15, 0.03)	0.09 (−0.06, 0.25)	0.40	0.03 (−0.13, 0.19)	0.95
Alcohol (g/d)	11.68±18.10	12.02±17.78	9.66±15.26	−1.62 (−2.60, −0.63)	−1.37 (−2.39, −0.35)	−1.10 (−1.96, −0.21)	−0.53 (−2.13, 1.07)	0.81	−0.28 (−1.91, 1.34)	0.97
14-unit Mediterranean diet score[b]	8.95±1.79	8.92±1.92	8.42±1.81	1.86 (1.70, 2.03)	2.26 (2.09, 2.43)	0.46 (0.28, 0.64)	1.40 (1.10, 1.70)	<0.001	1.80 (1.50, 2.10)	<0.001

[a]Of participants in the Mediterranean diet with virgin olive oil, Mediterranean diet with mixed nuts, and control groups, nine, nine, and five participants, respectively, were excluded from calculations of food intake because energy was outside the prespecified ranges. Dietary assessment was conducted using a food frequency questionnaire (136 items) previously validated for a Spanish population.
[b]Based on a 14-item assessment questionnaire on adherence to a Mediterranean diet (15). The range was zero (minimun) to 14 (maximum) points.

Table 3. Mean nutrient intake of elderly Spanish adults at baseline and 12 months after randomization to one of two Mediterranean diets and in the control group[a]

	Mediterranean Diet with Virgin Olive Oil (n=533)		Mediterranean Diet with Mixed Nuts (n=533)		Control Group (n=485)	
Nutrient	**Baseline**	**12 mo**	**Baseline**	**12 mo**	**Baseline**	**12 mo**
	← *mean± standard deviation* →					
Energy (kcal)	2,291±560	2,276±516	2,320±539	2,340±480	2,210±525	2,074±492
Total protein (% energy)	16.5±2.9	16.5±2.7	16.5±2.8	16.3±2.5	16.7±2.7	16.8±2.8
Total carbohydrate (% energy)	41.3±6.7	40.0±5.8	40.3±6.6	38.2±5.9	41.5±7.0	42.5±6.7
Fiber (g/d)	24.0±7.7	26.2±7.6	24.4±7.2	27.5±7.3	24.0±7.7	23.5±7.0
Total fat (% energy)	38.9±6.3	40.7±5.6	39.9±6.3	42.7±6.0	39.0±6.6	38.0±6.4
Saturated fatty acid (% energy)	9.8±2.2	9.3±1.8	10.1±2.1	9.4±1.9	9.9±2.3	9.5±2.2
Monounsaturated fatty acid (% energy)	19.6±4.2	21.7±3.7	20.0±4.2	21.6±3.9	19.5±4.4	19.2±4.1
Polyunsaturated fatty acid (% energy)	6.1±2.1	6.3±1.5	6.4±2.1	8.2±2.3	6.2±2.0	5.9±2.0
Monounsaturated/saturated fatty acid (% energy)	2.0±0.5	2.4±0.5	2.0±0.5	2.4±0.5	2.0±0.5	2.1±0.5
Linoleic acid (g/d)	13.0±5.72	13.11±4.77	13.94±6.64	17.67±5.22	12.8±6.19	11.43±5.74
α-linolenic acid (g/d)	1.42±0.68	1.53±0.70	1.57±0.78	2.17±0.67	1.34±0.66	1.21±0.66
Marine n-3 fatty acids (g/d)	0.71±0.44	0.77±0.40	0.71±0.41	0.77±0.42	0.65±0.40	0.64±0.40
Olive oil (% energy)	16.2±6.4	20.8±6.3	16.3±6.7	18.4±6.8	16.0±7.0	16.3±6.7
Nuts (% energy)	2.6±3.3	3.6±3.5	3.3±3.7	9.5±5.3	2.4±3.1	2.1±3.2
Cholesterol (mg/d)	360.4±106.3	338.7±100.6	371.2±111.1	340.0±98.5	359.9±116.1	337.1±110.4

[a]Of participants in the Mediterranean diet with virgin olive oil, Mediterranean diet with mixed nuts, and control groups, nine, nine, and five participants, respectively, were excluded from calculations of food intake because energy was outside the prespecified ranges.

sumption of refined-mixed olive oil for Mediterranean diets with olive oil vs the control group (Table 2).

Energy and Nutrient Intake

Table 3 shows the overall baseline and 12-month nutrient profiles for the three groups. As expected in a Spanish population, the customary diet was high in total fat and MUFA. The 12-month macronutrient composition of the diet in the Mediterranean diet groups showed increases in the intake of fiber, total fat due to a higher intake of healthy fats (MUFA and polyunsaturated fatty acid (PUFA), the ratio of MUFA to saturated fatty acid (SFA) also increased, as well as the energy derived from olive oil and nuts. In addition, these groups had the expected increase in PUFA intake from walnuts (ie, linoleic acid and α-linolenic acid) and a decreased intake of total carbohydrate, SFA, and cholesterol. The control group showed a small increase in the intake of total carbohydrate and a small decrease in total energy and overall fat intake, with reductions in the intake all types of fatty acids and cholesterol.

Regarding energy from olive oil, in the Mediterranean diet group supplied with virgin olive oil, 12-month data showed that >20% of total energy intake was derived from its consumption and that 96% of intake of MUFA corresponded to virgin olive oil.

Table 4 shows changes in the overall profile of nutrient intake for the two Mediterranean diet groups when compared with the control group. Total energy intake decreased more in the control group than in the two Mediterranean diet groups. PUFA increased significantly only in the group of mixed nuts and α-linolenic acid and n-3 long chain fatty acid intake also increased significantly in both intervention groups. Significant between-group differences for both Mediterranean diet groups vs the control group in the expected direction were found for the following variables: increased intake of fiber, total fat, MUFA, PUFA, linoleic acid, α-linolenic acid, marine n-3 fatty acids, and energy from olive oil and mixed nuts. A significant difference in the ratio MUFA/SFA was also observed. The intake of total carbohydrate decreased in the two intervention groups when compared to control.

The percentage of subjects who had modified their food habits is presented in Table 5. Subjects allocated to the Mediterranean diet intervention groups were significantly more likely to report the intended changes in the consumption of key foods and nutrients. They also were more likely to improve their body mass index, lipid profile, and blood pressure (Table 5).

Biomarkers of Compliance

Table 6 shows changes in biological markers of compliance in subgroups of participants in each group. Urinary tyrosol and hydroxytyrosol levels increased from baseline only in the group allocated to the Mediterranean diet plus virgin olive oil, indicating good adherence to the supplementary food given. The significant increase in the proportion of α-linolenic acid in the plasma of participants assigned the Mediterranean diet plus mixed nuts also supports their adherence to walnut intake. The propor-

Table 4. Within-group (95% confidence interval [CI]) changes and between-group changes in mean energy and nutrient intake in elderly Spanish adults after 12 months of being randomized into one of two groups receiving the Mediterranean diet intervention (vs the control group)[a]

	Within-Group Mean Changes after 12 mo			Between-Group Changes (Differences vs Control)			
	Mediterranean diet with virgin olive oil (n=533)	Mediterranean diet with mixed nuts (n=533)	Control group (n=485)	Mediterranean diet with olive oil vs control group		Mediterranean diet with mixed nuts vs control group	
	← mean (95% CI) →			*mean (95% CI)*	*P value*	*mean (95% CI)*	*P value*
Energy (kcal)	−15 (−57, 26)	20 (−23, 64)	−135 (−180, −90)	120 (45, 195)	<0.001	156 (80, 232)	<0.001
Total protein (% energy)	−0.1 (−0.3, 0.1)	−0.3 (−0.5, −0.03)	0.1 (−0.1, 0.4)	−0.2 (−0.6, 0.2)	0.56	−0.4 (−0.8, 0.0)	0.08
Total carbohydrate (% energy)	−1.3 (−1.8, −0.7)	−2.1 (−2.6, −1.5)	1.0 (0.4, 1.6)	−2.3 (−3.3, −1.3)	<0.001	−3.1 (−4.1, −2.1)	<0.001
Fiber (g/d)	2.2 (1.5, 2.8)	3.1 (2.4,3.7)	−0.5 (−1.2, 0.1)	2.7 (1.6, 3.9)	<0.001	3.6 (2.5, 4.7)	<0.001
Total fat (% energy)	1.8 (1.2, 2.4)	2.7 (2.1, 3.3)	−1.0 (−1.7, −0.4)	2.8 (1.8, 3.9)	<0.001	3.8 (2.7, 4.8)	<0.001
Saturated fatty acid (% energy)	−0.6 (−0.7, −0.4)	−0.7 (−0.8, −0.5)	−0.4 (−0.6, −0.2)	−0.2 (−0.5, 0.2)	0.58	−0.3 (−0.6, 0.1)	0.16
Monounsaturated fatty acid (% energy)	2.1 (1.7, 2.5)	1.6 (1.2, 2.0)	−0.3 (−0.7, 0.1)	2.4 (1.7, 3.1)	<0.001	1.9 (1.2, 2.6)	<0.001
Polyunsaturated fatty acid (% energy)	0.2 (−0.04, 0.4)	1.8 (1.5, 2.0)	−0.3 (−0.5, −0.1)	0.4 (0.1, 0.8)	0.01	2.1 (1.7, 2.4)	<0.001
Monounsaturated/Saturated fatty acid (% energy)	0.3 (0.3, 0.4)	0.3 (0.3, 0.4)	0.1 (0.02, 0.1)	0.3 (0.2, 0.4)	<0.001	0.3 (0.2, 0.3)	<0.001
Linoleic acid (g/d)	0.12 (−0.42, 0.66)	3.72 (3.12, 4.32)	−1.37 (−1.94, −0.81)	1.49 (0.54, 2.44)	<0.001	5.10 (4.09, 6.10)	<0.001
α-linolenic acid (g/d)	0.11 (0.04, 0.18)	0.60 (0.52, 0.67)	−0.12 (−0.19, −0.06)	0.24 (0.12, 0.35)	<0.001	0.72 (0.60, 0.84)	<0.001
Marine n-3 fatty acids (g/d)	0.06 (0.02, 0.10)	0.06 (0.18, 0.09)	−0.01 (−0.05, 0.02)	0.07 (0.01, 0.14)	0.03	0.07 (0.00, 0.14)	0.03
Olive oil (% energy)	4.6 (4.0, 5.2)	1.9 (1.2, 2.5)	0.3 (−0.3, 1.0)	4.2 (3.1, 5.3)	<0.001	1.5 (0.4, 2.6)	<0.001
Nuts (% energy)	1.0 (0.6, 1.3)	6.2 (5.7, 6.8)	−0.3 (−0.6, 0.04)	1.2 (0.7, 1.8)	<0.001	6.5 (5.7, 7.2)	<0.001
Cholesterol (mg/d)	−21.6 (−30.5, −12.8)	−31.3 (−40.1, −22.5)	−22.8 (−33.5, −12.1)	1.1 (−15.8, 18.0)	1.00	−8.5 (−25.4, 8.4)	0.54

[a]Of participants in the Mediterranean diet with virgin olive oil, Mediterranean diet with mixed nuts, and control group, nine, nine, and five participants, respectively, were excluded from calculations of energy and nutrient intake because reported energy was unrealistic.

tion of oleic acid in plasma was significantly reduced only in the control group (Table 7).

DISCUSSION

In this multicenter, randomized, primary prevention trial of cardiovascular disease, a behavioral intervention aimed to improve a Mediterranean-style diet enhanced by provision of palatable, healthful fat-rich foods (virgin olive oil or mixed nuts) was useful in achieving significant changes in the consumption of key food items, and participants who were assigned to Mediterranean diet groups showed a greater adherence to this food pattern. Our results show that the free provision of these foods, and the individual motivational interventions together with the group sessions, were effective in improving dietary habits, always moving toward a more healthful overall food pattern.

However, we acknowledge that our results do not provide evidence to indicate that these beneficial changes will be necessarily maintained after the intervention, when participants will no longer receive free provision of the key food items. Nevertheless, from a public health point of view our results can be extrapolated to suggest that interventions aimed at reducing the market prices of beneficial key food items might be part of an effective population-wide strategy to promote a better adherence to a Mediterranean-type diet.

We achieved only a modest reduction in total fat and SFA in the control group and similarly small increments in MUFA intake in the two Mediterranean diet groups, and there may be two reasons for this relatively small success. First, it is difficult to achieve substantial dietary modifications in healthy, elderly people during a 12-month period (28,29). Second, the participants' baseline diet scores showed that they had a high intake of meat and dairy products, but overall they already followed a reasonably good Mediterranean-style food pattern, with high intakes of vegetables, fruits, fish, and olive oil and an average of eight points out of a total of 14 points on adherence to the Mediterranean diet. Significantly improving this score would not be an easy task. In the Mediterranean area, it is common to use abundant olive oil as culinary fat or for dressing various dishes (18). This explains the consistently high intake of total fat and MUFA reported for Mediterranean populations in different surveys (7,16,30). To reduce the intake of total fat, MUFA, or SFA (as intended in the control group) is a more difficult challenge in Mediterranean populations than in other settings (10,28,31–34). In studies of nutrition counseling in younger participants and using more intense and longer interventions, greater changes in total fat and/or SFA intake were obtained (9,13,29,35). Despite these circumstances, the dietary changes achieved in our study, although small, were in the appropriate direction, and the proportion of participants who modified their dietary habits towards a more healthful pattern was substantially greater in the two Mediterranean diet groups than in the control group.

Our findings are consistent with previous dietary intervention studies. In trials of behavioral intervention to implement Mediterranean-type diets conducted in non-Mediterranean populations (28,32), the magnitude of observed changes was similar to that of our study. In the

Table 5. Percentage of elderly Spanish adult participants complying with the intended dietary changes and favorable changes in risk factors observed during the first year in the two intervention groups and in the control group

Variable	Mediterranean diet with virgin olive oil	Mediterranean diet with mixed nuts	Control group	*P* value[a]
	← % →			
Decreased total fat intake	37.5	34.1	57.9	<0.001
Increased monounsaturated fatty acid intake	69.0	63.4	44.3	<0.001
Increased monounsaturated/saturated fatty acid ratio	77.3	75.6	54.8	<0.001
Increased consumption of fruit	64.0	64.7	60.4	0.319
Increased consumption of vegetables	65.9	61.2	51.5	<0.001
Decreased consumption of meats	56.8	64.9	59.2	0.022
Decreased consumption of sweets and desserts	53.8	51.2	45.2	0.018
Decreased body mass index	37.7	40.9	41.2	0.464
Decreased total cholesterol level[b]	51.5	57.3	53.8	0.452
Decreased low-density lipoprotein cholesterol level[b]	45.5	47.7	35.8	<0.001
Decreased low-density lipoprotein cholesterol/ high-density lipoprotein cholesterol level[b]	50.6	49.2	35.8	<0.001
Decreased triglyceride level[b]	43.2	49.2	32.7	<0.001
Decreased systolic blood pressure[b]	58.0	59.3	36.6	<0.001
Decreased diastolic blood pressure[b]	49.8	51.6	43.2	<0.001

[a]Determined by χ^2 test for the difference between the groups.
[b]The changes in these risk factors were observed in the pilot study of the Prevención con Dieta Mediterránea (PREDIMED) study, 3 months after intervention. They are expressed here as percentages to avoid duplication of results published elsewhere (18).

Table 6. Biochemical markers of compliance by elderly Spanish adults to one of two Mediterranean diets or the control group: Tyrosol and hydroxytyrosol concentrations in urine at baseline and 12 months after randomization

Group	Tyrosol (μg/L)			Hydroxytyrosol (μg/L)		
	Baseline	12 mo	*P* value	Baseline	12 mo	*P* value
	← *mean*± *standard deviation* →			← *mean*± *standard deviation* →		
Mediterranean diet with virgin olive oil (n=127)	43.2±4.5	55.4±6.2	0.035	186.8±20.5	232.5±22.6	0.032
Mediterranean diet with mixed nuts (n=115)	42.1±5.4	41.7±3.8	0.944	212.8±31.9	225.8±35.2	0.767
Control group (n=102)	45.8±6.4	40.3±4.8	0.383	208.0±28.1	175.4±23.2	0.256

Table 7. Biochemical markers of compliance by elderly Spanish adults to one of two Mediterranean diets or the control group: Oleic acid and α-linolenic acid concentrations (as a percent of total fatty acids) in plasma at baseline and 12 months after randomization

Group	Oleic Acid			α-Linolenic Acid		
	Baseline	12 mo	*P* value	Baseline	12 mo	*P* value
	← *mean*± *standard deviation* →			← *mean*± *standard deviation* →		
Mediterranean diet with virgin olive oil (n=112)	29.3±4.2	29.9±3.9	0.281	0.43±0.16	0.41±0.19	0.181
Mediterranean diet with mixed nuts (n=102)	28.7±5.9	27.3±4.4	0.253	0.44±0.15	0.61±0.27	0.025
Control group (n=101)	30.1±5.3	29.2±4.9	0.021	0.41±0.16	0.42±0.19	0.398

Diabetes Prevention Study (29), 47% and 36% of participants in the intervention and control group, respectively, decreased their intake of total fat at 12 months after randomization. In the Diabetes Prevention Program (9), participants who received written information and a single individual session decreased their intake of total fat by a meager 0.8% at 12 months after randomization. The Women's Health Initiative study (13), the largest dietary intervention trial ever conducted, used a nutrition guidance approach similar to ours, but the aim was to decrease total fat intake instead of increasing the intake of healthy fats. After 12 months, the control group decreased total fat and SFA intake by 3.3% and 0.9% of energy, respectively, and there were minimal changes in the consumption of fruits, vegetables, and grains. Finally, the GISSI Prevenzione trial (36) showed that simple dietary counseling through a leaflet in more than 11,000 participants with myocardial infarction resulted in increased consumption of vegetables, fruit, fish, and olive oil after 6 months.

The PREDIMED study is the biggest randomized trial ever conducted on the effect of an overall Mediterranean dietary pattern and its key foods in primary cardiovascular prevention. An important strength of the study is that it stresses the consumption of healthy fats instead of aiming to reducing total fat intake. In addition, it reproduces real-life conditions with home-prepared foods, in a way that is similar to health-promoting lifestyle recommendations in primary care settings (37). The provision of healthful foods is an added strength, as judged by objective indexes of consumption. On the other hand, the dietary goals based exclusively on behavioral guidance were more difficult to implement, in part because the target population was a cohort of elderly people in free-living conditions and with deeply rooted dietary habits. Our study has other limitations. Dietary counseling in the control group was less intense and less frequent than in the Mediterranean diet groups. Despite this, significant reductions for the control group in the intake of total fat and SFA were observed. Another inherent limitation is related to the potential measurement error in the FFQ that we used, which provides only subjective information in comparison with the objective markers of supplementary food intake. However, both this study and our earlier report showed good agreement between the FFQ and the biomarker data (18). This is the main argument to reinforce the validity of the information collected by an FFQ (38).

CONCLUSIONS

Dietary changes after 12 months in the PREDIMED study indicate that individual motivational interventions together with group sessions and the free provision of high-fat and palatable key foods customary in a Mediterranean diet were effective in improving the dietary habits of participants in this trial, who already followed a Mediterranean-type diet in part. Dietary changes achieved after an intervention for 12 months were similar to those observed at 3 months, which led to substantial improvements in various surrogate markers of cardiovascular risk in the Mediterranean diet groups compared with the control group in the pilot study of the PREDIMED trial (39). After these results, we reinforced the intervention in the control group to reduce their intake of SFA to 7%. The final results of this large dietary trial after an expected 4-year follow-up of a larger number of participants will eventually show whether or not such beneficial dietary changes can be enhanced and if they are associated with a reduction in cardiovascular outcomes.

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