

A large randomized individual and grupal intervention conducted by dietitians increased the adherence to Mediterranean-type diets: The PREDIMED study

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ABSTRACT

Objective: Assessment of the effectiveness of an intervention aimed to increase adherence to the Mediterranean Diet (MeDiet).

Design: 12-month assessment of a randomized primary prevention trial

Subjects/settings: 1551 asymptomatic persons aged 55-80 years, with diabetes or ≥ 3 cardiovascular risk factors.

Intervention: Participants were randomly assigned to a control group or 2 MeDiet groups. Those allocated to the 2 MeDiet groups received individual motivational interviews every 3 months to negotiate nutritional goals, and group educational sessions also on a quarterly basis. One MeDiet group received free virgin olive oil (1 L/wk), the other received free mixed nuts (30 g/d). Participants in the control group received verbal instructions and a leaflet recommending the National Cholesterol Education Program-III dietary guidelines.

Main Outcome measures: changes in food and nutrient intake after 12-month.

Statistical analyses: Paired t-tests (Within-group changes) and ANOVA (between-group changes).

Results: Participants allocated to both MeDiets increased the intake of virgin olive oil, nuts, vegetables, legumes and fruits ($P < 0.05$; all within- and between-group differences). Participants in the 3 groups decreased their intake of meat and pastries, cakes and sweets ($P < 0.05$; all). Fiber, monounsaturated and polyunsaturated fatty acid intake increased in MeDiet groups ($P < 0.005$; all). Favorable, although nonsignificant, changes in intake of other nutrients occurred only in the MeDiet groups.

Conclusions: A 12-month behavioral intervention promoting the MeDiet can favorably modify the overall dietary pattern.

Applications: The individual motivational interventions together with the group sessions and the free provision of high-fat and palatable key foods customary to the MeDiet, were effective in improving the dietary habits of participants in this trial.

INTRODUCTION

Many observational studies have reported inverse associations of Mediterranean-type diets (MeDiet) 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 acids (MUFA) intake. This value was far from the 15-20 % MUFA content present in the traditional MeDiet. Moreover, no special consideration was given to olive oil, which is the major source of dietary fat in MeDiets (7). On the other hand, the American Heart Association has outlined that MeDiets 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 the dietitians 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. Finally, 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 nutritional 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 MeDiet among free-living elderly subjects at high cardiovascular risk.

At present, no large clinical trial has assessed the effect of a nutritional intervention on adherence to the Mediterranean-style diet and the effect of this food pattern on primary cardiovascular prevention. The PREDIMED (PREvencción con DIeta MEDiterránea) study is the first large trial to randomize high-risk individuals to follow either 2 MeDiets or a control diet for primary cardiovascular prevention. The PREDIMED trial 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 MeDiet and cardiovascular risk. The present study aims to evaluate the effectiveness of the dietary and nutritional 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 1511 participants who entered the PREDIMED trial.

METHODS

Overview of the PREDIMED study

The PREDIMED study is a multicenter, randomized, controlled, single-blinded 4-y clinical trial that aims to assess the effects of the MeDiet on the risk of major cardiovascular events. Two individual motivational interviews every 3 months to negotiate nutritional goals, and group educational sessions also on a quarterly basis, focused to adapt the customary diet to a traditional MeDiet, are compared with a control group, which received verbal instructions and a leaflet recommending the National Cholesterol Education Program-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 3 intervention groups: MeDiet with virgin olive oil; MeDiet with mixed nuts; or control group. The main outcome is an aggregate of cardiovascular events (cardiovascular death, nonfatal myocardial infarction, and/or nonfatal stroke).

Participants and recruitment

Eligible participants were community-dwelling men, 55 to 80 years of age, and women, 60 to 80 years of age, who were free of CHD at baseline and fulfilled at least one of the 2 following criteria: 1) type 2 diabetes; or 2) ≥ 3 of the following CHD risk factors (current smoker, hypertension [blood pressure $>140/90$ mm Hg or treatment with antihypertensive drugs], LDL cholesterol level ≥ 160 mg/dl (4.14 mmol/L), [or treatment with hypolipidemic drugs], HDL cholesterol ≤ 40 mg/dl (1.04 mmol/L), body mass index (BMI) ≥ 25 kg/m², or family history of premature CHD (before 55 years in men or 60 years in women). If the HDL-cholesterol level was ≥ 60 mg/dl (1.55 mmol/L), one risk factor was subtracted.

Exclusion criteria were 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 were included in the eligibility questionnaire: a) Are you able to change or to follow the diet which the doctors of the trial will advise you to follow? b) Do you habitually avoid eating a lot of animal fat (butter, fat, cakes etc.)? If this is not the case, would you be willing to try to do it? and c) Do you follow a fiber-rich diet, that is to say with abundant fruits, vegetables and legumes customarily? If this is not the case, would you be willing to try to do it? We used 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 8 Spanish cities and were randomized to 3 equally sized groups. After the screening visit, each

center randomly assigns eligible participants to 1 of 3 diet groups by using a computed-generated random-number sequence. The coordinating center constructs the stratified randomization table, which assigns each participant into blocks of 50 participants balanced by center, sex, and age group (<70 years and \geq 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 dietitians are directly responsible for the dietary and nutritional education intervention. They are registered dietitians, trained and certified to deliver the PREDIMED intervention protocol. Participants randomized to the control group have an interview with a PREDIMED dietitian, which includes: a) a simplified 14-item assessment questionnaire of adherence to the MeDiet (15), b) a leaflet with the written recommendations according to American Heart Association guidelines (21), and c) brief personal recommendations about how to follow this type of diet. For total fat intake, these recommendations are opposite to those given to participants in the 2 MeDiet groups. No further visits were scheduled for this group until the 12-month follow-up evaluation.

The intervention in the MeDiet groups is based on individual and group nutritional education. The individual motivational interview was administered quarterly and included both the 14-item questionnaire of adherence to the MeDiet and positive recommendations to follow this food pattern. The dietitian personalized the message by adapting it to the participant's clinical condition, preferences and beliefs. The general guidelines in the MeDiet group were: a) abundant use of olive oil for cooking and dressing dishes; b) consumption of \geq 2 servings of 125 g/d of vegetables (at least one of them as salad), without counting garnish c) \geq 3 serving of 125 g/d of fresh fruits (including natural juices); d) \geq 3 servings of 40 g/wk of legumes; e) \geq 3 servings of 150 g/wk of fish or seafood (at least 1 serving of fatty fish); f) \geq 3 servings of 25 g/wk of nuts or seeds; g) selected white meats (poultry without skin or rabbit) instead of red meats or processed meats (burgers, sausages); h) \geq 7 glasses/wk of wine if the participant is a wine consumer; i)

regularly cooking (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, industrial bakery products (sweet desserts, cakes, cookies, puddings, custard), French fries or potato chips, and out-of-home pre-cooked meals.

The quarterly group sessions with the MeDiet groups were run by the PREDIMED dietitians with up to 20 participants per session and separate sessions for each group. Each session consists of informative talks and provision of written material with elaborate descriptions of typical Mediterranean foods and seasonal shopping lists, meal plans, and cooking recipes. The participants also received free provision of typical Mediterranean fatty foods (virgin olive oil or mixed nuts). Depending on group assignment, participants were given 3-mo quantities of either virgin olive oil (1 L/wk) or mixed nuts (30 g/d, distributed as 15 g walnuts, 7.5 g almonds and 7.5 g hazelnuts). Throughout the study, all participants have free and continuous access to their center's dietitian for advice and consultation. At the 12-month visit and when consulted by participants, dietitians 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 1766 randomized participants who completed a food-frequency questionnaire (FFQ) at baseline, 1551 also completed the 12-month postrandomization FFQ and were included in the present analysis. The recruitment of these participants took place between July 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 dietitian in a face-to-face interview and included 2 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 to assess 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 (semi-quantitative assessment). Nine possibilities of frequency were offered from “never or less than once per month” to “ ≥ 6 times/d”. 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 twelve food groups: a) virgin olive oil, b) refined-mixed olive oil, c) total nuts, d) vegetables, e) cereals, f) legumes, g) fruits, h) fish or seafood, i) meat or meat products, j) pastries, cakes or sweets, k) dairy products, and l) alcohol.

Serum and anthropometric measurements

Trained personnel measured weight and height by using calibrated scales (TBF-300A Body Composition Analyzer/Scale, TANITA©, Tokyo, Japan, USA) 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. The blood pressure was measured in triplicate with a validated semi-automatic 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; HDL cholesterol level after precipitation with phosphotungstic acid and magnesium chloride. We performed all analyses in duplicate (18)

Biomarkers of compliance

Urinary (urine, 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 the 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 inter-assay CVs were 2.9 % and 3.8 % for tyrosol, and 5.7 % and 6.2% for hydroxytyrosol, respectively. Plasma fatty acids were performed on a Shimadzu GC-2010 Gas Chromatograph (Shimadzu, Kyoto, Japan) equipped with a flame ionization detector as described (25). Intra- and inter-assay CVs were 1.0 % and 1.8 % for oleic acid, and 3.2% and 3.9% for alfa-linolenic acid, respectively.

Statistical methods

Data were entered using optically scannable forms completed by the dietitians during their interviews with the participants. The completed forms were sent to the coordinator center and there they were first visibly examined to observe whether they were properly completed; failures to a proper completion have sporadically required to return the form to the corresponding center and rewriting a form, although usually forms were overmarked with a correct pencil to amend minor defects. We used descriptive statistics with means and SDs for participants' characteristics at baseline and 12-month after intervention. Participants whose baseline energy intake as estimated from the FFQs was outside pre-specified ranges (<500 kcal/d or >3,500 kcal/d for women and <800 kcal/d or >4,000 kcal/d for men) were excluded from the calculations (26). Within- and between-group differences are expressed as means and 95 % confidence intervals (CI). Within- and between-group changes were assessed with paired *t*-tests and ANOVA, respectively followed by the Dunnett post hoc test. All P values presented are 2-tailed; P<0.05 was considered statistically significant, unless otherwise specified. All analyses were performed using SPSS, version 13.0 (SPSS Inc, Chicago, Illinois).

RESULTS

The initial sample consisted initially of 1766 participants (643, 558 and 565 in the MeDiet plus olive oil, MeDiet 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 respectively 2507 and 2065. Among 299 non-eligible subjects, 148 did not meet inclusion criteria, 63 declined to participate, 38 could not change diet, 35 had chronic alcoholism, 9 had gastrointestinal disease and 6 had food allergies.

After excluding participants with baseline total energy intake outside the pre-specified 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 1551 of them (533, 533 and 485, in the MeDiet plus olive oil, MeDiet plus mixed nuts, and control groups, respectively). **Table 1** displays the baseline characteristics of the participants available at 12-month. The 3 groups were balanced with respect to demographic characteristics, cardiovascular risk factors, occupational status and educational level. The characteristics of participants in the 3 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 the following participants because their baseline values for total energy intake were outside the pre-specified limits: 9 in MeDiet plus virgin olive oil group, 9 in the MeDiet plus mixed nuts group, and 5 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 (>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 which deprive it of almost all its polyphenolic components (27).

After the 12-month intervention period, an increase of 3.25 servings/day of 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 MeDiet 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 2 groups assigned MeDiets. Participants in the 3 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 MeDiet score increased significantly in the participants included in the 2 MeDiet groups, while 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 MeDiet Score for both MeDiet groups versus the control group, and for decreased consumption of refined-mixed olive oil for MeDiet with olive oil versus the control group (**Table 2**).

Energy and nutrient intake

Table 3 shows the overall baseline and 12-month nutrient profiles for the 3 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 MeDiet 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 MUFA/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 (linoleic

acid and α -linolenic acid) and a decreased intake of total carbohydrate, saturated fatty acids (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 MeDiet group supplied with virgin olive oil, 12-month data showed that >20 percent of total energy intake was derived from its consumption and that 96 percent of the intake of MUFA corresponded to virgin olive oil.

Table 4 shows changes in the overall profile of nutrient intake for the 2 MeDiet groups when compared with the control group. Total energy intake decreased more in the control group than in the 2 MeDiet groups. PUFA increased significantly only in the group of mixed nuts and alpha-linolenic acid and n-3 long chain fatty acid intake also increased significantly in both intervention groups. Significant between-group differences for both MeDiet groups versus 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 2 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 MeDiet 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 BMI, 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 increased from baseline only in the group allocated to MeDiet 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 MeDiet plus mixed nuts also supports their adherence to walnut intake. The proportion 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, healthy 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 MeDiet 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 towards a healthier 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 the MeDiet.

We achieved only a modest reduction in total fat and SFA in the control group and similarly small increments in MUFA intake in the 2 MeDiet 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 over 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 food pattern, with high intakes of vegetables, fruits, fish, and olive oil and an average of 8 points out of a total of 14 points of adherence to the MeDiet. 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 nutritional counseling including 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 the present study, although small, were in the appropriate direction, and the proportion of participants who modified their dietary habits towards a healthier pattern was substantially greater in the 2 MeDiet groups than in the control group.

Our findings are consistent with previous dietary intervention studies. In trials of behavioral intervention to implement MeDiet conducted in non-Mediterranean populations (28, 32), the magnitude of observed changes was similar to that of our study. In the Diabetes Prevention Study (29), 47 % and 36 % of participants in the intervention and control group respectively, decreased their intake of total fat at 12-month. 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-month 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-month, 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-mo.

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 healthy foods is an added strength, as judged by objective indices 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 MeDiet groups. In spite of that, 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 a FFQ (38).

CONCLUSIONS AND APPLICATIONS

In conclusion, dietary changes after 12-month in the PREDIMED study indicate that the individual motivational interventions together with the group sessions and the free provision of high-fat and palatable key foods customary in the MeDiet were effective in improving the dietary habits of participants in this trial, who already followed a MeDiet in part. Dietary changes achieved after an intervention for 12-month were similar to those observed at 3-month, which led to substantial improvements in various surrogate markers of cardiovascular risk in the MeDiet 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 such beneficial dietary changes can be enhanced and if they are associated with a reduction in cardiovascular outcomes.

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Table 1. Baseline characteristics of participants in the three randomized groups.

	MeDiet with Virgin Olive Oil (n = 533)	MeDiet with Mixed Nuts (n = 533)	Control group (n = 485)
Age (year) [mean (SD) ^b]	67.2 (6.2) ^b	67.0 (5.6)	68.0 (6.1)
BMI ^a (kg/m ²) [mean (SD) ^b]	29.3 (3.5)	29.4 (3.4)	29.5 (3.6)
Gender [n (%) males]	246 (46.2)	272 (51.0)	205 (42.3)
Family history of CHD ^c [n (%)]	90 (16.9)	80 (15.0)	91 (18.8)
Overweight or obese (BMI \geq 25 kg/m ²) [n (%)]	486 (91.2)	488 (91.6)	438 (90.3)
Type 2 diabetes mellitus [n (%)]	272 (51.0)	253 (47.5)	232 (47.8)
Hypertension [n (%)]	420 (78.8)	407 (76.4)	390 (80.4)
Dyslipidemia [n (%)]	222 (41.7)	226 (42.4)	231 (47.6)
Current smokers [n (%)]	104 (19.5)	101 (19.0)	82 (16.9)
Total cholesterol level (mg/dL) ^d [mean (SD)]	219.7 (39.1)	214.4 (36.9)	217.2 (37.1)
HDL cholesterol level (mg/dL) ^d [mean (SD)]	54.8 (14.2)	54.8 (13.9)	54.8 (12.7)
LDL cholesterol level (mg/dL) ^d [mean (SD)]	136.8 (35.3)	132.3 (33.3)	134.3 (33.4)
Trygliceride level (mg/dL) ^e [mean (SD)]	141.3 (76.2)	137.8 (74.4)	141.7 (68.0)
Systolic BP (mm Hg) [mean (SD)]	155.1 (20.9)	156.3 (21.4)	155.9 (21.4)
Diastolic BP (mm Hg) [mean (SD)]	85.7 (10.5)	87.1 (11.1)	86.6 (11.1)
Occupation			
Worker [n (%)]	58 (10.9)	58 (10.9)	47 (9.7)
Housewife [n (%)]	165 (31.0)	160 (30.0)	160 (33.0)
Retired [n (%)]	302 (56.7)	309 (58.0)	269 (55.5)
Unemployed or unfit [n (%)]	8 (1.6)	6 (1.2)	9 (1.8)

Table 1 (continuation). Baseline characteristics of participants in the three randomized groups.

	MeDiet with Virgin Olive Oil (n = 533)	MeDiet with Mixed Nuts (n = 533)	Control group (n = 485)
Educational level			
None [n (%)]	6 (1.1)	3 (0.6)	7 (1.4)
Primary school [n (%)]	405 (76.0)	387 (72.6)	368 (75.9)
Secondary school [n (%)]	80 (15.0)	90 (16.9)	65 (13.4)
University [n (%)]	42 (7.9)	53 (9.9)	45 (9.3)

^a BMI = Body mass index;

^b SD = standard deviation;

^c CHD = coronary heart disease;

^d 1 mg/dL= 0.0259 mmol/L;

^e 1 mg/dL= 0.0113 mmol/L

Table 2. Mean Baseline values and changes after 12-month follow-up in the consumption of key food items and in the 14- Point Mediterranean Diet Score in the three randomized groups. Within group (95 % CI) changes and between-group changes for the 2 groups receiving the Mediterranean Diet intervention (versus the control group).

	Mean baseline			Within-group mean changes after 12-month			Between-group changes (differences vs.control)			
	MeDiet ^a with Virgin olive oil (n = 533)	MeDiet with Mixed Nuts (n = 533)	Control group (n = 485)	MeDiet with virgin olive oil (n = 533)	MeDiet with Mixed Nuts (n = 533)	Control group (n = 485)	MeDiet with virgin olive oil vs. Control group		MeDiet with mixed nuts vs. Control group	
	<i>Mean (standard deviation)</i>			<i>Mean (95% CI)</i>			<i>Mean (95% CI)</i>	<i>P value</i>	<i>Mean (95% CI)</i>	<i>P value</i>
Virgin olive oil (10 g) (s/d) ^b	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) (s/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) (s/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) (s/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) (s/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) (s/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, 0.014)	< 0.001
Fruits (125 g) (s/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

5 Table 2 (continuation). Mean Baseline values and changes after 12-month follow-up in the consumption of key food items and in the 14- Point Mediterranean Diet Score in the three randomized groups. Within group (95 % CI) changes and between-group changes for the 2 groups receiving the Mediterranean Diet intervention (versus the control group).

	Mean baseline			Within-group mean changes after 12-month			Between-group changes (differences vs.control)			
	MeDiet ^a with Virgin olive oil (n = 533)	MeDiet with Mixed Nuts (n = 533)	Control group (n = 485)	MeDiet with virgin olive oil (n = 533)	MeDiet with Mixed Nuts (n = 533)	Control group (n = 485)	MeDiet with virgin olive oil vs. Control group		MeDiet with mixed nuts vs. Control group	
	<i>Mean (standard deviation)</i>			<i>Mean (95% CI)</i>			<i>Mean (95% CI)</i>	<i>P value</i>	<i>Mean (95% CI)</i>	<i>P value</i>
Fish or seafood (125) (s/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) (s/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) (s/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) (s/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 MeDiet score ^c	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

NOTE: Of participants in the MeDiet with virgin olive oil, MeDiet with mixed nuts, and control groups, 9, 9 and 5 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 the Spanish population.

10 ^a MeDiet: Mediterranean diet;

^bs/d: serving/day;

^cThe range was 0 (minimum) to 14 (maximum) points.

Table 3. Mean nutrient intake at baseline and 12-month after randomization in the three groups randomized to the Mediterranean Diets (MeDiet) and in the control group.

	MeDiet with Virgin Olive Oil		MeDiet with Mixed Nuts		Control group	
	(n = 533)		(n = 533)		(n = 485)	
	Baseline	12-month	Baseline	12-month	Baseline	12-month
	<i>Mean (standard deviation)</i>		<i>Mean (standard deviation)</i>		<i>Mean (standard deviation)</i>	
Energy (kcal)	2291 (560)	2276 (516)	2320 (539)	2340 (480)	2210 (525)	2074 (492)
Total protein (% E ^a)	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 CH ^b (% E)	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 (% E)	38.9 (6.3)	40.7 (5.6)	39.9 (6.3)	42.7 (6.0)	39.0 (6.6)	38.0 (6.4)
SFA ^c (% E)	9.8 (2.2)	9.3 (1.8)	10.1 (2.1)	9.4 (1.9)	9.9 (2.3)	9.5 (2.2)
MUFA ^d (% E)	19.6 (4.2)	21.7 (3.7)	20.0 (4.2)	21.6 (3.9)	19.5 (4.4)	19.2 (4.1)
PUFA ^e (% E)	6.1 (2.1)	6.3 (1.5)	6.4 (2.1)	8.2 (2.3)	6.2 (2.0)	5.9 (2.0)
MUFA/ SFA (% E)	2.0 (0.5)	2.4 (0.5)	2.0 (0.5)	2.4 (0.5)	2.0 (0.5)	2.1 (0.5)

15 Table 3 (continued). Mean nutrient intake at baseline and 12-month after randomization in the three groups randomized to the Mediterranean Diets (MeDiet) and in the control group.

	MeDiet with Virgin Olive Oil				MeDiet with Mixed Nuts				Control group			
	(n = 533)								(n = 485)			
	Baseline		12-month		Baseline		12-month		Baseline		12-month	
	<i>Mean (standard deviation)</i>		<i>Mean (standard deviation)</i>		<i>Mean (standard deviation)</i>		<i>Mean (standard deviation)</i>		<i>Mean (standard deviation)</i>		<i>Mean (standard deviation)</i>	
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 (% E)	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 (% E)	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)

NOTE: Of participants in the MeDiet with virgin olive oil, MeDiet with mixed nuts, and control groups, 9, 9 and 5 participants, respectively,
20 were excluded from calculations of food intake because energy was outside the prespecified ranges;

^aE, energy intake;

^bCH, carbohydrates;

^cSFA, saturated fatty acids;

^dMUFA, monounsaturated fatty acids;

25 ^ePUFA, polyunsaturated fatty acids.

Table 4. Mean Baseline values and changes after 12-month follow-up in energy and nutrient intake in the three randomized groups. Within group (95 % CI) changes and between-group changes for the 2 groups receiving the Mediterranean Diet intervention (versus the control group).

	Within-group mean changes after 12-month			Between-group changes (differences vs. control)			
	MeDiet ^a with Virgin Olive Oil (n = 533)	MeDiet with mixed nuts (n = 533)	Control group (n = 485)	MeDiet with olive oil vs. Control group		MeDiet with mixed nuts vs. Control group	
	<i>Mean (95% CI)</i>			<i>Mean (95% CI)</i>	P value	<i>Mean (95% CI)</i>	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 (% E ^b)	-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 CH ^c (% E)	-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 (% E)	+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
SFA ^d (% E)	-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
MUFA ^e (% E)	+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
PUFA ^f (% E)	+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

Table 4 (continuation). Mean Baseline values and changes after 12-month follow-up in energy and nutrient intake in the three randomized groups.

Within group (95 % CI) changes and between-group changes for the 2 groups receiving the Mediterranean Diet intervention (versus the control group).

	Within-group mean changes after 12-month						Between-group changes (differences vs. control)					
	MeDiet with Virgin Olive Oil (n = 533)		MeDiet with mixed nuts (n=533)		Control group (n= 485)		MeDiet with olive oil vs. Control group			MeDiet with mixed nuts vs. Control group		
	<i>Mean (95% CI)</i>		<i>Mean (95% CI)</i>		<i>Mean (95% CI)</i>		<i>Mean (95% CI)</i>	P value	<i>Mean (95% CI)</i>	P value	<i>Mean (95% CI)</i>	P value
MUFA/ SFA (% E)	+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 (% E)	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 (% E)	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

NOTE: Of participants in the MeDiet with virgin olive oil, MeDiet with mixed nuts, and low-fat diet groups, 9, 9 and 5 participants, respectively, were excluded from calculations of energy and nutrient intake because reported energy was unrealistic.

^aMediet: Mediterranean diet;

^bE, energy intake;

35 ^cCH, carbohydrates;

^dSFA, saturated fatty acids;

^eMUFA, monounsaturated fatty acids;

^fPUFA, polyunsaturated fatty acids;

40 Table 5. Percentages of participants complying with the intended dietary changes and favorable changes in the risk factors during the first year in the 2 intervention groups and in the control group.

Variables	MeDiet ^a with Virgin Olive Oil	MeDiet with mixed nuts	Control group	<i>P value</i> ^b
<i>Percentage of participants</i>				
Decreased total fat intake	37.5	34.1	57.9	< 0.001
Increased MUFA ^c intake	69.0	63.4	44.3	< 0.001
Increased MUFA/SFA ^d ratio	77.3	75.6	54.8	< 0.001
Increased consumption of fruits	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 BMI ^e	37.7	40.9	41.2	0.464

Table 5 (continuation). Percentages of participants complying with the intended dietary changes and favorable changes in the risk factors during the first year in the 2 intervention groups and in the control group.

Variables	MeDiet ^a with Virgin Olive Oil	MeDiet with mixed nuts	Control group	<i>P value</i> ^b
<i>Percentage of participants</i>				
Decreased total cholesterol level	51.5	57.3	53.8	0.452
Decreased LDL- cholesterol level *	45.5	47.7	35.8	< 0.001
Decreased LDL- cholesterol/ HDL- cholesterol level *	50.6	49.2	35.8	< 0.001
Decreased Triglyceride level *	43.2	49.2	32.7	< 0.001
Decreased Systolic BP *	58.0	59.3	36.6	< 0.001
Decreased Diastolic BP *	49.8	51.6	43.2	< 0.001

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^a MeDiet: Mediterranean Diet;

^b P values were determined by the chi-square test for the difference between the groups;

^c MUFA, monounsaturated fatty acids;

^dSFA, saturated fatty acids;

50 ^eBMI = Body mass index

* The changes in these risk factors were observed in the pilot study of PREDIMED, 3-month after intervention. They are expressed here as percentages to avoid duplication of the published results (Ann Intern Med 2006;145:1-11).

Table 6. Biochemical markers of compliance: tyrosol and hydroxytyrosol concentrations in urine at baseline and 12-month after randomization

Group	Tyrosol (µg/L)			Hydroxytyrosol (µg/L)		
	Baseline	12-month	<i>P</i> value	Baseline	12-month	<i>P</i> value
	<i>Mean (standard deviation)</i>			<i>Mean (standard deviation)</i>		
MeDiet ^a 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
MeDiet 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

55 ^a MeDiet: Mediterranean Diet

Table 7. Biochemical markers of compliance: oleic acid and α -linolenic acid concentrations in plasma at baseline and 12-month after randomization

Group	Oleic acid (% total fatty acids)			α -linolenic acid (% total fatty acids)		
	Baseline	12-month	<i>P</i>	Baseline	12-month	<i>P</i>
	<i>Mean (standard deviation)</i>		<i>P value</i>	<i>Mean (standard deviation)</i>		<i>P value</i>
MeDiet ^a 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
MeDiet 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

60 ^a MeDiet: Mediterranean Diet

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