Prevention of Diabetes With Mediterranean Diets

A Subgroup Analysis of a Randomized Trial

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Background: Interventions promoting weight loss can reduce the incidence of type 2 diabetes mellitus. Whether dietary changes without calorie restriction also protect from diabetes has not been evaluated.

Objective: To assess the efficacy of Mediterranean diets for the primary prevention of diabetes in the Prevención con Dieta Mediterránea trial, from October 2003 to December 2010 (median follow-up, 4.1 years).

Design: Subgroup analysis of a multicenter, randomized trial. (Current Controlled Trials: ISRCTN35739639)

Setting: Primary care centers in Spain.

Participants: Men and women without diabetes (3541 patients aged 55 to 80 years) at high cardiovascular risk.

Intervention: Participants were randomly assigned and stratified by site, sex, and age but not diabetes status to receive 1 of 3 diets: Mediterranean diet supplemented with extra-virgin olive oil (EVOO), Mediterranean diet supplemented with mixed nuts, or a control diet (advice on a low-fat diet). No intervention to increase physical activity or lose weight was included.

Results: During follow-up, 80, 92, and 101 new-onset cases of diabetes occurred in the Mediterranean diet supplemented with EVOO, Mediterranean diet supplemented with mixed nuts, and control diet groups, respectively, corresponding to rates of 16.0, 18.7, and 23.6 cases per 1000 person-years. Multivariate-adjusted hazard ratios were 0.60 (95% CI, 0.43 to 0.85) for the Mediterranean diet supplemented with EVOO and 0.82 (CI, 0.61 to 1.10) for the Mediterranean diet supplemented with nuts compared with the control diet.

Limitations: Randomization was not stratified by diabetes status. Withdrawals were greater in the control group.

Conclusion: A Mediterranean diet enriched with EVOO but without energy restrictions reduced diabetes risk among persons with high cardiovascular risk.

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ype 2 diabetes mellitus represents a major health problem because worldwide prevalence has more than doubled in the past 3 decades, with nearly 347 million persons with diabetes in 2010 (1), and is a potent risk factor for cardiovascular disease (CVD), blindness, renal failure, and lower limb amputation (2).

Compelling evidence shows that diabetes can be prevented with lifestyle changes. Intensive lifestyle modification promoting weight loss through energy-restricted diets together with increased physical activity can decrease incident diabetes to as low as 50% (3). Indeed, lifestyle modification has performed better than pharmacologic approaches (such as metformin or rosiglitazone) in diabetes prevention (4–6). Of interest, the benefit of lifestyle changes in decreasing diabetes risk seems to extend beyond the termination of active intervention (6–8). However, there is little information on whether changes in the overall dietary pattern, without energy restriction, increased physical activity, and ensuing weight loss, may also be effective to prevent diabetes.

Prospective epidemiologic studies strongly suggest that dietary patterns characterized by high consumption of fruit, vegetables, whole grains, and fish and reduced consumption of red and processed meat, sugar-sweetened beverages, and starchy foods delay diabetes onset (9). In the last 6 years, the traditional Mediterranean diet has emerged as a healthy dietary pattern that is also associated with a decreased risk for diabetes (10–12). The Mediterranean diet is moderately rich in fat (35% to 40% of energy), especially from vegetable sources (rich in olive oil and nuts), and relatively low in dairy products. Moderate consumption of alcohol, mostly wine, and frequent use of sauces with tomato, onions, garlic, and spices for meal preparation are also typical.

Preliminary data from the PREDIMED (Prevención con Dieta Mediterránea) study (13–17) showed that traditional Mediterranean diets enriched with high-fat foods of vegetable origin decreased the incidence of diabetes (18). However, that report studied participants only from 1 of

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the 11 PREDIMED recruiting centers. In this analysis, we provide the final results on diabetes incidence in the whole multicenter trial after a median follow-up of 4.1 years.

**Methods**

**Design Overview**

The PREDIMED study is a parallel-group, randomized, primary cardiovascular prevention trial done in Spain in persons at high risk but without CVD at baseline. The protocol, design, objectives, and methods have been reported in detail elsewhere (13, 14). Briefly, participants were randomly assigned in a 1:1:1 ratio to 1 of 3 nutrition interventions: Mediterranean diet supplemented with extra-virgin olive oil (EVOO), Mediterranean diet supplemented with mixed nuts, or a control diet consisting of advice to reduce intake of all types of fat.

A complete list of PREDIMED study investigators is available in Supplement 1 (available at www.annals.org). The local institutional review boards approved the protocol at each study location, and all participants provided written informed consent.

**Setting and Participants**

Eligible participants were community-dwelling men (aged 55 to 80 years) and women (aged 60 to 80 years) without CVD at baseline who had either type 2 diabetes or at least 3 or more cardiovascular risk factors, namely current smoking, hypertension, hypercholesterolemia, low high-density lipoprotein cholesterol levels, overweight or obesity, and family history of premature CVD. Exclusion criteria have previously been reported (13).

**Randomization and Intervention**

From October 2003 to June 2009, 7447 suitable candidates were enrolled in the trial. The study nurse from each recruiting center randomly assigned each participant to the corresponding intervention group following computer-generated random numbers for allocation contained in sealed envelopes, which were centrally prepared for each center by the coordinating unit. Four strata of randomization were built by sex and age (cutoff, 70 years) but not by baseline diabetes status. The primary care physicians did not participate in the randomization process. The study nurses were independent of the nursing staff of the primary care health centers. Therefore, they were not involved in the usual clinical care of participants, and their exclusive role was to collect data for the trial. Given the nature of the interventions (nutritional advice and provision of foods), only investigators assessing outcomes were blinded with respect to intervention assignment. This was done by providing them with coded data sets and medical records blinded with respect to the personal identity of the participant and without any information on treatment allocation.

Because our main objective was to determine the effect of the 3 interventions on diabetes incidence, this report includes data only on participants who did not have diabetes at baseline and for whom we could ascertain the incidence of diabetes during follow-up (n = 3541) (Figure 1).

A behavioral intervention promoting the Mediterranean diet was implemented in the corresponding groups of the trial, as described (13). Dietitians gave personalized advice to participants about the amount and use of EVOO for cooking and dressing; weekly intake of nuts; increased consumption of vegetables, fruits, legumes, and fish; recommended intake of white meat instead of red or processed meat; avoidance of butter, fast food, sweets, pastries, or sugar-sweetened beverages; and the dressing of dishes with “sofrito” sauce (using tomato, garlic, onion, and spices simmered in olive oil). Reduction of alcoholic beverages other than wine was advised to all participants. Wine with meals was recommended with moderation only to habitual drinkers.

At baseline and quarterly thereafter, dietitians conducted individual and group dietary training sessions to provide information on typical Mediterranean foods, seasonal shopping lists, meal plans, and recipes for each group. In each session, a 14-item questionnaire was used to assess adherence to the Mediterranean diet (13, 14) so that personalized advice could be provided to upgrade participants’ adherence. The same questionnaire was assessed yearly in the control group. Participants assigned to the 2 Mediterranean diet groups received allotments of either EVOO (50 mL/d) or mixed nuts (30 g/d: 15 g of walnuts, 7.5 g of almonds, and 7.5 g of hazelnuts) at no cost. Participants assigned to the control diet received recommendations to reduce intake of all types of fat (from both animal and vegetable sources) and received nonfood gifts (kitchenware, tableware, aprons, or shopping bags). Through October 2006, participants in the control group received only a leaflet describing the low-fat diet.
Thereafter, participants assigned to the control diet also received personalized advice and were invited to group sessions with the same frequency and intensity as those in the Mediterranean diet groups. A separate 9-item dietary questionnaire (14) was used to assess adherence to the low-fat diet. Neither energy restriction nor increased physical activity was advised for any intervention group.

At baseline examination and yearly during follow-up, we administered a 137-item validated semiquantitative food-frequency questionnaire (19); the validated Spanish version of the Minnesota Leisure-time Physical Activity Questionnaire (20); and a 47-item questionnaire about education, lifestyle, medical history, and medication use.

At baseline, trained personnel performed electrocardiography and anthropometric and blood pressure measurements. Blood pressure was measured in triplicate by using a validated semiautomatic oscillometer with a 5-minute interval between measurements and the participant in a sitting position (Omron HEM-705CP, Omron, Hoofddorp, the Netherlands).

Fasting blood and spot urine were sampled at baseline and follow-up years 1, 3, 5, and 7. After an overnight fast, tubes for EDTA plasma, citrate plasma, and serum and urine samples were collected and aliquots were coded and stored at −80 °C in the central laboratory until analysis. Serum glucose, cholesterol, and triglyceride levels were measured using standard enzymatic methods. High-density lipoprotein cholesterol was measured after precipitation with phosphotungstic acid and magnesium chloride. Biomarkers of adherence to the supplemental foods, including urine hydroxytyrosol levels and plasma α-linolenic acid proportions, which are reliable biomarkers of EVOO and walnut intake, respectively, were measured in random subsamples of participants during the first 5 years of follow-up (by gas chromatography–mass spectrometry and by gas chromatography, respectively). Laboratory technicians were blinded to intervention group.

**Figure 1. Study flow diagram.**

EVOO = extra-virgin olive oil; MedDiet = Mediterranean diet.
Outcomes and Follow-up

Diabetes was a prespecified secondary outcome of the PREDIMED trial. It was considered to be present at baseline by clinical diagnosis or use of antidiabetic medication. New-onset diabetes during follow-up was diagnosed using the American Diabetes Association criteria, namely fasting plasma glucose levels of 7.0 mmol/L or greater (≥126.1 mg/dL) or 2-hour plasma glucose levels of 11.1 mmol/L or greater (≥200.0 mg/dL) after a 75-g oral glucose load. A review of all medical records of participants was completed yearly in each center by physician-investigators who were blinded to the intervention. When new-onset diabetes cases were identified on the basis of a medical diagnosis reported in the medical charts or on a glucose test during routine biochemical analyses (done at least once per year), these reports were sent to the PREDIMED Clinical Events Committee, whose members were also blinded to treatment allocation. Only when a second test using the same criteria and repeated within the next 3 months was available and confirmed the new diabetes case, the end point was definitively confirmed by the adjudication committee. Only confirmed diabetes events that occurred between 1 October 2003 and 1 December 2010 were included in the analyses.

Statistical Analysis

Sample size estimation (using sampsi in Stata, version 12.1, StataCorp, College Station, Texas) for the main PREDIMED trial on cardiovascular events was calculated as 7400 participants, with the assumption of a 6-year follow-up and underlying CVD event rates of 8.8% and 6.6% in the control and intervention groups, respectively. This was the estimate after a change introduced in April 2008 (14). For the subgroup analysis of diabetes incidence, with sample sizes of 1130 participants per group, we could obtain a statistical power greater than 90% under the following assumptions: 2-tailed α is 0.05, and expected proportions of new diabetes cases were 11% and 7% in the control and intervention groups, respectively (expected relative risk, 0.64).

Primary analyses were conducted for all randomly assigned participants without diabetes having follow-up assessments of glucose control (at least 1 assessment was needed), regardless of their adherence to the dietary intervention. Cox regression models (stset, stcox) were fitted to assess hazard ratios (HRs) for diabetes for the 2 Mediterranean diet groups in comparison with the control group. A crude age- and sex-adjusted model and 2 multivariate models with successive degrees of adjustment were fitted: Model A was adjusted for age, sex, and baseline body mass index (kg/m²); and model B was further adjusted for baseline smoking (never, current, or former smoker), fasting glucose level, presence of dyslipidemia (yes/no) or hypertension (yes/no), total energy intake level (kcal/d, continuous), adherence to Mediterranean diet (14-point score, continuous), physical activity level (metabolic equivalent of min/d, continuous), educational level (3 categories), and alcohol intake level (continuous in g/d, adding a quadratic term). All models were stratified by recruitment center and robust SEs (vce(robust)) were used. For the primary analysis of diabetes incidence, the time variable was the interval between randomization and the date of diabetes diagnosis or the date of the last visit for participants who were free of diabetes at the end of the study or when they were lost to follow-up. If a participant died after the last follow-up visit and had not been diagnosed with diabetes, the date of the death was used. For the analyses with death as a competing event for diabetes onset, the time variable was the interval between randomization and the date of diabetes diagnosis or date of death (if diabetes-free). For living participants who did not have diabetes, we used the date of the last visit. We repeated all analyses after merging the 2 Mediterranean diet groups into a single category for comparison with the control group.

Incidence curves (Nelson–Aalen) (sts graph, na) were plotted to estimate cumulative incidence of diabetes (and alternatively, either diabetes or death to take into account competing risks) by group allocation. Prespecified subgroup analyses were conducted within strata of sex and baseline age, dyslipidemia, smoking, family history of premature CVD, body mass index, waist, waist–height ratio, and adherence to the Mediterranean diet. Sensitivity analyses were conducted with multiple imputation (mi) procedures for missing values (including participants who lacked repeated measurements of glucose control during follow-up). We explain further details of the multiple imputation procedure in Supplement 2 (available at www.annals.org).

We applied marginal structural models with inverse probability weighting (21, 22), using the variables with small between-group imbalances to compute the weights (we computed the stabilized weights using logit, the postestimation command predict, and then generate). The weighted analyses were run with the option vce(robust). We also separately assessed persons who participated in the study before and after we changed the frequency and intensity of the contacts with the control group. All P values are 2-tailed at less than 0.050. Analyses were done using SPSS, version 19 (SPSS, Chicago, Illinois), and Stata, version 12.1.

Role of the Funding Source

This study was funded by the Spanish government’s Instituto de Salud Carlos III. The funding source had no role in the trial design, data analysis, reporting of the results, or decision to submit the manuscript for publication.

RESULTS

Among 7447 participants enrolled in the PREDIMED trial, 3833 did not have diabetes at baseline and 3541 had available information during follow-up to allow ascertainment of new cases of diabetes (Figure 1). A total of 252 participants had been lost to follow-up for 2 or more years.
(4.1% in the Mediterranean diet supplemented with EVOO group, 6.9% in the Mediterranean diet supplemented with mixed nuts group, and 10.5% in the control diet group). Compared with participants who remained in the trial, those who withdrew were younger (by 1.0 year) and had a greater body mass index (by 0.5 kg/m²), greater waist circumference (by 2.7 cm), and lower adherence to the Mediterranean diet (by 0.44 points in a range of 0 to 14) ($P < 0.050$ for all comparisons). Clinical characteristics at baseline by study group were similar (Table 1).

During follow-up (median, 4.1 years; interquartile range, 2.5 to 5.7 years), mean scores of adherence to the Mediterranean diet increased in both Mediterranean diet groups and were greater than in the control group ($P < 0.010$ for all yearly comparisons) (Figure of Supplement 3, available at www.annals.org). Also, the percentage of persons with a Mediterranean diet score of 10 or greater

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Table 1. Baseline Characteristics of the Study Population*

<table>
<thead>
<tr>
<th>Variable</th>
<th>MedDiet + EVOO Group (n = 1154)</th>
<th>MedDiet + Nuts Group (n = 1240)</th>
<th>Control Group (n = 1147)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age (SD), y</td>
<td>66.5 (6.0)</td>
<td>66.2 (6.0)</td>
<td>67.2 (6.1)</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>439 (38.0)</td>
<td>506 (40.8)</td>
<td>401 (35.0)</td>
</tr>
<tr>
<td>Female</td>
<td>715 (62.0)</td>
<td>734 (59.2)</td>
<td>746 (65.0)</td>
</tr>
<tr>
<td>Mean BMI (SD), kg/m²</td>
<td>30.10 (3.59)</td>
<td>29.78 (3.60)</td>
<td>30.17 (3.62)</td>
</tr>
<tr>
<td>Mean weight (SD), kg</td>
<td>76.71 (11.74)</td>
<td>76.37 (11.80)</td>
<td>76.37 (11.30)</td>
</tr>
<tr>
<td>Mean waist circumference (SD), cm</td>
<td>99.44 (10.08)</td>
<td>99.60 (10.58)</td>
<td>99.91 (10.23)</td>
</tr>
<tr>
<td>Mean waist-height ratio (SD)</td>
<td>0.62 (0.06)</td>
<td>0.62 (0.06)</td>
<td>0.63 (0.06)</td>
</tr>
<tr>
<td>Tobacco use†</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never smoker</td>
<td>715 (62.0)</td>
<td>762 (61.5)</td>
<td>723 (63.0)</td>
</tr>
<tr>
<td>Current smoker</td>
<td>180 (15.6)</td>
<td>205 (16.5)</td>
<td>181 (15.8)</td>
</tr>
<tr>
<td>Former smoker</td>
<td>259 (22.4)</td>
<td>273 (22.0)</td>
<td>243 (21.2)</td>
</tr>
<tr>
<td>Married status</td>
<td>883 (76.5)</td>
<td>957 (77.2)</td>
<td>854 (74.4)</td>
</tr>
<tr>
<td>Education level</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary education</td>
<td>875 (75.8)</td>
<td>903 (72.8)</td>
<td>904 (78.8)</td>
</tr>
<tr>
<td>Secondary education</td>
<td>185 (16.0)</td>
<td>217 (17.5)</td>
<td>168 (14.6)</td>
</tr>
<tr>
<td>Academic/graduate</td>
<td>94 (8.1)</td>
<td>120 (9.7)</td>
<td>75 (6.5)</td>
</tr>
<tr>
<td>Overweight/obesity‡</td>
<td>1092 (94.6)</td>
<td>1172 (94.5)</td>
<td>1097 (95.6)</td>
</tr>
<tr>
<td>Hypertension§</td>
<td>1037 (90.0)</td>
<td>1118 (90.2)</td>
<td>1060 (92.4)</td>
</tr>
<tr>
<td>Dyslipidemia†</td>
<td>593 (51.4)</td>
<td>672 (54.2)</td>
<td>606 (52.8)</td>
</tr>
<tr>
<td>Medication use</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antihypertensive agents</td>
<td>882 (76.4)</td>
<td>942 (76.0)</td>
<td>900 (78.5)</td>
</tr>
<tr>
<td>Statins or other hypolipidemic drugs</td>
<td>549 (47.6)</td>
<td>633 (51.0)</td>
<td>571 (49.8)</td>
</tr>
<tr>
<td>Mean blood biomarker level (SD)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fasting glucose</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>mmol/L</td>
<td>5.46 (0.95)</td>
<td>5.44 (0.85)</td>
<td>5.45 (0.85)</td>
</tr>
<tr>
<td>mg/dL</td>
<td>98.38 (17.12)</td>
<td>98.02 (15.32)</td>
<td>98.20 (15.32)</td>
</tr>
<tr>
<td>Total cholesterol</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>mmol/L</td>
<td>5.76 (1.12)</td>
<td>5.67 (0.94)</td>
<td>5.67 (1.04)</td>
</tr>
<tr>
<td>mg/dL</td>
<td>223.94 (43.24)</td>
<td>218.39 (36.29)</td>
<td>218.92 (40.15)</td>
</tr>
<tr>
<td>HDL cholesterol</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>mmol/L</td>
<td>1.45 (0.36)</td>
<td>1.45 (0.37)</td>
<td>1.43 (0.37)</td>
</tr>
<tr>
<td>mg/dL</td>
<td>55.98 (13.90)</td>
<td>55.98 (14.29)</td>
<td>55.21 (14.29)</td>
</tr>
<tr>
<td>LDL cholesterol</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>mmol/L</td>
<td>3.64 (1.02)</td>
<td>3.53 (0.85)</td>
<td>3.56 (0.93)</td>
</tr>
<tr>
<td>mg/dL</td>
<td>140.54 (39.38)</td>
<td>123.51 (32.82)</td>
<td>137.45 (35.91)</td>
</tr>
<tr>
<td>Triglycerides</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>mmol/L</td>
<td>1.46 (0.84)</td>
<td>1.50 (0.84)</td>
<td>1.53 (0.79)</td>
</tr>
<tr>
<td>mg/dL</td>
<td>129.20 (74.34)</td>
<td>132.74 (74.34)</td>
<td>135.40 (69.91)</td>
</tr>
<tr>
<td>Non-HDL cholesterol</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>mmol/L</td>
<td>4.30 (1.08)</td>
<td>4.21 (0.89)</td>
<td>4.24 (1.00)</td>
</tr>
<tr>
<td>mg/dL</td>
<td>166.02 (41.70)</td>
<td>162.55 (34.36)</td>
<td>163.71 (38.61)</td>
</tr>
<tr>
<td>Mean leisure-time physical activity level (SD), MET min/d</td>
<td>235.02 (221.36)</td>
<td>241.55 (234.63)</td>
<td>217.3 (213.22)</td>
</tr>
<tr>
<td>Mean total energy intake level (SD), kcal/d</td>
<td>2327 (589)</td>
<td>2339 (588)</td>
<td>2222 (567)</td>
</tr>
<tr>
<td>Mean MedDiet adherence score (SD)</td>
<td>8.77 (1.91)</td>
<td>8.80 (1.88)</td>
<td>8.40 (1.92)</td>
</tr>
</tbody>
</table>

BMI = body mass index; EVOO = extra-virgin olive oil; HDL = high-density lipoprotein; LDL = low-density lipoprotein; MedDiet = Mediterranean diet; MET = metabolic equivalent.
* Values are numbers (percentages) unless otherwise indicated. Characteristics are for all participants without diabetes (n = 3541).
† Current smoker was defined as $\geq 1$ cigarette, cigar, or pipe per day. Former smoker was defined as no smoking for $\geq 1$ y.
‡ Overweight was defined as BMI $\geq 25$ kg/m² and obesity as BMI $\geq 30$ kg/m².
§ Systolic blood pressure $\geq 140$ mm Hg, diastolic blood pressure $\geq 90$ mm Hg, or use of antihypertensive agents.
‖ LDL cholesterol levels $>4.14$ mmol/L ($>158.30$ mg/dL), HDL cholesterol levels $\leq 1.03$ mmol/L ($\leq 39.77$ mg/dL) in men or $\leq 1.29$ mmol/L ($\leq 49.81$ mg/dL) in women, or use of lipid-lowering therapy.

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was higher in both Mediterranean diet groups than in the control group ($P < 0.010$ for all yearly comparisons) (Table 1 of Supplement 3). During follow-up, a better achievement in 9 of the 14 items of the questionnaire measuring adherence to the Mediterranean diet was seen among persons in both Mediterranean diet groups than in the control group (Table 2 in Supplement 3).

Participants adhered to the supplemental foods, as shown by objective biomarkers measured in a small random sample during follow-up (Table 3 in Supplement 3). Urinary hydroxytyrosol levels increased from baseline among participants on the Mediterranean diet supplemented with EVOO ($P < 0.050$ at 3-year follow-up), and plasma α-linolenic acid levels increased in participants on the Mediterranean diet supplemented with mixed nuts ($P < 0.050$ at 3-year follow-up). No changes in these biomarkers occurred in the control group. The main nutrient changes in the Mediterranean diet groups reflected the fat content and composition of the supplemental foods (Table 4 in Supplement 3). Changes in body weight, waist circumference, and physical activity were minor and did not differ by study group (Table 5 in Supplement 3). Likewise, on-trial changes in medications that may influence development of diabetes, such as antihypertensives, statins, antiepileptic drugs, corticoids, or estrogens, were similarly distributed among the groups (Table 6 in Supplement 3).

During follow-up, 273 participants developed new-onset diabetes: 80 in the Mediterranean diet supplemented with EVOO group (6.9%), 92 in the Mediterranean diet supplemented with mixed nuts group (7.4%), and 101 in the control group (8.8%) (Table 2). Compared with those in the control group, unadjusted HRs for diabetes were 0.69 (95% CI, 0.51 to 0.92) for the Mediterranean diet supplemented with EVOO group and 0.81 (CI, 0.61 to 1.08) for the Mediterranean diet supplemented with mixed nuts group (Table 3). After adjustment for potential confounders, HRs for diabetes were 0.60 (CI, 0.43 to 0.85) for the Mediterranean diet supplemented with EVOO group and 0.82 (CI, 0.61 to 1.10) for the Mediterranean diet supplemented with mixed nuts group compared with the control group. When both Mediterranean diet groups were merged, a 30% relative risk reduction versus control was apparent (HR, 0.70 [CI, 0.54 to 0.92]). Figure 2 shows the cumulative incidence of diabetes and either diabetes or death. After adjustment for potential confounders, the HRs for diabetes and death were 0.70 (CI, 0.52 to 0.94) for the Mediterranean diet supplemented with EVOO group and 0.80 (CI, 0.59 to 1.06) for the Mediterranean diet supplemented with mixed nuts group compared with the control group.

Results were consistent among subgroups of sex, age, presence of comorbid conditions, smoking status, family history of CVD, and several indices of adiposity (Table 7 of Supplement 3). Sensitivity analyses included multiple imputations for participants without contact for 2 years or longer and for those who lacked repeated measurements of glucose control. The results (Table 8 of Supplement 3) were consistent with the findings of the primary analysis.
with relative risk estimates of 0.70 (CI, 0.52 to 0.94) for those on the Mediterranean diet supplemented with EVOO and 0.82 (CI, 0.62 to 1.09) for those on the Mediterranean diet supplemented with mixed nuts. When we imputed the outcome (diabetes onset) to all participants without contact for 2 years or longer plus those who lacked repeated measurements of glucose control, the estimates were 0.74 (CI, 0.55 to 0.99) and 0.86 (CI, 0.56 to 1.31), respectively.

**DISCUSSION**

We found that a long-term intervention with a high-quality dietary pattern akin to the traditional Mediterranean diet reduces the risk of diabetes onset.
nean diet and rich in EVOO could reduce the incidence of diabetes in older persons at high cardiovascular risk. This beneficial effect was mainly due to the overall composition of the dietary pattern, and not to calorie restriction, increased physical activity, or weight loss because such lifestyle changes were not part of the intervention and between-group changes were negligible. After a median 4.1-year follow-up, a statistically significant 40% relative risk reduction and a nonsignificant 18% risk reduction in diabetes risk was seen in the Mediterranean diet groups supplemented with EVOO and mixed nuts, respectively, in comparison with the control diet group.

The main focus of the intervention in the PREDIMED trial was to change the overall dietary pattern instead of focusing on changes in single macronutrients or micronutrients. Given that there were no specific restrictions on energy intake or counsel to increase physical activity for any study group, the observed benefit is likely attributable to the Mediterranean diet plus the supplementary foods given for free. Compared with participants in the control diet group, changes in objective biomarkers measured in a small, random sample indicated good adherence to the supplemental foods. Moreover, the 2 Mediterranean diet groups, but not the control diet group, increased adherence to the Mediterranean diet, as assessed by the 14-item Mediterranean diet screener. In fact, we saw better achievements in 9 of the 14 items of the questionnaire measuring adherence to the Mediterranean diet among persons in both Mediterranean diet groups than in the control group. Therefore, the PREDIMED interventions resulted in differences in the overall dietary pattern between the Mediterranean diet and control groups. These differences were probably critical to the dissimilar rates of incident diabetes seen by treatment allocation.

In a previous single-center PREDIMED publication (18), which was based on only 55 incident cases, we reported a protection by Mediterranean diets against diabetes. The present assessment with a considerably larger sample size provides stronger evidence. However, in our previous report (18), both Mediterranean diets afforded similar protection against diabetes. Here, we found a protective effect by the Mediterranean diet supplemented with EVOO but only a marginal effect for the Mediterranean diet supplemented with mixed nuts. The dissimilar benefit of the 2 Mediterranean diet interventions may be a chance finding because both EVOO and nuts contributed an extra load of unsaturated fatty acids that have been related to decreased diabetes risk (23). The Mediterranean diet pattern includes other dietary components reported to be beneficial in alleviating inflammation, oxidative stress, and insulin resistance and secretion, which are pathogenic factors in diabetes that add biological plausibility to the present results. For example, many vegetables, fruits, and seeds, such as cereals and legumes, contain minerals, polyphenols, and other phytochemicals that combat oxidative stress, inflammation, and insulin resistance (24, 25). Both EVOO and nuts exhibit potent anti-inflammatory (26) and antioxidant effects (27). Indeed, the PREDIMED Mediterranean diets have shown the same effects (28, 29). Many Mediterranean diet constituents are likely to be beneficial in terms of glucose metabolism, decreasing diabetes risk, as reviewed (30). Epidemiologic studies have suggested that greater adherence to the Mediterranean diet is associated with lower risk for abnormal glucose homeostasis (31, 32) and diabetes (10–12). Moreover, a recent systematic review of clinical trials reported that better adherence to the Mediterranean diet was associated with lower fasting glucose levels or insulin resistance compared with control diets (33), thus potentially decreasing diabetes risk.

Our study has limitations. First, diabetes incidence was a secondary end point, not the primary end point of the PREDIMED trial, and this was a secondary analysis conducted in the subgroup of persons without diabetes, making these analyses exploratory in nature. However, there are no reasons to believe that the randomization would not have worked in such a large subset of participants. Second, the study sample consisted of older white persons at high risk for coronary heart disease, which limits the generalizability of our results to other age groups or ethnicities. Third, we had greater losses during follow-up in the control group, but participants who withdrew had a worse cardiovascular risk profile at baseline than those who remained in the study, suggesting a bias toward benefit in the control group. Fourth, participants and study personnel were aware of group allocation because blinding is rarely feasible in feeding trials, but new-onset diabetes was ascertained by PREDIMED medical investigators and confirmed by the adjudication committee, and both were blinded to the intervention. Finally, we cannot discard measurement errors affecting physical activity and alcohol intake during follow-up.

The study also has strengths, such as its randomized design, which resulted in treatment groups being well-balanced for potential sources of confounding and being able to provide first-line evidence to support a causal association. This is a considerable advantage over previous studies assessing the association between high-quality dietary scores and diabetes incidence used in observational designs. Other strengths include the relatively long follow-up, control for many potential confounding variables, and inclusion of sensitivity analyses.

In conclusion, the PREDIMED trial provides strong evidence that long-term adherence to a Mediterranean diet supplemented with EVOO without energy restrictions, which is high in monounsaturated fat and bioactive polyphenols, results in a substantial reduction in the risk for type 2 diabetes among older persons with high cardiovascular risk. Of note, this dietary pattern is palatable and has a high potential for long-term sustainability, with obvious public health implications for primary prevention of diabetes.
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