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Reduction in the Incidence of Type 2-Diabetes with the Mediterranean Diet: Results of the PREDIMED-Reus Nutrition Intervention Randomized Trial

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Short running title: Mediterranean Diet and diabetes incidence

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Objective - To test the effects of two Mediterranean-diet interventions versus a low-fat diet on incidence of diabetes.

Research Design and Methods - Three-arm randomized trial in 418 nondiabetic subjects aged 55-80 years recruited in one center (PREDIMED-Reus, North-Eastern Spain) of the PREDIMED study, a large nutrition-intervention trial for primary cardiovascular prevention in persons at high cardiovascular risk. Participants were randomized to education on a low-fat diet (control group) or one of two Mediterranean diets, supplemented with either free virgin olive oil (1 liter/week) or nuts (30 g/day). Diets were *ad libitum* and no advice on physical activity was given. The main outcome was diabetes incidence diagnosed by the 2009 American Diabetes Association criteria.

Results - After a median follow-up of 4.0 years, diabetes incidence was 10.1% (95% confidence interval [CI], 5.1-15.1), 11.0% (5.9-16.1), and 17.9% (11.4-24.4) in the Mediterranean-diet with olive oil group, the Mediterranean-diet with nuts group, and the control group, respectively. Multivariable-adjusted hazard ratios of diabetes were 0.49 (0.25-0.97) and 0.48 (0.24-0.96) in the Mediterranean-diet groups supplemented with olive oil and nuts, respectively, compared to the control group. When pooling the two Mediterranean-diet groups compared to the control group, diabetes incidence was reduced by 52% (27-86). In all study arms, increased adherence to the Mediterranean-diet was inversely associated with diabetes incidence. Diabetes risk reduction occurred in the absence of significant changes in body weight or physical activity.

Conclusion - Mediterranean diets without calorie restriction appear to be effective in the prevention of diabetes in subjects at high cardiovascular risk.

Trial Registration**:** www.controlled-trials.com Identifier: ISRCTN35739639

The increasing incidence of type-2 diabetes throughout the world, closely linked to westernized dietary patterns, physical inactivity, and raising rates of obesity, is a challenging health problem. Lifestyle changes are effective measures to prevent diabetes and weight loss is the main predictor of success (1). Five clinical trials that examined the effects of reputedly healthy, energy-restricted diets together with increased physical activity in persons with impaired glucose tolerance, a prediabetic stage, showed risk reductions between 30% and 70% (2-6). The results of these studies provide convincing evidence that lifestyle modification reduces the incidence of diabetes among high-risk individuals. In four of these studies (2-5), diabetes rates decreased in relation to substantial reductions of body weight, while in the Indian trial (6) lifestyle intervention was successful in spite of no weight loss. Observational studies have also shown that diets rich in vegetables and low in red meat and whole-fat dairy products are associated with a decreased risk of diabetes, while dietary patterns rich in red meats, processed foods, refined grains, and sweets increase diabetes risk (7).

The traditional Mediterranean diet (MedDiet), characterized by a high consumption of vegetables, legumes, grains, fruits, nuts and olive oil, a moderate consumption of fish and wine, and low consumption of red and processed meat and whole-fat dairy products, is widely recognized as a healthy dietary pattern (8). Two prospective studies from Southern Europe suggest a lower incidence of diabetes with increasing adherence to the MedDiet in previously healthy persons (9) or myocardial infarction survivors (10). Recently, a clinical trial showed that, compared to a low-fat diet, a MedDiet achieved better glycemic control and delayed the need for antidiabetic drug treatment in patients with newly-diagnosed diabetes (11). However, the role of the MedDiet in the prevention of diabetes has not been tested in a clinical trial.

We conducted a randomized controlled trial to compare the effect on diabetes incidence of three non-calorie-restricted nutritional interventions: a low-fat diet (control diet), a MedDiet enriched with virgin olive oil, and a MedDiet enriched with mixed nuts.

RESEARCH DESIGN AND METHODS

Study Design. The PREDIMED (*PREvención con DIeta MEDiterránea*) study is a multicenter, randomized, parallel group primary prevention trial conducted in Spain to assess the effects of two MedDiets, supplemented with either extra virgin olive oil or mixed nuts, versus a low-fat control diet on cardiovascular and other chronic disease outcomes in persons at high cardiovascular risk. Full details of the PREDIMED protocol have been published elsewhere (12) and are available at www.predimed.org and www.predimed.es. Recruitment took place between October 2003 and June 2008, including 7,232 participants randomly assigned to the three interventions.

Only in one of the PREDIMED centers (PREDIMED-Reus) a yearly oral glucose tolerance test (OGTT) in non-diabetic participants was part of the protocol. The present report represents a nested substudy aimed at assessing the effects of the three interventions on the incidence of diabetes using a yearly OGTT as diagnostic tool. The local institutional review board approved the study protocol and all participants provided written informed consent.

Participants. Candidates were community-dwelling men aged 55-80 years and women aged 60-80 years, without prior cardiovascular disease but having at least three cardiovascular risk factors, namely smoking, hypertension, dyslipidemia, overweight (BMI ≥25 kg/m^2), and family history of premature cardiovascular disease (≤55 years in men and ≤60 years in women). Participants with d prevalent diabetes were excluded from the present analysis. Other exclusion criteria were any severe chronic illness, alcohol or drug abuse, BMI ≥40 kg/m^2, and history of allergy or intolerance to olive oil or nuts (12).

Procedures. A behavioral intervention promoting the MedDiet was implemented, as described (12). Briefly, on the basis of the initial assessment of individual scores of adherence using a 14-item questionnaire, dietitians gave personalized dietary advice to participants randomized to both MedDiets, with instructions directed to upscale the score, including, among others: 1) abundant use of olive oil for cooking and dressing; 2) increased consumption of fruit, vegetables, legumes, and fish; 3) reduction in total meat consumption, recommending white meat instead of red or processed meat; 4) preparation of home-made sauce with tomato, garlic, onion, and spices with olive oil to dress vegetables, pasta, rice, and other dishes; 5) avoidance of butter, cream, fast-food, sweets, pastries, and sugar-sweetened beverages; and 6) in alcohol drinkers, moderate consumption of red wine.

At inclusion and quarterly thereafter, dietitians administered both individual interviews and group sessions, separately for each group. Sessions consisted of informative talks and delivery of written material with elaborate descriptions of typical foods for each dietary pattern, seasonal shopping lists, meal plans, and recipes. Participants assigned to MedDiet groups were given free allotments of either virgin olive oil (1 liter per week) or mixed nuts (30 g per day). Participants allocated the low-fat diet received recommendations to reduce all types of fat, from both animal and vegetable sources, but no free foods. Instead, to encourage adherence, at quarterly visits they were given small gifts, such as oil dispensers, aprons, shopping bags, or cookbooks. Energy restriction was not advised, nor physical activity promoted.

At baseline and each annual visit we administered: a) a short-questionnaire about lifestyle variables, medical conditions and medication use; b) a 14-item questionnaire of adherence to the MedDiet (12); c) a 137-item validated food frequency questionnaire (13); and, d) the validated Spanish version of the Minnesota Leisure-Time Physical Activity questionnaire (14). Staff involved in collecting questionnaires and physical measures were unblinded to intervention group. Energy and nutrient intakes were calculated from Spanish food composition tables, as described (12). At yearly visits, weight was recorded, samples of fasting blood were taken, and an OGTT was scheduled. Plasma glucose concentrations were centrally analyzed by the glucose-oxidase method. Laboratory technicians were blinded to intervention group.

We assessed the proportion of participants in each group attaining pre-specific lifestyle goals on at least 50% of the follow-up visits. Goals included: 1) improved adherence to the MedDiet (≥10 points in the 14-point score), 2) a high (≥2) monounsaturated fatty acid (MUFA)-to-saturated fatty acid (SFA) ratio, 3) high olive oil consumption (≥20 g/1000 kcal/d), 4) high nut consumption (≥10 g/1000 kcal/d), 5) high dietary fiber intake (≥14 g/1000 kcal/d), 6) substantial weight loss (≥5% of initial body weight), 7) high physical activity (≥395 kcal/day, the top tertile). Changes in weight and physical activity were not intervention goals, but were assessed because of their well known association with diabetes.

The primary outcome was new-onset diabetes, diagnosed according to American Diabetes Association criteria (15), namely fasting plasma glucose ≥7.0 mmol/L or 2-h plasma glucose ≥11.1 mmol/L after a 75-g oral glucose load, measured yearly. A second test using the same criteria was required for confirmation. Case ascertainment was done by the PREDIMED Clinical Event Committee, whose members were blinded to intervention group. When diabetes was diagnosed, participants and their primary care physicians were informed and no further OGTTs were scheduled. Every effort was made to retain participants and to ascertain vital status, including telephone calls and home visits by PREDIMED investigators if necessary.

Statistical analysis. Comparisons among groups for qualitative variables were done with the χ^2 test. We fitted Cox regression models to assess the relative risk of diabetes by allocation group, estimating hazard ratios (HR) and 95% confidence intervals (CI). The time variable was the interval between randomization and the date of last follow-up, death, or diabetes diagnosis, whichever occurred first. Participants who were free of diabetes or lost during follow-up were censored at the date of the last visit. The assumption of proportional hazards was tested using time-dependent covariates. In all analyses, we fitted a Cox regression model adjusted for age and sex. In a subsequent model, we additionally adjusted for baseline energy intake, BMI, waist circumference, physical activity, smoking status, fasting serum glucose, use of lipid-lowering drugs, Mediterranean diet score, and weight change during the study. The last model was repeated after merging the two MedDiet groups into a single category. Multiplicative interaction (effect modification) between the intervention ("Mediterranean diets", i.e., the two groups merged into one category) and age, sex, BMI, and baseline fasting glucose were assessed using the likelihood ratio test for multiplicative product-terms introduced in fully-adjusted Cox models. Kaplan-Meier survival curves were plotted to estimate the probability of remaining free of diabetes during follow-up. Analyses were based on the intention-to-treat principle. All p-values are two-tailed at the <0.05 level. Statistics were done with SPSS version 17.0 (SPSS Inc, Chicago, IL) software.

RESULTS

Of 1125 eligible candidates, 870 fulfilled inclusion criteria and entered the trial. Of these, 452 were excluded because of a prior diagnosis of diabetes. A total of 418 nondiabetic volunteers were randomized into the three groups (Supplementary Figure 1 in the online appendix available at http://care.diabetesjournals.org). The first participant entered the study in October 2003 and the last one in June 2008. Most participants (98.8%) were enrolled for at least 1 year, 88.3% for ≥3 years and 19.9% for ≥6 years. The median follow-up was 4.0 years (interquartile range, 3.0-5.0). Attrition rates were low and were almost exclusively due major disease events or death.

Table 1 shows baseline characteristics of participants according to intervention arm. The mean age was 67.3 years and 58.4% were women. The groups were well balanced with respect to most relevant variables. However, participants in the control group used less lipid-lowering drugs and had a lower MedDiet score than the other two groups. Participants refused the OGTT in 17% of the scheduled occasions and 41 (9.8%) of them had none performed.

The diets were well tolerated. Up to 3% of participants in each treatment arm reported difficulties in following the prescribed diets, which were solved in all cases by the dietitians through individual counsel, negotiation, and small diet adjustments. The number of participants in each group who reported improved bowel motions (5.2%-8.1%) was approximately twice the number of those who complained of newly developed constipation (3.3%-3.7%). Supplementary Table 1 shows the proportion of participants in each group who attained pre-specified goals during the trial. The goals of higher MUFA-to-SFA ratios, higher intakes of total olive oil, nuts, fruit and vegetables, legumes, fish and a Mediterranean diet score ≥10 were achieved more frequently by participants allocated to the two Mediterranean diets than by those in the control group, while a small proportion of participants in each group reached substantial dietary fiber intakes. Only 21% of participants in the control group achieved the goal specific for this group of total fat intake <35% of energy. Weight changes among the 418 participants at the end of follow-up were -0.2±4.6 kg for the olive oil diet group, -0.6±4.2 kg for the nut diet group, and -0.6±4.3 kg for the low-fat diet group (P=.74 for the comparison between groups). Likewise, physical activity changes were similar in the three groups: -17.4±336, -58.8±297, and -35.8±257 kcal/day, respectively (P=.50). As shown in Supplementary Table 1, at the end of the study participants sustained weight loss >5% to a similar extent in the three groups, while a lower proportion of those in the control group were in the top tertile of physical activity. There were few changes in medication during the trial. Hypolipidemic and antihypertensive therapy was initiated by 15.6% and 6.1% of participants and discontinued by 5.4% and 3.2%, respectively, with a similar distribution among groups.

During the study, 54 persons developed new-onset diabetes. Supplementary Table 2 shows that the rate per 1000 person-years of diabetes incidence was 24.6 (95% CI, 13.5-40.8) for the MedDiet with virgin olive oil group, 26.8 (15.3-43.0) for the MedDiet with nuts group, and 46,6 (30.1-68.5) for the control group. Cumulative incidence of diabetes was 10.1 (5.1-15.1) in the MedDiet with olive oil and 11.0, (5.9-16.1) in the MedDiet with nuts group, while it was 17.9 (11.4-24.4) in the control group. Figure 1 shows that cumulative diabetes-free survival was lower in the control group compared to both MedDiet groups. After adjustment for various confounders, incident diabetes was reduced by 51% in the MedDiet with olive oil group and by 52% in the MedDiet with nuts group in comparison with the control group (table 2). Thus, when merging the two MedDiet groups into a single category in a similarly adjusted model, diabetes incidence was reduced by 52%. In multivariable regression models, sex, age, baseline obesity or baseline fasting glucose were unrelated to outcomes.

Diabetes incidence was lower in participants assigned the two MedDiets (considered together) who attained ≥4 out of the 7 pre-specified goals or achieved a MedDiet score ≥10 (Supplementary Figure 2). Thus, 6.3% of participants in the MedDiet groups developed diabetes if they attained ≥4 goals compared to 15.0% of those who reached <4 goals (P=.02). Rates depending on attainment or not of a high score (≥10) of adherence to the MedDiet were 9.4% versus 20.6% (P=.07) respectively in the control group. Changes in weight or physical activity did not differ among participants in each intervention arm developing or not developing diabetes at the end of the study. In the control group, however, subjects developing diabetes had sustained a mean weight gain of 1.8±3.3 kg, while those remaining diabetes-free had an average weight loss of 1.1±4.4 kg, a nearly significant difference (P=.10).

CONCLUSIONS

In this nutrition-intervention study we found that a non-calorie-restricted traditional MedDiet enriched with high-fat foods of vegetable origin decreased the incidence of diabetes in persons at high cardiovascular risk after a median follow-up of 4.0 years. Diabetes rates were reduced by 51% and 52% by the consumption of MedDiets supplemented with virgin olive oil or mixed nuts, respectively, compared with a control diet consisting of advice on a low-fat diet. When the results of the two MedDiet groups were merged, risk reduction was 52%. These results extend those of prior studies showing that lifestyle interventions can substantially reduce the incidence of diabetes in persons at high risk (2-6). However, in these studies the interventions consisted of advice on a calorie-restricted diet plus physical activity and, except for one study (6), weight loss was a major driving force in reducing the incidence of diabetes. Of note, in our study diabetes risk reduction occurred in the absence of significant changes in body weight or physical activity.

Our estimate of the magnitude of the effect of the MedDiet can be viewed as conservative because the data were analyzed by intention-to-treat, even though some participants in all treatment arms might not have been fully compliant with the intended dietary modifications. As described in other reports of the PREDIMED study (12,16), a sizable proportion of participants in the control group, despite being advised to follow the low-fat diet, did not substantially reduce total fat intake (Supplementary Table 1). This is because of a long-lasting preference for using olive oil in the kitchen and at the table in Mediterranean cultures. In fact, diabetes risk was reduced to a similar extent in participants of all treatment arms who reported higher scores of adherence to the Mediterranean diet (Supplementary Figure 2).

Our results are consistent with prior evidence suggesting a protective effect of the MedDiet on diabetes (7, 9-11). Characteristically, the MedDiet is a high-fat, high-unsaturated fat dietary pattern, a feature that was maximized in our study by the free provision of virgin olive oil (rich in MUFA) and mixed nuts (rich in MUFA and polyunsaturated fatty acids [PUFA]) to participants in the MedDiet groups. As suggested by the known associations between subtypes of dietary fat and diabetes risk (17), the increased unsaturated fat load of our MedDiets was probably instrumental in achieving diabetes risk reduction.

The results of a prior PREDIMED study report (12) support the protective role of olive oil and nuts on diabetes risk, as both MedDiets were associated with improved fasting glucose in diabetic participants and decreased insulin resistance in those without diabetes after a 3-month follow-up, again in the absence of weight loss. In the same study (12), a reduction in circulating inflammatory biomarkers was observed in the two MedDiet groups. Because chronic low-grade inflammation is a pathogenetic factor in diabetes, synergy among the anti-inflammatory properties of the MedDiet and those specific of virgin olive oil (18) and nuts (19) might also be relevant to diabetes risk reduction. Regarding nuts, reports from large prospective studies suggests that usual intake relates inversely to future diabetes risk in women (20), but not in men (21). No such data are available for olive oil consumption and risk of diabetes. However, a former report of the PREDIMED trial (16) showed that, compared to the control diet, both MedDiets, particularly the nut-enriched diet, had a favorable effect on metabolic syndrome status after intervention for 1 year. The fact that in our study participants in any treatment arm who were more compliant with the MedDiet had 2-3 times lower incidence of diabetes than those with lesser scores supports a beneficial effect of the whole MedDiet pattern.

There are some limitations to our study. First, the Mediterranean cohort studied was aged and at high risk for cardiovascular disease. The generalization of our findings to younger and/or healthier individuals from other geographical locations is uncertain. Nevertheless, it is plausible that the beneficial effect of the MedDiet on diabetes risk may be reproduced in other populations, as it has been shown for all-cause mortality, cardiovascular disease incidence, and cancer mortality in US populations (22). Second, the lifestyle score used in our study to determine whether changes in dietary goals related to diabetes incidence could not reflect the totality of dietary changes, thus making difficult to show significant differences among interventions. Third, some participants did not undergo an OGTT, thus limiting an eventual diagnosis of diabetes to a fasting blood sugar ≥7.0 mmol/L confirmed by a second test, which might have falsely lowered overall incident rates. Finally, our sample size was relatively small, because the results are based in less than 55 incident cases, and the CIs for our estimates are wide. Longer follow-up of the PREDIMED cohort may eventually provide stronger evidence of diabetes prevention by the MedDiet.

In conclusion, the results show that a non-energy-restricted traditional MedDiet high in unsaturated fat can be a useful tool for preventing diabetes. Because other studies have shown that the benefit of lifestyle modification in reducing diabetes risk extends beyond the termination of active intervention (23-25), education of the population on the MedDiet might be a safe public health approach to delay or prevent development of diabetes, as well as that of other prevalent chronic diseases (22). Further research is needed to elucidate the mechanisms leading to diabetes risk reduction independently of weight loss.

Contributions: J.S., M.B, N.B., M.A.M, N.I, R.E. and E.R. had full access to all the data in the study and take full responsibility for the

integrity and accuracy of the data analysis. *Study concept and design*: J.S., M.B., M.A.M., R.E., J.B., M.I.C., D.C., F.A., V.R. and E.R. *Acquisition of data*: J.S., M.B, N.B., N.I, J.B. *Analysis and interpretation of data*: J.S., M.B, N.B., M.A.M, N.I, R.E. and E.R. *Drafting of the manuscript*: J.S., N.B., M.A.M. and E.R. *Critical revision of the manuscript for important intellectual content*: All the authors. *Statistical analysis*: N.B., M.A.M. *Obtained funding*: J.S., M.A.M, R.E., V.R. and E.R.

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Table 1. Characteristics of the study population at baseline

	MedDiet with VOO group (n=139)	**MedDiet with nuts group (n=145)**	**Control diet group (n=134)**
Age (years)	67.4 ± 6.1	66.6 ± 5.8	67.8 ± 6.1
Male sex (%)	40	47	38
Current smoker (%)	11	15	15
Weight (kg)	75.3 ± 10.3	76.1 ± 10.5	76.2 ± 11.3
Body mass index (kg/m^2)	29.7 ± 3.3	29.6 ± 3.1	30.0 ± 3.3
Waist circumference(cm)	101.1 ± 8.6	100.3 ± 8.5	102.2 ± 9.4
Leisure-time physical activity (kcal/day)	372 ± 280	389 ± 267	338 ±209
Plasma biomarkers			
LDL cholesterol (mmol/L)	3.7 ± 0.9	3.5 ± 0.8	3.7 ± 0.9
HDL cholesterol (mmol/L)	1.5 ± 0.3	1.5 ± 0.4	1.5 ± 0.4
Triglycerides (mmol/L)	1.5 ± 0.6	1.6 ± 0.8	1.6 ± 0.8
Non-HDL cholesterol (mmol/L)	4.3 ± 0.9	4.2 ± 0.9	4.4 ± 1.0
Fasting glucose (mmol/L)	5.5 ± 0.8	5.5 ± 0.9	5.5 ± 0.9
2-hour post-load glucose (mmol/L)[*]	7.1 ± 2.6	6.9 ± 2.4	7.4 ± 2.9
Fasting insulin (μU/ml)[†]	5.8 ± 3.6	5.4 ± 3.2	6.2 ± 4.4
HOMA-IR[†]	1.41 ± 0.87	1.34 ± 0.87	1.60 ± 1.17
Medication use (%)			
Lipid-lowering drugs	46.8	47.6	40.3
Antihypertensive medication	82.0	82.1	78.4
Estrogen-replacement therapy	2.4	0.0	2.4
Energy, food and nutrient intake			
Total energy (kcal/d)	2320 ± 579	2365 ± 570	2314 ± 580
Carbohydrate (% energy)	41 ± 6	40 ± 6	41 ± 7
Protein (% energy)	16 ± 3	16 ± 2	16 ± 2
Fat (% energy)	41 ± 6	41 ± 6	40 ± 7
MUFA:SFA ratio	1.9 ± 0.4	2.0 ± 0.4	1.9 ± 0.5
Total fiber (g/day)	23.7 ± 7.6	23.6 ± 8.0	23.0 ± 7.7
Olive oil (g/day)	41.2 ± 17.7	42.0 ± 16.5	40.1 ± 20.4
Nuts (g/day)	13.1 ± 15.0	14.4 ± 15.4	9.3 ± 12.1
Vegetables (g/day)	309 ± 129	310 ± 141	286 ± 117
Fruits (g/day)	298 ± 185	315 ± 164	286 ± 168
Legumes (g/day)	18 ± 7.9	19 ± 9.0	18 ± 8.4
Cereals (g/day)	248 ± 98	245 ± 99	251 ± 105
Red meat and meat products (g/day)	80 ± 44	86 ± 46	84 ± 47
Milk and dairy products (g/day)	355 ± 201	348 ± 183	346 ± 207
Seafood (g/day)	107 ± 42	104 ± 43	99 ± 41
Alcohol (g/day)	8 ± 11	11 ± 14	9 ± 12
Red wine (ml/day)	57 ± 95	75 ± 101	64 ± 89
Score of adherence to the MedDiet	8.4 ± 1.9	8.4 ± 1.9	7.9 ± 1.9

Data are mean ± SD or %. Abbreviations; MedDiet, Mediterranean diet; VOO, virgin olive oil; HOMA-IR, homeostasis model assessment of insulin resistance; MUFA, monounsaturated fatty acids; SFA, saturated fatty acids. [*]Data available in 263 participants. [†]Data available in 307 participants.

Table 2. Hazard ratios (95% confidence intervals) of diabetes by intervention group*

	MedDiet with VOO versus control diet	**MedDiet with nuts versus control diet**	**Both MedDiets versus control diet**
Crude model	0.53 (0.27-1.09)	0.58 (0.31-1.10)	0.55 (0.32-0.95)
Age- and sex-adjusted model	0.52 (0.27-1.00)	0.55 (0.29-1.00)	0.53 (0.31-0.92)
Multivariate adjusted model†	0.49 (0.25-0.97)	0.48 (0.24-0.96)	0.48 (0.27-0.86)
Sex‡			
Male	0.48 (0.16-1.46)	0.65 (0.21-2.00)	0.55 (0.21-1.43)
Female	0.47 (0.19-1.17)	0.32 (0.11-0.93)	0.40 (0.18-0.90)
Age (years)‡			
≤67	0.50 (0.18-1.39)	0.65 (0.26-1.61)	0.58 (0.26-1.31)
>67	0.26 (0.08-0.83)	0.27 (0.07-0.98)	0.26 (0.09-0.76)
Body-mass index (kg/m^2)‡			
≤30	0.56 (0.21-1.49)	0.52 (0.19-1.41)	0.54 (0.24-1.22)
>30	0.50 (0.18-1.42)	0.62 (0.22-1.76)	0.56 (0.23-1.43)
Fasting glucose (mmol/L)‡			
≤6.1	0.44 (0.16-1.25)	0.60 (0.24-1.50)	0.53 (0.23-1.20)
>6.1	0.29 (0.09-0.95)	0.39 (0.11-1.37)	0.32 (0.11-0.98)

Abbreviations: MedDiet, Mediterranean diet; VOO, virgin olive oil.

*Cox regression models to assess the relative risk of diabetes by allocation group, estimating the hazard ratios and their 95% CIs were performed.

†Adjusted for sex, age, baseline energy intake, BMI, waist circumference, physical activity, smoking status, fasting serum glucose, use of lipid lowering drugs, Mediterranean diet score, and weight changes during the study.

‡Adjusted for the same variables as (†), except the variable of interest.

P for interaction (MedDiet * Sex): 0.496; P for interaction (MedDiet * Age): 0.195; P for interaction (MedDiet * Body-mass index): 0.592; P for interaction (MedDiet * Fasting glucose): 0.932.

FIGURE LEGENDS

Figure 1. Cumulative diabetes free-survival by group of intervention.

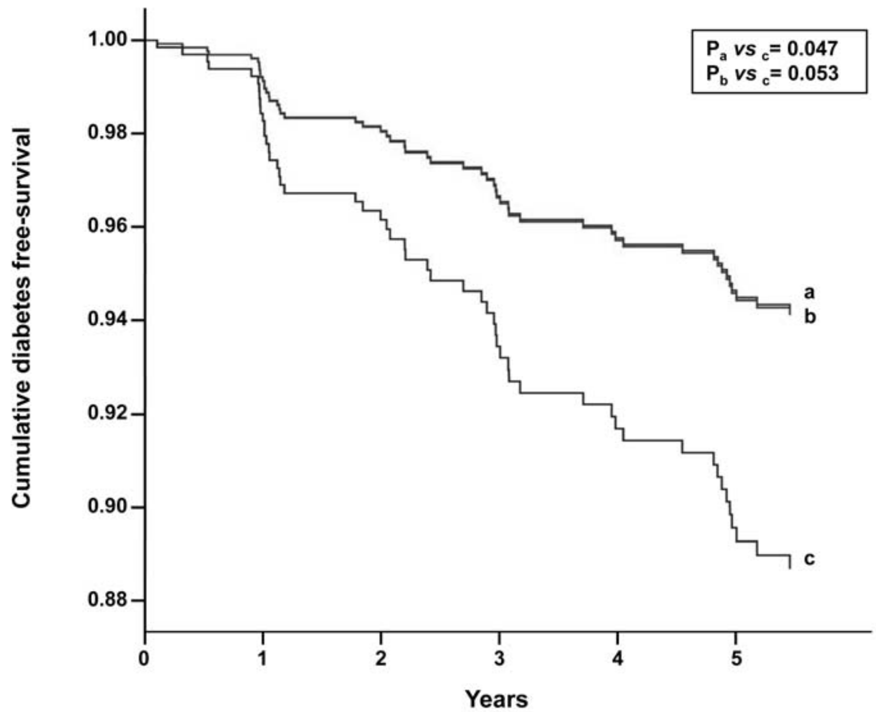
Cox regression models with outcome diabetes onset and exposure Mediterranean diet (MedDiet) intervention group versus control diet group, adjusted by sex, age, baseline energy intake, BMI, waist circumference, physical activity, smoking status, fasting serum glucose, use of lipid lowering drugs, Mediterranean diet score and weight change during the study.

(a) MedDiet + Virgin olive oil group

(b) MedDiet + Nuts group

(c) Control diet group

Figure



P_a *vs* $_c$= 0.047
P_b *vs* $_c$= 0.053
1.00
0.98
0.96
0.94
0.92
0.90
0.88
Cumulative diabetes free-survival
a
b
c
0
1
2
3
4
5
Years