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ORIGINAL RESEARCH

Comparison of an Energy-Reduced Mediterranean Diet and Physical Activity Versus an Ad Libitum Mediterranean Diet in the Prevention of Type 2 Diabetes

A Secondary Analysis of a Randomized Controlled Trial

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Background: Limited research has been done to evaluate the combined effect of energy reduction, Mediterranean diet (MedDiet), and physical activity on type 2 diabetes incidence.

Objective: To evaluate whether an energy-reduced MedDiet (erMedDiet) plus physical activity reduces diabetes incidence compared with a standard MedDiet.

Design: Prespecified secondary outcome analysis in the PREDIMED (Prevención con Dieta Mediterránea)-Plus randomized, single-blinded, controlled trial. (ISRCTN Registry: ISRCTN89898870)

Setting: 23 centers across Spain.

Participants: 4746 adults aged 55 to 75 years with metabolic syndrome and overweight or obesity, without prior cardiovascular disease or diabetes.

Intervention: Participants were randomly assigned 1:1 to an intervention group receiving an erMedDiet (planned reduction of 600 kcal per day), increased physical activity, and behavioral strategies for reducing weight, or a control group receiving ad libitum MedDiet advice.

Measurements: Diabetes incidence was based on the American Diabetes Association criteria. Anthropometric measurements were obtained annually. Cox regression models were used to assess the intervention effect.

Results: The 6-year absolute risk was 12.0% (95% CI, 11.9% to 12.1%) in the control group (349 cases) and 9.5% (CI, 9.4% to 9.5%) in the intervention group (280 cases). Over a median 6-year follow-up, diabetes incidence was 31% (CI, 18% to 41%) relatively lower in the intervention group compared with the control group, with an absolute risk reduction of −2.6 cases (CI, –2.7 to –2.4) per 1000 person-years. The intervention group attained better adherence to the erMedDiet, higher physical activity levels, and greater reductions in body weight and waist circumference.

Limitation: Secondary outcome, single-blinded design, and self-reported dietary adherence.

Conclusion: An intensive intervention with the MedDiet adding caloric reduction, physical activity, and modest weight loss was more effective than only an ad libitum MedDiet in reducing diabetes incidence in overweight/obese persons with metabolic syndrome.

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The rising prevalence, incidence, and burden of diabetes (1–3), driven by the obesity epidemic (2), underscore the need for simple, sustainable, preventive strategies (4).

Robust evidence shows that diabetes is preventable through lifestyle modifications aiming at weight loss (5–8). A meta-analysis including 19 randomized

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clinical trials confirmed the long-term beneficial effect of lifestyle interventions, even with modest weight loss (9). Most of these interventions targeted weight loss through an energy-reduced, healthy *low-fat* diet combined with increased physical activity (5). However, no previous trial has assessed the effect of energy reduction in the context of a relatively high-fat diet, such as the Mediterranean diet (MedDiet).

The PREDIMED (Prevención con Dieta Mediterránea) trial demonstrated that an ad libitum MedDiet supplemented with either extra-virgin olive oil or mixed nuts reduced diabetes incidence by 30%, compared with a low-fat diet (10, 11). However, this reduction occurred with only marginally reduced body weight (12). Building on this finding, the PREDIMED-Plus trial was designed to test whether adding caloric restriction and physical activity to the MedDiet would provide additional benefit beyond the effect observed only with the MedDiet. In a 1-year interim analysis, an energy-reduced MedDiet (erMedDiet) combined with increased physical activity significantly reduced body weight, waist circumference, and other cardiometabolic risk markers compared with an ad libitum MedDiet (13–15). The present analysis, conducted with data from all PREDIMED-Plus participants free of diabetes at baseline, tests whether an intensive lifestyle intervention aiming at weight loss reduces diabetes risk beyond the effects of an ad libitum MedDiet.

METHODS

Study Design

This is a secondary outcome analysis in the PREDIMED-Plus trial, whose methods were previously reported (13, 16). Briefly, the PREDIMED-Plus is a multicenter, randomized, parallel-group, single-blind, lifestyle intervention trial aiming to assess the effects of a weight-loss intervention with an erMedDiet and increased physical activity (intervention group) versus a control MedDiet group without energy reduction for primary cardiovascular prevention. Diabetes incidence was a predefined secondary end point.

The study protocol was approved by the research ethics committees of all recruitment centers, and all participants provided written informed consent. The ethics approval and study protocol are available at Annals.org and on the PREDIMED-Plus website.

Population and Randomization

Eligible participants were community-dwelling men aged 55 to 75 years and women aged 60 to 75 years, with overweight or obesity (body mass index [BMI] ≥27 and <40 kg/m^2), without documented cardiovascular disease or diabetes (for the present analysis), and with at least 3 metabolic syndrome components: waist circumference 80 cm or more in women and 94 cm or more in men, elevated triglycerides (≥1.69 mmol/L [≥150 mg/dL]), a reduced high-density lipoprotein cholesterol level (<1.04 mmol/L [<40 mg/dL]), elevated blood pressure (systolic ≥150 and diastolic ≥85 mm Hg), and an elevated fasting glucose level (≥5.55 mmol/L [≥100 mg/dL]) (17). Primary care physicians from 23 Spanish recruitment centers assessed eligibility. Participants were randomly allocated 1:1 to one of the study arms using a centralized computer-based system with stratification by center, sex, and age (<65, 65 to 70, >70 years) in blocks of 6. Couples sharing a household were randomly assigned as a cluster. Randomization was masked to center staff and investigators. Recruitment lasted from 5 September 2013 to 23 December 2016.

This study reports the intervention's effects on diabetes incidence in all participants without diabetes at baseline ($n = 4746$, from 6874 total participants in the trial). Prevalent diabetes cases at baseline were initially self-reported and subsequently confirmed through a review of their medical records. In addition, clinical records of potential new incident diabetes cases were reviewed to confirm that these diagnoses occurred after participants were enrolled in the study.

Intervention

The interventions were scheduled to last for an average of 6 years. Given the study design, neither dietitians nor participants were blinded to the randomized arm. Descriptions of the intervention and its effectiveness after 1 year were previously reported (13, 16, 18). Observed 1-year improvements in adiposity, glucose level, and lipids for the intervention versus control were reported in previous publications (13–15).

Participants in the intervention group were instructed to follow an erMedDiet with physical activity recommendations and behavioral support for weight loss (**Supplement Table 1**, available at Annals.org). The erMedDiet was defined as a traditional MedDiet with a planned reduction of 600 kcal per day, providing 35% to 40% of calories from fat, 40% to 45% from carbohydrates, and approximately 20% from protein. Participants were encouraged to consume more fruits, vegetables, whole cereals, legumes, nuts, and extra-virgin olive oil, while limiting meat, sugar-sweetened beverages, foods with added sugars, and cream. A validated 17-item questionnaire was used to assess adherence to the erMedDiet annually and to deliver recommendations (**Supplement Table 2**) (19). Physical activity recommendations included: a) progressively increased aerobic physical activity, mainly brisk walking, aiming for 45 minutes per day (or the equivalent) 6 days per week; b) strength exercises (≥2 days per week); and c) flexibility and balance exercises (≥3 days per week) (18).

The control group received educational sessions on the traditional MedDiet with ad libitum caloric intake following the PREDIMED-1 trial recommendations (20). Adherence to the MedDiet was assessed using a validated 14-item MedDiet adherence screener (21). No advice on physical activity or weight loss was provided to the control group.

The participants in the intervention group were contacted by dietitians 3 times a month (1 group session, 1 individual session, and 1 phone call) during the first year, then received monthly group sessions, individual sessions every 3 months, and 2 phone calls every 3 months. Control group participants had 1 individual visit, 1 phone call, and 1 group session every 6 months. Both groups received 1 L per month of extra-virgin olive oil to support adherence and retention. During the COVID-19 pandemic, the intervention was remotely delivered (22).

Variables

Self-reported dietary measurements were conducted at baseline, after 6 months, and then annually during the 6 years of the intervention and 2 additional years of follow-up, using a validated 143-item food-frequency questionnaire (23) and 2 MedDiet adherence questionnaires—one with 17 items to assess adherence to the erMedDiet (19) and one with 14 items to assess adherence to the traditional MedDiet (21). Physical activity was measured with the REGICOR short physical activity questionnaire (24) and the Physical Activity Readiness and Rapid Assessment of Physical Activity questionnaires (25).

Body weight, height, and waist circumference were measured by trained personnel, not blinded to group assignment, and medication use was recorded. Fasting blood glucose level, lipid profile, and hemoglobin A_{1c} (HbA_{1c}) level were determined by standard methods at baseline, after year 1, and every other year thereafter. Baseline insulin was centrally measured by an electrochemiluminescence immunoassay using an Elecsys immunoanalyzer (Roche Diagnostics). Insulin resistance was estimated using the Homeostasis Model Assessment of Insulin Resistance (HOMA-IR) index (26).

The definition of prediabetes was based on fasting plasma glucose (FPG) levels from 5.55 to 6.94 mmol/L (100 to 125 mg/dL) or HbA_{1c} levels between 5.7% and 6.4% (27, 28).

Outcome

Diabetes incidence was assessed yearly for 7 years of follow-up (a 6-year intervention period and 1 additional year of observation) (13). The American Diabetes Association criteria were used to ascertain incident diabetes (29): a) HbA_{1c} levels of 6.5% or more, performed in a laboratory using a method that is National Glycohemoglobin Standardization Program certified and standardized to the Diabetes Control and Complications Trial (DCCT) assay; b) a fasting plasma glucose level of 7.0 mmol/L or more (≥126 mg/dL); c) a 2-hour plasma glucose level of 11.1 mmol/L or more (≥200 mg/dL) during an oral glucose tolerance test using a glucose load containing the equivalent to 75 g of anhydrous glucose dissolved in water; or d) a random plasma glucose level of 11.1 mmol/L or more (≥200 mg/dL) in patients with classic symptoms of hyperglycemia or a hyperglycemic event. In the absence of unequivocal hyperglycemia, results should be confirmed by repeated testing.

Physicians, blinded to group assignment, reviewed participants' medical records annually. New-onset diabetes cases were identified based on medical diagnoses reported in medical charts or repeated glucose tests from routine analyses. Potential cases were reviewed by the Clinical Events Ascertainment Committee, blinded to treatment allocation. Only confirmed new-onset diabetes cases occurring between randomization and 31 December 2022 were included.

Statistical Analysis

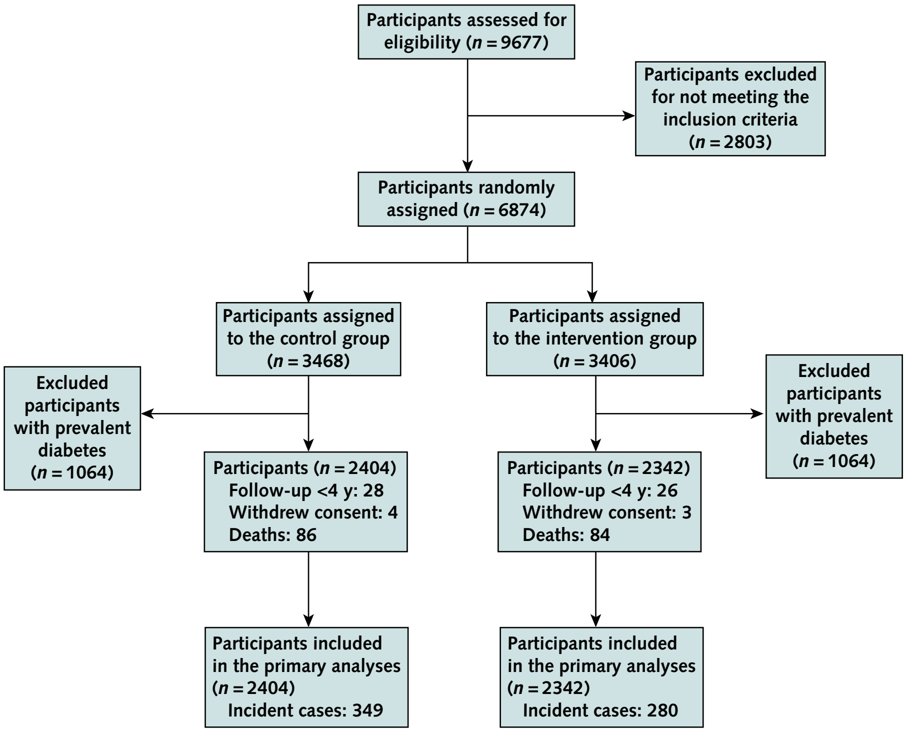
The original trial was designed to recruit approximately 6000 participants primarily to detect a 30% relative reduction in the incidence of cardiovascular disease in the intervention versus the control group (16). For incident diabetes, we anticipated sufficient statistical power based on projections from the Diabetes Prevention Impact Toolkit (29).

Primary between-group comparisons followed the intention-to-treat principle. Time-to-first event was defined as the time from randomization to diabetes diagnosis or the last follow-up date for those without this diagnosis (last visit or last date in the medical record, whichever occurred later, or date of death) (30). Cox models assessed the intervention's effect, with results expressed as hazard ratios and 95% CIs (31, 32). Robust SEs were used to account for intracluster correlations among participants from the same households (569 pairs out of the 4746 participants). Absolute risk differences at 6 years were estimated using Cox regression models, with robust SEs and the same covariate adjustments as described in the next paragraph for hazard ratios, to estimate standardized differences in incidence.

A multivariable model adjusted for sex, age, and baseline glucose level, and stratified according to recruitment center and educational level (5 categories), was fitted. To assess the robustness of the results, a second multivariable model included additional baseline covariates: BMI (continuous), leisure-time physical activity (metabolic equivalent of task minutes per week), smoking habit (never/current/former), hypercholesterolemia, hypertension, alcohol intake (grams per day, including a quadratic term), total energy intake (kilocalories per day), baseline erMedDiet adherence score (17-point score, continuous), and family history of diabetes.

Linear mixed models (with robust SEs) assessed changes in erMedDiet, physical activity, and anthropometric variables from baseline by intervention group during the first 6 years of active follow-up, with random intercepts at recruitment site and family cluster level, and time categorically modeled (visit number) to capture potential nonlinear trends (a sample of the STATA code is available in **Supplement 1**, available at Annals.org).

Figure 1. Flow chart of participants in the PREDIMED-Plus study.



PREDIMED = Prevención con Dieta Mediterránea.

A simple imputation method was applied for continuous variables with missing values included in multivariable models using the command *impute* from Stata: baseline fasting plasma glucose ($n = 31$), total energy intake ($n = 29$), alcohol intake ($n = 29$), erMedDiet adherence ($n = 7$), and body weight ($n = 2$). The impute command uses regression-based methods, assuming that missing values are missing at random or missing completely at random. The variables included in the imputation model were age, sex, waist-to-height ratio, waist circumference, BMI, blood pressure, alcohol intake, dietary fiber, and smoking status. Missing values from categorical variables were imputed assuming a negative response to questions about family history of diabetes ($n = 178$), hypercholesterolemia ($n = 46$), hypertension ($n = 35$), level of education (lowest, $n = 7$), and smoking ($n = 2$).

Subgroup analyses were conducted according to the following variables: age categories (≤65 vs. >65 years), sex, educational level (primary or less vs. secondary or higher), BMI (<30 vs. ≥30 kg/m^2), waist-to-height ratio (<0.5 vs. ≥0.5), and baseline glucose level (<5.55 vs. ≥5.55 mmol/L [<100 vs. ≥100 mg/dL]). An interaction term between intervention group and each one of these variables was included in the Cox model, and it was assessed using the likelihood ratio test.

Several ancillary analyses were conducted including a per protocol–like approach (Supplement Figure, available at Annals.org). In addition, a composite variable strategy was implemented to account for deaths occurring before the diagnosis of diabetes, and both absolute and relative risks were recalculated.

In all statistical analyses (performed with STATA v.16.1), the PREDIMED-Plus database version 21-11-2023 was used. All tests were 2-sided with a significance threshold of $P < 0.05$.

Role of the Funding Source

The funding organizations had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

RESULTS

Baseline Characteristics and Follow-up

Of the 6874 randomly assigned participants (Figure 1), 2128 with diabetes at baseline were F1
excluded, leaving 4746 participants without diabetes (mean age, 64.9 years [SD, 4.9]; 50% women). Baseline characteristics were similar between included participants and those excluded due to prevalent diabetes (Supplement Table 3). Retained participants' baseline characteristics were balanced between both groups (Table 1). Baseline medication use was similar between T1
groups (Supplement Table 4).

The number of participants with less than 6 years of follow-up was 241 (10.3%) in the intervention group

T2

Table 1. Baseline Characteristic of Participants Without Type 2 Diabetes at Baseline in the PREDIMED-Plus Trial*

Characteristic	Control Group (*n* = 2404)	Intervention Group (*n* = 2342)
Age, *y*	64.9 (4.9)	64.8 (5.0)
Sex, *n (%)*		
Female	1189 (49.5)	1170 (50.0)
Male	1215 (50.5)	1172 (50.0)
Body weight, *kg*	86.0 (13.0)	86.3 (13.1)
BMI, *kg/m^2*	32.5 (3.5)	32.5 (3.4)
Waist circumference, *cm*	106.9 (9.7)	106.8 (9.7)
Smokers, *n* (%)		
Former	1060 (44.1)	959 (40.9)
Current	269 (11.2)	315 (13.5)
Never	1075 (44.7)	1068 (45.6)
Physical activity, MET-min/wk	2582 (2352)	2383 (2186)
Primary education or less, *n (%)*	1165 (48.5)	1095 (46.8)
erMedDiet score	8.5 (2.7)	8.3 (2.7)
Alcohol intake, g/d	11.9 (15.8)	11.0 (15.0)
Total energy intake, kcal/d	2457 (678)	2425 (620)
Systolic blood pressure, *mm Hg*	138.7 (16.4)	139.4 (17.1)
Diastolic blood pressure, *mm Hg*	81.0 (9.8)	81.4 (9.9)
Baseline hypertension, *n (%)*	1946 (81.0)	1945 (83.1)
Baseline dyslipidemia, *n (%)*	1598 (66.5)	1583 (67.6)
Baseline prediabetes,† *n (%)*	585 (24.3)	595 (25.4)
Baseline prediabetes,‡ *n (%)*	1744 (72.6)	1670 (71.3)
Fasting plasma glucose level		
mmol/L	5.67 (0.72)	5.66 (0.75)
mg/dL	102.1 (13.0)	102.0 (13.6)
Fasting plasma insulin, *mIU/L*	18.5 (10.1)	18.2 (10.0)
HOMA-IR	4.8 (2.9)	4.8 (3.2)
HbA_{1c}, %	5.8 (0.4)	5.7 (0.4)
Total cholesterol level		
mmol/L	5.29 (0.94)	5.26 (0.93)
mg/dL	204.3 (36.3)	203.2 (35.9)
HDL cholesterol level		
mmol/L	1.27 (0.30)	1.27 (0.31)
mg/dL	49.2 (11.6)	49.0 (12.1)
LDL cholesterol level		
mmol/L	3.26 (0.81)	3.25 (0.81)
mg/dL	126.0 (31.1)	125.3 (31.2)
Triglycerides		
mmol/L	1.69 (0.85)	1.67 (0.81)
mg/dL	149.5 (75.2)	148.0 (72.1)
Family history of diabetes, *n (%)*	828 (34.4)	818 (34.9)

erMedDiet = energy-reduced Mediterranean diet (score, 0 to 17 points); HbA_{1c} = hemoglobin A_{1c}; HDL = high-density lipoprotein; HOMA-IR = Homeostasis Model Assessment for Insulin Resistance; LDL = low-density lipoprotein; MET-min/wk = metabolic equivalent task minutes per week; PREDIMED = Prevención con Dieta Mediterránea.
* Data are mean (SD) unless otherwise specified.
† According to World Health Organization (WHO) criteria.
‡ According to American Diabetes Association (ADA) criteria.

and 242 (10.1%) in the control group. No statistically significant differences were observed in terms of sex, age, weight, BMI, or adherence to the erMedDiet between participants with less than 6 years versus 6 or more years of follow-up.

Effect of the Intervention on Diabetes Risk

In the intention-to-treat analysis, after a median follow-up of 6.6 years (IQR, 6.0 to 7.1 years), 629 incident diabetes cases occurred. The incidence curves progressively diverged between the intervention and
F2 the control group starting at 6 months (**Figure 2**). **Table 2** shows the number of new cases, rates, absolute risks, and relative risks by groups. After 6 years, the adjusted absolute risk difference for incident diabetes between the intervention and control groups was −2.4% (95% CI, −3.1 to −1.8), corresponding to a 31% (CI, 18% to 41%) relative risk reduction in the intervention group as compared with the control group.

In prespecified subgroup analyses, no statistically significant interactions were found for age, educational level, BMI, waist-to-height ratio, or baseline glucose level, except for sex, with greater diabetes risk reduction in men than in women (*P* for interaction = 0.035) (**Supplement Table 5**).

Ancillary analyses yielded similar results (**Supplement Figure**). During follow-up, 148 participants died without a diagnosis of diabetes (77 in the control group and 71 in the intervention group). The intervention effect remained largely unchanged when either diabetes incidence or death occurring before diabetes diagnosis was used as a composite outcome (**Supplement Table 6**).

Both groups showed similar increased use of antihypertensive and hypolipidemic medication (**Supplement Table 4**). Participants in the control group had greater antidiabetic drug use than those in the intervention group during the follow-up (11.7% vs. 9.5% at year 6; *P* = 0.018).

Changes in erMedDiet Adherence and Physical Activity

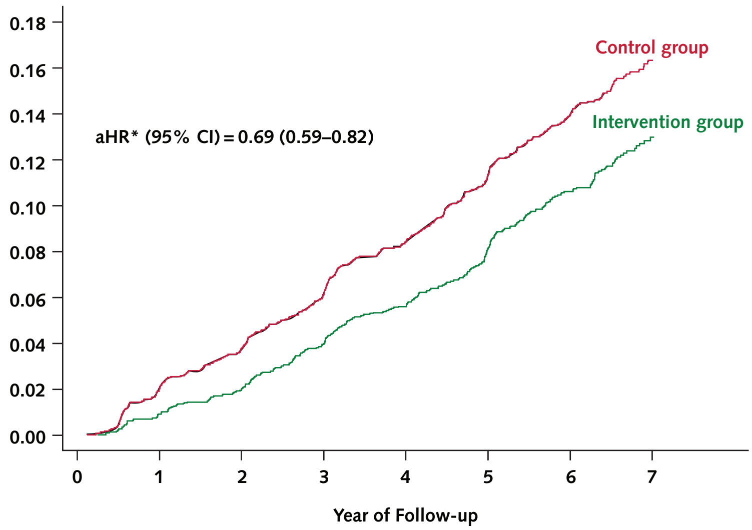
From year 1 on, both the intervention and the control groups improved their average adherence to the erMedDiet, although the former showed significantly
greater improvement (**Figure 3**). The mean between- F3
group difference in the erMedDiet score during the 6 years of intervention was 2.2 (CI, 2.0 to 2.3; *P* < 0.001). Detailed results for each of the 17 items of the erMedDiet score at baseline, and at years 1, 3, and 6 of follow-up, are shown in **Supplement Table 7**. An increase in the percentage of participants reaching the target for 16 of the 17 individual food items, excluding alcohol intake, was observed in both groups at years 3 and 6. However, this improvement was greater in the intervention than in the control group, with larger increments in the consumption of vegetables, fruits, legumes, fish, and whole grains, and reduced consumption of red and processed meat, refined grain, pasta, and white rice in the intervention than in the control group.

Compared with the control group, greater increases in physical activity were observed in the intervention group (**Figure 3**). During the first 6 years of intervention, the between-group mean difference was 800 (CI, 680 to 921) metabolic equivalent of task minutes per week (*P* < 0.001).

Effect on Adiposity Measures

Greater reductions in body weight and waist circumference occurred in the intervention group than in

Figure 2. Cumulative incidence of type 2 diabetes by randomized arm of the PREDIMED-Plus trial.



At risk, *n*								
Control	2404	2349	2306	2242	2183	2103	1853	676
Intervention	2342	2319	2288	2236	2189	2119	1868	670

aHR = adjusted hazard ratio; PREDIMED = Prevención con Dieta Mediterránea.
* Adjusted for age, sex, and fasting glucose level (≤5.55; >5.55 to <6.11; 6.11 to <6.99; and ≥6.99 mmol/L [≤100; >100 to <110; 110 to <126; and ≥126 mg/dL]), body mass index (kg/m^2), smoking status (never, former, current smoker), baseline prevalence of dyslipidemia (yes/no) and hypertension (yes/no), family history of diabetes, leisure-time physical activity level (metabolic equivalent of task minutes per day), adherence to energy-reduced MedDiet, and alcohol intake (grams per day, adding quadratic term), and stratified by center and educational level.

the control group (**Figure 3** and **Supplement Table 8**). In the analysis of completers, the 6-year mean body weight reduction was −3.3 kg (CI, −3.4 to -3.1 kg) in the intervention group and −0.6 kg (CI, −0.7 to −0.4 kg) in the control group, representing weight reductions of 3.7% in intervention and 0.6% in control. During this period, mean waist circumference was reduced by −3.6 cm (CI, −3.8 to −3.3 cm) in the intervention group and −0.3 cm (CI, −0.4 to −0.1 cm) in the control group.

DISCUSSION

In the PREDIMED-Plus randomized trial including adults aged 55 to 75 years with overweight or obesity and metabolic syndrome, an intervention consisting of advice on a calorie reduction using a traditional MedDiet pattern combined with increased physical activity and modest weight loss resulted in a 31% lower relative risk for incident diabetes compared with an ad libitum MedDiet replicating the PREDIMED trial intervention (20) after a median follow-up of almost 7 years. Moreover, analyses of adjusted risk differences revealed an absolute 2.4% reduction in the cumulative incidence of diabetes at 6 years, further reinforcing the clinical impact of the intervention. The reduction in diabetes incidence was consistent across subgroups of age, education, and baseline metabolic status, with a greater effect observed in men than women. The consistency of results across multiple ancillary analyses underscores the robustness of the PREDIMED-Plus intervention as a strategy to lower diabetes risk beyond the effects of a strong comparator, which was the conventional MedDiet.

Some postulated mechanisms could explain our results. The MedDiet, rich in fiber, whole grains, antioxidants, and anti-inflammatory compounds, is known to reduce diabetes risk, even in the absence of weight loss (12). The erMedDiet fosters low glycemic index foods as well as more fiber and whole grains, which are known to improve insulin sensitivity (33). In addition, moderate physical exercise may protect mitochondrial function and protect against obesity-induced insulin resistance (34). Synergistically, reductions in weight and visceral fat, achieved through caloric reduction and the increased physical activity implemented in our intervention, could significantly lower insulin resistance and inflammation (12, 35, 36). The MedDiet and physical activity also trigger the secretion of incretin hormones such as glucagon-like peptide-1, which plays a crucial role in glucose metabolism (37). Finally, the intervention effect could be modulated by favorable changes in gut microbiota and metabolome (38). However, in our study, we cannot disentangle whether the greater reduction in diabetes incidence resulted from weight loss, enhanced adherence to the MedDiet, physical activity promotion, or any combination of their effects.

Table 2. Absolute and Relative Risk Estimates for Incident Type 2 Diabetes After 6 Years of Intervention

Estimate	Control Group ($n = 2404$)	Intervention Group ($n = 2342$)
Cases, *n*	349	280
Person-years, *n*	15 022	14 989
Absolute risk (95% CI)	12.0 (11.9 to 12.1)	9.5 (9.4 to 9.5)
Crude RD (95% CI)	0 (reference)	−2.6 (−2.7 to −2.4)
Model 1,† RD (95% CI)	0 (reference)	−2.4 (−3.1 to −1.8)
Model 2,‡ RD (95% CI)	0 (reference)	−2.4 (−3.1 to −1.8)
Incidence rate (95% CI) per 1000 person-years	23.2 (20.9 to 25.8)	18.7 (16.6 to 21.0)
Crude HR (95% CI)	1 (reference)	0.80 (0.68 to 0.94)
Model 1,† HR (95% CI)	1 (reference)	0.71 (0.60 to 0.84)
Model 2,‡ HR (95% CI)	1 (reference)	0.69 (0.59 to 0.82)

HR = hazard ratio; RD = risk difference.
* Absolute risk and RDs were obtained from the predicted 6-year cumulative incidence derived from Cox models, using the baseline survival and average linear predictors for each group (see also Supplement Table 9).
† Adjusted for age (years), sex and fasting plasma glucose level at baseline (≤5.55; >5.55 to <6.11; 6.11 to <6.99; and ≥6.99 mmol/L [≤100; >100 to <110; 110 to <126; and ≥126 mg/dL]) and stratified by center and educational level (primary education vs. secondary or higher). Robust SEs to account for intracluster correlations (clusters are family members of the same household).
‡ Additionally adjusted for body mass index (kg/m^2), smoking status (never, former, current smoker), baseline prevalence of dyslipidemia (yes/no) and hypertension (yes/no), family history of diabetes, leisure-time physical activity level (metabolic equivalent of task minutes per day), adherence to the energy-reduced Mediterranean diet, and alcohol intake (grams per day, adding a quadratic term), and stratified by center and educational level (primary education vs. secondary or higher).

Previous landmark trials supported the efficacy of lifestyle interventions for diabetes prevention. The Diabetes Prevention Program (DPP) reported that an intensive lifestyle intervention, including a low-fat diet and enhanced physical activity, led to a 58% reduction in diabetes incidence compared with placebo over a mean follow-up of 2.8 years among persons with impaired glucose tolerance (8). Similarly, the Diabetes Prevention Study (DPS) reported comparable results after 3.2 years, also including patients with impaired glucose tolerance (7). More recently, 15-year follow-up of the DPP reported a 27% (CI, 17% to 35%) relative reduction in diabetes risk after lifestyle sessions were extended to all participants (39).

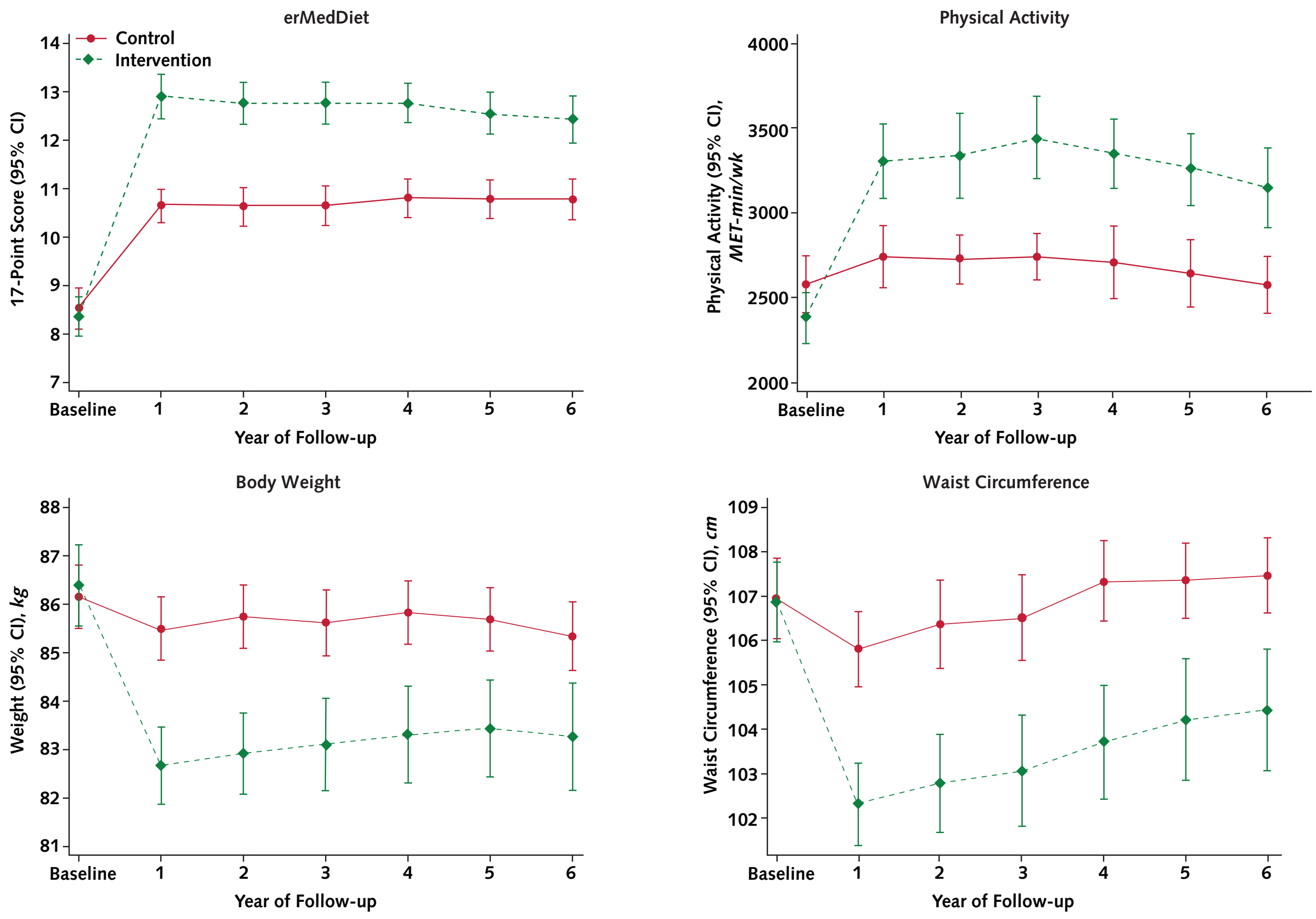
Our study differs from these previous trials in several important ways. First, we used a considerably stronger comparator, an ad libitum MedDiet supplemented with free extra-virgin olive oil, which has been previously shown to reduce diabetes risk by 30% (11). It is plausible that if the control intervention from the DPP trial had been used in PREDIMED-Plus, the observed risk reduction might have approached the 58% reduction reported in the DPP trial. The MedDiet is inherently high in fat (35% to 40% of daily energy), in contrast to the low-fat diets used in previous trials (40). Second, our participants were older persons with a mean age of 64.9 years versus 50.6 years in the DPP trial (8) and 53.0 years in the DPS trial (7), and they were selected on metabolic syndrome rather than impaired glucose tolerance. Third, we observed substantially lower incidence rates in both intervention and control groups (1.87 and 2.32 cases per 100 person-years, respectively) compared with those reported in the DPP trial (4.8 in the intervention and 11.0 cases per 100 person-years in the placebo group) (8). Therefore, it is challenging to directly compare the effect size of our interventions with those from these studies.

Nevertheless, in general, weight loss is crucial for reducing diabetes risk. The DPP trial achieved an average weight loss in the lifestyle intervention group of 5.6 kg (a 7% reduction of initial body weight) (8), whereas the DPS trial saw 5% weight loss (7). In PREDIMED-Plus, 3.7% body weight loss over a period of 6 years was associated with long-term diabetes risk reduction. Therefore, even modest weight losses can lead to reductions in diabetes risk, consistent with previous studies (41–43). The potential effect modification by sex may be explained by greater weight losses in men (3.4 kg) than in women (2.3 kg), which was also observed in the DPP trial (44). However, these subgroup findings should be interpreted cautiously considering the number of comparisons performed (45).

Our findings build on the previous PREDIMED-1 trial (11), showing that an ad libitum MedDiet versus a low-fat diet reduced diabetes incidence by 30%. The intensity of the intervention in the control group of PREDIMED-Plus was comparable to that of the active intervention group with MedDiet in the previous PREDIMED-1 trial. However, we acknowledge that the higher intensity and frequency in the intervention than in the control group of PREDIMED-Plus may partially explain the improved adherence and outcomes. Undoubtedly, weight loss, increased physical activity, and reduction in caloric intake represent greater challenges than only changing the dietary pattern. That was the reason why higher intensity and frequency were required in the protocol of PREDIMED-Plus for the intervention than for the control group.

Some limitations are acknowledged. Diabetes was a prespecified secondary outcome, but randomization was effective in balancing baseline characteristics in all participants without diabetes. Dietary adherence was self-reported; however, we strengthened assessments through periodic in-person administration of a validated tool specific for the trial (19). Staff performing anthropometric measures—though trained to follow a standardized protocol—were not blinded to group assignment. In addition, the multifaceted intervention makes it difficult to disentangle the proportion of benefits due to the changes in each of the 3 components (erMedDiet, physical activity, or weight loss) of the intervention or a potential synergistic effect among them. Lastly, our results derive from participants aged 55 to 75 years with metabolic syndrome, living in a European Mediterranean country, potentially limiting their generalizability to younger populations or those with different ethnic backgrounds or diverse dietary traditions.

Figure 3. Mean values (95% CIs) of adherence to the erMedDiet (17-point score), physical activity, body weight, and waist circumference during follow-up by intervention group.



erMedDiet = energy-reduced Mediterranean diet; MET-min/wk = metabolic equivalent of task minutes per week. Mixed linear model with random intercepts at recruitment site, participant, and cluster family level. Conducted with completers only. $P = 0.027$ (between-group differences at baseline); $P < 0.001$ (between-group differences during the follow-up period).

Future research should address several important questions, including the identification of which components of the intervention are most critical for diabetes prevention and which subgroups derive the greatest benefit. Implementation studies exploring how to effectively translate this approach into diverse clinical and community settings are essential. Longer-term follow-up studies would also help determine whether the observed benefits persist beyond the intervention period. Finally, the greater improvements in both MedDiet adherence scores and physical activity levels in the intervention group demonstrate that more frequent participant contact likely contributed to better adherence to lifestyle recommendations. This highlights the potential importance of contact intensity in lifestyle interventions, which should be considered when interpreting our results and designing future diabetes-prevention strategies.

In conclusion, among adults with overweight or obesity with metabolic syndrome, a MedDiet intervention including caloric reduction, physical activity, and modest weight loss reduced diabetes incidence beyond that achieved with only a traditional ad libitum MedDiet intervention, whose protective effects against diabetes were previously demonstrated. Although there is no “one-size-fits-all” dietary strategy plan for diabetes prevention (46), the MedDiet’s higher palatability and cultural acceptance (47) could make it a highly sustainable, long-term, weight loss option when combined with moderately reduced energy intake. Clinicians should consider recommending this approach for patients with overweight or obesity, particularly when conventional Mediterranean dietary advice alone has proven insufficient. This multicomponent lifestyle modification represents a practical and sustainable strategy that could be incorporated into routine clinical practice for diabetes prevention.

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Note: Drs. Ruiz-Canela and Salas-Salvadó had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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Data Sharing Statement: A controlled data sharing model is followed in the PREDIMED-Plus study using pseudoanonymized (deidentified) study data only, for collaborating with approved researchers. Requestors wishing to access the PREDIMED-Plus trial data used in this study for collaboration can request it from the PREDIMED-Plus Trial Steering Committee at predimed_plus_scommittee@googlegroups.com. Requests are considered by the PREDIMED-Plus Steering Committee composed of J. Salas-Salvadó (Chair), M.Á. Martínez-González, M. Fitó, E. Ros, F. Tinahones, D. Corella, and R. Estruch. Decisions on data access are based on the scientific legitimacy of the requester and of their institution, and on assurances on information security and governance; and with regard to the study's scientific reputation, the needs of funded study team research, the terms of participant consent, and regulatory requirements. All research using PREDIMED-Plus must be within the scope of the ethically approved PREDIMED-Plus Protocol. Studies where data and/or biological samples are requested are subject to ethics approval by the institutional review boards of the corresponding PREDIMED Plus recruitment centers.

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