Effect of a Lifestyle Intervention Program With Energy-Restricted Mediterranean Diet and Exercise on Weight Loss and Cardiovascular Risk Factors: One-Year Results of the PREDIMED-Plus Trial

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OBJECTIVE

The long-term impact of intentional weight loss on cardiovascular events remains unknown. We describe 12-month changes in body weight and cardiovascular risk factors in PREvención con DIeta MEDiterránea (PREDIMED)-Plus, a trial designed to evaluate the long-term effectiveness of an intensive weight loss lifestyle intervention on primary cardiovascular prevention.

RESEARCH DESIGN AND METHODS

Overweight/obese adults with metabolic syndrome aged 55–75 years ($n = 626$) were randomized to an intensive weight loss lifestyle intervention based on an energy-restricted Mediterranean diet, physical activity promotion, and behavioral support (IG) or a control group (CG). The primary and secondary outcomes were changes in weight and cardiovascular risk markers, respectively.

RESULTS

Diet and physical activity changes were in the expected direction, with significant improvements in IG versus CG. After 12 months, IG participants lost an average of 3.2 kg vs. 0.7 kg in the CG ($P < 0.001$), a mean difference of −2.5 kg (95% CI −3.1 to −1.9). Weight loss ≥5% occurred in 33.7% of IG participants compared with 11.9% in the CG ($P < 0.001$). Compared with the CG, cardiovascular risk factors, including waist circumference, fasting glucose, triglycerides, and HDL cholesterol, significantly improved in IG participants ($P < 0.002$). Reductions in insulin resistance, HbA_{1c}, and circulating levels of leptin, interleukin-18, and MCP-1 were greater in IG than CG participants ($P < 0.05$). IG participants with prediabetes/diabetes significantly improved glycemic control and insulin sensitivity, along with triglycerides and HDL cholesterol levels compared with their CG counterparts.

CONCLUSIONS

PREDIMED-Plus intensive lifestyle intervention for 12 months was effective in decreasing adiposity and improving cardiovascular risk factors in overweight/obese older adults with metabolic syndrome, as well as in individuals with or at risk for diabetes.

The current obesity pandemic entails a major impact on global morbidity and premature mortality linked to chronic diseases while severely impairing the quality of life of affected individuals and posing a significant burden to the health system (1,2). Thus, effective strategies to reduce the burden of obesity and its adverse health consequences are urgently needed.

Prior research has shown that moderate weight loss (5–10% of initial body weight) achieved through lifestyle changes is associated with improvement of cardiometabolic abnormalities characteristic of overweight/obesity (3,4) and reduction in the risk of type 2 diabetes (5). Expectedly, greater weight losses lead to greater cardiometabolic benefit (6,7). However, there are inconsistencies in the association between overweight/obesity and total or cardiovascular mortality, particularly after a controversial systematic review (8). Additionally, the lack of benefit on cardiovascular events or mortality of a recent large intervention trial focused on weight loss among individuals with type 2 diabetes casts doubts on the long-term cardiovascular impact of weight loss (9).

The current recommendation for patients with overweight or obesity, especially if they harbor the metabolic syndrome (MetS), is to establish a plan for weight loss through lifestyle changes. Although successful weight loss is expected to reduce cardiovascular risk, no large randomized controlled trial (RCT) has ever demonstrated that long-term intentional weight loss reduces the incidence of cardiovascular disease (CVD) events. In the only available trial (Look AHEAD) conducted to assess the long-term effects on CVD of weight loss and physical activity (PA), the results were null (9). Look AHEAD was conducted exclusively among individuals with diabetes, and the choice of a low-fat diet as active intervention has been argued as one explanation for its lack of cardiovascular benefit (10). Although not focused on weight loss, the Women's Health Initiative Dietary Modification Trial also used a low-fat diet and failed to show any benefit on cardiovascular events (11). Another nutritional strategy used to lose weight is carbohydrate restriction. However, low-carbohydrate diets are usually rich in saturated fat and poor in fiber and mineral content, are associated with increased LDL cholesterol, and tend to lose their weight-reducing efficacy after 12 months (12). Another dietary paradigm that may be an effective alternative to low-fat or low-carbohydrate diets in terms of weight loss is the Mediterranean diet (MedDiet), in which the quality of fat and carbohydrates is more important than the amounts of these macronutrients (13). A meta-analysis of RCTs suggests that the MedDiet is a useful tool to reduce body weight and obesity-related metabolic alterations, particularly when total energy intake is restricted (14). The Dietary Intervention Randomized Controlled Trial (DIRECT) trial and a recent meta-analysis (15,16) also provided further evidence supporting the stronger beneficial effects of the MedDiet on weight loss and long-term maintenance of modest weight loss as compared with a low-fat diet.

The PREvención con DIeta MEDiterránea (PREDIMED) intervention trial contributed to a large body of available evidence supporting the effectiveness of the MedDiet for cardiovascular prevention (17). A cardiovascular benefit of the MedDiet is plausible due to its beneficial impact on classical and emergent cardiovascular risk factors, such as hypertension, dyslipidemia, increased adiposity, MetS, type 2 diabetes, insulin resistance, and markers of oxidative stress, inflammation, and endothelial

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**A complete list of the PREDIMED-Plus investigators can be found in the Supplementary Data online.*

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dysfunction, respectively (13). The PREDIMED-Plus randomized trial, started in 2013, provides a unique opportunity to assess the long-term cardiovascular effects of an intensive weight loss intervention based on an energy-restricted MedDiet (erMedDiet), PA promotion, and behavioral support in comparison with a control group (CG). In this study, we report on a study within the PREDIMED-Plus trial on the 12-month effects of the intervention on weight loss, adiposity, and intermediate markers of cardiovascular risk in overweight/obese adults with MetS at high cardiovascular risk.

RESEARCH DESIGN AND METHODS

Study Design

The PREDIMED-Plus trial is a new 6-year parallel-group, multicenter RCT involving 6,874 participants recruited in 23 Spanish recruiting centers. The trial's main objective is to evaluate the effect of an intensive weight loss intervention based on an erMedDiet, PA promotion, and behavioral support (IG) on hard cardiovascular events in comparison with a CG receiving usual care, including the recommendation to follow an energy-unrestricted MedDiet without any advice to increase PA. The primary end point is a composite of CVD events (cardiovascular death, nonfatal myocardial infarction, and nonfatal stroke). The recruitment period lasted from 5 September 2013 to 30 November 2016. The intervention is scheduled to last for an average time of 6 years, with a further 2 years of extended follow-up for collection of clinical events. The PREDIMED-Plus protocol is available at http://predimedplus.com/. The institutional review boards of the 23 participating centers approved the study protocol, and all participants provided written informed consent.

The current report is the first longitudinal assessment of the PREDIMED-Plus RCT aimed to examine the 6- and 12-month effects of the intensive lifestyle intervention on body weight, adiposity parameters, and intermediate markers of cardiovascular risk (systolic and diastolic blood pressure, glucose metabolism–related variables, lipid profile, and peripheral levels of leptin, C-peptide, and some inflammatory markers) in comparison with usual care. This analysis was performed in 626 participants randomized into the trial belonging to the first 1,013 candidates assessed for eligibility. These participants were recruited from 13 out of the 23 PREDIMED-Plus recruiting centers because these centers were the first that started the recruitment of participants. The data were analyzed using the available complete PREDIMED-Plus database, dated 12 May 2017.

Participant Selection and Recruitment

From September 2013 until September 2014, medical doctors from primary health care centers associated with hospital or university recruiting centers assessed potential participants for eligibility. Eligible participants were men (aged 55–75 years) and women (aged 60–75 years), without documented history of CVD (except heart failure New York Heart Association class I and II or valvular heart disease) at enrollment, who were overweight/obese (BMI $\geq$27 and $<$40 kg/m^2) and disclosed at least three components of the MetS according to the harmonized definition of the joint statement from the International Diabetes Federation/National Heart, Lung, and Blood Institute/American Heart Association (2009), the most updated and largely recognized set of MetS criteria (18). Detailed inclusion and exclusion criteria are displayed in the Supplementary Data.

Potentially eligible candidates were contacted by telephone or interviewed in person in a clinical visit. A screening interview with a PREDIMED-Plus investigator was scheduled to inform in detail willing candidates about the study and obtain signed informed consent. Prior to randomization, potential participants entered a 4-week run-in period comprising three screening visits aimed at determining adherence to study procedures. Candidates were evaluated according to inclusion and exclusion criteria and received questionnaires assessing different lifestyle and sociodemographic variables to be returned at the last screening visit. In a second telephone-based visit, investigators ensured completion of the administered questionnaires. Importantly, in January 2014, following advice of the Data Safety and Monitoring Board, the Steering Committee decided to amend the protocol and omit the prerandomization requirement to sustain at least a 1.5-kg weight loss. Consequently, from this date onwards, recruits were advised to maintain their usual eating habits, PA level, and body weight. Such protocol change only affected the first 70 participants who were eligible and randomized in two vanguard centers (Supplementary Fig. 1). In the third screening face-to-face visit, candidates meeting eligibility criteria who had attended all screening visits and correctly filled in the administered questionnaires and records were randomized to either IG or CG.

Randomization and Intervention

Each recruiting center randomly allocated candidates in a 1:1 ratio to either the IG or the CG, using a centrally controlled, computer-generated random-number internet-based system with stratification by center, sex, and age ($<$65, 65–70, and $>$70 years). The randomization procedure was internet-based and blinded to all staff and to the principal investigators of each recruitment center. Couples sharing the same household were randomized together, using the couple as unit of randomization. The name, sex, age, center, and individual/couple randomization status of participants willing to participate and fulfilling inclusion criteria were submitted by the field team of each site to the internet-based system. This system applied the randomization algorithm and then returned to the site the automatically generated group assigned to the participant. With this system, no changes were possible regarding group assignments after the submission of the demographic data of the participant. In the specific cases of couples in which the first spouse was previously recruited at a different time, the last spouse entering the study was directly assigned (not randomized) to the same study arm as his/her partner (n = 73).

A 17-item questionnaire aimed at assessing adherence to the erMedDiet was delivered at baseline, 6, and 12 months in both study groups. The validated 14-item PREDIMED questionnaire was also used to assess adherence to the traditional MedDiet only in the CG participants (19) (Supplementary Data). A validated 143-item food frequency questionnaire was also completed, together with the validated Regicor Short Physical Activity Questionnaire (20) and the validated Spanish version of the Nurses' Health Study questionnaire to assess sedentary behaviors (21). Physical fitness was evaluated using the validated 30-s chair-stand

test (22). Additional information related to sociodemographic and lifestyle aspects, education level, individual and family medical history, and current medication use was collected. Anthropometric and blood pressure measurements were obtained, and samples of fasting blood and urine were collected.

Intervention

Participants allocated to the IG followed an erMedDiet plus PA promotion and behavioral support, with the purpose of accomplishing specific weight loss objectives. The objectives in terms of weight loss and the interventions are detailed in the Supplementary Data.

Participants in the CG received educational sessions on an ad libitum MedDiet with the same content as those used in the PREDIMED study (17). No specific advice for increasing PA or losing weight was provided to them (Supplementary Data).

In addition to the individual sessions (Supplementary Data), participants in both groups received periodical group sessions and telephone calls once per month in the IG and every 6 months in the CG. Briefly, group sessions for both study groups were conducted by the dietitians and consisted of informative talks addressing lifestyle-related topics, in which free extra virgin olive oil (1 L/month) and raw nuts (125 g/month) were provided in order to reinforce adherence to the protocol in both arms of the trial.

Outcomes and Assessments

The primary end point of the current study was between-group differences in weight loss at 6 and 12 months of intervention, expressed in absolute values (kilograms) and percentage as well as changes in BMI from baseline. Weight-related secondary end points at 6 and 12 months were the between-group differences in the proportions of participants who had either a stable weight or weight below baseline values, those who lost at least 5% or 10% of their initial weight, and those reversing obesity (changing BMI from $\geq$30 to $<$30 kg/m^2).

Other secondary outcomes were 6- and 12-month changes in waist circumference, body composition, systolic and diastolic blood pressure, fasting glucose, HbA_{1c}, insulin sensitivity, and lipid levels. Methods for anthropometry, body composition, and blood pressure measurements are described in the Supplementary Data.

After an overnight fast, blood samples were collected at baseline, 6, and 12 months. Tubes of serum and plasma were collected, and aliquots were coded and stored at -80°C in a central laboratory until analyses. Serum glucose, triglycerides, total cholesterol, and HDL cholesterol levels were measured using standard enzymatic methods, and LDL cholesterol concentrations were calculated with the Friedewald formula.

Other outcomes included 12-month changes in circulating levels of fasting serum insulin, leptin, C-peptide, hs-CRP, interleukin-6 (IL-6), IL-8, IL-18, tumor necrosis factor-α, MCP-1, and regulated on activation, normal T-cell expressed and secreted cytokines. The methods used for these determinations are shown in the Supplementary Data. Laboratory personnel performing all assays were blinded to group allocation.

Statistical Analyses

All analyses were performed using STATA software, version 15.0 (StataCorp LP, College Station, TX). Based on previous studies (6,15,23), and assuming that our intervention has only a small effect on weight change, achieving a weight loss of 3 kg in the IG and 1 kg in the CG, with a SD of 8 and a correlation of 0.7 between first and second measurements, 80% power, and α = 0.05, we would need a sample size of 151 in each group. Because the number of participants included in the present analysis is much higher than this figure, the study had 100% power to detect at least a 2-kg difference between groups.

We used descriptive statistics with mean ($\pm$ SD) or percentages (numbers) for participants' baseline characteristics. Data were analyzed by using the intention-to-treat principle and the completers-only framework. The small number of missing outcome data (3% for weight) were handled via multivariate imputation with chained equations (STATA "mi" command), generating 20 imputations for each missing measurement from regression equations to predict these outcomes. The imputation models included as predictors all variables in Table 1 and group allocation. Analyses of completers include only participants who had all measurements, without the inclusion of imputed data. Continuous outcomes were assessed for normality with the Shapiro-Wilk test, visual inspection of histograms, and scatter plots before each analysis.

Intervention effects on weight loss and BMI changes from baseline were evaluated using linear regression models based on between-group differences in mean changes. We used robust variance estimators to account for intracluster correlations in all regression models, considering as clusters the members of the same household. Prespecified subgroup analyses of the primary results were conducted within strata of sex, age, BMI, diabetes status, insulin use, statin treatment, and educational level. The proportions of participants in each group achieving the different weight loss categorical outcomes at 6 and 12 months were compared with the χ^2 test. The between-group differences in changes in cardiovascular risk markers, dietary variables, PA, sedentary behaviors, and medication use were compared using linear regression, χ^2 test, independent-samples *t* test, or median regression analyses if data were skewed to examine differences in medians (reporting median and interquartile range), as appropriate. Values are shown as mean and 95% CI, if not indicated otherwise. Significance for all statistical tests was set at $P < 0.05$ for bilateral contrast.

RESULTS

Between September 2013 and September 2014, 1,013 candidates were assessed for eligibility. Of these, 143 refused to participate, and 172 did not meet inclusion or randomization criteria. Thus, 698 participants were randomly allocated into two intervention groups of similar size, of whom 626 were included in the final analysis (n = 327, IG; and n = 299, CG). Approximately 98% of participants in each group completed 12 months of follow-up, without significant differences in attrition between groups (Supplementary Fig. 1).

Participants' Baseline Characteristics

Randomized participants were comparable to those not randomized due to ineligibility regarding body weight (mean 85 kg), waist circumference (107 cm), and proportion of men (44%). However, compared with nonrandomized participants, those randomized were slightly

Table 1—Characteristics of participants at randomization

Characteristic	All (n = 626)	Intervention group (n = 327)	Control group (n = 299)
Age (years)	65 ± 5	66 ± 5	65 ± 5
Male	46 (289)	45 (148)	47 (141)
Same household (couples)	12 (73)	12 (38)	12 (35)
Weight (kg)	86.3 ± 12.9	85.8 ± 13.1	86.9 ± 12.7
BMI (kg/m^2)	32.5 ± 3.5	32.3 ± 3.4	32.6 ± 3.6
Waist circumference (cm)	106.8 ± 9.3	106.3 ± 8.9	107.3 ± 9.6
Obese (BMI ≥30 kg/m^2)	73 (459)	73 (240)	73 (219)
Prediabetes*	40 (248)	39 (129)	40 (119)
Type 2 diabetes†	45 (281)	44 (144)	46 (137)
Hypertension	88 (551)	87 (285)	89 (266)
Dyslipidemia	74 (461)	72 (234)	76 (227)
Number of MetS components			
≤3 components	57 (354)	57 (185)	57 (169)
4 components	28 (175)	27 (90)	28 (85)
5 components	15 (97)	16 (52)	15 (45)
Current smokers	11 (68)	11 (36)	11 (32)
Former smokers	41 (260)	39 (126)	45 (134)
Medications			
Lipid-lowering drugs	55 (342)	52 (171)	57 (171)
Statin use	48 (298)	46 (150)	49 (148)
Antihypertensive therapy	78 (488)	76 (250)	80 (238)
Thiazide drugs‡	26 (163)	26 (86)	26 (77)
ACEi/ARB use	61 (381)	60 (195)	62 (186)
Oral antidiabetic medications§	36 (227)	36 (117)	37 (110)
Insulin treatment	7 (44)	6 (21)	8 (23)
Educational level			
Primary school	52 (324)	50 (165)	53 (159)
First-degree high school	28 (173)	27 (89)	28 (84)
High school or university	21 (129)	22 (73)	19 (56)

Data are mean ± SD or percentage (number). ACEi, ACE inhibitor; ARB, angiotensin type 2 receptor blocker. *Prediabetes was defined as fasting plasma glucose of 100–125 mg/dL (5.6–6.9 mmol/L) or glycated hemoglobin (HbA_{1c}) of 5.7–6.4% (39–47 mmol/mol). †Diabetes was defined as previous diagnosis of diabetes or HbA_{1c} ≥6.5% (48 mmol/mol), use of antidiabetic medication or having fasting glucose >126 mg/dL (7.0 mmol/L) in the screening visit plus fasting glucose >126 mg/dL (7.0 mmol/L) at baseline visit. ‡Thiazide drugs include thiazides and thiazide-like diuretics. §Oral antidiabetic medications include treatment with meglitinides, sulfonylureas, biguanides, thiazolidinediones, dipeptidyl peptidase IV inhibitors, and α-glucosidase inhibitors, each used as a single oral agent or combined with one or more oral antidiabetic drugs.

younger (by 1 year; $P < 0.001$). The IG and CG participants were well matched at randomization and showed similar baseline characteristics (Table 1).

Compliance With the Dietary and Lifestyle Interventions

At baseline, participants in the two groups reported similar adherence to the MedDiet and similar intakes of food groups, energy, and nutrients. At 6 and 12 months, participants in the IG reported a significantly greater achievement in 10 of the 17 items of the questionnaire of adherence to the erMedDiet, with a net increase of 2 points versus CG at 12 months ($P < 0.001$) (Supplementary Tables 1 and 2). Although the general food pattern improved in both IG and CG, the consumption of some key Mediterranean foods improved significantly more in IG than CG participants (Supplementary Table 3). At 12 months, reductions in daily energy intake were more pronounced in the IG than in CG ($P = 0.05$), and participants in the IG reported a lower intake of carbohydrates and higher intakes of protein, total fat, and monounsaturated fat (Supplementary Table 4).

Total leisure time PA increased significantly from baseline in the IG while decreasing in the CG ($P = 0.001$). A significant reduction from baseline of total sedentary time was observed in the IG, without significant differences versus CG (Supplementary Table 2). Mean time spent in television viewing was reduced significantly more among participants in the IG than in the CG. At baseline, the proportions of participants meeting the World Health Organization's 2010 recommendations of at least 150 min of moderate-vigorous PA/week were 52.6% in the IG and 51.5% in the CG. At 12 months, this proportion increased by 11.5% in the IG, whereas it decreased by 0.7% in the CG ($P = 0.001$). Changes in the 30-s chair-stand test were minor and did not differ between groups. Of note, during the 12 months of the study, participants in the IG attended 75% and 67% of the individual and group sessions, respectively, whereas respective rates for those in the CG were 95% and 78%.

Weight Loss and Maintenance

Because intention-to-treat (using multiple imputation methods) and completers-only analyses showed similar results, only intention-to-treat results are reported. Weight losses between the two groups differed significantly over time (Table 2): at 6 months, the mean weight losses from baseline among participants assigned to intervention and control were −2.4 (−2.7%) and −0.4 kg (−0.5%), respectively, whereas respective values at 12 months were −3.2 (−3.7%) and −0.7 kg (−0.8%). The maximum between-group difference in weight loss was reached at 12 months, with a mean difference in weight changes between the IG and CG of −2.5 kg (−3.1 to −1.9). Results were consistent among subgroups of sex, age, BMI, diabetes, insulin use, statin treatment, and educational level (Supplementary Table 5). Reductions in BMI from baseline to 6 and 12 months were greater in the IG (Table 2). Results were also qualitatively similar after adjusting by baseline values.

More participants in the IG than in the CG lost weight below their initial weight at 6 months (81.3% vs. 58.4%; $P < 0.001$) and 12 months (84.1% vs. 57.9%; $P < 0.001$) (Table 3). In all weight loss thresholds (losses of ≥5%, or ≥10%, and change of baseline BMI ≥30 to <30 kg/m^2) at 6 and 12 months, the proportions of participants attaining these targets were significantly higher in the IG than in the CG. At 12 months, 33.7 and 6.9% of participants in the IG achieved a weight loss of ≥5% and of at least 10%, respectively.

Table 2—Mean weight loss at 6 and 12 months of intervention, expressed as absolute body weight loss (kilograms), percent reduction relative to baseline, and absolute change in BMI by treatment group: intention-to-treat (multiple imputation) and completers-only

	Intervention group		Control group		Intervention vs. control			
					Between-group difference			
Variable	Intention-to-treat (MI) (n = 327)	Completers-only (n = 302)	Intention-to-treat (MI) (n = 299)	Completers-only (n = 282)	Intention-to-treat (MI)	P value	Completers-only	P value
Change in body weight (kg)								
At month 6	−2.4 (−2.8 to −2.0)	−2.4 (−2.8 to −2.0)	−0.4 (−0.8 to −0.1)	−0.4 (−0.8 to −0.1)	−1.9 (−2.4 to −1.4)	<0.001	−2.0 (−2.5 to −1.4)	<0.001
At month 12	−3.2 (−3.7 to −2.8)	−3.3 (−3.8 to −2.8)	−0.7 (−1.1 to −0.3)	−0.7 (−1.2 to −0.3)	−2.5 (−3.2 to −1.9)	<0.001	−2.6 (−3.2 to −1.9)	<0.001
Change in body weight (%)								
At month 6	−2.7 (−3.2 to −2.3)	−2.7 (−3.2 to −2.3)	−0.5 (−0.9 to −0.1)	−0.5 (−0.9 to −0.1)	−2.2 (−2.8 to −1.6)	<0.001	−2.2 (−2.8 to −1.6)	<0.001
At month 12	−3.7 (−4.3 to −3.2)	−3.8 (−4.3 to −3.2)	−0.8 (−1.3 to −0.3)	−0.8 (−1.3 to −0.3)	−3.0 (−3.6 to −2.3)	<0.001	−3.0 (−3.7 to −2.3)	<0.001
Change in BMI (kg/m^2)								
At month 6	−0.9 (−1.0 to −0.8)	−0.9 (−1.0 to −0.8)	−0.2 (−0.3 to −0.1)	−0.2 (−0.3 to −0.1)	−0.7 (−0.9 to −0.5)	<0.001	−0.7 (−0.9 to −0.5)	<0.001
At month 12	−1.2 (−1.4 to −1.0)	−1.2 (−1.4 to −1.1)	−0.3 (−0.4 to −0.1)	−0.3 (−0.4 to −0.1)	−1.0 (−1.2 to −0.7)	<0.001	−1.0 (−1.2 to −0.7)	<0.001

Data are mean (95% CI). P values for between-group differences were calculated using linear regression models with robust SE to account for intracluster correlations. MI, multiple imputation.

Compared with the CG, the IG experienced greater decreases in total body fat. Significant reductions in total lean mass were observed only in the IG, whereas no changes occurred in the CG. Compared with the CG, the IG showed greater improvement in total lean mass/total body fat ratio (Supplementary Table 6).

Waist Circumference, Blood Pressure, Glucose Metabolism–Related Parameters, and Lipid Profile

For several risk factors, between-group differences were most apparent at 12 months, when a maximum difference in weight loss was reached (Table 4). Waist circumference showed a greater reduction in the IG than in the CG both at 6 and 12 months. Significant reductions in all glucose metabolism–related parameters (fasting glucose, HbA_{1c}, insulin, and HOMA of insulin resistance [HOMA-IR] index) were observed in the IG after 12 months, whereas no changes occurred in the CG.

The IG experienced greater improvements in HDL cholesterol and triglyceride levels. Systolic and diastolic blood pressure and total and LDL cholesterol decreased in the two groups, without between-group differences. For all analyses, results were also qualitatively similar after adjusting by baseline values. We have further conducted subgroup analyses stratified according to diabetes status (normal glycemia, prediabetes, and diabetes) to assess the changes in glucose metabolism–related parameters and lipid profile (Supplementary Tables 7–9). Among participants with diabetes (n = 281) and prediabetes (n = 181), the intervention obtained improvements in glycemic control and insulin sensitivity, along with amelioration in triglyceride and HDL cholesterol levels significantly higher than the CG ($P < 0.05$) (Supplementary Tables 7 and 8).

On-trial changes in medications to control blood glucose, dyslipidemia, or hypertension were similarly distributed between the two groups (Supplementary Table 9).

Leptin, Pancreatic Insulin Secretion, and Inflammatory Markers

Novel cardiovascular risk biomarkers were measured only at baseline and 12 months. Circulating leptin had a greater reduction in the IG than in the CG. Levels of IL-18

and MCP-1 also decreased significantly versus control. Circulating C-peptide decreased significantly only in the IG, but without significant differences versus control. Changes in other inflammatory markers, such as hs-CRP, IL-6, IL-8, tumor necrosis factor-α, and regulated on activation, normal T-cell expressed and secreted, were minor and not statistically different between groups (Supplementary Table 10).

CONCLUSIONS

In this study conducted in the first participants recruited into the PREDIMED-Plus trial who had a 12-month follow-up, we show that the intensive lifestyle intervention was effective in producing a clinically meaningful weight loss among overweight/obese adults with MetS. As expected, participants allocated to the IG lost more weight and also showed greater improvements in some cardiovascular risk factors at 6 and 12 months than CG participants. Weight loss was maximal after 12 months, when improvements in risk factors were more evident, suggesting a strong relationship between the magnitude of weight loss achieved and changes in cardiovascular risk.

In most long-term weight loss studies using lifestyle (diet or/and exercise) interventions or drugs, maximum weight loss was typically achieved at 6 months of intervention, and thereafter a plateau or, more frequently, weight regain occurred (5,9,24,25). Notwithstanding, in our study, maximum weight loss was achieved at 12 months—for the entire study population and by subgroups of sex, age, BMI, diabetes status, insulin and statin treatment, and educational level—without any evidence of weight regain, thereby highlighting the sustained efficacy of our intensive lifestyle intervention based on an erMedDiet, PA, and behavioral enforcement. A maximum increase in adherence to the erMedDiet score was evident after 12 months in both groups, with a net increase in favor of the IG, as expected. In addition, the increase in the percentage of individuals achieving the goals for each of the 17 score items was apparent in 11 of the 17 items at 6 months, but also at 12 months, reflecting the large potential for long-term sustainability of the intervention in PREDIMED-Plus. These changes can be explained by a higher and

Table 3—Proportion of participants (%) who met different weight loss criteria at 6 and 12 months of intervention by treatment group: intention-to-treat (multiple imputation) and completers-only

	Proportion of participants (%)				Intervention vs. control			
	Intervention group		Control group		Between-group difference			
Criteria	Intention-to-treat (MI) (n = 327)	Completers-only (n = 302)	Intention-to-treat (MI) (n = 299)	Completers-only (n = 282)	Intention-to-treat (MI)	P value	Completers-only	P value
At or below baseline weight								
At month 6	81.3 (76.9–85.6)	81.4 (76.6–85.5)	58.4 (52.6–64.2)	58.5 (52.6–64.1)	22.9 (15.5–30.1)	<0.001	22.7 (15.3–30.0)	<0.001
At month 12	84.1 (80.0–88.2)	84.4 (80.3–88.5)	57.9 (52.2–63.7)	58.2 (52.4–63.9)	26.3 (19.1–33.5)	<0.001	26.0 (18.7–33.1)	<0.001
At least 5% below baseline weight								
At month 6	20.7 (16.2–25.3)	20.8 (16.3–25.4)	6.5 (3.6–9.3)	6.4 (3.5–9.2)	14.2 (8.6–19.7)	<0.001	14.5 (8.9–20.0)	<0.001
At month 12	33.7 (28.4–39.1)	34.1 (28.7–39.5)	11.9 (8.1–15.7)	11.7 (7.9–15.5)	21.8 (15.2–28.3)	<0.001	22.4 (15.7–29.0)	<0.001
At least 10% below baseline weight								
At month 6	4.2 (1.8–6.5)	3.6 (1.5–5.8)	0.9 (−0.3 to 2.2)	0.7 (−0.2 to 1.6)	3.3 (0.5–5.9)	0.02	2.9 (0.5–5.3)	0.02
At month 12	6.9 (4.1–9.8)	6.6 (3.8–9.4)	2.2 (0.4–3.9)	2.1 (0.4–3.8)	4.7 (1.3–8.1)	0.007	4.5 (1.2–7.8)	0.008
Change from baseline BMI ≥30 to BMI <30 kg/m^2								
At month 6	11.3 (7.8–14.8)	10.9 (7.3–14.5)	6.3 (3.4–9.1)	6.0 (3.2–8.8)	5.0 (0.4–9.6)	0.03	4.9 (0.3–9.4)	0.03
At month 12	15.7 (11.6–19.7)	15.6 (11.4–19.7)	6.7 (3.7–9.6)	6.4 (3.5–9.2)	9.0 (3.9–14.1)	0.001	9.2 (4.1–14.2)	<0.001

Data are percentage (95% CI). P values for between-groups differences were calculated using linear regression models with robust SE to account for intracluster correlations. MI, multiple imputation.

Table 4—Baseline and 6- and 12-month changes in adiposity, blood pressure, and cardiovascular risk factors by treatment group: intention-to-treat (multiple imputation) and completers-only

	Intervention group		Control group		Intervention vs. control			
					Between-group difference			
Variable	Intention-to-treat (MI)	Completers-only	Intention-to-treat (MI)	Completers-only	Intention-to-treat (MI)	*P* value	Completers-only	*P* value
Waist circumference (cm)	*n* = 327	*n* = 292	*n* = 299	*n* = 275				
Baseline	106.3 (105.3–107.2)	106.3 (105.2–107.3)	107.3 (106.2–108.4)	107.3 (106.1–108.4)				
6-month change	−3.0 (−3.6 to −2.5)	−3.1 (−3.7 to −2.5)	−0.9 (−1.5 to −0.3)	−0.9 (−1.4 to −0.3)	−2.1 (−2.9 to −1.3)	<0.001	−2.2 (−3.1 to −1.4)	<0.001
12-month change	−3.1 (−3.8 to −2.5)	−3.3 (−3.8 to −2.8)	−0.7 (−1.3 to 0.03)	−0.7 (−1.4 to −0.2)	−2.5 (−3.4 to −1.5)	<0.001	−2.5 (−3.5 to −1.6)	<0.001
Systolic BP (mmHg)	*n* = 327	*n* = 291	*n* = 299	*n* = 270				
Baseline	139.0 (137.0–140.7)	139.1 (137.2–140)	138.1 (136.2–140.0)	138.1 (136.1–140.1)				
6-month change	−0.8 (−2.6 to 1.0)	−0.7 (−2.5 to 1.1)	0.9 (−1.0 to 2.8)	0.8 (−1.0 to 2.7)	−1.7 (−4.3 to 0.9)	0.19	−1.6 (−4.2 to 0.9)	0.21
12-month change	−3.5 (−5.4 to −1.6)	−3.5 (−5.4 to −1.5)	−2.0 (−4.1 to 0.1)	−1.9 (−4.0 to 0.2)	−1.5 (−4.4 to 1.4)	0.24	−1.6 (−4.4 to 1.3)	0.28
Diastolic BP (mmHg)	*n* = 327	*n* = 291	*n* = 299	*n* = 270				
Baseline	79.9 (78.8–81.1)	79.8 (78.6–81)	79.0 (77.7–80.0)	79.0 (77.8–80.2)				
6-month change	−1.8 (2.8 to −0.8)	−1.7 (2.7 to −0.7)	−0.4 (−1.4 to 0.6)	−0.3 (−1.3 to 0.7)	−1.4 (−2.8 to −0.04)	0.05	−1.4 (−2.8 to 0.05)	0.06
12-month change	−2.1 (−3.0 to −1.2)	−2.2 (−3.1 to −1.3)	−1.4 (−2.4 to −0.3)	−1.3 (−2.4 to −0.2)	−0.7 (−2.1 to 0.7)	0.34	−0.9 (−2.3 to 0.5)	0.22
Glucose (mmol/L)	*n* = 327	*n* = 294	*n* = 299	*n* = 261				
Baseline	6.53 (6.34–6.72)	6.52 (6.331–6.72)	6.50 (6.30–6.70)	6.45 (6.25–6.65)				
6-month change	−0.13 (−0.24 to −0.01)	−0.13 (−0.24 to −0.01)	0.08 (−0.05 to 0.20)	0.07 (−0.05 to 0.21)	−0.21 (−0.37 to −0.03)	0.02	−0.20 (−0.38 to −0.03)	0.02
12-month change	−0.23 (−0.36 to −0.09)	−0.22 (−0.35 to −0.08)	0.12 (−0.04 to 0.29)	0.16 (−0.01 to 0.33)	−0.35 (−0.56 to −0.13)	0.002	−0.39 (−0.59 to −0.16)	0.001
HbA_{1c} (%)*	*n* = 327	*n* = 193	*n* = 299	*n* = 174				
Baseline	6.0 (5.6–6.5)	6.0 (5.7–6.5)	6.0 (5.6–6.6)	6.0 (5.7–6.6)				
6-month change	−0.10 (−0.33 to 0.10)	−0.10 (−0.30 to 0.10)	0.0 (−0.21 to 0.26)	0.0 (−0.20 to 0.10)	−0.10 (−0.17 to −0.03)	0.006	−0.10 (−0.18 to −0.02)	0.01
12-month change	−0.12 (−0.42 to 0.14)	−0.10 (−0.40 to 0.10)	0.0 (−0.23 to 0.22)	0.0 (−0.20 to 0.20)	−0.12 (−0.21 to −0.02)	0.01	−0.10 (−0.17 to −0.02)	0.01
HbA_{1c} (mmol/mol)*	*n* = 327	*n* = 193	*n* = 299	*n* = 174				
Baseline	42.07 (37.7–48.26)	42.07 (38.79–47.54)	42.07 (38.0–48.70)	42.07 (38.79–48.73)				
6-month change	−1.08 (−3.46 to 1.18)	−1.09 (−3.27 to 1.09)	0.04 (−2.19 to 3.12)	0.0 (−2.18 to 1.09)	−1.11 (−1.91 to −0.32)	0.006	−1.09 (−1.92 to −0.26)	0.01
12-month change	−1.25 (−4.61 to 1.54)	−1.09 (−4.37 to 1.09)	0.02 (−2.39 to 2.41)	0.0 (−2.18 to 2.19)	−1.27 (−2.29 to −0.25)	0.01	−1.09 (−1.92 to −0.26)	0.01
Insulin (pmol/L)†	*n* = 292	*n* = 237	*n* = 267	*n* = 212				
Baseline	132.8 (124.6–141.1)	132.9 (123.5–142.4)	133.2 (123.1–143.2)	132.4 (122.8–142.1)				
6-month change	—	—	—	—	—	—	—	—
12-month change	−26.2 (−34.3 to −18.1)	−27.0 (−34.7 to −19.2)	−7.4 (−15.8 to 1.1)	−6.9 (−15.3 to 1.5)	−18.8 (−30.7 to −6.9)	0.002	−20.1 (−31.5 to −8.7)	0.001
HOMA-IR index‡	*n* = 292	*n* = 237	*n* = 267	*n* = 212				
Baseline	5.20 (4.8–5.58)	5.19 (4.83–5.57)	5.12 (4.73–5.51)	5.09 (4.72–5.47)				
6-month change	—	—	—	—	—	—	—	—
12-month change	−1.16 (−1.51 to −0.81)	−1.12 (−1.45 to −0.79)	−0.07 (−0.48 to 0.33)	−0.11 (−0.47 to 0.26)	−1.09 (−1.60 to −0.58)	<0.001	−1.02 (−1.52 to −0.52)	<0.001
HOMA-IR index§	*n* = 183	*n* = 150	*n* = 162	*n* = 126				
Baseline	4.57 (4.14–4.99)	4.50 (4.13–4.88)	4.79 (4.33–5.25)	4.85 (4.39–5.31)				
6-month change	—	—	—	—	—	—	—	—
12-month change	−1.03 (−1.42 to −0.64)	−0.93 (−1.27 to −0.58)	−0.18 (−0.65 to 0.29)	−0.29 (−0.67 to 0.10)	−0.85 (−1.45 to −0.26)	0.005	−0.64 (−1.16 to −0.13)	0.01

Continued on p. 785

Table 4—Continued

	Intervention group		Control group		Intervention vs. control: Between-group difference			
Variable	Intention-to-treat (MI)	Completers-only	Intention-to-treat (MI)	Completers-only	Intention-to-treat (MI)	*P* value	Completers-only	*P* value
Total cholesterol (mmol/L)	*n* = 327	*n* = 292	*n* = 299	*n* = 257				
Baseline	5.14 (5.03–5.25)	5.09 (4.98–5.20)	5.12 (5.01–5.24)	5.19 (5.07–5.31)				
6-month change	−0.05 (−0.14 to 0.04)	−0.03 (−0.12 to 0.06)	−0.07 (−0.15 to 0.01)	−0.07 (−0.16 to −0.01)	0.02 (−0.10 to 0.13)	0.76	0.04 (−0.08 to 0.16)	0.49
12-month change	−0.13 (−0.22 to −0.04)	−0.12 (−0.21 to −0.03)	−0.15 (−0.24 to −0.06)	−0.16 (−0.26 to −0.07)	0.02 (−0.11 to 0.15)	0.72	0.04 (−0.08 to 0.17)	0.48
HDL cholesterol (mmol/L)	*n* = 327	*n* = 290	*n* = 299	*n* = 254				
Baseline	1.26 (1.22–1.29)	1.26 (1.23–1.30)	1.28 (1.24–1.31)	1.27 (1.23–1.30)				
6-month change	0.07 (0.05–0.09)	0.07 (0.05–0.09)	0.04 (0.02–0.06)	0.04 (0.02–0.06)	0.03 (0.01–0.06)	0.02	0.03 (0.01–0.06)	0.02
12-month change	0.06 (0.04–0.08)	0.06 (0.04–0.08)	0.0 (−0.02 to 0.02)	0.01 (−0.01 to 0.02)	0.06 (0.03–0.09)	<0.001	0.06 (0.03–0.09)	<0.001
LDL cholesterol (mmol/L)	*n* = 327	*n* = 289	*n* = 299	*n* = 253				
Baseline	3.13 (3.04–3.23)	3.08 (2.98–3.18)	3.08 (2.99–3.18)	3.14 (3.04–3.24)				
6-month change	−0.06 (−0.14 to 0.02)	−0.04 (−0.12 to 0.04)	−0.08 (−0.15 to 0.0)	−0.08 (−0.16 to −0.01)	0.02 (−0.09 to 0.12)	0.76	0.04 (−0.07 to 0.14)	0.48
12-month change	−0.12 (−0.19 to −0.04)	−0.11 (−0.19 to −0.02)	−0 0.16 (−0.24 to −0.07)	−0.15 (−0.24 to −0.07)	0.04 (−0.08 to 0.15)	0.48	0.05 (−0.07 to 0.16)	0.42
Total cholesterol/HDL cholesterol ratio	*n* = 327	*n* = 290	*n* = 299	*n* = 253				
Baseline	4.27 (4.15–4.39)	4.21 (4.08–4.33)	4.17 (4.05–4.28)	4.23 (4.11–4.35)				
6-month change	−0.26 (−0.34 to −0.18)	−0.25 (−0.33 to −0.16)	0.19 (−0.26 to −0.11)	0.18 (−0.26 to −0.11)	−0.07 (−0.18 to 0.04)	0.19	−0.06 (−0.17 to 0.05)	0.28
12 month change	−0.30 (−0.38 to −0.21)	−0.29 (−0.37 to −0.20)	−0.14 (−0.23 to −0.05)	−0.15 (−0.23 to −0.06)	−0.16 (−0.28 to −0.03)	0.01	−0.14 (−0.26 to −0.02)	0.02
Triglycerides (mmol/L)	*n* = 327	*n* = 291	*n* = 299	*n* = 259				
Baseline	1.64 (1.57–1.72)	1.62 (1.54–1.69)	1.67 (1.59–1.74)	1.69 (1.60–1.77)				
6-month change	−0.13 (−0.19 to −0.07)	−0.14 (−0.20 to −0.07)	−0.06 (−0.13 to 0.01)	−0.05 (−0.13 to 0.02)	−0.07 (−0.16 to 0.02)	0.13	−0.08 (−0.18 to 0.01)	0.09
12-month change	−0.17 (−0.23 to −0.10)	−0.16 (−0.22 to −0.10)	0.0 (−0.08 to 0.09)	0.0 (−0.08 to 0.09)	−0.17 (−0.27 to −0.06)	0.002	−0.16 (−0.27 to −0.06)	0.003
Triglyceride/HDL cholesterol ratio	*n* = 327	*n* = 289	*n* = 299	*n* = 254				
Baseline	1.43 (1.34–1.53)	1.41 (1.32–1.50)	1.45 (1.35–1.56)	1.45 (1.35–1.56)				
6-month change	−0.16 (−0.23 to −0.10)	−0.17 (−0.24 to −0.10)	−0.10 (−0.18 to −0.03)	−0.10 (−0.17 to −0.02)	−0.06 (−0.16 to 0.04)	0.22	−0.07 (−0.18 to 0.03)	0.19
12-month change	−0.20 (−0.27 to −0.12)	−0.19 (−0.26 to −0.12)	0.0 (−0.09 to 0.09)	−0.02 (−0.11 to 0.07)	−0.19 (−0.31 to −0.08)	0.001	−0.17 (−0.29 to −0.05)	0.004

Data are mean (95% CI) unless otherwise indicated. BP, blood pressure; MI, multiple imputation. *For HbA_{1c}, data are median (interquartile range), and the between-group difference is median (95% CI). †,‡Determined only in participants without insulin treatment. §Determined only in participants without diabetes. *P* values for between-groups differences were calculated using linear regression with robust SE to account for intracluster correlations or median regression analyses if data were skewed.

sustained increase in the consumption of nuts, whole-grain cereals, and fish along with a higher reduction in the consumption of refined cereals, red meat, pastries, cakes, and sweets in participants assigned to the IG compared with those in the CG. These data demonstrate the effect of the intervention increasing the consumption of foods typical of the MedDiet and decreasing the consumption of those characteristic of an unhealthy dietary pattern (e.g., red and processed meat, soft drinks, and refined foods).

Our study also showed a sustained effect of the PA intervention. Compared with control, a significant and higher decrease in time spent in television viewing and a higher increase in leisure-time PA was observed in the IG, and these changes were most apparent at 12 months. In fact, the proportion of participants meeting the World Health Organization's 2010 recommendations of at least 150 min of moderate-vigorous PA/week was maximal at 12 months and higher in the IG than CG.

Although we observed a weight loss effect maintained over time, only a median 3.7% decrease in body weight was achieved in the IG compared with the 8% decrease aimed at. In addition, only a 3% between-group difference in weight loss was observed compared with the objective of 5%. The modest effect of the PREDIMED-Plus intervention on body weight and waist circumference in relation to our a priori objectives can be explained in part because our population was aged, had a low educational level (~50% only have primary-school level), and 45% of participants had diabetes at baseline. All of these factors have been recognized as predictors of suboptimal adherence to and efficacy of the intervention in weight loss trials (26). A considerable strength of our study is that there were very few dropouts in comparison with previous weight loss trials. In addition, attendance to the scheduled individual and group sessions during follow-up was also higher than in previous weight loss trials. High retention into the trial provides sound evidence of the long-term palatability and sustainability of an erMedDiet. In our study, the IG achieved weight loss especially at expenses of total body fat. Participants in the IG showed improvements in the lean body mass/total body fat ratio, which is typically considered as a more favorable body composition, hereby suggesting that lifestyle interventions for weight loss should include the use of lean body mass–preserving strategies (e.g., PA) in order to prevent or delay sarcopenia.

Many RCTs have reported the beneficial effects of losing 5–10% body weight irrespective of intervention on cardiovascular risk factors associated with overweight/obesity, including abdominal adiposity, blood pressure, triglycerides, HDL cholesterol, and insulin resistance (3,4). Moderate weight loss in our study had the same beneficial effects in these parameters except for blood pressure. These findings suggest that an intensive weight loss lifestyle intervention based on an erMedDiet and increased PA is a safe strategy for treating the MetS and ameliorate some associated cardiovascular risk factors. Weight-losing low-carbohydrate diets are usually rich in saturated fatty acids and cholesterol and thereby have the unwanted effect of increasing LDL cholesterol (12,27), a potent and recognized risk factor for atherosclerotic CVD. However, as in other studies using low-fat (7) or MedDiets (15,28), in the current study, no deleterious effects of losing weight on LDL cholesterol were observed. A relevant beneficial effect of the intervention in our study occurred on fasting glucose, insulin levels, and HbA_{1c}, reinforcing the hypothesis that an erMedDiet intervention has long-term beneficial effects on insulin resistance and glucose control in overweight and obese elderly people at high risk for cardiovascular events. In this regard, it is worth noting that for individuals with both prediabetes and diabetes, our intervention, although exerting a modest weight loss, importantly resulted in improvements in glycemic control and insulin sensitivity, along with improvements in triglyceride and HDL cholesterol levels. Our findings support prior results from RCTs (5–7,9), confirming the potential of weight loss–based intensive lifestyle interventions in the management of diabetes as well as in the delay or prevention of diabetes in those people at risk.

Yet, intervention in our study resulted in little changes of medications to control blood glucose, dyslipidemia, or hypertension. Possibly greater and sustained weight loss over time is necessary to reduce use of medications against obesity-associated risk factors.

Our results also demonstrate beneficial effects of the intensive intervention on some circulating proinflammatory parameters related to obesity, such as leptin and IL-18. Leptin is a proinflammatory protein produced mainly by adipocytes, which reflects the degree of adiposity and insulin resistance and is implicated in the pathogenesis of several of its major complications (29). IL-18 is another proinflammatory cytokine produced by macrophages and other cells that has been shown to increase in obesity (30) and decrease after weight loss (31). Reduction of leptin and IL-18 in the intervention arm can be explained in part by weight loss, but we cannot discount effects derived from a higher adherence to the MedDiet and increased PA. The intervention was also associated with reduced concentrations of MCP-1, one of the key chemokines regulating inflammation via migration and infiltration of monocytes/macrophages (32). This protein is increased in obesity and diabetes and reduced by weight loss (31). Given that high levels of MCP-1 and IL-18 are also implicated in the development of atherosclerosis (31,33), their sustained reduction over time might be associated with decreased cardiovascular events.

Our findings are limited to adults with high BMI who also meet the criteria for MetS and were living in a Mediterranean country. Therefore, they cannot be generalized to other populations or to all individuals with MetS.

In conclusion, we have shown in overweight/obese adults with MetS that an intensive lifestyle intervention using an erMedDiet, PA promotion, and behavioral support resulted in clinically meaningful weight loss, high adherence to recommendations, and improvements in MetS components and other intermediate markers of cardiovascular risk after a 6-month follow-up, with these beneficial effects being enhanced after intervention for 12 months. Additionally, such lifestyle intervention caused modest, yet potentially important, improvements in glycemic control, insulin sensitivity, and dyslipidemia in individuals with or at risk for diabetes. Based on these results and past research on the cardiovascular effects of the MedDiet (13,17), we hypothesize that long-term weight loss maintenance in response to the PREDIMED-Plus lifestyle program

might provide the same or even greater benefit in terms of hard cardiovascular events.

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