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Effect of a Nutritional and Behavioral Intervention on Energy-Reduced Mediterranean Diet Adherence Among Patients With Metabolic Syndrome
Interim Analysis of the PREDIMED-Plus Randomized Clinical Trial

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IMPORTANCE High-quality dietary patterns may help prevent chronic disease, but limited data exist from randomized trials about the effects of nutritional and behavioral interventions on dietary changes.

OBJECTIVE To assess the effect of a nutritional and physical activity education program on dietary quality.

DESIGN, SETTING, AND PARTICIPANTS Preliminary exploratory interim analysis of an ongoing randomized trial. In 23 research centers in Spain, 6874 men and women aged 55 to 75 years with metabolic syndrome and no cardiovascular disease were enrolled in the trial between September 2013 and December 2016, with final data collection in March 2019.

INTERVENTIONS Participants were randomized to an intervention group that encouraged an energy-reduced Mediterranean diet, promoted physical activity, and provided behavioral support (n = 3406) or to a control group that encouraged an energy-unrestricted Mediterranean diet (n = 3468). All participants received allotments of extra-virgin olive oil (1 L/mo) and nuts (125 g/mo) for free.

MAIN OUTCOMES AND MEASURES The primary outcome was 12-month change in adherence based on the energy-reduced Mediterranean diet (er-MedDiet) score (range, 0-17; higher scores indicate greater adherence; minimal clinically important difference, 1 point).

RESULTS Among 6874 randomized participants (mean [SD] age, 65.0 [4.9] years; 3406 [52%] men), 6583 (96%) completed the 12-month follow-up and were included in the main analysis. The mean (SD) er-MedDiet score was 8.5 (2.6) at baseline and 13.2 (2.7) at 12 months in the intervention group (increase, 4.7 [95% CI, 4.6-4.8]) and 8.6 (2.7) at baseline and 11.1 (2.8) at 12 months in the control group (increase, 2.5 [95% CI, 2.3-2.6]) (between-group difference, 2.2 [95% CI, 2.1-2.4]; *P* < .001).

CONCLUSIONS AND RELEVANCE In this preliminary analysis of an ongoing trial, an intervention that encouraged an energy-reduced Mediterranean diet and physical activity, compared with advice to follow an energy-unrestricted Mediterranean diet, resulted in a significantly greater increase in diet adherence after 12 months. Further evaluation of long-term cardiovascular effects is needed.

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The disease burden of elevated body mass index (BMI) has increased rapidly during the past 3 decades[1,2] in close association with excess caloric intake and poor nutritional quality. Evaluations of lifestyle interventions to mitigate overweight and obesity are among the top priorities in public health. High adherence to high-quality dietary patterns coupled with reduced calorie intake may represent a sound solution for confronting adiposity-associated chronic diseases that can compromise the sustainability of most health systems.[3]

Good adherence to the traditional Mediterranean diet presents an optimal nutrient profile[4-6]; has been associated with reduced all-cause mortality,[3] nonfatal cardiovascular disease,[4,7-9] type 2 diabetes and its long-term complications,[10,11] and overweight/obesity[12]; and has demonstrated long-term sustainability and nutritional quality.[13] An energy-reduced Mediterranean diet may represent an optimal model for participants with overweight or obesity to be evaluated in large long-term randomized clinical trials (RCTs). This was the rationale behind the PREDIMED-Plus trial.[14] However, the main challenge for feasibility of large RCTs examining nutritional interventions using a whole dietary pattern is the expected adherence with the intended goals. Because randomly allocating thousands of healthy, free-living participants to follow a diet that was not their choice for several years may not be an easy endeavor, the selected dietary goals should have sufficient appeal. In this context, the traditional Mediterranean diet seems sufficiently attractive and realistic for individuals to adhere to. Initial results of the pilot study of 626 participants of this trial were previously reported.[15]

The aim of this study was to examine adherence and changes in risk factors after the 12-month intervention of an energy-reduced Mediterranean diet vs a control Mediterranean diet. This study reports interim 1-year results focused on exploratory end points of a larger ongoing RCT.

Key Points

Question What is the effect of a nutritional and behavioral intervention focused on encouraging an energy-reduced Mediterranean diet and physical activity on the dietary pattern of participants after 12 months?

Findings In this preliminary analysis of an ongoing randomized clinical trial involving 6874 participants, an intervention focused on encouraging an energy-reduced Mediterranean diet and promoting physical activity, compared with advice to follow an energy-unrestricted Mediterranean diet, resulted in a significant increase in a measure of diet adherence, the 17-item energy-reduced Mediterranean diet score, at 12 months (4.7 points vs 2.5 points; score range, 0-17; minimal clinically important difference, 1 point).

Meaning A nutritional and behavioral intervention focused on encouraging an energy-reduced Mediterranean diet and physical activity led to a significant improvement in a measure of diet adherence at 12 months. Further evaluation of the effects on long-term cardiovascular and other health outcomes is needed.

Methods

The methods have been published[14,15] and are described in detail in Supplement 1 and Supplement 2. Briefly, this multicenter, parallel-group, randomized, single-blind clinical trial is evaluating the long-term effects of a lifestyle intervention including an energy-reduced Mediterranean diet, promotion of physical activity, and behavioral support for weight loss (intervention group) vs a control group following a traditional Mediterranean diet without any caloric restriction on cardiovascular events. This trial was approved by the institutional review board of all participating institutions. All participants provided written informed consent.

Eligible participants were community-dwelling men aged 55 to 75 years and women aged 60 to 75 years without cardiovascular disease at baseline who had an initial BMI of 27 to 40 and met at least 3 criteria for metabolic syndrome.[16] Between September 2013 and December 2016, participants were recruited in 23 Spanish National Health System research centers in Spain. Participants were randomized in a 1:1 ratio to the intervention group or to the control group using a computer-generated random number internet-based system with stratification by center, sex, and age (<65 years, 65-70 years, and >70 years) in blocks of 6 participants. The randomization procedure was blinded to all staff members and principal investigators and was audited for all centers. For participant couples sharing the same household, randomization was done by cluster, with the couple as the unit of randomization.

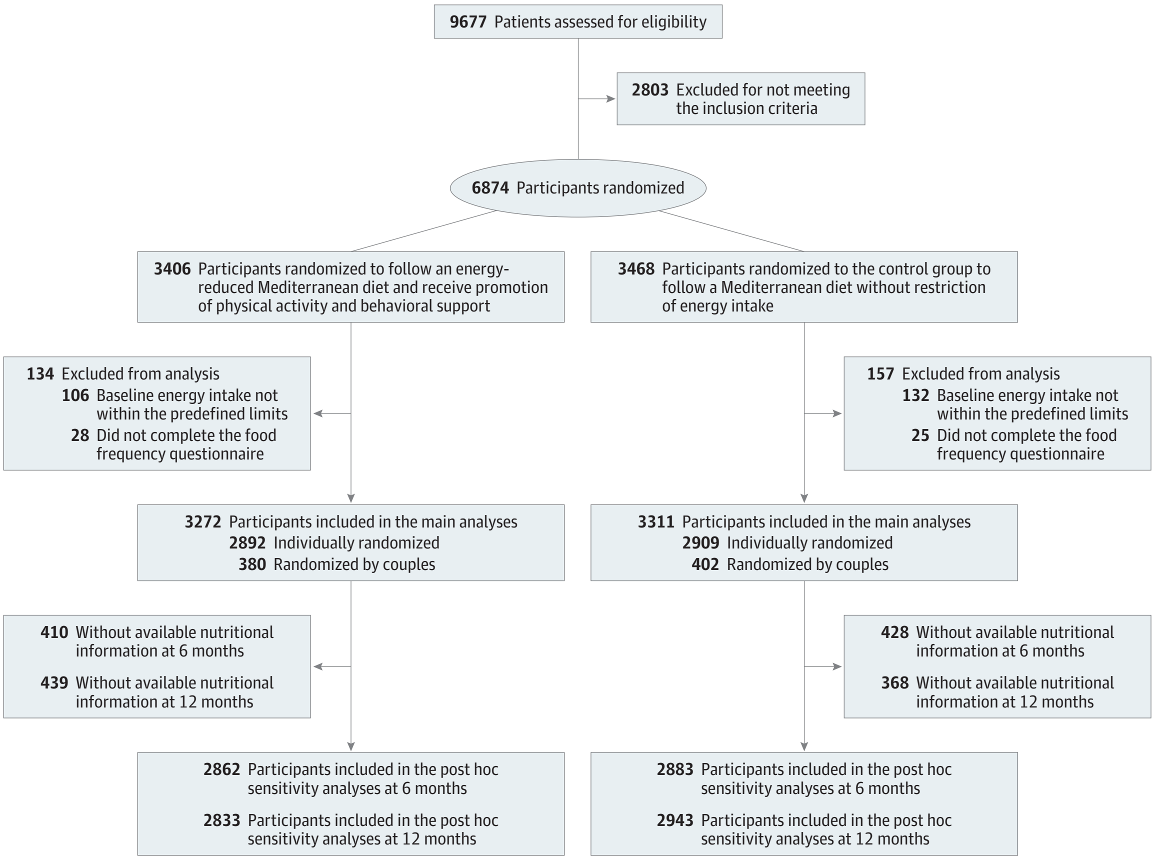
Dietary Intervention

Participants randomized to the intervention group were instructed to follow an energy-reduced Mediterranean diet, accompanied by physical activity promotion and behavioral support, with the purpose of accomplishing specific weight loss objectives.[14,15] Trained dietitians conducted a group session, an individual motivational interview, and a phone call each month during the first year. Considering basal metabolic rate and level of physical activity of each participant in the intervention group, a reduction of approximately 30% of estimated energy requirements, which represents a reduction of approximately 600 kcal/d, was recommended. However, actual energy intake reduction was expected to be modest because the trial was conducted among free-living participants and levels of physical activity were expected to increase.

Participants in the control group attended 2 educational sessions per year on the traditional Mediterranean diet with ad libitum caloric intake, all contents previously used in PREDIMED trial[8] and general lifestyle recommendations according to usual care practices in the Spanish National Health System. This group received an individual visit, telephone call, and group session every 6 months during the first year.

The energy-reduced Mediterranean diet differed from the diet recommended to the control group in that there were more restrictive limits for red and processed meats, butter, margarine or cream, and carbonated sweetened beverages. Also, for participants following the energy-reduced Mediterranean diet, it was recommended to not add sugar to beverages and to limit white bread and refined cereal consumption, while promoting the consumption of whole grains. Participants in both groups

Figure 1. Flow of Participants in a Study of the Effect of an Energy-Reduced Mediterranean Diet Among Adults With Metabolic Syndrome



were provided with an allotment of extra-virgin olive oil (1 L/mo) and almonds (125 g/mo) for free. However, we recommended that all participants consume a total of 500 g/mo of mixed nuts.

Dietary Assessment

Baseline and follow-up examinations were conducted by trained dietitians and included the assisted completion of different questionnaires by the participant. Results of a validated 143-item semiquantitative food frequency questionnaire were collected at baseline and at 6 and 12 months[17] during face-to-face visits to assess food habits during the preceding 6 months. Food composition tables were used to derive energy and nutrient intake.[18]

Changes in 4 dietary scores[19-21] (eTable 1 in Supplement 3) that reflected adherence to dietary patterns were assessed. Three of the scores measured adherence to the Mediterranean diet and a 17-item questionnaire was used to assess adherence to the energy-reduced Mediterranean diet (er-MedDiet score). This 17-item questionnaire is a modified version of the previously validated 14-item Mediterranean Diet Adherence Screener (MEDAS) questionnaire, which was also used in this trial.[20] In the 17-item version,[14] more restrictive cutoffs for some caloric-dense items were used and a few additional items aimed to reduce caloric intake were added. The third measure was the Mediterranean Diet Score (MDS),[19] a well-known measure that has repeatedly shown to be inversely associated with all-cause mortality and the risk of clinical cardiovascular events in large prospective cohort studies. The fourth measure was the Prime Diet Quality Score (PDQS), which is based on the Prime Screen questionnaire and tries to meet both simplicity in assessing dietary habits and high discriminative ability to identify associations with the risk of noncommunicable diseases.[21]

Nondietary Variables

At baseline and the 6- and 12-month follow-up visits, information was collected on physical activity,[22,23] lifestyle, medication use, and other variables. At each visit, nurses measured waist circumference (midway between the lowest rib and the iliac crest, using an anthropometric tape), weight (using high-quality electronic calibrated scales), and height (using a wall-mounted stadiometer) twice. Blood pressure was measured 3 times using a validated semiautomatic oscillometer (Omron HEM-705CP). At baseline, 6 months, and 12 months, plasma total cholesterol, low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol, and triglycerides concentrations were measured in blood samples collected after an overnight fast and using standard enzymatic methods.

Outcomes

The primary end point for this interim analysis was change from baseline to 12 months in adherence to the energy-reduced Mediterranean diet, measured with the er-Med Diet score (range, 0-17; higher scores indicate greater adherence; minimally clinically important difference, 1 point). Secondary end points included the MEDAS score (range, 0-14), the MDS (range, 0-9), and the PDQS (range, 0-42) (eTable 1 in Supplement 3). For all secondary end point measures, higher scores indicate better dietary quality. Other secondary outcomes were changes in nutrients (measured via total energy intake; percentage of energy from macronutrients and alcohol; and the intake of fiber, long-chain Ω-3 fatty acids, dietary cholesterol, and sodium); consumption of key food items, including refined and extra-virgin olive oil, nuts, fruits, vegetables, cereals (whole grain and refined), legumes, fish, meat (red and processed), pastries, dairy (yogurt and fermented, low-fat, and whole-fat dairy), and alcohol (red wine); and cardiovascular risk factors, including body weight, waist circumference, body mass index (BMI), total serum cholesterol, HDL cholesterol, LDL cholesterol, non-HDL cholesterol, total cholesterol:HDL cholesterol ratio, triglycerides, and systolic and diastolic blood pressure.

We compared the percentage of participants in each group who achieved any favorable dietary changes (ie, any change in the desirable direction) and also the percentage of participants with clinically meaningful changes in classic risk factors. We considered reductions of at least 5% in BMI,[24] body weight,[25] waist circumference,[25] total cholesterol, LDL cholesterol,[26] non–HDL cholesterol, and cholesterol:HDL cholesterol ratio; reductions of at least 5 mm Hg in systolic or at least 2.5 mm Hg in diastolic blood pressure[27]; and an increase of at least 5% in HDL cholesterol as minimal clinically important differences.[28] For triglycerides, we considered a 10% reduction as the minimal clinically important difference.[29]

Statistical Analysis

Calculation of sample size was done for the primary end point of the overall trial (composite of nonfatal myocardial infarction, nonfatal stroke, or cardiovascular death).[14] We used the database from the overall trial, which was dated on March 12, 2019. Principal analyses included all randomized participants with baseline nutritional data, regardless of whether they had incomplete information at follow-up visits, with multiple imputation procedures for missing data. Secondary analyses included only participants with complete information available at each follow-up visit.

For the principal analysis, we excluded participants who did not complete food frequency questionnaires at baseline and who had total energy intake beyond prespecified limits (500-3500 kcal/d for women and 800-4000 kcal/d for men).[30] For the post hoc sensitivity analyses (completers only), we further excluded participants without nutritional information at follow-up (**Figure 1**).

In the main analyses, multiple imputation methods used an iterative Markov chain Monte Carlo method (STATA "mi" command). We generated 8 imputations for each missing measurement. Imputed missing values were used for follow-up data but not for baseline data. The imputation models included sex, age, smoking status, education level, BMI, physical activity, study group, total energy intake, and the baseline value of the variable that was imputed as predictors.

Table 1. Baseline Characteristics of Participants Included in the Main Analyses in a Study of the Effect of an Energy-Reduced Mediterranean Diet Among Adults With Metabolic Syndrome on Diet Adherence

Characteristic	No. (%) Intervention Group (n = 3272)	Control Group (n = 3311)
Men	1702 (52)	1704 (51)
Women	1570 (48)	1607 (49)
Age, mean (SD), y	65.0 (4.9)	65.0 (4.9)
Smoker		
Current	436 (13)	379 (11)
Former	1366 (42)	1486 (45)
Education	(n = 3240)	(n = 3285)
Primary or less	1540 (48)	1647 (50)
Secondary	997 (31)	902 (28)
University	703 (21)	736 (22)
Weight, mean (SD), kg	86.7 (13.0)	86.4 (13.0)
BMI, mean (SD)	32.5 (3.4)	32.5 (3.5)
Waist circumference, mean (SD), cm	108 (9.6)	108 (9.7)
Physical activity, median (IQR), MET min/wk	1709 (839-3202)	1902 (867-3371)

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); IQR, interquartile range; MET, metabolic equivalent.

Mixed-effects linear models were used to assess changes in nutritional variables from baseline to 6- and 12-month follow-up in all randomized participants and completer-only analyses. We fitted a 3-level mixed linear model with random intercepts at site, participant, and cluster family level. All secondary analyses were exploratory; therefore, no additional adjustment was conducted to adjust for type I error.

Post hoc sensitivity analyses were conducted by (1) including only participants with complete information available at 6- or 12-month follow-up (completers only; eTables 3, 4, and 5 in Supplement 3) and (2) repeating all analyses after replacing all missing values with baseline values (eTables 6, 7, and 8 in Supplement 3). All analyses were conducted with Stata, version 15.0 (Stata Corp). All statistical tests were 2-sided and $P < .05$ was deemed statistically significant.

Results

Of 6874 patients who were recruited and randomized, 53 who did not complete the food frequency questionnaire at baseline (28 from the intervention group and 25 from the control group) and 238 with total energy intake beyond prespecified limits (106 from the intervention and 132 from the control group) were excluded. A total of 6583 participants (3406 men and 3177 women; 3272 in the intervention group and 3311 in the control group) were analyzed (Figure 1). Imputed missing values for nutritional variables were 12.7% at 6 months and 12.2% at 12 months. Baseline characteristics of participants in the intervention and control groups were similar (**Table 1**).

Table 2. Baseline Dietary Pattern Scores and Changes by Randomized Treatment Group in a Study of the Effect of an Intervention Promoting an Energy-Reduced Mediterranean Diet Among Patients With Metabolic Syndrome on Diet Adherence

Dietary Pattern Score	Multiple Imputation: All Randomized Included Participants[a] Intervention Group (Energy-Reduced Mediterranean Diet; n = 3272)	Control Group (Mediterranean Diet; n = 3311)	Between-Group Difference (95% CI)[b]	*P* Value
er-MedDiet Score[c]				
Baseline, mean (SD)	8.5 (2.6)	8.6 (2.7)		
6 Months				
Score	12.9 (2.8)	10.8 (2.8)		
Score change	4.4 (3.4)	2.2 (3.5)	2.2 (2.0 to 2.3)	<.001
12 Months				
Score	13.2 (2.7)	11.1 (2.8)		
Score change	4.7 (3.5)	2.5 (3.4)	2.2 (2.1 to 2.4)	<.001
MDS[d]				
Baseline, mean (SD)	4.3 (1.7)	4.3 (1.6)		
6 Months				
Score	5.0 (1.6)	4.6 (1.6)		
Score change	0.7 (2.4)	0.3 (2.5)	0.4 (0.3 to 0.5)	<.001
12 Months				
Score	5.1 (1.6)	4.5 (1.6)		
Score change	0.8 (2.5)	0.2 (2.4)	0.6 (0.5 to 0.7)	<.001
MEDAS Score[e]				
Baseline, mean (SD)	7.6 (1.9)	7.6 (1.9)		
6 Months				
Score	10.6 (1.8)	9.6 (1.9)		
Score change	3.0 (2.4)	2.0 (2.5)	1.0 (0.9 to 1.1)	<.001
12 Months				
Score	10.8 (1.7)	9.7 (1.9)		
Score change	3.2 (2.4)	2.1 (2.5)	1.1 (1.0 to 1.2)	<.001
PDQS[f]				
Baseline, mean (SD)	21.1 (3.7)	21.1 (3.7)		
6 Months				
Score	27.8 (3.6)	25.8 (3.7)		
Score change	6.7 (6.8)	4.7 (7.4)	2.0 (1.6 to 2.3)	<.001
12 Months				
Score	28.0 (3.5)	25.5 (3.6)		
Score change	6.9 (7.0)	4.4 (7.0)	2.4 (2.1 to 2.8)	<.001

Abbreviations: er-MedDiet, energy-reduced Mediterranean diet; MDS, Mediterranean Diet Score; MEDAS, Mediterranean Diet Adherence Screener; PDQS, Prime Diet Quality Score.

[a] For the er-MedDiet score, 463 values were imputed at 6 months and 517 values were imputed at 12 months. For the MDS, MEDAS score, and the PDQS, 838 values were imputed at 6 months and 807 were imputed at 12 months.

[b] Calculated using mixed-effect models with site and intracluster correlations (couples) as random factors.

[c] The er-MedDiet score ranges from 0-17, with a higher score indicating a higher level of adherence. The 17-item er-MedDiet score captures the 14 items of MEDAS with some additions that have been repeatedly associated with cardiovascular health benefits in previous observational studies with good control for confounding. Therefore, a 1-point difference can be accepted as a minimal clinically important difference.

[d] The MDS ranges from 0-9, with a higher score indicating better dietary quality. The minimum clinically important difference can be considered 1 point because a 2-point increment (roughly corresponding to 1 SD) was associated in the fully adjusted model with a 25% relative reduction in all-cause mortality[19] (coefficient = log(0.75) = −0.2877). Therefore, 1 point in the MDS (corresponding to 0.5 SD) will lead to a 13% relative risk reduction corresponding to a hazard ratio of 0.87, namely exp(−0.2877/2) = 0.87, which can be considered higher than a minimal clinically significant effect from the subjective point of view of a patient.

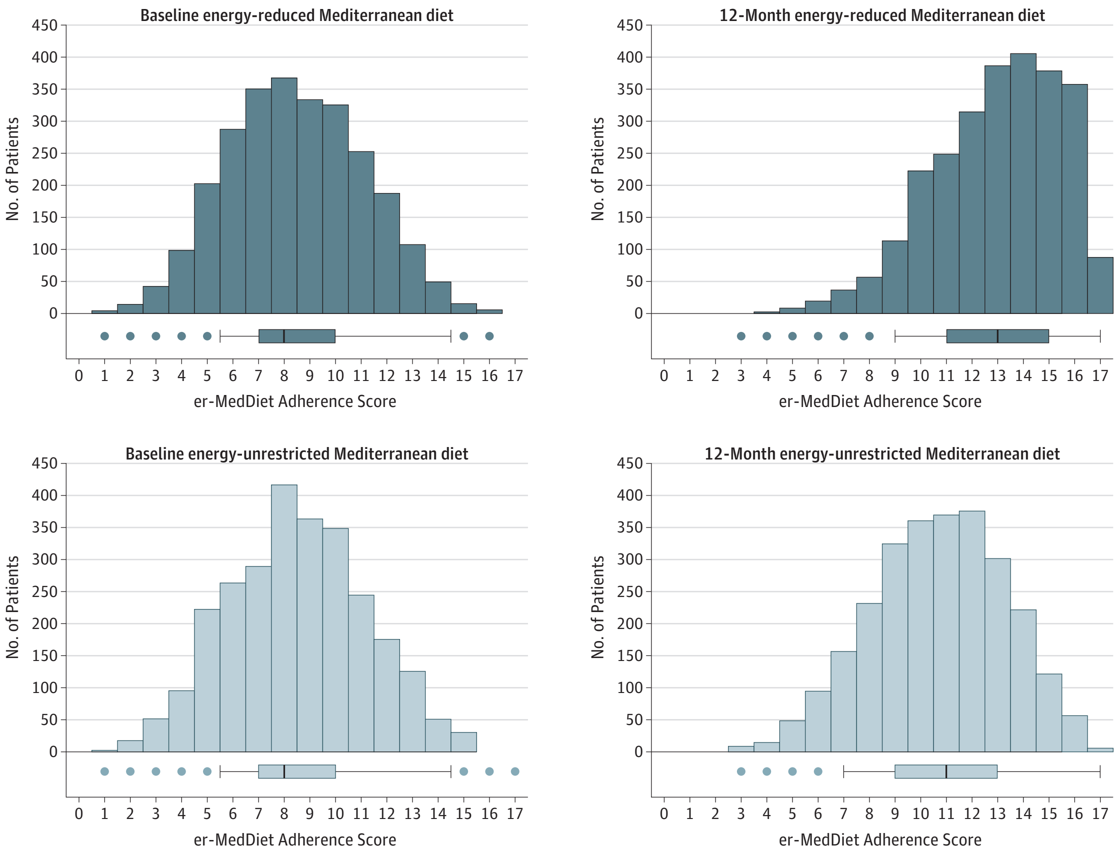
[e] The MEDAS score ranges from 0-14, with a higher score indicating better dietary quality. In the PREDIMED trial, assessed as an observational study, and controlling for potential confounding, a 1-point increment was associated with a 10% reduction in the risk of the composite primary cardiovascular end point (multivariable-adjusted hazard ratio, 0.90 [95% CI, 0.85-0.96]) and with a 6% reduction in total mortality (multivariable-adjusted hazard ratio, 0.94 [95% CI, 0.89-0.99]) (PREDIMED-Plus investigators, unpublished data, 2019). Therefore, 1 point should represent a sufficiently important difference for an individual patient.

[f] The PDQS ranges from 0-42, with a higher score indicating better dietary quality. The minimal clinically important difference will likely represent a 2-point increment in the PDQS, given its wider range.

Primary Outcome

The mean (SD) er-MedDiet score was 8.5 (2.6) at baseline and 13.2 (2.7) at 12 months in the intervention group (increase, 4.7 [95% CI, 4.6-4.8]) and 8.6 (2.7) at baseline and 11.1 (2.8) at 12 months in the control group (increase, 2.5 [95% CI, 2.3-2.6]) (between-group difference, 2.2 [95% CI,

Figure 2. Changes in the Primary End Point of Diet Adherence in a Study of the Effect of an Energy-Reduced Mediterranean Diet (er-MedDiet) Among Adults With Metabolic Syndrome



Horizontal box plots are shown in which the middle line represents the median er-MedDiet score (range, 0-17; higher score indicates higher adherence), boxes represent the interquartile range (IQR), whiskers extend to the most extreme observed values with 1.5 × IQR of the nearer quartile, and the dots represent observed values outside that range.

2.1-2.4]; *P* < .001; eFigure 1 in Supplement 3). The improvements in the er-MedDiet score in the intervention group represented a significant 55% ([95% CI, 55%-56%]; *P* < .001) relative increase over 12 months (**Table 2**). **Figure 2** shows the distribution of er-MedDiet scores at baseline and at the 12-month follow-up in each group. The intervention group exhibited greater improvements in the overall distribution of this score.

Secondary Outcomes

Other Dietary Scores

The mean (SD) baseline PDQS value was 21.1 (3.7) in both groups. Within-group changes in PDQS scores were significant at 12 months in the control group (difference, 4.4 [95% CI, 4.2-4.7]; *P* < .001) and in the intervention group (difference, 6.9 [95% CI, 6.6-7.1]; *P* < .001). There was a statistically significant difference in the PDQS score at 12 months between the groups (difference, 2.4 [95% CI, 2.1-2.8]; *P* <.001). These differences were maintained in post hoc sensitivity analyses (eFigure 1, eTable 3, and eTable 6 in Supplement 3). Results for the other dietary scores can be seen in Table 2.

Foods and Food Groups

Significant reductions in the consumption of specific foods or food groups after 12 months were observed (eTable 2 in Supplement 3). Baseline consumption of refined grains was 779 g/wk in both groups and reductions after 12 months were −535 g/wk (95% CI, −559 to −510) in the intervention group compared with −226 g/wk (95% CI, −249 to −203) in the control group, with a significant between-group difference of −309 g/wk ([95% CI, −340 to −277]; *P* <.001). For pastries, mean baseline consumption was 114 g/wk in the control group and 121 g/wk in the intervention group, with significant within-group differences after 12 months of −60 g/wk ([95% CI, −67 to −53]; *P* < .001) in the control group and −109 g/wk ([95% CI, −116 to −102]; *P* < .001) in the intervention group. The between-group difference of −49 g/wk in pastry consumption was also statistically significant ([95% CI, −59 to −39]; *P* <.001). Significant reductions in red meat consumption were also observed; the between-group difference after 12 months was −39 g/wk ([95% CI, −51 to −28]; *P*<.001). Some of the greatest increases were observed for vegetables, with mean baseline consumption of 2130 g/wk in the control group and 2168 g/wk in the intervention group and within-group differences after 12 months of

Table 3. Baseline Energy and Nutrient Intake and Their Changes by Randomized Treatment Group

	Multiple Imputation: All Randomized Participants[a]			
Energy Intake	Intervention Group (Energy-Reduced Mediterranean Diet; n = 3272)	Control Group (Mediterranean Diet; n = 3311)	Between-Group Difference (95% CI)[b]	*P* Value
Total Energy, Mean (SD), kcal/d				
Baseline	2355 (555)	2369 (555)		
6-mo change	−173 (537)	−76 (501)	−97 (−122 to −72)	<.001
12-mo change	−176 (543)	−74 (501)	−102 (−129 to −75)	<.001
Total Protein, Mean (SD), %/d				
Baseline	16.8 (2.8)	16.8 (2.8)		
6-mo change	1.2 (2.9)	0.2 (2.7)	1.0 (0.9 to 1.2)	<.001
12-mo change	1.1 (3.0)	0 (2.7)	1.1 (1.0 to 1.3)	<.001
Total Carbohydrate, Mean (SD), %/d				
Baseline	40.7 (6.8)	40.4 (6.9)		
6-mo change	−3.4 (7.0)	−1.9 (6.8)	−1.5 (−1.8 to −1.1)	<.001
12-mo change	−3.7 (6.9)	−2.3 (6.8)	−1.4 (−1.8 to −1.0)	<.001
Total Fat, Mean (SD), %/d				
Baseline	39.5 (6.6)	39.7 (6.5)		
6-mo change	2.5 (7.1)	1.9 (6.9)	0.6 (0.3 to 1.0)	<.001
12-mo change	2.9 (7.1)	2.4 (6.9)	0.5 (0.1 to 0.9)	.007
SFA, Mean (SD), %/d				
Baseline	9.9 (2.0)	10.0 (2.0)		
6-mo change	−1.0 (2.0)	−0.6 (2.0)	−0.5 (−0.6 to −0.4)	<.001
12-mo change	−0.9 (2.0)	−0.6 (1.9)	−0.4 (−0.5 to −0.3)	<.001
MUFA, Mean (SD), %/d				
Baseline	20.5 (4.7)	20.6 (4.6)		
6-mo change	3.5 (5.6)	2.4 (5.3)	1.1 (0.9 to 1.4)	<.001
12-mo change	3.9 (5.6)	3.0 (5.3)	0.9 (0.6 to 1.2)	<.001
MUFA:SFA Ratio, Mean (SD)				
Baseline	2.1 (0.5)	2.1 (0.5)		
6-mo change	0.6 (0.7)	0.4 (0.6)	0.3 (0.2 to 0.3)	<.001
12-mo change	0.7 (0.7)	0.5 (0.7)	0.2 (0.2 to 0.2)	<.001
PUFA, Mean (SD), %/d				
Baseline	6.4 (1.9)	6.4 (1.8)		
6-mo change	1.3 (2.3)	0.8 (2.1)	0.5 (0.4 to 0.6)	<.001
12-mo change	1.3 (2.2)	0.8 (2.1)	0.4 (0.3 to 0.5)	<.001
Total Alcohol, %/d				
Baseline, median (IQR)	1.0 (0 to 4)	2.0 (0 to 4)		
6-mo change, mean (SD)	−0.3 (3.0)	−0.1 (3.0)	−0.2 (−0.4 to 0)	.01
12-mo change, mean (SD)	−0.3 (3.0)	−0.1 (3.0)	−0.2 (−0.4 to 0.1)	.01
Fiber, Mean (SD), g/wk				
Baseline	184 (62.7)	182 (59.9)		
6-mo change	40 (70.8)	16 (60.6)	23 (20 to 27)	<.001
12-mo change	37 (68.5)	18 (62.8)	19 (16 to 23)	<.001
Long-Chain Ω-3 Fatty Acids, g/wk				
Baseline, median (IQR)	5 (4 to 9)	5 (4 to 9)		
6-mo change, mean (SD)	1.1 (3.9)	0.5 (3.6)	0.6 (0.4 to 0.8)	<.001
12-mo change, mean (SD)	1.1 (4.1)	0.4 (3.6)	0.7 (0.5 to 0.9)	<.001

(continued)

Table 3. Baseline Energy and Nutrient Intake and Their Changes by Randomized Treatment Group (continued)

Energy Intake	Multiple Imputation: All Randomized Participants[a] Intervention Group (Energy-Reduced Mediterranean Diet; n = 3272)	Control Group (Mediterranean Diet; n = 3311)	Between-Group Difference (95% CI)[b]	*P* Value
Cholesterol, Mean (SD), mg/wk				
Baseline	2651 (793)	2687 (825)		
6-mo change	−224 (779)	−169 (780)	−54 (−94 to −14)	.008
12-mo change	−216 (823)	−209 (784)	−7 (−49 to 35)	.74
Sodium, g/wk				
Baseline, median (IQR)	22 (18 to 27)	22 (18 to 27)		
6-mo change, mean (SD)	−3.0 (6.8)	−1.8 (6.5)	−1.2 (−1.6 to −0.9)	<.001
12-mo change, mean (SD)	−3.2 (7.1)	−1.9 (6.9)	−1.3 (−1.6 to −0.9)	<.001

Abbreviations: IQR, interquartile range; MUFA, monounsaturated fatty acids; PUFA, polyunsaturated fatty acids; SFA, saturated fatty acids.

[a] For all energy intake variables, 838 values were imputed at 6 months and 807 were imputed at 12 months.

[b] Calculated using mixed-effect models with site and intracluster correlations (couples) as random factors.

137 g/wk (95% CI, 100-175) in the control group and 347 g/wk (95% CI, 306-389) in intervention group; the between-group difference of 210 g/wk was significant ([95% CI, 157-263]; *P* <.001). The 12-month between-group difference was also significant for fruits (difference, 197 g/wk [95% CI, 118-276]; *P* <.001) and for nuts (baseline consumption in both groups, 60 g/wk; 12-month between-group difference, 35 g/wk [95% CI, 27-43]; *P* <.001) (eTable 2 in Supplement 3). Post hoc sensitivity analyses showed similar results (eTable 4 and eTable 7 in Supplement 3).

Energy Intake and Nutrients

Mean (SD) total energy intake at baseline was 2369 (555) kcal/d in the control group and 2355 (555) kcal/d in the intervention group; the 12-month between-group difference in energy intake was statistically significant (difference, −102 kcal/d [95% CI, −129 to −75]; *P* <.001) (**Table 3**; eTable 5 and eTable 8 in Supplement 3). The mean percentage of energy from carbohydrates decreased in both groups, with a statistically significant 12-month between-group difference of −1.4% ([95% CI, −1.8 to −1.0]; *P* <.001). Increases in energy from monounsaturated fatty acids were observed from the mean (SD) baseline intake of 20.6% (4.6) of total energy intake in the control group and 20.5% (4.7) in the intervention group; within-group significant increases after 12 months were observed in the control group (difference, 3.0% [95% CI, 2.8%-3.2%]; *P* <.001) and the intervention group (difference, 3.9% [95% CI, 3.7%-4.1%]; *P* <.001), with a significant between-group difference of 0.9% ([95% CI, 0.6%-1.2%]; *P* < .001). The proportion of participants achieving any favorable dietary changes was significantly higher in the intervention than in the control group for most comparisons (eFigure 2 in Supplement 3).

eFigure 3 in Supplement 3 shows differences in total energy and nutrient intake between both groups, comparing changes at the 6-month and 12-month follow-up with all differences expressed in common units of baseline SD of each nutritional variable for the sake of comparability.

Risk Factors

The mean changes after 6 and 12 months in cardiovascular risk factors and the percentage of participants who attained a clinically meaningful change in risk factors after 12 months are presented in **Figure 3** and **Figure 4**.

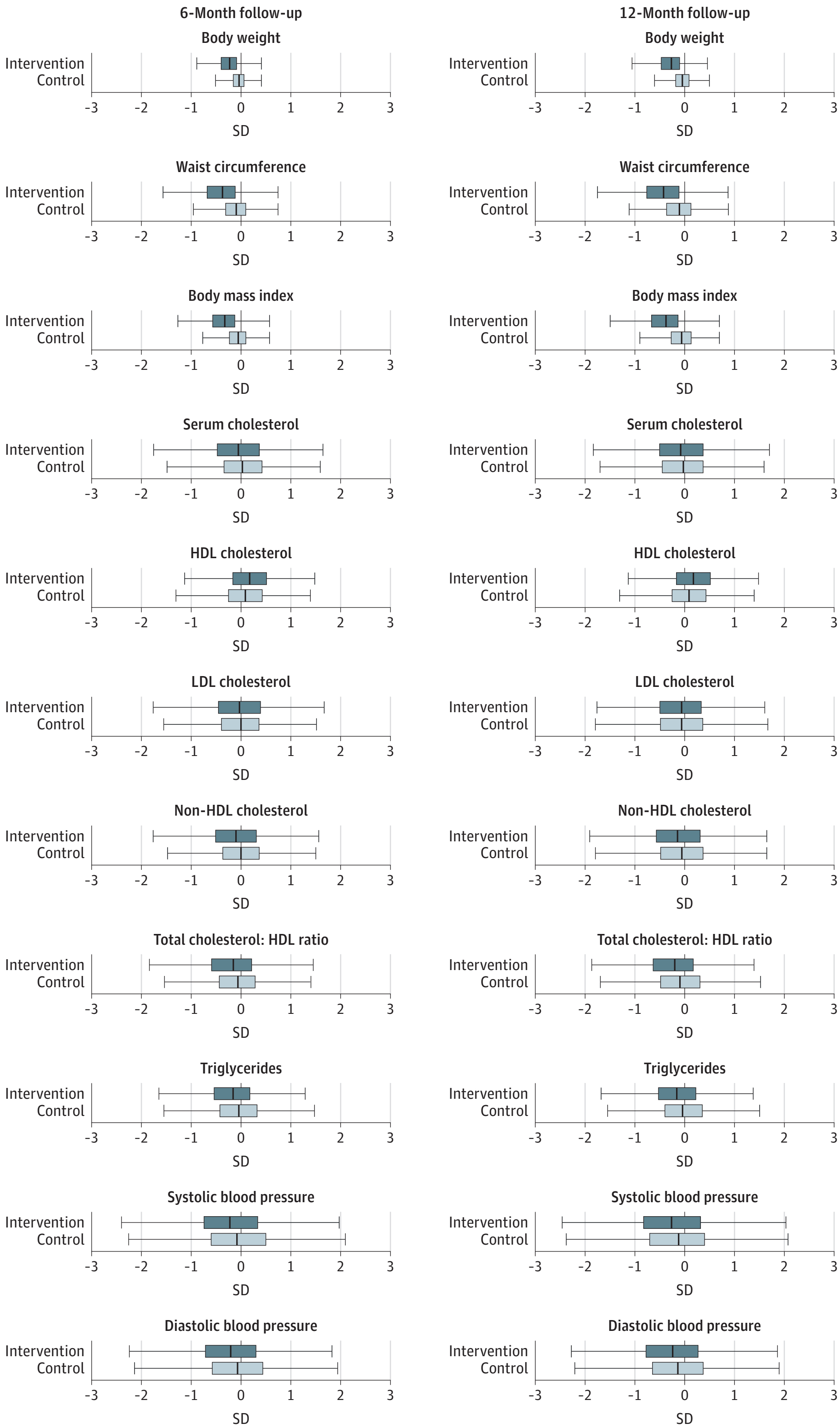
With few exceptions, such as LDL cholesterol, significant and clinically meaningful favorable changes for the intervention vs the control group in body weight, waist circumference, BMI, HDL cholesterol, non-HDL cholesterol, total cholesterol:HDL cholesterol ratio, serum triglycerides, and systolic and diastolic blood pressure after 12 months were observed (Figure 3; eTable 9 in Supplement 3). For example, mean waist circumference was 108 cm at baseline in both the control and intervention groups, and the between-group difference at 12 months was −3.3 cm ([95% CI, −3.6 to −2.9]; *P* <.001). Mean systolic blood pressure was 139 mm Hg at baseline in the control group and 140 mm Hg in the intervention group, with a between-group difference at 12 months of −1.9 ([95% CI, −2.7 to −1.1]; *P* <.001).

Discussion

In this preliminary analysis of an ongoing clinical trial, an intervention that encouraged an energy-reduced Mediterranean diet and physical activity, compared with advice to follow an energy-unrestricted Mediterranean diet, resulted in a significantly greater increase in diet adherence to an energy-reduced Mediterranean diet at 12 months. Improvements in diet quality, energy intake, and cardiovascular risk factors also were observed in the energy-reduced Mediterranean diet group. These findings are consistent with the previously reported preliminary findings from the pilot study of 626 participants of this trial.[14]

The intervention program included individual interviews and group motivational sessions with counseling to follow the traditional Mediterranean diet and reduce caloric intake and showed meaningful and sustainable short- and long-term changes in overall dietary quality and risk factors. The control group only received a low-intensity intervention promoting a traditional Mediterranean diet, without any special effort in energy reduction, physical activity, or weight loss beyond the usual care received in the Spanish National Health System. Because of this, the level of participant interaction was 6-fold higher in the intervention than in the control group, with 18 interactions in the intervention group vs 3 in the control group in 6 months. Participants in both groups received free extra-virgin olive oil and nuts.

Figure 3. Changes in Risk Factors in a Study of the Effect of an Intervention Promoting an Energy-Reduced Mediterranean Diet Among Adults With Metabolic Syndrome



Participants in the intervention group were encouraged to follow an energy-reduced Mediterranean diet, accompanied by physical activity promotion and behavioral support, while participants in the control group were encouraged to follow the traditional Mediterranean diet with ad libitum caloric intake. Horizontal box plots are shown in which the middle line represents the within-group median change in observed risk factors, boxes represent the interquartile range (IQR), and whiskers extend to the most extreme observed values with 1.5 × IQR of the nearer quartile. All differences are expressed in common units of baseline SD of each factor for comparability. HDL indicates high-density lipoprotein; LDL, low-density lipoprotein.

Change at 12 months in the 17-item MedDiet score, which measured adherence to an energy-reduced Mediterranean diet, was the primary end point. In the intervention group, the MedDiet score increased significantly more in the intervention

Figure 4. Risk Factors at 12 Months of Follow-up in a Study of the Effect of an Energy-Reduced Mediterranean Diet Among Adults With Metabolic Syndrome

	Patients With Clinically Meaningful Changes, % (95% CI) Reduction >5%	P Value
Intervention	40.6 (38.7-42.5)	<.001
Control	12.2 (11.0-13.5)	

	Patients With Clinically Meaningful Changes, % (95% CI) Reduction >5%	P Value
Intervention	39.5 (37.6-41.3)	<.001
Control	13.5 (12.2-14.8)	

	Patients With Clinically Meaningful Changes, % (95% CI) Reduction >5%	P Value
Intervention	40.5 (38.6-42.4)	<.001
Control	12.5 (11.3-13.8)	

	Patients With Clinically Meaningful Changes, % (95% CI) Reduction >5%	P Value
Intervention	37.5 (35.7-39.4)	.02
Control	34.3 (32.5-36.1)	

	Patients With Clinically Meaningful Changes, % (95% CI) Increase >5%	P Value
Intervention	45.6 (43.7-47.6)	<.001
Control	40.0 (38.1-41.8)	

	Patients With Clinically Meaningful Changes, % (95% CI) Reduction >5%	P Value
Intervention	41.4 (39.5-43.3)	.36
Control	40.2 (38.3-42.1)	

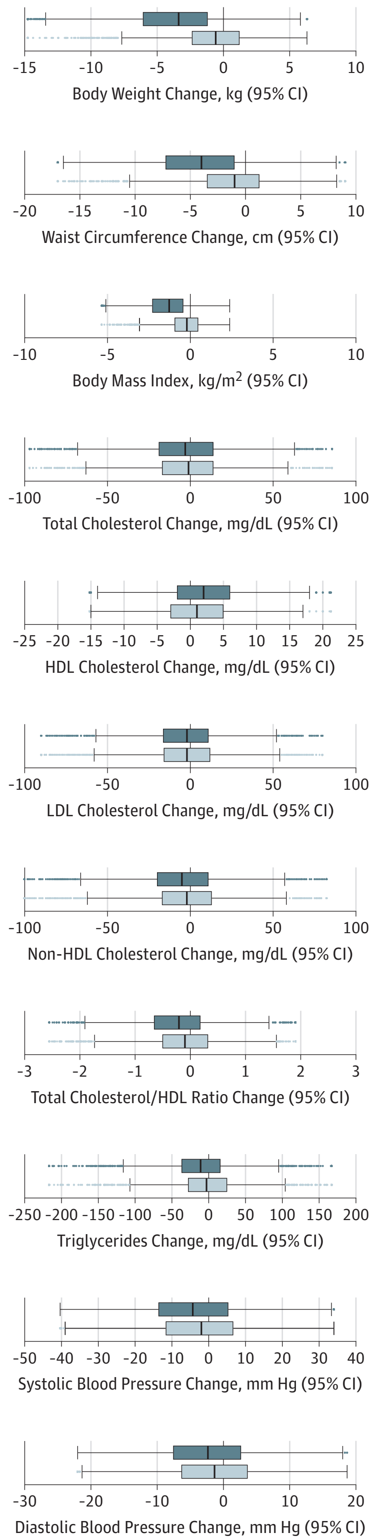
	Patients With Clinically Meaningful Changes, % (95% CI) Reduction >5%	P Value
Intervention	43.6 (41.7-45.5)	<.001
Control	37.5 (35.7-39.4)	

	Patients With Clinically Meaningful Changes, % (95% CI) Reduction >5%	P Value
Intervention	48.4 (46.5-50.4)	<.001
Control	41.3 (39.4-43.2)	

	Patients With Clinically Meaningful Changes, % (95% CI) Reduction >10%	P Value
Intervention	47.3 (45.4-49.2)	<.001
Control	38.2 (36.3-40.0)	

	Patients With Clinically Meaningful Changes, % (95% CI) Reduction >5 mm Hg	P Value
Intervention	47.5 (45.6-49.5)	<.001
Control	41.8 (39.9-43.7)	

	Patients With Clinically Meaningful Changes, % (95% CI) Reduction 2.5 mm Hg	P Value
Intervention	48.1 (46.2-50.1)	.005
Control	44.3 (42.4-46.2)	



Horizontal box plots are shown in which the middle line represents the median change in observed risk factors, boxes represent the interquartile range (IQR), whiskers extend to the most extreme observed values with 1.5 × IQR of the nearer quartile, and the dots represent observed values outside that range. HDL indicates high-density lipoprotein; LDL, low-density lipoprotein.

group than in the control group. These results showing sufficient contrast support the effectiveness of this study intervention to overcome the most difficult challenge in dietary intervention trials, namely the adherence of participants to the intervention. Furthermore, these dietary changes were paralleled by successful changes in most classic risk factors.

Both randomized groups were educated in following a Mediterranean diet. Therefore, it is of no surprise that olive oil consumption, the hallmark of a Mediterranean diet, increased in both groups. Many beneficial effects attributed to the Mediterranean diet were due to the consumption of extra-virgin olive oil, which contains high amounts of dietary bioactive phenolic compounds with antioxidant and anti-inflammatory properties.[31] These compounds are not present in common, refined varieties of olive oil. Participants in both groups reduced their consumption of this suboptimal refined variety of olive oil. The energy reduction applied only to the intervention group may in part explain why no meaningful between-group differences in extra-virgin olive oil consumption were observed.

The effectiveness of the intervention, reflected by significant changes in dietary habits and reduced cardiovascular risk factors, support that nutritional interventions and behavioral therapies in patients at high cardiovascular risk, including patients with diabetes and metabolic syndrome, are likely to facilitate modifications of targeted dietary habits, reductions in body weight, and improvements in risk factors.[32,33] A 2019 systematic review[34] concluded that the most effective dietary interventions should avoid low participation rates and promote high retention rates, have long study duration, intervene at multiple levels, and include multiple face-to-face interactions. This trial, with 36 interactions during the first year, represents one of the largest RCTs in which all these characteristics were present. These continuous interactions between trained personnel and the participants of the PREDIMED-Plus trial partially explain the attained results. However, because this is an interim exploratory analysis of an ongoing trial, these results should be considered preliminary. Also, further analyses are needed to assess whether the effect size and adherence are maintained after a longer follow-up.

The principal strengths of the present study are its randomized design and its large sample size. Repeated data collection and main analyses based on inclusion of all randomized participants are additional strengths.

Limitations

This study has several limitations. First, the use of self-reported data to evaluate nutritional changes could be a source of information bias. Second, recall bias, social desirability bias, and other potential reporting biases may have affected the results. However, the tools used to repeatedly evaluate food and nutrient intake were previously validated,[17,20] and it seems reasonable to assume that these biases, if they existed, would be similar in both groups because both groups received advice encouraging a Mediterranean diet. Importantly, dietary results were paralleled by changes in objectively measured risk factors that are free from these potential issues. Third, the strategy of donating food items was used as an incentive for attendance to educational sessions and to foster adherence. However, this strategy can also represent a limitation regarding the generalizability of these results to populations in which access to or affordability of high-quality olive oil and tree nuts might be a barrier. Fourth, these findings are based on interim and preliminary analyses within the context of the overall main outcomes of an ongoing RCT, and whether and how these results may be related to long-term cardiovascular and other health outcomes are unknown. Fifth, the dietary intervention was multifaceted and it is not possible to determine which aspects of the intervention may be influencing the outcomes.

Conclusions

In this preliminary analysis of an ongoing trial, an intervention that encouraged an energy-reduced Mediterranean diet and physical activity, compared with advice to follow an energy-unrestricted Mediterranean diet, resulted in a significantly greater increase in diet adherence after 12 months. Further evaluation of long-term cardiovascular effects is needed.

ARTICLE INFORMATION

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Correction: This article was corrected on November 1, 2021, to correct an error in eTable 1 in Supplement 2 in which it was not indicated that the outcome "Bone density and body composition measured with DXA" was measured at 1- and 3-year follow-up.

Author Contributions: Drs Martínez-González and Salas-Salvadó had full access to all of the data in the study, take responsibility for the integrity of the data and the accuracy of the data analysis. Drs Martínez-González and Salas-Salvadó equally contributed as co–senior authors.
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