"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".

Running title: Effectiveness of the PREDIMED-Plus nutritional and behavioral intervention

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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 6,874 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 er-MedDiet 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.

Abstract

Importance: Adoption of high-quality dietary patterns may help prevent some chronic medical conditions, but limited data exist from randomized trials about the effects of nutritional and behavioral interventions on dietary changes**.**

Objective: To assess the effect of an intensive nutritional and physical activity education program on dietary quality and cardiovascular risk factors.

Design, Setting and Participants: Preliminary exploratory interim analysis of an ongoing randomized trial. In 23 Spanish centers, the trial enrolled 6,874 men and women (55 to 75 years) with metabolic syndrome, but free of cardiovascular disease, between September 2013 to December 2016 (last data collection: March 2019).

Intervention: Participants were randomly allocated to an intervention group based on an energy-reduced Mediterranean diet (er-MedDiet), physical activity promotion, and behavioral support (n= 3,406) or to an energy unrestricted Mediterranean diet control group (n=3,468). Participants in both groups received allotments of extra-virgin olive oil (1 l/mo) and nuts (125 g/mo) for free.

Main Outcome and Measure: The primary outcome was 12-month change in adherence to er-MedDiet score (range: 0 to 17 points, higher scores indicate greater adherence; minimal important difference: 1 point).

Results: Among 6,874 randomized participants [mean age 65.0 (SD: 4.9) years; 3,539 (52%) men], 6,583 (96 %) completed 12-month follow up and were included in the analyses. The mean (SD) er-MedDiet score was 8.5 (2.6) at baseline and 13.2 (3.5) at 12 months in the intervention group (increase, 4.7 (95% CI 4.6 to 4.8), and it was 8.6 (2.7) at baseline and 11.1 (3.4) at 12 months in the control group (increase, 2.5 (2.3 to 2.6), between group difference 2.2 (2.1 to 2.4, $p < 0.001$). This difference was objectively confirmed by beneficial changes in cardiovascular risk factors.

Conclusion and Relevance: In this preliminary analysis on an ongoing clinical trial, an intervention focused on encouraging 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.

Trial Registration: isrctn.com Identifier: ISRCTN89898870

Key words: PREDIMED-Plus, dietary intervention, Mediterranean diet, cardiovascular disease, randomized clinical trial.

Introduction

The disease burden of elevated body mass index (BMI) has increased rapidly during the last three decades[1-2] in close association with excess caloric intake but poor nutritional quality. Evaluations of lifestyle interventions to mitigate overweight and obesity are among the top priorities in public health. High scores in diet quality 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 (MedDiet) presents an optimal nutrient profile[4-6], has been associated with reduced all-cause mortality[3], non-fatal 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 MedDiet (er-MedDiet) may represent an optimal model for participants with overweight/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 about nutritional interventions using a whole dietary pattern is the actually expected adherence with the intended goals. Because placing thousands of apparently healthy free-living participants during several years on a diet which is not of their choice, but was randomly allocated, does not seem an easy endeavor, the selected dietary goals should have sufficient appeal. In this context, the traditional MedDiet seems sufficiently realistic and attractive. Initial results of the pilot study in 626 participants of this trial were previously reported[15]. The aim of this study was to evaluate the effect of a large RCT testing an er-MedDiet (versus control group) regarding adherence and changes in risk factors after a 12-month intervention. This article reports interim 1-year results focused on exploratory endpoints of a larger ongoing RCT.

Methods

The methods are described in detail elsewhere[14-15], including the protocol (on-line Supplement 1), the statistical analysis plan (Supplement 2), a Data Sharing Statement (Supplement 3) and other information (Supplement 4). Briefly, a multicenter, parallel-group, randomized, single-blind clinical trial is evaluating the long-term effects on cardiovascular events of a lifestyle intervention (intervention group) including: a) er-MedDiet; b) physical activity promotion; and c) a behavioral support for weight loss in comparison to a control group receiving a traditional MedDiet without any caloric restriction. This trial was approved by each institutional review board of all participating institutions. All participants provided written informed consent.

Eligible participants were community-dwelling men (aged 55-75) and women (60-75 years), free from CVD at baseline, with initial BMI between 27-40 kg/m^2 and meeting >=3 criteria for metabolic syndrome[16]. Between September 2013 and December 2016, 6,874 participants were recruited in 23 Spanish centers. Participants were randomized in a 1:1 ratio to the intervention group or to the usual-care control group, using a computer-generated random number internet-based system with stratification by center, sex and age (<65, 65-70, and >70 years) in blocks of 6 participants. The randomization procedure was blinded to all staff members and principal investigators. This randomization procedure was audited for all centers. For couples sharing the same household, randomization was done by cluster, with the couple as unit of randomization.

Dietary intervention

Participants allocated to the intervention group were prescribed an er-MedDiet, accompanied by physical activity promotion and behavioral support, with the purpose of accomplishing specific weight-loss objectives[14,15]. Trained dietitians delivered three interventions per month during the first year (a group session, an individual motivational interview and a phone call) using problem-solving interviews for successful weight loss. Considering basal metabolic rate and level of physical activity of each participant in the intervention group, a reduction of ~ 30% of estimated energy requirements was recommended (which represents a reduction of ~ 600 kcal/day). However, actual energy intake reduction was expected to be modest, given that the trial was conducted among free-living participants and that levels of physical activity were expected to increase.

Participants in the control group received educational sessions on the traditional MedDiet with ad libitum caloric intake, all contents previously used in PREDIMED[8] and general lifestyle recommendations according to usual care practices in the Spanish National Health System. This group received one individual visit, one telephone call and one group session every 6 months during the first year. We provided participants in both groups with an allotment of extra-virgin olive oil (1 liter/month) and nuts (almonds) (125 g/month) for free. However, we recommend all participants to consume a total of 500 g/month of mixed nuts.

The er-MedDiet differed from the diet recommended to the control group in more restrictive limits for red and processed meats, butter, margarine or cream and carbonated sweetened beverages. Also, it recommended not adding sugar to beverages, limiting white bread and refined cereals, while promoting the consumption of whole grains.

Dietary assessment

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

Changes in four dietary scores[19-21] (eTable 1), reflecting adherence to food patterns, were assessed. Three of them captured adherence to the MedDiet. We used a 17-item questionnaire to assess adherence to an er-MedDiet. This 17-item tool is a modified version of a previously validated 14-item questionnaire[20], also known as the Mediterranean Diet Adherence Screener (MEDAS). But in this new 17-item version[14], more restrictive cutoff points for some caloric-dense items were used and a few additional items aimed to reduce caloric intake were added. The Mediterranean Diet Score (MDS, range: 0-9 points)[19] is a well-known score 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 score that we assessed was the Prime Diet Quality Score (PDQS). It 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 non-communicable diseases, adopting a world-wide perspective[21].

Non-dietary variables

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

Outcomes

The primary end-point in the present article was change from baseline to 12 months in adherence to the er-Med Diet score ranging 0-17 point. Secondarily, we assessed the MEDAS (0 to 14 points), the MDS (0 to 9 points) and the PDQS (0 to 42 points) (eTable1). In all cases a higher score meant a better dietary quality. The minimum clinically important difference (MCID) or detectable difference can be considered as 1 point for the er-MedDiet (see Table2, footnote). Other secondary outcomes were changes in nutrients [total energy intake and % of energy from macronutrients and alcohol, and the intake of fiber, long chain w-3 fatty acids, dietary cholesterol and sodium], key food items [olive oil (refined and extra virgin), nuts, fruits, vegetables, cereals (whole grain and refined), legumes, fish, meat (red and processed), pastries, dairy (yogurt, fermented, low-fat and whole-fat dairy) and alcohol (red wine)], and cardiovascular risk factors (body weight, waist circumference, BMI, total serum cholesterol, HDL-c, LDL-c, non HDL-c, ratio between cholesterol and HDL-c, triglycerides, systolic and diastolic blood pressure). We compared percentages of participants with clinically meaningful changes in classical risk factors. We considered as MCID all changes of at least 5% in BMI[24], body weight[25], WC[25], total cholesterol, LDL-c[26], non HDL-c, cholesterol:HDL ratio, and HDL-c (increases)[27], or reductions >=5 mmHg in systolic or >=2.5 mmHg in diastolic blood pressure[28]. For triglycerides, we considered 10% change as the MCID[29].

Statistical Analysis

Calculation of sample size was done for the primary end-point of the overall trial (composite of non-fatal myocardial infarction, non-fatal stroke or cardiovascular death)[14]. We used the data base of this trial dated on March 12, 2019. Principal analyses included all randomized participants with baseline nutritional data, regardless of whether they had incomplete information on follow-up visits or not, with multiple imputation procedures for missing data. Secondary analyses included only those participants with complete information in each follow-up visit.

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

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

Mixed-effects linear models were used to assess changes in nutritional variables from baseline to 6- and 12-month follow-up in both all randomized participants and completer-only analyses. We fitted a three-level mixed linear model with random intercepts at site, and at the cluster family level.

All secondary analyses were exploratory; therefore, no additional adjustment was conducted to handle type-1 error.

Post hoc sensitivity analyses were conducted by 1) Including only participants with complete information (Completers only) (eTables 3-5), 2) repeating all analyses after replacing all missing values with baseline value (eTables 6-8). All analyses were conducted with Stata, version 15.0 (Stata Corp). All statistical tests were 2-sided and $p<0.05$ were deemed as statistically significant.

Results

We excluded 53 participants (28 from the intervention group, 25 from the control group) who did not complete the food frequency questionnaire at baseline, and 238 participants (106 from the intervention and 132 from the control group) with total energy intake beyond pre-specified limits. A final sample of 6,583 participants (3,406 men and 3,177 women) was analyzed (Figure 1). Imputed missing values for nutritional variables were 12.7% at 6-month and 12.2% at 12-month. For sensitivity analyses in completers only, we also excluded participants without nutritional information at follow-up (eTables 3-5) or without information on risk factors (eTable9).

As Table 1 shows, both groups were well balanced at randomization showing similar baseline characteristics.

Primary outcome

At baseline, the mean score of 17-item er-MedDiet was 8.6 (SD:2.7) points in the control group and 8.5 (SD:2.6) in the intervention group. The mean (SD) er-MedDiet score was 8.5 (2.6) at baseline and 13.2 (3.5) at 12 months in the intervention group (increase, 4.7 (95%CI 4.6 to 4.8), and it was 8.6 (2.7) at baseline and 11.1 (3.4) at 12 months in the control group (increase, 2.5 (2.3 to 2.6), between group difference 2.2 (2.1 to 2.4, p <0.001) (eFigure1). These improvements in the intervention group represented a significant 55% (95% CI: 55 to 56) relative increase over 12 months (Table 2). Figure 2 graphically represents the distribution of scores of adherence to the er-MedDiet at baseline and after 12-month follow-up in each group. The intervention group exhibited considerably greater improvements in the overall distribution of this score.

Secondary outcomes

Other Dietary scores

Mean baseline adherence to the PDQS was 21.1 (SD:3.7) in both groups. Within-group significant changes at 12-month were 4.4 (95% CI:4.2 to 4.7) in the control group and 6.9 (95% CI:6.6 to 7.1) in the intervention group. Between-group differences were statistically significant: 2.4 (95% CI:2.1 to 2.8). In post hoc sensitivity analyses these changes were maintained (eFigure1, eTable3, eTable6).

Foods and food groups

Significant reductions in the consumption of specific foods or food groups after 12 months of intervention were observed (eTable2). For example, baseline consumption of refined grains was 779 g/wk in both groups and reductions (95% CI) after 12 months were -535 g/wk (-559 to -510) in the intervention group compared to -226 (-249 to -203) in control, with significant between-group differences of -309 (-340 to -277). 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 changes after 12 months of -60 (-67 to -53) g/wk in control and -109 (-116 to -102) in intervention. Between-group differences were statistically significant: -49 (-59 to -39). Significant reductions in red meat consumption were also observed. Some of the greatest increases were observed for vegetables, with mean baseline consumption 2,130 g/wk in control and 2,168 in the intervention group; within-group differences after 12 month were 137 g/wk (100 to 175) in control and 347 (306 to 389) in intervention; the between-group significant difference was 210 (157 to 263) g/week. For fruits, the 12-month between-group significant difference was similar 197 (118 to 276) g/week. For nuts, with baseline consumption 60 g/wk in both groups; the 12-month between-group difference was also statistically significant: 35 (27 to 43) g/wk (eTable2). Post hoc sensitivity analyses showed that these results were robust (eTable4 and eTable7).

Energy intake and nutrients

Mean total energy intake at baseline intake was 2,369 (SD: 555) kcal/d in the control group and 2,355 (SD: 555) in the intervention group; 12-month between-group differences were statistically significant: -102 (-129 to -75) kcal/day (Table 3, eTable5 and eTable8). The percentage of energy from carbohydrates decreased in both groups, with 12-month between-group differences which were statistically significant: -1.4 (-1.8 to -1.0). Relative increases in energy from monounsaturated fatty acids (MUFA) were observed the mean baseline intake was 20.6% (SD: 4.6) of total energy intake in the control group and 20.5% (SD: 4.7) in intervention; within-group significant increases after 12 months were observed in control group: 3.0 (2.8 to 3.2) and the intervention group: 3.9 (3.7 to 4.1), with between-group significant differences of 0.9 (0.6 to 1.2). The proportion of participants achieving favorable dietary changes was significantly higher in the intervention than in the control group for most comparisons (eFigure2). eFigure3 shows differences in total energy intake and nutrient intake between both randomized groups, comparing changes at 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 change after 6 and 12 months in cardiovascular risk factors and the proportion of participants attaining a clinically meaningful change in risk factors after 12-month intervention are presented in Figure 3.

With few exceptions, such as LDL-c, significant and clinically meaningful favorable changes for the intervention versus the control group in body weight, waist circumference, BMI, HDL-c, non HDL-cholesterol, total cholesterol:HDL-c ratio, serum triglycerides, systolic and diastolic blood pressure after 12-month were observed (Figure 3 and eTable9). For example, mean waist circumference (cm) was 108 at baseline in both control and intervention groups, and between-group differences at 12 months were -2.9 cm (-3.2 to -2.6, p value<0.001). Mean systolic blood pressure was 139 mmHg at baseline in control and 140 in intervention, with between-group differences at 12 months of -1.9 (-2.7 to -1.1, p value <0.001).

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 at 12 months. In addition, improvements in diet quality, energy intake, and cardiovascular risk factors also were observed. These findings are consistent with the previously reported preliminary findings from the pilot study of 626 participants in this trial[14].

The special intervention program included individual interviews and group motivational sessions with counseling to follow the traditional MedDiet and reduce caloric intake. It 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 MedDiet, without any special effort in energy reduction, physical activity or weight loss beyond the usual care received at the Spanish National Health System. In this way the level of participant interaction was considerably higher (6-fold higher) in the intervention than in the control group, with 18 vs 3 contacts in 6 months in the intervention and control group, respectively. Both groups received for free extra-virgin olive oil and nuts.

Changes at 12 months in the 17-item score appraising adherence to an er-MedDiet were the primary end-point. In the intervention group, this 17-item score increased significantly more in the intervention 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 such a trial, namely the adherence of participants to the intervention. Furthermore, these dietary changes were paralleled by successful changes in most classical risk factors.

Both randomized groups were educated in following a MedDiet. Therefore, it is of no surprise that olive oil consumption –the hallmark of MedDiet– increased in both groups. Many beneficial effects attributed to the MedDiet are due to the consumption of the extra-virgin variety of olive oil, that contains high amounts of dietary bioactive phenolic compounds with anti-oxidant and anti-inflammatory properties[31]. These compounds are not present in common, refined, varieties of olive oils. 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.

These findings support that nutritional interventions and behavioral therapies in patients at high cardiovascular risk, including diabetics and patients with metabolic syndrome, are likely to facilitate modifications of targeted dietary habits, reductions in body weight, and improvements in risk factors[32-33]. A recent 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 should include multiple face-to face contacts. This trial, with 36 contacts during the first year represents one of the largest RCTs where all these characteristics were present. They contribute to explain the attained results. However, as this is an interim exploratory analysis of an on-going trial, these results should be considered preliminary. Also, further analyses are deserved 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 including all randomized participants are additional strengths.

Limitations

This study has several limitations. First, the use of self-reported data to evaluate nutritional changes. Second, recall bias, social desirability bias and other potential reporting biases might have affected our 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 actually existed, would be similar in both groups, because both groups received advice encouraging a MedDiet. 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 transferability of these results to populations where access or affordability of high-quality olive oil and tree nuts might be a barrier to some participants. Fourth, these are interim and preliminary analyses, within the context of the overall main outcomes of the RCT. Therefore, the lack of long-term cardiovascular and other health outcomes represents an additional limitation. Another challenge is the understanding of which aspect(s) of a multifaceted intervention may be influencing the outcomes. However, the final results of the trial with cardiovascular outcomes will be better suited to address the potential mediation of the effects through each different aspect of the multidimensional intervention.

Conclusions

In this preliminary analysis on an ongoing clinical trial, 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 significant improvements in measures of diet adherence, which were objectively confirmed by beneficial changes in cardiovascular risk factors. Further evaluation of the effect on long-term cardiovascular and other health outcomes is needed.

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Conflicts of interest

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Figure legends

Figure 1. Flow-chart of participants.

Figure 2. Changes in the primary end-point (adherence to the energy-reduced Mediterranean diet) according to randomized group).

Figure 3. Changes in risk factors.

Figure 3A. Within-group changes expressed in common units of baseline standard deviations.

Figure 3B. Twelve-month changes in risk factors by randomized group, with percentages of clinically meaningful changes.

Table 1. Baseline characteristics of participants in the PREDIMED-PLUS trial included in the main analyses.

	Energy-reduced Mediterranean diet, physical activity, and behavioral support (Intervention group) (n=3,272)	Control group (Mediterranean diet with ad libitum energy intake) (n=3,311)
Female, n (%)	1,570 (48)	1,607 (49)
Male, n (%)	1,702 (52)	1,704 (51)
Age, years mean (SD)	65.0 (4.9)	65.0 (4.9)
Smoker, n (%)		
Current	436 (13)	379 (11)
Former	1,366 (42)	1,486 (45)
Education, n (%)		
Primary or less	1,540 (48)	1,647 (50)
Secondary	997 (31)	902 (28)
University	703 (21)	736 (22)
Weight, kg mean (SD)	86.7 (13.0)	86.4 (13.0)
BMI, kg/m^2, mean (SD)	32.5 (3.4)	32.5 (3.5)
Waist, cm, mean (SD)	108 (9.6)	108 (9.7)
Physical activity, METs-min/wk, median (IQR)	1,709 (839, 3,202)	1,902 (867, 3,371)

BMI, Body mass index; MET, metabolic equivalent of task; Categorical, and continuous variables are expressed as n (proportion), and mean (standard deviation) or median (IQR), respectively

Table 2. Baseline dietary pattern scores and their changes by randomized treatment group.

	MULTIPLE IMPUTATION: all randomized participants			
Dietary patterns	**Energy-reduced Mediterranean diet, physical activity, and behavioral support (Intervention group) N=3,272**	**Control group (Mediterranean diet with ad libitum energy intake) N=3,311**	**Between-group difference (95% CI)**	**p value**
17-item er-MedDiet (0 to 17)				
Baseline, mean (SD)	8.5 (2.6)	8.6 (2.7)		
6-month change	4.4 (3.4)	2.2 (3.5)	2.2 (2.0 to 2.3)	<0.001
12-month change	4.7 (3.5)	2.5 (3.4)	2.2 (2.1 to 2.4)	<0.001
MDS (Trichopolou 0 to 9)				
Baseline, mean (SD)	4.3 (1.7)	4.3 (1.6)		
6-month change	0.7 (2.4)	0.3 (2.5)	0.4 (0.3 to 0.5)	<0.001
12-month change	0.8 (2.5)	0.2 (2.4)	0.6 (0.5 to 0.7)	<0.001
MEDAS (0 to 14)				
Baseline, mean (SD)	7.6 (1.9)	7.6 (1.9)		
6-month change	3.0 (2.4)	2.0 (2.5)	1.0 (0.9 to 1.1)	<0.001
12-month change	3.2 (2.4)	2.1 (2.5)	1.1 (1.0 to 1.2)	<0.001
PDQS (0 to 42)				
Baseline, mean (SD)	21.1 (3.7)	21.1 (3.7)		
6-month change	6.7 (6.8)	4.7 (7.4)	2.0 (1.6 to 2.3)	<0.001
12-month change	6.9 (7.0)	4.4 (7.0)	2.4 (2.1 to 2.8)	<0.001

MI, Multiple imputation.
Baseline data are means (SD)
6-month and 12-month change within groups are means (SD), changes between groups are means (95% confidence intervals [CI]) calculated using mixed effect models taking into account site and intra-cluster correlations (couples) as random factors.
er-MedDiet, Energy reduced Mediterranean Diet; MDS, Mediterranean Diet Score, MEDAS, Mediterranean Diet Adherence Screener; PDQS,
The direction of all 4 food patterns is the same: a higher score means a higher quality of the overall dietary pattern. The possible ranges were 0-17 for er-MedDiet, 0-9 for the MDS, 0-14 for MEDAS, and 0-42 for PDQS, Prime Diet Quality Score.

The minimum clinically important difference (MCID) can be considered 1 point for the MDS, because a 2 point increment (roughly corresponding to one standard deviation) was associated in the fully adjusted model with a 25% relative reduction in all-cause mortality (Trichopoulou et al. N Engl J Med 2003;348:2599-608, Table 4), 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.

For the MEDAS, in the PREDIMED trial, assessed as an observational study, and controlling for potential confounding, 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) (unpublished data). Therefore, 1 point should represent a sufficiently important difference for an individual patient.

The 17-item er-MedDiet score basically captures the 14-items of MEDAS with some additions (sufficiently explained in our main manuscript) that have been repeatedly associated with benefits in previous observational studies with good control for confounding. Therefore, a 1-point difference can be also accepted as a minimum clinically important difference.

For the PDQS (range 0 to 42, SD=3.7), the minimum clinically important difference will represent probably a 2-point increment, given its wider range.

Table 3. Baseline energy and nutrient intake and their changes by randomized treatment group.

	MULTIPLE IMPUTATION: all randomized participants			
Energy and nutrients	**Energy-reduced Mediterranean diet, physical activity, and behavioral support (Intervention group) N=3,272**	**Control group (Mediterranean diet with ad libitum energy intake) N=3,311**	**Between-group difference (95% CI)**	**p value**
Total Energy Intake (kcal/d)				
Baseline, mean (SD)	2,355 (555)	2,369 (555)		
6-month change	-173 (537)	-76 (501)	-97 (-122 to -72)	<0.001
12-month change	-176 (543)	-74 (501)	-102 (-129 to -75)	<0.001
Total protein (%E)				
Baseline, mean (SD)	16.8 (2.8)	16.8 (2.8)		
6-month change	1.2 (2.9)	0.2 (2.7)	1.0 (0.9 to 1.2)	<0.001
12-month change	1.1 (3.0)	0 (2.7)	1.1 (1.0 to 1.3)	<0.001
Total carbohydrate (%E)				
Baseline, mean (SD)	40.7 (6.8)	40.4 (6.9)		
6-month change	-3.4 (7.0)	-1.9 (6.8)	-1.5 (-1.8 to -1.1)	<0.001
12-month change	-3.7 (6.9)	-2.3 (6.8)	-1.4 (-1.8 to -1.0)	<0.001
Total fat (%E)				
Baseline, mean (SD)	39.5 (6.6)	39.7 (6.5)		
6-month change	2.5 (7.1)	1.9 (6.9)	0.6 (0.3 to 1.0)	<0.001
12-month change	2.9 (7.1)	2.4 (6.9)	0.5 (0.1 to 0.9)	0.007
SFA(%E)				
Baseline, mean (SD)	9.9 (2.0)	10.0 (2.0)		
6-month change	-1.0 (2.0)	-0.6 (2.0)	-0.5 (-0.6 to -0.4)	<0.001
12-month change	-0.9 (2.0)	-0.6 (1.9)	-0.4 (-0.5 to -0.3)	<0.001
MUFA				
Baseline, mean (SD)	20.5 (4.7)	20.6 (4.6)		
6-month change	3.5 (5.6)	2.4 (5.3)	1.1 (0.9 to 1.4)	<0.001
12-month change	3.9 (5.6)	3 (5.3)	0.9 (0.6 to 1.2)	<0.001

Baseline data are means and (SD)
E, energy; SFA, saturated fatty acids; MUFA, unsaturated fatty acids
6-month and 12-month change within groups are means (SD), changes between groups are means (95% confidence intervals [CI]) calculated using mixed effect models taking into account site and intra-cluster correlations (couples) as random

Table 3 (cont.). Baseline dietary variables and their changes by randomized treatment group.

	MULTIPLE IMPUTATION: all randomized participants			
Energy and nutrients	**Energy-reduced Mediterranean diet, physical activity, and behavioral support (Intervention group) N=3,272**	**Control group (Mediterranean diet with ad libitum energy intake) N=3,311**	**Between-group difference (95% CI)**	**p value**
Ratio MUFA:SFA				
Baseline, mean (SD)	2.1 (0.5)	2.1 (0.5)		
6-month change	0.6 (0.7)	0.4 (0.6)	0.3 (0.2 to 0.3)	<0.001
12-month change	0.7 (0.7)	0.5 (0.7)	0.2 (0.2 to 0.2)	<0.001
PUFA (%E)				
Baseline, mean (SD)	6.4 (1.9)	6.4 (1.8)		
6-month change	1.3 (2.3)	0.8 (2.1)	0.5 (0.4 to 0.6)	<0.001
12-month change	1.3 (2.2)	0.8 (2.1)	0.4 (0.3 to 0.5)	<0.001
Total alcohol (%E)				
Baseline, median (IQR)	1.0 (0, 4)	2.0 (0, 4)		
6-month change	-0.3 (3.0)	-0.1 (3.0)	-0.2 (-0.4 to 0)	0.01
12-month change	-0.3 (3.0)	-0.1 (3.0)	-0.2 (-0.4 to 0.1)	0.01
Fiber (g/week)				
Baseline, mean (SD)	184 (62.7)	182 (59.9)		
6-month change	40 (70.8)	16 (60.6)	23 (20 to 27)	<0.001
12-month change	37 (68.5)	18 (62.8)	19 (16 to 23)	<0.001
Long chain w-3 fatty acids (g/week)				
Baseline, median (IQR)	5 (4, 9)	5 (4, 9)		
6-month change	1.1 (3.9)	0.5 (3.6)	0.6 (0.4 to 0.8)	<0.001
12-month change	1.1 (4.1)	0.4 (3.6)	0.7 (0.5 to 0.9)	<0.001
Cholesterol (mg/week)				
Baseline, mean (SD)	2,651 (793)	2,687 (825)		
6-month change	-224 (779)	-169 (780)	-54 (-94 to -14)	0.008
12-month change	-216 (823)	-209 (784)	-7 (-49 to 35)	0.74
Sodium (g/week)				
Baseline, median (IQR)	22 (18, 27)	22 (18, 27)		
6-month change	-3.0 (6.8)	-1.8 (6.5)	-1.2 (-1.6 to -0.9)	<0.001
12-month change	-3.2 (7.1)	-1.9 (6.9)	-1.3 (-1.6 to -0.9)	<0.001

Baseline data are means and (SD) or median (IQR).
E, energy; SFA, saturated fatty acids; MUFA, unsaturated fatty acids; PUFA, polyunsaturated fatty acids;

w-3, omega-3
6-month and 12-month change within groups are means (SD), changes between groups are means (95% CI) calculated using mixed effect models taking into account site and intra-cluster correlations (couples) as random factors.