THELANCETDE-D-16-00306R1

S2213-8587(16)30085-7

Embargo: June 6, 2016 [23:30] BST

Effect of a high-fat Mediterranean diet on bodyweight and waist circumference: a prespecified secondary outcomes analysis of the PREDIMED randomised controlled trial

Ramon Estruch, Miguel Angel Martínez-González, Dolores Corella, Jordi Salas-Salvadó, Montserrat Fitó, Gemma Chiva-Blanch, Miquel Fiol, Enrique Gómez-Gracia, Fernando Arós, José Lapetra, Lluis Serra-Majem, Xavier Pintó, Pilar Buil-Cosiales, José V Sorlí, Miguel A Muñoz, Josep Basora-Gallisá, Rosa María Lamuela-Raventós, Mercè Serra-Mir, Emilio Ros*, for the PREDIMED Study Investigators†*

Summary

Background Because of the high density of fat, high-fat diets are perceived as likely to lead to increased bodyweight, hence health-care providers are reluctant to recommend them to overweight or obese individuals. We assessed the long-term effects of ad libitum, high-fat, high-vegetable-fat Mediterranean diets on bodyweight and waist circumference in older people at risk of cardiovascular disease, most of whom were overweight or obese.

Methods PREDIMED was a 5 year parallel-group, multicentre, randomised, controlled clinical trial done in primary care centres affiliated to 11 hospitals in Spain. 7447 asymptomatic men (aged 55–80 years) and women (aged 60–80 years) who had type 2 diabetes or three or more cardiovascular risk factors were randomly assigned (1:1:1) with a computer-generated number sequence to one of three interventions: Mediterranean diet supplemented with extra-virgin olive oil (n=2543); Mediterranean diet supplemented with nuts (n=2454); or a control diet (advice to reduce dietary fat; n=2450). Energy restriction was not advised, nor was physical activity promoted. In this analysis of the trial, we measured bodyweight and waist circumference at baseline and yearly for 5 years in the intention-to-treat population. The PREDIMED trial is registered with ISRCTN.com, number ISRCTN35739639.

Findings After a median 4·8 years (IQR 2·8–5·8) of follow-up, participants in all three groups had marginally reduced bodyweight and increased waist circumference. The adjusted difference in 5 year changes in bodyweight in the Mediterranean diet with olive oil group was –0·43 kg (95% CI –0·86 to –0·01; p=0·044) and in the nut group was 0·08 kg (–0·50 to 0·35; p=0·730), compared with the control group. The adjusted difference in 5 year changes in waist circumference was –0·55 cm (–1·16 to –0·06; p=0·048) in the Mediterranean diet with olive oil group and –0·94 cm (–1·60 to –0·27; p=0·006) in the nut group, compared with the control group.

Interpretation A long-term intervention with an unrestricted-calorie, high-vegetable-fat Mediterranean diet was associated with decreases in bodyweight and less gain in central adiposity compared with a control diet. These results lend support to advice not restricting intake of healthy fats for bodyweight maintenance.

Funding Spanish Government, CIBERobn, Instituto de Salud Carlos III, Hojiblanca, Patrimonio Comunal Olivarero, California Walnut Commission, Borges SA, and Morella Nuts.

Lancet Diabetes Endocrinol 2016

Published Online
June 6, 2016
http://dx.doi.org/10.1016/S2213-8587(16)30085-7

See Online/Comment
http://dx.doi.org/10.1016/PII

*Contributed equally

†Members listed in the appendix

Centro de Investigación Biomédica en Red Fisiopatologia de la Obesidad y la Nutrición, Instituto de Salud Carlos III, Madrid, Spain (R Estruch MD, Prof M A Martínez-González MD, Prof D Corella PharmD, Prof J Salas-Salvadó MD, M Fitó MD, M Fiol MD, E Gómez-Gracia MD, F Arós MD, J Lapetra MD, Prof L Serra-Majem MD, X Pintó MD, J V Sorlí MD, J Basora-Gallisá MD, P Buil-Cosiales MD, R M Lamuela-Raventós PharmD, M Serra-Mir RD, E Ros MD); **Department of Internal Medicine and Lipid Clinic, Department of Endocrinology and Nutrition** (M Serra-Mir, E Ros), **Hospital Clinic, Institut d'Investigacions Biomèdiques August Pi Sunyer, University of Barcelona, Barcelona, Spain** (R Estruch, G Chiva-Blanch PhD); **Department of Preventive Medicine and Public Health, Universidad de Navarra-Institute of Health Research of Navarra, Pamplona, Spain** (M A Martínez-González); **Department of Preventive Medicine, School of Medicine, University of Valencia, Valencia, Spain** (D Corella, J V Sorlí); **Human Nutrition Department, Hospital Universitari Sant Joan, Institut d'Investigació Sanitària Pere Virgili, University Rovira i Virgili, Reus, Spain**

Introduction

Obesity is a key risk factor for morbidity and mortality from cardiovascular disease and for the development of type 2 diabetes, some cancers, and musculoskeletal disorders.[1] The standard recommendation for the prevention and treatment of obesity is restricting dietary energy intake and increasing physical activity. Because of the high energy of fat, the belief persists that increased dietary fat intake will lead to weight gain, whereas reduced fat intake will promote weight loss.[2] Thus, nutritional advice to obese individuals has often emphasised the avoidance of all types of dietary fat and their replacement with carbohydrate or protein.[3] By sharp contrast with this view, results from two clinical trials testing low-fat diets for the prevention of cardiovascular disease in postmenopausal women[4] and patients with diabetes[5] did not show any benefit of reduced fat intake with respect to prevention of cardiovascular disease outcomes. Moreover, these studies provided only marginal evidence of weight loss over time compared with control diets. The results of a meta-analysis[6] of trials comparing low-fat versus high-fat dietary interventions favoured high-fat diets for weight loss, albeit only in the context of calorie restriction.

Some scientific societies,[7] but not the American Diabetes Association,[8] still recommend low-fat diets to promote overall health and the loss of excess bodyweight. However, long-term adherence to energy-restricted diets low in fat and high in complex carbohydrates to achieve weight loss is generally poor[9] and weight regain usually ensues 6–12 months after commencing such diets.[5] In the past few decades, the perception of dietary fat as unhealthy has resulted in decreased fat consumption in the US population, but the epidemics of obesity and diabetes have continued to grow.[10] Higher-fat diets can be beneficial for cardiovascular health if salutary

(J Salas-Salvadó); **Cardiovascular and Nutrition Research Group, Institut de Recerca Hospital del Mar, Barcelona, Spain** (M Fitó); **Institute of Health Sciences, University of Balearic Islands and Hospital Son Espases, Palma de Mallorca, Spain** (M Fiol); **Department of Preventive Medicine, University of Málaga, Málaga, Spain** (E Gómez-Gracia); **Department of Cardiology, University Hospital of Alava, Vitoria, Spain** (F Arós); **Department of Family Medicine, Primary Care Division of Sevilla, San Pablo Health Center, Sevilla, Spain** (J Lapetra); **Research Institute of Biomedical Research and Health Services and School of Medicine, University of Las Palmas de Gran Canaria, Spain** (L Serra-Majem); **Lipids and Vascular Risk Unit, Internal Medicine, Hospital Universitario de Bellvitge, Hospitalet de Llobregat, Spain** (X Pintó); **Primary Care Division, Valencia Institute of Health, Burjassot, Valencia, Spain** (J V Sorlí); **Primary Health Care Division, Institut Català de la Salut and Idiap-Jordi Gol, Barcelona, Spain** (M A Muñoz MD); **Primary Health Care Division, Institut Català de la Salut and Idiap-Jordi Gol, Tarragona, Spain** (J Basora-Gallisá); **Primary Health Care Division, Institute of Health Research of Navarra, Pamplona, Spain** (P Buil-Cosiales); **and Department of Nutrition and Bromatology, School of Pharmacy, Xarxa de Referència en Tecnologia dels Aliments, Instituto de Investigación en Alimentación y Seguridad Alimentaria, University of Barcelona, Barcelona, Spain** (R M Lamuela-Raventós)

Correspondence to: Dr Ramon Estruch, Department of Internal Medicine, Hospital Clinic, University of Barcelona, Barcelona 08036, Spain **restruch@clinic.ub.es**

See **Online** for appendix

For more on the **PREDIMED trial** see http://www.predimed.es/

Research in context

Evidence before this study

We searched MEDLINE (via PubMed) for articles published in any language between Jan 1, 1950, and March 1, 2016, using the search terms ("bodyweight"[MeSH Terms] OR "overweight"[MeSH Terms] OR "obesity"[MeSH Terms] OR "waist-hip ratio"[MeSH Terms] OR "waist circumference"[MeSH Terms] OR "body mass index"[MeSH Terms]) AND ("mediterranean diet"[All Fields]). All articles were screened and only systematic reviews, meta-analyses, clinical trials, and cohort studies were reviewed. Although evidence from prospective cohort studies and clinical trials shows that adherence to the high-fat Mediterranean diet might be associated with reduced rather than increased bodyweight, intake of all types of fat is still widely believed to promote weight gain. Systematic reviews and meta-analyses of randomised controlled trials that have assessed the effects of the Mediterranean diet on adiposity are limited by a follow-up timeframe of 2 years or less. No previous randomised trial has analysed the long-term effects of an unrestricted-calorie Mediterranean diet on bodyweight and waist circumference.

Added value of this study

This study provides first-level evidence that plant-based, unrestricted-calorie, high-fat diets, such as the traditional Mediterranean diet, do not promote weight gain. After analysis of the nearly 5 years of follow-up of a large cohort of older individuals (n=7447), of whom more than 90% were overweight or obese, our results show that intervention with an ad libitum Mediterranean diet enriched with healthy fatty foods has little effect on bodyweight or waist circumference. In fact, compared with participants following the control diet, based on advice to reduce all dietary fat, those in the Mediterranean diet plus olive oil group significantly reduced bodyweight while experiencing a minor and lesser increase of waist circumference, whereas those allocated to the Mediterranean diet with nuts showed no weight changes and stable waist circumference, compared with a mean 1·2 cm increase in the control group.

Implications of all the available evidence

There is accruing scientific evidence of the beneficial role of high-vegetable-fat dietary patterns such as the Mediterranean diet on cardiovascular disease, diabetes, and obesity. Our results have practical implications because the fear of weight gain often associated with a high-fat diet such as the Mediterranean diet need no longer be an obstacle to adherence to a dietary pattern known to provide much clinical and metabolic benefit, Our results are also relevant for public health guidance, in so much as they support unrestricted fat intake as appropriate for bodyweight maintenance and overall cardiometabolic health, as acknowledged by the Dietary Guidelines for Americans 2015 Advisory Committee.

vegetable fats are consumed.[11] However, even when low-fat diets are not explicitly recommended, specific guidance on high-fat foods, including nuts and vegetable oils, remains highly focused on concerns about weight gain.[12] In this context, a radical reassessment of the low-fat approach applied for the past 40 years in nutrition policy is needed.[12]

Ample epidemiological evidence shows that the Mediterranean diet—a dietary pattern that includes high consumption of vegetable fats—is associated with reduced all-cause mortality and reductions in cardiovascular disease and cancer.[13] The PREvención con DIeta MEDiterránea (PREDIMED) trial[14] has also provided first-level evidence of cardiovascular protection by the Mediterranean diet. Additionally, despite its high fat content, there is evidence from prospective cohort studies[15] and clinical trials[16] that adherence to the Mediterranean diet might also reduce bodyweight. However, results from a meta-analysis[17] of short-term randomised controlled trials of the Mediterranean diet for weight loss suggested that there was no effect on bodyweight when the diet was not calorie restricted. No previous randomised trial has analysed the long-term effects of an unrestricted-calorie Mediterranean diet on adiposity measures. Here we assess long-term changes in bodyweight and waist circumference in the PREDIMED trial.[14]

Methods

Study design and participants

The study design of the PREDIMED trial has been reported elsewhere.[14] Briefly, PREDIMED was a 5-year, parallel-group, multicentre, randomised clinical trial done in participants at high cardiovascular risk, comparing the effects of two unrestricted-calorie Mediterranean diets, enriched with extra-virgin olive oil or mixed nuts, with a control diet (advice to avoid all dietary fat) for the primary prevention of cardiovascular disease.[14] The trial was done in primary care centres affiliated to 11 hospitals in Spain during 2003–10 and included 7447 participants who were assigned to one of the three nutritional interventions. PREDIMED was approved by the institutional review boards of the 11 participating centres.[14]

In this prespecified secondary outcomes analysis of PREDIMED, we assessed the long-term effects of the Mediterranean diet interventions compared with the control diet on bodyweight and waist circumference over 5 years during which the assigned interventions were given. Eligible participants for PREDIMED were community-dwelling men (aged 55–80 years) and women (aged 60–80 years) who had either type 2 diabetes or at least three of the following cardiovascular risk factors: current smoking, hypertension (blood pressure >140/90 mmHg or treatment with antihypertensive drugs), high plasma LDL cholesterol concentration (≥4·14 mmol/L), low plasma HDL cholesterol concentration (<1·04 mmol/L for men and <1·30 mmol/L for women), overweight or obesity (BMI ≥25 kg/m²), or family history of premature coronary heart disease. More detailed criteria for enrolment have been reported elsewhere.[14] Of 8420 eligible candidates identified, 7447 (88%) agreed to participate and provided written informed consent.

Randomisation and masking

Candidates were randomly assigned (1:1:1) to one of three interventions: Mediterranean diet supplemented with extra-virgin olive oil, Mediterranean diet supplemented with nuts, or a control diet (advice to reduce dietary fat). Randomisation was done centrally by means of a computer-generated random-number sequence.[14] The clinical investigators and laboratory technicians were masked to intervention allocations.

Procedures

Trained dietitians were responsible for all aspects of the behavioural intervention promoting the Mediterranean diet, as previously described.[14] Briefly, on the basis of the initial assessment of individual scores of adherence to the Mediterranean diet with a 14-item questionnaire,[18,19] dietitians gave personalised dietary advice to participants randomly assigned to the two Mediterranean diet interventions, with instructions directed to improve adherence by face-to-face intervention every 3 months by registered dietitians. Participants assigned to the control diet received personal advice and written recommendations to reduce all types of dietary fat once a year; however, during the trial, this frequency of dietary advice in the control group was perceived as a limitation by reviewers, and the protocol was modified to increase the intensity and frequency of the intervention of the control group so that intervention in the three groups was similar. The change of the intervention was made on Oct 1, 2006, when 1626 participants were already included in the control group (appendix).

The intended goals of the interventions were to reduce fat intake to less than 30% of energy in the control diet group and to increase it to more than 40% of energy in the two Mediterranean diet groups. Participants in the two Mediterranean diet groups received at no cost either extra-virgin olive oil (1 L per week for the participants' family needs as each participant should consume 50 mL a day) or 30 g of nuts per day (15 g of walnuts, 7·5 g of almonds, and 7·5 g of hazelnuts, with additional 1 kg sachets of mixed nuts every 3 months to account for family needs), whereas those in the control group were given small non-food gifts every 3 months (such as, books, kitchen clocks, spoons, etc). Neither energy restriction nor increased physical activity was advised for any of the study groups. The duration of the trial was prespecified as 6 years; however, the Data and Safety Monitoring Board decided to stop the trial after analysing the results during the meeting done at year 5, according to prespecified rules to stop (appendix).

Participants completed a general medical questionnaire, a 137-item validated food frequency questionnaire,[20] and the validated Spanish version of the Minnesota Leisure Time Physical Activity Questionnaire[21] at baseline and at 1 year, 3 years, and 5 years. Information from the 137-item validated food frequency questionnaire was used to calculate energy and nutrient intake. Total physical activity was expressed as metabolic equivalent tasks.

Blood and urine samples were obtained after an overnight fast on the same day that the questionnaires were collected. To assess compliance to supplemental foods, we measured urinary hydroxytyrosol (a biomarker of extra-virgin olive oil consumption) and plasma α-linolenic acid (a fatty acid characteristic of walnuts) in random subsamples of participants at 1 year, 3 years, and 5 years and compared this with baseline levels.

Outcomes

The main outcomes of interest in this prespecified secondary outcomes analysis were bodyweight and waist circumference at a mean of 5 years of follow-up. Trained personnel measured weight and height to the nearest 0·5 kg and 0·5 cm with calibrated scales and a wall-mounted stadiometer, respectively; waist circumference was measured to the nearest 0·5 cm midway between the lowest rib and the iliac crest with an anthropometric tape at baseline, 1 year, 2 years, 3 years, 4 years, and 5 years of follow-up. Changes in bodyweight and waist circumference at the end of intervention were prespecified secondary outcomes in the PREDIMED study.

Statistical analysis

The sample size was calculated to detect significant differences in the primary outcome (cardiovascular disease), as detailed in the appendix. A sample size of 6999 with randomisation to three equally sized groups (two intervention groups and one control group with 2333 patients each) was estimated to provide sufficient statistical power to assess the effects of the Mediterranean diets on the primary outcome assuming 80% power and a two-sided p value of 0·05. For the secondary outcomes analysed here (weight and waist circumference), the study was powered to detect clinically relevant mean differences. The final sample size of 7447 participants included at baseline and 3985 participants with follow-up data at 5 years (n=1501 in the extra-virgin olive oil group, n=1241 in the nuts group, and n=1243 in the control group) allowed detection of statistically significant differences at a two-sided α of 0·05 and 20% β for between-group mean differences in 5 year changes from baseline in the intervention groups compared with the control group of 0·6 kg in weight and 0·7 cm in waist circumference. At 1 year and 3 years as well as for yearly changes, the study had more than 80% power to detect these differences.

We used descriptive statistics with means and SDs or percentages for the participants' baseline characteristics. Within-group and between-group differences are expressed as means and 95% CIs. Missing data for outcome variables were handled in accordance with the method described by Groenwold and colleagues[22] by doing multiple imputations (20 sets) for missing values in participants who dropped out out or had missing measurements in each year, provided that they had entered the trial sufficiently early as to be assessable on that year. Thus, 20 datasets with computed outcomes were created and each was analysed by standard statistical methods (including the multiple imputations procedure) to fit the model of interest. Estimated associations in each of the imputed datasets were averaged together to give the overall associations. First, ordinary least-squares linear regression models for multiple imputed data were used to compare mean between-group changes (at 1, 3, or 5 years, minus baseline) in bodyweight and waist circumference and run separately at the 1, 3, and 5 year assessments. Two dummy variables (one for each of the two Mediterranean diet groups with the control group as reference category) were used in this model. We adjusted these linear models for sex, age, centre, smoking status (never, former, or current smoker), diabetes, dyslipidaemia, and hypertension. In a subsequent model, we additionally adjusted for baseline BMI and baseline waist-to-height ratio, total energy intake (kcal per day; both at baseline and at 1 year follow-up), leisure-time physical activity (metabolic equivalent tasks per h per week), educational level, and alcohol consumption.

In addition to the ordinary least-squares models for one timepoint changes, we also considered all timepoints (ie, each of the 5 years of follow-up and at baseline) to compare changes in bodyweight and waist circumference during follow-up by intervention group. As the ordinary least-squares models do not take into account the correlation of within-participant data (longitudinal measurements), we used generalised estimating equations, which allow specification of the correlation structure. We assumed an exchangeable or an autoregressive correlation matrix, as suggested by the actually observed correlations between

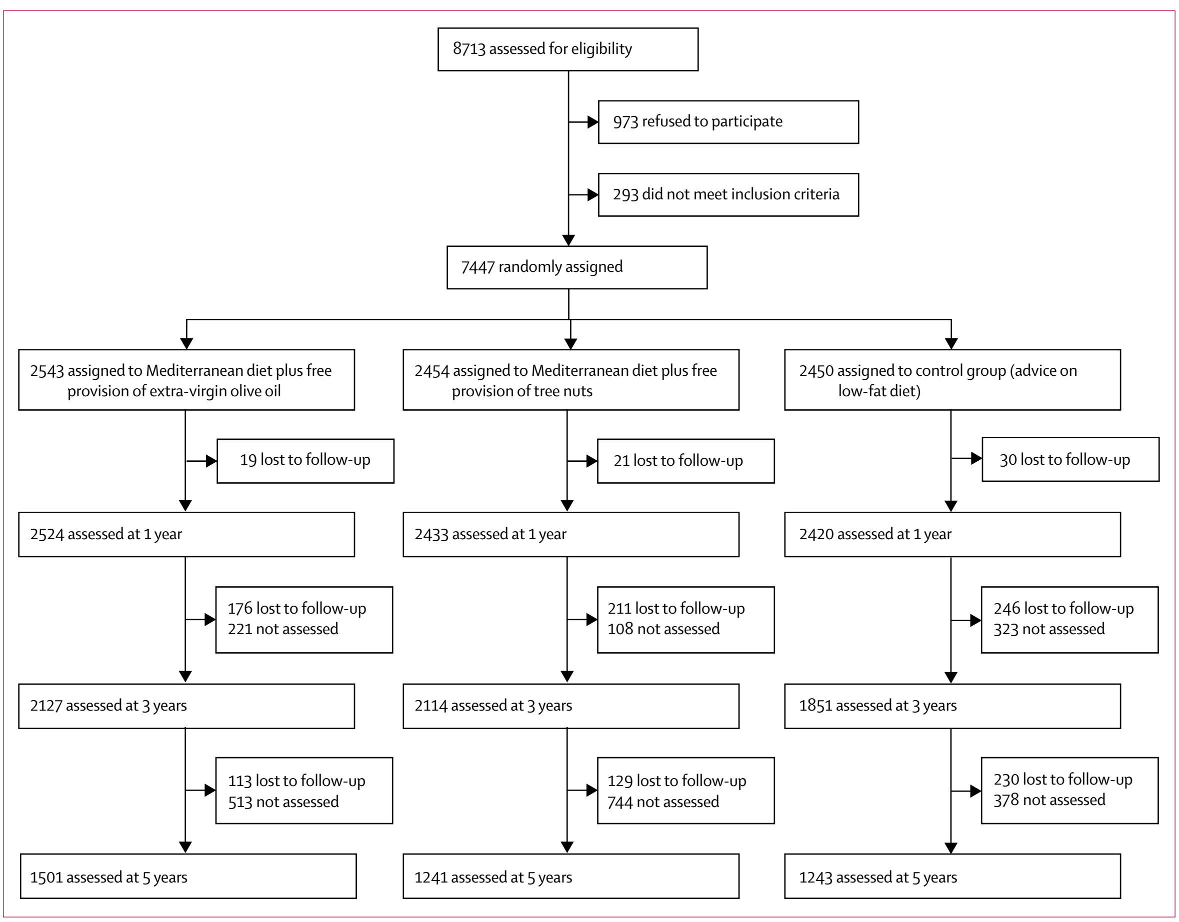

Figure 1: **Trial profile for the PREDIMED study**
The median follow-up was 4·8 years. Numbers of patients in each group at the close of the trial were 2452 in the extra-virgin olive oil group, 2299 in the nuts group, and 2173 in the control group. The long recruitment period in the trial (the last participant was recruited approximately 2 years before the trial was stopped) meant that participants recruited later were not evaluated at 3 or 5 years, hence the lower numbers at these timepoints.

 www.thelancet.com/diabetes-endocrinology **Published online June 6, 2016 http://dx.doi.org/10.1016/S2213-8587(16)30085-7**

repeated measurements of bodyweight or waist circumference. These models were first computed for the observed data and then repeated with multiple imputation methods for missing data. The dependent variable was bodyweight or waist circumference (at years 1, 2, 3, 4, 5, and at baseline) and the predictors were time (as continuous from baseline to 5 years) and intervention (including two dummy variables, as described). We also introduced an interaction term between intervention and time. Analyses were adjusted for age, sex, educational level, leisure-time physical activity, cigarette smoking, diabetes, dyslipidaemia, hypertension, total energy intake, alcohol consumption, and baseline bodyweight or waist circumference. Additional adjustments including baseline waist-to-height ratio, 1 year follow-up leisure-time physical activity, and 1 year follow-up energy intake were done when appropriate. Rules for stopping the trial are included in the appendix.

When we repeated the generalised estimating equation analyses with multiple imputation, we treated bodyweight or waist changes as the dependent variable, with models adjusted for age, sex, educational level, leisure-time physical activity, cigarette smoking, diabetes, dyslipidaemia, hypertension, total energy intake, alcohol consumption, and baseline bodyweight or waist circumference. Additional adjustments including baseline waist-to-height ratio, 1 year follow-up leisure-time physical activity, and 1 year follow-up energy intake were done when appropriate. All statistical analyses were done with Stata version 12.0. The PREDIMED trial is registered with ISRCTN.com, number ISRCTN35739639.

Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing the report. The corresponding author had full access to all the data in the study and had final responsibility to submit for publication.

Results

Between Oct 1, 2003, and June 30, 2009, we assessed 8713 candidates for eligibility. Of these, 973 refused to participate and 293 did not meet inclusion criteria. Thus, 7447 participants were included in the trial (4282 women and 3165 men) and were randomly allocated to the three intervention groups: 2543 to the Mediterranean diet plus extra-virgin olive oil group, 2454 in the Mediterranean diet plus nuts groups, and 2450 in the control group (figure 1). Baseline characteristics are detailed in table 1. The mean age of participants was 67 years (SD 6), 97% were of white European ethnic origin, and all were at high cardiovascular risk. More than 90% of the participants were overweight or obese. No between-group clinically relevant differences in age, sex, cardiovascular risk factors, or drug treatment regimens were noted. Participants in the three groups reported similar baseline adherence to the Mediterranean diet, as assessed with the 14-point screener.

Participants were followed up for a median of 4·8 years (IQR 2·8–5·8). At the end of the trial, 523 participants (7%) had been lost to follow-up for 2 or more years. 277 (11%) participants withdrew from the control group, compared with 91 (4%) in the extra-virgin olive oil group and 155 (6%) in the nut groups. Mean follow-up times were 4·66 (SD 1·69) years in the control group, 4·22 (1·84) years in the extra-virgin olive oil group, and 3·98 (1·95) years in the nut group.

In the control group, 1605 (66% of the total group) participants recruited in the first 3 years were receiving a low intensity intervention and were in the trial for a mean of 1·6 years (40% of the total follow-up time).

Participants in the extra-virgin olive oil group largely increased consumption of polyphenol-rich extra-virgin olive oil, while reciprocally decreasing consumption of common olive oil (p<0·0001 for both). Nut intake significantly increased in both Mediterranean diet groups (p<0·0001 for both), especially in the group assigned the Mediterranean diet plus nuts. Additionally, participants in both Mediterranean diet groups increased consumption of vegetables, legumes, fruits, and fish and decreased

	Control diet (n=2450)	Mediterranean diet plus extra-virgin olive oil (n=2543)	Mediterranean diet plus nuts (n=2454)
Male sex	987 (40%)	1050 (41%)	1128 (46%)
Age (years)	67·3 (6·3)	67·0 (6·2)	66·7 (6·1)
Bodyweight (kg)	77·0 (12·2)	76·7 (11·8)	76·6 (11·9)
Waist circumference (cm)	100·9 (10·8)	100·2 (10·4)	100·2 (10·5)
BMI (kg/m²)	30·2 (4·0)	29·9 (3·7)	29·7 (3·8)
BMI <25 kg/m²	161 (7%)	193 (8%)	203 (8%)
BMI 25 kg/m² to <30 kg/m²	1084 (44%)	1147 (45%)	1159 (47%)
BMI ≥30 kg/m²	1205 (49%)	1203 (47%)	1092 (44%)
Waist-to-height ratio*	0·63 (0·07)	0·63 (0·06)	0·63 (0·06)
Smoking status			
Never smoked	1527 (62%)	1572 (62%)	1465 (60%)
Former smoker	584 (24%)	618 (24%)	634 (26%)
Current smoker	339 (14%)	353 (14%)	355 (14%)
Physical activity (minutes of metabolic equivalent tasks per day)	214·1 (240·3)	230·2 (230·0)	247·5 (246·2)
Energy intake (kcal per day)	2219 (599)	2286 (606)	2318 (611)
Total carbohydrate (g per day)	235·6 (79·3)	239·9 (81·5)	241·8 (81·9)
Total protein (g per day)	90·2 (22·3)	93·3 (24·0)	94·0 (23·0)
Total fat (g per day)	95·9 (30·7)	99·3 (30·2)	101·1 (30·2)
Saturated fat (g per day)†	10·0 (2·3)	10·0 (2·3)	10·0 (2·1)
Monosaturated fat (g per day)	19·3 (4·7)	19·6 (4·6)	19·6 (4·3)
Polyunsaturated fat (g per day)†	6·2 (2·1)	6·1 (2·1)	6·4 (2·0)
Score for adherence to Mediterranean diet†	8·4 (2·1)	8·7 (2·0)	8·7 (2·0)

Data are n (%) or mean (SD). *Waist-to-height ratio (an index of central obesity) is the waist circumference divided by height in cm. †The score for adherence to the Mediterranean diet is based on the 14-item dietary screener (a score of zero indicates minimum adherence, a score of 14 indicates maximum adherence).

Table 1: **Baseline characteristics of study participants**

consumption of meat, sweets, and dairy products (appendix). However, only differences in legumes and fish or seafood were significant between the Mediterranean diet groups and the control group (p<0·0001 for all).

Although estimated energy intake significantly decreased in all groups, self-reported reduction was more pronounced in the control group than in the two Mediterranean diet groups (p<0·0001 for both; appendix). Median total fat intake as a percentage of energy decreased after 5 years from 40·0% to 37·4% in the control group, even though the goal was to reduce fat intake to less than 30% of energy; in the extra-virgin olive oil and nut groups it increased from 40·0% to 41·8% and from 40·4% to 42·2%, respectively (p<0·0001 for all). Compared with the control group, monounsaturated and polyunsaturated fatty acid intake increased in both Mediterranean diet groups (p<0·0001 for all). Accordingly, the percentage of energy intake from protein and carbohydrate decreased in both Mediterranean diet groups (p<0·0001 for all).

During follow-up, scores of adherence to the Mediterranean diet increased in the two Mediterranean diet groups (both p<0·0001), but did not change in the control group. Changes in objective biomarkers of consumption of supplemental foods (extra-virgin olive oil and walnuts) measured in random samples of participants (750 [10%] in the extra-virgin olive oil group and 375 [5%] in the nut group) indicated good compliance in the corresponding Mediterranean diet groups at 1, 3, and 5 years (p<0·0001 for comparison between means of biomarkers of compliance between the corresponding Mediterranean diet intervention group and control group each year). No between-group differences in estimated energy expenditure from leisure-time physical activity were recorded.

Bodyweight changes from baseline to 1, 3, and 5 years with multiple imputation of missing values (13%) are shown in table 2. Participants in the extra-virgin olive oil group had a significant decrease in bodyweight during the trial, but average between-group changes were only significant at 3 years (p=0·026) and 5 years (p=0·044). Participants in the nut group showed a non-significant decrease in bodyweight at 3 years (–0·155 kg [95% CI

	Control diet	Mediterranean diet plus extra-virgin olive oil	p value (extra-virgin olive oil *vs* control)	Mediterranean diet plus nuts	p value (nuts *vs* control)
Baseline *vs* 1 year					
Participants assessed	2420	2524	..	2433	..
Participants imputed	449	158	..	267	..
Mean bodyweight change (crude, kg)	–0·231 (–0·398 to –0·064)	–0·190 (–0·331 to –0·048)	0·704	0·014 (–0·141 to 0·169)	0·029
Difference *vs* control (multivariable-adjusted, kg)*	1	0·047 (–0·169 to 0·264)	0·667	0·247 (0·025 to 0·468)	0·029
Difference *vs* control (multivariable-adjusted, kg)†	1	–0·017 (–0·234 to 0·200)	0·876	0·138 (–0·088 to 0·364)	0·231
Baseline *vs* 3 years					
Participants assessed	1851	2127	..	2114	..
Participants imputed	514	195	..	286	..
Mean bodyweight change (crude, kg)	–0·244 (–0·500 to 0·012)	–0·526 (–0·726 to –0·326)	0·078	–0·155 (–0·371 to 0·061)	0·604
Difference *vs* control (multivariable-adjusted, kg)*	1	–0·256 (–0·574 to 0·055)	0·105	0·065 (–0·271 to 0·401)	0·703
Difference *vs* control (multivariable-adjusted, kg)†	1	–0·359 (–0·675 to –0·044)	0·026	–0·064 (–0·402 to 0·275)	0·712
Baseline *vs* 5 years					
Participants assessed	1243	1501	..	1241	..
Participants imputed	230	113	..	129	..
Mean bodyweight change (crude, kg)	–0·604 (–0·904 to –0·304)	–0·880 (–1·149 to –0·612)	0·188	–0·402 (–0·696 to –0·108)	0·346
Difference *vs* control (multivariable-adjusted, kg)*	1	–0·264 (–0·679 to 0·150)	0·211	0·113 (–0·307 to 0·533)	0·597
Difference *vs* control (multivariable-adjusted, kg)†	1	–0·433 (–0·855 to –0·011)	0·044	–0·075 (–0·500 to 0·350)	0·730

Data were analysed by linear regression (two dummy variables for the two Mediterranean diet intervention groups, whereas the control group was the reference category). The intervention effect (95% CI) in all cases was assessed after multiple imputation (20 sets) for missing values in participants who dropped out dropped out or had missing weight measurements in each year. Each dataset was analysed by standard statistical methods (including the multiple imputations procedure) to fit the model of interest to each of the imputed datasets. Estimated associations in each of the imputed datasets were averaged together to give the overall associations. *Adjusted for sex, age, centre, smoking status, diabetes, dyslipidaemia, and hypertension. †Additionally adjusted for educational level, leisure-time physical activity, baseline BMI, total energy intake (both at baseline and at 1 year follow-up), and alcohol consumption.

Table 2: **Bodyweight changes from baseline to 1 year, 3 year, and 5 year follow-up visits**

	Control diet	Mediterranean diet plus extra-virgin olive oil	p value (extra-virgin olive oil *vs* control)	Mediterranean diet plus nuts	p value (nuts *vs* control)
Baseline *vs* 1 year					
Participants assessed	2420	2524	..	2433	..
Participants imputed	597	276	..	374	..
Mean waist circumference change (crude, cm)	–0·447 (–0·729 to –0·166)	–0·659 (–0·898 to –0·419)	0·272	–0·406 (–0·655 to –0·157)	0·836
Difference versus control (multivariable-adjusted, cm)*	1	–0·229 (–0·603 to +0·145)	0·230	0·003 (–0·384 to 0·390)	0·987
Difference versus control (multivariable-adjusted, cm)†	1	–0·351 (–0·702 to –0·001)	0·050	–0·080 (–0·449 to 0·290)	0·671
Baseline *vs* 3 years					
Participants assessed	1857	2127	..	2114	..
Participants imputed	819	380	..	535	..
Mean waist circumference change (crude, cm)	0·805 (0·404 to 1·205)	0·143 (–0·188 to 0·474)	0·008	0·442 (0·091 to 0·793)	0·169
Difference versus control (multivariable-adjusted, cm)*	1	–0·699 (–1·187 to –0·212)	0·005	–0·380 (–0·894 to 0·134)	0·147
Difference versus control (multivariable-adjusted, cm)†	1	–0·707 (–1·162 to –0·252)	0·002	–0·372 (–0·858 to 0·114)	0·133
Baseline *vs* 5 years					
Participants assessed	1243	1501	..	1241	..
Participants imputed	621	322	..	394	..
Mean waist circumference change (crude, cm)	1·198 (0·677 to 1·719)	0·851 (0·427 to 1·275)	0·293	0·372 (–0·123 to 0·868)	0·021
Difference versus control (multivariable-adjusted, cm)*	1	–0·428 (–1·068 to 0·211)	0·188	–0·802 (–1·490 to –0·115)	0·022
Difference versus control (multivariable-adjusted, cm)†	1	–0·549 (–1·162 to –0·063)	0·048	–0·936 (–1·600 to –0·271)	0·006

Data was analysed by linear regression (two dummy variables for the two Mediterranean diet intervention groups, whereas the control group was the reference category). The treatment effect (95% CI) in all cases was assessed after multiple imputation (20 sets) for missing values in participants who dropped dropped out or had missing waist measurements in each year. Each dataset was analysed by standard statistical methods (including the multiple imputations procedure) to fit the model of interest to each of the imputed datasets. Estimated associations in each of the imputed datasets were averaged together to give the overall associations. *Adjusted for sex, age, centre, smoking status, diabetes, dyslipidaemia, and hypertension. †Additionally adjusted for educational level, leisure-time physical activity, baseline BMI, total energy intake (both at baseline and at 1 year follow-up), and alcohol consumption.

Table 3: **Waist circumference changes from baseline to 1-year, 3-year, and 5-year follow-up visits**

–0·371 to 0·061]) and a significant decrease at 5 years (–0·402 kg [–0·696 to –0·108]) compared with baseline, but did not differ from the control group (p=0·712 at 3 years and p=0·730 at 5 years). Changes in waist circumference (table 3) initially paralleled those of bodyweight. However, after 3 years and 5 years, absolute, albeit small, increases in waist circumference were noted. The multivariable adjusted differences with respect to the control group showed significantly lower waist circumference increases at 3 years and 5 years for the extra-virgin olive oil group and at 5 years for the nut group (table 3).

When we considered all yearly weight measurements with observed data (no imputations for missing values) using multivariable generalised estimating equations (figure 2), we identified no significant interactions between time and intervention (p=0·70 for the extra-virgin olive oil group and p=0·40 for the nut group). We then removed the interaction term from the model and estimated the global time effect (–0·13 kg per year [95% CI –0·16 to –0·10]), which indicated significant reductions in bodyweight in the three groups, without between-group differences in the intervention effect being identified in stratified analyses: –0·17 kg per year (–0·23 to –0·13) for the extra-virgin olive oil group, –0·09 kg per year (0·13 to –0·04) for the nut group, and –0·12 kg per year (–0·18 to –0·07) for the control group. When we considered all yearly waist circumference measurements with no imputations using multivariable generalised estimating equations (figure 3), we noted no significant time interaction effects by group (p=0·90 for the extra-virgin olive oil group and p=0·43 for the nut group). The time effect for the three groups was (0·16 cm per year [95% CI 0·12–0·21]), showing an increase in all the groups. The time effect in the stratified analysis by intervention was 0·16 cm per year (0·10 to 0·23) for the extra-virgin olive oil group, 0·13 cm per year (0·06 to 0·20) for the nut group, and –0·18 cm per year (0·10 to 0·26) for the control group, with no significant differences between groups.

Likewise, when we applied multiple imputations for missing values in generalised estimating equations

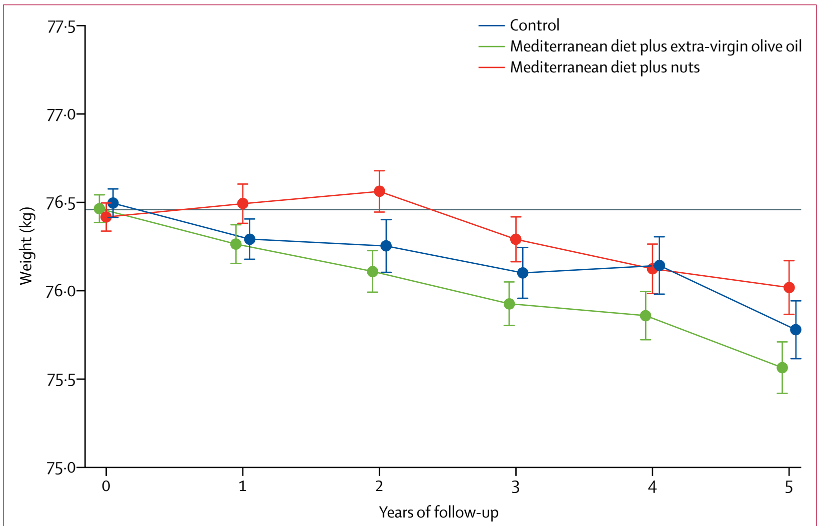

Figure 2: **Multivariable-adjusted average bodyweight of PREDIMED participants during follow-up, by intervention group**
Error bars show 95% CI. Generalised estimating equations with exchangeable correlation matrix including time, intervention, and the interaction term between time (as categorical for plotting the figure) and intervention group, adjusted for age, sex, centre, educational level, leisure-time physical activity, smoking, diabetes, hypertension, dyslipidaemia, total energy intake, alcohol consumption, and baseline bodyweight, were used to estimate the intervention effect on yearly bodyweight. Estimates were unchanged after additional adjustment for waist-to-height ratio, total energy intake after 1 year, and leisure-time physical activity after 1 year. The horizontal black line represents the mean weight of all participants at baseline.

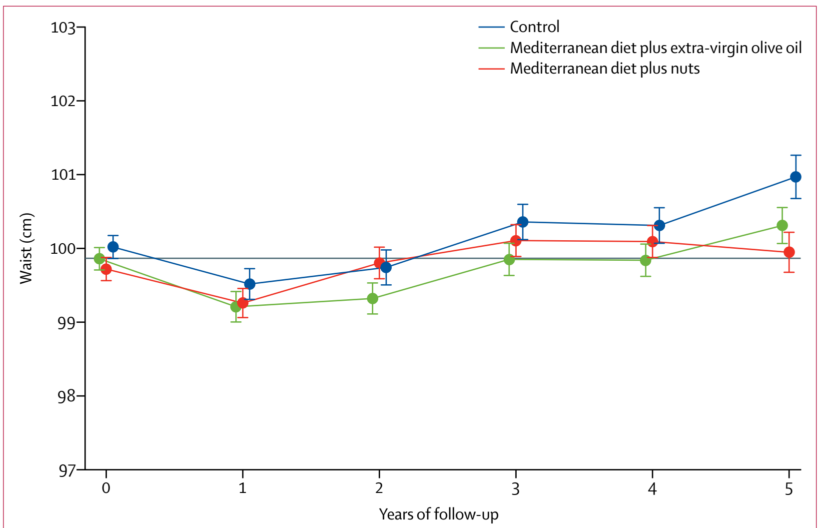

Figure 3: **Multivariable-adjusted average waist circumference of PREDIMED participants during follow-up, by intervention group**
Error bars show 95% CI. Generalised estimating equations with exchangeable correlation matrix including time, intervention, and the interaction term between time (as categorical for plotting the figure) and intervention group, adjusted for age, sex, centre, educational level, leisure-time physical activity, smoking, diabetes, hypertension, dyslipidaemia, total energy intake, alcohol consumption, and baseline waist circumference were used to estimate the intervention effect on yearly waist circumference. Estimates were unchanged after additional adjustment for waist-to-height ratio, total energy intake after 1 year, and leisure-time physical activity after 1 year. The horizontal black line represents the mean waist circumference of all participants at baseline.

(table 4) and adjusted the models for sex, age, centre, baseline weight, smoking status, education, diabetes, dyslipidaemia, and hypertension, we found similar results to those for non-imputed generalised estimating equation models, with no significant time-by-intervention group interaction for weight or waist circumference. Bodyweight and waist circumference changes during 5-year follow-up (averaged for the whole period) for the intervention groups in comparison with the control group are shown in table 4. For weight, interaction terms (time by intervention) for the whole period did not differ (p=0·45 for the extra-virgin olive oil group and p=0·90 for the nut group). The effects, expressed as changes in kg per year in comparison with the control group were essentially null for both intervention groups: –0·03 kg per year (95% CI –0·12 to 0·05) for the extra-virgin olive oil group and 0·01 kg per year (–0·08 to 0·09) for the nut group. Yearly changes in weight are reported in the appendix. Likewise, for waist circumference, interaction terms for the whole period did not differ (p=0·80 for the extra-virgin olive oil group and p=0·30 for the nut group). The effects, expressed as changes in cm per year in comparison with the control group, were essentially null for both intervention groups: 0·02 (–0·14 to 0·18) for the extra-virgin olive oil group and –0·09 (–0·26 to 0·08) for the nut group. No substantial differences in results were seen when we additionally adjusted for total energy intake, physical activity, and alcohol consumption, or when we repeated the analyses assuming an autoregressive correlation matrix instead of an exchangeable matrix (data not shown). Finally, we did a stratified analysis to explore the associations in predefined strata and identified no between-group differences in bodyweight or waist circumference changes in subgroups of age, sex, or diabetes status (table 4).

Discussion

Despite accruing scientific evidence on the beneficial role of a high-fat, high-vegetable fat dietary pattern such as the Mediterranean diet on cardiovascular disease, diabetes and obesity,[15–17] it is still widely feared that intake of all types of fat may promote weight gain and adiposity. In the PREDIMED trial, we followed up a large cohort of older individuals, of whom more than 90% were overweight or obese, for nearly 5 years and showed that a high-vegetable-fat, unrestricted-calorie Mediterranean diet enriched with healthy fatty foods does not increase bodyweight. Waist circumference increased slightly with ageing in all three groups, as seen in any general population. Compared with participants following the control diet (based on advice to reduce all dietary fat), those in the Mediterranean diet plus extra-virgin olive oil group significantly reduced bodyweight, those in the Mediterranean diet plus nuts group maintained stable bodyweight, and both Mediterranean diet groups showed lower waist circumference increases, particularly the nut group. These results provide first-level evidence that ad libitum plant-based, high-fat diets do not promote weight gain or visceral adiposity.

Adults in developed countries tend to gain weight gradually over decades,[23] although older people usually

 www.thelancet.com/diabetes-endocrinology **Published online June 6, 2016 http://dx.doi.org/10.1016/S2213-8587(16)30085-7**

lose weight because of an age-related decline in lean body mass.[24] Indeed, waist circumference is better than bodyweight as a measure of adiposity in older populations. In this 5-year trial, we report average losses of 0·88 kg, 0·40 kg, and 0·60 kg in bodyweight and increases of 0·85 cm, 0·37 cm, and 1·2 cm in waist circumference in the Mediterranean diet with extra-virgin olive oil group, Mediterranean diet with nuts group, and control group, respectively. Notably, responses were similar by sex, age, and diabetes status. Consistent with our findings, most prospective studies assessing weight gain over time or the risk of developing overweight or obesity in relation to Mediterranean diet adherence have reported a beneficial effect on adiposity measures.[15–17] The absence of weight gain with the Mediterranean diet might be expected, since this diet is enriched in foods that have not been associated with long-term deleterious effects on adiposity, such as nuts, vegetables, fruits, and whole grains, and it does not include many foods and beverages that have been associated with long-term weight gain, such as fast-foods, sweets and desserts, butter, red meat and processed meat, and sugar-sweetened beverages.[25]

In the PREDIMED trial, slight weight loss was similar in the three study groups (figure 2), which supports the idea that the high-fat Mediterranean diet is at least equally beneficial for weight control as a diet with a lower fat content. The slight weight loss and increased waist circumference after 5-year Mediterranean diet intervention in our ageing population might be explained in part by regular visits with dietitians for dietary counsel and anthropometric measures, leading to enhanced eating competence and control of energy balance, as attested by reduced overall energy intake despite the increased fat load. The satiating effects of fat-rich foods, with ensuing displacement of other foods and beverages, might have played a part. Diet-induced changes in the microbiota might also affect adiposity.[26] Increases in diet quality have also been associated with less weight gain over time in large observational cohorts such as the Nurses' Health Study and the Health Professionals Follow-up Study.[27] Our results confirm that the Mediterranean diet is a high-quality dietary pattern useful to limit future adiposity gains.

Our study has several limitations. First, total energy intake was included as a covariate in the model to achieve the equivalent of an isocaloric diet and reduce measurement error in the final score. However, total energy is not well estimated from food-frequency questionnaires, nor does it reflect energy balance because of measurement error and within-individual differences in body size, physical activity, and lean muscle mass.[28] In any case, measurement error should be similar in the three study groups. Second, in any feeding trial in free-living people, there can be difficulties in ensuring compliance with dietary instructions. We acknowledge that the size of the reported changes in fat intake as percentage of total energy intake was quite small. However, these changes

	Weight changes (kg)		Waist changes (cm)	
	Coefficient (95% CI)	p value	Coefficient (95% CI)	p value
Total sample (n=7447)				
Control group	1	..	1	
Mediterranean diet plus extra-virgin olive oil	−0·11 (−0·40 to 0·18)	0·46	−0·47 (−0·97 to 0·03)	0·07
Mediterranean diet plus nuts	0·12 (−0·18 to 0·43)	0·43	−0·26 (−0·80 to 0·27)	0·33
Time effect (per year)	−0·12 (−0·18 to −0·06)	<0·0001	0·33 (0·22 to 0·45)	<0·0001
Interaction term time by control	1		1	
Interaction term time by extra-virgin olive oil	−0·03 (−0·12 to 0·05)	0·45	0·02 (−0·14 to 0·18)	0·80
Interaction term time by nuts	0·01 (−0·08 to 0·09)	0·90	−0·09 (−0·26 to 0·08)	0·30
Age strata				
<70 years (n=4776)				
Control group	1	..	1	..
Mediterranean diet plus extra-virgin olive oil	−0·07 (−0·36 to 0·22)	0·63	−0·58 (−1·21 to 0·05)	0·07
Mediterranean diet plus nuts	0·20 (−0·10 to 0·50)	0·20	−0·22 (−0·85 to 0·42)	0·51
Time effect (per year)	−0·08 (−0·16 to −0·02)	0·02	0·34 (0·19 to 0·50)	<0·0001
Interaction term time by control	1	..	1	..
Interaction term time by extra-virgin olive oil	−0·03 (−0·11 to 0·05)	0·46	0·05 (−0·15 to 0·24)	0·65
Interaction term time by nuts	0·01 (−0·08 to 0·09)	0·89	−0·10 (−0·31 to 0·11)	0·35
≥70 years (n=2671)				
Control group	1	..	1	..
Mediterranean diet plus extra-virgin olive oil	−0·24 (−0·71 to 0·23)	0·32	−0·18 (−0·98 to 0·62)	0·66
Mediterranean diet plus nuts	0·09 (−0·40 to 0·59)	0·71	−0·30 (−1·23 to 0·63)	0·52
Time effect (per year)	−0·19 (−0·29 to −0·09)	<0·0001	0·32 (0·11 to 0·52)	0·002
Interaction term time by control	1		1	
Interaction term time by extra-virgin olive oil	−0·10 (−0·23 to 0·04)	0·16	−0·02 (−0·28 to 0·24)	0·87
Interaction term time by nuts	−0·04 (−0·18 to 0·10)	0·59	−0·07 (−0·38 to 0·24)	0·66
Sex strata				
Women (n=4281)				
Control group	1	..	1	..
Mediterranean diet plus extra-virgin olive oil	0·11 (−0·34 to 0·56)	0·63	−0·49 (−1·16 to 0·18)	0·15
Mediterranean diet plus nuts	0·31 (−0·15 to 0·76)	0·19	−0·33 (−1·05 to 0·38)	0·36
Time effect (per year)	−0·11 (−0·21 to −0·02)	0·02	0·40 (0·25 to 0·55)	0·0002
Interaction term time by control	1		1	..
Interaction term time by extra-virgin olive oil	−0·01 (−0·14 to 0·11)	0·82	0·02 (−0·18 to 0·23)	0·83
Interaction term time by nuts	0·02 (−0·11 to 0·15)	0·73	−0·07 (−0·29 to 0·15)	0·53
Men (n=3166)				
Control group	1	..	1	..
Mediterranean diet plus extra-virgin olive oil	−0·20 (−0·58 to 0·18)	0·31	−0·41 (−1·13 to 0·32)	0·27
Mediterranean diet plus nuts	0·15 (−0·26 to 0·55)	0·48	−0·19 (−0·92 to 0·55)	0·62
Time effect (per year)	−0·12 (−0·21 to −0·04)	0·004	0·23 (0·05 to 0·41)	0·01
Interaction term time by control	1	..	1	..
Interaction term time by extra-virgin olive oil	−0·04 (−0·15 to 0·07)	0·44	0·02 (−0·23 to 0·26)	0·90
Interaction term time by nuts	−0·01 (−0·13 to 0·10)	0·83	−0·08 (−0·33 to 0·16)	0·51

(Table 4 continues on next page)

	Weight changes (kg)		Waist changes (cm)	
	Coefficient (95% CI)	p value	Coefficient (95% CI)	p value
(Continued from previous page)				
Diabetes strata				
No diabetes at baseline (n=3833)				
Control group	1	..	1	..
Mediterranean diet plus extra-virgin olive oil	−0·12 (−0·52 to 0·28)	0·55	−0·44 (−1·13 to 0·25)	0·21
Mediterranean diet plus nuts	0·18 (−0·22 to 0·58)	0·38	−0·04 (−0·73 to 0·65)	0·92
Time effect (per year)	−0·05 (−0·14 to 0·04)	0·29	0·38 (0·22 to 0·54)	0·0003
Interaction term time by control	1	..	1	..
Interaction term time by extra-virgin olive oil	−0·01 (−0·12 to 0·11)	0·93	0·06 (−0·16 to 0·28)	0·57
Interaction term time by nuts	0·01 (−0·11 to 0·12)	0·94	−0·15 (−0·38 to 0·07)	0·19
Diabetes at baseline (n=3614)				
Control group	1	..	1	..
Mediterranean diet plus extra-virgin olive oil	−0·01 (−0·44 to 0·42)	0·96	−0·44 (−1·14 to 0·28)	0·23
Mediterranean diet plus nuts	0·26 (−0·19 to 0·72)	0·26	−0·45 (−1·25 to 0·35)	0·27
Time effect (per year)	−0·19 (−0·28 to −0·10)	<0·0001	0·29 (0·12 to 0·46)	0·001
Interaction term time by control	1	..	1	..
Interaction term time by extra-virgin olive oil	−0·05 (−0·17 to 0·06)	0·37	−0·01 (−0·23 to 0·21)	0·91
Interaction term time by nuts	−0·01 (−0·13 to 0·12)	0·96	−0·01 (−0·27 to 0·24)	0·91

Time was treated as a continuous variable for the estimations, and the regression coefficient for time indicates the averaged changes in bodyweight or waist circumference (depending on the model) and the analysed strata per year. The control group was considered as the reference category for dummy variables for intervention and interaction terms. Models were adjusted for baseline values (of bodyweight and waist circumference, respectively), age, sex, centre, educational levels, smoking, diabetes, hypertension, and dyslipidaemia. Main terms for time (as continuous from 0 years to 5 years) and intervention (two dummy variables for extra-virgin olive oil and nuts groups) were considered as well as for their interaction terms (interaction between each dietary intervention and time). An exchangeable correlation matrix was assumed for bodyweight changes, whereas an autoregressive correlation matrix was assumed for waist circumference changes. Multiple imputation procedures based on multivariable normal distributions were used to build 20 datasets with the imputed values for participants with missing data for bodyweight or waist circumference in any of the visits. Each dataset was analysed by standard statistical methods (including the multiple imputations procedure) to fit the model of interest to each of the imputed datasets. Estimated associations in each of the imputed datasets were averaged together to give the overall associations.

Table 4: **Weight and waist circumference changes during 5-year follow-up in the intervention groups compared with the control group**

were statistically significant in the expected direction and adherence to the recommended diets was good, as judged by self-report and changes in objective biomarkers of consumption of supplemental foods.[14] Third, there was unequal loss to follow-up, which could have biased results toward less weight gain in the control group, given the more likely loss of less healthy and less compliant participants. This limitation could have caused an underestimation of the benefits of the Mediterranean diet on bodyweight and waist circumference. Finally, the initial study design called for a minimum intervention in the control group (yearly delivery of instructions to follow a low-fat diet), but after 3 years the protocol was modified and control participants received dietary intervention with the same frequency and intensity as those in the Mediterranean diet groups, which accounted for 60% of the time they were in the trial. Besides the randomised design, strengths of our study are its setting, which reproduces real-life conditions, and the long duration of follow-up, allowing the examination of long-term adiposity changes. The use of multiple imputation procedures is an additional strength, since this statistical method increases the validity of the results of clinical trials.[29]

Overall, our results show that an increase in vegetable fat intake from natural sources in the setting of a Mediterranean diet had little effect on bodyweight or central adiposity in older individuals who were mostly overweight or obese at baseline. Instead, small but significant reductions in weight and lesser increases in waist circumference were seen in patients given the Mediterranean diet interventions compared with the control group. Even small changes in bodyweight have implications for long-term adiposity-related conditions, including diabetes and cardiovascular disease.[30] These results have practical implications, because the fear of weight gain from high-fat foods need no longer be an obstacle to adherence to a dietary pattern such as the Mediterranean diet, which is known to provide much clinical and metabolic benefit.[14,18] They are also relevant for public health, because they lend support to not restricting intake of healthy fats in advice for bodyweight maintenance and overall cardiometabolic health, as acknowledged by the Dietary Guidelines for Americans 2015 Advisory Committee.[12]

Contributors
RE, MAM-G, DC, and ER had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data and the accuracy of the analysis. RE, MAM-G, DC, JS-S, MFit, MFio, EG-G, FA, JL, LS-M, XP, and ER designed and conducted the study. RE, MAM-G, DC, JS-S, MFit, MFio, EG-G, FA, JL, JVS, LS-M, XP, MAM, JB-G, PB-C, RML-R, MS-M, and ER collected, managed, and interpreted the data. MAM-G, DC, and GC-B did the statistical analysis. RE, MAM-G, and ER prepared the report. RE, MAM-G, DC, JS-S, MFit, and ER reviewed the report. All authors approved the final submitted version of the report.

Declaration of interests
RE reports serving on the board of and receiving lecture fees from the Research Foundation on Wine and Nutrition (FIVIN); serving on the boards of the Beer and Health Foundation and the European Foundation for Alcohol Research (ERAB); receiving lecture fees from Instituto Cerventes, Fundación Dieta Mediterránea, Cerveceros de España, Lilly Laboratories, AstraZeneca, and Sanofi-Aventis; consultancy fees from KAO coorporation, and receiving grant support through his institution from Novartis, Amgen, Bicentury, and Grand Fountaine. JS-S reports serving on the board of and receiving grant support through his institution from the International Nut and Dried Fruit Council; receiving consulting fees from Danone, Font Vella Lanjaron, Nuts for Life, and Eroski; and receiving grant support through his institution from Nut and Dried Fruit Foundation and Eroski. FA reports receiving payment for the development of educational presentations from Menarini and AstraZeneca. LS-M reports serving on the boards of the Mediterranean Diet Foundation and the Beer and Health Foundation. XP reports serving on the board of and receiving grant support through his institution from the Residual Risk Reduction Initiative (R3i) Foundation; serving on the board of Omegafort; serving on the board of and receiving payment for the development of educational presentations, as well as grant support through his institution, from Ferrer International; receiving consulting fees from Abbott Laboratories; receiving lecture fees, as well as grant support through his institution, from Merck and Roche; receiving lecture fees from Danone and Esteve; receiving payment for the development of educational presentations from Menarini, Mylan, LACER, and Rubio Laboratories; and receiving grant support through his institution from

Sanofi-Aventis, Kowa, Unilever, Boehringer Ingelheim, and Karo Bio. RML-R reports serving on the board of and receiving lecture fees from FIVIN; receiving lecture fees from Cerveceros de España; and receiving lecture fees and travel support from Brewers of Europe (Belgium) and Wissotsky Tea (Israel). ER reports grants, non-financial support, and other fees from California Walnut Commission; grants, personal fees, non-financial support, and other fees from Merck, Sharp & Dohme, Alexion, and Ferrer International; personal fees, non-financial support and other fees from Aegerion; grants and personal fees from Sanofi Aventis; and; grants from Amgen and Pfizer, outside of the submitted work. All other authors declare no competing interests.

Acknowledgments
This work was supported by the official funding agency for biomedical research of the Spanish Government, Instituto de Salud Carlos III, through grants provided to research networks specifically developed for the trial (RTIC G03/140 to RE; RTIC RD 06/0045 to MAM-G; and through Centro de Investigación Biomédica en Red Fisiopatología de la Obesidad y Nutrición [CIBERobn]), and by grants from Centro Nacional de Investigaciones Cardiovasculares (CNIC 06/2007), Fondo de Investigación Sanitaria–Fondo Europeo de Desarrollo Regional (PI04-2239, PI 05/2584, CP06/00100, PI07/0240, PI07/1138, PI07/0954, PI 07/0473, PI10/01407, PI10/02658, PI11/01647, and P11/02505), Ministerio de Ciencia e Innovación (AGL-2009-13906-C02, AGL2010-22319-C03, and AGL2013-49083-C3-1-R), Fundación Mapfre 2010, Consejería de Salud de la Junta de Andalucía (PI0105/2007), Public Health Division of the Department of Health of the Autonomous Government of Catalonia, Generalitat Valenciana (ACOMP06109, GVACOMP2010-181, GVACOMP2011-151, CS2010- AP-111, and CS2011-AP-042), and Regional Government of Navarra (P27/2011). CIBERobn is an initiative of Instituto de Salud Carlos III. Food companies, Hojiblanca and Patrimonio Comunal Olivarero, donated extra-virgin olive oil and California Walnut Commission, Borges SA, and Morella Nuts donated nuts. We thank the participants for their enthusiastic collaboration and all the PREDIMED personnel for excellent assistance with all aspects of the trial.

References

1 WHO. Global health risks: mortality and burden of disease attributable to selected major risks. Geneva: World Health Organization, 2009.
2 Hill JO, Wyatt HR, Petey JC. Energy balance and obesity. *Circulation* 2012; **126:** 126–32.
3 Expert panel on the identification, evaluation, and treatment of overweight in adults. National Heart, Lung, and Blood Institute. Clinical guidelines on the identification, evaluation, and treatment of overweight and obesity in adults: executive summary. *Am J Clin Nutr* 1998; **68:** 899–917.
4 Howard BV, Van Horn L, Hsia J, et al. Low-fat dietary pattern and risk of cardiovascular disease: the Women's Health Initiative randomized controlled dietary modification trial. *JAMA* 2006; **295:** 655–66.
5 Look AHEAD Research Group. Cardiovascular effects of intensive lifestyle intervention in type 2 diabetes. *N Engl J Med* 2013; **369:** 145–54.
6 Tobias DK, Chen M, Manson JE, Ludwig DS, Willett W, Hu FB. Effect of low-fat diet interventions versus other diet interventions on long-term weight change in adults: a systematic review and meta-analysis. *Lancet Diabetes Endocrinol* 2015; **3:** 968–79.
7 Gonzalez-Campoy JM, St Jeor ST, et al. Clinical practice guidelines for healthy eating for the prevention and treatment of metabolic and endocrine diseases in adults: cosponsored by the American Association of Clinical Endocrinologists/the American College of Endocrinology and the Obesity Society. *Endocr Pract* 2013; **19** (suppl 3): 1–82.
8 Evert AB, Boucher JL, Cypress M, et al. Nutrition therapy recommendations for the management of adults with diabetes. *Diabetes Care* 2014; **37** (suppl 1): S120–43.
9 McManus K, Antinoro L, Sacks F. A randomized controlled trial of a moderate-fat, low-energy diet compared with a low fat, low-energy diet for weight loss in overweight adults. *Int J Obes Relat Metab Disord* 2001; **25:** 1503–11.
10 Cohen E, Cragg M, de Fonseka J, Hite A, Rosenberg M, Zhou B. Statistical review of US macronutrient consumption data, 1965–2011: Americans have been following dietary guidelines, coincident with the rise in obesity. *Nutrition* 2015; **31:** 727–30.
11 Halton TL, Willett WC, Liu S, et al. Low-carbohydrate-diet score and the risk of coronary heart disease in women. *N Engl J Med* 2006; **355:** 1991–2002.
12 Mozaffarian D, Ludwig DS. The 2015 US dietary guidelines: lifting the ban on total dietary fat. *JAMA* 2015; **313:** 2421–22.
13 Sofi F, Abbate R, Gensini GF, Casini A. Accruing evidence on benefits of adherence to the Mediterranean diet on health: an updated systematic review and meta-analysis. *Am J Clin Nutr* 2010; **92:** 1189–96.
14 Estruch R, Ros E, Salas-Salvadó J, et al. Primary prevention of cardiovascular disease with a Mediterranean diet. *N Engl J Med* 2013; **368:** 1279–90.
15 Buckland G, Bach A, Serra-Majem L. Obesity and the Mediterranean diet: a systematic review of observational and intervention studies. *Obes Rev* 2008; **9:** 582–93.
16 Shai I, Schwarzfuchs S, Henkin Y, et al. Weight loss with low-carbohydrate, Mediterranean or low-fat diet. *N Engl J Med* 2008; **359:** 229–41.
17 Esposito K, Kastorini CM, Panagiotakos DB, Giugliano D. Mediterranean diet and weight loss: meta-analysis of randomized controlled trials. *Metab Syndr Relat Disord* 2011; **9:** 1–12.
18 Estruch R, Martínez-González MA, Corella D, et al. Effects of a Mediterranean-style diet on cardiovascular risk factors: a randomized trial. *Ann Intern Med* 2006; **145:** 1–11.
19 Schröder H, Fitó M, Estruch R, et al. A short screener is valid for assessing Mediterranean diet adherence among older Spanish men and women. *J Nutr* 2011; **141:** 1140–45.
20 Fernández-Ballart JD, Piñol JL, Zazpe I, et al. Relative validity of a semi-quantitative food-frequency questionnaire in an elderly Mediterranean population of Spain. *Br J Nutr* 2010; **103:** 1808–16.
21 Elosua R, Marrugat J, Molina L, Pons S, Pujol E, MARARTHOM Investigators. Validation of the Minnesota Leisure Time Physical Activity Questionnaire in Spanish men. *Am J Epidemiol* 1994; **139:** 1197–209.
22 Groenwold RH, Donders AR, Roes KC, Harrell FE Jr, Moons KG. Dealing with missing outcome data in randomized trials and observational studies. *Am J Epidemiol* 2012; **175:** 210–17.
23 Finucane MM, Stevens GA, Cowan MJ, et al. National, regional, and global trends in body-mass index since 1980: systematic analysis of health examination surveys and epidemiological studies with 960 country-years and 9·1 million participants. *Lancet* 2011; **377:** 557–67.
24 Janssen I, Heymsfield SB, Wang Z, Ross R. Skeletal muscle mass and distribution in 468 men and women aged 18–88 years. *J Appl Physiol* 2000; **89:** 81–88.
25 Mozzafarian D, Hao T, Rimm EB, Willett WC, Hu FB. Changes in diet and lifestyle and long-term weight gain in women and men. *N Engl J Med* 2011; **364:** 2392–404.
26 Power SE, O'Toole PW, Stanton C, Ross RP, Fitzgerald GF. Intestinal microbiota, diet and health. *Br J Nutr* 2014; **111:** 387–402.
27 Fung TT, Pan A, Hou T, et al. Long-term change in diet quality is associated with body weight change in men and women. *J Nutr* 2015; **145:** 1850–56.
28 Dhurandhar NV, Schoeller D, Brown AW, et al. Energy balance measurement: when something is not better than nothing. *Int J Obes* 2015; **39:** 1–5.
29 Little RJ, D'Agostino R, Cohen ML, et al. The prevention and treatment of missing data in clinical trials. *N Engl J Med* 2012; **367:** 1355–60.
30 Perk J, De Backer G, Gohlke H, et al. European guidelines on cardiovascular disease prevention in clinical practice (version 2012). The Fifth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of nine societies and by invited experts). *Eur Heart J* 2012; **33:** 1635–701.