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Cohort Profile

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Cohort Profile: Design and methods of the PREDIMED-Plus randomized trial

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Why was the cohort set up?

The PREDIMED (in Spanish: PREvención con DIeta MEDiterránea) primary prevention trial[1–3] reported in 2013 that long-term adherence to an energy-unrestricted Mediterranean diet (MedDiet), supplemented with either extra-virgin olive oil (EVOO) or nuts, reduced cardiovascular disease (CVD). PREDIMED showed a 30% relative reduction in the composite cardiovascular primary endpoint (stroke, myocardial infarction or cardiovascular death).[2,3] However, the PREDIMED trial tested only the composition of the diet, but did not test other lifestyle interventions (i.e. energy reduction, increased physical activity (PA) and behavioural modification) frequently applied in the context of the current unprecedented obesity pandemic.[4,5] With the exception of the null results of the Look-AHEAD trial,[6] and the successful results of the EXERDIET-HTA study that found improvements in blood pressure, cardio-respiratory fitness and body composition (though they encouraged adherence to an hypocaloric DASH diet, instead of a Mediterranean diet),[7] lifestyle interventions including such components have never been tested in long-term randomized trials using hard cardiovascular events as endpoints.

The rationale for a new randomized trial ('PREDIMED-Plus') is to go beyond the previous PREDIMED trial, and to answer one of the most important questions in current medical practice: is an intentional body mass reduction through PA promotion and energy reduction, able to bring about in the long term a substantial reduction in hard cardiovascular clinical events? Our main hypothesis is that by addressing three lifestyle aspects (energy reduction with a high-quality dietary pattern, recommendations on PA and motivational behaviour changes, based on providing persuasion and tools for solving problems, potentially derived from avoiding high calorie foods and sedentary lifestyles), an even stronger reduction in the risk of hard cardiovascular events will be attained, as compared with that observed with only a MedDiet.

The worldwide prevalence of obesity has almost tripled since 1975.[4,5,8,9] More than one in three adults is now obese in the USA[9] and the obesity epidemic has become global.[4,5] Increased risks of CVD, several cancers, diabetes, depression and impaired cognitive function have been found related to a high body mass index.[4,5,10–14] On the basis of long-standing and good quality evidence that

lifestyle changes that result in modest, sustained body mass reductions of 5% to 10% produce clinically meaningful reductions in the potency of cardiovascular risk factors,[15] expert panels set up by the National Institutes of Health and the World Health Organization advise that overweight and obese adults with comorbid conditions should lose 5–10% of their initial body mass, with lifestyle interventions as primary treatment.[16,17] These interventions should include an energy-restricted diet, PA and behavioural education.[18,19]

The global failure in addressing and combating overweight/obesity during the past three decades is a great setback for public health, and is probably due to a wrong conventional approach that needs to be revised.[20] During the 1990s and early 2000s, scientific societies usually recommended low-fat diets to promote body mass reduction and prevention of chronic disease.[19] However, long-term adherence to low-fat diets proved limited[21] and, for those who lost body mass, body mass regain usually occurred after 6–12 months.[21–25] Low-fat diets are also far from optimal because it is difficult to sustain a high consumption of vegetables unless dressed with sizeable amounts of vegetable oils. Alternative approaches with low-carbohydrate diets resulted in nutritional profiles usually poor in several micronutrients and requiring multivitamin supplements.[26–29]

The Look AHEAD trial[6] was unique in testing an intensive body mass reduction lifestyle programme based on a low-fat diet and PA in obese adults with type 2 diabetes. This intervention was ineffective in reducing incident CVD (the primary outcome) and, even though an absolute 5% loss of initial body mass was attained, the trial was stopped after the 9.6-year median follow-up due to futility. As summarized in a recent meta-analysis, body mass reduction interventions based on low-fat diets have been ineffective in reducing CVD events.[30]

In summary, novel alternative approaches for confronting the unprecedented obesity pandemic are needed. Extreme body mass reduction diets do not seem a solution because they represent large departures from the usual diet, are difficult to follow in the long term and their safety has not been well documented.[28,29] An alternative approach in the dietary control of overweight and obesity for CVD prevention could include well-known, healthy and palatable dietary patterns, such as the traditional MedDiet. The MedDiet is relatively rich in fat from vegetable sources [EVOO, nuts], includes an abundance of plant foods (vegetables, fruits, whole grains, legumes), moderate fish consumption and red wine in moderation (usually consumed with meals), but set limitations on the consumption of red and processed meats, refined grains, potatoes, whole-fat dairy, and ultra-processed foods such as ice-creams, sweets, creamy desserts, commercial bakery and sugar-sweetened beverages.[31] According to a substantial and increasing body of scientific evidence, the MedDiet has passed the tests of long-term sustainability, effectiveness and nutritional quality.[31–34] In addition, several studies have shown that a closer adherence to the MedDiet is usually associated in the long term with slowing down age-related body mass gain or obesity incidence (Supplementary Table 1, available as Supplementary data at *IJE* online). A systematic review of five trials suggested that a MedDiet was a feasible alternative to a low-fat diet for achieving weight loss after a 12-month follow-up.[35] The excellent long-term results of the energy-reduced MedDiet (erMedDiet) in the DIRECT trial,[36,37] and the modest but encouraging results of the PREDIMED trial after 5 years of adherence to a calorie-unrestricted MedDiet,[38] also support that an erMedDiet might be the ideal approach for body mass reduction and cardiovascular prevention in patients with overweight/obesity and metabolic syndrome. No clinical trial has assessed the long-term impact of body mass reduction with an erMedDiet on hard cardiovascular events. Thus, the PREDIMED-Plus trial seeks to provide a new, affordable and sustainable approach to reduce excess cardiovascular morbidity in overweight/obese patients with metabolic syndrome by implementing lifestyle changes within the context of an erMedDiet.

With regard to behaviour modification, previous studies have described the role of motivational enhancement strategies in interventions aimed to reduce adiposity in obese participants.[39] Armstrong *et al.*,[40] in a meta-analysis, reported a significant beneficial effect of motivational interviewing on reductions of body mass in overweight/obese participants. In addition, a review of randomized controlled trials suggested the potential of motivational interview to help primary care adult patients lose weight and improve weight-related variables.[41] As we aimed to recruit senior participants, who are likely to show deep-rooted habits, a behavioural intervention could be effective in reducing dropping out due to poor motivation, and provide tools to help better embrace the different components of the intervention.

PREDIMED-Plus is expected to take advantage of the synergy of a high-quality diet (a supplemented erMedDiet) plus a weight-loss intervention (using energy restriction, PA recommendations and behavioural modifications) on the incidence of hard cardiovascular endpoints. Considering the rising obesity-related healthcare costs,[42] the proposed strategy could provide a means for substantially reducing the economic burden of obesity. Moreover, our research aims to intervene at the primary care level, the setting best suited for an intensive body mass reduction intervention from the perspective of national health systems (NHS).

PREDIMED-Plus is an ongoing trial conducted in the 23 Spanish study centres listed in Table 1. General practitioners

Table 1. Participants recruited per centre in the PREDIMED-Plus trial

Location of the centre (department)	Principal investigator	Number of participating PCPH	Number of participants recruited
Navarra (Epidemiology)	Martínez-González MA	11	628
Valencia (Genetics)	Corella D	14	465
Reus (Nutrition)	Salas-Salvadó J	5	460
Barcelona (Molecular biology)	Fitó M	40	407
Alicante (Epidemiology)	Vioque J	6	361
Balearic (Cardiology)	Romaguera D	7	335
Navarra (Nutrition)	Martinez JA	8	331
Málaga (Nutrition)	Wärnberg J	3	326
Córdoba (Internal medicine)	López-Miranda J	1[a]	308
Barcelona (Internal medicine)	Estruch R	7	302
Granada (Epidemiology)	Bueno-Cavanillas A	6	296
Vitoria (Cardiology)	Arós F	18	274
Balearic (Physiology)	Tur JA	7	270
Málaga (Endocrinology)	Tinahones FJ	6	268
Canary Islands (Epidemiology)	Serra-Majem L	5	266
León (Public Health)	Martín V	9	258
Sevilla (Primary care)	Lapetra J	10	232
Madrid (Endocrinology)	Vázquez C	12	230
Barcelona (Internal medicine)	Pintó X	11	207
Barcelona (Endocrinology)	Vidal J	5	205
Madrid (Nutrition)	Daimiel L	6	169
Jaén (Epidemiology)	Delgado-Rodríguez M	6	152
Madrid (Endocrinology)	Matía P	5	124
Total		208	6874

PCHC, primary care health centres.
[a]Lipids and Atherosclerosis Unit, Department of Internal Medicine, Reina Sofia University Hospital.

from over 200 primary healthcare centres contributed to the recruitment of participants. This trial is supported by a European Research Council Advanced Research Grant (PI: MAM-G, grant #349018) and other competitive grants from the official agency of the Spanish Government (Instituto de Salud Carlos III), detailed at the end of the manuscript. In accordance with the previous PREDIMED trial, participants receive free allowances of extra-virgin olive oil provided by Fundación Patrimonio Comunal Olivarero.

Who is in the cohort?

A large cohort of 6874 participants (mean age 65.0 ± 4.9, range: 55–75 years) with overweight or obesity, harbouring the metabolic syndrome, has been assembled for long-term follow-up. After the run-in period (see below), the randomization started in October 2013 and finished in December 2016 (Figure 1). Trial close will take place after 6 years of intervention (March 2022). Subsequent follow-up will continue as an observational multi-purpose cohort to explore other hypotheses and to develop nested case-control analyses for studies of biomarkers and gene-nutrient interactions.

The primary endpoint is a combined cardiovascular outcome: myocardial infarction (acute coronary syndromes with positive troponin test), stroke or cardiovascular mortality. We hypothesize that the active lifestyle intervention will be effective in body mass reductions and long-term weight-loss maintenance, including reductions in waist circumference.

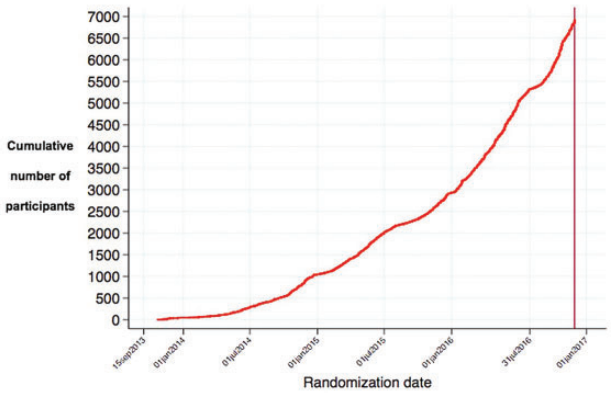

Figure 1. Recruitment: number of recruited participants by randomization date in the PREDIMED-Plus trial.

Secondary endpoints and intermediate outcomes are listed in Supplementary Table 2, available as Supplementary data at *IJE* online. Moreover, we are storing plasma, serum, buffy coat and nail and urine samples to evaluate additional risk factors and outcomes in the future, depending on available funding.

Participants are men aged 55–75 years and women aged 60–75 years, with overweight or obesity (body mass index 27–40 kg/m^2), who at baseline met at least three components of the metabolic syndrome.[43] Our initial goal was that diabetic participants (reporting diabetes or taking medication to control diabetes) comprised <30%, approximately 25% of the sample. Exclusion criteria are shown in Supplementary Table 3, available as Supplementary data at *IJE* online.

After the institutional review boards of all participating institutions had approved the study protocol, the selection process began by identifying names of potential participants from the records of primary care health centres (PCHC) in more than 200 PCHC. The facts that the Spanish NHS is universal, and free access to PCHC is offered to all citizens, strengthen this study in terms of follow-up and easy access to medical records. The clinical records of these persons were individually reviewed to exclude those who did not meet eligibility criteria. Family doctors approached potential participants via telephone call or during clinical visits. If candidates were interested in participating, a face-to-face interview was scheduled. During this interview, the purpose and characteristics of the study were explained, and willing participants were asked to sign two informed consent forms (one for the general protocol and another for genetic research and biobanking). A brief description of the study, including the explanation that participants would receive free allowances of EVOO and mixed tree nuts for the duration of the trial, was given at this first visit. Most (>70 %) candidates approached in this way agreed to return for the screening visit.

A 4-week run-in period starting immediately after the screening visit was scheduled, before randomization. This period aimed to assess willingness to participate in the study, and to predict compliance with the intended intervention. We evaluated in this period the likelihood of participants attending the scheduled sessions and completing correctly the assessment tools (including self-monitoring and recording of lifestyles and food habits).

The main obstacles when setting up the cohort were the difficulties in finding participants with the predefined inclusion criteria (men and women aged 55–75 and 60–75 years, respectively, with overweight or obesity, who at baseline met at least three components of the metabolic syndrome), the recruitment of more diabetic participants than expected (27.2%; above the objective of no more than 25% of participants with diabetes at baseline), the slowness of recruitment that lasted longer than expected (3 years, as against the expected 2 years) and the difficulties in finding participants who showed eagerness and willingness to comply with the interventions.

Sample size and statistical power estimation

Assuming a two-tailed alpha error of 0.05, a cumulative incidence in the control group after 6 years of at least 10%,[1] an anticipated hazard ratio (HR) for the combined primary cardiovascular end point of 0.70, and dropout rates of up to 20%, the required sample size was approximately 1600 participants per group (Supplementary Figure 1, available as Supplementary data at *IJE* online). To be conservative, we aimed to recruit at least 6000 participants, 3000 in each group. The final sample included 6874 participants distributed over 23 centres (Table 1).

Study participants were randomized 1:1 into two equally sized groups. Computer-generated random allocation was centrally elaborated in blocks of six subjects and stratified by sex, age (<65, 65–70, >70) and centre. The randomization procedure was internet-based and blinded to all staff and to the principal investigators of each centre. Participants were correctly randomized within each stratum of centre, sex and age. Spouses of participants who wished to belong to the same group were randomized together, and we used the couple as unit of randomization among 806 participants (403 couples). In the specific cases of couples in which the first spouse was previously recruited at a different time, the last spouse entering the study was directly assigned (not randomized) to the same study arm than his/her partner. The comparisons of observed versus expected proportions in each stratum gave all *P*-values above 0.05 (Supplementary Figure 2, available as Supplementary data at *IJE* online).

Baseline characteristics of participants by group allocation are shown in Table 2. The randomization procedure was successful, and the baseline covariates were well balanced between groups. As expected after multiple comparisons, some statistically significant differences in baseline characteristics existed. The proportion of current smokers at baseline was higher in the intervention (13.5%) than in the control group (11.5%), and baseline leisure-time PA was lower in the intervention [2485 metabolic equivalents (METs)-min/week] than in the control group (2705 METs-min/week). In any case, this potential confounding will be controlled for in the analyses. Compared with those who were excluded during the run-in period, randomized participants were more likely to be male, former smokers, significantly younger, had higher mean body mass at baseline, reported more frequently hypertension and family history of coronary heart disease and showed higher willingness to change their diet (Supplementary Table 4, available as Supplementary data at *IJE* online). The research ethics committees of all centres approved the study protocol during 2013 and 2014. The trial was registered in 2014 at [www.isrctn.com/ISRCTN89898870].

How often have they been followed up?

The frequency of contacts with participants is twice a year for the control group and three times a month (one group

Table 2. Baseline characteristics of participants in the PREDIMED-Plus study by group allocation

Characteristics at baseline	Control	Intervention	*P*-value
N	3467	3407	–
Subjects individually randomized	3051	3017	–
Subjects randomized in couples	416	390	–
Age (mean years, SD)	65.0 (4.9)	64.9 (4.9)	0.337
Female sex (%)	48.6	48.4	0.830
Baseline weight (mean kg, SD)	86.5 (13.0)	86.7 (13.0)	0.465
Baseline waist (mean cm, SD)	107.6 (9.7)	107.6 (9.6)	0.851
Waist-to-height ratio (mean, SD)	66.5 (5.5)	66.3 (5.5)	0.300
Baseline body-mass index (kg/m^2; mean, SD)	32.6 (3.5)	32.6 (3.4)	0.848
Obesity (%)	73.4	73.7	0.793
Smoking			0.004
Current smoker (%)	11.5	13.5	
Former smoker (%)	52.4	47.6	
Self-reported diabetes at baseline (%)	26.6	27.8	0.280
Family history of premature CHD (%)	17.4	16.1	0.132
High blood cholesterol (%)	68.5	70.1	0.130
Total cholesterol (mean mg/dl, SD)	197.6 (40.3)	196.9 (37.6)	0.521
LDL cholesterol (mean mg/dl, SD)	121.4 (40.9)	121.8 (43.6)	0.719
HDL cholesterol (mean mg/dl, SD)	48.2 (11.7)	47.9 (11.9)	0.272
Triglycerides (mean mg/dl, SD)	153.4 (79.0)	151.4 (76.9)	0.306
Glucose (mean mg/dl, SD)	113.7 (30.1)	113.2 (28.2)	0.524
Systolic blood pressure (mean mmHg, SD)	139.4 (16.7)	139.6 (17.2)	0.701
Diastolic blood pressure (mean mmHg, SD)	80.8 (9.9)	80.9 (10.0)	0.609
Hypertension (%)	82.7	83.5	0.393
Physical activity (METs/min-week; mean, SD)	2705 (2430)	2485 (2234)	<0.001
Chair test (#/30 sec; mean, SD)	13.2 (5.5)	13.3 (5.0)	0.393
Adherence to the erMedDiet (mean, SD)	8.5 (2.7)	8.4 (2.6)	0.109
Adherence to the MedDiet (mean, SD)	7.4 (1.9)	7.4 (1.9)	0.212
Total energy intake (kcal/d; mean, SD)	2417 (626)	2393 (603)	0.108
Fat intake (%E; mean, SD)	39.5 (6.5)	39.4 (6.6)	0.311
Carbohydrate intake (%E; mean, SD)	40.8 (6.9)	41.1 (6.8)	0.147
Protein intake (%E; mean, SD)	16.6 (2.8)	16.5 (2.8)	0.648
Alcohol intake (mean g/d, SD)	11.4 (15.5)	10.9 (15.2)	0.206
Dietary fibre intake (mean g/d, SD)	26.2 (9.0)	26.3 (9.2)	0.665
Primary education (%)	49.3	46.7	0.029
Non-European origin (%)	2.7	2.3	0.340
Willingness to change diet (mean, SD)	2.7 (0.5)	2.7 (0.5)	0.958
Married (%)	77.0	75.3	0.108
Living alone (%)	11.9	13.1	0.137
Retired (%)	56.4	54.9	0.203
Self-reported previous depression (%)	21.4	20.1	0.186
Previous weight-loss dieting (%)	43.0	42.6	0.743

CHD, coronary heart disease;d, day; erMedDiet, energy-reduced Mediterranean diet (based on the 17-item questionnaire); MedDiet, Mediterranean diet (based on the 14-item questionnaire);[44,45] E, energy intake; LDL, low-density lipoprotein; HDL, high-density lipoprotein.

session, one phone call and one face-to-face interview) for the intervention group during the first year. During years 2 to 6, contacts with the intervention group are twice a month: one group session and alternate phone calls or personal interviews). At baseline, at 6 months and every year after randomization, general medical and validated food frequency questionnaires (FFQ)[46–48] are obtained and an electrocardiogram is performed. This annual check-up lasts around 1 h. Blood and urine samples are collected at baseline, at 6 months, 1 year and every 2 years thereafter. Toenail samples are collected at baseline and every 2 years thereafter (Table 3).

After the trial formally terminates, we will continue to ascertain vital status through yearly personal interviews by

Table 3. Measurements in the PREDIMED-Plus study

Measurements	Number of repeated measurements											
	S1	S2	S3	Baseline	6 months	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6	Year 7	Year 8
Eligibility questionnaire	1												
3-day food register	D		1										
Anthropometric measurements[a]	1		2	3	4	5	6	7	8	9	10	11	12
General questionnaire				1									
143-item FFQ			1		2	3	4	5	6	7	8	9	10
Mediterranean diet questionnaire (17/14-items)[b]				1	2	3	4	5	6	7	8	9	10
Physical activity questionnaires[c]	D[d]		1[d]	2	3	4	5	6	7	8	9	10	11
Chair test (physical activity evaluation)				1	2	3	4	5	6	7	8	9	10
Accelerometers			D	1	2	3	4	5	6	7	8	9	10
Follow-up questionnaire					1	2	3	4	5	6	7	8	9
Electrocardiogram	1				2	3	4	5	6	7	8	9	10
Blood pressure measurement	1		2	3	4	5	6	7	8	9	10	11	12
Blood sample collection				1	2	3		4		5		6	7
Morning spot urine collection				1	2	3		4		5		6	7
Nail collection				1		2		3		4		5	6
Cognitive-neuropsychological tests[e]			1				2		3		4		5
Psychopathological questionnaires[f]	D		1			2	3	4	5	6	7	8	9
Quality of life questionnaires[g]	D		1			2		3		4		5	

S: screening visit; FFQ: food frequency questionnaire; D: delivery.

[a]Anthropometric measurements include: weight, height, waist circumference and hip circumference.

[b]Short questionnaires on adherence to the Mediterranean diet. The control group will use the same 14-item questionnaire that was used in the PREDIMED trial.[44,45] The intervention group will use the 17-item energy-restricted Mediterranean diet questionnaire. (Table 3).

[c]PAR-Q (Physical Activity Readiness Questionnaire), RAPA (Rapid Assessment of Physical Activity) (RAPA-1 and RAPA-2) questionnaires;[49] the NHS (Nurses' Health Study) sedentary lifestyle questionnaire;[50] and the REGICOR Short Physical Activity questionnaire.[51]

[d]Long version of the Minnesota leisure time physical activity questionnaire.

[e]Mini-Mental Status Evaluation, clock test, phonological verbal fluency test (animals + P), the reverse series of digits test (WAIS-III), and the trail-making test.

[f]Beck Depression Inventory (BDI-II), multidimensional scale of weight locus of control and lifetime eating disorders diagnostic criteria.

[g]SF-36 quality of life scale.

PREDIMED-Plus personnel, close contact with family doctors who care for the participants and reviews of medical records. On a yearly basis, the Spanish official mortality index (Indice Nacional de Defunciones) will also be reviewed.

What has been measured?

Table 3 shows the variables collected in the PREDIMED-Plus trial. The annually administered food frequency questionnaire (FFQ) provides information about compliance with food and nutrient targets. This FFQ was previously and repeatedly validated in Spain.[46–48] Clinical evaluations are limited to yearly follow-up visits including the same examinations as performed at baseline, with the exception of the general questionnaire which is replaced by a follow-up questionnaire and a tolerance/adverse events questionnaire.

For PA, the Rapid Assessment of Physical Activity,[49] the questionnaire for sedentary behaviours of the Nurses' Health Study,[50] and the Minnesota-REGICOR Short Physical Activity questionnaire,[51] are completed after the first 6 months and yearly thereafter. In addition, a field test to assess functional strength which approximates to the way the body works in everyday life (the 30-s chair-stand test) is repeated with the same frequency. Participants were given a pedometer (Yamax SW200 Digi-Walker) to self-monitor the number of steps they walked. Accelerometers were provided to a random subset of participants at the third screening visit during the run-in period (50% of participants in the intervention group and 20% in the control group) to quantify PA at baseline. Accelerometer measurements are repeated at 6 months, 1 year, and at each yearly visit thereafter.

Blood and urine samples are extracted in tubes for EDTA plasma, Citrate plasma, and serum aliquots of 200 µl and 500 µl are stored at -80°C for future analyses. Toenail samples to study heavy metals and other chemicals are also collected.

For the neuropsychological evaluation, a battery of six cognitive tests (the Mini-Mental State Evaluation,[52–58] the

semantic verbal fluency test 'animals in one minute', the phonemic verbal fluency test "words in one minute starting with letter 'p' ", the reverse series of digits test (WAIS-III),[54] the trail making test and the clock drawing test,[54–58] were collected in personal interviews by the study nurses at the third screening visit, and will be administered every 2 years thereafter. For the psychopathological evaluation, three questionnaires (the Beck Depression Inventory (BDI-II),[59] the Multidimensional Scale of Weight of Locus Control[60] and the screening for comorbid lifetime eating disorders with diagnostic criteria (DSM-V),[61] were completed by the participants at the third screening visit and will be collected again at year 1 and each year thereafter. Validated tools in Spanish to assess quality of life[62] were delivered at the first screening visit, completed by all participants during the run-in period and collected at the third screening visit. They will be repeated at 1 year, and every 2 years thereafter.

Outcomes are ascertained on a yearly basis by a Clinical Events Ascertainment Committee whose members are blinded to the assignment of participants to the two arms of the study.

Regarding the interventions, the recommended dietary pattern for the two treatment groups is the MedDiet, implemented as in the PREDIMED trial with the exception of energy reduction (erMedDiet) in the intervention arm but not in the control arm. Free provision of supplemental foods is provided in similar amounts to the two groups, EVOO (1 l/month) and mixed nuts (specifically almonds, 125 g/month). Participants receive these foods together with instructions about their use and conservation, during their educational group sessions.

Participants in the control arm receive all the written material and all recommendations to follow the MedDiet implemented in the previous PREDIMED trial, and they are specifically encouraged to adhere to the 14-point scale (MEDAS)[44,45] used in PREDIMED (Table 4). In group sessions every 6 months lead by dietitians, they receive the above-mentioned free supply of EVOO and nuts, in order to help promote the MedDiet and encourage compliance. Participants in the intervention group are prescribed a traditional MedDiet similar to that of the PREDIMED study, but in contrast with the control group wherein total energy is *ad libitum*, an erMedDiet is encouraged according to a 17-point scale (Table 5).

During scheduled visits, participants in the intervention group also receive PA counselling. Participants were encouraged to gradually increase their levels of physical activity to eventually reach at least 150 min/week of moderate-to-vigorous PA (MVPA), in order to meet the World Health Organization recommended levels of physical activity for adults aged 65 and above,[63] with the ultimate goal of walking at least 45 min per day during 6 days

Table 4. 14-point questionnaire to assess adherence to the non-energy restricted Mediterranean diet (in the control group) of the PREDIMED-Plus study[44,45]

Questions	Criteria for 1 point
1. Do you use olive oil as culinary fat?	Yes
2. How much olive oil do you consume in a given day (including oil used for frying, salads, out-of-house meals etc.)?	≥4 tablespoons
3. How many vegetable servings do you consume per day? [1 serving: 200 g (consider side dishes as half a serving)]	≥2 (≥1 portion raw or as a salad)
4. How many fruit units (including natural fruit juices) do you consume per day?	≥3
5. How many servings of red meat, hamburger or meat products (ham, sausage, etc.) do you consume per day?	<1
6. How many servings of butter, margarine or cream do you consume per day? (1 serving: 12 g)	<1
7. How many sweetened and/or carbonated beverages do you drink per day?	<1
8. How much wine do you drink per week?	≥7 glasses
9. How many servings of legumes do you consume per week? (1 serving: 150 g)	≥3
10. How many servings of fish or shellfish do you consume per week? (1 serving: 100-150 g of fish or 4-5 units or 200 g of shellfish)	≥3
11. How many times per week do you consume commercial sweets or pastries (not homemade), such as cakes, cookies, biscuits or custard?	<2
12. How many servings of nuts (including peanuts) do you consume per week? (1 serving: 30 g)	≥3
13. Do you preferentially consume chicken, turkey or rabbit meat instead of veal, pork, hamburger or sausage?	Yes
14. How many times per week do you consume vegetables, pasta, rice or other dishes seasoned with sofrito (sauce made with tomato and onion, leek or garlic and simmered with olive oil)?	≥2

Table 5. Energy-restricted Mediterranean diet used in the intervention arm of the PREDIMED-Plus trial: 17-point questionnaire to assess adherence to the energy-restricted Mediterranean diet

Questions	Criteria for 1 point
1. Do you use only extra-virgin olive oil for cooking, salad dressings, and spreads?	Yes
2. How many fruit units (including natural fruit juices) do you consume per day?	≥3
3. How many servings of vegetables/garden produce do you consume per day? [1 serving: 200 g (consider side dishes as half a serving)]	≥2 (≥1 portion raw or in a salad)
4. How many servings of white bread do you consume per day? (1 serving: 75 g)	≤1
5. How many times per week do you consume whole-grain cereals and pasta?	≥5
6. How many servings of red meat, hamburgers, or meat products (ham, sausage, etc.) do you consume per week? (1 serving: 100-150 g)	≤1
7. How many servings of butter, margarine or cream do you consume per week? (1 serving: 12 g)	<1
8. How many sugary beverages or sugar-sweetened fruit juices do you drink per week?	<1
9. How many servings of legumes do you consume per week? (1 serving: 150 g)	≥3
10. How many servings of fish or shellfish do you consume per week? (1 serving: 100-150 g of fish or 4-5 units or 200 g of shellfish)	≥3
11. How many times per week do you consume commercial sweets or pastries (not homemade), such as cakes, cookies, sponge cake or custard?	<3
12. How many servings of nuts (including peanuts) do you consume per week? (1 serving: 30 g)	≥3
13. Do you preferentially consume chicken, turkey or rabbit instead of beef, pork hamburgers or sausages?	Yes
14. How many times per week do you consume vegetables, pasta, rice or other dishes seasoned with sofrito (sauce made with tomato and onion, leek or garlic and simmered in olive oil)?	≥2
15. Do you avoid adding sugar to beverages (coffee, tea)?	Yes
16. How many times per week do you consume non-whole grain pasta or white rice?	<3
17. How many glasses of wine do you drink per day? (1 glass: 200 ml)	2-3 for men; 1-2 for women

of the week and conducting also static exercises of strength, flexibility and balance according to specific instructions.

The PA recommendations include aerobic activities, such as gentle walking or equivalent activities of moderate intensity, and resistance training.[64] Regarding resistance training, participants in the intervention group are encouraged to perform physical activities to develop the strength of the main muscles at least 2 days/week, with a duration of 30–40 min/day. Participants are also recommended to perform physical activities for the development of flexibility and balance, carried out at the end of physical exercises, three or more times/week. They are also advised to perform directed balanced activities, such as yoga or tai chi, if they are motivated and have access to these activities.

In addition, participants receive behavioural and motivational support strategies including self-monitoring, goal setting and problem solving.[65,66] Participants also undergo individual motivational interviews[67,68] in which suitable dietary and lifestyle changes are incorporated, and attainable goals are set tailored to each participant's clinical conditions, preferences and beliefs. The main framework for the behavioural intervention is the 'eudaimonic' paradigm of fulfilment. Previous investigations have determined that a eudaimonic well-being, which emphasizes proactive engagement in life, a sense of purpose and meaning and the perception that personal talents and abilities are being realized, was linked to benefits for multiple health outcomes and showed protective effects for metabolic syndrome and improvements in lipid profiles.[69–71] The individual sessions usually last for 15–30 min, depending on participant's needs.

Tailored charts to self-monitor and periodically record body mass and waist circumference are provided to participants in the intervention group. During this period, if participants do not achieve the established weight-loss goals (at least 5% of their initial body mass), they are encouraged to replace one meal a day by very-low-calorie foods, providing them with ample and palatable alternatives in line with the culinary tradition of the MedDiet. No maximal goals for weight reduction (i.e. no minimum body mass index) goals are proposed, and participants are free to continue with the body mass reduction beyond the established objective. However, the theoretical minimum level of a body mass index = 22 is considered as a reference.[4] The group sessions in the intervention group include explanations of the recipes, menus and other characteristics of the proposed dietary intervention and lifestyle modification. These sessions last for 30–45 min. The PREDIMED-Plus dietitians manage the

sessions with no more than 20 participants per group separately in each arm of the trial. Usually, the 12 group sessions in the intervention arm during 1 year include:

- six sessions on the erMedDiet;
- three sessions on PA, including audio-visual resources to explain each activity;
- three sessions on behaviour, attitudinal and lifestyle modification techniques.

After the first year of follow-up, participants allocated to the intervention group are scheduled to a monthly group session (30–45 min) and an individual session (15–30 min) every 3 months. Additionally, they receive two telephone calls (15–30 min) every three months. Participants in the control group are scheduled to one annual individual session and two group sessions.

An organization depending on the Ministry of Agriculture - Government of Spain (Fundación Patrimonio Comunal Olivarero) provides and is committed to supply for free the necessary amount of olive oil used in the trial. Nuts are also freely provided to the participants and included in the budget of the project. None of the investigators has any commercial interest with these companies.

The main focus of the intervention with an erMedDiet is to increase the overall quality of the diet through the avoidance of foods that have been consistently shown to be associated with weight gain and/or to increase cardiovascular risk,[72,73] and to replace them with foods known to be associated with weight loss and reduced cardiovascular risk in large epidemiological studies with good control for confounding.[72–77] A reduction of 600 kcal/day in energy intake (or about 30% of estimated energy requirements) was planned from the estimation of energy requirements by the WHO equation, taking into account the basal metabolic rate, PA and observed weight changes of each participant at baseline and during follow-up.[78]

What is the attrition?

Of the 9677 participants assessed for eligibility initially and during the run-in period, 6874 (71%) were randomized (Figure 2). High retention rates among these participants are expected because the run-in period contributed to selecting collaborative and motivated participants. The fact that all participants in both the control and intervention groups receive a free provision of Mediterranean foods (EVOO and nuts) was implemented to favour retention. Other retention strategies include permanent feedback to usual health care providers to share relevant participants' findings during follow-up, and non-coercive material incentives in both groups. Also, in the intervention group continuous contact is maintained and self-monitoring is expected to reinforce compliance with the intervention. In early 2018, after a median follow-up of 1.9 years, the 2-year retention rate is above 85%, which is superior to that of most shorter-term body mass reduction trials. Furthermore, strategies to recover the contact with lost-to-follow-up participants will be applied during the intervention period.

What has it found? Key findings and publications

Within the framework of the PREDIMED-Plus trial, the relative validity and repeatability of a new beverage-specific questionnaire was assessed, and findings suggest that it is a relatively valid and highly reliable tool.[79] In addition, in a cross-sectional analysis, greater time spent on moderate-vigorous PA and fewer sedentary behaviours were inversely associated with obesity, type 2 diabetes and some components of the metabolic syndrome (abdominal obesity, low HDL-c).[80] Publications are available at [www.predimedplus.com/en/publications/].

What are the main strengths and weaknesses?

A major strength is the multimodal approach to address overweight/obesity.[4,5,20] In addition, given that the most important current challenge for tackling the obesity epidemic is the long-term sustainability of body mass reduction attainments,[78] this trial is unique because it is specifically designed for determining the long-term effect of a body mass reduction intervention tailored for prolonged sustainability. We propose a novel paradigm for nutritional and lifestyle recommendations with strong potential for long-term compliance.[21,27,34–37] At any rate, given that the primary endpoint is not body mass reduction but hard clinical cardiovascular endpoints, PREDIMED-Plus is not a weight-loss trial. The good environmental sustainability of the MedDiet is another strength of the PREDIMED-Plus trial.[81–83] Furthermore, the research team comprises investigators with experience in lifestyle intervention trials (e.g. PREDIMED), which attests to the viability of the trial. Finally, if proven in efficacy, the interventions tested are feasible to be adopted and integrated by the primary care system.

This trial has also several weaknesses. First, the generalization to younger age and healthier population groups is limited due to the age range of participants (55–75 years) and the fact that all of them had metabolic syndrome at baseline. Second, there is an inherent difficulty in attaining a homogeneous intervention across the 23 centres, because it is based on three components (diet, PA and behaviour

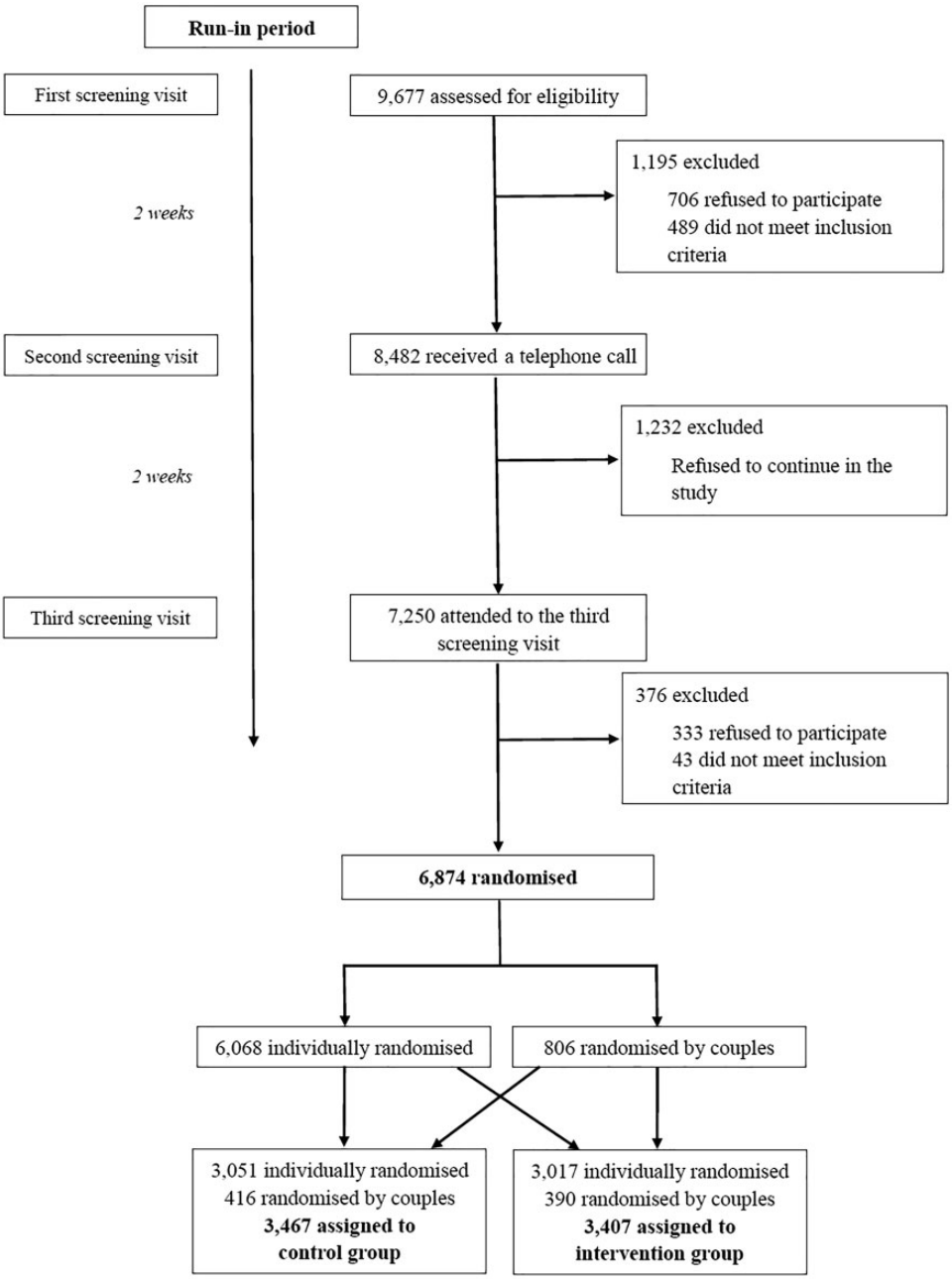

Figure 2. Flow chart of the PREDIMED-Plus trial.

modification techniques) and the expertise, motivation and circumstances of the staff in charge of the interventions (mainly dietitians) might potentially introduce some small degree of heterogeneity. In addition, not all centres count on physical activity specialists to conduct the PA recommendations. In a small number of centres where no physical activity specialist is available, the dietitians are in charge also of the physical activity component of the intervention. This should be acknowledged as a limitation. However, for this reason, a detailed protocol for the physical activity intervention has been developed, including booklets, videos and instructions on how to use the pedometers, questionnaires, tests and accelerometers. Also, intensive and comprehensive staff training sessions were conducted at the trial's inception and are repeated on a yearly basis.

Another limitation is that, despite the blind randomization, not only participants know their assigned group but also caregivers; in particular, those who are delivering the intervention will know if a participant belongs or not to the intervention group. However in any case, the adjudicators of the final hard clinical events will be completely blinded because they are not the caregivers responsible for the intervention or the usual care of patients. They are

completely independent of the fieldwork conducted in the study. Also, the high number of contacts (individual and group sessions, and telephone calls) in the intervention group (36 contacts in the first year of follow-up, and 20 yearly contacts thereafter), may limit the applicability of this intervention in some settings. Finally, the combination of PA, energy restriction and behavioural support is needed to obtain sustained body mass reductions, but this combination will represent a potential obstacle for the interpretation of findings, because it will be impossible to separate the effect of each of these three components using the randomized design. However, current causal models would permit us to isolate the specific contribution of each component by applying pertinent per-protocol analyses.[84]

Profile in a nutshell

- PREDIMED-Plus is a 6-year randomized clinical trial assessing the effect of an energy-reduced Mediterranean diet, physical activity recommendations and body mass loss goals on the primary prevention of hard cardiovascular clinical events.
- PREDIMED-Plus included 6874 participants (aged 55-75 years for men; 60-75 for women), with overweight or obesity (body mass index 27 to 40 kg/m^2) and metabolic syndrome.
- The dataset includes comprehensive yearly repeated assessments of diet, physical activity, biological samples, repeated neuropsychological evaluations and quality of life questionnaires.
- Participants in the intervention group attend one group session and two individual sessions (one of them as a telephone call) monthly during the first year of the trial, and one group session per month and alternate phone calls or personal interviews thereafter.
- Participants in the control group have group sessions and individual interviews every 6 months.
- More information about the PREDIMED-Plus trial can be found in its webpage [www.predimedplus.com].

Can I get hold of the data? Where can I find out more?

Collaboration with national and international studies is welcomed and can be proposed to [mamartinez@unav.es] or to [jordi.salas@urv.cat]. All publications and further relevant information can be found at [www.predimedplus.com].

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Supplementary Data

Supplementary data are available at *IJE* online.

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