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CORONARY DIET INTERVENTION WITH OLIVE OIL AND CARDIOVASCULAR PREVENTION STUDY (THE CORDIOPREV STUDY): RATIONALE, METHODS, AND BASELINE CHARACTERISTICS:

A CLINICAL TRIAL COMPARING THE EFFICACY OF A MEDITERRANEAN DIET RICH IN OLIVE OIL VERSUS A LOW-FAT DIET ON CARDIOVASCULAR DISEASE IN CORONARY PATIENTS.

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Abstract

Coronary heart disease (CHD) represents a major global health burden. However, despite the well-known influence that dietary habits exert over the progression of this disease, there are no well-established and scientifically sound dietary approaches to prevent the onset of clinical outcomes in secondary prevention. The objective of the CORonary Diet Intervention with Olive oil and cardiovascular PREvention study (CORDIOPREV study, clinical trials number NCT00924937) is to compare the ability of a Mediterranean diet rich in virgin olive oil versus a low-fat diet to influence the composite incidence of cardiovascular events after 7 years, in subjects with

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documented CHD at baseline. For this purpose, we enrolled 1002 coronary patients from Spain. Baseline assessment (2009–12) included detailed interviews and measurements to assess dietary, social and biological variables. Results of baseline characteristics: The CORDIOPREV study in Spain describes a population with a high BMI (37.2% overweight and 56.3% obesity), with a median of LDL-cholesterol of 88.5 mg/dL (70.6% of the patients having <100 mg/dL, and 20.3% patients < 70 mg/dL). 9.6% of the participants were active smokers, and 64.4% were former smokers. Metabolic Syndrome was present in 58% of this population. To sum up, we describe here the rationale, methods and baseline characteristics of the CORDIOPREV study, which will test for the first time the efficacy of a Mediterranean Diet rich in extra virgin olive oil as compared with a low-fat diet on the incidence of CHD recurrence in a long term follow-up study.

Keywords

Mediterranean Diet; Coronary Secondary Prevention; Public Health Interventions; Coronary Heart Disease

INTRODUCTION

Atherosclerosis is the leading cause of death in Western countries, and according to current estimates, its overall prevalence will continue growing¹. The development of this disease is linked to the presence of several risk factors, among them high blood pressure, high low-density cholesterol (LDL), low high-density cholesterol (HDL), Type 2 Diabetes Mellitus, smoking and physical inactivity. Of these, the first four are closely related to the type of diet, and their appearance is often associated with the presence of overweight or obesity². Dietary interventions to reduce the incidence or recurrence of cardiovascular events have been tested, mainly by substituting saturated fatty acid diets for high-carbohydrate or high polyunsaturated fatty acid (PUFA) diets^{3–10}. A third dietary model, the so-called Mediterranean diet, is characterized by a relatively high proportion of fruit, cereals and vegetables; fish and poultry as the main sources of protein, and the use of virgin olive oil as the main source of fat. This dietary pattern is relatively high in total fat (35%) but low in saturated fats (<10%)¹¹. Although the epidemiological evidence points towards a reduction of the incidence of cardiovascular events resulting from this diet^{12–19}, no evidence from large-scale, long-term clinical trials exists. A recent study, the PREDIMED trial, showed that, after an average of 4.8 years' follow-up, two slightly different Mediterranean diet models reduced the incidence of a composite of major cardiovascular events (myocardial infarction, stroke or death from cardiovascular causes) versus a control diet (following AHA dietary recommendations) in a Spanish population of 7000 participants in primary prevention in subjects at high cardiovascular risk²⁰. However, evidence of the favorable effect of the Mediterranean diet in secondary prevention is much less established. The Lyon study reported a decrease of 50–70% in the recurrence of cardiovascular events after 4 years' follow-up of a "Mediterranean diet"²¹. However, this study used canola oil as the main source of fat, a food that is not commonly used in Mediterranean countries. In fact, some of the potential favorable effects of the Mediterranean Diet have been ascribed to the extra virgin olive oil, due to its combination of a high MUFA (MUFA) fat content with minor compounds with various biological properties, such as polyphenols. These include

compounds which affect cardiovascular risk factors like blood pressure, lipids, inflammation, oxidation and those which even modulate favourably the relative expression of certain genes^{22–27}.

With the above background, it becomes evident that there is a need for long-term follow up studies evaluating the efficacy of this dietary model on cardiovascular outcomes in secondary prevention. We report here the methods and baseline characteristics of the CORDIOPREV study, which was designed to investigate the efficacy of the Mediterranean diet in the secondary prevention of CHD as compared with a low-fat diet.

OBJECTIVES

The primary outcome of the CORDIOPREV study is to compare the appearance of a composite of cardiovascular events after an average follow-up of 7 years in secondary prevention with two dietary models: a Mediterranean diet (rich in olive oil) and a low-fat diet. The composite outcome includes the following cardiovascular events: myocardial infarction, revascularization, ischemic stroke, documented peripheral artery disease and cardiovascular death.

Pre-specified secondary outcomes include clinical, biochemical and biological factors, and are defined below in the section entitled “Measuring the Effectiveness”.

METHODS AND DESIGN

Overall Design

The CORDIOPREV study (Clinicaltrials.gov number NCT00924937) is a randomized, single blind, controlled dietary intervention trial in CHD patients with high cardiovascular risk, with an intention to treat analysis basis.

The study is being conducted at the *Instituto Maimonides de Investigacion Biomedica de Cordoba* (IMIBIC), a scientific institute which carries out research into biomedical areas for the Reina Sofia University Hospital, and the University of Cordoba, Spain. The lipids and atherosclerosis unit, internal medicine unit, is also a member of the CIBER Fisiopatologia de la Obesidad y Nutrición (CIBERObn), a national research organization studying obesity and nutrition and their impact on health and disease. Moreover, the leading researchers have established collaboration agreements with national and international research groups to conduct additional ancillary studies.

Study Population

The inclusion and exclusion criteria are detailed in Table 1. To sum up, patients were eligible if they were over 20 years old, but under 76, had established CHD without clinical events in the last six months, were believed to be following a long-term dietary intervention and had no severe illnesses or an expected life expectancy of under five years. All the patients gave their written informed consent to participate in the study.

Randomization

The procedure of randomization was carried out so that the assignment to both diets is well-balanced. The randomization was based on the following variables: sex (male, female), age (under and over 60 years old) and previous myocardial infarction (yes, no). With this distribution, eight distinct groups were created, with all the possible combinations of the above factors, and eight different blocks were created to assign the diets (en-bloc randomization). The process of randomization was performed by the Andalusian School of Public Health. The procedure for assigning a diet was as follows: when there was a candidate for randomization, the study dietitians phoned the person in charge of the study in the Andalusian School of Public Health, which communicated the assigned diet to the dietitian. The dietitians were the only members of the intervention team to be aware of the dietary group of each participant. The School of Public Health gave the head of the dietary staff weekly reports with the progress of randomization, and the assigned diets were crossed between each other to validate the correctness of each assignment.

Interventions, subsequent care and follow up visits

A total of 1002 patients, aged between 20 and 75 years old, were included between July 2009 and February 2012 (Fig 1). The intervention phase is still in progress, and will have a median follow up of seven years. Dietary and clinical monitoring will be carried out by nutritionists and dietitians, as well as internists and cardiologists.

Study diets and dietary assessment: The models of healthy diet are: 1) the Mediterranean diet, with a minimum 35% of calories as fat (22% MUFA fat, 6% PUFA fat and <10% saturated fat), 15% proteins and a maximum of 50% carbohydrates, and 2) the low-fat high complex carbohydrate diet recommended by the National Cholesterol Education Program and the American Heart Association, comprising of <30% total fat (<10% saturated fat, 12–14% MUFA fat and 6–8% PUFA fat), 15% protein and a minimum 55% carbohydrates. In both diets, the cholesterol content was adjusted to <300 mg/day (summarized in Table 2). The objective was not to compare the two different diets defined by a certain percentage of nutrients, but to compare two different dietary models or patterns or two different food pyramids: the dietary pattern of the Mediterranean diet food pyramid versus the dietary pattern recommended by the American Heart Association. Both therapeutic diets should provide a wide variety of foods, including vegetables, fruit, cereals, potatoes, legumes, dairy products, meat and fish. Participants in both intervention groups receive the same intensive dietary counselling. Dietitians administered personalized individual interviews at inclusion and every 6 months, and quarterly group education sessions with up to 20 participants per session and separate sessions for each group. These sessions consisted of informative talks accompanied by written information with detailed descriptions of typical foods for each dietary pattern, seasonal shopping lists, meal plans and recipes. In brief, on the basis of the initial assessment of individual scores of adherence using a 14-item questionnaire, dietitians gave personalized dietary advice to participants randomly assigned to the Mediterranean Diet, with instructions directed to increasing the score, by including, among others, 1) abundant use of olive oil for cooking and dressing, 2) increased consumption of fruit, vegetables, legumes, and fish, 3) reduction in total meat consumption, with white meat recommended instead of red or processed meat, 4) preparation of homemade sauces with

tomato, garlic, onion, and spices with olive oil to dress vegetables, pasta, rice and other dishes, 5) avoidance of butter, cream, fast food, sweets, pastries and sugar-sweetened beverages, and 6) in alcohol drinkers, a moderate consumption of red wine. The participants assigned to the Mediterranean Diet were given free extra virgin olive oil (1 litre/week). This amount was not intended to be for the exclusive use of the participant, but for the family to use at home if needed. The participants were not told to use all the oil, but just as much as they needed in their regular diet. The extra virgin olive oil was provided by the Fundación Patrimonio Comunal Olivarero, and always contained >75% of MUFA, > 300 ppm of phenolic compounds and <12% saturated fats (laboratory authorization number A-033-AU, Consejería De Agricultura, Pesca Y Desarrollo Rural, Junta de Andalucía). The participants randomized to the low-fat diet received recommendations focused on limiting all types of fat, from both animal and vegetable sources, and on increasing the intake of complex carbohydrates. The participants also received free food packs incorporating the main food components of this dietary pattern. No energy restriction was administered, nor was physical activity promoted specifically by the study team. Energy and nutrient intakes were calculated from Spanish food composition tables^{28–29}. A table of interventions and follow-up is described in Table 3. Baseline and annual visit included: 1) collection of biological samples; 2) a short questionnaire about lifestyle variables, medical conditions, and use of medication, 3) a 14-item questionnaire of adherence to the Mediterranean Diet³⁰ 4) a 137-item validated food frequency questionnaire^{31–32}, and 5) the validated Spanish version of the Minnesota Leisure-Time Physical Activity questionnaire³³ and the validated SF36 quality of life questionnaire³⁴. Weight, height and waist circumference were measured using standardized procedures. Regular medical visits to ascertain the existence of clinical, prescription drugs or other health changes of the patients are carried out (see Table 3), or additionally on demand, when the patients attend dietary visits and report any changes in their health or treatment.

Measuring the Effectiveness

The primary outcome of the CORDIOPREV study is to compare the appearance of a number of cardiovascular events after a median follow-up of 7 years in secondary prevention with two dietary models: a Mediterranean diet (rich in olive oil) or a low-fat diet. The composite outcome includes the following cardiovascular events: myocardial infarction, revascularization, ischemic stroke, documented peripheral artery disease and cardiovascular death.

Pre-specified secondary outcomes are: incidence of intermittent claudication; concentration of LDL cholesterol; lipid-related atherogenic ratios: total cholesterol/HDL and LDL/HDL; metabolic control of carbohydrates (assessed by glycemic and insulin responses to tolerance tests to glucose); metabolic control of lipids and postprandial lipaemia; blood pressure; incidence of malignancy; incidence of Type 2 Diabetes Mellitus; incidence of metabolic syndrome; arrhythmias; an extended composite of heart events (cardiac death, myocardial infarction, unstable angina, revascularization, heart failure, heart transplantation and cardiac arrest), an extended composite of cardiovascular disease progression (cardiac death, myocardial infarction, unstable angina, revascularization, heart failure, heart transplantation, cardiac arrest, stroke and peripheral artery disease), progression of cognitive decline and

changes in microbiota. (Supplemental material) Additional secondary outcome measures will be performed in the light of present and/or future knowledge about CHD risk factors, prognostic factors and patho-physiological pathways, and will include, but not be limited to, endothelial function, inflammation, cell biology, molecular biology, proteomics, genetics and epigenetics.

Statistical Methods

Sample Size and Power Calculations:

The sample size and power calculation have been calculated on the following assumptions: an incidence rate in the control group (Low Fat) of 4 events/100 person-years that will amount to 24.9% of absolute cumulative incidence after 7 years, a hazard ratio of 0.7 and a statistical power of 80%, with two tailed $\alpha=0.05$. Under these assumptions, the required sample size was 491 patients in each of the two groups.

The size of the sample for the CORDIOPREV study was initially calculated for a cardiovascular disease recurrence of 35% in the control group (Low Fat) and of 25% in the intervention (Mediterranean Diet) in 5 years, with an annual loss of 2%, an alpha error = 0.05 and a power of 0.90 (minimum sample size: 874 patients) of a composite endpoint that included cardiac death, myocardial infarction, unstable angina, revascularization, heart failure, heart transplantation, cardiac arrest, stroke, peripheral artery disease or any other manifestation of cardiovascular disease. In the meeting of the external advisory board in the third year of the study, and according to recent cardiovascular studies, the advisory board recommended limiting the definition of cardiovascular events to those finally included in the study, and which are defined above. Subsequently, based on the lower number of expected events, the final calculations for sample size and power were set as above.

Primary statistical analysis

This study will be analyzed under the principle of “intention-to-treat”

Statistical comparisons will be performed using 2-sided significance tests.

The primary statistical comparison will be the log-rank analysis using the Kaplan-Meier survival estimates, and the “time-to event” analysis using the Cox proportional hazards model. To adjust for heterogeneity among the subjects, the Cox model will be adjusted for several baseline covariates including age and sex. The level of significance for all the analyses will be $\alpha=0.05$. If the study does not meet the superiority significance criterion, the non-inferiority of the Mediterranean Diet will be tested and established if the upper 95% CI for the estimated hazard ratio falls below 1.10.

Secondary statistical analysis

Due to the heterogeneity of the secondary outcomes, statistical tests will be chosen individually for each outcome. As an example, recently published papers from CordioPrev dealing with genetics or postprandial lipemia used ANOVA tests for quantitative variables and Chi-square for qualitative variables^{35–40}. As a general rule, all levels of significance for regular tests will be set at $\alpha=0.05$, and Parametric tests will be used whenever possible.

Individual specific statistical tests will be performed when needed. An example of this could be the case of large-scale genetic tests or GWA (genome wide analysis). These types of tests are dependent on the specific hypothesis and cannot be pre-specified.

Intermediate analysis

The interim analysis has been planned for October 2016 and 2017. Following the O'Brien Fleming rule, the pre-specified α s for the anticipated end of the study are 0.014 and 0.045 respectively.

Rationale for collaborations, ascertaining events and ethics

The excellent characterization and control of the CORDIOPREV study, with biological, psychological, vascular, genetic, metabolic and socio-economic tests will allow us to study the effects of the dietary intervention in CHD patients using an integrated approach. This wealth of data and the uniqueness of the study will draw the interest of other researchers and facilitate collaborations to investigate other aspects of the study which were not contemplated in the original design.

The existence of primary and secondary outcomes will be monitored by the information provided by the researchers in the case report forms, the scheduled visits in Table 3 and the institutional computer records. In any case, all patients who do not attend a programmed visit will be contacted to find out the cause of the absence, and to carry out a final study visit. The outcomes are ascertained on a yearly basis by a Clinical Events Committee whose members are blinded to the intervention group. During the programmed visits, patient compliance is checked, based on the scores of adherence to the Mediterranean and low-fat dietary patterns, and by measuring selected biological plasma variables, such as the fatty acids profile. The dietary patterns are based on those used in the PREDIMED study^{20, 30}. The characteristics of the CORDIOPREV study have been previously released in Clinicaltrials.gov (NCT00924937). The local Ethics Committee approved the trial protocol, which follows the Helsinki declaration and the charter of good clinical practices. The experimental protocol conforms to international ethical standards and written informed consent was obtained from all the subjects.

RESULTS OF BASELINE MEASUREMENTS

Up to February 2012, a total of 1002 participants were included in the CORDIOPREV study. Table 4 shows baseline characteristics. The mean age was 59.5 years. The subjects were predominantly male (83.5%), former smokers (64.6%) and consumers of alcohol (82.6%), mostly in moderation (<14 g/d, mainly red wine). Adherence to the Mediterranean diet and the low-fat scores were 8.78 and 3.81 for the whole sample (regardless of the randomization group to which they were assigned), on scores that ranged from 0–14 for the Mediterranean^{20, 30} and 0–9 for the low fat²⁰ diet. The prevalence of Metabolic Syndrome was 58% (n=581) in this set of patients, which is in accordance with similar studies⁴¹.

DISCUSSION AND CONCLUSIONS

The evidence for the influence of the Mediterranean diet on the clinical course of CHD is sparse. Despite the well-established healthy effects of this dietary pattern on multiple cardiovascular risk factors, either traditional ones such as lipids or hypertension, or new emerging ones (endothelial function, oxidative stress, inflammation, obesity, metabolic syndrome or type 2 diabetes mellitus)^{14–15, 24, 42–44}, there is a paucity of studies evaluating its effectiveness in reducing the onset of cardiovascular complications in coronary patients. The CORDIOPREV study will explore the ability of the Mediterranean diet to reduce the progression of CHD, comparing its results with the low-fat model, in a long-term (7 years) intervention study. The results of the CORDIOPREV study may test the existence of a causal link between the Mediterranean diet and the reduction in cardiovascular events observed in epidemiological studies. Although, due to the longitudinal character of CORDIOPREV, the clinical outcomes will not be unveiled until the end of the intervention periods, several papers have been already published from baseline data from the CORDIOPREV study which have yielded useful insights about genetics, human metabolism or inflammation.^{35–40} From the conceptual point of view, this study will fill the gap in long-term studies on secondary prevention using dietary approaches. Moreover, it will contribute to our understanding of the use of more personalized strategies. In terms of the methodological components, we should highlight the randomization process carried out by an external body, the large sample size of the study, the strict follow-up protocols and the array of biological samples collected and stored, ranging from microbiota to urine, DNA or endothelial cells, etc. The main weaknesses of the study are those inherent to all long-term intervention studies. On the one hand, it is impossible to guarantee that no patients tell their doctor what their dietary intervention group is; although the standard operation procedures of the study prohibits patients from telling their GP about the diet and from telling those involved in the study (except dietitians) what their dietary intervention group is, it could occur. On the other hand, it is difficult to maintaining the initial sample size, due to losses in the follow up. This is especially important in the subset of patients randomized to the low-fat diet, as this is not a usual dietary pattern in a Mediterranean setting. Although we have established several layers of internal controls to ascertain adherence to the diet, the nature of the study in the “real world setting” contributes to potential deviations from a strict dietary adherence. However, they will also provide more useful results, as they will be applicable to real-life scenarios.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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there were many observational studies and studies evaluating risk factors which indicated that it could have a favourable effect. The sponsor was not involved in the design or carrying out the study, and its participation was limited to funding and providing the olive oil used in the study. We also received additional funding from CITOLIVA, CEAS, Junta de Andalucía (Consejería de Salud, Consejería de Agricultura y Pesca, Consejería de Innovación, Ciencia y Empresa), Diputaciones de Jaén y Córdoba, Centro de Excelencia en Investigación sobre Aceite de Oliva y Salud and Ministerio de Medio Ambiente, Medio Rural y Marino and the Spanish Government. It was also partly supported by research grants from the Ministerio de Ciencia e Innovación (AGL2009-122270 to J L-M, FIS PI10/01041 to P P-M, FIS PI13/00023 to J D-L); Ministerio de Economía y Competitividad (AGL2012/39615 to J L-M); Consejería de Salud, Junta de Andalucía (PI0193/09 to J L-M, PI-0252/09 to J D-L, and PI-0058/10 to P P-M, PI-0206-2013 to A G-R); Proyecto de Excelencia, Consejería de Economía, Innovación, Ciencia y Empleo (CVI-7450 to J L-M); Francisco Gomez-Delgado is supported by an ISCIII research contract (Programa Río-Hortega). The study was also co-financed by the Fondo Europeo de Desarrollo Regional (FEDER). The CIBEROBN is an initiative of the Instituto de Salud Carlos III, Madrid, Spain. The authors have declared no conflict of interest. There are no ties with industry regarding this paper. We would like to thank to the Cardiology Unit at IMIBIC/University Hospital Reina Sofia, for their valuable help in the recruitment for the present study.

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Highlights

- We present the rationale and methods of the CORDIOPREV study.
- Mediterranean versus Low-fat diet on cardiovascular outcomes, secondary prevention.
- 1st large (n=1002), long-term (median 7 years) study with these characteristics.

Fig 1.
Screening and randomization of the CordioPrev study

Table 1

Inclusion and exclusion criteria for CORDIOPREV study.

Inclusion Criteria in the CORDIOPREV study:	
<p>1.- Informed Consent: All participants will agree to being included in the study by signing the protocol approved by the Reina Sofia University Hospital Clinical Research Ethics Committee. In this written statement of consent, it will state that patients will be chosen for inclusion in the groups on a random basis.</p> <p>2.- Diagnostic Criteria: The patients were selected with acute coronary syndrome (unstable angina, acute myocardial infarction) and high-risk chronic coronary heart disease, according to the following criteria:</p>	
a.	Acute myocardial infarction: The existence of at least two of the following three signs: angina-type chest pain (or anginal equivalents), typical ECG changes (appearance of new Q waves and/or changes in ST segments and/or T waves), and a rise in myocardial enzymes (CPK and/or CPK/MB > of twice the normal laboratory limits). The MB value criterion will prevail in case of discrepancies over the total CPK.
b.	Unstable angina: Admission to hospital for angina-type chest pains lasting at least 15 minutes, both at rest and after exercise, which have increased in frequency and duration in recent days or weeks. The latest episode must have occurred at least 48 hours prior to admission and must be accompanied by at least one of the following electrocardiographic or analytical changes: <ul style="list-style-type: none"> • ST depression of at least 0.5 mm in 2 contiguous leads. • ST elevation of at least 1 mm in 2 contiguous leads. • T-wave inversion of at least 2 mm in 2 contiguous leads. • Positive troponin result.
c.	Chronic high-risk ischemic heart disease: patients will be included who have been hospitalized for a coronary event and/or stable angina, at least once in the past 2 years and who have undergone diagnostic coronary angiography with evidence of severe coronary disease, which is defined as the existence of an epicardial vessel greater than 2.5 mm in diameter with stenosis of over 50%.
Exclusion Criteria	
1	Patients under 20 years of age or over 75 years old with a life expectancy of over 5 years.
2	Severe heart failure, NYHA functional class III or IV, with the exception of self-limited episodes of acute heart failure at the time of the acute ischemic event.
3	Severe left ventricular systolic dysfunction (with ejection fraction equal to or under 35%).
4	Patients with restricted capacity to follow the protocol: those unable to follow the prescribed diet for whatever reason, due to personal or family circumstances.
5	Risk factors which are severe or difficult to control: patients with hypertension and diabetes, where there is organ involvement that limits their survival, will be excluded (chronic renal failure with creatinine which is persistently >2.5 mg/dl) and disabling clinical manifestations of cerebral atherosclerosis.
6	Chronic diseases unrelated to coronary risk: severe psychiatric illnesses, chronic conditions requiring treatment that could modify the lipid metabolism (chronic renal failure, chronic liver disease, neoplasia under treatment, chronic obstructive pulmonary disease involving respiratory pulmonary failure with home oxygen therapy, endocrine diseases susceptible to decompensation and diseases of the digestive tract that involve episodes of diarrhea).
7	Participants in other studies: patients taking part in other studies will be excluded, at the time of selection or up to 30 days before the study begins.

Table 2

Energy composition of the two dietary models.

NUTRIENTS	MEDITERRANEAN DIET	LOW FAT DIET
Energy	Usual intake, no energy restriction	Usual intake, no energy restriction
Carbohydrates	<50 % of total calories	> 55 % of total calories
Proteins	15 % of total calories	15 % of total calories
Total Fat	>35 % of total calories	< 30% of total calories
SAFA	< 10% of total calories	< 10% of total calories
MUFA	22 % of total calories	12–14 % of total calories
PUFA	6 % of total calories	6–8 % of total calories
Cholesterol	< 300 mg	< 300 mg

SAFA: saturated fatty acid; MUFA: monounsaturated fatty acid; PUFA: polyunsaturated fatty acid; mg: milligrams

Table 3

Table of interventions and follow up. BP, blood pressure. (a) includes direct measurements of weight, height and waist circumference, and (b) only if necessary.

Item/Measurements	Brief description	Baseline	Number of yearly measurements				
			Year 1	Year 2	Year 3	Year 4	Year 5
Eligibility questionnaire	Inclusion/Exclusion Criteria	1	0	0	0	0	0
General questionnaire ^a	Personal and family history, medical conditions, medications, anthropometry, BP, smoking, alcohol intake	1	0	0	0	0	0
Informed Consent		1	0	0	0	0	0
Randomization		1	0	0	0	0	0
Follow-up questionnaire ^a	Symptoms and conditions, marital status, job, medications, anthropometry, BP	0	2	2	2	2	2
Review prior/concomitant medications and Event Questionnaire ^b							
Tolerance questionnaire	Adverse experiences	0	1	1	1	1	1
Socio-economic questionnaire	Socio-demographic and economic characteristics, marital status, job, level of education	1	0	0	0	0	0
Circadian chronotype questionnaires	Horne-Östberg Morningness- Eveningness Questionnaire (Spanish version), sleep diaries	1	0	0	0	0	0
Mini-mental state examination (MMSE)	Validated tool for screening cognitive function	1	0	0	0	0	1
Geriatric Depression Scale (GDS) or Yesavage	Validated tool for identifying depression in the elderly (Spanish version)	1	0	0	0	0	0
Health related quality of life	Validated 36-Item Short Form Health Survey (SF-36)	1	0	0	1	0	1
Physical activity questionnaire	Validated Minnesota questionnaire	1	1	1	1	1	1
Food frequency questionnaire (FFQ)	Validated 137-item FFQ	1	1	1	1	1	1
14-item MedDiet questionnaire	MedDiet adherence tool	1	6	6	6	6	6
9-item Low Fat Diet questionnaire	Low-fat Diet adherence tool	1	6	6	6	6	6
Dietary reinforcement	Face-to-face and telephone interviews	1	6	6	6	6	6
Group education sessions	Separate sessions for each group (20 participants/session)	0	3	3	3	3	3
Dispensing study foods		1	2	2	2	2	2
Blood sample	Lipids, glucose, renal function, transaminases, blood count and others	1	1	1	1	1	1
Urine sample		1	1	1	1	1	1
Stool sample		1	1	1	1	1	1
Insulin resistance test/Oral Glucose Tolerance Test (OGTT)		1	1	1	1	1	1

Item/Measurements	Brief description	Baseline	Number of yearly measurements				
			Year 1	Year 2	Year 3	Year 4	Year 5
Postprandial lipaemia		1	0	0	1	0	1
Intima-media thickness (IMT) study	Carotid-Wall Intima-Media Thickness measurement	1	0	0	0	0	1
Brachial Artery Reactivity study	Ultrasound assessment of endothelial-dependent flow- mediated vasodilation of the brachial artery	1	0	0	0	0	1
Ankle-brachial index (ABI)		1	0	1	0	0	1
Microvascular endothelial function	Laser doppler flowmetry	1	1	1	1	1	1
Echocardiography		1	0	0	1	0	0

Table 4

Baseline characteristics of the CORDIOPREV study.

	All patients (n=1002)	Mediterranean Diet group (n=502)	Low-Fat Diet group (n=500)	p-value
Age, years	59.5 (0.2)	59.7 (0.4)	59.5 (0.4)	NS
Male/Female, n	837/165	420/82	417/83	NS
Metabolic Syndrome, %	58.0	55.6	60.4	NS
SBP, mmHg	138.8 (0.6)	138.5 (0.9)	139.0 (0.9)	NS
DBP, mmHg	77.2 (0.3)	77.2 (0.5)	77.3 (0.5)	NS
Weight, Kg	85.1 (0.4)	84.9 (0.6)	85.4 (0.7)	NS
Height, m	1.7 (0.0)	1.7 (0.0)	1.7 (0.0)	NS
Waist circumference, cm	105.1 (0.3)	104.9 (0.5)	105.4 (0.5)	NS
BMI, kg/m ²	31.1 (0.1)	31.0 (0.1)	31.2 (0.2)	NS
Total Cholesterol, mg/dl	159.0 (1.0)	159.1 (1.5)	159.0 (1.3)	NS
HDL-c, mg/dl	42.2 (0.3)	42.3 (0.5)	42.1 (0.5)	NS
LDL-c, mg/dl	88.5 (0.8)	88.9 (1.2)	88.2 (1.1)	NS
APO-A, mg/dl	129.6 (0.7)	129.7 (1.0)	129.5 (0.9)	NS
APO-B, mg/dl	73.6 (0.5)	73.6 (0.8)	73.7 (0.8)	NS
TG, mg/dl	135.4 (2.2)	134.8 (3.1)	136.0 (3.2)	NS
Fasting Plasma Glucose, mg/dl	113.7 (1.2)	114.7 (1.8)	112.8 (1.6)	NS
Family history of premature coronary artery disease, %	14.9	14.9	14.8	NS
Family history of DM, %	46.7	45.6	47.8	NS
Diabetes mellitus, %	32.3	31.9	32.8	NS
Hypertension, %	68.5	69.2	67.9	NS
Normal systolic function (LVEF ≥ 50%), %	94.9	94.3	95.6	NS
History of myocardial infarction, %	61.9	62.2	61.6	NS
History of CABG, %	3.2	3.8	2.6	NS
history of PCI, %	91.5	91.2	91.8	NS
Current smoker, %	9.7	8.7	10.7	NS
Former smoker, %	64.6	63.9	65.2	NS
History of stroke or TIA, %	5.1	5.2	5.0	NS
History of peripheral vascular disease, %	2.9	3.0	2.8	NS
History of prior malignancy, %	2.6	3.6	1.6	0.04
Baseline medication, %				
Antiplatelets	96.6	96.9	96.4	NS
Statins	85.6	84.9	86.4	NS

* Data are given as Mean (SE) value or percentage of participants unless otherwise specified.

Abbreviations: APO-A, apolipoprotein A1; APO-B, apolipoprotein B; BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); CABG, Coronary artery bypass grafting; DBP, diastolic blood pressure; DM, diabetes mellitus; HDL-C, high-density lipoprotein cholesterol; LDL-c, low-density lipoprotein; LVEF, left ventricular ejection fraction; NS, not significant (p-value>0.05); PCI, percutaneous coronary intervention; SBP, systolic blood pressure; TIA, transient ischemic attack; TG, triglycerides. SI conversion factors: To convert to millimol per liter, multiply by 0.0259 for HDL-C, by 0.0113 for triglycerides, and by 0.0555 for glucose; to convert insulin to picomol per liter, multiply by 6.945.

We used unpaired T-tests for quantitative variables and Chi-Square for categorical.

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