Long-term secondary prevention of cardiovascular disease with a Mediterranean diet and a low-fat diet (CORDIOPREV): a randomised controlled trial

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Summary

Background Mediterranean and low-fat diets are effective in the primary prevention of cardiovascular disease. We did a long-term randomised trial to compare the effects of these two diets in secondary prevention of cardiovascular disease.

Methods The CORDIOPREV study was a single-centre, randomised clinical trial done at the Reina Sofia University Hospital in Córdoba, Spain. Patients with established coronary heart disease (aged 20–75 years) were randomly assigned in a 1:1 ratio by the Andalusian School of Public Health to receive a Mediterranean diet or a low-fat diet intervention, with a follow-up of 7 years. Clinical investigators (physicians, investigators, and clinical endpoint committee members) were masked to treatment assignment; participants were not. A team of dietitians did the dietary interventions. The primary outcome (assessed by intention to treat) was a composite of major cardiovascular events, including myocardial infarction, revascularisation, ischaemic stroke, peripheral artery disease, and cardiovascular death. This study is registered with ClinicalTrials.gov, NCT00924937.

Findings From Oct 1, 2009, to Feb 28, 2012, a total of 1002 patients were enrolled, 500 (49·9%) in the low-fat diet group and 502 (50·1%) in the Mediterranean diet group. The mean age was 59·5 years (SD 8·7) and 827 (82·5%) of 1002 patients were men. The primary endpoint occurred in 198 participants: 87 in the Mediterranean diet group and 111 in the low-fat group (crude rate per 1000 person-years: 28·1 [95% CI 27·9–28·3] in the Mediterranean diet group *vs* 37·7 [37·5–37·9] in the low-fat group, log-rank p=0·039). Multivariable-adjusted hazard ratios (HRs) of the different models ranged from 0·719 (95% CI 0·541–0·957) to 0·753 (0·568–0·998) in favour of the Mediterranean diet. These effects were more evident in men, with primary endpoints occurring in 67 (16·2%) of 414 men in the Mediterranean diet group versus 94 (22·8%) of 413 men in the low-fat diet group (multiadjusted HR 0·669 [95% CI 0·489–0·915], log-rank p=0·013), than in 175 women for whom no difference was found between groups.

Interpretation In secondary prevention, the Mediterranean diet was superior to the low-fat diet in preventing major cardiovascular events. Our results are relevant to clinical practice, supporting the use of the Mediterranean diet in secondary prevention.

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Introduction

Besides drugs and invasive interventional measures (eg, revascularisation), lifestyle is a clear determinant of both incidence and recurrence of cardiovascular events. Among its components, diet is the most studied and supported factor.[1–10] The composition of the optimal diet for cardiovascular prevention has been evolving over the past decades. In the first part of the 2000s, reducing fat consumption was the standard approach in patients with cardiovascular disease. This approach was based on two main guidelines: the National Cholesterol Education Program II and the Adult Treatment Panel III guidelines.[11,12] Although the National Cholesterol Education Program II was stricter in fat reduction, the Adult Treatment Panel III emphasised the type of carbohydrates (eg, complex carbohydrates) used to replace saturated fats and correct fibre composition. However, the guideline did not raise the lower recommended limit for fats, keeping it to 25% (desirable limits are 25–35%). Therefore, a low-fat diet was the recommended option. A Mediterranean diet, characterised by a relatively high proportion of fruits, vegetables, legumes, and cereals, white meat and fish as the primary source of protein, and olive oil as the main source of fat, traditionally had been identified as a diet with a potential healthy composition. In the PREDIMED study, the Mediterranean diet has also proven effective in primary prevention in people at high risk of cardiovascular disease[13] compared with a control

Research in context

Evidence before this study

Evidence from clinical trials of the effect of a Mediterranean diet in secondary prevention of cardiovascular disease is scarce. Two reviews highlight the need for clinical data from clinical trials. A Cochrane Library report evaluated current knowledge about the effects of the Mediterranean diet on primary and secondary prevention. The authors conclude that there is a paucity of evidence for secondary prevention and that the ongoing studies might provide more certainty in the future. In that report, accumulated data were available from 605 patients on the Mediterranean diet for 4 years versus usual care, and 101 patients on the Mediterranean diet for 2 years versus an active comparator, compared with the 1002 patients on the Mediterranean diet versus low-fat diet for 7 years in our CORDIOPREV study. A 2019 critical review by Martinez-Gonzalez and colleagues analysing the effect of the Mediterranean diet highlights the need for new data on secondary prevention, because the only two significant existing studies were either too short (de Lorgeril and colleagues, 1999) or they presented some concerns (Singh and colleagues, 2002). Although clinical guidelines recommend the Mediterranean diet for secondary prevention, there have been no clinical trials in the past 20 years to support this recommendation.

Added value of this study

The CORDIOPREV study is the only trial in the past 23 years (excluding one subjected to an expression of concern) evaluating the effect of the Mediterranean diet versus any other active comparator in the secondary prevention of cardiovascular disease. This implies that the effect of the Mediterranean diet in the set of current treatment guidelines has not been tested until the CORDIOPREV study. The results of our study provide evidence that the Mediterranean diet is better than the low-fat diet in preventing cardiovascular recurrence. Our study is the most extensive study on secondary prevention with a Mediterranean diet, has the longest follow-up, and had more reported events.

Implications of all the available evidence

This study is a hallmark for the effect of the Mediterranean diet on secondary prevention of cardiovascular disease and can be used to change clinical guidelines on diet recommendations and follow-up of patients with coronary heart disease.

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See **Online** for appendix

diet (which had advice to reduce dietary fat). Active intervention by dietitians was done to equalise the intensity of the intervention between groups.[13] However, despite epidemiological and mechanistic studies showing similar results,[14–21] no evidence from large-scale, long-term clinical trials exists on the efficacy of the Mediterranean diet on secondary cardiovascular prevention, especially when compared with another active group. The CORDIOPREV study, a long-term, large-scale clinical trial aimed to compare the efficacy of two healthy dietary interventions (a low-fat diet and a Mediterranean diet) in secondary cardiovascular prevention.

Methods

Study design

The CORDIOPREV study was a single centre, randomised, dietary intervention clinical trial in patients with coronary heart disease developed at Reina Sofia University Hospital in Córdoba, Spain. Details of the trial design are provided elsewhere.[22] Extra-virgin olive oil was provided free of charge to the participants in the Mediterranean diet group (1 L per week per household). Healthy food bag packs, rich in complex carbohydrates, were provided, free of charge, to the participants in the low-fat diet group, with similar commercial value. The ethics approval and study protocol can be found on the IMIBIC website.

Participants

The inclusion and exclusion criteria have been previously published.[22] Eligible patients included men and women aged 20–75 years who had established coronary heart disease, were free of clinical events related to coronary heart disease in the previous 6 months, were able to follow a long-term dietary intervention, and had no severe illnesses or an expected life expectancy lower than the length of the study. The upper age limit was set on the basis of the life expectancy at the conception of the trial (2007) and according to the usual practice in contemporary long-term cardiovascular studies. Patients gave their written informed consent to participate in the study. The three criteria for established coronary heart disease in the CORDIOPREV study were: acute myocardial infarction, hospitalisation for unstable angina, or chronic high-risk ischaemic heart disease (patients with hospitalisation for a coronary event or stable angina with an image diagnostic test showing an epicardial vessel greater than 2·5 mm in diameter with stenosis of more than 50%). More details on these criteria have been published.[22]

Randomisation and masking

The process of randomisation (1:1) to the low-fat diet or the Mediterranean diet was done by the Andalusian School of Public Health (Granada, Spain), with fixed randomisation stratified in blocks, based on sex, age, and the existence of previous acute myocardial infarction (appendix).

Randomisation was blinded to dietitians, physicians, or any other personnel in the CORDIOPREV team. The procedure for assigning a diet was as follows: when there was a candidate for randomisation, the study dietitians telephoned the person in charge of the study in the Andalusian School of Public Health who then communicated the assigned diet to the dietitian. The CORDIOPREV team, including dietitians, did not know if randomisation

For the **ethics approval** see https://www.imibic.org/documents/cordioprevethic.pdf

For the **study protocol** see https://www.imibic.org/documents/cordioprevprotocol.pdf

	Mediterranean diet group	Low-fat diet group
Oil (including the oil used for cooking, dressing, and meals consumed outside the home)	Four or more tablespoons of extra virgin olive oil per day (40–60 g per day)	Less than two tablespoons of vegetable oils (eg, sunflower oil or regular olive oil) per day (20–30 g per day)
Fruit	Three or more servings of fresh fruit and natural fruit juices per day	Three or more servings of fresh, frozen, canned, or dried fruits per day
Vegetables	Two or more servings per day (at least one serving raw or as a salad)	Two or more servings per day (fresh, frozen, or canned, without added fat, sauce, or salt)
Grains and potatoes	Six servings of preferably whole grains per day	Six to 11 servings of grains (preferably whole grains), potatoes, and legumes per day
Legumes	Three or more servings per week	Six to 11 servings of grains (preferably whole grains), potatoes, and legumes per day
Dairy	Two servings per day	Two to three servings of low-fat or fat-free dairy products per day
Tree nuts	Three or more servings of raw, non-roasted, or fried nuts per week	Occasional consumption (one serving or less) of raw, non-roasted, or fried nuts per week
Fish and seafood	Three or more servings of especially fatty fish per week	Choose lean fish; limit fatty fish and seafood canned in oil to one serving or fewer per week
White meat	Consume white meat (eg, chicken, turkey, or rabbit) instead of red meat; remove skin and visible fat	Choose skinless poultry and lean cuts (eg, loin or round)
Red or processed meats	Less than one serving per week	One serving or fewer per week
Eggs	Two to four units per week	Two or fewer egg yolks per week
Commercial bakery products, sweets, and pastries	One serving or fewer per week	One serving or fewer per week
Butter and margarine	Not allowed	One serving or fewer per week
Wine	Optional consumption, only in case of a habitual wine drinker (one glass per day for women and two glasses per day for men)	Not allowed
Sweet or carbonated beverages	Less than one drink per day	Less than one drink per day
Culinary techniques	Use of sofrito (a homemade sauce with garlic, onion, aromatic herbs, and tomato slow cooked in olive oil) two or more times a week	Use low-fat cooking methods (eg, broiling, grilling, roasting, baking, microwaving, and poaching); avoid frying and use of sofrito; remove the visible fat before cooking

Table 1: **Summary of dietary recommendations to the patients in the two intervention groups of the CORDIOPREV study**

was done by blocks or other methods. Individual allocation documents were recorded in both institutions, and then by weekly telephone calls to ensure the correct allocations were done. The only physician auditing the randomisation was the clinical coordinator, who, together with the head of the randomisation team at the Andalusian School of Public Health, reviewed the allocations. The clinical coordinator did not make clinical visits.

Regarding masking, dietitians were the only members of the intervention team who knew the diet of each patient. Physicians and other members of the CORDIOPREV team who carried out clinical follow-up and analysis of the patients were unaware of the diets. Participants were instructed not to comment to the physicians on anything related to diet. This was a crucial point of our study, and even separate rooms for the visits related to diet or clinical follow-up were used. The clinical endpoint committee was also unaware of the diets consumed by the patients.

Procedures

The intervention had a median follow-up of 7 years. Dietary and clinical monitoring was carried out by dietitians, internists, and cardiologists. The dietary models were (1) the Mediterranean diet, comprising a minimum of 35% of the calories as fat (22% monounsaturated fatty acids, 6% polyunsaturated fatty acids, and <10% saturated fat), 15% proteins, and a maximum of 50% carbohydrates, and (2) the low-fat, high complex carbohydrates diet, comprising less than 30% of total fat (<10% saturated fat, 12–14% monounsaturated fatty acids, and 6–8% polyunsaturated fatty acids), 15% protein, and a minimum of 55% carbohydrates. In both diets, the cholesterol content was adjusted to less than 300 mg per day.[22] Dietary adherence was assessed with the 14-point Mediterranean Diet Adherence Screener and 9-point low-fat diet adherence.[13] No energy restriction was implemented and the study team explicitly did not promote physical activity. The dietary intervention in the CORDIOPREV study included individual face-to-face visits every 6 months, group sessions every 3 months, and telephone calls every 2 months, all of which aimed at guaranteeing frequent contact between the patients and dietitians (at least 12 interactions per year). During the study, the following interventions were done: regular contacts, group sessions, monitoring of adherence, goal setting, social support, and the provision of foods. Based on previous studies,[23,24] we consider that the intervention was of high intensity. Table 1 shows a summary of dietary recommendations to the patients in the two intervention groups. Further details on the dietary intervention, along with the results of the adherence of the dietary models during the first 7 years, are in the appendix (pp 7–17, 22–30).

Outcomes

The primary outcome of the CORDIOPREV study was a composite of major cardiovascular events, including myocardial infarction, revascularisation, ischaemic stroke, documented peripheral artery disease, and cardiovascular death, for 7 years. Prespecified secondary outcomes are in the appendix (pp 18–20).

Statistical analysis

The sample size and power calculation were calculated on the following assumptions: an incidence rate in the low-fat group of 4 events per 100 person-years that would amount to 24·9% of absolute cumulative incidence after 7 years, a hazard ratio (HR) of 0·7, and statistical power of 80%, with two-tailed α=0·05. Under these assumptions, the required sample size was 491 patients in each of the two groups. This sample size was

	All patients (n=1002)	Mediterranean diet group (n=502)	Low-fat diet group (n=500)
Age, years	59·5 (0·2)	59·7 (0·4)	59·5 (0·4)
Sex			
Male	827 (82·5%)	414 (82·5%)	413 (82·6%)
Female	175 (17·5%)	88 (17·5%)	87 (17·4%)
Metabolic syndrome	581 (58·0%)	279 (55·6%)	302 (60·4%)
Systolic blood pressure, mm Hg	138·8 (0·6)	138·5 (0·9)	139·0 (0·9)
Diastolic blood pressure, mm Hg	77·2 (0·3)	77·2 (0·5)	77·3 (0·5)
Weight, kg	85·1 (0·4)	84·9 (0·6)	85·4 (0·7)
Height, m	1·65 (0·0)	1·65 (0·0)	1·65 (0·0)
Waist circumference, cm	105·1 (0·3)	104·9 (0·5)	105·4 (0·5)
Body-mass index, kg/m²	31·1 (0·1)	31·0 (0·1)	31·2 (0·2)
Total cholesterol, mg/dL	159·0 (1·0)	159·1 (1·5)	159·0 (1·3)
HDL cholesterol, mg/dL	42·2 (0·3)	42·3 (0·5)	42·1 (0·5)
LDL cholesterol, mg/dL	88·5 (0·8)	88·9 (1·2)	88·2 (1·1)
Apolipoprotein A1, mg/dL	129·6 (0·7)	129·7 (1·0)	129·5 (0·9)
Apolipoprotein B, mg/dL	73·6 (0·5)	73·6 (0·8)	73·7 (0·8)
Triglycerides, mg/dL	135·4 (2·2)	134·8 (3·1)	136·0 (3·2)
Fasting plasma glucose, mg/dL	113·7 (1·2)	114·7 (1·8)	112·8 (1·6)
Family history of premature coronary artery disease	149 (14·9%)	75 (14·9%)	74 (14·8%)
Family history of diabetes	468 (46·7%)	229 (45·6%)	239 (47·8%)
Diabetes*	540 (53·9%)	256 (51·0%)	284 (56·8%)
Hypertension	683 (68·2%)	346 (68·9%)	337 (67·4%)
Normal systolic function (left ventricular ejection fraction ≥50%)	951 (94·9%)	473 (94·3%)	478 (95·6%)
History of myocardial infarction	620 (61·9%)	312 (62·2%)	308 (61·6%)
(Continued from previous column)			
History of coronary artery bypass grafting	32 (3·2%)	19 (3·8%)	13 (2·6%)
History of percutaneous coronary intervention	914 (91·2%)	456 (90·8%)	458 (91·6%)
Current smoker	95 (9·7%)	43 (8·7%)	52 (10·7%)
Former smoker	635 (64·6%)	317 (63·8%)	318 (65·4%)
History of stroke or transient ischaemic attack	51 (5·1%)	26 (5·2%)	25 (5·0%)
History of peripheral vascular disease	29 (2·9%)	15 (3·0%)	14 (2·8%)
History of previous malignancy	26 (2·6%)	18 (3·6%)	8 (1·6%)
Baseline medication			
Antiplatelets or anticoagulants	963 (98·2%)	479 (98·4%)	484 (98·0%)
Statins	858 (86·6%)	426 (84·9%)	432 (86·4%)
Other lipid-lowering drugs	231 (23·1%)	123 (24·5%)	108 (21·6%)
Angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers	834 (83·2%)	414 (82·5%)	420 (84·0%)
β-blockers	803 (80·1%)	404 (80·5%)	399 (79·8%)
Calcium antagonist	295 (29·4%)	145 (28·9%)	150 (30·0%)
Diuretics	526 (52·5%)	261 (52·0%)	265 (53·0%)
Insulin	114 (11·4%)	58 (11·6%)	56 (11·2%)
Oral antidiabetics	329 (32·8%)	160 (31·9%)	169 (33·8%)

Data are mean (SE) or n (%). We used unpaired t tests for quantitative variables and χ^2 for categorical variables. This table was adapted from Delgado-Lista et al[22] with permission from the American Heart Journal. *Including patients who self-reported as previously diagnosed with diabetes and those who met the American Diabetes Association diagnostic criteria of HbA_{1c} concentrations of 6·5% or more, fasting blood glucose of 126 mg/dL or more, or a 2 h blood glucose of 200 mg/dL or more after 75 g of oral glucose overload done at baseline.

Table 2: **Baseline characteristics**

recalculated over the original, based on a reduction of criteria applying as primary endpoint components to hardpoints and increasing the follow-up to 7 years, which was decided upon external advisory board suggestion in the third year, and according to the prespecified sample size revision made in the study protocol. Subsequently, two interim analyses were added to the two planned initially, and they were established for years 3, 4, 5, and 6 (O'Brien-Fleming, prespecified p values for the anticipated end of the study were 0·001, 0·004, 0·019, and 0·043, respectively). Power curves for the original assumptions of the number of events are in the appendix (p 20).

The analysis was done under the principle of intention-to-treat. All patients were included in the primary analysis. Treatment of patients who abandoned the dietary intervention was as follows: if the patient allowed follow-up by electronic health records, we treated the data as patients included in the study, scouting data from electronic health records until their seventh year from recruitment. If the patient denied permission to be followed up, we analysed the data until abandonment of the dietary intervention and censored the patient at that moment. Statistical comparisons were done using two-sided significance tests. The primary statistical comparison was made by log-rank analysis with Kaplan-Meier survival estimates and several Cox proportional hazards models were adjusted for the following covariates: model 1: age and sex; model 2: age, sex, family history of early coronary heart disease, and smoking; model 3: age, sex, family history of early cardiovascular disease, smoking, body-mass index (BMI), LDL cholesterol, diabetes, and hypertension; model 4: age,

sex, hypertension, LDL cholesterol (<100 mg/dL), BMI, smoking, statins (intensity), and diabetes; model 5: model 2 plus pharmacological treatments at baseline; model 6: model 4 plus changes in weight and physical activity during follow-up; and model 7: all covariates used in the different models and randomisation order. The significance level for all the analyses was α=0·05. Sensitivity analyses were done for these cases: primary endpoint excluding cases in the first month; cases in the first 6 months; patients with a mean adherence greater than 80% during the study; patients with an extended composite of a cardiovascular endpoint; and extended composite of heart events and randomisation order. SPSS (version 25.0) and R statistical software (version 3.6.1) were used for the statistical study. This study is registered with ClinicalTrials.gov, NCT00924937.

Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

From Oct 1, 2009, to Feb 28, 2012, 1850 patients were screened for eligibility and 1002 were included in the CORDIOPREV study. 500 (49·9%) of 1002 patients were assigned to the low-fat diet group and 502 (50·1%) to the Mediterranean diet group.[22] The population was mostly men (82·5%), and the average age was 59·5 years (table 2). By the end of the study, on July 1, 2018, a total of 132 (13·8%) of 1002 participants had abandoned the dietary intervention (figure 1). These cases were higher in the low-fat group (86 [17·2%]) than in the Mediterranean diet group (46 [9·2%]; p=0·0002; appendix p 21). 112 (84·8%) of 132 participants who left the dietary intervention were followed up by electronic health records or phone calls after giving their permission. 14 (2·8%) of 500 participants in the low-fat diet and six (1·2%) of 502 in the Mediterranean diet abandoned the dietary intervention and denied their permission to be followed up by electronic health records or phone calls, and therefore were censored at that point. The median follow-up of the whole population of the study (n=1002) was 2557 days (IQR 173).

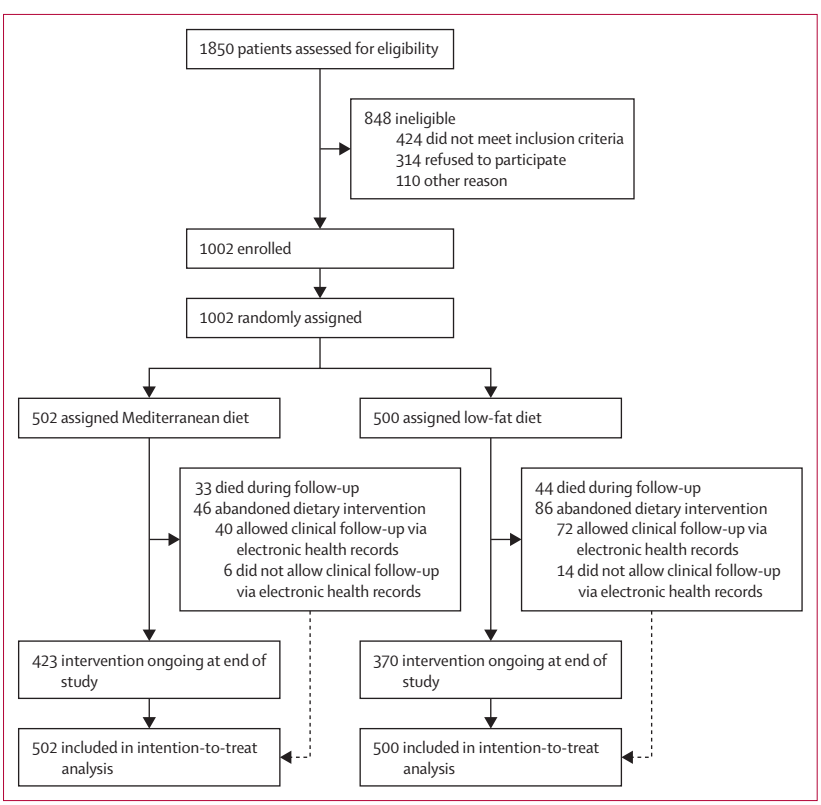

Figure 1: **Trial profile**

Baseline adherence of the whole population to the Mediterranean diet was 8·78 on the 0–14 scale[25,26] (14 being the best possible adherence rate for the Mediterranean scale) and 3·81 on the 0–9 scale for the low-fat diet (9 being the best possible adherence rate for the low-fat diet score).[22] Participants adhered to the group they were randomly assigned to and maintained this adherence during the study. Most of the dietary change happened during the first year, with increases of 1·99 points in the Mediterranean diet group and 2·53 points in the low-fat group.[27] Data for all 7 years are in appendix (pp 22–23).

At the end of the study, patients in the Mediterranean diet group had significantly increased their intake of total fat (from 37·4% to 40·5% of the total energy intake), monounsaturated fatty acids (from 18·4% to 21·4% of the total energy intake), and polyunsaturated fatty acids (from 6·4% to 7·4% of the total energy intake), which was related to higher intakes of extra-virgin olive oil (from 31 g to 48 g per day), nuts (from 2·1 to 3·9 servings per week), and oily fish (from 2·8 to 3·2 servings per week) in comparison with those in the low-fat diet group. In addition, the Mediterranean diet group reduced their consumption of total carbohydrates (from 41·4% to 39·4% of the total energy intake) and saturated fatty acids (from 9·0% to 7·9% of the total energy intake). As expected, the low-fat diet group showed an increased intake of carbohydrates (from 41·7% to 45·5% of the total energy intake), mainly complex carbohydrates, and a decreased consumption of total fat (from 36·7% to 32·1% of the total energy intake), monounsaturated fatty acids (from 17·9% to 15·1% of the total energy intake), and saturated fatty acids (from 8·9% to 7·1% of the total energy intake). Both the Mediterranean and the low-fat diet groups increased their fibre intake (by 2·3 g per 1000 kcal *vs* 3·2 g per 1000 kcal) due to a higher intake of vegetables, fruits, and legumes. In addition, decreases in the intake of red or processed meats, sweet or carbonated beverages, and fat spreads were observed in the two intervention groups (appendix pp 24–31).

The different pre-established interim analyses did not reach the threshold to stop the study. In the seventh year,

a decision was made to stop the study after registering a total of 198 primary-outcome events: 87 (17·3%) in the Mediterranean diet group and 111 (22·2%) in the low-fat group. The unadjusted HR was 0·745 (95% CI 0·563–0·986). The crude rate per 1000 person-years was 28·1 (95% CI 27·9–28·3) for the Mediterranean diet group and 37·7 (37·5–37·9) for the low-fat diet group (log-rank p=0·039; figure 2A).

Table 3 shows the results of the multivariable adjusted Cox HRs. In all models, the Mediterranean diet was superior to the low-fat diet. HRs for the primary endpoint ranged from 0·719 to 0·753 in the different models. When evaluating the different components of the composite primary outcome, we did not find any significant statistical difference between diets. The specific number of events for each component was: non-fatal myocardial infarction (Mediterranean diet 19, low-fat 24, p=0·366); cardiovascular death (Mediterranean diet 11, low-fat 20, p=0·120); revascularisation (Mediterranean diet 64, low-fat 77, p=0·171); ischaemic stroke (Mediterranean diet 8, low-fat 15, p=0·123); and peripheral artery disease (Mediterranean diet 11, low-fat 17, p=0·223; appendix p 32).

We did different sensitivity analyses to test cases at the beginning of the study (cases in the first month and the first 6 months), with results similar to those of the primary analysis. In people with a high dietary adherence during the study (mean adherence ≥80% during the study, excluding time 0), the Mediterranean diet was superior to the low-fat diet (HR 0·602, 95% CI 0·385–0·941, p=0·026). In the evaluation of the extended composite of heart events (ie, myocardial infarction, unstable angina, cardiac arrest, and heart failure), the Mediterranean diet was superior to the low-fat diet (HR 0·745, 95% CI 0·580–0·956, p=0·021; appendix pp 33–34).

When evaluating patient subgroups, the Mediterranean diet was superior to the low-fat diet in patients without a family history of coronary heart disease, in those without hypertension at baseline, in those younger than age 70 years at study entry, and those with an LDL cholesterol lower than 100 mg/dL (appendix p 38). Lipid and glucose parameters did not change significantly during the study (appendix p 35). Three sensitivity analyses were done regarding missing data analysis, not varying for main results (appendix p 36).

In the male population (n=827), a total of 161 primary endpoints occurred: 67 (16·2%) in the Mediterranean diet group and 94 (22·8%) in the low-fat diet group. The log-rank p value for the primary endpoint was 0·013 favouring the Mediterranean diet group (figure 2b). Cox-regression multiadjusted HRs for the primary endpoint in the different adjusted models ranked from 0·669 (95% CI 0·489–0·915, p=0·012) to 0·684 (0·500–0·936, p=0·018) for the Mediterranean diet group versus the low-fat diet group (appendix p 39). We did not find statistical differences in women (appendix p 38). The use of medication and anthropometric measurements during the study are in the appendix (p 40).

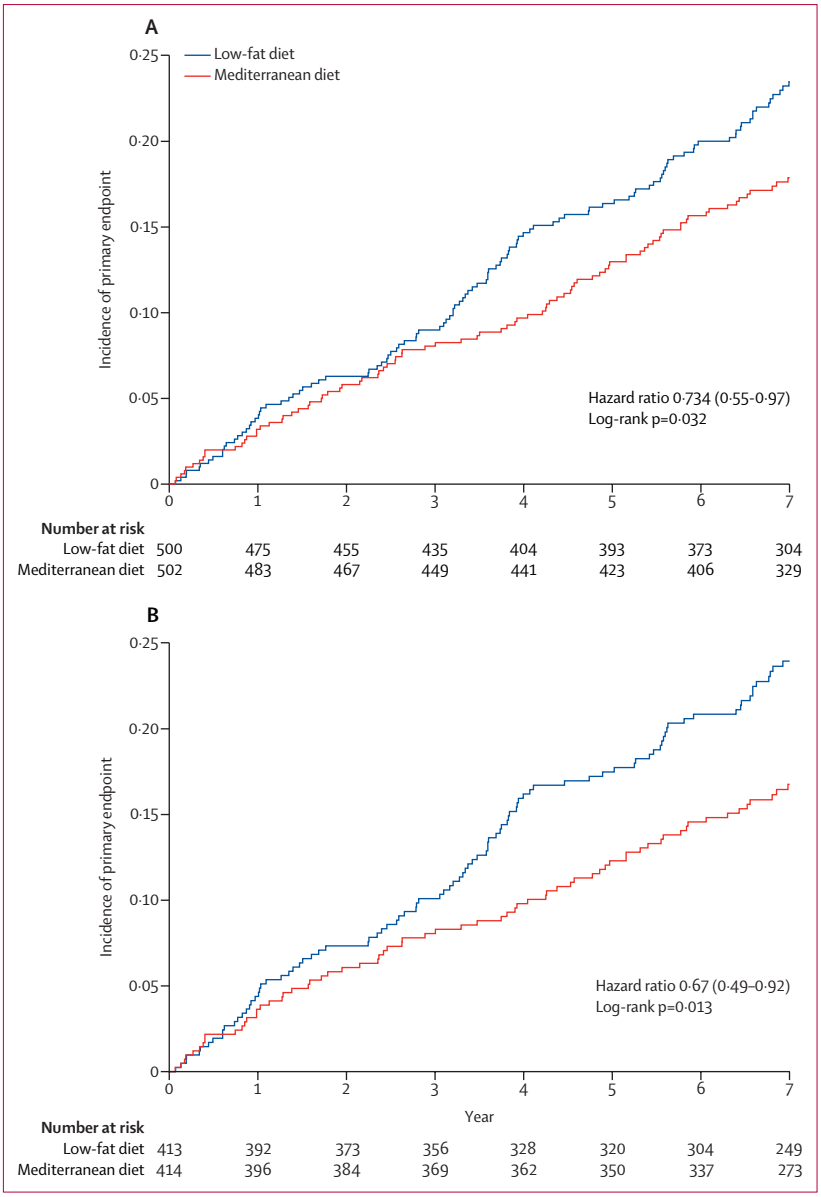

Figure 2: **Kaplan-Meier estimates of the incidence of the composite primary endpoints of myocardial infarction, revascularisation, ischaemic stroke, documented peripheral artery disease, and cardiovascular death events**
(A) Total study population of the CORDIOPREV study. (B) Male population (827 [82·5%] of 1002) of the CORDIOPREV study. Hazard ratios and confidence intervals are from the multivariable-adjusted Cox model (adjusted for diet, age, family history of coronary disease, and smoking).

Discussion

In our study, evaluating the effects of a comprehensive, high-intensity dietary intervention with a Mediterranean diet or a low-fat diet over 7 years of follow-up in 1002 patients with coronary heart disease, the Mediterranean diet was superior to the low-fat diet in preventing a major cardiovascular event, with a decrease of HR of 26%. In men, the Mediterranean diet showed an

	Mediterranean diet (n=502)	Low-fat diet (n=500)	p value
Unadjusted	0·745 (0·563–0·986)	1 (ref)	0·040
Multivariable adjusted for age and sex	0·738 (0·558–0·978)	1 (ref)	0·034
Multivariable adjusted for age, sex, family history of early coronary heart disease, and smoking	0·734 (0·555–0·974)	1 (ref)	0·032
Multivariable adjusted for age, sex, family history of early cardiovascular disease, smoking, BMI, LDL cholesterol, diabetes, and hypertension	0·753 (0·568–0·998)	1 (ref)	0·049
Multivariable adjusted for age, sex, hypertension, LDL cholesterol (<100 mg/dL), BMI, smoking, statins (intensity), and diabetes	0·747 (0·564–0·990)	1 (ref)	0·042
Multivariable adjusted for age, sex, family history of early coronary heart disease, smoking, and pharmacological treatments* at baseline	0·748 (0·562–0·997)	1 (ref)	0·048
Multivariable adjusted for age, sex, hypertension, LDL cholesterol (<100 mg/dL), BMI, smoking, statins (intensity), diabetes, and changes in weight and physical activity during follow-up	0·740 (0·558–0·982)	1 (ref)	0·035
Multivariable adjusted for all covariates used in the different models and randomisation order	0·719 (0·541–0·957)	1 (ref)	0·024

Data are hazard ratio (95% CI) or p value. All p values were calculated with Cox proportional-hazards models. The primary endpoint was a composite of myocardial infarction, revascularisation, ischaemic stroke, documented peripheral artery disease, and cardiovascular death events. BMI=body-mass index. *Statins, other lipid-lowering drugs, angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, β-blockers, calcium antagonists, diuretics, insulin, oral antidiabetics, antiplatelets, and anticoagulants.

Table 3: **Hazard ratios for the main outcome of the Mediterranean diet and low-fat diet groups**

even higher superiority than the low-fat diet, with a nearly 33% reduction in major cardiovascular events. The Mediterranean diet also showed higher efficacy in the total cohort (men and woman) without a family history of coronary heart disease, in participants with an LDL less than 100 mg/dL at baseline, in patients younger than age 70 years at study entry, and those with a dietary adherence of more than 80% to the assigned diet throughout the study.

The CORDIOPREV study was a secondary prevention trial. Therefore, the use of a control diet was not ethically appropriate. Consequently, the experimental approach investigated two high-intensity dietary interventions with equal intensity in both groups. All patients received comprehensive, tailored, and continuous dietary support, regardless of the study group. As our results show, the intervention effectively changed the dietary habits for both the Mediterranean and the low-fat diet groups resulting in significant dietary changes towards the assigned diet. Participants in the low-fat diet group managed to reduce their total fat intake from 36·7% to 32·1% (mean decrease of 12·5% of fat consumption), which was higher than that reported in similar intervention studies.[13] Because both intervention groups were submitted to a high-intensity dietary intervention with participants reaching and maintaining a high adherence to the two healthy dietary patterns during the study, on top of the optimal medical treatment, we had a lower-than-expected rate of cardiovascular events in our trial. Our results were collected in the setting of a controlled environment, where adherence to diets, meetings with dietitians, and positive reinforcement might have contributed significantly to our results. Therefore, our results should be extrapolated with caution to other environments.

Our study did not find differences in glucose or main lipids between diets at the beginning or at the end of the dietary intervention. A Mediterranean diet has been associated with an improvement in lipids profile and glucose when compared with diets rich in saturated fats. However, this improvement has not been so uniform when compared with low-fat diets, primarily when an adequate fibre intake has been provided and complex carbohydrates were the main source of energy. Also, the fact that these patients were in secondary prevention and mostly taking hypolipidaemic drugs (mostly statins) might have influenced the differential effects on lipids and glucose of both groups of dietary intervention.

To our knowledge, this study is the most extensive to date evaluating the effects of a Mediterranean diet and a low-fat diet in the prevention of recurrent cardiovascular events in the context of two high-intensity dietary interventions. It is important to highlight that the Mediterranean diet used in the Lyon Diet Heart Study, for example, was supplemented with canola oil, which is not a traditional source of fat in the Mediterranean region. Moreover, the comparator was a "prudent Western-type diet" and not a healthy comparator.[28] A 2019 Cochrane report evaluated current knowledge about the effects of the Mediterranean diet on primary and secondary prevention.[29] The authors concluded that, "There is a paucity of evidence for secondary prevention. The ongoing studies might provide more certainty in the future".[29] Accumulated data included in the Cochrane report were from 605 patients at 4 years for the Mediterranean diet versus usual care, and 101 patients during 2 years for the Mediterranean diet versus an active group, compared with 1002 patients from the CORDIOPREV study on the Mediterranean diet versus the low-fat diet for 7 years. Another review analysing the effect of the Mediterranean diet[30] highlights the need for new data on secondary prevention, as the only two significant existing studies were either too short[28] or show some concerns.[31]

In our study, the primary endpoint occurred in 19·8% of the population, and death occurred in less than 8% of participants. In comparison, a retrospective study evaluating the cardiovascular prognosis of coronary patients in our setting, and in the same timeframe of the CORDIOPREV study, reported a 20% mortality after 6 years of follow-up, which was more than double the percentage of deaths in the CORDIOPREV study.[32] Similarly, other large studies evaluating the efficacy of different drugs in this type of patient reported higher major cardiovascular event rates than our population, both in the active and the placebo groups of these studies.[33,34] The fact that primary endpoint rates were lower than

expected might support the hypothesis that the two diets had high efficacy in preventing cardiovascular recurrences and support the previous results of studies with low-fat diet versus control diets,[3–10] or with the Mediterranean diet in participants at high risk in primary prevention.[13]

Our study found that the superiority of the Mediterranean diet was higher in the male participants, suggesting that either there was not enough power in the female group or that sex is a factor in the dietary response. In this sense, our study was designed to represent the population with ischaemic heart disease and all patients who met the recruitment criteria were included, regardless of sex. Future studies should be created with sufficient power to unveil specific sex-related effects in women. Although other subgroup analyses also showed differences in the outcomes between diets, these findings were not primary endpoints of the study and should be taken as hypothesis-generating results.

Our study has limitations. First, this study included people with established coronary disease and, thus, the generalisability of our findings to other patient groups should be made with caution. Additionally, the study was done in a Mediterranean country with a higher acceptance for the Mediterranean lifestyle intervention. However, the low-fat diet study group was also well accepted by participants. The high acceptance of the Mediterranean diet in non-Mediterranean countries has been repeatedly reported;[35] therefore, our results should be generalised with caution to other geographical areas.

Our study also had some remarkable characteristics. First, the length of the study, which was challenging in itself, and even more so in a high-intensity dietary intervention. Second, the strict uniformity in the comprehensive characterisation, the medical treatment, and the dietary management of the cohort. This was done by planning the study as a single-centre study, which allowed the standardised high-intensity strategy, the homogenised and standardised care, and the thorough characterisation of the population. Finally, we were able to maintain follow-up through electronic medical records for 112 (85%) of 132 patients who abandoned the dietary intervention during the 7 years of the study, increasing the validity of the results of the intention-to-treat analysis. In summary, the CORDIOPREV study reports that a Mediterranean diet is superior to a low-fat diet in preventing major cardiovascular events in secondary prevention of cardiovascular disease.

Contributors

JD-L, FL-S, FP-J, PP-M, and JL-M contributed to the study conceptualisation. JD-L, JFA-D, JDT-P, EMY-S, OAR-Z, AC, FR-C, and JL-M were responsible for the data curation. JD-L, JFA-D, GMQ-N, and JL-M developed the formal analysis. JD-L, EMY-S, OAR-Z, AC, FL-S, FP-J, PP-M, and JL-M participated in funding acquisition. JD-L, JFA-D, GMQ-N, FF, AG-R, AMO-M, AIG-R, AIP-C, EMY-S, OAR-Z, AC, FP-J, PP-M, and JL-M participated in the clinical trial. JD-L, JFA-D, JDT-P, EMY-S, AC, OAR-Z, FP-J, PP-M, and JL-M were responsible for the methodology. JD-L, EMY-S, OAR-Z, AC, and JL-M handled the project administration. FR-C was responsible for resources. JD-L and JFA-D took responsibility for software. JD-L, PP-M, and JL-M supervised the entire project. JD-L, JFA-D, GMQ-N, EMY-S, AC, OAR-Z, FR-C, FP-J, PP-M, and JL-M took responsibility for validation process. EMY-S, OAR-Z, and AC developed the visualisation process. JD-L, JFA-D, and JDT-P were involved in writing the original draft. JD-L, JFA-D, LB, JMO, FP-J, PP-M, and JL-M were involved in writing, review, editing. JD-L, JFA-D, and JL-M have accessed and verified the data. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Declaration of interests

JD-L reports a research grant from Instituto de Salud Carlos III (PI13/00023) and has received fees for lectures and educational activities from Novo-Nordisk, Amgen, Laboratorios Dr Esteve, Ferrer, Servier, Mylan–Viatrix, Instituto Cervantes, and the Spanish Society of Internal Medicine, all unrelated to this work. JFA-D reports research grants from Servicio Andaluz de Salud (B-0009-2017) and Insituto de Salud Carlos III (CM12/00202), and has received fees for lectures and educational activities from Bayer, Grunenthal Pharma, Laboratorios Dr Esteve, Ferrer, and Boehringer Ingelheim, all unrelated to this work. JDT-P has received fees for lectures and educational activities from Laboratorios Dr Esteve, Amgen, Sanofi, and the Spanish Society of Internal Medicine, all unrelated to this work, and is a board member of the Andalusian Society of Internal Medicine. FF has received fees for lectures and educational activities from Laboratorios Dr Esteve, Mylan, Novartis, Menarini, Servier, Novo-Nordisk, and Amgen, all unrelated to this work. AG-R reports a research grant from Consejería de Salud Junta de Andalucía (PI-0206-2013) and has received fees for lectures and educational activities from Laboratorios Dr Esteve and Instituto Cervantes, all unrelated to this work. EMY-S reports grants from Consejería de Salud-Junta de Andalucía (PC-0283-2017), Carlos III Health Institute (PI18/01822), and Servicio Andaluz de Salud-Junta de Andalucia (Nicolas Monardes Programme Contract C1-0005-2019). OAR-Z reports research grants from Ministerio de Ciencia e Innovacion (PI15/00733), Fundación para la investigación Biomédica de Córdoba (PI-0170-2018-FIB), and de Instituto de salud Carlos III (Miguel Servet Program CP19/00142). AC reports research grants from Instituto de Salud Carlos III (CP14/00114, PI19/00299, and DTS19/00007) and Ministerio de Economía y Competitividad (AGL2015-67896-P). FL-S has received fees for lectures and educational activities from Pfizer, Novartis, Mylan–Viatris, and Boehringer Ingelheim, all unrelated to this work. LB reports a research grant from AstraZeneca, has served on scientific advisory boards of Sanofi, Bayer, and AstraZeneca, has received speaker fees from Lilly, MSD–Boehringer, and AstraZeneca, and founded the spin-offs for Glycardial Diagnostics and Ivastatin Therapeutics S, all unrelated to this work. JMO has received research funding from the US Department of Agriculture on personalised nutrition, and from Archer Daniels Midland on probiotics, has served on the scientific advisory board or as a consultant for Nutrigenomix, the Predict Study, General Nutrition Centres, Weight Watchers, Metagenics, and Reckitt Group, all unrelated to this work. FP-J reports research grants from Instituto de Salud Carlos III (PI10/02412 and PI13/00619) and has received fees for lectures and educational activities from Mylan and Instituto Cervantes, unrelated to this work. PP-M reports research grants from Instituto de Salud Carlos III (PI13/00185, PI10/01041, and PI16/01777) and Consejería Salud Junta de Andalucía (PI058/10), and has received fees for lectures and educational activities for Novo-Nordisk, Boehringer Ingelheim, Amgen, Laboratorios Dr Esteve, MSD, Ferrer, Menarini, Servier, Mylan–Viatrix, Instituto Cervantes, and the Spanish Society of Internal Medicine, all unrelated to this work. JL-M reports research grants from Instituto de Salud Carlos III (PIE14/00005 and PIE14/00005), Ministerio de Ciencia e Innovación (PID2019-104362RB-I00, AGL2009-122270, PCIN-2016-084, and AGL2012/39615), Consejería de Salud Junta de Andalucia (PI0193/09), Ministerio de Ciencia e Innovación (AGL2015-67896-P), and Consejería de Economía, Innovación, Ciencia y Empleo (P20_00256 and CVI-7450), has received fees for lectures and educational activities from Novo-Nordisk, Sanofi, Amgen, Laboratorios Dr Esteve, MSD, and Instituto Cervantes, and has received consulting fees from Amgen and Sanofi, all unrelated to this work. All other authors declare no competing interests.

Data sharing

Collaborations with the Cordioprev Study are open to Biomedical Institutions, always after an accepted proposal for a scientific work. Depending on the nature of the collaboration, electronic data, hard copy data, or biological samples should be provided. All collaborations will be made after a collaboration agreement. Terms of the collaboration agreement will be specific for each collaboration, and the extent of the shared documentation (ie, deidentified participant data, data dictionary, biological samples, hard copy, or other specified data sets) will be also specifically set on the light of each work.

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References

1 Mach F, Baigent C, Catapano AL, et al. 2019 ESC/EAS guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk. *Atherosclerosis* 2019; **290:** 140–205.
2 Mach F, Baigent C, Catapano AL, et al. 2019 ESC/EAS guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk. *Eur Heart J* 2020; **41:** 111–88.
3 Burr ML, Fehily AM, Gilbert JF, et al. Effects of changes in fat, fish, and fibre intakes on death and myocardial reinfarction: diet and reinfarction trial (DART). *Lancet* 1989; **2:** 757–61.
4 de Lorgeril M, Renaud S, Mamelle N, et al. Mediterranean alpha-linolenic acid-rich diet in secondary prevention of coronary heart disease. *Lancet* 1994; **343:** 1454–59.
5 Hjermann I, Velve Byre K, Holme I, Leren P. Effect of diet and smoking intervention on the incidence of coronary heart disease. Report from the Oslo Study Group of a randomised trial in healthy men. *Lancet* 1981; **2:** 1303–10.
6 Leren P. The Oslo diet-heart study. Eleven-year report. *Circulation* 1970; **42:** 935–42.
7 Ornish D, Brown SE, Scherwitz LW, et al. Can lifestyle changes reverse coronary heart disease? The Lifestyle Heart Trial. *Lancet* 1990; **336:** 129–33.
8 Turpeinen O, Karvonen MJ, Pekkarinen M, Miettinen M, Elosuo R, Paavilainen E. Dietary prevention of coronary heart disease: the Finnish Mental Hospital Study. *Int J Epidemiol* 1979; **8:** 99–118.
9 Watts GF, Jackson P, Mandalia S, et al. Nutrient intake and progression of coronary artery disease. *Am J Cardiol* 1994; **73:** 328–32.
10 Watts GF, Lewis B, Brunt JN, et al. Effects on coronary artery disease of lipid-lowering diet, or diet plus cholestyramine, in the St Thomas' Atherosclerosis Regression Study (STARS). *Lancet* 1992; **339:** 563–69.
11 Grundy SM, Bilheimer D, Chait A, et al. Summary of the second report of the National Cholesterol Education Program (NCEP) Expert Panel on detection, evaluation, and treatment of high blood cholesterol in adults (Adult Treatment Panel II). *JAMA* 1993; **269:** 3015–23.
12 National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) final report. *Circulation* 2002; **106:** 3143–421.
13 Estruch R, Ros E, Salas-Salvadó J, et al. Primary prevention of cardiovascular disease with a Mediterranean diet supplemented with extra-virgin olive oil or nuts. *N Engl J Med* 2018; **378:** e34.
14 Babio N, Bulló M, Basora J, et al. Adherence to the Mediterranean diet and risk of metabolic syndrome and its components. *Nutr Metab Cardiovasc Dis* 2009; **19:** 563–70.
15 Díez-Espino J, Buil-Cosiales P, Serrano-Martínez M, Toledo E, Salas-Salvadó J, Martínez-González MA. Adherence to the Mediterranean diet in patients with type 2 diabetes mellitus and HbA1c level. *Ann Nutr Metab* 2011; **58:** 74–78.
16 Estruch R. Anti-inflammatory effects of the Mediterranean diet: the experience of the PREDIMED study. *Proc Nutr Soc* 2010; **69:** 333–40.
17 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.
18 Martínez-González MA, Corella D, Salas-Salvadó J, et al. Cohort profile: design and methods of the PREDIMED study. *Int J Epidemiol* 2012; **41:** 377–85.
19 Salas-Salvadó J, Bulló M, Babio N, et al. Reduction in the incidence of type 2 diabetes with the Mediterranean diet: results of the PREDIMED-Reus nutrition intervention randomized trial. *Diabetes Care* 2011; **34:** 14–19.
20 Sofi F, Cesari F, Abbate R, Gensini GF, Casini A. Adherence to Mediterranean diet and health status: meta-analysis. *BMJ* 2008; **337:** a1344.
21 Sofi F, Macchi C, Abbate R, Gensini GF, Casini A. Mediterranean diet and health status: an updated meta-analysis and a proposal for a literature-based adherence score. *Public Health Nutr* 2014; **17:** 2769–82.
22 Delgado-Lista J, Perez-Martinez P, Garcia-Rios A, et al. 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. *Am Heart J* 2016; **177:** 42–50.

23 Zazpe I, Sanchez-Tainta A, Estruch R, et al. A large randomized individual and group intervention conducted by registered dietitians increased adherence to Mediterranean-type diets: the PREDIMED study. *J Am Diet Assoc* 2008; **108:** 1134–44.

24 Lara J, Hobbs N, Moynihan PJ, et al. Effectiveness of dietary interventions among adults of retirement age: a systematic review and meta-analysis of randomized controlled trials. *BMC Med* 2014; **12:** 60.

25 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.

26 Martínez-González MA, Fernández-Jarne E, Serrano-Martínez M, Wright M, Gomez-Gracia E. Development of a short dietary intake questionnaire for the quantitative estimation of adherence to a cardioprotective Mediterranean diet. *Eur J Clin Nutr* 2004; **58:** 1550–52.

27 Quintana-Navarro GM, Alcala-Diaz JF, Lopez-Moreno J, et al. Long-term dietary adherence and changes in dietary intake in coronary patients after intervention with a Mediterranean diet or a low-fat diet: the CORDIOPREV randomized trial. *Eur J Nutr* 2020; **59:** 2099–110.

28 de Lorgeril M, Salen P, Martin JL, Monjaud I, Delaye J, Mamelle N. Mediterranean diet, traditional risk factors, and the rate of cardiovascular complications after myocardial infarction: final report of the Lyon Diet Heart Study. *Circulation* 1999; **99:** 779–85.

29 Rees K, Takeda A, Martin N, et al. Mediterranean-style diet for the primary and secondary prevention of cardiovascular disease. *Cochrane Database Syst Rev* 2019; **3:** CD009825.

30 Martínez-González MA, Gea A, Ruiz-Canela M. The Mediterranean diet and cardiovascular health. *Circ Res* 2019; **124:** 779–98.

31 Singh RB, Dubnov G, Niaz MA, et al. Effect of an Indo-Mediterranean diet on progression of coronary artery disease in high risk patients (Indo-Mediterranean Diet Heart Study): a randomised single-blind trial. *Lancet* 2002; **360:** 1455–61.

32 Sánchez Fernández JJ, Ruiz Ortiz M, Ogayar Luque C, et al. Long-term survival in a Spanish population with stable ischemic heart disease. *Rev Esp Cardiol (Engl Ed)* 2019; **72:** 827–34.

33 Cannon CP, Blazing MA, Giugliano RP, et al. Ezetimibe added to statin therapy after acute coronary syndromes. *N Engl J Med* 2015; **372:** 2387–97.

34 Sabatine MS, Giugliano RP, Keech AC, et al. Evolocumab and clinical outcomes in patients with cardiovascular disease. *N Engl J Med* 2017; **376:** 1713–22.

35 Murphy KJ, Parletta N. Implementing a Mediterranean-style diet outside the Mediterranean region. *Curr Atheroscler Rep* 2018; **20:** 28.