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RESEARCH ARTICLE

Mediterranean diet and risk of heart failure: results from the PREDIMED randomized controlled trial

**Angeliki Papadaki[1], Miguel Ángel Martínez-González[2,3,4], Angel Alonso-Gómez[3,5], Javier Rekondo[3,5], Jordi Salas-Salvadó[3,6], Dolores Corella[3,7], Emilio Ros[3,8], Montse Fitó[3,9], Ramon Estruch[3,10], José Lapetra[3,11], Antonio García-Rodriguez[12], Miquel Fiol[3,13], Lluís Serra-Majem[3,14], Xavier Pintó[3,15], Miguel Ruiz-Canela[2,3], Monica Bulló[3,6], Mercè Serra-Mir[3,8], Jose V. Sorlí[3,7], and Fernando Arós[3,5]*

[1]Centre for Exercise, Nutrition and Health Sciences, School for Policy Studies, University of Bristol, Bristol, UK; [2]University of Navarra, Department of Preventive Medicine and Public Health, Faculty of Medicine, IdiSNA, Pamplona, Spain; [3]CIBER Fisiopatología de la Obesidad y Nutrición (CIBEROBN), Instituto de Salud Carlos III (ISCIII), Madrid, Spain; [4]Department of Nutrition, Harvard TH Chan School of Public Health, Boston, MA, USA; [5]Department of Cardiology, University Hospital Araba, Vitoria, Spain; [6]Human Nutrition Unit, Faculty of Medicine and Health Sciences, IISPV, Rovira i Virgili University, Reus, Spain; [7]Department of Preventive Medicine, University of Valencia, Valencia, Spain; [8]Lipid Clinic, Endocrinology and Nutrition Service, Institut d'Investigacions Biomèdiques August Pi Sunyer (IDIBAPS), Hospital Clinic, University of Barcelona, Barcelona, Spain; [9]Cardiovascular Risk and Nutrition (Regicor Study Group), Hospital del Mar Medical Research Institute (IMIM), Barcelona, Spain; [10]Department of Internal Medicine, IDIBAPS, Hospital Clinic, University of Barcelona, Barcelona, Spain; [11]Department of Family Medicine, Research Unit, Distrito Sanitario Atención Primaria Sevilla, Sevilla, Spain; [12]Department of Preventive Medicine, University of Malaga, Malaga, Spain; [13]Palma Institut of Health Research (IdISPa), Hospital Son Espases, Palma de Mallorca, Spain; [14]Research Institute of Biomedical and Health Sciences, University of Las Palmas de Gran Canaria, Las Palmas, Spain; and [15]Internal Medicine Department, Hospital Universitari de Bellvitge-IDIBELL, Universidad de Barcelona, Barcelona, Spain

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Aims The aim of this study was to evaluate the effect of the Mediterranean diet (MedDiet) on the incidence of heart failure (HF), a pre-specified secondary outcome in the PREDIMED (PREvención con DIeta MEDiterránea) primary nutrition-intervention prevention trial.

Methods and results Participants at high risk of cardiovascular disease were randomly assigned to one of three diets: MedDiet supplemented with extra-virgin olive oil (EVOO), MedDiet supplemented with nuts, or a low-fat control diet. Incident HF was ascertained by a Committee for Adjudication of events blinded to group allocation. Among 7403 participants without prevalent HF followed for a median of 4.8 years, we observed 29 new HF cases in the MedDiet with EVOO group, 33 in the MedDiet with nuts group, and 32 in the control group. No significant association with HF incidence was found for the MedDiet with EVOO and MedDiet with nuts, compared with the control group [hazard ratio (HR) 0.68; 95% confidence interval (CI) 0.41–1.13, and HR 0.92; 95% CI 0.56–1.49, respectively].

Conclusion In this sample of adults at high cardiovascular risk, the MedDiet did not result in lower HF incidence. However, this pre-specified secondary analysis may have been underpowered to provide valid conclusions. Further randomized controlled trials with HF as a primary outcome are needed to better assess the effect of the MedDiet on HF risk. **Trial registration:** ISRCTN35739639.

Keywords Mediterranean diet • Heart failure • Cardiovascular disease • PREDIMED study

*Corresponding author. Department of Cardiology, University Hospital Araba, c/ José Achotegui s/n. 01009 Vitoria-Gasteiz, Spain. Tel: +34 945007304, Fax: +34 945007359, Email: aborau@secardiologia.es

Introduction

The prevalence of heart failure (HF) has been increasing during the last decades.[1] Heart failure is also the leading cause of hospitalization in older adults and it is associated with an enormous burden of disability and healthcare costs.[2] This emerging epidemic represents an insurmountable public health challenge that can compromise the sustainability of national health systems.[1,2]

Primary prevention of HF should be a priority.[3] Hypertension, obesity, and type 2 diabetes (T2D)[4] are strong risk factors not only for HF, but also for stroke, myocardial infarction (MI), atrial fibrillation (AF),[5] and peripheral arterial disease.[6] Multimorbidity is common in HF, and higher cardiovascular disease (CVD) mortality is observed when several of these CVD manifestations co-exist.[7] Therefore, effective preventive interventions against MI or stroke seem also likely to reduce HF.

In this context, there is increasing evidence that changes in overall dietary patterns, and, specifically, interventions using the traditional Mediterranean diet (MedDiet), are a useful tool in CVD prevention.[8,9] Two cohort studies reported a lower HF risk associated with better adherence to MedDiet.[10,11] However, no randomized controlled trial to date has examined the effect of the MedDiet on the primary prevention of HF. One-year results from the PREvención con DIeta MEDiterránea (PREDIMED) randomized controlled trial showed that the MedDiet favourably affected HF biomarkers compared with a low-fat diet.[12] In PREDIMED, the MedDiet also favourably influenced major HF risk factors, such as T2D,[13] obesity,[14] and hypertension.[15] The aim of this study was to investigate with a randomized design the effect of the MedDiet on HF incidence, a protocol-specified secondary outcome of the PREDIMED trial.[16] We hypothesized that the MedDiet would result in lower HF incidence, compared with a control, low-fat, diet.

Methods

Study design

The detailed methods of this trial (www.predimed.es) have been described.[9,16] In brief, PREDIMED was a large, parallel-group, randomized controlled trial conducted in 11 centres in Spain, designed to examine the effect of the MedDiet on primary CVD prevention. The trial was registered (ISRCTN35739639) and conformed with the principles outlined in the Declaration of Helsinki. The protocol was approved by the Institutional Review Boards of participating centres, and all participants provided written informed consent to take part in the study. Participants were recruited between October 2003 and March 2009 from Spanish primary care centres. The study was planned to last 6 years, but was stopped at 4.8 years of median follow-up (December 2010), because of evidence of early benefit.[9] Yearly follow-up measurements continued until October 2012.

Participants and randomization

Participants were men (55–80 years) and women (60–80 years) who were free of CVD at enrolment but who were at high CVD risk, as defined by the presence of T2D and/or ≥3 CVD risk factors, namely smoking, hypertension, elevated LDL-cholesterol, low HDL-cholesterol, overweight/obesity (body mass index ≥25 kg/m^2), or family history of premature coronary heart disease. Detailed inclusion and exclusion criteria are provided elsewhere.[9,16]

Participants were randomly assigned to one of three dietary intervention groups (1:1:1 ratio): (i) MedDiet supplemented with extra-virgin olive oil (EVOO); (ii) MedDiet supplemented with mixed nuts; or (iii) low-fat control diet. Randomization was conducted centrally using a computer-generated random-number sequence. All clinical investigators, laboratory technicians, and members of Committees assessing clinical events were blinded to intervention allocation.

Intervention description

The PREDIMED dietary intervention has been detailed elsewhere.[9,16] Briefly, all participants received repeated and continuous advice from trained dietitians to follow their allocated diets (during both individual and group sessions, separately for each group) on a quarterly basis.[9,16] The diets were *ad libitum* regarding total energy intake. Physical activity was assessed but not promoted.

Participants assigned to the MedDiet + EVOO group were provided with 1 L of EVOO/week (including family needs), whereas those in the MedDiet + nuts group received 30 g/day of mixed nuts. These supplementary foods were given for free in order to facilitate adherence. Participants in the control group received small non-food gifts.

Measurements

All measurements were carried out at baseline and yearly, and comprised a 47-item questionnaire assessing socio-demographic characteristics, medical conditions, medication use, and lifestyle habits, a 14-item questionnaire assessing MedDiet adherence,[17] a 137-item food frequency questionnaire, used to assess nutrient and energy intake,[18] and the Spanish version of the Minnesota Leisure-Time Physical Activity questionnaire.[9,16] Trained nurses collected fasting blood samples and measured blood pressure, body weight, height, and waist circumference to calculate the waist-to-height ratio (WtHR).

Clinical endpoints

The primary outcome for the present study was HF incidence, a protocol-specified secondary outcome of the PREDIMED trial.[16] All HF events were evaluated according to the 2005 (time of study design) guidelines on the diagnosis and treatment of acute and chronic HF of the European Society of Cardiology.[19,20] The diagnostic criteria for ascertaining HF events are presented in the Supplementary material online, *Appendix S1*.

All endpoints of the PREDIMED trial, including HF, were identified prospectively through contacts with participants and family physicians, annual reviews of all participants' outpatient and inpatient medical records, and linkage to the National Death Index, and were analysed by events. If an HF diagnosis was an explicit medical diagnosis, all relevant documentation, including clinical records of hospital discharge, outpatient clinics, and family physicians' records, was sent to the Clinical Adjudication Committee. This documentation was independently reviewed and blindly evaluated by two cardiologists. If there was disagreement regarding the acceptance or rejection of an event, a third cardiologist (the Committee's Chair) intervened until agreement was reached (in some cases, more information was requested to complete the ascertainment). All members of the Clinical Adjudication Committee and the adjudication process were blinded to group allocation.

This paper reports on HF events that occurred during the trial's active intervention (October 2003–July 2010).

Statistical analyses

Cox regression models with robust variance estimators were fitted to estimate hazard ratios (HRs) and 95% confidence intervals (CIs) for the incidence of HF by group assignment (using the control group as reference).

The assumption of proportional hazards was tested using time-dependent covariates. We stratified all models by centre and baseline T2D. A crude model was followed by an age- and sex-adjusted model. We further adjusted for pre-randomization values of education, smoking, WtHR, physical activity, dyspnoea, and non-AF arrhythmias (model 1), and, additionally for history of hypertension, history of dyslipidaemia, family history of premature coronary heart disease, and baseline prevalence of AF (model 2), and additionally for total energy intake (model 3). We evaluated potential effect modification by sex, age, CVD risk factors, WtHR, and baseline MedDiet adherence.

Follow-up time was the interval between randomization and diagnosis, death, or the last visit, whichever occurred first. We defined event rates as the number of participants diagnosed with an event over the follow-up time in each group. All analyses were performed on an intention-to-treat basis.

Results

After excluding 44 participants with prevalent HF at baseline, 7403 were included in the present analyses (Supplementary material online, *Figure S1*). The three groups were well balanced regarding baseline characteristics (*Table 1*).

Ninety-four participants developed HF during the trial period with active intervention (*Table 2*). Of these, 19 (20.2%) had preceding ischaemic heart disease and 58 (61.7%) were hospitalized. Data on receipt of treatment following HF diagnosis were available for 79 participants, who received ACE inhibitors/ARBs (74.7%), diuretics (65.8%), beta-blockers (26.6%), calcium channel blockers (20%), antiplatelet therapy (29.1%), and oral anticoagulants (25%). Ventricular function information after HF diagnosis (as assessed by echocardiography) was available for 80 participants, who presented with preserved EF (>45–50%) (60%) and reduced EF (40%). Twenty-one (out of 94) participants (22.3%) died by 2012 (end of extended follow-up).

The baseline characteristics of participants who developed HF during the active intervention period and those who did not are shown in the Supplementary material online, *Table S1*. Those who developed HF were generally older and had higher WtHR and BNP levels. The unadjusted HRs did not indicate significant associations for the MedDiet + EVOO (HR 0.68; 95% CI 0.41–1.13) and MedDiet + nuts (HR 0.92; 95% CI 0.56–1.49) compared with the control group. Multivariate analyses did not alter these results (*Table 2*; *Figure 1*). There was no evidence of a significant association for the two MedDiets combined, compared with the control group, in the unadjusted (HR 0.79; 95% CI 0.51–1.22) and multivariable-adjusted models (Supplementary material online, *Table S2*).

In subgroup analyses (Supplementary material online, *Table S3*), the effect of the MedDiet on reducing HF, though statistically not significant, was stronger among participants without T2D (*P* for interaction = 0.010). A higher baseline WtHR was associated with a risk reduction related to the MedDiet + nuts and higher baseline MedDiet adherence was associated with an inverse association of MedDiet + EVOO with HF. In both cases, the *P* for interaction was significant, but the effect within subgroups was not.

Overall, 141 HF events occurred during the trial period with active intervention and extended follow-up (Supplementary material online, *Table S4*). The unadjusted HRs were 0.71 (95% CI 0.47–1.07) for the MedDiet + EVOO and 0.99 (95% CI 0.67–1.48) for the MedDiet + nuts compared with the control diet. Adjusting for different covariates (Supplementary material online, *Table S4*) and examining the combined effect of the two MedDiet groups, compared with the control group (Supplementary material online, *Table S2*), did not alter these findings.

Discussion

This secondary analysis of a pre-specified outcome of the PREDIMED trial showed no evidence of a significant effect on HF incidence for the intervention using a MedDiet + EVOO or a MedDiet with nuts compared with the control diet. Our hypothesis of a beneficial effect of the MedDiet on HF incidence in this sample of high CVD risk individuals was therefore not confirmed for this secondary endpoint of the trial. However, the explanation for the non-significant results for HF might stem from the relatively small number of observed HF events ($n = 94$) and it should be given the interpretation that our findings are inconclusive.

To our knowledge, PREDIMED is the first randomized controlled trial in which the potential effect of an intervention with the traditional MedDiet on primary HF prevention could be explored (as HF was a secondary, and not a primary outcome of PREDIMED). An earlier report of the PREDIMED trial showed that the intervention with the MedDiet reduced the levels of HF biomarkers, including NT-proBNP, oxidized LDL-cholesterol, and lipoprotein(a).[12] Despite this beneficial effect on HF biomarkers,[12] as well as on HF risk factors such as hypertension,[15] T2D,[13] and obesity,[14] we may have had here limited statistical power to demonstrate an effect on the incidence of new-onset clinical cases of HF considered alone. Nevertheless, the finding that HF incidence was consistently lower in the point estimates during the trial for the MedDiet + EVOO, regardless of the factors we adjusted for (risk reduction range, 22–32%), generates a hypothesis for future randomized controlled trials to examine the potential effect of the traditional MedDiet on HF as a primary outcome, in a sufficiently powered study.

Two recent prospective cohorts with up to 10 years of follow-up reported inverse associations of the MedDiet with HF incidence and mortality (1648 events) in men[11] and HF incidence (1269 events) in women.[10] An exploratory meta-analysis of prospective cohort studies[21,22] conducted for the purposes of the current study suggested that, according to previous evidence, for each two additional points of MedDiet adherence (0 to 9 score), the relative risk of HF decreased by 8% (95% CI 0.90–0.95, without evidence

Table 1 Baseline characteristics of participants by intervention group

	Mediterranean diet + EVOO (n = 2527)	Mediterranean diet + nuts (n = 2444)	Control diet (n = 2432)
Age, years	67.0 (6.2)	66.7 (6.1)	67.3 (6.3)
Sex, female, *n* (%)	1484 (58.7)	1319 (54.0)	1455 (59.8)
Smoking, *n* (%)			
Current	346 (13.7)	354 (14.5)	338 (13.9)
Education, *n* (%)			
University or higher	186 (7.4)	201 (8.2)	144 (5.9)
Secondary school	370 (14.6)	412 (16.9)	334 (13.7)
Primary school	1851 (73.2)	1733 (70.9)	1853 (76.2)
No education	120 (4.8)	98 (4.0)	101 (4.2)
Waist-to-height ratio	0.63 (0.06)	0.63 (0.06)	0.63 (0.07)
History of diabetes, *n* (%)	1281 (50.7)	1145 (46.9)	1184 (48.7)
History of hypertension, *n* (%)	2075 (82.1)	2014 (82.4)	2036 (83.7)
History of dyslipidaemia, *n* (%)	1811 (71.7)	1792 (73.3)	1751 (72.0)
Family history of premature coronary heart disease, *n* (%)	571 (22.6)	531 (21.7)	557 (22.9)
Leisure-time physical activity, METs-min/day	231 (231)	247 (247)	214 (241)
Total energy intake, kcal/day	2281 (591)	2315 (599)	2216 (590)
Baseline Mediterranean diet adherence score*	8.7 (2.0)	8.7 (2.0)	8.4 (2.1)

Values indicate means (standard deviations), unless otherwise stated.
EVOO, extra virgin olive oil; MET, metabolic equivalent task.
*Based on a 14-item dietary screener (a score of 0 indicates minimum adherence and a score of 14 indicates maximum adherence).

Table 2 Incidence of heart failure during the trial period with active intervention (2003–2010) by intervention group

	Mediterranean diet + EVOO (*n* = 2527)	Mediterranean diet + nuts (*n* = 2444)	Control diet (*n* = 2432)	*P*-value	
				Mediterranean diet + EVOO vs. control	Mediterranean diet + nuts vs. control
Cases (*n* = 94)	29	33	32		
Person-years of follow-up	11 737	10 279	9664		
Crude rate/1000 person-years (95% CI)	2.5 (1.7–3.5)	3.2 (2.2–4.5)	3.3 (2.3–4.7)		
Hazard ratios (95% CI)					
Crude model*	0.68 (0.41–1.13)	0.92 (0.56–1.49)	1 (ref.)	0.139	0.725
Age- and sex-adjusted model*	0.71 (0.43–1.19)	0.98 (0.60–1.61)	1 (ref.)	0.193	0.943
Multivariate adjusted model 1*[a]	0.77 (0.46–1.28)	1.04 (0.64–1.71)	1 (ref.)	0.312	0.864
Multivariate adjusted model 2*[b]	0.78 (0.46–1.30)	1.07 (0.65–1.76)	1 (ref.)	0.336	0.792
Multivariate adjusted model 3*[c]	0.74 (0.44–1.24)	1.01 (0.61–1.66)	1 (ref.)	0.248	0.981

CI, confidence interval; EVOO, extra-virgin olive oil.
*All models were stratified according to centre and history of diabetes, and used robust variance estimators.
[a]Adjusted for age, sex, education (four categories), smoking (three categories), waist-to-height ratio (continuous), physical activity (METS-min/day), dyspnoea symptoms at baseline (three categories), and non-AF arrhythmias at baseline.
[b]Adjusted for (a), history of hypertension, history of dyslipidaemia, family history of premature coronary heart disease, and baseline prevalence of AF.
[c]Adjusted for (a), (b), and baseline energy intake (kcal/day).

of heterogeneity, $I^2 = 0\%$) (Supplementary material online, *Figure S2*). The difference in the number of observed events and the length of follow-up between these studies and the PREDIMED randomized trial might explain why our study was probably not sufficiently powered to confirm these previous observational findings. Although the findings of the current study are inconclusive, when they are considered together with the results from other prospective studies, they may suggest a potential beneficial role of the MedDiet in HF prevention. The advantage and novelty of PREDIMED is that our results come from a randomized intervention. Additionally, the PREDIMED trial started on the basis of a relatively high baseline adherence to the MedDiet in the three arms of the trial, which might have attenuated the findings. In an exploratory secondary analysis of the association between

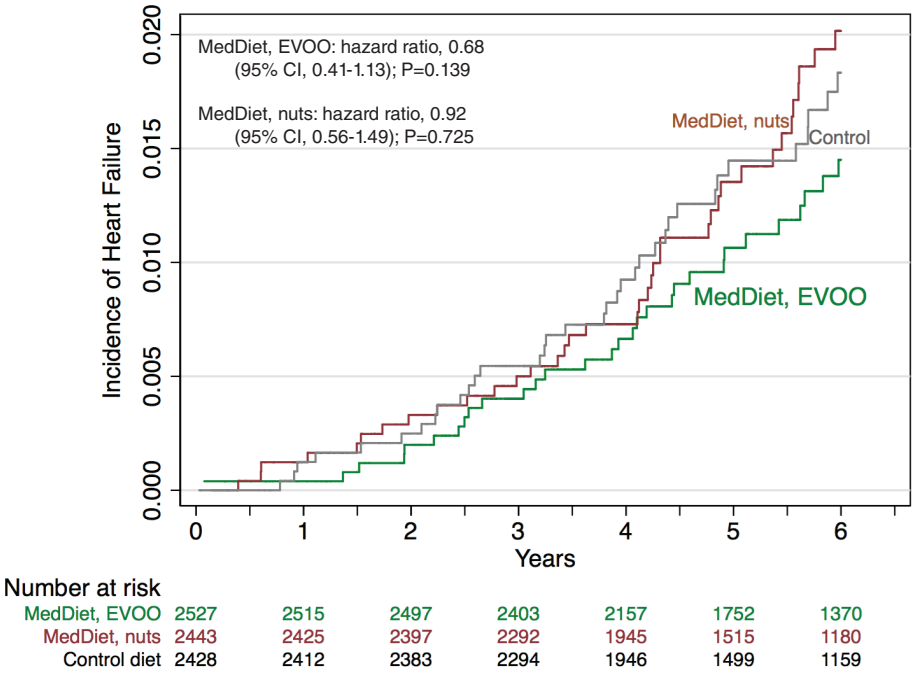

Figure 1 Kaplan–Meier estimates of the incidence of heart failure in the total study population (trial intervention period, 2003–2010). Hazard ratios were stratified by centre and history of diabetes (Cox model with robust variance estimators). CI, confidence interval; EVOO, extra-virgin olive oil; MedDiet, Mediterranean diet.

participant baseline characteristics and HF, we found that older age at baseline and T2D history were significantly associated with higher HF rates, whereas higher baseline MedDiet adherence (assessed in an observational approach) might have been associated with a 37% (HR 0.63; 95% CI 0.40–0.98) lower HF rate (Supplementary material online, *Figure S3*). It might be, however, that this high baseline adherence reflected better compliance with other lifestyle factors that may have an influence on HF, and residual confounding cannot be excluded in this observational approach.

Several mechanisms might explain a potential beneficial role of the MedDiet for HF prevention, as suggested by our exploratory meta-analysis, including the MedDiet's anti-inflammatory[23] and antioxidant[24] properties. Oxidative stress[25] and inflammation[26] accompany HF, and olive oil, in particular, has been associated with reduced HF risk.[27] Earlier PREDIMED reports showed that biomarkers of inflammation[28] and oxidation[12] were reduced with the MedDiet + EVOO compared with the other two groups. In the current analyses, the difference in the size of the association with HF incidence between the MedDiet + EVOO and MedDiet + nuts groups (although both not significant) might have resulted from the fact that participants in the MedDiet + EVOO group were provided (at no cost) with EVOO with a highly constant content of polyphenols. In contrast, that was not the case for participants in the MedDiet + nuts group who bought their own oils, with potentially varied polyphenol content. The anti-inflammatory and antioxidant properties of EVOO, attributed to its polyphenol content, have been well documented[29] and add biological plausibility to the hypothesis of a protection against HF by a MedDiet high in EVOO. As results from the current study were inconclusive, this hypothesis should be studied further by future randomized controlled trials with longer follow-up periods and sufficient statistical power to examine whether this protective effect exists.

Heart failure shares common risk factors with other cardiovascular conditions, and earlier studies have included HF as part of a composite CVD endpoint. For example, the Lyon Diet Heart Study showed that a MedDiet reduced the risk of a composite endpoint that included HF by 67% (RR 0.33; 95% CI 0.21–0.52).[8] A recent randomized controlled trial, Look AHEAD,[30] also included HF in its composite CVD endpoint. An exploratory secondary analysis of our data that examined the effect of the MedDiet on a composite outcome of 634 observed total CVD events (i.e. MI, stroke, CVD death, HF, AF, or peripheral arterial disease) showed that the unadjusted HRs were 0.62 (95% CI 0.51–0.75) for the MedDiet + EVOO and 0.77 (95% CI 0.63–0.93) for the MedDiet + nuts, compared with the control diet (Supplementary material online, *Table S5* and *Figure S4*). Although this specific exploratory analysis might be prone to bias, as it was not a pre-specified outcome of the PREDIMED trial, it might allow useful comparisons with existing or future studies examining the effect of the MedDiet on composite CVD outcomes that include HF.

Our study also has limitations. HF was a pre-specified secondary endpoint of the PREDIMED trial, and the trial was probably underpowered, taking into account the small number of observed HF events. Further, HF is a syndrome with various clinical aetiologies

and symptoms, as well as definitions,[19,20,31] and the effect of dietary patterns might differ according to the type, severity, and pathogenesis of the condition.[1,2] We could not determine HF aetiology or severity in PREDIMED and the possibility of some degree of HF misclassification may exist. In addition, we used the 2005 HF guidelines to adjudicate HF events, concomitant with the time of the PREDIMED trial design.[16] Nevertheless, our HF diagnostic criteria are in agreement with the recently published American College of Cardiology/American Heart Association clinical data standards, where 'HF can be diagnosed when a patient demonstrates or there is objective evidence of new or worsening HF symptoms and receives HF-specific treatment, with objective evidence results from at least two physical examination findings'.[31] In any case, the use of specific criteria to adjudicate events and the adjudication by an independent committee in the context of a large and well-known randomized trial reduce the potential for misclassification. Finally, our results are not generalizable to other populations (e.g. non-Mediterranean countries, younger adults, or adults without CVD risk).

In conclusion, we were not able to show that an intervention with MedDiet reduced the risk of clinical cases of HF. However, this pre-specified secondary analysis of the PREDIMED trial may have been underpowered to provide valid conclusions. Further randomized controlled studies with HF as a primary endpoint are needed to better assess the specific effect of the traditional MedDiet on HF risk.

Supplementary Information

Additional Supporting Information may be found in the online version of this article:

Appendix S1. Diagnostic criteria for the trial endpoint.

Figure S1. Flow chart of participants.

Figure S2. Exploratory meta-analysis of observational cohort studies examining the association between Mediterranean diet adherence and heart failure incidence.

Figure S3. Factors independently associated with heart failure.

Figure S4. Kaplan–Meier estimates of total cardiovascular events (stroke, myocardial infarction, cardiovascular death, heart failure, atrial fibrillation, or peripheral arterial disease) in the total study population (trial intervention period, 2003–2010).

Table S1. Baseline characteristics of participants who developed heart failure during the trial period with active intervention (2003–2010) and those who did not.

Table S2. Incidence of heart failure during the trial period with active intervention (2003–2010) and trial period with active intervention and extended follow-up (2003–2012): combined Mediterranean diets compared with control diet.

Table S3. Subgroup analyses of the incidence of heart failure during the trial period with active intervention (2003–2010) by intervention group.

Table S4. Incidence of heart failure during the trial period including both the active intervention period and the extended follow-up (2003–2012) by intervention group.

Table S5. Incidence of total cardiovascular events (stroke, myocardial infarction, cardiovascular death, heart failure, atrial fibrillation, or peripheral arterial disease) during the trial period with active intervention (2003–2010) by intervention group.

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