Papadaki, A., Martínez-González, M. Á., Alonso-Gómez, A., Rekondo, J., Salas-Salvadó, J., Corella, D., Ros, E., Fitó, M., Estruch, R., Lapetra, J., García-Rodriguez, A., Fiol, M., Serra-Majem, L., Pintó, X., Ruiz-Canela, M., Bulló, M., Serra-Mir, M., Sorlí, J. V., & Arós, F. (2017). Mediterranean diet and risk of heart failure: Results from the PREDIMED randomized controlled trial. *European Journal of Heart Failure*, *19*(9), 1179-1185. https://doi.org/10.1002/ejhf.750

Peer reviewed version

Link to published version (if available):
10.1002/ejhf.750

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

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Manuscript type: Full length article

Running title: Mediterranean diet and heart failure risk

Abbreviations: AF, atrial fibrillation; BMI, body mass index; CHD, coronary heart disease; CVD, cardiovascular disease; EVOO, extra virgin olive oil; FFQ,

food frequency questionnaire; HDL, high-density lipoprotein; HF, heart failure; LDL, low-density lipoprotein; MedDiet, Mediterranean diet; MI, myocardial infarction; PAD, peripheral arterial disease; PREDIMED, Prevención con Dieta Mediterránea; T2D, type 2 diabetes; WtHR, waist-to-height ratio

The study has been registered at http://www.controlled-trials.com (ISRCTN 35739639).

Abstract

Aims: 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 (CVD) were randomly assigned to one of three diets: MedDiet supplemented with extra-virgin olive oil (EVOO), MedDiet supplemented with nuts, or 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% CI, 0.41-1.13 and HR 0.92; 95% CI, 0.56-1.49, respectively].

Conclusion: In this sample of adults at high CVD 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 randomised controlled trials with HF as a primary outcome are needed to better assess the effect of the MedDiet on HF risk.

Keywords: Mediterranean diet; heart failure; cardiovascular disease; PREDIMED study

Introduction

The prevalence of heart failure (HF) is increasing during the last decades.[1] HF is also the leading cause of hospitalisation 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 stroke, myocardial infarction (MI), atrial fibrillation (AF)[5] and peripheral arterial disease (PAD).[6] Multi-morbidity is common in HF and higher cardiovascular (CVD) mortality is observed when several of these CVD manifestations coexist.[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 randomised 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) randomised controlled trial showed that the MedDiet favourably affected HF biomarkers compared to 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 randomised design the effect of the MedDiet on HF incidence, a protocol-specified secondary outcome of the PREDIMED trial.[16] We hypothesised that the MedDiet would result in lower HF incidence, compared to 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, randomised 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 10/2003 and 03/2009 from Spanish primary care centres. The study was planned for 6 years, but was stopped at 4.8 years of median follow-up (12/2010), because of evidence of early benefit.[9] Yearly follow-up measurements continued until 10/2012.

Participants and randomisation

Participants were men (55-80 years) and women (60-80 years) who were free of CVD at enrollment but who were at high-CVD-risk, as defined by the presence of T2D and/or ≥3 CVD risk factors, namely smoking, hypertension, elevated low-density lipoprotein (LDL) cholesterol, low high-density lipoprotein (HDL) cholesterol, overweight/obesity (body mass index, BMI≥25kg/m^2), or family history of premature coronary heart disease (CHD). 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.

Randomisation 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 litre of EVOO/week (including family needs), whereas those in the MedDiet+nuts group received 30 grams/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 sociodemographic characteristics, medical conditions, medication use and lifestyle habits, a 14-item questionnaire assessing MedDiet adherence,[17] an 137-item FFQ, 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 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 Supplementary Appendix 1.

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 (10/2003-07/2010).

Statistical analyses

Cox regression models with robust variance estimators were fitted to estimate Hazard Ratios (HR) 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-randomisation values of education, smoking, WtHR, physical activity, dyspnea and non-AF arrhythmias (model 1), and, additionally for history of hypertension, history of dyslipidaemia, family history of premature CHD 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 randomisation 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 Appendix 2). 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 ischemic heart disease and 58 (61.7%) were hospitalised. Data on receipt of treatment following HF diagnosis were available for 79 participants, who received ACE inhibitors/ARA II (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 (assessed via echocardiography) was available for 80

participants, who presented with preserved ejection fraction (>45-50%) (60%) and reduced ejection fraction (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 Supplementary Appendix 3. Those who developed HF were generally older and had higher WtHR and B-type natriuretic peptide levels. The unadjusted HR 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 Appendix 4).

In subgroup analyses (Supplementary Appendix 5), 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 Appendix 6). 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 Appendix 6) and examining the combined effect of the two

MedDiet groups, compared with the control group (Supplementary Appendix 4), 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 to 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 not 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 randomised 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 N-terminal pro-brain natriuretic peptide, oxidised 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 newly-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

174 future randomised controlled trials to examine the potential effect of the traditional
175 MedDiet on HF as a primary outcome, in a sufficiently powered study.
176 Two recent prospective cohorts with up to 10 years of follow-up reported
177 inverse associations of the MedDiet with HF incidence and mortality (1648 events) in
178 men[11] and HF incidence (1269 events) in women.[10] An exploratory meta-analysis of
179 prospective cohort studies[21,22] conducted for the purposes of the current paper
180 suggested that, according to previous evidence, for each 2 additional points of
181 MedDiet adherence (0 to 9 score), the relative risk of HF decreased by 8% (95% CI,
182 0.90-0.95, without evidence of heterogeneity, I^2=0%) (Supplementary Appendix 7).
183 The difference in the number of observed events and the length of follow-up between
184 these studies and the PREDIMED randomised trial might explain why our study was
185 probably not sufficiently powered as to confirm these previous observational findings.
186 Although the findings of the current study are inconclusive, when they are considered
187 together with the results from other prospective studies, they may suggest a potential
188 beneficial role of the MedDiet in HF prevention. The advantage and novelty of
189 PREDIMED is that our results come from a randomised intervention. Additionally,
190 the PREDIMED trial started on the basis of a relatively high baseline adherence to the
191 MedDiet in the three arms of the trial, which might have attenuated the findings. In an
192 exploratory secondary analysis of the association between participant baseline
193 characteristics and HF, we found that older age at baseline and T2D history were
194 significantly associated with higher HF rates, whereas higher baseline MedDiet
195 adherence (assessed in an observational approach) might have been associated with a
196 37% (HR=0.63; 95% CI, 0.40-0.98) lower HF rate (Supplementary Appendix 8). It
197 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 to 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 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 randomised controlled trials with longer follow-up periods and sufficient statistical power to examine whether this protective effect exists.

HF 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 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 randomised 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 PAD) 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 to the control diet (Supplementary Appendix 9; Supplementary Appendix 10). 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 etiologies 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 etiology 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's 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 randomised trial reduce the potential for misclassification. Finally, our

results are not generalisable 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 randomised controlled studies with HF as a primary endpoint are needed to better assess the specific effect of the traditional MedDiet on HF risk.

Acknowledgements

The supplemental foods used in the study were generously donated by Patrimonio Comunal Olivarero and Hojiblanca from Spain (EVOO); the California Walnut Commission from Sacramento, CA (walnuts); and Borges S.A. (almonds) and La Morella Nuts (hazelnuts), both from Reus, Spain. CIBEROBN and RTIC RD 06/0045 are initiatives of ISCIII, Spain. The funding sources had no role in the design, collection, analysis, or interpretation of the data or in the decision to submit the manuscript for publication.

Supplementary Information

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

Supplementary Appendix S1: Diagnostic criteria for trial endpoint.

Supplementary Appendix S2: Flow chart of participants.

Supplementary Appendix S3: Baseline characteristics of participants who developed heart failure during the trial period with active intervention (2003-2010) and those who did not.

Supplementary Appendix S4: 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

Supplementary Appendix S5: Subgroup analyses of the incidence of heart failure during the trial period with active intervention (2003-2010) by intervention group

Supplementary Appendix S6: Incidence of heart failure during the trial period including both the active intervention period and the extended follow-up (2003-2012) by intervention group

Supplementary Appendix S7: Exploratory meta-analysis of observational cohort studies examining the association between Mediterranean diet adherence and heart failure incidence

Supplementary Appendix S8: Factors independently associated with heart failure

Supplementary Appendix S9: 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

Supplementary Appendix S10: 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)

Funding

This work was supported by the Official Funding Agency for Biomedical Research of the Spanish government (ISCIII) through grants provided to research networks specifically developed for the trial: [RTIC G03/140 to R.E., RTIC RD 06/0045 to

M.A.M.]. All investigators of the PREDIMED trial belong to CIBEROBN, an initiative of ISCIII. We also acknowledge grants from the National Institute of Health [1R01HL118264-01]; Fondo de Investigación Sanitaria–Fondo Europeo de Desarrollo Regional [PI04/0233, PI05/0976, PI07/0240, PI10/01407, PI10/02658, PI11/00049, PI11/02505 and AGL2010-22319-C03-03]; Consejería de Salud de la Junta de Andalucía [PI0105/2007], and the Generalitat Valenciana, Spain [ACOMP/2013/165 and ACOMP/2013/159].

Conflict of interest

Dr Ros is a consultant for the California Walnut Commission and Dr Salas-Salvadó is a consultant for the International Nut Council. Dr Papadaki reports travel reimbursement from the California Walnut Commission. Dr Ros reports grants from the California Walnut Commission and Dr Salas-Salvadó reports grants from the International Nut Council. The other authors report no conflicts of interest.

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452 **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[a]	8.7 (2.0)	8.7 (2.0)	8.4 (2.1)

453 EVOO, extra virgin olive oil; MET, metabolic equivalent tasks

454 Values indicate means (standard deviations), unless otherwise stated

[a] 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**	
During the trial intervention period (2003-2010)				Mediterranean diet+EVOO vs. Control	Mediterranean diet+nuts vs. Control
Cases (n=94)	29	33	32		
Person-years of follow-up	11737	10279	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; HF, Heart Failure

*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/d), dyspnea 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 atrial fibrillation.

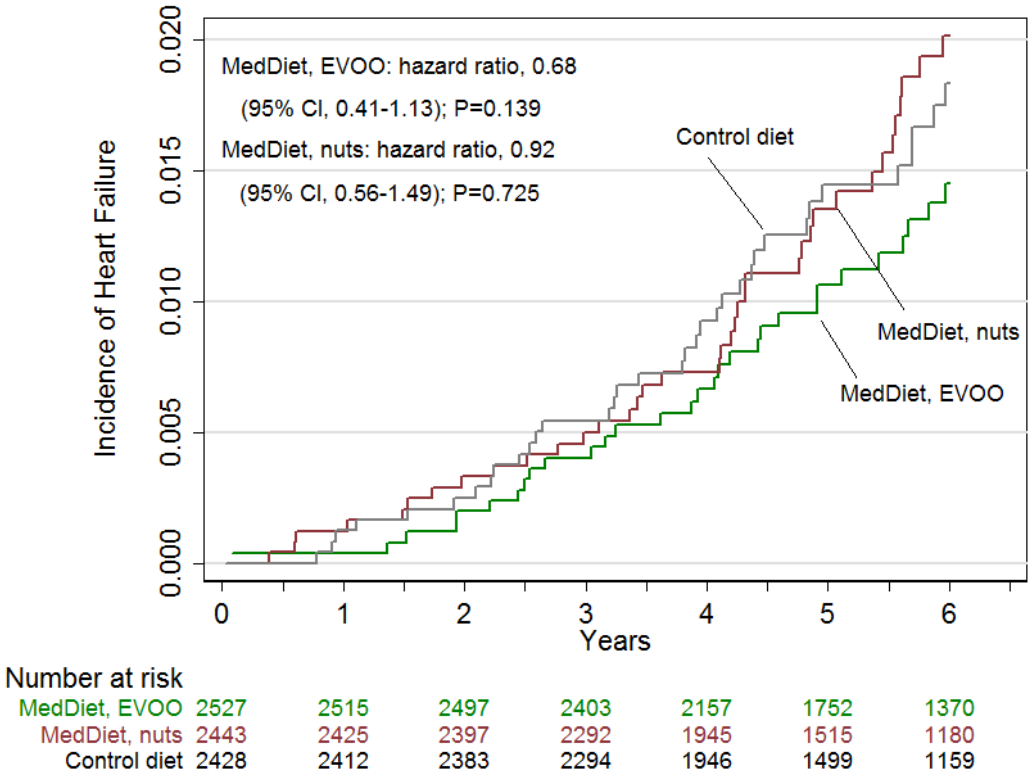
(c) Adjusted for (a), (b) and baseline energy intake (kcal/day).

Legends

Figure 1 Kaplan–Meier estimates of the incidence of heart failure in the total study population (trial intervention period, 2003-2010)

Footnote to Figure 1:

Hazard ratios were stratified by centre and history of diabetes (Cox model with robust variance estimators).



Supplementary Appendix 1

Diagnostic criteria for trial endpoint

(Version July, 2005 – Modified December, 2006)

Heart failure (HF)

Based on the 2005 guidelines of the European Society of Cardiology, an event was classified as HF if patients had symptoms and/ or signs of HF (frequent breathlessness or fatigue at rest or during exertion, or ankle swelling) attributable to objective evidence of cardiac dysfunction at rest (preferably by echocardiography). The clinical picture may appear suddenly or in a progressive way.

For a definition of the other cardiovascular endpoints of the PREDIMED trial, we would like to refer the readers to the following citations:

Myocardial infarction (MI), stroke, cardiovascular (CVD) death:

Estruch R, Ros E, Salas-Salvadó J, Covas MI, Corella D, Arós F, Gómez-Gracia E, Ruiz-Gutiérrez V, Fiol M, Lapetra J, Lamuela-Raventos RM, Serra-Majem L, Pintó X, Basora J, Muñoz MA, Sorlí JV, Martínez JA, Martínez-González MA. Primary prevention of cardiovascular disease with a Mediterranean diet. *New Engl J Med* 2013; **368**:1279-1290.

Atrial fibrillation (AF):

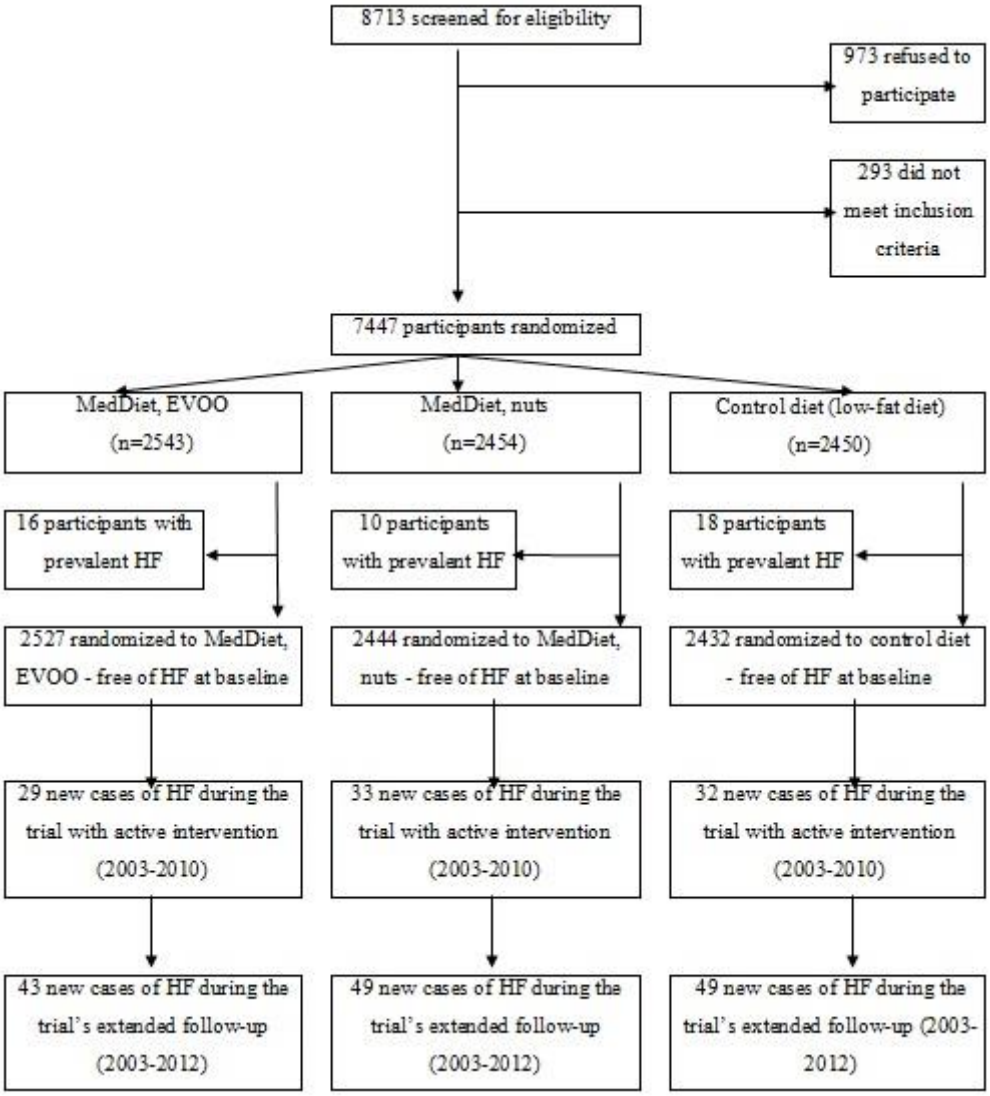
Martínez-González MA, Toledo E, Arós F, Fiol M, Corella D, Salas-Salvadó J, Ros E, Covas MI, Fernández-Crehuet J, Lapetra J, Muñoz MA, Fitó M, Serra-Majem L, Pintó X, Lamuela-Raventós RM, Sorlí JV, Babio N, Buil-Cosiales P, Ruiz-Gutierrez V, Estruch R, Alonso A. Extra-virgin olive oil consumption reduces risk of atrial

fibrillation: The PREDIMED (Prevención con Dieta Mediterránea) trial. *Circulation* 2014; **130**:18-26.

Peripheral arterial disease (PAD)

Ruiz-Canela M, Estruch R, Corella D, Salas-Salvadó J, Martínez-González MA. Association of Mediterranean diet with peripheral artery disease: The PREDIMED randomized trial. *JAMA* 2014; **311**:415-417.

Supplementary Appendix 2



Supplementary Appendix 3

Table S3 Baseline characteristics of participants who developed heart failure during the trial period with active intervention (2003-2010) and those who did not

	Participants who developed heart failure (n=94)	**Participants who did not develop heart failure (n=7309)**	**P value**
Age, years	71.0 (5.9)	66.9 (6.2)	<0.001
Sex, female, n (%)	50 (53.2)	4208 (57.6)	0.390
Smoking, n (%)			0.506
Current	11 (11.7)	1027 (14.1)	
Education, n (%)			0.124
University or higher	5 (5.3)	526 (7.2)	
Secondary school	9 (9.6)	1107 (15.2)	
Primary school	75 (79.8)	5362 (73.4)	
No education	5 (5.3)	314 (4.3)	
Waist-to-height ratio	0.65 (0.06)	0.63 (0.07)	0.006
BT-pro-BNP, pg/mL	635.9 (314.7)	589.4 (170.6)	0.009
History of diabetes, n (%)	61 (64.9)	3549 (48.6)	0.002
History of hypertension, n (%)	81 (86.2)	6044 (82.7)	0.372
History of dyslipidaemia, n (%)	57 (60.6)	5297 (72.5)	0.010
Family history of premature coronary heart disease, n (%)	18 (19.2)	1641 (22.5)	0.446
Leisure-time physical activity, METs-min/day	187 (184)	231 (240)	0.076

Total energy intake, kcal/day	2344 (716)	2270 (592)	0.230
Baseline Mediterranean diet adherence score[a]	8.2 (2.5)	8.6 (2.0)	0.054

527 BT-pro-BNP, B-type natriuretic peptide; EVOO, extra virgin olive oil; MET, metabolic
528 equivalent tasks
529 Values indicate means (standard deviations), unless otherwise stated
530 [a] Based on a 14-item dietary screener (a score of 0 indicates minimum adherence and a
531 score of 14 indicates maximum adherence).
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533

Supplementary Appendix 4

Table S4 Incidence of heart failure during the trial period with active intervention (2003-2010) and trial period including both the active intervention period and the extended follow-up (2003-2012): both Mediterranean diets combined versus the control diet

	Combined Mediterranean diets (n=4971)	**Control diet (n=2432)**	**P value***
During the trial intervention period (2003-2010)			
Cases (n=94)	62	32	
Person-years of follow-up	22016	9664	
Crude rate/1000 person-years (95% CI)	2.8 (2.2-3.6)	3.3 (2.3-4.7)	
Hazard ratios (95% CI)			
Crude model*	0.79 (0.51-1.22)	1 (ref.)	0.283
Age- and sex-adjusted model*	0.84 (0.54-1.29)	1 (ref.)	0.415
Multivariate adjusted model 1* (a)	0.89 (0.58-1.38)	1 (ref.)	0.616
Multivariate adjusted model 2* (b)	0.91 (0.59-1.41)	1 (ref.)	0.673
Multivariate adjusted model 3* (c)	0.86 (0.55-1.34)	1 (ref.)	0.504
Trial intervention period plus extended follow-up (2003-2012)			
Cases (n=141)	92	49	
Person-years of follow-up	29326	13940	
Crude rate/1000 person-years (95% CI)	3.1 (2.5-3.8)	3.5 (2.6-4.6)	
Hazard ratios (95% CI)			
Crude model*	0.84 (0.59-1.19)	1 (ref.)	0.316
Age- and sex-adjusted model*	0.88 (0.62-1.25)	1 (ref.)	0.476
Multivariate adjusted model 1* (a)	0.94 (0.66-1.34)	1 (ref.)	0.723
Multivariate adjusted model 2* (b)	0.96 (0.67-1.36)	1 (ref.)	0.801

Multivariate adjusted model 3* (c)	0.94 (0.66-1.34)	1 (ref.)	0.725

CI, confidence interval; HF, Heart Failure

*All models were stratified according to recruiting centre and history of diabetes and used robust variance estimators. All P values were calculated using Cox proportional-hazards models with robust variance estimators.

(a) Adjusted for age, sex, education (University or higher, secondary school, primary school or no education), smoking (never, current or former smoker), waist-to-height ratio (continuous), physical activity (METS-min/d), dyspnea symptoms at baseline (no symptoms, symptoms after high effort and symptoms after moderate/minimal effort or symptoms, not specified) and non-AF arrhythmias at baseline.

(b) Adjusted for the above, in addition to history of hypertension, history of dyslipidaemia, family history of premature coronary heart disease and baseline prevalence of atrial fibrillation.

(c) Adjusted for (a) and (b), in addition to baseline energy intake (kcal/day).

Supplementary Appendix 5

Table S5 Subgroup analyses of the incidence of heart failure during the trial period with active intervention (2003-2010) by intervention group

	HF events/Total			Hazard Ratios (95% CI)		P value for interaction*
	MedDiet, EVOO	**MedDiet, nuts**	**Control**	**MedDiet, EVOO**	**MedDiet, nuts**	**Combined Mediterranean diets**
Sex						
Male	12/1043	20/1125	12/977	0.86 (0.38-1.96)	1.40 (0.67-2.92)	0.490
Female	17/1484	13/1319	20/1455	0.68 (0.34-1.34)	0.80 (0.39-1.67)	
Age, years						
<67	10/1256	7/1235	8/1117	0.86 (0.33-2.24)	0.62 (0.21-1.79)	0.130
≥ 67	19/1271	26/1209	24/1315	0.71 (0.38-1.33)	1.18 (0.66-2.09)	
Smoking						
Never	19/1565	16/1458	21/1517	0.75 (0.39-1.42)	0.81 (0.41-1.60)	0.480
Ever	10/962	17/986	11/915	0.74 (0.31-1.78)	1.34 (0.61-2.94)	
History of diabetes						
No	9/1246	11/1299	13/1248	0.48 (0.20-1.17)	0.66 (0.29-1.51)	0.010
Yes	20/1281	22/1145	19/1184	0.82 (0.43-1.56)	1.21 (0.64-2.27)	
History of hypertension						
No	3/452	5/430	5/396	0.63 (0.13-3.05)	1.29 (0.29-5.67)	0.650
Yes	26/2075	28/2014	27/2036	0.75 (0.43-1.32)	1.02 (0.60-1.76)	
History of dyslipidaemia						
No	11/716	13/652	13/681	0.71 (0.31-1.63)	1.02 (0.46-2.27)	0.990
Yes	18/1811	20/1792	19/1751	0.69 (0.36-1.36)	0.92 (0.48-1.77)	

Family history of premature CHD						
No	26/1956	26/1913	24/1875	0.91 (0.51-1.61)	1.06 (0.60-1.89)	0.330
Yes	3/571	7/531	8/557	0.37 (0.09-1.52)	1.09 (0.36-3.30)	
History of AF						
No	28/2510	32/2423	32/2409	0.71 (0.42-1.19)	0.99 (0.60-1.64)	0.190
Yes	1/17	1/21	0/23	-	-	
Body mass index, kg/m^2						
<30	13/1335	18/1353	16/1233	0.67 (0.32-1.41)	1.04 (0.52-2.09)	0.610
≥30	16/1192	15/1091	16/1199	0.85 (0.41-1.77)	1.04 (0.50-2.18)	
Waist-to-height ratio						
<0.63	9/1366	20/1369	12/1272	0.62 (0.25-1.52)	1.75 (0.83-3.69)	0.040
≥ 0.63	20/1161	13/1075	20/1160	0.70 (0.36-1.34)	0.57 (0.27-1.19)	
Baseline score for MedDiet adherence						
<9 (low)	19/1113	13/1055	20/1250	1.00 (0.52-1.93)	0.75 (0.36-1.54)	0.040
≥ 9 (high)	10/1414	20/1389	12/1182	0.59 (0.25-1.39)	1.38 (0.66-2.89)	

AF, atrial fibrillation; CHD, coronary heart disease; CI, confidence interval; EVOO, Extra-virgin olive oil; HF, Heart Failure; MedDiet, Mediterranean diet

All models were stratified according to recruiting centre and history of diabetes (apart from when history of diabetes was examined as a subgroup) and used robust variance estimators.

All models were adjusted for age, sex, education (University or higher, secondary school, primary school or no education), smoking (never, current or former smoker), waist-to-height ratio (continuous), physical activity (METS-min/d), dyspnea symptoms at baseline (no symptoms, symptoms after high effort and symptoms after moderate/minimal effort or symptoms, not specified), non-AF arrhythmias at baseline, history of hypertension, history of dyslipidaemia, family history of premature coronary heart disease, baseline prevalence of

atrial fibrillation and baseline energy intake (kcal/day).

* P values were calculated using Cox proportional-hazards models with robust variance estimators. Interactions for both MedDiet groups were assessed by a likelihood ratio test with 2 degrees of freedom: grouping variable x (MedDiet with EVOO) and grouping variable x (MedDiet with nuts).

572 **Supplementary Appendix 6**

573 **Table S6** Incidence of heart failure during the trial period including both the active

574 intervention period and the extended follow-up (2003-2012) by intervention group

	Mediterranean diet+EVOO (n=2527)	**Mediterranean diet+nuts (n=2444)**	**Control diet (n=2432)**	**P value**	
Trial intervention period plus extended follow-up (2003-2012)					
Cases (n=141)	43	49	49		
Person-years of follow-up	15261	14064	13940		
Crude rate/1000 person-years (95% CI)	2.8 (2.0-3.8)	3.5 (2.6-4.6)	3.5 (2.6-4.6)		
Hazard ratios (95% CI)					
Crude model*	0.71 (0.47-1.07)	0.99 (0.67-1.48)	1(ref.)	0.100	0.970
Age- and sex-adjusted model*	0.73 (0.49-1.11)	1.06 (0.71-1.58)	1(ref.)	0.146	0.771
Multivariate adjusted model 1*(a)	0.79 (0.52-1.19)	1.13 (0.75-1.69)	1(ref.)	0.260	0.562
Multivariate adjusted model 2*(b)	0.80 (0.53-1.21)	1.16 (0.77-1.73)	1(ref.)	0.290	0.485
Multivariate adjusted model 3*(c)	0.78 (0.52-1.19)	1.14 (0.76-1.70)	1(ref.)	0.252	0.540

575 CI, confidence interval; EVOO, Extra-virgin olive oil; HF, Heart Failure

576 *All models were stratified according to centre and history of diabetes and used robust

577 variance estimators.

578 (a) Adjusted for age, sex, education (four categories), smoking (three categories), waist-to-

579 height ratio (continuous), physical activity (METS-min/d), dyspnea symptoms at baseline

580 (three categories) and non-AF arrhythmias at baseline.

581 (b) Adjusted for (a), history of hypertension, history of dyslipidaemia, family history of

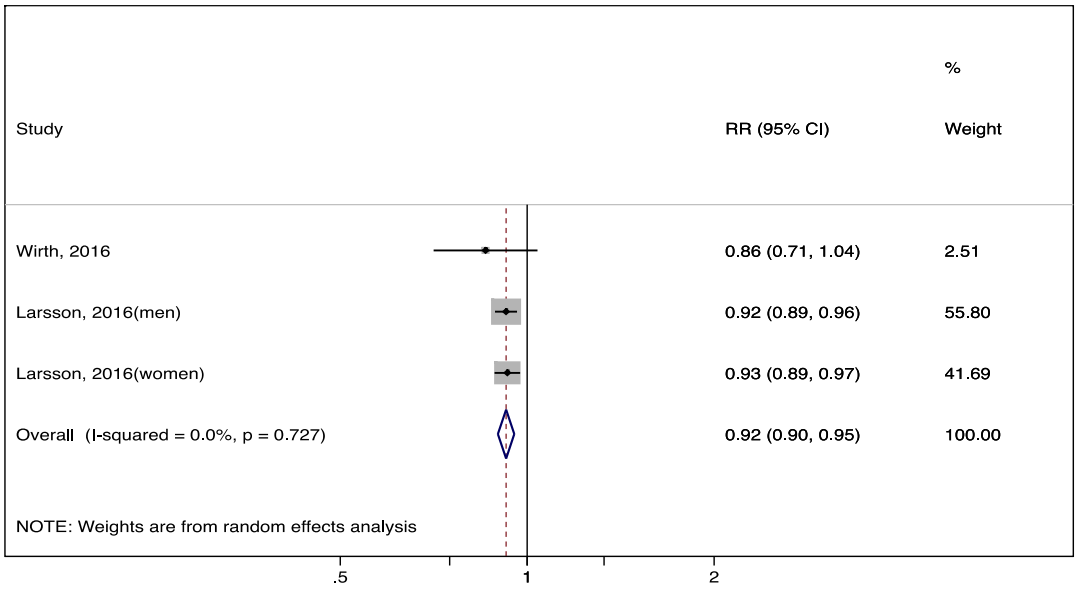
582 premature coronary heart disease and baseline prevalence of atrial fibrillation.

583 (c) Adjusted for (a), (b) and baseline energy intake (kcal/day).

584

Supplementary Appendix 7

Figure S7 Exploratory meta-analysis of observational cohort studies examining the association between Mediterranean diet adherence and heart failure incidence

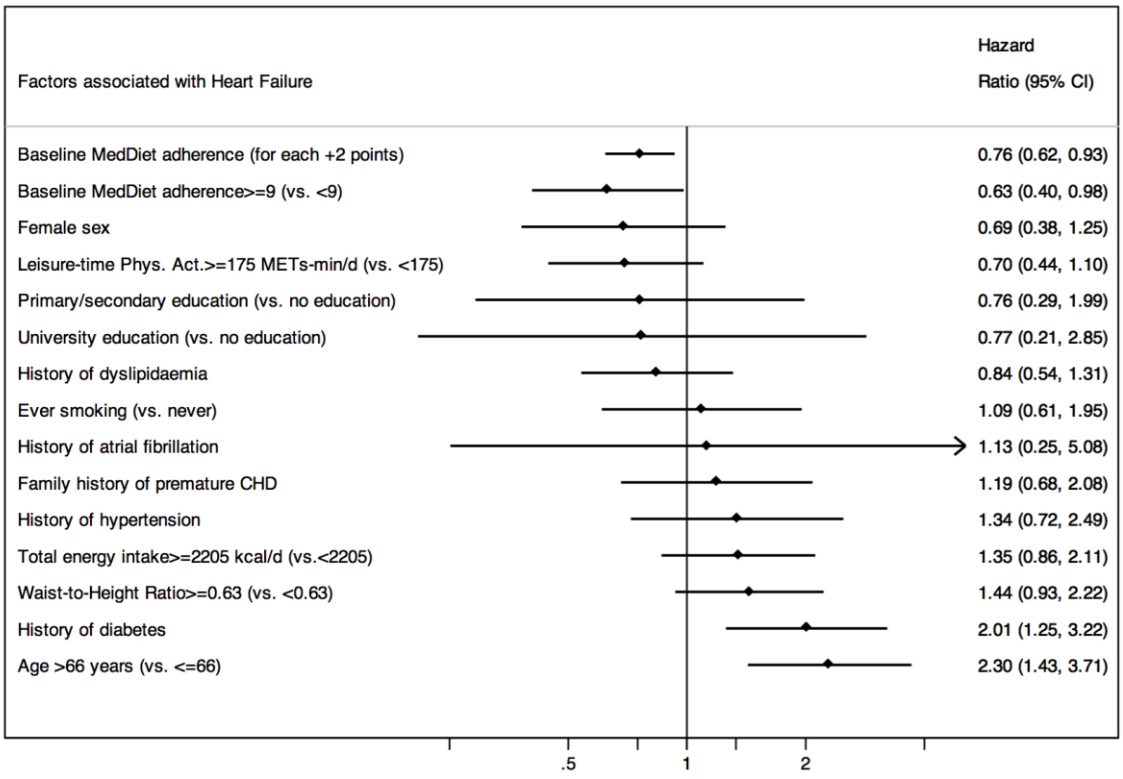


A random effects model was used. The estimates of each study included in the meta-analysis were transformed to capture the effect on the risk of HF (or mortality in patients with HF) for an additional +2 point increment in a 0 to 9 score of adherence to the MedDiet.

The two studies by Tektonidis et al [Tektonidis et al (2015) A Mediterranean diet and risk of myocardial infarction, heart failure and stroke: A population-based cohort study. Atherosclerosis 243:93-98 and Tektonidis et al (2016) Adherence to a Mediterranean diet is associated with reduced risk of heart failure in men. Eur J Heart Fail 18:253-259] were excluded because Larsson [Larsson et al (2016) Healthy lifestyle and risk of heart failure: results from 2 prospective cohort studies. Circ Heart Fail 9:e002855] analysed the same cohorts, but using a slightly larger sample size in updated databases.

Supplementary Appendix 8

Figure S8 Factors independently associated with heart failure



Cut-off values indicate medians, unless otherwise stated.

*All models were stratified by centre, intervention group and history of diabetes (apart from when history of diabetes was examined as a predictor) and used robust variance estimators. All models were adjusted for age, sex, education (four categories), smoking (three categories), waist-to-height ratio (continuous), physical activity (METS-min/d), dyspnea symptoms at baseline (no symptoms, symptoms after high effort and symptoms after moderate/minimal effort or symptoms, not specified), non-AF arrhythmias at baseline, history of hypertension, history of dyslipidaemia, family history of premature coronary heart disease, baseline prevalence of atrial fibrillation and baseline energy intake (kcal/day). Confidence intervals were estimated using Cox proportional-hazards models with robust variance estimators.

Supplementary Appendix 9

Table S9 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

	Mediterranean diet+EVOO (n=2510)	**Mediterranean diet+nuts (n=2423)**	**Control diet (n=2409)**	**P value**	
				Mediterranean diet+EVOO vs. Control	Mediterranean diet+nuts vs. Control
Cases (n=634)	196	202	236		
Person-years of follow-up	11479	10038	9397		
Crude rate/1000 person-years (95% CI)	1.7 (1.5-2.0)	2.0 (1.7-2.3)	2.5 (2.2-2.8)		
Hazard ratios (95% CI)					
Crude model†	0.62 (0.51-0.75)	0.77 (0.63-0.93)	1(ref.)	<0.001	0.006
Age- and sex-adjusted model†	0.63 (0.52-0.76)	0.76 (0.63-0.92)	1(ref.)	<0.001	0.005
Multivariate adjusted model 1†(a)	0.64 (0.53-0.78)	0.78 (0.64-0.94)	1(ref.)	<0.001	0.011
Multivariate adjusted model 2†(b)	0.65 (0.53-0.78)	0.79 (0.66-0.96)	1(ref.)	<0.001	0.019
Multivariate adjusted model 3†(c)	0.65 (0.53-0.78)	0.79 (0.65-0.96)	1(ref.)	<0.001	0.018

CI, confidence interval; CVD, cardiovascular disease; EVOO, Extra-virgin olive oil

† All models were stratified according to centre and history of diabetes.

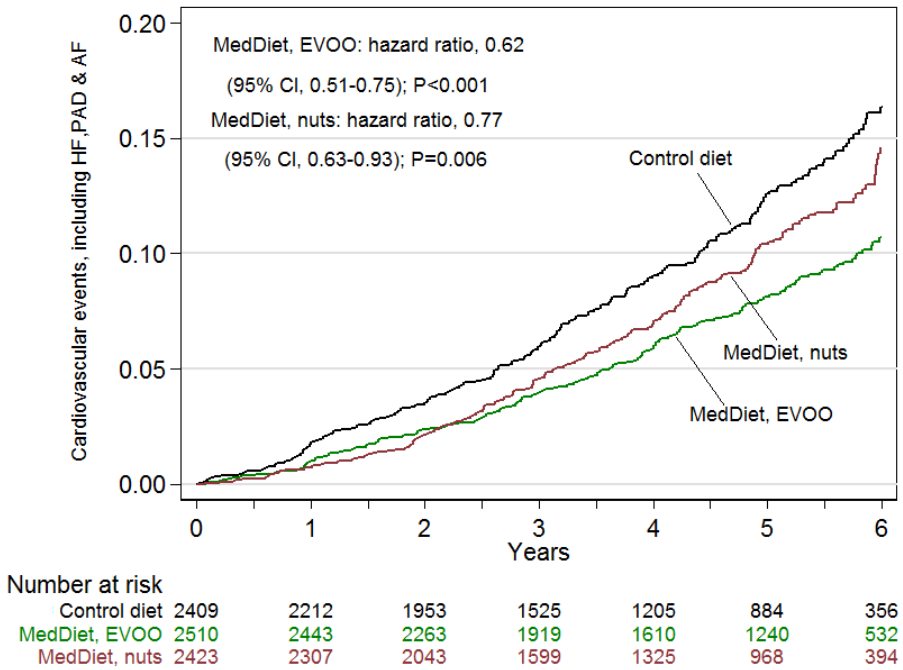
(a) Adjusted for age, sex, education (four categories), smoking (three categories), waist-to-height ratio (continuous), physical activity (METS-min/d), dyspnea symptoms at baseline (three categories) and non-AF arrhythmias at baseline.

(b) Adjusted for (a), family history of premature coronary heart disease, history of dyslipidaemia and history of hypertension.

(c) Adjusted for (b) and baseline energy intake (kcal/day).

Supplementary Appendix 10

Figure S10 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)



Hazard ratios were stratified by centre and sex (Cox model with robust variance estimators).