Extravirgin Olive Oil Consumption Reduces Risk of Atrial Fibrillation

The PREDIMED (Prevención con Dieta Mediterránea) Trial

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Background—The PREDIMED (Prevención con Dieta Mediterránea) randomized primary prevention trial showed that a Mediterranean diet enriched with either extravirgin olive oil or mixed nuts reduces the incidence of stroke, myocardial infarction, and cardiovascular mortality. We assessed the effect of these diets on the incidence of atrial fibrillation in the PREDIMED trial.

Methods and Results—Participants were randomly assigned to 1 of 3 diets: Mediterranean diet supplemented with extravirgin olive oil, Mediterranean diet supplemented with mixed nuts, or advice to follow a low-fat diet (control group). Incident atrial fibrillation was adjudicated during follow-up by an events committee blinded to dietary group allocation. Among 6705 participants without prevalent atrial fibrillation at randomization, we observed 72 new cases of atrial fibrillation in the Mediterranean diet with extravirgin olive oil group, 82 in the Mediterranean diet with mixed nuts group, and 92 in the control group after median follow-up of 4.7 years. The Mediterranean diet with extravirgin olive oil significantly reduced the risk of atrial fibrillation (hazard ratio, 0.62; 95% confidence interval, 0.45–0.85 compared with the control group). No effect was found for the Mediterranean diet with nuts (hazard ratio, 0.89; 95% confidence interval, 0.65–1.20).

Conclusions—In the absence of proven interventions for the primary prevention of atrial fibrillation, this post hoc analysis of the PREDIMED trial suggests that extravirgin olive oil in the context of a Mediterranean dietary pattern may reduce the risk of atrial fibrillation.

Clinical Trial Registration—URL: http://www.controlled-trials.com. Unique identifier: ISRCTN35739639.

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Atrial fibrillation (AF) is the most common arrhythmia found in clinical practice, with an estimated lifetime risk of 25%.[1,2] Increasing lifespan, prolonged survival after heart disease, and other factors have resulted in a steady increase in the prevalence of AF.[3] Recent estimates suggest that by 2050, almost 16 million individuals in the United States and 25 to 30 million in Europe will have AF.[4,5]

Clinical Perspective on p 26

In spite of advances in our understanding of the pathophysiological mechanisms that cause AF, preventive strategies are virtually nonexistent.[6] Lifestyle factors, especially dietary habits, have been recognized as important determinants of other major cardiovascular diseases (CVDs; stroke, coronary heart disease, and peripheral artery disease). Some of the salutary effects of diet and lifestyle modification for cardiovascular risk reduction are hypothesized to be mediated by reduction of inflammation and oxidative stress in association with the metabolic syndrome.[7]

Interestingly, the same mechanisms have been implicated in the pathogenesis of AF.[8–10] In this context, adherence to the traditional Mediterranean dietary pattern, with abundant consumption of vegetable fats such as extravirgin olive oil (EVOO), has been proven to reduce the incidence of major CVDs.[11,12] Recently, the PREDIMED (Prevención con Dieta Mediterránea) randomized primary prevention trial[13] showed that a Mediterranean diet (MeDiet) supplemented with either EVOO or mixed nuts was superior to a low-fat diet for prevention of stroke, myocardial infarction, or cardiovascular mortality[12] and for the reduction of peripheral artery disease.[14] In a secondary analysis, we assessed the effect of the 2 supplemented MeDiets on the incidence of AF.

Methods

The PREDIMED Trial: Study Design and Participants

The design, objectives, methods, and protocol of the PREDIMED study (http://www.predimed.es) have been reported in detail elsewhere.[12,13] This was a multicenter trial conducted in 11 recruiting centers affiliated with 11 Spanish university hospitals. Participants were 7447 men (aged 55–80 years) and women (aged 60–80 years) initially free of CVD but who were at high cardiovascular risk because they had either type 2 diabetes mellitus or ≥3 of the following cardiovascular risk factors: Current smoking, hypertension, hypercholesterolemia, low high-density lipoprotein cholesterol, overweight/obesity, or family history of premature coronary heart disease. Exclusion criteria have been reported previously.[12,13] Patients were randomly assigned (1:1:1) to receive 1 of 3 nutrition interventions: MeDiet supplemented with EVOO (MeDiet+EVOO), MeDiet supplemented with mixed nuts (MeDiet+nuts), or a control intervention that consisted of advice to reduce intake of all types of fat. Investigators and members of all committees were blinded to individual participant treatment assignments. Participants allocated to the MeDiet+EVOO had a goal of consuming 50 g (≈4 tbsp) or more per day of a polyphenol-rich olive oil that they received free of cost. Both the food frequency questionnaires (including a previously validated 14-item dietary screener) and biomarkers of compliance showed that the intervention changed the overall dietary pattern of participants, as we have reported previously.[12,15] Specifically, adherence to the MeDiet+EVOO intervention was assessed by measuring urinary hydroxytyrosol, the main phenolic compound in EVOO, whereas the plasma proportion of α-linolenic acid was used as a measure of adherence to the MeDiet+nuts intervention. Measurements were performed at 1, 3, and 5 years of follow-up in a random sample of participants.[12]

The primary end point of the PREDIMED trial was a composite of stroke, myocardial infarction, or death of cardiovascular causes. In December 2010, the trial was stopped because of early evidence of benefit by both MeDiets after a median follow-up of 4.8 years.[12] Secondary end points included death of any cause, incidence of angina that led to a revascularization procedure, heart failure, peripheral artery disease,[14] diabetes mellitus,[16] dementia, and cancer. Among the initial 7447 participants, we excluded 75 participants with prevalent AF at baseline. In 1 of the 11 centers, AF was not assessed systematically as a relevant end point. Therefore, the 667 participants from that center were excluded, and the sample size was reduced from 7372 to 6705 participants (Figure 1). All cardiovascular end points were adjudicated according to prespecified criteria by the PREDIMED End-Point Adjudication Committee, chaired by a cardiologist. Members of this committee were blinded to the intervention and dietary habits of participants.[12–14,16] Potential incident cases of

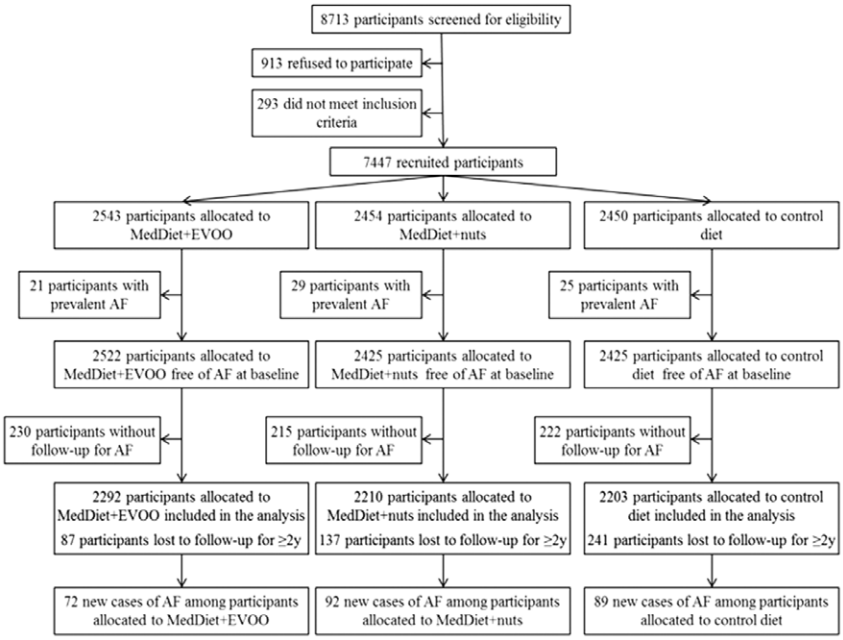

Figure 1. Flow-chart of the PREDIMED (Prevención con Dieta Mediterránea) trial. AF indicates atrial fibrillation; EVOO, extravirgin olive oil; and MedDiet, Mediterranean diet.

AF through December 1, 2010, were identified initially from an annual review of all outpatient and inpatient medical records of each participant and from yearly ECGs performed during follow-up examinations in the healthcare centers. If AF was mentioned anywhere in the medical record or AF was present in the ECG, all relevant documentation was submitted to the Adjudication Committee. Even though AF was not a primary end point in the trial, the Adjudication Committee reviewed the medical charts and ECGs from potential AF cases and made a final decision about the presence or absence of AF. For the purposes of the PREDIMED trial and the present analysis, a diagnosis of AF was made only if both AF was present in an ECG tracing and an explicit medical diagnosis of AF was made by a physician. AF events associated with myocardial infarction or cardiac surgery were not included.

Statistical Analysis

The main analyses included all randomly assigned participants from 10 centers without prevalent AF at baseline, regardless of their compliance with the intended intervention (intention to treat). We included in the analyses all incident AF events from the time of randomization until the end of the trial. We assessed the effect of the intervention on AF using a Cox proportional hazards model with robust variance estimators (Huber-White sandwich estimators),[17–19] stratified by center. We adjusted the models for the following known predictors of AF using their baseline values: Age, sex, smoking (never, current, or former smoker), educational level, height, body mass index, waist-to-height ratio, diabetes mellitus, hypertension, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, baseline systolic and diastolic blood pressure, antihypertensive treatment, statin use, baseline adherence to the MeDiet, and previous history of arrhythmia (any previous diagnosis of arrhythmia other than AF present in the medical record of the participant at inception of the trial).[20] This multivariable model was considered the primary analysis, as prespecified in the PREDIMED trial protocol. We defined event rate as the number of participants who developed AF during follow-up divided by the sum of days to AF diagnosis or end of follow-up. We repeated these analyses after including either AF or the primary cardiovascular end point as outcome. We evaluated effect modification according to subgroups of sex, age, diabetes mellitus, body mass index, statin use, antihypertensive medication, and baseline adherence to the MeDiet. To determine whether any effect of the MeDiet interventions on AF risk was mediated through reductions in overall CVD, we conducted additional analyses with AF as the outcome, with inclusion of the nonfatal component of the trial primary end point (myocardial infarction or stroke) as a time-dependent covariate and censoring of participants at the time of the primary CVD end point.

In the per protocol analyses, we used time-dependent Cox models to assess the association between attained consumption of EVOO during follow-up and subsequent incidence of AF. We conducted sensitivity analyses, including stratified analyses by follow-up periods, competing risk analyses,[21] Poisson regression models, and multiple imputation of AF events to participants lost to follow-up for ≥2 years, as well as for those participants belonging to the center that did not monitor the occurrence of new cases of AF (online-only Data Supplement Methods).[22] We used the Kaplan-Meier method to describe the incidence of AF during follow-up and to estimate AF-free survival. We also assessed the risk of AF according to actual categories of attained consumption of EVOO, nuts, or overall adherence to the MeDiet during follow-up using time-dependent Cox models. Finally, we assessed whether the effect of the MeDiet interventions on AF risk mediated the observed reduction of stroke incidence described in the main results of the PREDIMED trial,[12] with incident AF included as a time-dependent covariate in a Cox model that had incident stroke as the dependent variable. We used STATA (version 12.1). PREDIMED is registered in Current Controlled Trials (http://wwww.controlled-trials.com, number ISRCTN35739639).

Role of the Funding Source and Ethical Issues

Recruitment took place between October 1, 2003, and June 30, 2009. Approval of the institutional review boards at each participating center was obtained before the inception of the study, patients' recruitment, data analysis, data interpretation, and writing of the report. All participants provided written informed consent. The corresponding author had full access to all data, and the coauthors and steering committee members had final responsibility for the decision to submit the manuscript for publication. The authors vouch for the completeness and accuracy of all analyses. The trial was funded by competitive grants and research networks from the Spanish official agency for funding biomedical research (Instituto de Salud Carlos III, http://www.isciii.es). Food companies donated the supplemental foods (extravirgin olive oil by Hojiblanca and Patrimonio Comunal Olivarero; walnuts by the California Walnut Commission; almonds by Borges; and hazelnuts by La Morella Nuts). None of the sponsors played any role in the trial's design, data analysis, or the decision to report the results.

Results

We assessed 2292, 2210, and 2203 participants from the MeDiet+EVOO, MeDiet+nuts, and control diet, respectively. They had been recruited in10 of the 11 PREDIMED centers and were free of AF at baseline (Figure 1). The 3 groups were well balanced with regard to baseline characteristics (Table 1).

After a median follow-up of 4.7 years (interquartile range, 2.8–5.8 years), a total of 253 new cases of AF occurred: 72 in the group assigned to MeDiet+EVOO, 92 in the group assigned to MeDiet+nuts, and 89 in the control diet group. Taking into account differences in the accrual of person-years among the 3 groups, AF rates were 6.8, 9.9, and 10.1 per 1000 person-years, respectively (Table 2). The unadjusted hazard ratios (HRs) were 0.62 (95% confidence interval [CI], 0.45–0.85; P=0.003) for MeDiet+EVOO and 0.89 (95% CI, 0.65–1.20; P=0.43) for MeDiet+nuts (Figure 2) compared with the control diet. Further adjustment for multiple covariates rendered similar results, as expected from the randomized design (Table 2). When the primary event of the PREDIMED trial (ie, stroke, myocardial infarction, or cardiovascular death) was added to AF as the combined outcome for this model, the protective effect of MeDiet+EVOO was unchanged. Similarly, the protective effect of MeDiet+EVOO remained when the primary event was included as an independent covariate and treated as time-dependent exposure and when follow-up was censored when the primary end point occurred (Table 2).

The observed associations between some covariates introduced in the multivariable models and AF paralleled those of a recently proposed prediction model based on several large cohorts.[20] We found positive associations for age (HR, 1.29; P<0.001 per 5 years), height (HR, 1.29; P=0.039 per 10 cm), weight (HR, 1.37; P=0.004, per 15 kg), and treatment with antihypertensive agents (HR, 1.70; P=0.005), as well as an inverse association (consistent with the Framingham Heart Study and other cohorts)[16] with diastolic blood pressure (HR, 0.84; P=0.007 per 10 mm Hg). A nonsignificant positive association (HR, 1.06, P=0.22 per 10 mm Hg) was found for systolic blood pressure, and a nonsignificant inverse association was found for statin use (HR, 0.84; P=0.22; Table I in the online-only Data Supplement). Male sex (HR, 1.69; P<0.001) in an age-adjusted model and previous diagnosis of

Table 1. Summary of Participants' Baseline Characteristics According to Randomized Interventions: PREDIMED, 2003 to 2010

	MeDiet + EVOO (n=2292)	MeDiet + Nuts (n=2210)	Control Group (n=2203)
Female sex	1343 (58.6)	1200 (54.3)	1323 (60.1)
Age, y	66.9±6.2	66.6±6.1	67.4±6.3
Educational level: primary education or less	1795 (78.3)	1687 (76.3)	1787 (81.1)
Smoking status			
Current smokers	318 (13.9)	315 (14.3)	296 (13.4)
Former smokers	561 (24.5)	556 (25.2)	523 (23.7)
Body mass index, kg/m^2	30.0±3.8	29.8±3.8	30.3±4.1
Weight, kg	76.8±11.8	76.7±11.9	77.2±12.2
Height, cm	160±8.8	160±8.8	159±8.9
Waist to height ratio	0.63±0.06	0.63±0.07	0.63±0.07
Hypertension	1897 (82.8)	1839 (83.2)	1855 (84.2)
Systolic BP, mm Hg	147±19	148±18	148±19
Diastolic BP, mm Hg	92±14	93±14	93±14
Type 2 diabetes mellitus	1150 (50.2)	1022 (46.2)	1071 (48.6)
LDL cholesterol, mg/dL	131±34	128±34	127±37
HDL cholesterol, mg/dL	54±14	54±14	54±15
Triglycerides, mg/dL	137±79	136±78	138±75
Adherence to MeDiet (14 items)	8.8±2.0	8.8±2.0	8.3±2.0
Physical activity, MET·min/d	225±227	245±247	206±233
Use of statins	930 (40.6)	876 (39.6)	882 (40.0)
Use of digoxin, antiarrhythmic drugs, or AV nodal blocking agents	334 (14.6)	329 (14.9)	346 (15.7)
Use of aspirin/antiplatelet drugs	428 (18.7)	444 (20.1)	451 (20.5)
Previous history of arrhythmia*	154 (6.7)	164 (7.4)	163 (7.4)

Values are n (%) or mean±SD. AV indicates atrioventricular; BP, blood pressure; EVOO, extravirgin olive oil; HDL, high-density lipoprotein; LDL, low-density lipoprotein; MeDiet, Mediterranean diet; MET, metabolic equivalents; and PREDIMED, Prevención con Dieta Mediterránea.

*Previous history of arrhythmia did not include atrial fibrillation.

hypertension (HR, 1.53; *P*=0.030) in a sex- and age-adjusted model were also significantly associated with higher risk.

The observed reduction in the risk of AF in the MeDiet+EVOO group was similar across the assessed subgroups, with no evidence of statistical interaction (Table 3). Sensitivity analyses showed that the effect of MeDiet+EVOO was robust under different analytic scenarios (Table 4).

Participants who during any of the yearly follow-up visits attained a higher consumption of energy-adjusted EVOO exhibited the strongest reductions in the incidence of AF (Figure I and Table II in the online-only Data Supplement). In these ancillary analyses with updated dietary information, for each additional 5% of energy intake from EVOO, the HR was 0.90 (95% CI, 0.84–0.96; *P*=0.002).

Finally, in an analysis that considered incident stroke as the outcome, adjustment for incident AF as a time-dependent covariate did not impact the magnitude of the effect of the dietary interventions (Table III in the online-only Data Supplement).

Discussion

In this secondary analysis of the PREDIMED randomized trial, we found that significant protection against AF was afforded by a MeDiet supplemented with EVOO. The advantages of a traditional MeDiet rich in EVOO compared with the advice to reduce all types of fat with respect to stroke, myocardial infarction, or cardiovascular death were also extended to a significant 38% reduction in the relative risk of AF. A high consumption of EVOO (≥15% of total energy intake) was instrumental for obtaining this significant protection. Only a small, nonsignificant risk reduction was observed with the MeDiet enriched with nuts.

We found no previous trial that assessed the effect of a MeDiet on AF. Previous epidemiological assessments of dietary exposures in relation to AF have obtained inconsistent results.[23–25] A potential protective effect of long chain omega-3 fatty acids from fish, especially docosahexaenoic acid, has been suggested in some[26,27] but not all[23–25,28,29] studies. To the best of our knowledge, there are no data from observational epidemiological studies to support or refute an association between EVOO consumption and reduced AF risk. A recent case-control study conducted in Italy[30] found an inverse association between adherence to the MeDiet and AF. The MeDiet score used in that study included high consumption of olive oil as one of its components, but no specific estimate for the association between olive oil consumption and the risk of AF was reported.

Table 2. Incidence of AF According to Intervention: Intention-to-Treat Analyses—PREDIMED Trial, 2003 to 2010

	MeDiet + EVOO (n=2292)	MeDiet + Nuts (n=2210)	Control (n=2203)
Cases, n	72	92	89
Person-years of follow-up	10 634	9333	8851
Crude rate/1000 person-years (95% CI)	6.8 (5.3–8.5)	9.9 (8.0–12.1)	10.1 (8.1–12.4)
Hazard ratios of AF by intervention group (95% CI)			
Crude model	0.62 (0.45–0.85)	0.89 (0.65–1.20)	1 (Reference)
Age- and sex-adjusted model	0.64 (0.46–0.88)	0.90 (0.66–1.22)	1 (Reference)
Multivariate-adjusted model 1*	0.62 (0.44–0.85)	0.86 (0.63–1.17)	1 (Reference)
Multivariate-adjusted model 2†	0.62 (0.44–0.86)	0.87 (0.64–1.18)	1 (Reference)
Multivariate-adjusted model 3‡	0.62 (0.45–0.88)	0.90 (0.66–1.23)	1 (Reference)
Hazard ratios of AF or major CVD event			
Crude model	0.67 (0.54–0.84)	0.83 (0.67–1.03)	1 (Reference)
Multivariate adjusted model 1*	0.71 (0.57–0.88)	0.85 (0.68–1.05)	1 (Reference)

All models were stratified by center and used robust variance estimators. AF indicates atrial fibrillation; CI, confidence interval; CVD, cardiovascular disease (stroke, myocardial infarction or cardiovascular death); EVOO, extravirgin olive oil; MeDiet, Mediterranean diet; and PREDIMED, Prevención con Dieta Mediterránea.

*Model 1 adjusted for age, sex, smoking (never, current, or former smoker), educational level, baseline height, body mass index, waist to height ratio, diabetes mellitus, hypertension, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, baseline systolic blood pressure, diastolic blood pressure, antihypertensive treatment, statin use, baseline adherence to the MeDiet, and preexisting arrhythmias.

†Model 2 was additionally adjusted for the nonfatal component of the primary end point (myocardial infarction, stroke) of the PREDIMED trial as a time-dependent covariate.

‡As in model 1 but with censoring of individuals at the time of nonfatal primary end points (myocardial infarction, stroke).

The strong relative risk reduction against AF found in the PREDIMED trial for EVOO in the context of a MeDiet pattern is highly relevant given the need for interventions aimed at the primary prevention of AF. Several potential mechanisms could explain the observed inverse association. First, the present results are congruent with the hypothesis of an inflammatory component in the pathogenesis of AF[8,31] and with the demonstrated anti-inflammatory effects of EVOO, attributed to its richness in phenolic compounds.[7,32,33] The association between a proinflammatory state and incidence of AF has been demonstrated extensively. For instance, higher levels of inflammatory markers, such as C-reactive protein or interleukin 6, have been associated with the risk of AF in prospective studies. The frequent occurrence of AF after cardiac surgery and the association between pericardial fat volume and AF also support the inflammatory origin of this arrhythmia. EVOO, in the context of a MeDiet pattern, could decrease this inflammatory response. Second, oxidative stress can play a role in the development of AF.[34] Markers of oxidative stress have been found to be higher in

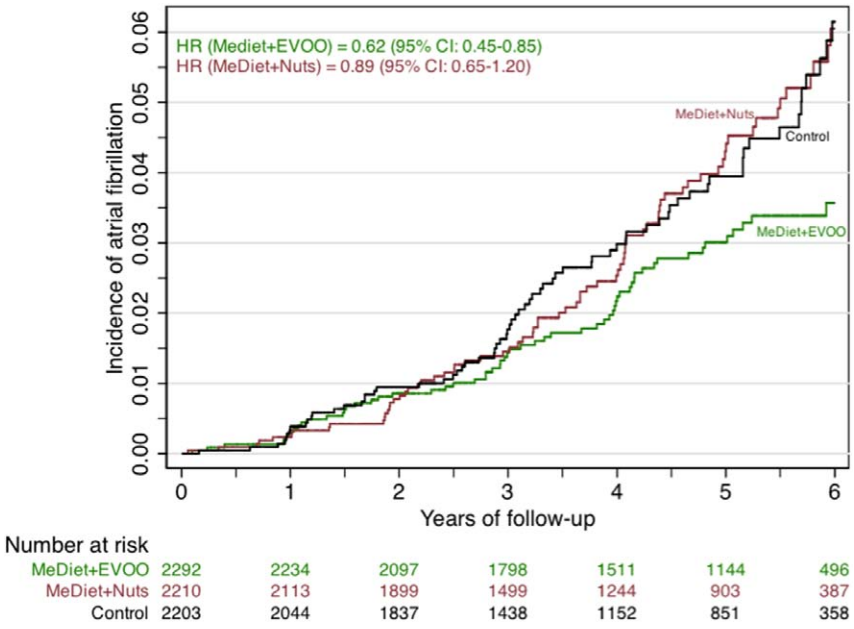

Figure 2. Incidence of atrial fibrillation by randomized group. Crude hazard ratios (95% confidence intervals) for the PREDIMED (Prevención con Dieta Mediterránea) trial, 2003 to 2010. CI indicates confidence interval; EVOO, extravirgin olive oil; HR, hazard ratio; and MeDiet, Mediterranean diet.

Table 3. Subgroup Analyses of the Incidence of AF by Intervention Group: PREDIMED Trial, 2003 to 2010

	Events/Total			Hazard Ratios (95% CI)		*P* for Interaction	
	MeDiet + EVOO	MeDiet + Nuts	Control	MeDiet + EVOO	MeDiet + Nuts	EVOO	EVOO + Nuts
Sex							
Male	36/949	54/1010	46/880	0.66 (0.42–1.03)	0.87 (0.57–1.33)	0.61	0.87
Female	36/1343	38/1200	43/1323	0.55 (0.33–0.90)	0.85 (0.54–1.34)		
Age, y†							
<70	35/1484	59/1476	37/1353	0.80 (0.50–1.29)	1.20 (0.77–1.85)	0.48†	0.16†
≥70	37/808	33/734	52/850	0.48 (0.30–0.77)	0.59 (0.36–0.96)		
Diabetes mellitus							
No	38/1142	46/1188	46/1132	0.70 (0.44–1.10)	0.87 (0.55–1.37)	0.38	0.68
Yes	34/1150	46/1022	43/1071	0.47 (0.29–0.77)	0.78 (0.50–1.21)		
BMI, kg/m^2							
<30	31/1204	42/1212	43/1106	0.50 (0.31–0.80)	0.69 (0.43–1.09)	0.71	0.38
≥30	41/1088	50/998	46/1097	0.72 (0.45–1.15)	1.10 (0.71–1.69)		
Statin use							
No	52/1362	60/1334	55/1321	0.73 (0.49–1.09)	0.89 (0.60–1.30)	0.22	0.46
Yes	20/930	32/876	34/882	0.43 (0.22–0.81)	0.86 (0.51–1.44)		
BP-lowering drugs							
No	18/741	26/723	16/660	0.90 (0.45–1.81)	1.30 (0.67–2.52)	0.81	0.52
Yes	54/1551	66/1487	73/1543	0.58 (0.40–0.83)	0.79 (0.55–1.13)		
MeDiet adherence at baseline (0 to 14 score)							
<9	43/1432	54/1354	62/1568	0.61 (0.40–0.92)	0.87 (0.59–1.29)	0.83	0.93
≥9	29/860	38/856	27/635	0.63 (0.37–1.08)	0.85 (0.50–1.44)		

All models are fully adjusted for the confounders shown in model 1 in Table 2, stratified by center and estimated with use of robust standard errors.

AF indicates atrial fibrillation; BMI, body mass index; BP, blood pressure; CI, confidence interval; EVOO, extravirgin olive oil; MeDiet, Mediterranean diet; and PREDIMED, Prevención con Dieta Mediterránea.

*Two interactions were assessed: (1) Only for the effect of MeDiet + EVOO (1 degree of freedom) and (2) for both groups (2 degrees of freedom).

†The interaction with age was assessed with age as a continuous variable.

AF patients than in control subjects, and higher levels of reactive oxygen species have been associated with atrial remodeling and increased vulnerability to AF. The antioxidant effects of virgin olive oil are well demonstrated.[32,33,35–37] In this context, a dietary pattern with strong anti-inflammatory and antioxidant effects is likely to be beneficial. Finally, the effect could have been mediated through a decrease in CVD, which is a known risk factor for AF.[20] However, an analysis that adjusted for the primary end point of the PREDIMED trial (myocardial infarction, stroke, or CVD death) provided similar results, which suggests that other mechanisms might be responsible.

The difference in the effects of the 2 active interventions using an identical MeDiet pattern as the background diet is also consistent with an inflammatory and oxidative pathogenesis for AF. The anti-inflammatory effects of EVOO supplements given in the PREDIMED trial are likely to be superior to those of tree nuts. EVOO represented 22% of total calories in the MeDiet+EVOO group at the end of the trial, whereas nuts only accounted for 8% of calories in the MeDiet+nuts group.[12] This superiority can be explained not only on these quantitative terms but also by the higher content of polyphenols with known anti-inflammatory and antioxidant properties in EVOO.[32–37] Moreover, a previous analysis of the PREDIMED trial found a significant reduction in C-reactive protein among participants assigned to the MeDiet+EVOO group but not in those assigned to the MeDiet+nuts group.[38]

The strengths of the present study are many, including the randomized design and the adjustment for a wide array of potential confounders in multivariable analyses with little indirect evidence of residual confounding. Similarly, the large sample size and the long follow-up period allowed us to obtain relatively precise estimates. Finally, the consistency of predictors of AF with previous findings, the concordance of intention-to-treat and per protocol analyses pointing in the same direction, the robustness of the protection afforded by MeDiet+EVOO in several sensitivity analyses, and the strong magnitude of the observed risk reduction make our results less likely to be attributed to bias.

We also acknowledge limitations. First, AF was not the primary end point of the PREDIMED trial, and the present assessment should be considered only as a secondary analysis of a previous trial. In addition, no specific study on the validity or reliability of the adjudication process for AF cases was conducted. Thus, despite the review of medical records and ECGs by the Adjudication Committee, false-positive diagnoses may have occurred, and some undiagnosed cases may have been missed. In addition, AF events that may occur in the context of some reversible causes, such as hyperthyroidism or sepsis, were not excluded by the protocol for event

Table 4. Sensitivity Analyses: Incidence of AF by Intervention Group—PREDIMED Trial, 2003 to 2010

	Multivariable-Adjusted HRs (95% CI) vs Control Diet Group*	
	MeDiet + EVOO	MeDiet + Nuts
All participants	0.62 (0.44–0.85)	0.86 (0.63–1.17)
Adjustment for the same variables included in the predictive model of Salas-Salvadó et al[16]	0.63 (0.46–0.88)	0.91 (0.67–1.24)
Excluding AF occurring in the first year	0.60 (0.42–0.85)	0.88 (0.64–1.22)
Excluding AF occurring after ≥6 y	0.62 (0.43–0.89)	0.88 (0.63–1.24)
According to follow-up time†		
<2 y (51 events)	0.92 (0.49–1.73)	0.80 (0.41–1.59)
2–4 y (73 events)	0.51 (0.29–0.91)	0.70 (0.40–1.21)
>4 y (118 events)	0.55 (0.33–0.92)	1.06 (0.67–1.68)
P for time-varying covariate	0.25	0.91
Excluding previous arrhythmias	0.61 (0.43–0.87)	0.86 (0.61–1.19)
Excluding incident CVD events	0.61 (0.44–0.86)	0.91 (0.66–1.24)
Competing risk analysis‡	0.64 (0.46–0.88)	0.89 (0.66–1.20)
Using center as a random effect	0.66 (0.48–0.91)	0.92 (0.68–1.24)
Poisson regression model (rate ratios)	0.61 (0.45–0.84)	0.96 (0.72–1.30)
Excluding those without contact for ≥2 y	0.70 (0.50–0.98)	0.95 (0.69–1.31)
Imputed AF for all without contact for ≥2 y	0.43 (0.34–0.53)	0.60 (0.49–0.74)
Multiple imputation if without contact for ≥2 y	0.64 (0.46–0.89)	0.99 (0.73–1.34)
Multiple imputation including the excluded recruiting center	0.65 (0.48–0.89)	0.90 (0.67–1.17)

AF indicates atrial fibrillation; CI, confidence interval; CVD, cardiovascular disease; EVOO, extravirgin olive oil; HR, hazard ratio; MeDiet, Mediterranean diet; and PREDIMED, Prevención con Dieta Mediterránea.

*Unless otherwise stated, all models were adjusted for age, sex, smoking (never, current, or former smoker), educational level, baseline height, body mass index, waist to height ratio, diabetes mellitus, hypertension, low-density-lipoprotein cholesterol, high-density-lipoprotein cholesterol, baseline systolic blood pressure, diastolic blood pressure, antihypertensive treatment, statin use, baseline adherence to the MeDiet, and preexistent arrhythmias.

†Although no association was apparent during the first 2 years of the trial, no evidence of a departure from the proportionality of hazards was found, and the test for time-varying covariates was not statistically significant.

‡Considering death as a competing risk.

adjudication. Notwithstanding this secondary approach, randomization resulted in comparable groups in such a large sample. Additionally, the blinded assessment of the outcome by a specific independent Adjudication Committee, which used highly specific criteria, allays the fear of potential misclassification biases. Consequently, the randomized design provides strong internal validity to the present findings. Second, 1 of the 11 recruiting centers of the PREDIMED trial did not collect information on AF incidence during follow-up; hence, the 667 participants from that center were not assessed. However, these subjects were evenly distributed in the 3 randomized groups (230, 215, and 222; Figure 1) and they represented only 9% of the total cohort. Their baseline characteristics were similar to those of participants from the other 10 recruiting centers. Third, the study sample consisted of older white individuals at high cardiovascular risk, with limited generalizability of the present results to other age groups or ethnicities, healthy subjects, or individuals with other pathologies. Fourth, we may have missed some diagnoses of AF, especially among participants lost to follow-up for ≥2 years; however, we obtained the available information on AF from their medical records, and the number of dropouts was larger in the control group (241) than in the MeDiet+EVOO group (87). Thus, there would have been more undetected new cases of AF in the control group, and we possibly underestimated rather than overestimated the protection afforded by EVOO. Finally, the present study does not define the minimal amount of EVOO intake required to have an effect on AF risk, which hinders direct translation of these findings to clinical practice.

In summary, the PREDIMED trial provides suggestive evidence of a reduction in the risk of AF by increased consumption of EVOO in the context of a traditional MeDiet pattern. This finding deserves further assessment and replication in future trials. Future research should also explore the underlying mechanisms and the implications of these findings in the prevention of AF complications, including heart failure, stroke, dementia, and overall mortality.

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Disclosures

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CLINICAL PERSPECTIVE

Currently, no established interventions exist for the primary prevention of atrial fibrillation (AF). The PREDIMED (Prevención con Dieta Mediterránea) randomized primary prevention trial showed that a Mediterranean diet supplemented with either extravirgin olive oil or mixed nuts reduces the incidence of stroke, myocardial infarction, and cardiovascular mortality in a high-risk population. We assessed in the PREDIMED trial the effect of these diets on the incidence of AF. During an average follow-up of 4.7 years, 246 incident AF events were identified among 6705 eligible participants. Incidence of AF was lower in individuals assigned to the Mediterranean diet supplemented with extravirgin olive oil (hazard ratio, 0.62; 95% confidence interval, 0.45–0.85) than in those in the control diet group. No effect was found for the Mediterranean diet with nuts (hazard ratio, 0.89; 95% confidence interval, 0.65–1.20). The anti-inflammatory and antioxidant effects of extravirgin olive oil in the context of a Mediterranean diet may explain this effect. Further studies replicating these results and exploring the underlying mechanisms are necessary. This analysis provides suggestive evidence to recommend the Mediterranean diet rich in extravirgin olive oil as a strategy in the primary prevention of AF.

Extravirgin Olive Oil Consumption Reduces Risk of Atrial Fibrillation: The PREDIMED (Prevención con Dieta Mediterránea) Trial

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SUPPLEMENTAL MATERIAL

Supplemental Methods

Multiple imputation analysis

We conducted the multiple imputation procedures only as sensitivity analyses as recommended by Groenwold RH et al (Am J Epidemiol 2012;175(3):210-7). In the first analysis using multiple imputation ("Multiple imputation if without contact for >=2 y" in Table 4), we imputed the end-point for 447 participants. We used the multivariate normal regression procedure and the logistic regression procedure for length of follow-up and event, respectively, in Stata 12.1 (*mi estimate* command). The imputation methods available in Stata obtain imputations by simulating from a Bayesian posterior predictive distribution of the missing data (or its approximation) under the conventional (or chosen) prior distribution. When a pattern of missing values is arbitrary, iterative methods are used by Stata to fill in missing values. The multivariate normal method uses multivariate normal data augmentation to impute missing values of continuous imputation variables. Predictors for the imputations were: sex, age, smoking, height, body mass index, waist-to-height-ratio, blood lipids (LDL and HDL), systolic and diastolic blood pressure, hypertension, educational level and group allocation. We were aware that a common mistake that may lead to biased estimates is when an outcome variable of the analysis model is not used in the imputation model used to impute independent covariates. However, we imputed here the outcome, not the independent covariates (which only had <1% of missing values), and we used the allocated dietary groups as predictors. We run 20 sets of random imputations.

Supplemental Table 1. Association of selected baseline characteristics with the incidence of AF. Hazard Ratios (HR) and 95% confidence intervals (CI). The PREDIMED Trial, 2003-2010.

	HR (95% CI)	P-value
Male sex	1.01 (0.68, 1.52)	0.95
Age, 5 years increment	1.29 (1.16, 1.44)	<0.001
Smoking		
Never smoker	1 (ref.)	
Former smoker	1.17 (0.83, 1.65)	0.38
Current smoker	1.27 (0.83, 1.96)	0.27
Height, 10 cm increment	1.29 (1.01, 1.64)	0.04
Weight, 15 kg increment	1.37 (1.11, 1.68)	0.004
Diabetes	0.96 (0.73, 1.27)	0.77
Hypertension	1.05 (0.65, 1.69)	0.84
Systolic blood pressure, 10 mmHg increment	1.06 (0.97, 1.15)	0.22
Diastolic blood pressure, 10 mmHg increment	0.84 (0.73, 0.95)	0.007
BP lowering medication	1.70 (1.18, 2.46)	0.005
Use of statins	0.84 (0.63, 1.11)	0.22

Cox proportional hazards model adjusting for all covariates in the table plus assigned treatment, education, LDLc, and HDLc, stratified by center and using robust variance estimators.

Supplemental Table 2. Incidence of AF according to attained consumption of extra-virgin olive oil during the follow-up period. Per protocol analysis. The PREDIMED trial 2003-2010.

	Attained consumption of energy-adjusted EVOO (>= 3 upper quintiles)	
	No	Yes
Cases	109	144
Person-years of follow-up	7 014	21 805
Crude rate/1000 person-years (95% CI)	15.5 (12.8-18.7)	6.6 (5.6-7.8)
Hazard ratios of AF (95% CI) *entire sample*		
Crude model*	1 (ref.)	0.34 (0.26-0.45)
Age- and sex-adjusted model*	1 (ref.)	0.36 (0.27-0.47)
Multivariate adjusted model* (a)	1 (ref.)	0.35 (0.27-0.47)
Additionally adjusted for both intervention groups (a)	1 (ref.)	0.36 (0.26-0.50)
Hazard ratios of AF (95% CI) *in each arm*		
Within the MeDiet+EVOO* (a)	1 (ref.)	0.15 (0.08-0.31)
Within the MeDiet+Nuts* (a)	1 (ref.)	0.41 (0.25-0.69)
Within the Control group* (a)	1 (ref.)	0.39 (0.24-0.64)
p for interaction (2 df)		0.068
p for interaction (1 df)		0.023

EVOO: Extra-virgin olive oil

CI: confidence interval

MeDiet: Mediterranean diet

AF: atrial fibrillation

df: degrees of freedom

(a) Adjusted for age, sex, smoking (never, current or former smoker), educational level, baseline height, body mass index, waist-to-height ratio, diabetes, hypertension, low-density-lipoprotein-cholesterol, high-density-lipoprotein-cholesterol, baseline systolic blood pressure, diastolic blood pressure, anti-hypertensive treatment, statin use, baseline adherence to the MeDiet and pre-existent arrhythmias.

*All models were stratified by centre and used robust variance estimators.

Supplemental Table 3. Incidence of stroke according to intervention.

Intention to treat analyses. The PREDIMED trial 2003-2010

	MedDiet + EVOO (n=2292)	MedDiet + Nuts (n=2210)	Control (n=2203)
Incident cases of **stroke**	45	27	52
Person-years of follow-up	10 731	9 353	8 856
Crude rate/1000 person-years (95% CI)	4.2 (3.1-5.6)	2.9 (1.9-4.2)	5.9 (4.4-7.7)
Hazard ratios of **stroke** by intervention group (95% CI)			
Crude model*	0.68 (0.46-1.02)	0.48 (0.30-0.78)	1 (ref.)
Additionally adjusted for incident AF**	0.69 (0.46-1.02)	0.49 (0.30-0.78)	1 (ref.)
Age- and sex-adjusted model*	0.70 (0.47-1.04)	0.50 (0.31-0.80)	1 (ref.)
Additionally adjusted for incident AF**	0.70 (0.47-1.05)	0.50 (0.31-0.80)	1 (ref.)
Multivariate adjusted model* (a)	0.72 (0.48-1.07)	0.52 (0.32-0.84)	1 (ref.)
Additionally adjusted for incident AF**	0.73 (0.49-1.08)	0.52 (0.32-0.84)	1 (ref.)

AF: atrial fibrillation; CI: confidence interval; CVD: cardiovascular disease (stroke, myocardial infarction or cardiovascular death); MeDiet: Mediterranean diet; EVOO: Extra-virgin olive oil

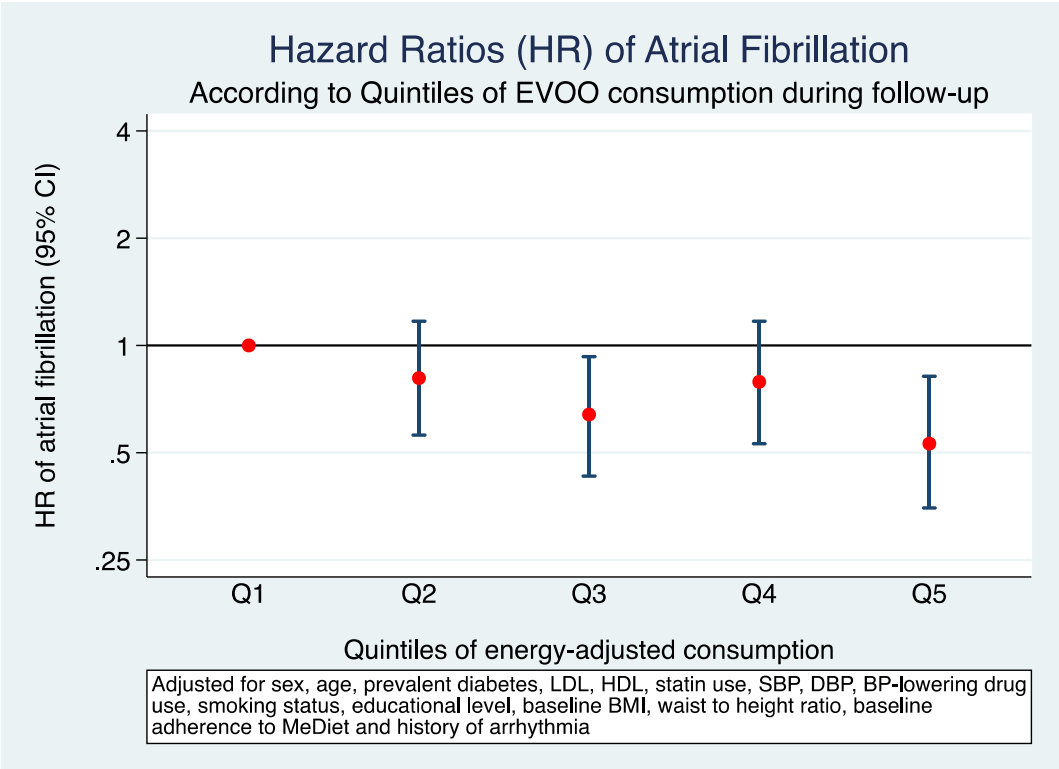
(a) Adjusted for age, sex, smoking (never, current or former smoker), educational level, baseline height, body mass index, waist-to-height ratio, diabetes, hypertension, low-density lipoprotein-cholesterol, high-density lipoprotein-cholesterol, baseline systolic blood pressure, diastolic blood pressure, anti-hypertensive treatment, statin use, baseline adherence to the MeDiet and pre-existing arrhythmias.

*All models were stratified by center and used robust variance estimators.

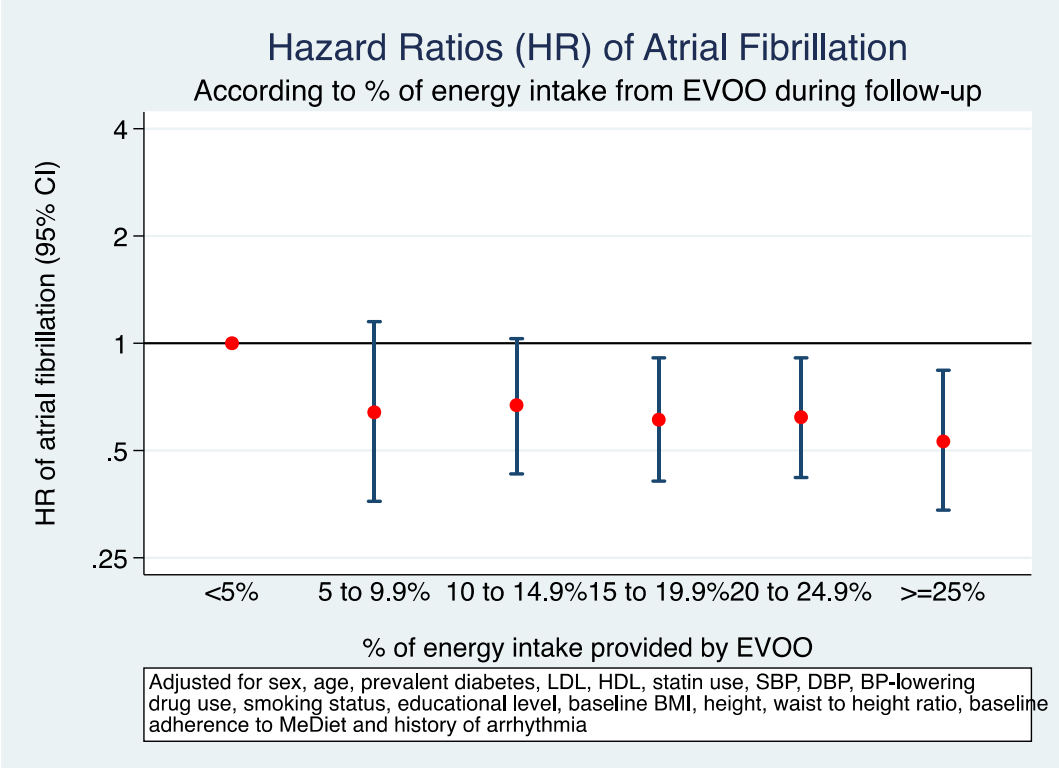
**Atrial fibrillation (used as a time-dependent exposure)

Supplemental Figure 1. Hazard ratio (HR) of AF according to observed exposures in the previous year during follow-up. Cox models with time-dependent exposures. The PREDIMED trial 2003-2010

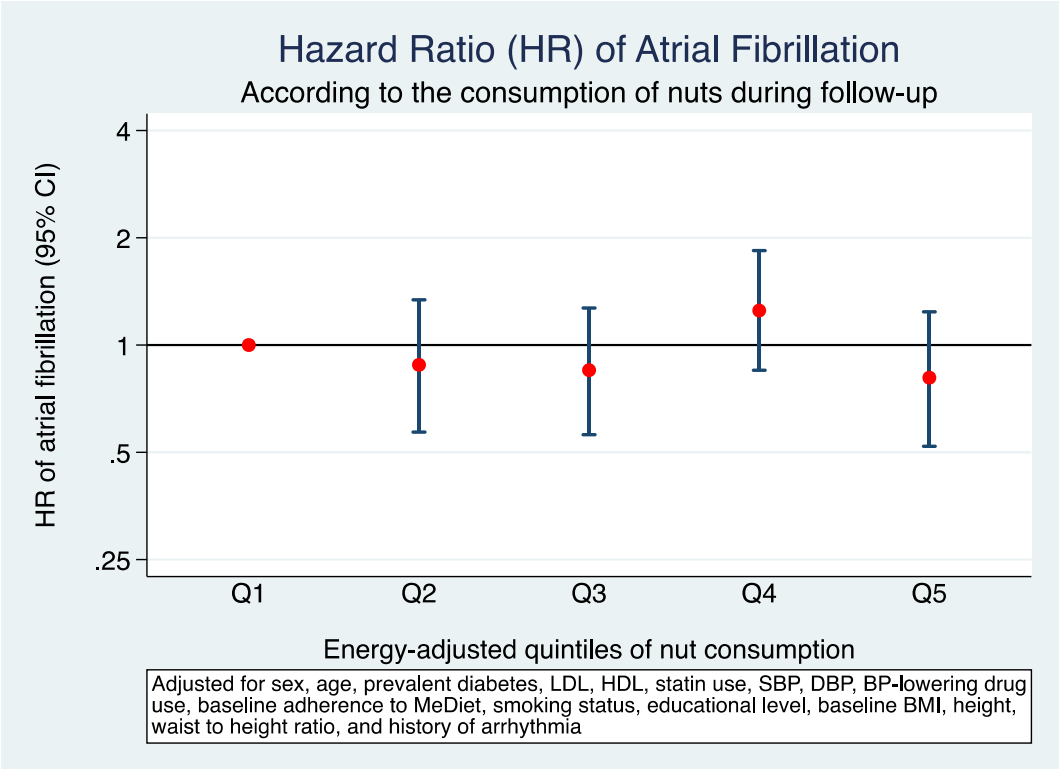
Panel A) Hazard ratio (HR) of AF by attained consumption (energy-adjusted quintiles) of extra-virgin olive oil.



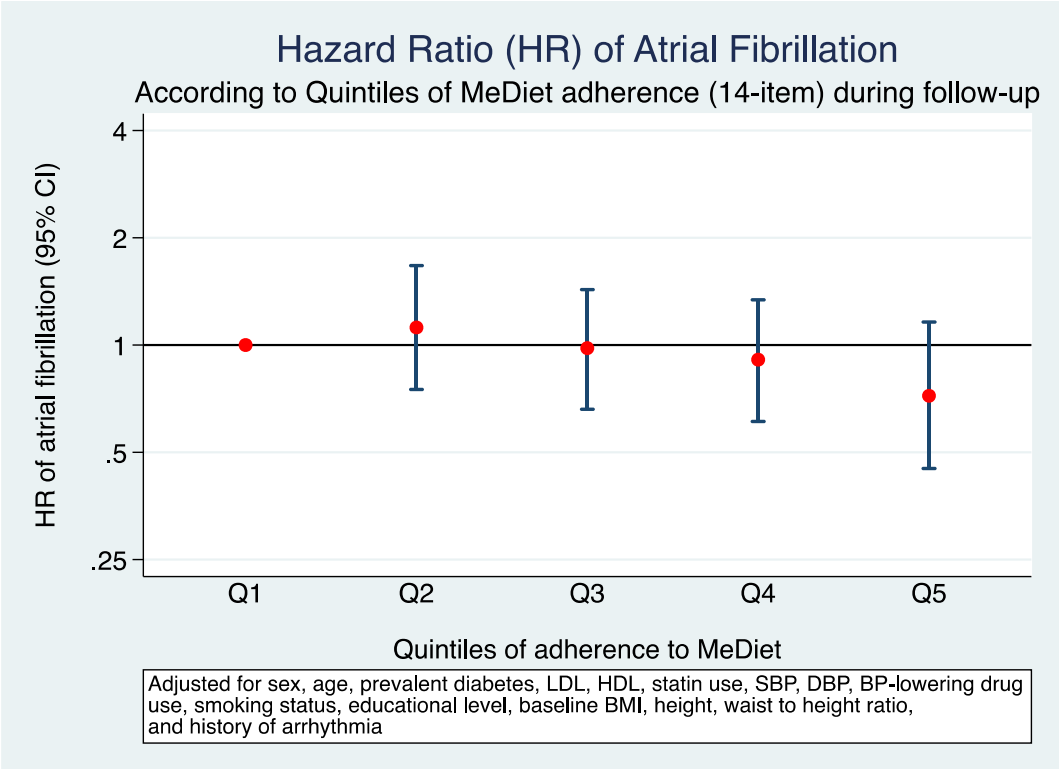
Panel B) Hazard ratio (HR) of AF by attained consumption (percentage of total energy intake) of extra-virgin olive oil.



Panel C) Hazard ratio (HR) of AF by attained consumption (energy-adjusted quintiles) of mixed nuts.



Panel D) Hazard ratio (HR) of AF by attained adherence to the Mediterranean diet during follow-up.



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