Extra-virgin olive oil and additional cardiovascular outcomes in the PREDIMED Trial: An outcome-wide perspective

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ABSTRACT

Background Olive oil, increasingly consumed in the U.S., has been inversely associated with cardiovascular disease (CVD) risk. However, previous studies did not assess a broad spectrum of CVD outcomes, incorporated repeated annual dietary assessments, or distinguished between polyphenol-rich EVOO and common olive oil (COO), which lacks these compounds.

Methods We assessed 7102 high-risk participants from the PREDIMED trial (57.5% women; aged 55-80 years), all free of CVD at baseline. Olive oil consumption was assessed annually, and cumulative average intakes of EVOO and COO were calculated. The primary outcome was a composite of myocardial infarction, stroke, peripheral arterial disease, heart failure, atrial fibrillation, or cardiovascular death, whichever occurred first. Individual outcomes were also evaluated. Time-dependent Cox models were adjusted for major confounders, including trial intervention arm.

Results Over a median follow-up of 4.7 years, 621 participants experienced at least one CVD event. Participants in the highest tertile of cumulative EVOO intake (mean: 49.2 g/d) had a 25% lower risk of the composite outcome (HR: 0.75; 95% CI: 0.60-0.94), with significant reductions in several individual CVD outcomes. In the decile analysis, the highest (mean: 60.9 g/d) versus lowest decile had a 48% lower risk (HR: 0.52; 95% CI: 0.35 to 0.79). COO consumption was not significantly associated with CVD risk when mutually adjusted for EVOO ($HR_{per\ 10\ g/d}$: 0.93; 95% CI: 0.87-1.00).

Conclusions High consumption of EVOO is associated with a substantial reduction in the risk of an outcome-wide composite of CVD events among high-risk individuals. In contrast, COO, which lacks polyphenols, showed weaker associations, highlighting the importance of differentiating olive oil types in CVD prevention strategies.

Trial Registration This trial was registered in the ISRCTN registry (ISRCTN 35739639): https://www.isrctn.com/ISRCTN35739639. (Am Heart J 2026;291:175–185.)

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The traditional Mediterranean diet (MedDiet) has long been recognized as a model for healthy eating and cardiovascular disease (CVD) prevention, supported by a robust body of epidemiological and clinical trial evidence, particularly over the past three decades. A central feature of this dietary pattern is the emphasis on fat quality, with olive oil as the primary source of fat.[1]

Olive oil consumption has risen sharply outside Mediterranean countries, including the United States, where intake increased from about 28,000 metric tons in the 1970s to over 400,000 metric tons in the 2020s.[2] Extra-virgin olive oil (EVOO) is obtained through mechanical cold pressing of olives—without chemical solvents or heat—thereby preserving a wide range of bioactive phenolic compounds. These polyphenols, such as oleocanthal and hydroxytyrosol, are efficiently absorbed and may contribute to EVOO's health benefits beyond its high monounsaturated fat content.[3,4] In contrast, common olive oil (COO) typically consists of refined olive oil (≥80%) blended with a small proportion of virgin olive oil (≤20%). The refining process—often involving heat, chemical solvents, and deodorization—removes nearly all polyphenols and other bioactive compounds, leaving primarily monounsaturated fats.

Although their fat composition is similar, EVOO and COO differ markedly in their antioxidant and anti-inflammatory properties, which may translate into different cardiovascular effects.[5,6] As a result, EVOO has gained increasing recognition for its potential to reduce the risk of CVD—including myocardial infarction (MI), stroke, and cardiovascular death—in individuals at high CVD risk.[7] Despite these findings, important gaps remain. To date, no clinical study has comprehensively evaluated the associations between different olive oil types and a broad spectrum of major CVD outcomes—including peripheral artery disease (PAD), heart failure (HF), and atrial fibrillation (AF). Moreover, previous studies have largely relied on baseline dietary data, without accounting for dietary changes over time.

For instance, Guasch-Ferré et al.[7] analyzed only baseline olive oil consumption and a limited composite CVD endpoint—MI, stroke, or CVD death—in the PREDIMED trial, which recorded 277 total events. Their analysis did not include other CVD outcomes such as PAD, HF, or AF, nor did it account for cumulative intake throughout follow-up. Other cohort studies using repeated dietary assessments did not distinguish between EVOO and COO and were conducted in U.S. populations with substantially lower olive oil consumption.[8,9] Furthermore, dietary data were collected every four years rather than annually. In contrast, yearly repeated dietary assessments may provide a more accurate and time-sensitive characterization of diet as a dynamic exposure.[10]

Observational data from the PREDIMED study provide a valuable opportunity to address these limitations. While intention-to-treat effects of the MedDiet interventions on CVD incidence have been previously reported,[11-14] those analyses did not account for actual adherence to dietary recommendations, particularly regarding EVOO consumption. Importantly, unlike most previous studies, PREDIMED allows for separate analyses of EVOO and COO, enabling a more nuanced assessment of their respective associations with CVD outcomes.

The aim of this study was to provide a robust evaluation of the associations between each olive oil type—EVOO and COO—and a wide range of adjudicated CVD outcomes, using annually repeated validated measures of intake in the context of a well-known randomized primary prevention trial (PREDIMED). By applying an outcome-wide analytical approach, we assessed both a composite CVD endpoint and its individual components: MI, stroke, PAD, HF, AF, and cardiovascular death.

Methods

Data source and ethical considerations

The design and primary results of the PREDIMED study (ISRCTN: 35739639) have been published.[11] The Institutional Review Boards of all the recruitment centers approved the overall PREDIMED trial design according to the ethical guidelines of the Declaration of Helsinki. All participants gave written informed consent. The present study adhered to most of the items in the SAGER (Sex and Gender Equity in Research) guidelines checklist. Our sample was sex-balanced, with 57.5% women. Sex differences were specifically analyzed and considered in the data analysis and interpretation where relevant. The completed SAGER checklist is provided in the Supplementary Material.

Study design and population

The PREDIMED study was a multicenter randomized primary CVD prevention trial conducted in Spain in 7,447 participants between 55 and 80 years of age, without prevalent CVD at the time of recruitment but at high CVD risk.[11,15] Participants were randomized to one of the following three dietary interventions: a Mediterranean diet supplemented with extra-virgin olive oil (MedDiet with EVOO), a Mediterranean diet supplemented with nuts (MedDiet with nuts), or a control diet consisting of advice to follow a low-fat diet. Recruitment began in June 2003 and concluded in June 2009.

This observational analysis was conducted as a prospective cohort study assessing PREDIMED trial participants. In subtype-specific analyses, participants who developed CVD outcomes other than the one being analyzed, were censored at that point in time. Additionally, AF was not consistently assessed as a relevant endpoint at one of the eleven research centers, resulting in the exclusion of 674 participants from our AF analysis.

Ascertainment of cardiovascular disease

We included only CVD events that were reviewed and blindly adjudicated by the Clinical Event Committee until December 1, 2010. Committee members were blinded to both treatment allocation and participants' dietary information. CVD outcomes included MI, stroke, PAD, HF, AF, and cardiovascular mortality. Detailed diagnostic criteria are provided in the Supplementary Material.

Dietary evaluation

A 137-item validated food frequency questionnaire (FFQ) was administered yearly in face-to-face interviews by trained dietitians. The FFQ included questions about "olive oil," "pomace olive oil," and "extra-virgin olive oil," with intake measured in tablespoons (10 g each). Participants reported their consumption frequency using nine categories: never, 1-3 times per month, weekly (1, 2-4, 5-6 times), or daily (1, 2-3, 4-6, > 6 times). Responses were converted into grams per day. COO intake was determined by summing the first two items, while the third item was used to assess EVOO intake. Information from the FFQ was also used to estimate total energy intake. The FFQ's reproducibility and validity have been previously confirmed .[16] Additionally, olive oil consumption as measured through the FFQ has been associated with a distinct metabolomic profile in the PREDIMED study. This profile has been linked to a reduced risk of incident CVD.[17] More recently, dietary patterns, with particular attention to refined carbohydrates and their overall quality, derived from the same FFQ in the PREDIMED-Plus study, have also been associated with favorable changes in CVD risk factors.[18]

Refined carbohydrate intake was estimated from FFQ items corresponding to white bread, refined breakfast cereals, white rice, refined pasta, pizza, biscuits and cookies (plain or chocolate), cakes, muffins, donuts, croissants, pastries, sponge cakes, chocolate bars, churros, savory snacks, custards, ice cream, canned fruits in syrup, sugar-sweetened beverages, packaged fruit juices, nougat, marzipan, table sugar, jams, and honey. For each item, carbohydrate content was calculated using standard portion sizes and nutrient composition values and then summed to obtain total refined carbohydrate intake (g/d).

Adherence to the traditional MedDiet was also assessed annually using the validated 14-item Mediterranean Adherence Screener (MEDAS). To evaluate dietary patterns independent of olive oil consumption, two olive oil-related items were excluded, resulting in a 12-point MEDAS score. This modified version of the MEDAS was used as a covariate in statistical models to adjust for overall adherence to the MedDiet.[19]

Anthropometric measures and other covariates

Blood pressure and anthropometric measurements, including weight, height, and waist circumference, were recorded in accordance with the study protocol by trained personnel. Other covariates collected in the PREDIMED trial have been previously described .[15]

Statistical analyses

The present observational analysis was conducted as a prospective cohort study. Participants with extreme reported total energy intake at baseline—defined as exceeding 4,000 or falling below 800 kcal per day for men and exceeding 3,500 or falling below 500 kcal per day for women—were excluded from the current analysis.[20]

We used multivariable time-dependent Cox models to estimate hazard ratios (HR) for developing total CVD and each of its individual components. Person-years of follow-up were calculated from the baseline visit date until the occurrence of a CVD event, death, or the end of follow-up. Olive oil consumption was adjusted for total energy intake using the residual model.[21] In the main models, the relevant exposure for each type of olive oil was the cumulative mean of intake, equivalent to the average values from each year up to the last follow-up visit. In an ancillary analysis, we used updated intake data, reflecting only the most recent measurement at each time point, without averaging previous values.

To control for potential confounding factors, a multivariable model was adjusted for age, educational level, body mass index (BMI), waist-to-height ratio, physical activity level at baseline, cumulative total energy intake, cumulative 12-point MEDAS score, smoking status, baseline prevalence of type 2 diabetes, dyslipidemia, hypertension, and family history of early-onset CHD. A second model was additionally adjusted for the use of statins, other lipid-lowering agents, angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs), diuretics, other antihypertensive agents, acetylsalicylic acid, insulin, and oral hypoglycemic agents. Finally, a third model further adjusted for propensity scores (based on 30 baseline variables estimating the probability of assignment to each intervention group) and by the randomized intervention group. All models were stratified by sex and recruitment center and used robust variance estimators, to account for intra-cluster correlations.

Hazard ratios were computed across three categories according to sex-specific tertiles of each type of olive oil intake, with the first tertile as the reference category. To examine linear trends, we conducted a Wald test for linearity by considering the median intake within each tertile as a continuous variable. An additional HR was computed for each 10-gram per day increment in olive oil intake. We also conducted isocaloric substitution analyses to estimate the effect of replacing 100 kcal/d of COO with EVOO, and 100 kcal/d of refined carbohydrates with EVOO.

We conducted subgroup analyses using predefined subgroups, including sex, age, intervention group, BMI, and smoking status. Potential interactions between these

stratification factors were assessed through likelihood ratio tests.

The cumulative incidence of CVD was plotted using Nelson-Aalen incidence curves, based on the joint classification of participants by average EVOO intake (< 40 g/d or ≥ 40 g/d) from baseline to the 7th year of follow-up, and by the randomized intervention arm of the trial (MedDiet or control group). These graphs were adjusted using inverse probability weighting, employing the same covariables as in the Cox regression models.

Results were presented with 95% confidence intervals (CI), and statistical significance was determined by a two-tailed p-value less than 0.05. All analyses were performed using STATA statistical software version 16 (StataCorp. 2019. Stata Statistical Software: Release 16, College Station, TX: StataCorp LLC).

Results

Description of participants

Following the exclusion of individuals with total energy intake out of predefined limits (n = 153), incomplete baseline dietary data (n = 78), and pre-existing symptoms of HF, AF, or intermittent claudication (n = 114), 7,102 participants remained for analysis (see Supplementary Figure 1 for the flowchart).

The mean age of the participants was 67 years and 57.5% of them were women. Baseline characteristics of participants, categorized by tertiles of average EVOO intake during follow-up, are detailed in Table 1. A higher average intake of EVOO during follow-up was correlated with younger age, a lower percentage of women, higher level of education, lower BMI, lower waist-to-height ratio, lower percentage of obesity, higher physical activity at baseline, higher adherence to the MedDiet (based on the 14-point MEDAS score) at baseline, a higher percentage of former smokers, and a lower percentage of dyslipidemia.

Detailed changes in cumulative EVOO intake by year throughout the follow-up period for each trial arm are available in Supplemental Figure 2. In the control group, only 20.7% of participants achieved an average EVOO intake equal to or exceeding 40 g per day during the follow-up period. In contrast, in the MedDiet with nuts group, a higher percentage of participants (32.8%) reached this goal of EVOO intake, while in the MedDiet with EVOO group, 83.1% of participants met this threshold.

Outcome data

Over a median follow-up of 4.7 years (interquartile range, 2.8-5.8 years), we identified 621 participants (8.7% of the cohort) who experienced at least one component of the CVD composite outcome—a substantially higher number than the 277 cases (3.9% of the cohort) included in prior PREDIMED assessments focused solely on MI, stroke, and cardiovascular death.[7] In our current analysis, we included 103 adjudicated cases of myocardial infarction (MI), 135 of stroke, 87 of peripheral arterial disease (PAD), 90 of heart failure (HF), 245 of atrial fibrillation (AF), and 81 cardiovascular-related mortality events (the total exceeds 621 because some participants experienced more than one event).

Crude incidence rates of the composite CVD endpoint per 100 person-years were 2.5 for the lowest tertile of cumulative EVOO intake, 2.1 for the second tertile, and 1.5 for the third tertile (Table 2). These rates showed, therefore, a consistent decreasing trend as cumulative EVOO intake increased. In the multivariable-adjusted model, which accounted for total energy intake, participants in the highest tertile of cumulative EVOO intake (mean: 49.2 g/d) had a 32% relative reduction in the risk of CVD events as compared to those in the lowest tertile (hazard ratio [HR]: 0.68; 95% confidence interval [CI]: 0.55 to 0.85; P for trend = .001). Further adjustment for the randomized intervention group slightly attenuated these results, resulting in an HR of 0.75 (95% CI: 0.60-0.94; P for trend = .02) for the highest versus the lowest tertile. When cumulative EVOO intake was divided into deciles instead of tertiles, a linear dose-response relationship emerged between EVOO intake and CVD risk, with no apparent threshold for the beneficial effects of EVOO consumption (Table 3). Comparing the highest (mean: 60.9 g/d) versus lowest deciles of cumulative EVOO intake, the HR was 0.52 (95% CI: 0.35-0.79) in the multivariable model, which included adjustment for the randomized intervention group. Ancillary analyses using updated intake data (i.e., considering only the most recent measurement at each time point) showed nearly identical results as compared to cumulative intake (see **Supplementary Table 1**).

In the continuous analysis, each 10 g/d increase in cumulative EVOO intake was associated with a 9% lower risk of the composite CVD endpoint (HR: 0.91; 95% CI: 0.87-0.95). By contrast, each 10 g/d increase in COO intake was associated with a 5% higher risk of CVD (HR: 1.05; 95% CI: 1.00-1.10). However, when both EVOO and COO were included in the regression model, the HR was 0.87 (95% CI: 0.82-0.93) for EVOO and 0.93 (95% CI: 0.87-1.00) for COO, reflecting the effect of each oil type while holding the other constant.

The isocaloric substitution analysis–including cumulative intake of EVOO, COO, and refined carbohydrates–showed that replacing 100 kcal/d of COO by EVOO was associated with a 7% lower risk of CVD (HR: 0.93; 95% CI: 0.87-0.98). Replacing refined carbohydrates by an equivalent amount of EVOO was associated with a 14% lower risk (HR: 0.86; 95% CI: 0.79-0.93). In contrast, replacing refined carbohydrates by COO showed no significant association with CVD risk (HR: 0.93; 95% CI: 0.85-1.02).

Adjusted HRs and their 95% CIs for the association between cumulative EVOO intake and each clinical ma-

Table 1. Baseline characteristics of participants according to tertile of average EVOO intake during follow-up

Tertile of average EVOO intake during follow-up	T1	T2	T3
N	2,368	2,367	2,367
Mean follow-up EVOO intake (SD), g/d	8.5 (8.0)	33.0 (5.5)	50.9 (6.6)
Female sex %	60.60 %	59.5 %	52.9 %
Mean age (SD), years	67.5 (6.3)	66.9 (6.1)	66.6 (6.1)
Mean education level (SD), years	3.7 (2.0)	3.9 (2.2)	4.2 (2.4)
Marital status, % married	73.9 %	76.1 %	78.9 %
Mean BMI (SD), kg/m²	30.1 (4.0)	29.9 (3.9)	29.8 (3.7)
Mean waist-to-height ratio (SD)	0.64 (0.07)	0.63 (0.07)	0.62 (0.06)
Mean leisure-time physical activity level (SD), MET min/d	220 (242)	220 (235)	252 (237)
Mean total energy intake level (SD), kcal/d	2,151 (438)	2,171 (390)	2,234 (377)
Mean MEDAS score (SD)	9.5 (2.0)	10.1 (1.9)	10.7 (1.8)
Current smoker % *	14.6 %	13.0 %	14.1 %
Former smoker % *	21.3 %	23.7 %	28.2 %
Type 2 diabetes †	50.3 %	47.7 %	47.8 %
Overweight ‡	92.9 %	92.2 %	92.4 %
Obesity ‡	48.5 %	46.9 %	45.2 %
Family history of early-onset CHD §	22.1 %	23.9 %	21.0 %
Dyslipidaemia ‖	72.8 %	73.5 %	70.6 %
Hypertension #	82.6 %	82.3 %	83.1 %
Medication use			
Statins	40.0 %	40.8 %	40.0 %
Diuretics	21.2 %	20.6 %	21.8 %
Other lipid-lowering agents	5.1 %	5.7 %	5.2 %
ACE inhibitors or ARBs	49.6 %	47.5 %	51.0 %
Other antihypertensive agents	28.6 %	30.3 %	28.2 %
Acetylsalicylic acid	19.6 %	19.8 %	18.5 %
Insulin	5.7 %	4.9 %	4.9 %
Oral hypoglycaemic agents	30.9 %	29.6 %	28.9 %

SD: Standard deviation. BMI = Body mass index. MET = Metabolic equivalent. MEDAS = Mediterranean diet adherence score (on a scale of 0 to 14). ACE = Angiotensin-converting enzyme. ARB = Angiotensin receptor blockers.

* Current smoker was defined as more than one cigarette, cigar, or pipe per day. Former smoker was defined as no smoking for at least 1 year.

† Diabetes was defined as a fasting blood glucose level of 126 mg per decilitre (7.0 mmol per litre) or higher on two occasions, a 2-hour plasma glucose level of 200 mg per decilitre (11.1 mmol per litre) or higher during a 75 g oral glucose-tolerance test, or the use of antidiabetic medication.

‡ Overweight was defined as BMI ≥ 25 kg/m² and obesity as BMI ≥ 30 kg/m².

§ A family history of early-onset coronary heart disease (CHD) was defined as a diagnosis of the disease in a male first degree relative younger than 55 years of age or in a female first-degree relative younger than 65 years of age.

‖ Dyslipidaemia was defined as LDL cholesterol levels ≥ 4.14 mmol/L (≥158.30 mg/dL), HDL cholesterol levels < 1.03 mmol/L (<39.77 mg/dL) in men or < 1.29 mmol/L (< 49.81 mg/dL) in women or use of lipid-lowering therapy.

Hypertension was defined as Systolic blood pressure ≥ 140 mm Hg, diastolic blood pressure ≥ 90 mm Hg, or use of antihypertensive agents.

jor CVD subtype are presented in **Supplementary Table 2**. In multivariable-adjusted analyses, cumulative consumption of EVOO was significantly inversely associated with the risk of stroke (HR $_{T3\ vs.\ T1}$: 0.58; 95% CI: 0.36-0.91; *P* for trend = .028), peripheral arterial disease (HR $_{T3\ vs.\ T1}$: 0.33; 95% CI: 0.17-0.63; *P* for trend <.001), and atrial fibrillation (HR $_{T3\ vs.\ T1}$: 0.71; 95% CI: 0.51-0.99; *P* for trend = .04). For myocardial infarction (HR $_{T3\ vs.\ T1}$: 0.75; 95% CI: 0.44-1.27; *P* for trend = .41) and cardiovascular mortality (HR $_{T3\ vs.\ T1}$: 0.69; 95% CI: 0.39-1.23; *P* for trend = .24), point estimates suggested potential inverse associations; whereas for heart failure (HR $_{T3\ vs.\ T1}$: 1.22; 95% CI: 0.69-2.14; *P* for trend = .82), a higher risk was observed. However, all three associations had wide confidence intervals, likely due to the limited number of events, and none reached statistical significance.

Subgroup analyses, which assessed the effect of the highest versus the lowest tertile of cumulative EVOO intake, showed a consistent inverse association with overall CVD risk (Figure 1). However, in certain subgroups, the results included the null value, possibly due to limited sample sizes. Of note, no significant interactions were detected with stratifying variables, which included sex, age, trial arm, BMI, and smoking status.

The cumulative risk of CVD, as estimated by weighted-adjusted Nelson-Aalen estimates, is illustrated in Figure 2, categorized by average EVOO intake during follow-up and intervention arm. In this analysis, both MedDiet groups were combined. High average EVOO intake (≥ 40 g/d) in the MedDiet groups exhibited the lowest CVD incidence rate, while the control group with low average EVOO intake (< 40 g/d) exhibited the highest rates. For a more detailed breakdown, a separate analysis was performed considering each of the three intervention groups individually (**Supplementary Figure 3**).

Table 2. Time-dependent Cox regression models assessing the risk of overall CVD by energy-adjusted tertiles of cumulative EVOO intake (g/d) during follow-up and as a continuous variable (per 10 g/d)

	Tertiles for cumulative EVOO intake				Per 10 g/d increase in EVOO intake
	T1	T2	T3		
N	2368	2368	2366		
Mean cumulative EVOO intake (g/d)	6.3 (7.3)	27.5 (5.1)	49.2 (9.4)		
N of cases	261	209	151		
Person-years	10256	9822	9910		
Incidence rate per 100 person-years (95% CI)	2.5 (2.3 - 2.9)	2.1 (1.9 - 2.4)	1.5 (1.3 - 1.8)		
Models				p for trend	
Multivariate adjusted A*	1 (ref.)	0.93 (0.77 - 1.13)	0.68 (0.55 - 0.85)	0.001	0.91 (0.87 - 0.95)
Multivariate adjusted B†	1 (ref.)	0.92 (0.76 - 1.12)	0.68 (0.55 - 0.85)	0.001	0.91 (0.87 - 0.95)
Multivariate adjusted C§	1 (ref.)	0.99 (0.81 - 1.21)	0.75 (0.60 - 0.94)	0.02	0.93 (0.89 - 0.97)

Results were presented as Hazard Ratios (95% CI).

* Adjusted for age (years), educational level (classified into six categories), BMI (kg/m²), waist-to-height ratio (continuous), physical activity level at baseline (in quintiles), cumulative total energy intake (kcal/d), cumulative 12-point MEDAS score, smoking status (never smoked, former smoker, or current smoker), prevalence of type 2 diabetes (yes/no), dyslipidaemia (yes/no), hypertension (yes/no), and family history of early-onset CHD (yes/no).

† Additionally adjusted for use of statins (yes/no), other lipid-lowering agents (yes/no), ACE inhibitors or ARBs (yes/no), diuretics (yes/no), other antihypertensive agents (yes/no), acetylsalicylic acid (yes/no), insulin (yes/no), and oral hypoglycaemic agents (yes/no). All models were stratified by sex and recruitment centre and used robust standard errors.

§ Additionally adjusted for propensity scores (based on 30 baseline variables estimating the probability of assignment to each intervention group) and by intervention group.

Table 3. Time-dependent Cox regression models assessing the risk of overall CVD by energy-adjusted deciles of cumulative EVOO intake (g/d) during follow-up. Results were presented as Hazard Ratios (95% CI).

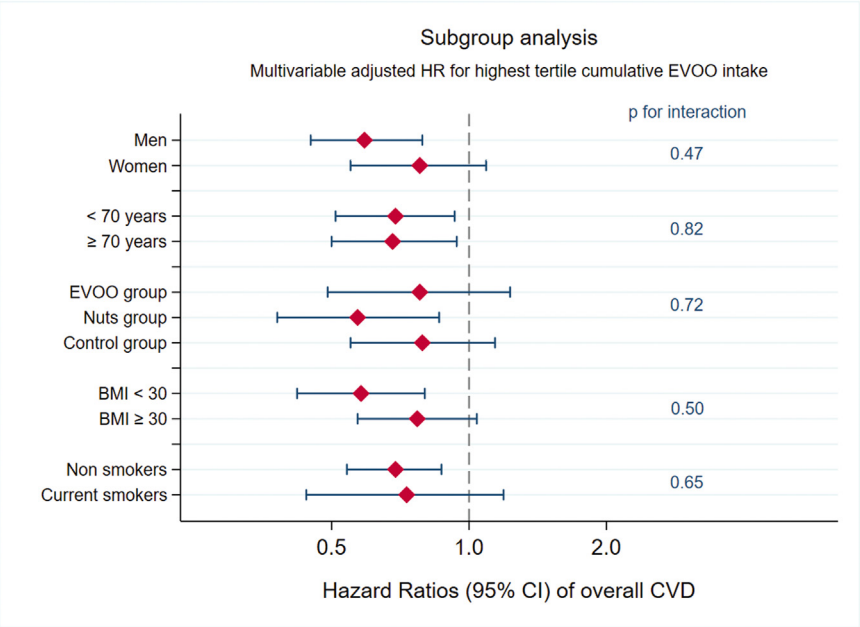
	Deciles for cumulative EVOO intake				
	D1	D2	D3	D4	D5
N	711	710	711	709	711
Mean cumulative EVOO intake (g/d)	0.0 (3.3)	4.7 (2.3)	12.4 (3.0)	19.4 (2.4)	25.2 (1.8)
N of cases	88	86	68	78	59
Person-years	3113	3082	3075	3028	2967
Incidence rate per 100 person-years (95% CI)	2.8 (2.3 - 3.5)	2.8 (2.3 - 3.4)	2.2 (1.7 - 2.8)	2.6 (2.1 - 3.2)	2.0 (1.5 - 2.6)
Models					
Multivariate adjusted A*	1 (ref.)	0.98 (0.72 - 1.32)	0.81 (0.59 - 1.11)	0.94 (0.70 - 1.28)	0.78 (0.55 - 1.10)
Multivariate adjusted B†	1 (ref.)	0.97 (0.72 - 1.31)	0.79 (0.57 - 1.08)	0.92 (0.68 - 1.26)	0.76 (0.54 - 1.07)
Multivariate adjusted C§	1 (ref.)	0.98 (0.73 - 1.33)	0.83 (0.60 - 1.14)	0.98 (0.72 - 1.34)	0.82 (0.58 - 1.17)
	D6	D7	D8	D9	D10
N	710	710	710	711	709
Mean cumulative EVOO intake (g/d)	29.9 (1.7)	35.3 (2.0)	41.3 (2.5)	49.4 (2.9)	60.9 (5.6)
N of cases	51	55	48	50	38
Person-years	2906	2888	2897	2926	3107
Incidence rate per 100 person-years (95% CI)	1.8 (1.3 - 2.3)	1.9 (1.5 - 2.5)	1.7 (1.2 - 2.2)	1.7 (1.3 - 2.3)	1.2 (0.9 - 1.7)
Models					
Multivariate adjusted A*	0.74 (0.52 - 1.05)	0.78 (0.55 - 1.09)	0.67 (0.47 - 0.96)	0.69 (0.48 - 0.98)	0.47 (0.32 - 0.71)
Multivariate adjusted B†	0.72 (0.51 - 1.02)	0.77 (0.55 - 1.09)	0.66 (0.46 - 0.95)	0.70 (0.49 - 0.99)	0.47 (0.31 - 0.71)
Multivariate adjusted C§	0.79 (0.55 - 1.13)	0.85 (0.60 - 1.20)	0.73 (0.50 - 1.04)	0.78 (0.54 - 1.12)	0.52 (0.35 - 0.79)

* Adjusted for age (years), educational level (six categories), BMI (kg/m²), waist-to-height ratio (continuous), physical activity level at baseline (in quintiles), cumulative total energy intake (kcal/d), cumulative 12-point MEDAS score, smoking status (never smoked, former smoker, or current smoker), prevalence of type 2 diabetes (yes/no), dyslipidemia (yes/no), hypertension (yes/no), and family history of early-onset CHD (yes/no).

† Additionally adjusted for use of statins (yes/no), other lipid-lowering agents (yes/no), ACE inhibitors or ARBs (yes/no), diuretics (yes/no), other antihypertensive agents (yes/no), acetylsalicylic acid (yes/no), insulin (yes/no), and oral hypoglycemic agents (yes/no). All models were stratified by sex and recruitment center and used robust standard errors.

§ Additionally adjusted for propensity scores (based on 30 baseline variables estimating the probability of assignment to each intervention group) and by intervention group.

Figure 1. Subgroup analysis for highest versus lowest tertile of EVOO cumulative intake. Adjusted for age (years), educational level (classified into six categories), BMI (kg/m²), waist-to-height ratio (continuous), physical activity level at baseline (in quintiles), cumulative total energy intake (kcal/d), cumulative 12-point MEDAS score, smoking status (never smoked, former smoker, or current smoker), prevalence of type 2 diabetes (yes/no), dyslipidemia (yes/no), hypertension (yes/no), family history of early-onset CHD (yes/no), use of statins (yes/no), other lipid-lowering agents (yes/no), ACE inhibitors or ARBs (yes/no), diuretics (yes/no), other antihypertensive agents (yes/no), acetylsalicylic acid (yes/no), insulin (yes/no), and oral hypoglycemic agents (yes/no). The analysis was also stratified by sex and recruitment center and employed robust standard errors.



Discussion

In this longitudinal analysis of the PREDIMED trial, higher EVOO intake during the intervention period—measured through annually repeated assessments—was significantly associated with a reduced risk of CVD events. Subtype-specific analyses also showed notable reductions in the incidence of stroke, PAD, and AF. However, no significant associations were identified for MI, HF, or cardiovascular mortality. In contrast to EVOO, cumulative consumption of COO was not linked to a significant decrease in the risk of CVD events.

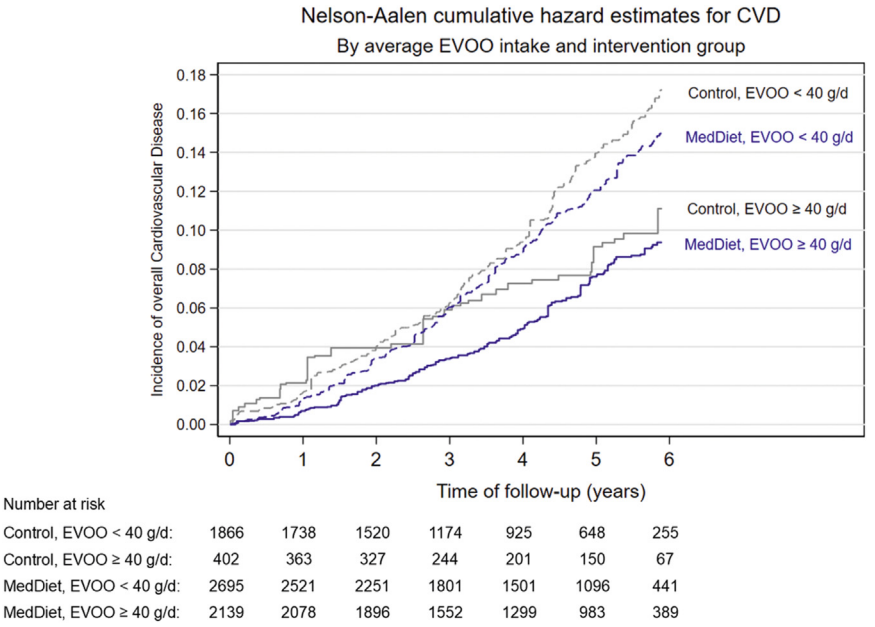
While previous findings from the PREDIMED trial provided first-level evidence that a MedDiet supplemented with EVOO reduces the incidence of major CVD events in high-risk individuals,[11] our current study builds on these findings by incorporating annual measures of EVOO intake and adopting an outcome-wide definition of CVD that includes PAD, HF, and AF—conditions not assessed in prior analyses. As a result, the number of adjudicated CVD events increased from 277 in earlier reports[7,11] to 621 in the present study.

This approach aligns with current methodological recommendations for pragmatic trial analysis, which emphasize the importance of evaluating actual compliance to the intervention.[22] It also follows the principles of outcome-wide epidemiology[23] and addresses a key limitation in nutritional epidemiology, the infrequent use of repeated exposure assessments.[10] By integrating these methodological advances, our analysis reduces confounding, provides a more accurate estimate of long-term dietary exposure, and offers a more comprehensive understanding of the cardiovascular benefits of EVOO consumption.

Our results align with extensive research, reinforcing the favorable influence of olive oil consumption—particularly EVOO—on CVD incidence. This consistent pattern has been observed across a substantial number of cohort studies, such as the Nurses' Health Study (NHS), the Health Professionals' Follow-up Study (HPFUS), the European Prospective Investigation into Cancer and Nutrition study (EPIC), the Study on Nutrition and Cardiovascular Risk in Spain (ENRICA), and the "Seguimiento Universidad de Navarra" (SUN) study.[8,9,24-26]

Regarding subtype-specific analyses, prior studies have also demonstrated beneficial outcomes of olive oil intake for stroke [25] and cardiovascular death.[9,24] While the protective effect for MI or coronary heart disease (CHD) was significant in the study by Guasch-Ferre et al.,[8] it was weaker and non-significant in the study by Donat-Vargas et al.[25] However, when it comes to the effect of olive

Figure 2. Nelson-Aalen curves of overall CVD incidence according to average EVOO (g/d) intake during follow-up and intervention group (MedDiet and control group). Inverse probability weighting was used to adjust for the following variables: age (years), educational level (six categories), BMI (kg/m²), waist-to-height ratio (continuous), physical activity level at baseline (in quintiles), average total energy intake (kcal/d), average 12-point MEDAS score, smoking status (never smoked, former smoker, or current smoker), prevalence of type 2 diabetes (yes/no), dyslipidemia (yes/no), hypertension (yes/no), family history of early-onset CHD (yes/no), use of statins (yes/no), other lipid-lowering agents (yes/no), ACE inhibitors or ARBs (yes/no), diuretics (yes/no), other antihypertensive agents (yes/no), acetylsalicylic acid (yes/no), insulin (yes/no), and oral hypoglycemic agents (yes/no). The analysis was also stratified by sex and recruitment centre and employed robust standard errors.



oil on PAD, HF, or AF, there is less available evidence. In the cross-sectional InCHIANTI study, high intake of vegetable lipids, mainly from olive oil, was associated with a reduced likelihood of PAD, defined as an ankle brachial index (ABI) of less than 0.9.[27] The same effect was found for total olive consumption in the PREDIMED-Plus study.[28] Similarly, two population-based cohort studies in Sweden reported that adherence to a MedDiet with a high EVOO intake was linked to a decreased risk of HF in individuals without CVD at baseline.[29,30] Finally, the SUN cohort study found no association between olive oil consumption and AF .[31]

Regarding the specific effects of COO, there is very limited information in the literature due to its frequent analysis alongside EVOO. Nevertheless, studies conducted by Donat-Vargas et al. have also reported either detrimental effects or non-significant beneficial effects of COO on CVD.[24,25] Our analyses suggest that the apparent adverse effect of COO is unlikely to represent a true causal relationship, but instead likely reflects lower EVOO consumption or reduced health consciousness among individuals preferring COO, rather than intrinsic harm from COO. This interpretation is supported by our analyses showing that, when EVOO intake was held constant (included as a covariate), no harm was observed for COO. Thus, while COO may provide some cardiovascular benefits through its monounsaturated fat content, these are considerably less pronounced than those associated with EVOO. Isocaloric substitution analyses further support this interpretation. Replacement of COO by EVOO was associated with reduced CVD risk, whereas replacing refined carbohydrates by COO showed a modest, though non-significant, inverse association.

An important difference between our study and U.S. cohorts such as the NHS and HPFUS is the much higher absolute intake of olive oil among PREDIMED participants. In the aforementioned U.S. cohorts, more than half of participants reported consuming one tablespoon of olive oil per month or less,[9] whereas in our study even the lowest tertile of EVOO intake averaged 6.3 g/d (approximately half a tablespoon per day). This relatively high baseline consumption in our reference group may have attenuated the strength of observed associations compared with what might be expected across a wider intake range.

The present study provides new evidence that high intake of EVOO (approximately >40 g/d), assessed through annual measurements, reduces overall CVD

risk—including stroke, PAD, and AF—in high-risk individuals. Unlike previous studies focusing mainly on CHD or stroke, our study also investigates EVOO's impact on PAD, HF, and AF.

Importantly, EVOO showed clear cardiovascular benefits, whereas COO conferred only small, if any, benefits, despite their similar monounsaturated fat content. This contrast suggests that bioactive compounds—particularly polyphenols—play a central role in the cardioprotective effects of EVOO, which are largely absent in COO due to the refining process.

The high polyphenol and antioxidant content of EVOO may explain its protective effects against stroke and PAD, as it helps reduce inflammation and oxidative stress. In stroke, its antioxidant properties may counteract ischemia-induced damage, improving cerebral circulation and reducing thrombus formation. Similarly, in PAD, EVOO may slow atherosclerosis progression by enhancing endothelial function and reducing local inflammation, key factors in peripheral artery health.

However, conditions like CHD and HF involve more complex and heterogenous mechanisms, such as endothelial dysfunction and cardiac remodeling. While EVOO offers anti-inflammatory benefits, these conditions likely require broader therapeutic approaches beyond dietary intervention alone.

Lastly, it is important to note that EVOO consumption is only one of many factors influencing CVD outcomes. Social determinants related to lower socioeconomic status, such as precarious employment, unpaid caregiving, and chronic stress, significantly contribute to CVD risk.[32] These factors often interact with traditional CVD risk factors, including hypertension, dyslipidemia, obesity, diabetes, and smoking, amplifying their impact.

In terms of the limitations of this study, several considerations should be noted. First, our study exclusively involved older men and women at a high CVD risk. Therefore, while our findings are consistent with existing literature, caution is warranted when generalizing them to younger individuals, non-Mediterranean populations, or groups with lower olive oil consumption. Second, despite the extensive multivariable analysis conducted, residual confounding cannot be completely ruled out. While we adjusted for key variables, such as educational level as a proxy for socioeconomic status, other factors, such as household income or employment status, might still influence CVD outcomes. Third, we did not account for certain comorbidities known to be associated with CVD, such as chronic obstructive pulmonary disease (COPD) and sleep apnea. Fourth, although we used validated food frequency questionnaires (FFQs) administered by qualified dietitians, measurement errors in dietary exposure remain a possibility. Fifth, while we adjusted for the MEDAS (Mediterranean Diet Adherence Screener) score, we cannot exclude the possibility that the observed effect of EVOO may be partly due to the displacement of other foods in the diet. Sixth, over time, dietary recommendations and diagnostic criteria for CVD have evolved, which may affect the interpretation of our findings in the current clinical context. Seventh, it's important to acknowledge the potential for undetected diagnoses among some participants. Finally, the relatively small number of events for some CVD outcomes may have limited statistical power, as reflected by the wide confidence intervals.

Among the strengths of this study, we highlight its prospective longitudinal design and substantial follow-up duration, conducted within the framework of a randomized trial. Olive oil consumption was assessed annually, and cumulative intake was calculated to provide a more accurate representation of long-term dietary habits. Importantly, our results were consistent across different exposure assessments (cumulative vs. updated) and categorizations (tertiles vs. deciles). Unlike much of the existing literature on olive oil, we conducted separate analyses for different types of olive oil. Additionally, our study population exhibited relatively high olive oil consumption with notable between-subject variability. Moreover, we investigated not only the impact of olive oil on overall CVD incidence but also its effects on specific subtypes, including some that are less studied, such as PAD, HF, and AF. Lastly, a major strength of our study is the extensive multivariable adjustment, which included a wide range of sociodemographic variables, CVD risk factors, medication use, total energy intake, and adherence to the Mediterranean diet (assessed via the MEDAS score), among others.

Conclusion

In conclusion, a high intake of EVOO (approximately >40 g/d) is associated with a substantial reduction in the risk of overall CVD, stroke, peripheral artery disease, and atrial fibrillation among older individuals at high CVD risk in a Mediterranean population. In contrast, COO intake may not yield similar benefits. These findings emphasize the cardioprotective effects of EVOO as a key component of the Mediterranean diet.

Data availability statement

The data underlying this article cannot be shared publicly due to the privacy of individuals who participated in the PREDIMED trial and the signed consent agreements around data sharing. These agreements only allow access to external researchers for studies aligned with the project's purposes. Those wishing to access the PREDIMED trial data used in this study can make a request to the PREDIMED trial Steering Committee chair. You can contact PREDIMED coordinator Miguel Ángel Martínez-González at mamartinez@unav.es.

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Conflict of interest

None reported.

CRediT authorship contribution statement

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ahj.2025.08.021.

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