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Olive oil intake and risk of atrial fibrillation in the SUN cohort

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Abstract *Background and aims:* A Mediterranean-type diet enriched with extra virgin olive oil has been associated with a reduction in the incidence of atrial fibrillation (AF) in a population at high cardiovascular risk. However, no study has replicated these findings. In our study, we analyzed the association between olive oil consumption and AF in the SUN project, a cohort with young Spanish adults at low cardiovascular risk.
Methods and results: We included all participants without prevalent AF at baseline (18,118 participants). Incident AF cases were confirmed by a cardiologist following a prespecified protocol. We used multivariable repeated-measurement Cox models adjusted for possible confounders (sex, age, BMI, and several classic cardiovascular risk factors).

After a mean follow-up of 10.1 years, 94 AF incident cases were confirmed. Comparing to the lowest category of consumption (<7.9 g/d), the multivariable models showed hazard ratios (IC 95%) of 1.52 (0.93–2.48) for low-to-moderate, 1.44 (0.83–2.47) for moderate-to-high and 1.27 (0.56–2.86) for high olive oil intake. In a subgroup analysis stratified by overweight, an inverse although non-significant association was found only among overweight participants when we compared the highest vs the lowest category of consumption (p for interaction = 0.043).
Conclusion: No association between olive oil and AF was found in this low-risk cohort, although the effect of extra-virgin olive oil on AF prevention especially among people with overweight deserves further investigation.

Introduction

Atrial fibrillation (AF) is the most frequent cardiac arrhythmia worldwide and the burden of this disease is growing in terms of increased prevalence, reduced quality of life, and increased premature mortality and total health care costs [1]. Primary prevention of AF focusing on lifestyle interventions is a public health priority but there is not a clear set of prevention strategies to avoid this disease. This is partly explained because of an incomplete understanding of the etiology and pathogenesis of this disease [2]. We know that promoting a healthy diet is one of the most effective strategies for CVD prevention [3]. However, the level of evidence is lower for AF because results from available studies have been inconsistent [4].

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The Mediterranean Diet (MedDiet) is one of the most well-studied dietary patterns with demonstrated cardiometabolic benefits [5]. The beneficial effect of a MedDiet would be predicted based on its ability to improve lipid levels and anti-inflammatory and anti-oxidant properties [6,7]. Although this effect is explained by the synergistic combination of all its foods and nutrients [8], the use of extra-virgin olive oil (EVOO) as the main culinary fat is an essential component of the traditional MedDiet [9,10]. The consumption of olive oil has been associated with multiple health benefits [11]. In fact, the PREDIMED trial suggested that, in the context of a MedDiet pattern, EVOO may reduce the risk of AF among high-risk subjects [12]. However, no further studies have replicated these results.

The relationship between AF and inflammation seems to be complex and bidirectional. On one hand, AF has been related to a higher pro-inflammatory status [13,14]. On the other hand, the American and European guidelines for the management of patients with AF assume inflammatory infiltration of the atrium as a crucial mechanism to increase fibroblast activity and atrium fibrosis that may contribute to atrial remodeling which is in the origin of the pathophysiology of AF [15,16]. In fact, some inflammatory mediators (TNF, IL-2, PDGF, IL-6) are related with atrial remodeling. Changes in these inflammatory biomarkers could explain the increase risk of AF in systemic inflammatory diseases such as rheumatoid arthritis [17,18]. Thus, interventions with anti-inflammatory properties could be helpful to prevent AF [14]. Some studies have shown the role of anti-inflammatory drugs, such as dexamethasone or colchicine, in the prevention of postoperative and post-ablation AF [19–21]. Furthermore, factors that could simultaneously exert anti-oxidant and anti-inflammatory effects are likely to offer a potential for the prevention of AF. In fact, a short-term randomized controlled trial with dietary supplements of n-3 fatty acids plus antioxidant vitamin supplementation found a significant reduction on post-operative AF [22].

Several studies have shown the anti-inflammatory and anti-oxidative properties of EVOO, specifically by decreasing inflammatory mediators plasma levels, some of them (e.g. TNF and IL6) involved in AF pathogenesis [23–25]. This protective effect of EVOO is mainly attributed to phenolic compounds [26,27] including bioactive components such as oleocanthal [28], oleuropein and hydroxytyrosol [24,29]. In this context, our hypothesis is that a higher consumption of olive oil will be associated with a lower risk of AF, based on its anti-inflammatory and antioxidant properties. In this study we assess the association between the consumption of olive oil and the incidence of AF in a young-adult population recruited in the Seguimiento Universidad de Navarra (SUN) cohort."

Methods

Population

The SUN Project is a young cohort of university graduates from Spain. It was designed to assess the relation between diet and lifestyle habits and different health disorders. Information is self-reported using biennial mailed questionnaires [30]. Since the beginning of the project in December 1999 to the last update a total of 22,280 participants (39% men, mean age 37.5 years) were recruited [31].

In this study we included all participants at risk of a first diagnosis of AF at baseline. Participants with prevalent AF or without follow-up were excluded (2202 participants). We also excluded all participants with a previous diagnose of heart failure (67 participants) or those who did not comply with the Willet criteria energy intake limits: $<$800 kcal or $>$4200 kcal in men and $<$600 kcal and $>$3600 kcal in women (1893 participants). Out of 22,280 participants in the SUN cohort we included 18,118 participants for the present study.

Ethical standards

The study was approved by the Research Ethics Committee at University of Navarra. The response to the baseline questionnaire was considered as an informed consent to participate in the study. Regarding the obtention of informed consent of potential participants, we duly informed these potential candidates of their right to refuse to participate in the SUN study or to withdraw their consent to participate at any time without reprisal, according to the principles of the Declaration of Helsinki. Special attention was given to the specific information needs of individual potential candidates as well as to the methods used to deliver their information and the feedback that may receive in the future from the research team. After ensuring that the candidate had understood the information, we sought their potential freely-given informed consent, and their voluntary completion of the baseline questionnaire. These methods were accepted by our Institutional Review Board as to imply an appropriately-obtained informed consent.

Ascertainment of AF incident cases

We sent a letter to all participants who self-reported an AF diagnosis during the follow-up of the study. Participants with a positive self-report of a medically diagnosed AF were requested by letter or by phone to send the diagnostic ECG or a medical report with the specific diagnosis and the date of the first diagnosis. All the ECGs and medical records were reviewed by a trained cardiologist completely blinded to the nutritional variables. The cardiologist requested more information by phone to all participants who did not answer the letter or who sent incomplete information. An AF case was confirmed if the participant could answer at least two of the three following questions: 1) They were able to name the specific arrhythmia (AF); 2) they informed about their medication used for AF (anticoagulation, anti-arrhythmics…); 3) they were able to describe their symptoms related to AF (irregular palpitations associated or not to dyspnea or asthenia). The information about the date of diagnosis was obtained from the information

collected in the medical records. If this information was missing we obtained it from the self-reported questionnaire or by phone call. If there was a conflict between both answers we considered the first date for the diagnosis of AF.

Olive oil consumption

Participants were asked about the average intake of olive oil during the previous year, taking in to account the consumption of olive oil alone or with bread or used to dress the salad [32]. This question was asked at baseline and at years 6 and 10 of follow-up and it had 9 possible options: never/almost never, 1–3 spoons/month, 1/week, 2–4/week, 5–6 week, 1/day, 2–3/day, 4–6/day and >6/day. The consumption was then transformed into grams per day. The same question was repeated in questionnaires sent to participants after 6 and 10 years of follow-up.

Covariates

A baseline questionnaire was used to asses socio-demographic factors and health related habits (employment status, smoking habits, alcohol consumption…) as well as extensive diet information.

Anthropometric variables (weight and height) were also self-reported. Body mass index (BMI) was then calculated with the information obtained as the result of the weight (kilograms) by the square of height (meters).

Hypertensive status was established by previous validated self-reported medical diagnosis of hypertension. Other variables as physical activity, previous diagnoses (sleep apnea, cardiovascular disease, diabetes) and family medical history were also obtained from the baseline questionnaire.

Statistical analyses

Baseline characteristics were described using means and standard deviations for numeric variables and percentages for categorical variables, using Anova and Chi-squared tests respectively to compare different groups of olive oil consumption.

On the present study, participants were classified for the analyses attending to different categories (roughly quartiles) of total olive oil consumption.

Cox proportional hazards regression models were used to assess the association between olive oil and AF, using first quartile (lowest consumption) as the reference category. As olive oil consumption may not be constant through the years we decided to use repeated-measurements Cox models taking in to account the consumption at baseline and at years 6 and 10 of follow up. We estimated hazard ratios (HR) and 95% confidence intervals (CI). We calculated person-years of follow-up from the date of the baseline questionnaire to the date of AF diagnosis, death, or the end of follow-up, whichever occurred first.

We performed three repeated-measurements Cox regression models to assess the association between olive oil and AF. First, adjusted for age and sex. Second, additionally adjusting for smoking habit (non-smokers, former and current smokers), body mass index (kg/m^2), physical activity (METS-min/day), hypertension (yes/no), prevalent type 2 diabetes, and prevalent cardiovascular disease (myocardial infarction, coronary disease or stroke). Third, we added additional risk factors related to AF including height (cm), sleep apnea (yes/no) and alcohol consumption (grams/week).

We assessed the effect of olive oil consumption in stratified analyses according to sex, overweight (bmi≥25) and level of physical activity (using the median of physical activity as cut off value). To assess the modification of the effect of olive oil according to these variables we compared two models, model 2 previously described and the same model with the product term of the variable used for stratification (sex, overweight or physical exercise) and quartiles of olive oil consumption. We applied the log-likelihood ratio test to estimate the p value for interaction.

In order to evaluate the consistence of our results we performed several sensitivity analyses: 1) repeating the multivariable Cox regression models without participants younger than 45 years, 2) stratifying by cardiovascular risk (using Framingham equation) and 3) excluding participants with prevalent cardiovascular risk factors. Subgroups of olive oil consumption were merged for these sub-analyses in order to obtain higher statistical power.

Finally, we performed an additional ancillary analysis to evaluate the effect that the adherence to the Mediterranean diet pattern could have in addition to olive oil consumption. We repeated the analyses stratifying by adherence to a Mediterranean diet and olive oil consumption (low adherence and low olive oil consumption vs. high adherence and high olive oil consumption).

Results

Out of 22,280 participants in the SUN cohort we included 18,118 participants for the present study without AF at baseline. Compared with the lowest category of olive oil consumption, participants with higher consumptions were more likely to be women, younger and consumed alcohol more frequently. Most of AF risk factors (hypertension, obesity, diabetes, prevalent ECV, sleep apnea, height) had a low prevalence and presented a heterogeneous distribution, being significantly higher in the lowest category of olive oil consumption (Table 1).

A total of 94 new incident self-reported AF cases were confirmed after a mean follow up of 10.1 years. Among all incident cases of AF, 38 participants correspond to the lowest consumption, 28 participants to the second category, 21 participants in 3rd quartile category and 7 participants to the upper category.

We found no significant association in the multivariable model after the update of the exposure in a repeated-

Table 1 Baseline characteristics according to olive oil intake categories in the SUN cohort.

	Low (mean: 4.4 g/d)	Low-moderate (mean: 10 g/d)	Moderate-high (mean: 25 g/d)	High (mean: 53.9 g/d)	p
N	6802	5082	5051	1183	
Age (years)	38.0 (12.6)	37.5 (11.8)	37.2 (11.7)	37.4 (11.7)	<0.01
sex					<0.01
Men (%)	49.6	39.7	29.22	24.85	
Women (%)	49.6	60.2	70.78	75.15	
Smoking (%)					<0.01
current	27.3	26.2	27.4	30.9	
former	23.3	25.2	26	28.6	
Diabetes (%)	1.9	1.8	1.7	1.9	0.95
Dyslipidemia (%)	21	19.6	21	20.5	0.35
Hypertension (%)	12	10.1	9.32	9.72	<0.01
Height (cm)	170 (9)	168 (9)	168 (9)	167 (8)	<0.01
BMI	23.9 (3.6)	23.4 (3.3)	23.3 (3.5)	23.2 (3.6)	<0.01
BMI >30 (%)	5.41	3.86	4.41	4.82	<0.01
Obstructive sleep apnea	2.1	1.7	1.3	1.3	<0.01
Prevalent CVD (%)	1.5	1.18	1.27	0.93	0.267
Physical activity METS min/day	150.3 (161)	155.6 (159)	155.5 (155)	152.3 (159)	0.04
Total alcohol intake	6.8 (10.7)	6.6 (9.9)	6.4 (9.4)	6.8 (10.3)	<0.01
Alcohol drinking (%)					<0.01
Non drinker	22.2	20.5	20.1	20.4	
Moderate drinker	66.8	66.9	66.1	64.2	
Heavy drinkers	10.8	12.5	13.8	15.3	

Data are mean (SD) unless otherwise stated BMI: body mass index (kg/cm^2). Prevalent CVD: prevalent cardiovascular disease (coronary artery disease or cerebrovascular stroke).

measure model. A decreasing risk trend was found with higher olive oil intake quartiles, but none of them reached statistical significance (Table 2).

In the subgroup analyses similar results were obtained after stratifying by sex and physical activity. However, an inverse association was observed only among initially overweight participants with the highest category of olive oil intake. Though this association did not reach statistical significance, a significant effect modification was observed (P for interaction: 0.040) (Table 3).

Non-significant results were also found in additional sensitivity analyses (Supplementary Table 1) and in an ancillary analysis taking into account adherence to Mediterranean diet. The HR for high adherence to Mediterranean diet and high olive oil consumption was 1.2 (95% CI 0.73–1.97) compared to the group of participants with low adherence to Mediterranean diet and low olive oil consumption.

Discussion

In this prospective study we did not find any significant association between olive oil consumption and the risk of incident AF among young low-risk adults from Spain. We observed a statistically significant effect modification by overweight in the association between olive oil and AF (p for multiplicative interaction = 0.04). Among participants with overweight (BMI≥25) we detected a lower AF risk in those in the category with the highest olive oil consumption in comparison with participants in the lowest category. However, this association was not statistically significant (HR 0.59; 95% CI (0.13–2.62))

Scarce evidence exists regarding the association between olive oil or a MedDiet pattern and the risk of AF. The PREDIMED trial has previously demonstrated an inverse association in direct relationship with the amount of EVOO consumed in the context of a large study assessing a

Table 2 AF incidence risk (HR, 95% CI) according to different categories of olive oil intake*.

	Low (mean: 4.4 g/d)	Low-moderate (mean: 10 g/d)	Moderate-high (mean: 25 g/d)	High (mean: 53.9 g/d)
Number cases	38	28	21	7
Total	6802	5082	5051	1183
Crude	1. (reference)	1.25 (0.76–2.04)	1.04 (0.61–1.79)	0.76 (0.33–1.74)
Age, sex adjusted	1. (reference)	1.53 (0.93–2.51)	1.51 (0.87–2.62)	1.33 (0.6–3)
Multivar. Adjusted 1[a]	1. (reference)	1.52 (0.93–2.48)	1.44 (0.83–2.47)	1.27 (0.56–2.86)
Multivar. Adjusted 2[a]	1. (reference)	1.52 (0.93–2.48)	1.44 (0.83–2.47)	1.27 (0.56–2.86)

(*) Repeated-measurements Cox models were used to estimate the average of olive oil intake through the follow-up.
[a] Multivariable model 1: adjusted for age, sex, body mass index, physical activity, diabetes, arterial hypertension, cardiovascular disease: previous diagnosis of coronary artery disease or cerebrovascular stroke and adherence to Mediterranean diet. Multivariable model 2: additionally adjusted for sleep apnea, height, and alcohol consumption.

Table 3 Atrial fibrillation risk (HR, 95% CI) according to different quartiles of olive oil intake and stratified by sex, BMI and physical activity.

		Low	Low-Moderate		Moderate-High		High		P for interaction
			Events/ total	HR (95% CI)	Events/ total	HR (95% CI)	Events/ total	HR (95% CI)	
Sex	Women	1. (ref.)	6/3056	1.60 (0.54–4.76)	8/3567	1.81 (0.61–5.3)	2/887	1 (0.24–4.22)	0.943
	Men	1. (ref.)	25/1995	1.5 (0.88–2.57)	19/1457	1.36 (0.7–2.65)	7/287	1.43 (0.54–3.76)	
BMI>25	no	1. (ref)	10/3647	2.24 (0.98–5.11)	12/3668	2.44 (0.96–6.19)	6/867	2.65 (0.93–7.55)	0.043
	yes	1. (ref.)	21/1404	1.23 (0.66–2.32)	15/1356	1.06 (0.52–2.17)	3/307	0.59 (0.13–2.62)	
Physical activity (METS/d)	<15.4	1. (ref.)	15/2500	1.49 (0.75–2.98)	16/2398	1.92 (0.93–3.93)	5/575	1.17 (0.35–3.96)	0.479
	>15.4	1. (ref.)	16/2551	1.53 (0.75–3.13)	11/2626	0.95 (0.39–2.28)	4/599	1.4 (0.45–4.33)	

Multivariable model: adjusted for age, sex, body mass index, physical activity, diabetes, arterial hypertension, cardiovascular disease: previous diagnosis of coronary artery disease or cerebrovascular stroke and adherence to Mediterranean diet.
BMI: body mass index.

MedDiet intervention [12]. A previous case-control study showed that higher adherence to a MedDiet and a higher intake of antioxidants was associated with spontaneous conversion of AF [33]. One reason to explain the lack of significant associations found in our study is that we were not able to specifically measure the consumption of EVOO where phenolic contents and other bioactive compounds are found in higher concentrations, but were assessing together in a single category the consumption of EVOO and the refined variety of olive oil which is devoid of these bioactive components [34]. Another potential explanation is that participants in our study were young adults at low risk with a mean age of 37 years and therefore a low incidence of AF was to be expected. Moreover, among younger subjects with a small burden of risk factors, probably the role of predisposing genetic factors is a more important determinant of AF than dietary factors, whereas in older populations structural heart disease anomalies and inflammatory disorders are likely to be more common [35].

Lack of significant results may reflect that there is no association between olive oil and AF or, on the contrary, it could be explained buy insufficient statistical power due to the low number of incident cases observed in this cohort. Two studies have recently examined the association between the American Heart Association's Life's Simple 7 (LS7) metrics and incident AF [36,37]. In both studies a higher LS7 score was associated with lower risk of AF but no apparent effect was found for diet. In our study we found an interaction between being overweight and olive oil consumption. A recent study has found that overweight and obesity are the factors with the biggest impact on the occurrence of AF [38]. It is possible that olive oil consumption may counteract the harmful effects of being overweight or obese on the occurrence of AF [39].

The cardiovascular benefits of olive oil, probably mediated through an anti-oxidative and anti-inflammatory pathway, are well known. This cardioprotective effect seems to be more evident in the context of atherosclerotic disease by reducing the oxidative stress on the artery wall and stabilizing the plaque [6,26,27]. However, it is known that AF and arterial disease share common risk factors. Moreover one of the main mechanism that has been related with the development of AF is local and systemic inflammation [14,40,41]. Inflammatory biomarkers as interleukine 2 (IL-2), tumor necrosis factor (TNF) and platelet-derive growth factor have been related with electroanatomical changes in the atrium, promoting atrial apoptosis and fibrosis and provoking an auspicious electrical substrate due to changes in calcium conductance and intracellular concentration [13].

Some studies have found an association between higher plasma concentration of oleic acid and an increase of atherogenicity as well as cardiovascular and all-cause mortality [42,43]. High concentrations of plasma oleic acid may also contribute to some degree of atrial arrhythmogenesis [44,45]. However, although olive oil is a major source of dietary oleic acid, there is a low correlation between the consumption of olive oil and the levels of oleic acid in plasma [46]. In addition, in Non-mediterranean Western countries, beef and pork represent important sources of dietary oleic acid [47]. A number of studies have consistently shown a protective cardiovascular effect of EVOO [9,26,48,49], and this is mainly explained by the combined effect of other minor components beyond oleic acid [50]. Since plasma oleic acid also comes from other foods as well as from endogenous synthesis, it is important to further explore the mechanisms underlying the detrimental health effect associated with high plasma levels of this fatty acid.

Our study may contribute to the knowledge of AF epidemiology and prevention. One strength in our study is the update of the information about olive oil intake through repeated measurements at baseline, 6 years and 10 years. We also applied an AF confirmation algorithm for this cohort, being all AF cases previously revised and confirmed by the same cardiologist blinded to the exposure. This protocol reduces the probability of possible false positive self-reported cases on the questionnaire. However, more studies with larger sample size are needed to further explore the potential effect of extra-virgin olive oil on AF prevention as well as the interaction with other cardiovascular lifestyle factors.

This study has also some limitations. First, the lack of association maybe due to the very small sample size and therefore a suboptimal power to detect small effects of olive oil on AF risk. The observed low incidence of AF in our cohort could be explained by the healthy characteristics of our study population with high educational levels, low BMI

and, in general, a very low cardiovascular risk. It may also, in part, be potentially explained by some degree of under-detection, but this possibility would be merely speculative. In fact, on a large register made on Spanish population, prevalence in the youngest range requested (40–49 years) was very low (0.3%) [51], even lower than the one registered on our baseline questionnaire (0.6%). Since this is the first study conducted with young adults, further research is needed in order to know if our non-significant results reflect a lack of association between olive oil and AF among young adults, in contradiction with the inverse association found in the PREDIMED trial which included only older adults at high cardiovascular risk. Due to the small sample size, we should also be cautious regarding the potential modification of the effect of olive oil consumption by overweight status.

Second, information on the SUN project was self-reported and AF cases were only confirmed if a previous diagnosis was previously communicated by a participant. The absence of regular ECG registries may preclude the diagnosis of asymptomatic AF, and thus we cannot exclude a possible underestimation of asymptomatic AF.

Third, some self-reported AFs cases were confirmed in a phone call according to the participant's description of the diagnosis, treatment and symptoms of AF. However, this confirmation was undertaken by the same cardiologist, following a pre-specified protocol and more than 50% of the SUN participants are health professionals themselves.

Four, the SUN cohort did not collect blood samples and therefore we were not able to use a biomarker for olive oil consumption. Moreover, olive oil information was self-reported and we could not quantify specifically the consumption of extra-virgin olive oil or refined olive oil, with different compositions. Olive oil loses the vast majority of small components with anti-inflammatory properties during the refining process. In our assessment, due to the design of the FFQ, we could not separate the different types of olive oil. Instead, we used all kinds of olive oil merged together as the main exposure. Therefore, we could not appraise the specific effect of extra-virgin olive oil. This fact may explain our negative results, but we admit that further studies are needed to answer this question.

Finally, our data cannot be extrapolated to high risk populations and further observational and experimental studies are needed to explore the potential association between extra-virgin olive oil and AF prevention, specially in the context of overweight or obesity.

Our results did not show any association between olive oil and AF in this low-risk cohort. However, the significant interaction with overweight may suggest that olive oil consumption might show the inverse association selectively in the context of overweight or high cardiometabolic risk, although this finding has to be further explored in future studies with larger number of AF cases.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.numecd.2019.02.002.

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