MEDITERRANEAN ALCOHOL-DRINKING PATTERN, LOW TO MODERATE ALCOHOL INTAKE AND RISK OF ATRIAL FIBRILLATION IN THE PREDIMED STUDY

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Clinical Trials: URL: http://www.controlled-trials.com. Unique identifier: ISRCTN35739639

Word counts: abstract (234 words), Text (2996 words), figures(1), Tables(4)

Key Words: Alcohol, atrial fibrillation, Mediterranean, red wine, antioxidant

ABSTRACT

a) Background and Aims: There is ongoing controversy about the effect of a low to moderate alcohol consumption on atrial fibrillation (AF). Our aim is to assess the association between adherence to a Mediterranean alcohol drinking pattern and AF incidence.

b) Methods and Results: A total 6527 out of the 7447 participants on the PREDIMED trial met our inclusion criteria. A validated frequency food questionnaire was used to measure alcohol consumption. Participants were classified as non-drinkers, Mediterranean alcohol drinking pattern (MADP) (10-30g/d in men and 5-15 g/day in women, preferably red wine consumption with low spirits consumption), low-moderate drinking (<30 g/day men y <15 g/day women), and heavy drinking. We performed multivariable Cox regression models to estimate hazard ratios (HR) with 95% confidence intervals (95% CI) of incident AF according to alcohol drinking patterns.

After a mean follow up of 4.4 years, 241 new incident AF cases were confirmed. Alcohol consumption was not associated to AF incidence among low-moderate drinkers (HR: 0.96; 95%CI: 0.67-1.37), adherents to MADP (HR: 1.15 95%CI: 0.75-1.75), or heavy drinkers (HR: 0.92; 95%CI: 0.53-1.58), compared with non-drinkers.

c) Conclusions: In a high cardiovascular risk adult population, a meditteranean alcohol consumption pattern (low to moderate red wine consumption) was not associated with an increased incidence of AF.

d) Registration number for clinical trials: PREDIMED trial, NCT02669602 (clinicalTrials.gov)

a) INTRODUCTION

Alcohol consumption is considered a risk factor for atrial fibrillation (AF). It is well known that excessive drinking, including binge drinking and a daily high amount of alcohol consumption, increases the risk of AF [1–5] as well as the recurrences of AF after an ablation[5]. Three meta-analyses have suggested a linear dose-response relation between the amount of alcohol habitually consumed and AF [6–8]. However, several studies and a recent meta-analysis have found that moderate-to-low consumption of alcohol does not show any association with the risk of AF [4,5,9–11]. Moreover, a curvilinear instead of a linear association has been suggested in a recent cohort study [10].

The type of alcoholic beverages and drinking pattern could also be important factors, but studies assessing these aspects in detail are scarce. A prospective study found that consumption of liquor or wine but not beer was significantly associated with AF risk[8]. More recently, a cohort study found relevant differences in the association between AF and a moderate to high consumption of specific beverage types [10]. However, the influence of these factors and other aspects such us the alcohol drinking pattern and the regular consumption of small amounts of alcohol, preferably of non-distilled alcoholic beverages have less well studied.

It is well-recognized that low-to-moderate alcohol consumption has cardiovascular benefits, specially based on an inverse association with ischaemic heart disease. The American Heart Association recommends limit alcoholic beverages to no more than 2 drinks per day for men and 1 drink per day for women, ideally consumed within meals [12], in those with a regular consumption. This pattern is associated with lower levels of blood pressure and inverse associations with incident cardiovascular disease and it is sometimes recommended in cardiovascular prevention (only for subjects who already consume alcohol and are older than 40 years and have a high cardiovascular risk) [13,14]. However, there is currently a debate regarding the limits for a moderate alcohol drinking and if there is a difference between specific types of alcoholic beverages. It can be also questionable whether a healthy alcohol consumption pattern exists and if alcohol itself can provide cardioprotective benefits [15].

As far as we know, no previous study has specifically assessed the association between AF and the pattern of alcohol consumption which captures diverse aspects of the characteristics of alcohol intake, including the amount and type of alcohol consumed in the context of a Mediterranean population. The aim of our study was to describe the association between AF and several alcohol consumption patterns including the Mediterranean alcohol-drinking pattern (MADP) [13,14]. Our hypothesis is that the cardioprotective effect of a healthy alcohol-drinking pattern could be offset in the case of AF due to its potential proarrhytmogenic effect.

b) METHODS

Population

The PREDIMED study was a Spanish multicentre trial conducted in 11 recruiting centers[16]. Participants were 7447 men and women (55-80 years) at a high cardiovascular risk, because they had either prevalent type 2 diabetes mellitus or ≥3 of any of the following cardiovascular risk factors: current smoking habit, prevalent hypertension, hypercholesterolemia, low high-density lipoprotein cholesterol, overweight/obesity, or family history of premature coronary heart disease[17].

We studied all participants at risk of AF at the beginning of the PREDIMED trial. As shown in the flow-chart (figure 1), 75 participants with self-reported diagnosis of AF at baseline were excluded. We also excluded 667 participants from one recruitment center (site 05) where AF was not systematically assessed, 78 participants without alcohol intake information, and 100 participants that did not comply with predefined energy intake limits (we exclude participants with extreme values of energy consumption using Willet criteria: <800 kcal or > 4200 kcal in men and <600 kcal and >3600 kcal in women). Out of 7447 recruited participants, we included 6,527 for the present study, and we analysed the PREDIMED trial as an observational study, including the intervention group as two dummy independent covariates in the models.

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.

<u>Mediterranean alcohol-drinking pattern</u>

A validated 137-item food-frequency questionnaire (FFQ) was used to measure alcohol consumption at baseline, and every year [17,18]. Alcohol consumption was estimated from this FFQ. Participants were asked for the frequency on the consumption of different alcoholic beverages (50 cc for liquor or spirits, 100 cc for wine and 330 cc for beer). A total of 9 answers were possible: never, 1-3 monthly, three categories for weekly consumption (1; 2-4; 5-6) and four categories for daily consumption (1; 2-3; 4-6; >6). Global daily amount of alcohol was estimated by adding all different beverages.

Participants were classified according to the following categories: 1) abstainers at baseline, 2) participants following a predefined Mediterranean alcohol-drinking pattern (MADP), 3) participants with a low to moderate drinking pattern (LMD), with alcohol intake <30 g/day in men and <15 g/day in women but not following the MADP, or 4) participants with a heavy drinking pattern (HD), including ≥30 g/day in men and ≥15 g/day in women. MADP was operationalized similarly to previous publications [14]. This pattern was defined using the following criteria: 1) Moderate alcohol intake (10-30 g/day in men and 5-15 g/day in women), 2) preferably wine (>75% alcohol consumed as wine), 3) selection of red wine over other types of wine (>75% of wine consumed as red wine), 4) low consumption of spirits (<25% of total alcohol), 5) consuming wine preferentially during meals, 6) alcohol intake spread out over the week, and 7) avoidance of excess drinking occasions. In our study we only included criteria 1 to 4 because the information required for criteria 5 to 7 was not collected in the questionnaires used in the PREDIMED study. Only the participants that complied with all these premises were included in the MADP group.

We alternatively repeated the analyses after classifying the participants according to their amount of alcohol intake (alcohol beverage units, or units of drinking [ud]= 10 grams of alcohol)[9,19] in 3 categories: abstainers, low-moderate drinkers: 70 grams/week or less in women (>0 and ≤7 ud/week) and 140 grams/week or less in men (>0 and ≤14 ud/week), and heavy drinkers: more than 70 grams/week in women and more than 140 grams/week in men (>7 ud/week and >14 ud/week respectively).

Covariates

Participants, at baseline and yearly thereafter, completed a general questionnaire including lifestyle and clinical variables, a validated Spanish version of the Minnesota Leisure-Time Physical Activity[20] and a validated 137-item semi-quantitative food frequency questionnaire. Questionnaire includes information about prevalent diseases. In our study we used depression and sleep apnea, self-reported at baseline, as covariates. Trained personnel measured, at baseline and yearly, weight and height using calibrated scales. Blood pressure was measured in triplicate after 5 min of rest by using a validated semiautomatic sphygmomanometer.

Outcome

Incident AF cases were assessed on annual medical review of medical records and from ECGs performed yearly during the follow-up visits in the study. If AF was suggested in the medical record or diagnosed by ECG, all the information was submitted to a blinded Adjudication Committee. A new case was confirmed only if AF was present on the ECG and an explicit diagnosis of a physician was made. Further information about the confirmation of AF incidence cases is discussed elsewhere[21].

Statistical analyses

We included in the analyses all incident AF events from the baseline visit until the end of the trial in December of 2010. We described baseline characteristics using means and standard deviations for numeric variables and percentages for categorical variables, and we used Chi-squared and ANOVA tests to compare those variables among groups of alcohol exposure.

In order to assess the association between different alcohol patterns and AF we used Cox proportional hazards regression models to estimate the hazard ratio (HR) and 95% confidence intervals (CI) using abstainers as the reference category. We imputed 4 participants with missing values for baseline hypertension as non-hypertensive at baseline and 2 participants with missing values for physical activity (imputing the mean of physical activity). We calculated person-years of follow-up from the date of the baseline visit to the date of AF diagnosis, death, or the end of follow-up, whichever occurred first. We fitted a first model adjusted for age, and sex. A second model additionally adjusted for intervention group (Mediterranean diet enriched with extra virgin oil, MedDiet+EVOO; Mediterranean diet with nuts, MedDiet+nuts; and control group), smoking habit (non-smokers, former and current smokers), body mass index (kg/m^2), height, depression, sleep apnea, physical activity (METS-min/day), diastolic and systolic blood pressure, use of antihypertensive agents (yes/no), and previous diagnosis of diabetes, heart failure or non-atherosclerotic coronary disease. In a third model, we adjusted for propensity scores that used all the variables, included in the previous multivariable model, to estimate the probability of belonging to each of the categories of alcohol consumption patterns (abstainers, MADP, low-to-moderate drinkers and heavy drinkers).

In all Cox models we used the option “strata” from Stata to account for the multicenter design and we used robust standard errors which are recommended when there are some kinds of misspecification.

As daily alcohol intake and different risk factors may not be constant through the years, we repeated the Cox regression models using time-varying models with yearly repeated dietary measurements this is a unique characteristic of this study, because we had the advantage of using yearly repeated full-length food-frequency questionnaires and, to our knowledge, no other cohort has this possibility.

We assessed the potential effect modification by sex, age (>70 vs. equal or <70 years), diabetes, body mass index (BMI equal or >30 vs. <30), smoking habit (former or current smoker vs. non-smokers), and prevalent depression. To test for these interactions, we compared the multivariable model with and without the interaction term using the likelihood ratio test.

Finally, we performed different sensitivity analyses to assess the robustness of our results. We repeated the Cox multivariable regression analyses changing the energy intake limits criteria, excluding the early incident cases of AF (cases that appeared before one year of follow-up, because the induction period can be assumed to be longer than one year), excluding late incidence cases (diagnosed later than five years of follow-up, because the induction period can be assumed to be shorter), including prevalent AF cases (and controlling for this variable in the multivariable analyses), and excluding heavy drinkers.

c) RESULTS

We assessed 6077 participants from the PREDIMED study without prevalent AF at the beginning of the trial. Most of the participants were non-drinkers (34.3%, n=2,086) or low-moderate drinkers (42.06 %, n=2,556) whereas 14.8% (n=901) followed the MADP and 8.79% (n=534) were heavy drinkers. Compared with non-drinkers, participants following a MADP were more frequently men, smokers and presented higher levels of physical activity. On the contrary, they were less likely to be type 2 diabetics, to use anti-hypertensive treatment, and had lower average BMI. The prevalence of a previous cardiopathy was lower in the Mediterranean alcohol-drinking pattern group than in the abstainer group (Table 1).

After a mean follow up of 4.4 year, 241 incident cases of AF were confirmed. Among them, 85 were diagnosed and confirmed among non-drinkers, 92 among low to moderate drinkers, 41 were confirmed among the group adherent to the MADP and 23 occurred among heavy drinkers. Using non-drinkers as the reference category, we observed a slightly higher incidence of AF in all categories of alcohol consumption, but these associations were not statistically significant (Table 2). No substantial differences were observed when we used a Cox regression model adjusting for propensity scores to estimate the probability of being in each of the categories of alcohol consumption patterns (supplementary table 4). Similarly, non-significant associations were found in the models considering repeated measurements of the exposure to alcohol (Table 2).

As an ancillary analysis we observed the association between AF and light or moderate drinkers not following the MADP as separated categories (Supplemental Table 1). We observed a lower AF risk for moderate drinkers who not followed the MADP, although all the associations were not statistically significant.

We assessed the effect of the MADP in different subgroups according to sex, age, previous diagnosis of depression, obesity, hypertension and diabetes. Compared to non-drinkers we obtained in all subgroups, a non-significant direct association, without evidence of significant interaction (Figure 1 and supplementary tables 2 and 3).

No relevant differences were found in sensitivity analyses (Table 3).

We also studied the incidence of AF across levels of alcohol consumption. Compared to the group of non-drinkers, the groups of low-to-moderate or heavy drinkers did not show any association with a higher incidence of AF (Table 4). Similar results were found for all the subgroup analyses (Supplementary tables 2 and 3).

d) DISCUSSION

In a longitudinal study of an elderly Mediterranean population at high cardiovascular risk we found no association between a Mediterranean alcohol-drinking pattern and the incidence atrial fibrillation. This association remained non-significant even after adjustment for potential confounders and taking into account the variation through the years of the main exposure. These results were consistent in all sensitivity analyses and they were also independent of the type of alcoholic beverage consumed in low-moderate drinkers.

Although moderate alcohol consumption has been sometimes recommended for cardiovascular disease prevention in older subjects at high risk who already consume alcohol, some authors have expressed doubts about the real benefit of this recommendation due to the lack of association and even a possible increase on AF cases associated with alcohol intake [22]. Currently, there is controversy regarding the effect of a low to moderate alcohol drinking pattern and even the possible effect that different types of alcohol beverages could have on AF. Recent meta-analyses suggest a linear dose-response relation between the total amount of alcohol intake and the risk of atrial fibrillation, increasing a 8% on the risk of AF with each additional daily alcoholic drink [8,23]. However when they specifically assessed a moderate alcohol intake they were not able to find any significant increase on AF risk. Similarly, our study shows no significant association between a moderate consumption of alcohol, even within a Mediterranean alcohol-drinking pattern, and the risk of AF risk. Moreover, a recent study performed in a big Norwegian cohort suggested a possible curvilinear relation between alcohol and AF[10], concluding that a low-moderate could not have the harmful effect that some authors expected.

It is well-known that the pro-arrhythmogenic effect of alcohol intake is mediated through different anatomical and electric changes in the left atrium. A high alcohol consumption produces a direct toxic and inflammatory effect on atrial myocardium and also an indirect effect, promoting changes on the autonomic system and left ventricle remodelling, increasing the arterial blood pressure, and provoking an increase in left ventricular pressures and diastolic dysfunction. All of this pathophysiological changes may provoke left atrium remodelling (dilatation and fibrosis), and this may form the electro-anatomical substrate that facilitates the appearance of AF [23–27].

The possible cardioprotective mechanism for light consumption of alcohol, especially with red wine, is complex and still not well known. In the case of red wine seems to be related with an antioxidant effect of polyphenols [28,29]. Moreover, moderate consumption of ethanol have been associated to a anti-atherosclerotic effect due to a increase of high density lipoprotein levels and a anti-inflammatory effect [30,31]. This beneficial effect has been found in the context of cardiovascular disease (CVD) and heart failure (HF), but never with AF [11,13]. AF shares risk factors with CVD and HF, and both HF and CVD are associated with an increased risk of AF. Thus, it is possible that a decrease in cardiovascular risk factors, CVD and HF could also reduce the occurrence of new cases of AF or at least partially compensate the proarrhythmogenic effect of alcohol. Participants recruited in our study are elderly and at high cardiovascular risk, thus, if this cardiovascular benefit is finally confirmed and they already drink alcohol, they could be good candidates to promote a MADP for the prevention of cardiovascular diseases. However, our lack of association does not prove the absence of a harmful effect of a moderate alcohol consumption on AF risk. Thus, any recommendation on moderate alcohol consumption can be provided according to our results.

The strengths in our study include the prospective design, the use of a validated FFQ, the relatively large sample size, and the long follow-up period. However, our study has also several limitations. First, the number of AF cases is relatively low and we can not preclude that lack of association is explained but a lack of statistical power. Second, the PREDIMED excluded participants with excessive drinking or alcoholism according to the CAGE questionnaire and therefore our results cannot be extrapolated to a population with heavy alcohol drinking or binge drinking and they cannot be interpreted in any way as a proof that alcohol consumption is not associated with AF, because there were almost no heavy drinkers in our cohort. Third, alcohol consumption was self-reported and we could have underestimated the true level of consumption. However, we obtained similar results when we used repeated-measures analyses. Four, three questions previously used in the SUN cohort to build the MADP were not available in the PREDIMED study. Two of these questions are related to binge drinking (alcohol intake spread out over the week, and avoidance of excess drinking occasions). We could not estimate the frequency of binge drinking in our population although it was probably low since this pattern is less frequent among people at older ages, who screened negatively in the CAGE questionnaire (as all participants in PREDIMED did), and who are conscious of having cardiovascular risk factors. Moreover, the misclassification of a small number of binge drinkers in the MADP group would, in any case, bias our results towards the null. Another question was consuming wine preferably during meals and therefore a higher cardioprotective effect could be found among participants following the MADP. Five, no information about former drinkers was obtained at baseline. Abusive drinkers, who are those who probably would try to stop drinking due to health reasons, were not included in the trial, and probably an abusive drinking pattern might be more detrimental for AF risk. Although we cannot exclude a possible residual effect of former drinkers who were previously low or moderate alcohol drinkers included in the abstainers group, a recent study in a Mediterranean cohort did not find any association between former drinking and AF [11]. Six, the arrhythmogenic effect of alcohol could be underestimated due to the highest proportion of AF risk factors in the reference group (non-drinkers). Although we adjusted for these factors, residual confounding is still possible in our study.

Our results could suggest that a MADP in a high cardiovascular risk population may not have the pro-arrhythmogenic effect described in previous publications. However, according to our negative results we can not assume or recommend any alcohol consumption Further studies are needed to conclude whether a low to moderate consumption of alcohol, and preferably red wine, does not increase AF risk in a population at high cardiovascular risk

In summary, in a high cardiovascular risk adult population, a low to moderate red wine drinking pattern was not associated with an increased incidence of AF.

ACKNOWLEDGEMENTS

Sources of Funding: PREDIMED trial was supported by the official funding agency for biomedical research of the Spanish government (Instituto de Salud Carlos III) RTIC G03/140 (Coordinator: Dr Estruch) and RTIC RD 06/0045 (Coordinator: Dr Martínez-González). We also acknowledge grants from the National Institutes of Health (1R01HL118264-01); Fondo de Investigación Sanitaria– Fondo Europeo de Desarrollo Regional (PI04/0233, PI05/0976, PI07/0240, PI10/01407, PI10/02658, PI11/00049, PI11/02505 and AGL2010-22319-C03-03); Consejería de Salud de la Junta de Andalucía (PI0105/2007), and by the Generalitat Valenciana, Spain (ACOMP/2013/165 and ACOMP/2013/159).

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TABLES

Table 1. Baseline characteristics according to different alcohol patterns

	Non drinkers	Low–moderate drinkers	Mediterranean pattern	Heavy drinkers	p
n	2086	2,556	901	534	
Age	68.34 (6.06)	66.3 (6.14)	67.32 (6.03)	64.85 (5.97)	<0.01
Sex					
Men (%)	17.5	52.3	58.8	73.6	<0.01
Women (%)	82.5	47.7	41.2	26.4	
Intervention Group					
Medit+NUTS (%)	28.9	35.2	36.3	34.9	<0.01
Medit+ VOO (%)	35.3	33.7	35.3	35.7	0.64
Smoking (%)					
Current smoker	6.6	15.9	14.8	32.6	<0.01
Former smoker	11.9	29.1	36	36.7	
Diabetes (%)	51.3	48.4	42.1	41.2	<0.01
Non-atherosclerotic cardiopathy (%)	3.7	2.7	2.7	2.6	0.18
SBP mmHg	147.98 (19.21)	147.89 (18.43)	148.8 (17.73)	149.45 (18.93)	0.23
DBP mmHg	91.83 (14.08)	93.11 (13.67)	93.69 (13.34)	93.34 (13.7)	<0.01
Anti-hypertensive medication (%)	76.5	70.9	67.7	69.1	<0.01
Height	156.14 (7.74)	161.68 (8.82)	162.11 (8.54)	164.6 (8.11)	<0.01
BMI	30.45 (4.13)	29.93 (3.74)	29.45 (3.54)	29.38 (3.44)	<0.01
BMI >30 (%)	52.7	46.8	39.4	40.2	<0.01
Physical activity METS min/day	184.52 (192.56)	234.47 (250.92)	266.01 (250.28)	300.08 (267.66)	<0.01
Sleep apnea (%)	1.1	2.4	1.2	2.6	<0.01
Total alcohol intake (g/d)	0	6.1 (6.7)	14.9 (7.7)	43.5 (18.9)	<0.01
Drink subtypes (g/day)					
Wine	0	3.4 (4.4)	14.2 (7.5)	31.6 (18.9)	<0.01
Beer	0	1.9 (3.6)	0.4 (0.5)	6.1 (9.7)	<0.01
Spirits	0	0.8 (2.5)	0.3 (0.7)	5.8 (10.8)	<0.01

Data are mean (SD) unless otherwise stated. SBP: systolic blood pressure. DBP: diastolic blood pressure. *P value from comparisons was calculated with Pearson's chi-square test and ANOVA, as appropriate. Non-atherosclerotic cardiopathy: heart failure and non-atherosclerotic coronary disease.

Table 2. Risk of atrial fibrillation (HR, 95% CI) according to different alcohol patterns (*)

	Non drinkers (n=2,086)	Low-moderate drinkers (n=2,556)	Mediterranean pattern (n= 901)	Heavy drinkers (n=534)
Number cases	85	92	41	23
Person-years	10,629	10,988	3,999	2,504
Age, sex adjusted	1 (reference)	1.05 (0.75-1.48)	1.19 (0.79-1.79)	1.03 (0.63-1.67)
Multivar. Adjusted (**)	1 (reference)	0.96 (0.67-1.37)	1.15 (0.75-1.75)	0.92 (0.53-1.58)
Repeated measures Multivar. Adjusted	1 (reference)	1.07 (0.76-1.51)	1.03 (0.67-1.58)	1.06 (0.61-1.85)

(*) Alcohol pattern defined as low-moderate drinkers: women <15 gr/day; men <30 gr/day, Medit. Pattern Medit. Pattern participants that complies all the Med. Pattern criteria. Heavy drinkers > 30 g/day in men and >15 g/day in women

(**) Multivariable model: adjusted for age, sex, intervention group, smoking, body mass index, height, physical activity, sleep apnea, depression, diabetes, diastolic and systolic blood pressure, hypertension, non-atherosclerotic coronary disease and heart failure

Table 3. Sensitivity analyses exploring the association between atrial fibrillation (HR 95% CI) and different alcohol patterns (**)

		Non drinkers	Low-moderate drinkers	Mediterranean pattern	Heavy drinkers	Events/total
Other energy limits as exclusion criteria§	HR (95% CI)	1.00 (ref.)	0.94 (0.66-1.36)	1.14 (0.75-1.75)	0.94 (0.54-1.62)	238/6,041
	Person-years	9,203	10,989	4,016	2,510	
Excluding early FA cases	HR (95% CI)	1.00 (ref.)	1.02 (0.71-1.48)	1.3 (0.83-2.01)	0.94 (0.53-1.67)	221/6057
	Person-years	9,362	10,984	3,999	2,501	
Excluding late FA cases	HR (95% CI)	1.00 (ref.)	0.97 (0.64-1.49)	0.89 (0.53-1.49)	0.84 (0.45-1.59)	169/6,005
	Person-years	9,182	10,838	3,908	2,465	
Including Prevalent FA cases	HR (95% CI)	1.00 (ref.)	0.96 (0.67-1.38)	1.16 (0.76-1.77)	0.93 (0.54-1.61)	241/6,769
	Person-years	9,369	10,988	3,999	2,504	
Excluding heavy drinkers	HR (95% CI)	1.00 (ref.)	0.94 (0.65-1.34)	1.14 (0.75-1.74)	-	218/5,543
	Person-years	9,369	10,988	3,999	-	
Excluding Heart failure	HR (95% CI)	1.00 (ref.)	1 (0.69-1.44)	1.21 (0.79-1.85)	0.93 (0.53-1.63)	231/5,893
	Person-years	9,070	10,719	3,897	2,452	

§ Excluding participants with a energy consumption below de centile 1 and above de 99 centile
(*) Multivariable model: adjusted for age, sex, intervention group, smoking, body mass index, height, physical activity, sleep apnea, depression, diabetes, diastolic and systolic blood pressure, hypertension, non-atherosclerotic coronary disease and heart failure
(**) Alcohol pattern defined as: Low-moderate drinkers: women <15 gr/day; men <30 gr/day, Medit. Pattern participants that complies all the Med. Pattern criteria. Heavy drinkers > 30 g/day in men and >15 g/day in women

Table 4. Risk of AF according to level of alcohol consumption (**)

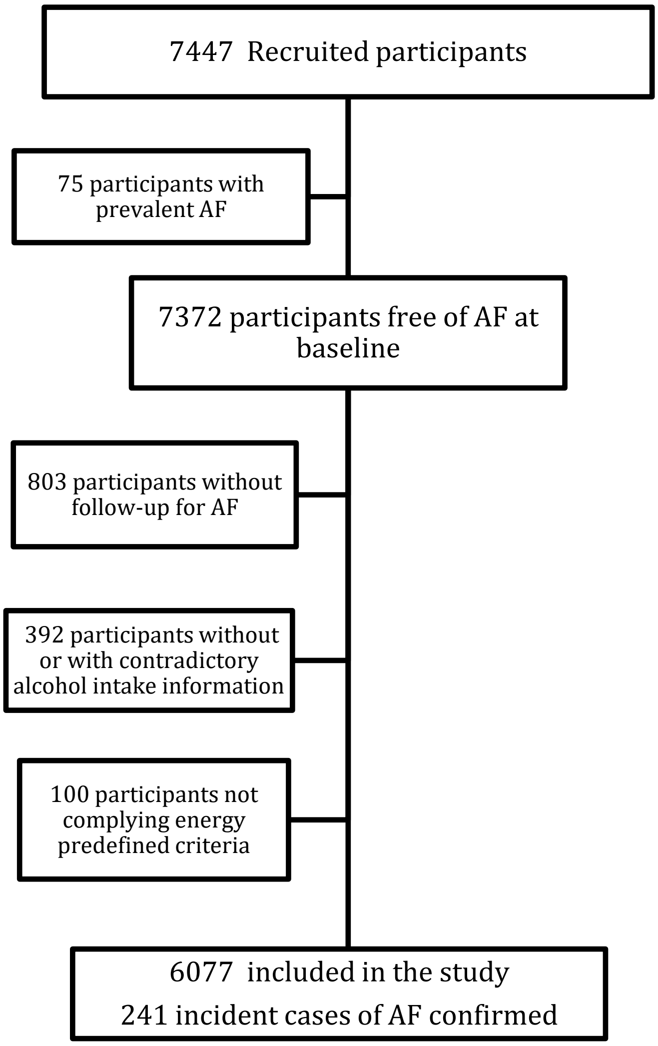
	Non drinkers (n=2,086)	**Low-moderate drinkers (n=2,694)**	**Heavy drinkers (n=1,297)**
Number cases	85	104	52
Person-Yrs	9,369	11,547	5,944
Age, sex adjusted HR (95% CI)	1. (reference)	0.95 (0.69-1.31)	0.93 (0.64-1.36)
Multivar. Adjusted HR (95% CI)	1. (reference)	1.04 (0.74-1.47)	0.94 (0.64-1.37)
Repeated measures Multivar. Adjusted HR (95% CI)	1. (reference)	1.09 (0.77-1.5)	0.98 (0.67-1.44)

(*)Multivariable model: adjusted for age, sex, intervention group, smoking, body mass index, height, physical activity, sleep apnea, depression, diabetes, diastolic and systolic blood pressure, hypertension, non-atherosclerotic coronary disease and heart failure

(**) Alcohol pattern defined as: Moderate: women 10-70 grams/week (1-7 ud/week) men 10-140 grams/week (1-14 ud/week); Heavy: women >70 grams/week (>7 ud/week) and men >140 grams/week (>14 ud/week)

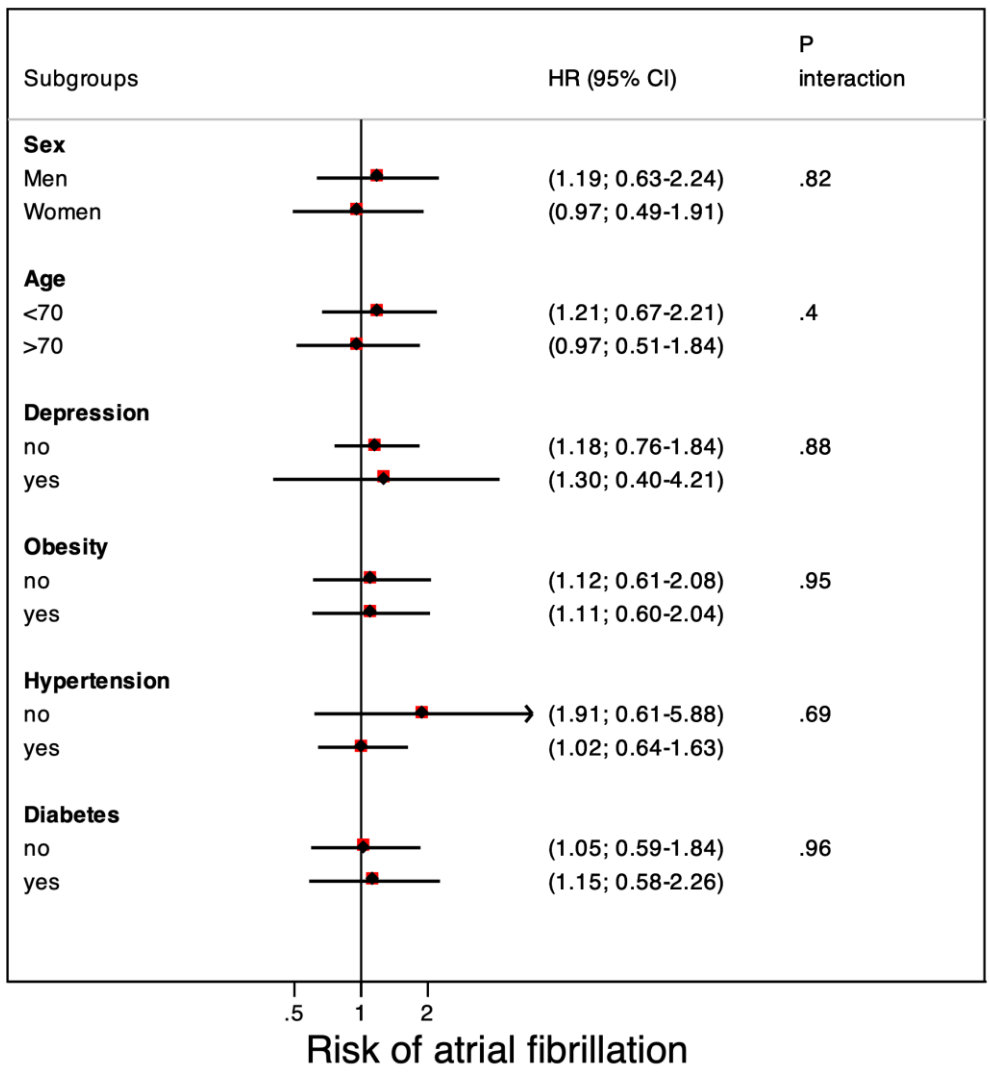
FIGURE

Figure1: Flow Chart



AF: atrial fibrillation

Figure 2: Atrial fibrillation risk (HR 95% CI) in participants following a Mediterranean alcohol-drinking pattern stratified by different subgroups (reference: non-drinkers)



SUPPLEMENTARY MATERIAL

Supplementary Table 1. Ancillary analyses: Risk of atrial fibrillation in different alcohol patterns (Reference: non drinkers) HR 95% CI

	Light drinkers (n=1,873)	Moderate drinkers Not MADP (n=683)	Mediterranean pattern (MADP) (n= 901)	Heavy drinkers (n=534)
Number cases	71	21	41	23
Person-years	8,015	2,972	3,999	2,504
Age, sex adjusted	1.09 (0.76-1.55)	0.95 (0.56-1.6)	1.19 (0.79-1.79)	1.03 (0.63-1.67)
Multivar. Adjusted (*)	0.99 (0.69-1.43)	0.85 (0.5-1.47)	1.15 (0.75-1.75)	0.92 (0.53-1.57)

(*) Multivariable model: adjusted for age, sex, intervention group, smoking, body mass index, height, physical activity, sleep apnea, depression, diabetes, diastolic and systolic blood pressure, hypertension, non-atherosclerotic coronary disease and heart failure
(**) Alcohol pattern defined as: Light drinkers < 10 grams in men and <5 grams/day in women, moderate drinkers: women >5 and <15 gr/day; men >10 and <30 gr/day, Medit. Pattern Medit. Pattern participants that complies all the Med. Pattern criteria. Heavy drinkers > 30 g/day in men and >15 g/day in women

Supplementary Table 2: Subgroup Analyses of the AF incidence by different alcohol pattern (reference group: non-drinkers)

		Events/Total			Hazard ratios (95% CI)		
		Non drinkers	**Moderate drinkers**	**Heavy drinker**	**Moderate drinkers**	**Heavy drinkers**	**P interaction**
Sex							
	Men	21/366	67/1,458	41/801	0.99 (0.56-1.77)	0.94 (0.5-1.81)	0.59
	Women	64/1,720	37/1,236	11/496	1.13 (0.73-1.78)	0.71 (0.36-1.41)	
Age							
	>70	53/909	42/884	20/394	0.76 (0.47-1.26)	0.77 (0.41-1.42)	0.33
	<70	32/1,177	61/1810	32/903	1.25 (0.74-2.12)	1.07 (0.58-1.96)	
Smoke (%)							
	current	5/138	19/407	16/309	0.48 (0.14-1.58)	0.41 (0.10-1.64)	0.39
	former	11/250	37/812	22/450	0.95 (0.44-2.04)	1.03 (0.43-2.49)	
Diabetes							
	yes	41/1070	51/1312	21/524	1.07 (0.64-1.78)	1.01 (0.52-1.97)	0.81
	no	44/1016	53/1382	31/773	1.18 (0.72-1.92)	0.95 (0.55-1.65)	
HTA							
	Yes	77/1786	89/2212	45/1061	0.98 (0.66-1.43)	0.84 (0.53-1.32)	0.93
	no	8/300	15/482	7/236	0.98 (0.59-1.62)	0.77 (0.44-1.37)	
BMI>30							
	yes	53/1100	55/1237	22/530	1.12 (0.69-1.81)	0.92 (0.49-1.69)	0.75
	no	32/896	49/1457	30/767	0.98 (0.58-1.66)	0.92 (0.52-1.64)	
Depression							
	yes	18/463	13/393	4/155	0.88 (0.34-2.24)	0.58 (0.19-1.74))	0.29
	no	67/1623	91/2301	48/1142	1.1 (0.76-1.59)	1.05 (0.7-1.58)	
Beverages types							
	beer	165/4004	71/1939	5/134	0.83 (0.61-1.14)	1.09 (0.43-2.73)	
	wine	102/2573	95/2459	44/1045	1.09 (0.79-1.51)	0.94 (0.63-1.42)	
	spirits	193/5,067	47/967	1/34	1.04 (0.71-1.51)	0.54 (0.07-4.22)	

HTA: arterial hypertension, BMI: body mass index
(*) Multivariable model: adjusted for age, sex, intervention group, smoking, body mass index, height, physical activity, sleep apnea, depression, diabetes, diastolic and systolic blood pressure, hypertension, non-atherosclerotic coronary disease and heart failure

Supplementary Table 3: Subgroup Analyses of the AF incidence by different alcohol pattern (reference group: non-drinkers)

	Events/Total			Hazard ratios (95% CI)			
	Low-moderate drinkers	Mediterranean pattern	Heavy drinkers	Low-moderate drinkers	Mediterranean pattern	Heavy drinkers	P Interact.
Sex							
Men	55/1,336	32/530	21/393	0.89 (0.49-1.61)	1.19 (0.63-2.24)	0.99 (0.47-2.05)	0.82
Women	37/1,220	9/371	2/141	1.1 (0.7-1.71)	0.97 (0.49-1.91)	0.24 (0.02-2.08)	
Age							
>70	35/810	19/334	9/134	0.71 (0.42-1.18)	0.97 (0.51-1.84)	1.02 (0.45-2.29)	0.40
<70	57/1746	22/567	14/400	1.18 (0.67-2.21)	1.21 (0.67-2.21)	0.93 (0.43-1.98)	
Smoke (%)							
current	14/408	14/134	7/174	0.32 (0.09-1.06)	0.99 (0.27-3.56)	0.18 (0.03-0.84)	0.49
former	36/740	12/325	11/197	1.12 (0.49-2.54)	0.83 (0.33-2.06)	1.16 (0.43-3.14)	
Diabetes							
yes	46/1,237	16/379	10/220	1.03 (0.61-1.71)	1.15 (0.58-2.26)	1.16 (0.48-2.81)	0.96
no	46/1,319	25/522	13/314	0.89 (0.53-1.48)	1.05 (0.59-1.84)	0.67 (0.31-1.41)	
HTA							
Yes	79/2,103	34/737	21/433	0.91 (0.61-1.35)	1.02 (0.64-1.63)	0.89 (0.49-1.61)	0.69
no	13/453	7/164	2/101	1.09 (0.41-2.92)	1.91 (0.61-5.88)	0.47 (0.04-5.88)	
BMI>30							
yes	49/1,197	17/355	11/215	1.04 (0.64-1.7)	1.11 (0.6-2.04)	1.12 (0.49-2.56)	0.95
no	43/1,359	24/546	12/319	0.94 (0.55-1.58)	1.12 (0.61-2.08)	0.77 (0.37-1.63)	
Depression							
yes	11/399	4/99	2/50	0.7 (0.27-1.85)	1.3 (0.4-4.21)	0.83 (0.20-3.42)	0.88
no	81/2,157	37/802	21/484	1.0 (0.68-1.47)	1.18 (0.76-1.84)	0.96 (0.54-1.71)	
Heart failure							
no	90/2,487	41/877	22/520	1 (0.69-1.44)	1.21 (0.79-1.85)	0.93 (0.53-1.6)	

HTA: arterial hypertension, BMI: body mass index
(*)Multivariable model: adjusted for age, sex, intervention group, smoking, body mass index, height, physical activity, sleep apnea, depression, diabetes, diastolic and systolic blood pressure, hypertension, non-atherosclerotic coronary disease and heart failure

Supplementary table 4: Risk of atrial fibrillation in different alcohol patterns (*) using propensity scores model

	Non drinkers (n=2,086)	**Low-moderate drinkers (n=2,556)**	**Mediterranean pattern (n= 901)**	**Heavy drinkers (n=534)**
Number cases	85	92	41	23
Person-years	10,629	10,988	3,999	2,504
Age, sex adjusted	1 (reference)	1.05 (0.75-1.48)	1.19 (0.79-1.79)	1.03 (0.63-1.67)
Propensity scores model (***)	1 (reference)	1.01 (0.71-1.43)	1.20 (0.79-1.81)	0.89 (0.53-1.50)

(*) Alcohol pattern defined as low-moderate drinkers: women <15 gr/day; men <30 gr/day, Medit. Pattern Medit. Pattern participants that complies all the Med. Pattern criteria. Heavy drinkers > 30 g/day in men and >15 g/day in women

(***) Propensity scores using all the variables included in the multivariable model to estimate the probability of being in each of the categories of alcohol consumption patterns (abstainers, MADP, low-to-moderate drinkers and heavy drinkers).