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Moderate Alcohol Consumption Is Associated With Lower Risk for Heart Failure But Not Atrial Fibrillation

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ABSTRACT

OBJECTIVES The aim of this study was to assess the hypothesis that alcohol consumption is associated with onset of atrial fibrillation (AF) and/or heart failure (HF).

BACKGROUND The connection between ethanol intake and AF or HF remains controversial.

METHODS The study population was 22,824 AF- or HF-free subjects (48% men, age ≥35 years) randomly recruited from the general population included in the Moli-sani study, for whom complete data on HF, AF, and alcohol consumption were available. The cohort was followed up to December 31, 2015, for a median of 8.2 years (183,912 person-years). Incident cases were identified through linkage to the Molise regional archive of hospital discharges. Hazard ratios were calculated using Cox proportional hazard models and cubic spline regression.

RESULTS A total of 943 incident cases of HF and 554 of AF were identified. In comparison with never drinkers, both former and occasional drinkers showed comparable risk for developing HF. Drinking alcohol in the range of 1 to 4 drinks/day was associated with a lower risk for HF, with a 22% maximum risk reduction at 20 g/day, independent of common confounders. In contrast, no association of alcohol consumption with onset of AF was observed. Very similar results were obtained after restriction of the analyses to regular or only wine drinkers or according to sex, age, social status, or adherence to the Mediterranean diet.

CONCLUSIONS Consumption of alcohol in moderation was associated with a lower incidence of HF but not with development of AF. (J Am Coll Cardiol HF 2017;■:■-■) © 2017 by the American College of Cardiology Foundation.

Heavy alcohol drinking is associated with cardiovascular disease (CVD) (1,2), cardiomyopathy (3), heart failure (HF) (4,5), and atrial fibrillation (AF) (6,7). In contrast, alcohol in moderation is associated with reduced risk for CVD, as consistently shown in many epidemiological studies and supported by extensive experimental work (1,3,8-10). Nevertheless, the epidemiological data on the relationship between moderate alcohol intake and risk for AF or HF remain controversial (1,4-7,11,12).

A recent dose-response meta-analysis based on 8 prospective studies, with more than 200,000 subjects and 6,211 cases of HF, observed a nonlinear relationship between alcohol consumption and risk for HF, with maximum protection (−16%) at

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ABBREVIATIONS AND ACRONYMS

AF = atrial fibrillation

CI = confidence interval

CVD = cardiovascular disease

HF = heart failure

HR = hazard ratio

10 drinks/week (13). Mechanisms of potential benefit of alcohol consumption in HF are unclear. They include the risk reduction for CVD, neurohormonal changes, and blood pressure lowering (14-16).

A dose-response meta-analysis of 7 prospective studies, including 12,554 AF cases, showed that alcohol consumption, even at moderate intake, is a risk factor for AF (6). Several mechanisms have been suggested to contribute to this association, including depression of heart function, cardiac conduction abnormalities and morphologic changes, dilated cardiomyopathy, alterations in oxidative stress, electrolyte imbalances, shortening of atrial refractoriness, and hypertension (17,18). However, whether alcohol itself affects the progression of AF, including electric and structural remodeling, remains unclear (19-22).

HYPOTHESIS AND PURPOSE. Several aspects of the relation between alcohol consumption and HF or AF remain to be clarified. In particular, it is unclear whether a role for different types of alcoholic beverages exists and whether a modification of effect due to sex, social status, or diet is present. The Moli-sani study recruited 24,325 citizens living in southern Italy and paid particular attention to the role played by social status indicators and dietary behaviors in accounting for the risk for major chronic diseases (23-25). We investigated whether categories of alcohol consumption are associated with onset of HF or AF in the follow-up of the Moli-sani study.

METHODS

STUDY PARTICIPANTS. The Moli-sani study is a population-based cohort study recruiting 24,325 citizens (men and women ≥35 years of age) of the Molise region, an area between central and southern Italy, between March 2005 and April 2010, with the purpose of investigating genetic and environmental risk factors in the onset of cardiovascular, cerebrovascular, and tumor diseases (26). Among environmental factors, the study paid particular attention to the role played by dietary behaviors in accounting for the risk for major chronic diseases. Exclusion criteria at recruitment level were pregnancy at the time of recruitment, disturbances in understanding or willingness, current polytrauma or coma, and refusal to provide informed consent. For the present study, participants with unreliable medical questionnaires (1.0%), those with missing values for alcohol assessment (5.3%), those lost to follow-up (0.8%), and those with histories of HF (1.1%, for the study on HF) or AF (1.7%, for the study on AF) were excluded from the analysis. The final sample sizes were 22,824 for the HF analysis and 22,628 for the AF analysis. The mean age of subjects was 55 ± 12 years, and 48.1% were men. The Moli-sani study complies with the Declaration of Helsinki and was approved by the Catholic University (Rome, Italy) ethics committee. All participants enrolled provided written informed consent.

CASE ASCERTAINMENT AND FOLLOW-UP. Mortality, HF, and AF events were recorded until December 31, 2015 (the pre-established end date for follow-up). Incident events were adjudicated by a centralized events committee using inpatient medical records. Overall mortality was assessed through the Italian mortality registry and validated through Italian death certificates. Incident HF or AF at follow-up was defined as HF or AF hospitalization or HF or AF death (27). Validation of HF required diagnosis by a physician, HF symptoms (shortness of breath, paroxysmal nocturnal dyspnea, orthopnea, or fatigue), and medical therapy for HF.

ALCOHOL CONSUMPTION. Alcohol intake during the year before enrollment was assessed using the validated Italian EPIC food frequency questionnaire, complemented by specific questions on pattern of beverage (28). In calculating the amount of alcohol consumed (in grams per week), it was assumed that 120 ml of wine, 330 ml of beer, or 40 ml of liquor contains 12 g of ethanol. Thus, 12 g/day of ethanol is equivalent to 1 alcoholic beverage. Subjects were classified into 6 categories: former drinkers, abstainers, occasional drinkers (drinkers of up to 1 g/day or equivalently 2.5 alcoholic drinks per month), ≥1 to 12, ≥12.1 to 24, ≥24.1 to 48, and >48 g/day. We identified exclusive consumers of wine, beer, or liquor and analyzed the association with incident HF or AF, having as a reference category the abstainers in each group. "Irregular drinkers" were identified as those who reported consumption >4 alcoholic units (48 g/day) for women and >5 alcoholic units for men on a single occasion.

RISK FACTOR ASCERTAINMENT. Adherence to the Mediterranean diet was evaluated using the Mediterranean diet score developed by Trichopoulou et al. (29). In the present study, alcohol intake was not included in the score, to test for a modification of the alcohol effect due to high or low adherence to the Mediterranean diet. Education was based on the highest qualification attained and was categorized as low (secondary school or lower) or high (high school or higher). Household income was divided into 4 categories as low (≤€10,000 per year), low-medium (>€10,000 to ≤€25,000 per year), medium-high

(>25,000 to ≥€40,000 per year), and high (>€40,000 per year). Cigarette smoking was defined by self-report of currently smoking every day or some days and having smoked >100 cigarettes over a lifetime. Body mass index was calculated as weight (kilograms) divided by height (meters) squared. Physical activity was assessed using a structured questionnaire and expressed as daily energy expenditure in metabolic-equivalent task-hours. Hypertensive status was defined as diastolic or systolic blood pressure ≥90 or ≥140 mm Hg, respectively, or by the use of antihypertensive medications. Diabetic status was defined as glucose level ≥126 mg/dl or by the use of relevant medications. Blood pressure was measured using an automatic device (HEM-705CP, OMRON, Kyoto, Japan) 3 times on the nondominant arm, with the patient lying down for about 5 min; the average of the last 2 measurements was used. Serum lipids were assayed using enzymatic reaction methods with an automatic analyzer (ILab 350, Diamond Diagnostics, Holliston, Massachusetts).

STATISTICAL METHODS. Baseline characteristics are expressed as percentages or as mean ± SD. The associations between alcohol categories and baseline covariates were adjusted for age and sex using linear models. Hazard ratios (HRs) of HF or AF for alcohol categories were calculated using Cox proportional hazard models adjusted for age, sex, smoking (never, former, or current, modeled by dummy variables with never as the referent), education (high vs. low), income (4 categories), physical activity (continuous), body mass index (continuous), total calorie intake (continuous), history of CVD (acute myocardial infarction or unstable angina or stroke revascularization procedure, or yes or no), hypertension (yes or no), and diabetes (yes or no), comparing each level of drinking with abstainers. We additionally adjusted the association of alcohol consumption with AF (HF) for personal history of HF (AF) at baseline or if an event of HF (AF) occurred during follow-up; that is, we treated the presence of AF (in analysis of HF) or of HF (in analysis of AF) as a time-varying covariate. Tests for violation of the proportional hazards assumption were conducted through the introduction of linear interaction between categories of alcohol consumption and the time variable. Appropriate terms of interaction were included in the models to test for a modification of the effect. A curvilinear association between the continuous measure of alcohol consumption (grams per day) at baseline and incident HF or AF was tested using an adjusted Cox model with a restricted cubic spline. For the purpose of the spline analysis, former drinkers were excluded, with abstainers (0 g/week) as the reference group. The number of knots used in the cubic spline model was chosen on the basis of maximizing goodness of fit (i.e., minimizing the Akaike information criterion). Two-sided p values <0.05 were considered to indicate statistical significance. The data analysis was performed using SAS/STAT version 9.4 of the SAS System for Windows (SAS Institute, Cary, North Carolina).

RESULTS

Characteristics of the study population according to alcohol categories are listed in Table 1. Prevalence rates of men, smoking, total physical activity, hypertension, and diabetes increased according to alcohol consumption (from never drinkers to heavy drinkers). High income and high education were more prevalent in light to moderate drinkers. Total and high-density lipoprotein cholesterol levels were higher in drinkers. In comparison with abstainers, former drinkers had higher prevalence rates of men, smokers, high income, hypertension, diabetes, and history of cardiovascular events (Table 1).

ALCOHOL AND HF. During follow-up (median 8.2 years, for a total of 183,913 person-years), 943 events of HF were identified (crude rate 4.13%). Drinkers of >12 g/day had a higher rate of HF in comparison with abstainers (Table 2); accordingly, univariate HRs increased along with crude rates (Table 2). This result is largely explained because subjects with greater alcohol consumption were worse off with respect to several CVD risk factors (sex, age, smoking, total cholesterol, hypertension, diabetes, and previous CVD) (Table 1). Multivariate HRs are deemed to be used for better elucidate the association of alcohol categories with HF or AF.

In comparison with never drinkers, both former and occasional drinkers showed an equal multivariate risk for developing HF (Table 2). Categories of alcohol intake were associated with a 13% to 21% lower multivariate risk for HF (test for overall significance of association, p = 0.049), although statistical significance was observed only for the category 24.1 to 48 g/day (HR: 0.80; 95% confidence interval [CI]: 0.65 to 0.99).

After further adjustment for the presence of AF as a time-varying covariate, the findings were practically unchanged (HR: 0.80; 95% CI: 0.65 to 0.99 for the category 24.1 to 48 g/day vs. abstention).

Among drinkers (n = 14,513), 10.8% (n = 1,572) were identified as "irregular drinkers." In this group we observed 71 incident events of HF (4.5%). In comparison with abstention, irregular drinking was not

TABLE 1 General Characteristics at Baseline, According to Alcohol Categories

	Alcohol Category							
	Former Drinkers (n = 759 [3.3%])	Never Drinkers (n = 6,104 [26.4%])	Occasional Drinkers (n = 1,448 [6.3%])	1-12 g/day (n = 4,565 [20.0%])	12.1-24 g/day (n = 3,508 [15.4%])	24.1-48 g/day (n = 4,207 [18.4%])	>48 g/day (n = 2,233 [9.8%])	p Value*
Men	32.3	19.6	32.5	41.6	51.6	76.1	96.5	<0.0001
Age (yrs)	57 ± 12	54 ± 12	53 ± 11	54 ± 12	57 ± 12	57 ± 12	57 ± 11	<0.0001
Current smokers	22	20	24	23	22	26	32	<0.0001
Total physical activity (MET-h/day)	43 ± 7	43 ± 8	42 ± 7	42 ± 7	43 ± 8	43 ± 8	45 ± 12	<0.0001
High income (>€40,000 per yr)	12	9	14	16	14	13	8	<0.0001
High education (upper to secondary education or higher)	44	45	55	57	51	45	34	<0.0001
BMI (kg/m^2)	28.5 ± 5	28.5 ± 5	28.0 ± 5	27.9 ± 5	27.6 ± 4	27.7 ± 4	28.2 ± 4	<0.0001
Total cholesterol (mg/dl)	206 ± 41	207 ± 42	211 ± 41	211 ± 40	213 ± 41	218 ± 42	226 ± 43	<0.0001
HDL cholesterol (mg/dl)	54 ± 14	54 ± 15	56 ± 15	56 ± 15	58 ± 15	60 ± 15	63 ± 14	<0.0001
Hypertension	61	51	48	52	57	62	67	<0.0001
Diabetes	11.1	8.3	6.8	7.2	8.6	11.9	13.2	<0.0001
Cardiovascular disease	6.4	4.6	3.7	3.8	5.7	7.1	5.2	<0.0001

Values are % or mean ± SD. *Means and p values are adjusted for age and sex.
BMI = body mass index; HDL = high-density lipoprotein; MET-h = metabolic-equivalent task-hrs.

associated with any multivariate risk for HF (HR: 0.92; 95% CI: 0.68 to 1.24). Lower risk for HF was actually confined to regular drinkers (HR: 0.84; 95% CI: 0.70 to 0.99).

Wine is the prevailing alcoholic beverage in our population: among drinkers, subjects who consume wine but no (or very rarely, <10 g/week) other alcoholic beverages account for 63%, whereas drinkers of beer or other alcoholic beverages but wine account for only 2%; drinkers of wine and beer represented 25% and those of wine or spirits 10%. After restriction of the analysis to wine drinkers, the multivariate association with HF incidence remained practically unchanged (Table 2). Additional beverage-specific analyses in non-wine drinkers were not performed, because of very small numbers.

Findings were similar in men and women and in younger and older subjects separately, in those with low or high adherence to the Mediterranean diet, and according to income or education (p values for difference >0.26) (Table 3).

Restricted cubic spline regression clearly showed a J-shaped relationship between alcohol intake and HF risk (Figure 1A) (overall effect p = 0.036, nonlinear effect p = 0.018), with a nadir of 20% relative protection at 20 g/day (corresponding to an absolute risk reduction of 1%). The statistical significance of the role of alcohol vanished at 55 g/day. The cubic spline curve models HF risk as a continuous function of grams per day of alcohol, whereas in Table 2, a separate HR for each alcohol category is presented. As a consequence of the difference in these 2 techniques,

TABLE 2 Incidence Rates and Hazard Ratios for Heart Failure (943 of 22,824; 4.13%), According to Alcohol Categories

	Alcohol Category						
	Former Drinkers (n = 759)	Never Drinkers (n = 6,104)	Occasional Drinkers (n = 1,448)	1-12 g/day (n = 4,565)	12.1-24 g/day (n = 3,508)	24.1-48 g/day (n = 4,207)	>48 g/day (n = 2,233)
Rate of event	53 (7.0%)	224 (3.7%)	59 (4.1%)	151 (3.3%)	153 (4.4%)	198 (4.7%)	105 (4.7%)
Person-years	6,484	47,421	11,697	38,136	28,503	33,765	17,908
Unadjusted hazard ratio (95% CI)	1.67 (1.24-2.52)	1.00 (reference)	1.06 (0.79-1.41)	0.82 (0.67-1.01)	1.12 (0.91-1.37)	1.22 (1.01-1.48)	1.23 (0.97-1.55)
Multivariate hazard ratio* (95% CI)	1.24 (0.91-1.67)	1.00 (reference)	1.17 (0.88-1.57)	0.87 (0.71-1.08)	0.85 (0.68-1.05)	0.80 (0.65-0.99)	0.79 (0.60-1.04)
Wine consumer	(n = 759)	(n = 6,104)	(n = 1,365)	(n = 3,040)	(n = 2,244)	(n = 2,507)	(n = 783)
Rate of event	53 (7.0%)	224 (3.7%)	58 (4.3%)	114 (3.8%)	120 (5.4%)	141 (5.6%)	54 (6.9%)
Multivariate hazard ratio* (95% CI)	1.24 (0.92-1.68)	1.00 (reference)	1.19 (0.89-1.66)	0.82 (0.65-1.03)	0.86 (0.68-1.08)	0.78 (0.62-0.99)	0.88 (0.63-1.23)

*Adjusted for age, sex, smoking, education, income, physical activity, body mass index, total cholesterol, total calorie intake, adhesion to Mediterranean diet (deprived of alcohol), history of cardiovascular disease, hypertension, and diabetes. Twelve grams per day of ethanol is equivalent to 1 drink.
CI = confidence interval.

TABLE 3 Hazard Ratios for Heart Failure, According to Alcohol Categories, in Different Subgroups

Subgroup	Never Drinkers	1-12 g/day	12.1-24 g/day	24.1-48 g/day	>48 g/day	p Value for Difference
All (943/22,824*)	1	0.87 (0.71-1.08)	0.85 (0.68-1.05)	0.80 (0.65-0.99)	0.79 (0.60-1.04)	
<65 yrs (347/17,739)	1	0.78 (0.56-1.08)	0.76 (0.52-1.11)	0.77 (0.54-1.10)	0.89 (0.58-1.36)	0.26
≥65 yrs (596/5,085)	1	0.97 (0.73-1.27)	1.07 (0.82-1.40)	1.01 (0.77-1.33)	0.91 (0.63-1.31)	
Men (525/10,977)	1	0.94 (0.66-1.36)	0.87 (0.62-1.23)	0.86 (0.63-1.18)	0.84 (0.59-1.20)	0.65
Women (418/11,847)	1	0.85 (0.65-1.12)	0.89 (0.66-1.18)	0.79 (0.54-1.18)	1.07 (0.33-3.44)	
Low MD adherence (≤4 points) (575/14,047)	1	0.91 (0.70-1.18)	0.91 (0.70-1.19)	0.78 (0.59-1.04)	0.98 (0.69-1.38)	0.66
High MD adherence (>4 points) (368/8,777)	1	0.84 (0.59-1.19)	0.76 (0.52-1.10)	0.83 (0.58-1.18)	0.58 (0.37-0.91)	
Low income (≤€25,000 per year) (392/8,315)	1	0.81 (0.58-1.13)	1.00 (0.72-1.39)	0.74 (0.52-1.04)	0.75 (0.49-1.15)	0.43
High income (>€25,000 per year) (190/7,557)	1	0.70 (0.44-1.13)	0.52 (0.31-0.87)	0.75 (0.47-1.18)	0.58 (0.32-1.08)	
Up to lower secondary school (701/11,860)	1	0.95 (0.74-1.22)	0.93 (0.72-1.19)	0.83 (0.64-1.08)	0.91 (0.66-1.24)	0.68
Upper to secondary education or higher (241/10,946)	1	0.74 (0.50-1.10)	0.72 (0.47-1.08)	0.81 (0.54-1.21)	0.50 (0.26-0.95)	

*Number of heart failure events/total number of exposed subjects; the sum does not add to total because of missing data.
MD = Mediterranean diet.

the cubic spline 95% confidence band is not in sync with each category's 95% CI in Table 2. The reason for the marginally significant (p = 0.049) overall association between categories of alcohol intake and HF is that in Figure 1A, the 95% confidence band dips slightly below an HR of 1.0 between 0 and 55 g/day.

ALCOHOL AND AF. New events of AF were identified in 554 subjects (crude rate 2.45%). We failed to observe overall multivariate association of alcohol categories with incidence of AF (p = 0.42) (Table 4), although significantly lower AF multivariate risk was observed for the category 24.1 to 48 g/day (HR: 0.73; 95% CI: 0.55 to 0.98). Restricted cubic spline regression failed to find a relationship between alcohol intake and AF risk (Figure 1B) (overall effect p = 0.30, nonlinear effect p = 0.12). There was no significant association between grams per day of alcohol consumption and AF, as the upper confidence band in Figure 1B is always above 1.00.

Further adjustment for the presence of HF as a time-varying covariate left the findings virtually unaffected (HR: 0.71; 95% CI: 0.53 to 0.95 for the category 24.1 to 48 g/day vs. abstention).

Very similar results were found after restriction of the analysis to wine drinkers or regular drinkers (data not shown).

The findings also remained unchanged when analyses were restricted to men, women, or wine drinkers or according to age, income, or education (p values for difference >0.50; data not shown).

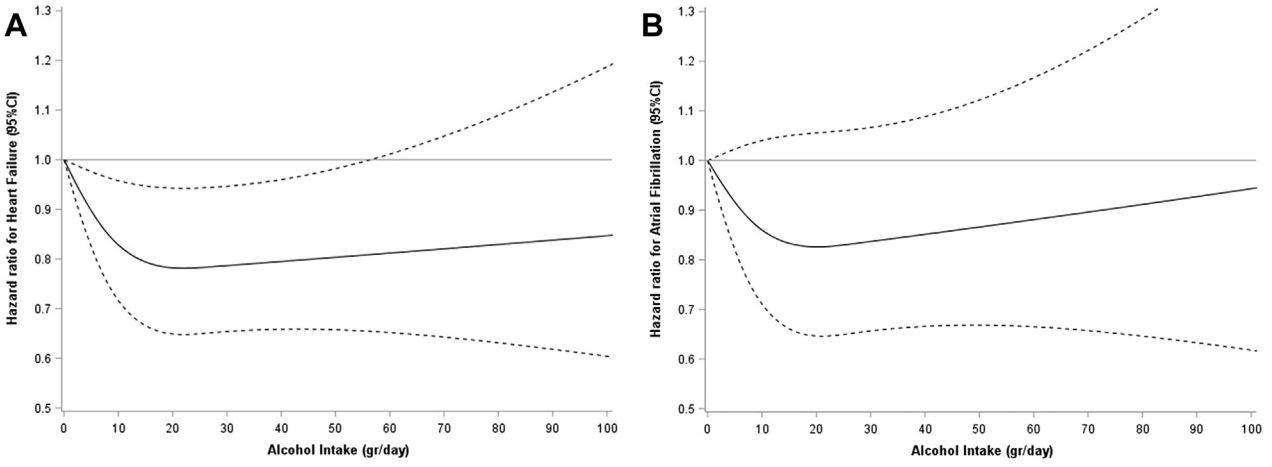
DISCUSSION

ALCOHOL AND HF. In this prospective study of more than 22,800 men and women ≥35 years of age, we found that moderate alcohol intake, in comparison with abstention, was associated with reduced risk for HF events when adjusted for a large panel of confounding variables. The association was manifest up to 4 drinks/day. Either former or very rare or heavy drinker categories were not associated with a lower risk for HF compared with abstainers. The association was not modified by sex, age, type of alcoholic beverage, diet, or social status.

Our findings are in agreement with a large dose-response meta-analysis in which the investigators observed a nonlinear relationship between alcohol consumption and risk for HF, with maximum protection (−16%) at 10 drinks/week (13). Of interest, all the studies included in the meta-analysis were from the United States or northern European countries. Our results extend these findings to a Mediterranean population, in which wine was to a large extent the alcoholic beverage of preference. This fact may explain why in our study, protection against HF was detected up to 4 drinks/day, a limit higher than that observed in populations in which wine is not the predominant alcoholic beverage. The hypothesis that wine exerts a beneficial effect to a higher intake in comparison with other drinks, at least for HF, is fascinating and may rely upon potential healthy properties of nonalcoholic components present in wine in larger amounts than in other beverages (2). However, this hypothesis remains to be more thoroughly investigated in both experimental and epidemiological studies (9,10).

Alcohol's effects may be different in men and women or modified by age or environmental factors (2). However, we failed to observe any modification of effect due to sex, age, diet, or social status. In fact,

FIGURE 1 Restricted Cubic Spline Regression for the Association Between Alcohol Intake and Heart Failure or Atrial Fibrillation



(A) Heart failure; **(B)** atrial fibrillation. **Solid line** = hazard ratio; **dashed line** = 95% confidence interval. Knots were placed at the 25th, 50th, and 75th percentiles (0, 7.64, and 26.75 g/day). The reference value was 0 g/day. Former drinkers were excluded. The model was adjusted for age, sex, smoking, education, income, physical activity, body mass index, total cholesterol, total calorie intake, history of cardiovascular disease, hypertension, and diabetes.

the risk for HF associated with heavy intake was higher in women than in men, and the lower HF risk associated with moderate alcohol intake was more evident in subjects with poor adherence to the Mediterranean diet compared with those with greater adherence (**Table 3**); although the modification of effect was not statistically significant, this result suggests possible overlapping mechanisms of alcohol consumption and the Mediterranean diet in cardiovascular protection. Further studies are required to elucidate this finding.

The mechanisms through which alcohol in moderation may exert a role in HF are composite and are not entirely understood; previous studies have shown beneficial effects of alcohol on endothelial function, insulin sensitivity, high-density lipoprotein cholesterol, and atrial natriuretic peptide, which may prevent the clinical onset of HF (13-15).

ALCOHOL AND AF. We failed to observe an overall multivariate association of alcohol consumption with AF. Concerning the consumption of alcohol up to 1 drink/day, our findings are in agreement with those of a recent Swedish prospective study including 79,019 subjects with 7,245 incident AF cases, in which the investigators failed to observe an association between low alcohol intake and AF (30). In contrast, although both in the Swedish study and in a recent meta-analysis (6), intake of alcohol higher than 1 drink/day was associated with an increase in AF risk, we failed to observe an augmentation of AF risk at increasing intake of alcohol. As a possible partial

TABLE 4 Incidence Rates and Hazard Ratios for Atrial Fibrillation (n = 554 of 22,628; 2.45%), According to Alcohol Categories

	Alcohol Category						
	Former Drinkers (n = 753)	Never Drinkers (n = 6,052)	Occasional Drinkers (n = 1,442)	1-12 g/day (n = 4,526)	12.1-24 g/day (n = 3,481)	24.1-48 g/day (n = 4,167)	>48 g/day (n = 2,207)
Rate of event	26 (3.5%)	120 (2.0%)	24 (1.6%)	99 (2.2%)	101 (2.9%)	113 (2.7%)	71 (3.2%)
Person-years	6,486	47,410	11,765	38,050	28,417	33,642	17,797
Univariate hazard ratio (95% CI)	1.54 (1.01-2.35)	1.00 (reference)	0.80 (0.52-1.24)	1.01 (0.77-1.32)	1.39 (1.07-1.81)	1.31 (1.02-1.70)	1.56 (1.16-2.09)
Multivariate hazard ratio* (95% CI)	1.05 (0.69-1.62)	1.00 (reference)	0.98 (0.74-1.28)	0.92 (0.75-1.52)	0.96 (0.70-1.21)	0.73 (0.55-0.98)	0.85 (0.60-1.20)

*Adjusted for age, sex, smoking, education, income, physical activity, body mass index, total cholesterol, total calorie intake, history of cardiovascular disease, hypertension, and diabetes. Twelve grams per day of ethanol is equivalent to 1 drink.

CI = confidence interval.

explanation of this contrasting result, we notice that almost all studies included in the meta-analysis (6) were from the United States or northern European countries, where wine is not the alcoholic beverage of preference (as it is in our population) and the tendency toward irregular drinking, or drinking outside meals, is higher compared with our setting. However, the latter is only a conjecture, and further studies are required to assess whether a different effect of alcohol on AF across countries does exist.

STUDY STRENGTHS AND LIMITATIONS. As strengths of this study, we recognize that it derives from a large population-based cohort enrolled in a Mediterranean country, a setting where the association of alcohol with HF or AF had not been previously studied; it was a prospective study, and a large panel of potential confounders were available to adjust for.

A major limitation of our study is the relatively small number of events. Moreover, alcohol consumption information was self-reported and was based only on a single baseline ascertainment, although this is common in large population-based studies. Lack of data on HF type (HF with altered vs. normal ejection fraction) and imperfect ability to identify lifetime abstainers also must be disclosed as limitations. We should also note that outpatient AF events were not captured. This could explain the lack of association, as a certain proportion of AF is diagnosed in clinics, not by way of hospital admission. Ultimately, we recognize that the association of moderate alcohol intake with HF we found is only marginal and does not meet a significance criterion of 2-sided $p = 0.05/2 = 0.025$ possibly required for significance in the presence of 2 tested outcomes (HF and AF).

CONCLUSIONS

In a large Mediterranean population, in which wine is largely the alcoholic beverage of preference, consumption of alcohol in moderation was associated with a lower incidence of HF, whereas it was not associated with the development of AF.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: In adults ≥35 years of age who are regular light to moderate alcohol consumers (up to 2 drinks/day), the risk for developing HF is 20% lower in comparison with abstention or heavy drinking (absolute risk reduction 1%).

TRANSLATIONAL OUTLOOK: Randomized trials investigating alcohol intake in more detail for the prevention of HF in older adults are needed.

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KEY WORDS alcohol consumption, atrial fibrillation, heart failure

APPENDIX For a list of Moli-sani Project investigators, please see the online version of this paper.