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ORIGINAL RESEARCH

Associations of Alcohol Consumption With Left Atrial Morphology and Function in a Population at High Cardiovascular Risk

Aniqa B. Alam, MPH; Estefania Toledo-Atucha, MD, PhD; Dora Romaguera, MSc, PhD; Angel M. Alonso-Gómez, MD, PhD; Miguel A. Martínez-Gonzalez, MD, PhD; Lucas Tojal-Sierra, MD; Marta Noris Mora, MD; Caterina Mas-Llado, MD; Linzi Li, MPH, MSPH; Ines Gonzalez-Casanova, PhD; Jordi Salas-Salvadó, PhD; Montserrat Fitó, MD, PhD; Alvaro Alonso, MD, PhD

BACKGROUND: Excessive alcohol consumption has been associated with increased risk of atrial fibrillation, although the underlying mechanisms remain unclear. An enlarged left atrium and impaired left atrial function may lead to atrial fibrillation. The association of alcohol consumption with structural and functional left atrial measures, however, has received limited attention.

METHODS AND RESULTS: We studied 503 participants from the PREDIMED-Plus (Prevención con Dieta Mediterránea) trial, a randomized trial testing intensive weight loss intervention with an energy-reduced Mediterranean diet and physical activity promotion in preventing cardiovascular disease in adults with metabolic syndrome. Participants underwent transthoracic echocardiography at baseline, year 3, and year 5 of the study. Outcomes of interest included volume index and reservoir, conduit, and contractile strains of the left atrium. Alcohol consumption was calculated through food frequency questionnaires and presented as drinks consumed per day. Multiple linear regression and mixed models estimated the association of alcohol consumption with left atrial measurements at baseline and through follow-up. Cross-sectionally, higher alcohol consumption (per 1 drink/day increases) was associated with larger left atrial volume (0.65 mL/m^2 [95% CI, 0.18–1.11]) and lower left atrial reservoir and contractile strain (−0.44% [95% CI, −0.87 to −0.01]; and −0.44% [95% CI, −0.75 to −0.14]). Baseline alcohol consumption was not associated with changes in left atrial measurements, but increases in alcohol consumption (per 1 drink/day increase) during follow-up were associated with left atrial enlargement (0.71 mL/m^2 [95% CI, 0.17–1.26]).

CONCLUSIONS: In a population at high cardiovascular risk, increased alcohol consumption was associated with left atrial enlargement and worsening atrial function.

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Key Words: alcohol consumption ■ atrial fibrillation ■ atrial structure and function

See Editorial by Petzl and Deo.

Alcohol consumption is widespread in Western countries. Excessive alcohol consumption is associated with cardiovascular pathologies such as cardiomyopathy,[1] stroke,[2,3] myocardial infarction,[4,5] and atrial fibrillation (AF).[6] Even moderate drinking has been associated with incident AF,[7,8] though to a lesser extent compared with heavy drinking, suggesting a dose–response relationship. It is important to note, however, that the classification of drinking severity varies across studies.

Correspondence to: Aniqa B. Alam, MPH, Department of Epidemiology, Emory University School of Public Health, 1518 Clifton Rd NE, CNR 3040B, Atlanta, GA 30322. Email: abalam@emory.edu

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CLINICAL PERSPECTIVE

What Is New?

- In a population at high risk of cardiovascular disease, we found elevated alcohol consumption to be associated with left atrial enlargement and worsening atrial strain function.
- Participants who increased alcohol consumption over 5 years, starting at a baseline of low consumption, experienced the greatest volumetric enlargement and atrial strain worsening.

What Are the Clinical Implications?

- Alcohol consumption behaviors should be taken into consideration when managing and treating those at higher risk of developing atrial fibrillation.

Nonstandard Abbreviations and Acronyms

LAVi	left atrial volume index
MedDiet	Mediterranean diet
PREDIMED	Prevención con Dieta Mediterránea

The mechanisms linking alcohol consumption and AF are not well characterized. Previous studies have shown that increased left atrial (LA) diameter and dysfunction are associated with both excessive alcohol consumption and AF, with nearly 24% of the association of alcohol and AF being explained by increased LA diameter.[9,10] Prior studies, however, did not consider that more relevant measures of LA structure (such as LA volume) were performed in small samples or were merely cross sectional. Furthermore, the effects of different types of alcohol on LA structure and function or AF risk are not well studied.[7] Thus, we propose examining the association of alcohol consumption, as well as consumption of alcohol from different sources, with volumetric and functional measures of the left atrium, both cross sectionally and longitudinally.

METHODS

Study Population

Due to issues of consent regarding data sharing, data from the PREDIMED-Plus (Prevención con Dieta Mediterránea) trial cannot be made widely available, but researchers wishing to access data for research purposes may make a request to the principal coordinator of the PREDIMED-Plus trial (Jordi Salas-Salvadó at jordi.salas@urv.cat). The PREDIMED-Plus study is an ongoing, randomized, and controlled lifestyle intervention trial being conducted in several centers throughout Spain with the primary aim of testing an intensive lifestyle intervention focusing on weight loss in the context of increasing adherence to an energy-reduced Mediterranean diet (MedDiet) and physical activity among individuals who are overweight or obese with the metabolic syndrome.[11] Participants in the control group received a nutritional intervention to foster their adherence to the MedDiet with no total energy reduction or advice on physical activity. Results from the analysis evaluating the effect of the intervention on measures of LA structure and function have been reported elsewhere.[12] The institutional review boards at each of the associated study centers have approved the current study protocol, and all participants have provided written informed consent to be part of the study.

A subgroup of 566 participants recruited from 3 sites of the PREDIMED-Plus cohort (Navarra, Balearic Islands, and Vitoria) who agreed to be included in the study underwent 2-dimensional transthoracic echocardiography at baseline, year 3, and year 5 of the study. After excluding those missing LA measurements at baseline (N=51) and those with AF at baseline (N=12), 503 participants were included in the present analysis (Figure 1).

LA Structure and Volume

Measurements at all sites were performed by trained personnel using GE Vivid machines, with studies sent to a central laboratory for reading by 2 dedicated cardiologists. Outcomes of interest included structural (left atrial volume index [LAVi]) and functional (reservoir, conduit, and contractile atrial strains) measures of the left atrium. Maximal LA volume was measured before mitral valve opening using 2-dimensional speckle tracking analysis of the left atrium, with 4- and 2-chamber apical views analyzed using AFI LA (GE EchoPAC)[13] and indexed to body surface area to calculate LAVi. LA strain indices were calculated with speckle-tracking software with an autostrain algorithm (GE Echopac). Detailed descriptions of the imaging process can be found elsewhere.[14] Intra- and interobserver variability was evaluated by calculating the coefficient of variation for 29 baseline studies read twice by the same reader at separate time points and 76 baseline studies read by 2 different individuals. Intraobserver coefficient of variation was 7.4% for LA volume and 4.4% for LA reservoir strain, while interobserver coefficient of variation was 18.9% for LA volume and 19.1% for LA reservoir strain.

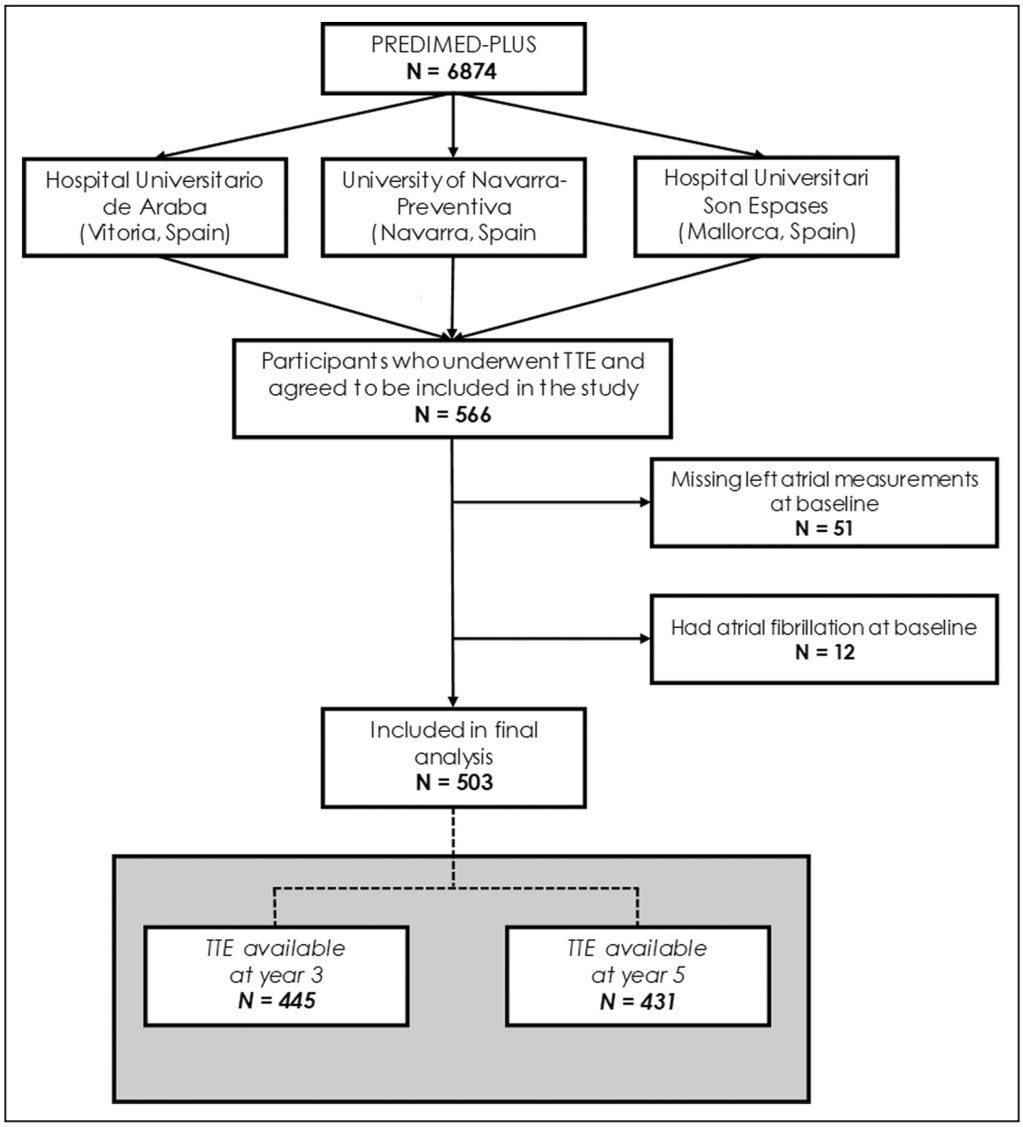

Figure 1. Flowchart of PREDIMED-Plus participants included in study.
PREDIMED-Plus indicates Prevención con Dieta Mediterránea; and TTE, transthoracic echocardiography.

Alcohol Consumption

Alcohol consumption was calculated with a validated 143-item semiquantitative food frequency questionnaire, which participants filled out at baseline and every yearly follow-up visit.[15] Specific categories of alcohol included wine (red wine [aged and young], other wine [white, rosé, muscatel, cava]), beer, and spirits (liquor, whiskey). Since the pure alcohol content varies depending on the type of drink, standard sizes of each type of beverage in the food frequency questionnaire were as follows: 1 glass of wine, 100 cc, except for muscatel, 50 cc; 1 bottle of beer, 330 cc; 1 shot of liquor or other spirits, 50 cc. In this analysis, 1 standard drink was equivalent to 14 g of pure alcohol. For estimated alcohol intake, the intraclass correlation between the food frequency questionnaire and four 3-day dietary records was 0.82.[15]

Covariates

Education and marital status served as markers of socioeconomic status in this study. Physical activity was assessed at baseline in metabolic equivalents of task in minutes per day.[16] Body mass index was calculated from weight and height at baseline. Smoking status was self-reported at baseline. Diet adherence was calculated using a 17-item questionnaire evaluating adherence to an energy-reduced MedDiet,[17] but was recalculated to exclude alcohol intake to avoid redundancy. Systolic and diastolic blood pressure were taken 3 times at every visit and then averaged.

Diabetes was based on self-reported information at baseline, use of antidiabetic medication, and measures of fasting blood glucose and glycosylated hemoglobin. The presence of depressive symptoms was evaluated using the 21-question Beck Depression Inventory. Assignment to the study intervention group was also taken into consideration.

Statistical Analysis

Analyses were conducted using a data set with follow-up data up to 5 years generated on August 10, 2022. Multivariable linear regression was used to estimate the cross-sectional association of baseline alcohol consumption with baseline LA measures. To evaluate the association of baseline alcohol consumption with changes in LA measures from baseline to year 3 to year 5, we employed mixed models with baseline alcohol consumption and LA measures at each time as dependent variables (with the data structured as one observation per visit), with time being modeled continuously, and used an unstructured covariance matrix to avoid model misspecification. We also evaluated the impact of changes in drinking amount over the course of the study by using the difference in alcohol consumption from baseline to year 5 as a predictor of changes in LA measures from baseline to year 5. We also modeled change in alcohol consumption over time as restricted cubic splines via linear regression to visualize the association with change in LA measurements. Furthermore, we must consider the impact of physical activity and energy reduction on cardiac structure and function. We therefore estimated associations by intervention assignment. All analyses were repeated to also produce estimates for each type of alcohol. Alcohol consumption was categorized into 0 (reference group), 1, 2 to 3, and ≥4 drinks consumed per day. Models were also run using alcohol consumption as a continuous variable (modeled in drinks/day).

All models were initially adjusted for age, sex, education, and intervention group, except for cross-sectional analyses in which intervention group assignment would have no impact on baseline outcomes. They were further adjusted for marital status, smoking, physical activity, height, body mass index, systolic and diastolic blood pressure, diabetes, depression, adherence to the energy-reduced MedDiet, and intervention group. Longitudinal analysis also considered interaction of all covariates with time. Changes in these covariates, however, may also influence LA structure and functioning, so differences from baseline to year 5 for the following covariates were also incorporated in our models: smoking, physical activity, body mass index, systolic and diastolic blood pressure, diabetes, depression, and diet adherence.

All analyses were performed using SAS 9.4 (SAS Institute Inc., Cary, NC), while splines were generated using STATA, version 17 (StataCorp LP, College Station, TX).

RESULTS

Of 503 participants included in this study (mean age [SD], 65.1 [4.9] years), 40% were women, and 51% were randomized to the intervention group. Heavier drinkers at baseline were younger, more educated, and more likely to be men than their nondrinking counterparts (Table 1). Echocardiographic measurements were available in 445 participants at year 3 (88%) and 431 participants at year 5 (86%) (Figure 1).

Cross-sectionally, modeling of alcohol consumption as a continuous variable showed larger LAVi with higher alcohol consumption (β, 0.65 mL/m^2 [95% CI, 0.18–1.11] per 1 drink/day), after adjustment for demographic, lifestyle, and clinical variables (Table 2). Considering categories of alcohol intake suggested a J-shaped association, with higher LAVi observed only at the highest levels of alcohol consumption (Table 2). Higher baseline alcohol consumption showed linear associations with reduced LA reservoir strain and LA contractile strain, but not with LA conduit strain (Table 2). One drink/day was associated with reductions of −0.44% (95% CI, −0.87 to −0.01) of LA reservoir strain and −0.44% (95% CI, −0.75 to −0.14) of LA contractile strain.

Baseline alcohol consumption was not associated with changes in LA volume nor with strain measures (Table 3). However, changes in alcohol consumption over 5 years were associated with changes in LA structure and function. Increasing alcohol consumption by at least 1 drink per day was associated with 0.71 mL/m^2 (95% CI, 0.17–1.26) increases in LAVi compared with participants who did not change their amount of alcohol consumption (Table 4). Increasing alcohol consumption from baseline to year 5 was also nonsignificantly associated with worsening LA function, as determined by LA strain measurements (Table 4). Analyses modeling change in alcohol intake as a spline variable once again suggested a J-shaped association, with increases in LAVi observed only with exposure to heavy alcohol consumption (Table 4 and Figure 2). The associations of change in alcohol intake (when modeled as a spline variable) with strain measures were mostly linear (Figure 2).

Heavy wine consumption was associated with significantly elevated LAVi at baseline (β, 2.56 mL/m^2 [95% CI, 0.32–4.80], comparing ≥4 drinks/day to 0 drinks), but no such associations were present with beer or spirits (Table S1). Heavy wine consumption was also

Table 1. Cohort Descriptives, by Daily Drinking Frequency

Characteristic	0 Drinks (N=99)	1 Drink/day (N=228)	2–3 Drinks/day (N=105)	≥4 Drinks/day (N=71)
Intervention group, %	54	51	48	52
Age, y	66 (4)	65 (5)	65 (5)	64 (5)
Female, %	71	50	14	4
Education, %				
College	11	13	16	20
Technical school	4	5	9	6
High school	25	28	30	49
Primary school	60	54	46	25
Marital status, %				
Single	5	5	5	7
Married	73	75	82	86
Widower	15	12	8	3
Divorced	6	6	4	3
Other	1	1	2	1
Height, cm	160 (9)	163 (9)	168 (8)	170 (7)
Body mass index, kg/m^2	32.5 (3.6)	32.2 (3.3)	32.0 (3.0)	32.3 (3.0)
Systolic blood pressure, mm Hg	142 (17)	140 (17)	141 (16)	143 (16)
Diastolic blood pressure, mm Hg	77 (9)	78 (10)	81 (9)	83 (10)
Smoking, %				
Current smoker	5	10	9	13
Former smoker (0–5 years ago)	4	5	8	10
Former smoker (>5 years ago)	31	42	56	58
Never smoker	60	43	28	20
Physical activity (MET min/wk)	2244 (1906)	2398 (2066)	3104 (2966)	2471 (2163)
Diabetes, %	43	29	18	20
Beck Depression Inventory (0–63)	9.3 (7.3)	8.3 (7.3)	7.9 (7.7)	6.7 (5.6)
Diet adherence* (1–16)	8.1 (2.7)	7.6 (3.0)	6.7 (2.9)	5.5 (2.6)
Daily wine consumption, g/d	0	35 (34)	170 (107)	452 (181)
Daily beer consumption, g/d	0	49 (74)	192 (245)	280 (474)
Daily spirits consumption, g/d	0	1 (3)	6 (10)	13 (25)
LA outcomes				
LAVi, mL/m^2	22.6 (6.8)	22.6 (7.2)	22.0 (6.8)	25.1 (6.9)
LA reservoir strain, %	27.4 (6.5)	27.6 (6.7)	28.2 (6.8)	27.3 (5.2)
LA conduit strain, %	11.4 (3.7)	12.0 (4.8)	12.4 (4.7)	11.8 (3.4)
LA contractile strain, %	15.9 (5.0)	15.6 (4.7)	15.7 (4.4)	15.5 (4.3)

Data presented as either mean (SD) for continuous measures or as frequencies for categorical variables. 1 drink: 1–14 g; 2–3 drinks: 15–42 g; 4 or more drinks: ≥43 g. LA indicates left atrial; LAVi, left atrial volume index; and MET metabolic equivalent of tasks.

*Sum of 16 questions concerning adherence to an energy-reduced Mediterranean diet. Does not include alcohol intake.

associated with poorer reservoir (β, −2.06% [95% CI, −4.11 to −0.01]) and contractile strain (β, −1.50% [95% CI, −2.97 to −0.02]) at baseline. The different types of alcoholic beverage did not show any association with changes in LA measures from baseline to year 5 (Table S2).

Higher alcohol consumption was associated with larger LA volumes (β, 3.71 mL/m^2 [95% CI, 0.65–6.77]) and poorer contractile strains (β, −2.31% [95% CI, −4.42 to −0.21]) at baseline in men but not in women (Table S3). There was, however, no evidence of sex interaction (P=0.76 [volume] and P=0.20 [contractile]). Once again, there was no evidence of longitudinal associations of alcohol consumption and changes in LA measures when analyses were stratified by sex (Table S4).

Participants were also stratified by drinking intensity at baseline. Participants who began with 0 to 1 drinks per day and progressed to ≥2 drinks per day by year 5 had higher volumes (β, 0.73 mL/m^2 [95% CI, 0.11–1.34]) and worse reservoir strains (β, −0.58% [95% CI, −1.18 to 0.01]) compared with those who remained light drinkers (Table S5). Participants who began with ≥2 drinks per day and reduced their intake to 0 to 1 drinks per day by

Table 2. Multiple Linear Regression Estimates of Overall Alcohol Consumption with LA Measures at Baseline

		0 Drinks	1 Drink/day	2–3 Drinks/day	≥4 Drinks/day	Per 1-drink* increase
LAVi, mL/m^2	Model 1	0 (ref.)	0.09 (–1.60 to 1.77)	–0.44 (–2.54 to 1.66)	2.74 (0.38 to 5.10)	0.67 (0.21 to 1.13)
	Model 2	0 (ref.)	–0.09 (–1.79 to 1.60)	–0.75 (–2.90 to 1.39)	2.35 (–0.08 to 4.78)	0.65 (0.18 to 1.11)
LA reservoir strain, %	Model 1	0 (ref.)	–0.32 (–1.85 to 1.20)	–0.50 (–2.40 to 1.40)	–1.51 (–3.65 to 0.63)	–0.40 (–0.81 to 0.02)
	Model 2	0 (ref.)	–0.75 (–2.31 to 0.81)	–0.98 (–2.95 to 0.99)	–1.94 (–4.17 to 0.29)	–0.44 (–0.87 to –0.01)
LA conduit strain, %†	Model 1	0 (ref.)	0.40 (–0.64 to 1.44)	0.52 (–0.77 to 1.82)	–0.07 (–1.52 to 1.39)	–0.06 (–0.35 to 0.22)
	Model 2	0 (ref.)	0.55 (–0.50 to 1.60)	0.93 (–0.39 to 2.24)	0.48 (–1.01 to 1.98)	–0.01 (–0.29 to 0.28)
LA contractile strain, %	Model 1	0 (ref.)	–0.57 (–1.67 to 0.53)	–1.06 (–2.43 to 0.31)	–1.36 (–2.90 to 0.19)	–0.34 (–0.64 to –0.04)
	Model 2	0 (ref.)	–0.96 (–2.08 to 0.16)	–1.65 (–3.06 to –0.23)	–2.09 (–3.69 to –0.49)	–0.44 (–0.75 to –0.14)

Model 1: adjusted for age, sex, and education. Model 2: adjusted for age, sex, education, marital status, smoking, physical activity, height, body mass index, systolic and diastolic blood pressure, diabetes, depression, and adherence to the energy-reduced Mediterranean diet. LA indicates left atrial; LAVi, left atrial volume index; and ref., reference.

*1 drink=14 g of alcohol.

†Association not linear, based on per 1-drink increase.

year 5 had lower volumes, but also worse strain function compared with those who remained heavy drinkers; these estimates, however, were not significant.

Stratification based on assignment to the intervention did not yield significantly different results between either arm of the intervention (Table S6). Heavy drinkers in the control group experienced greater increases in LA reservoir strains (β, 0.57% [95% CI, –0.33 to 1.46]), while heavy drinkers in the intervention group experienced less of an increase over the 5 years (β, 0.22% [95% CI, –0.55 to 0.98]); neither of these estimates were significant, and there was no evidence of significant interactions between intervention assignment and LA outcomes.

DISCUSSION

In a study of 503 Spanish adults at high cardiovascular risk, we found that higher alcohol intake was cross sectionally associated with LAVi following a J-shaped association and with impaired LA function. Baseline alcohol intake was not associated with changes in LA structure or function longitudinally over a 5-year period. However, increases in alcohol consumption during the

Table 3. Mixed-Model Estimates of Overall Alcohol Consumption at Baseline With Change in LA Measures From Baseline to Year 5

		0 Drinks	1 Drink/day	2–3 Drinks/day	≥4 Drinks/day	Per 1-drink* increase
Change in LAVi, mL/m^2†	Model 1	0 (ref.)	–0.24 (–0.61 to 0.13)	0.14 (–0.32 to 0.60)	0.07 (–0.44 to 0.58)	0.06 (–0.04 to 0.16)
	Model 2	0 (ref.)	–0.21 (–0.59 to 0.18)	0.14 (–0.35 to 0.62)	–0.01 (–0.55 to 0.53)	0.04 (–0.06 to 0.14)
	Model 3	0 (ref.)	–0.19 (–0.60 to 0.22)	0.17 (–0.34 to 0.69)	–0.09 (–0.67 to 0.49)	0.02 (–0.09 to 0.13)
Change in LA reservoir strain, %†	Model 1	0 (ref.)	–0.02 (–0.38 to 0.33)	–0.15 (–0.58 to 0.29)	0.31 (–0.18 to 0.80)	0.08 (–0.02 to 0.17)
	Model 2	0 (ref.)	–0.04 (–0.40 to 0.33)	–0.19 (–0.66 to 0.27)	0.27 (–0.25 to 0.79)	0.08 (–0.02 to 0.18)
	Model 3	0 (ref.)	–0.02 (–0.42 to 0.37)	–0.14 (–0.64 to 0.36)	0.37 (–0.19 to 0.93)	0.09 (–0.02 to 0.20)
Change in LA conduit strain, %†	Model 1	0 (ref.)	–0.05 (–0.29 to 0.20)	–0.14 (–0.44 to 0.16)	0.18 (–0.16 to 0.51)	0.03 (–0.03 to 0.10)
	Model 2	0 (ref.)	–0.07 (–0.32 to 0.18)	–0.22 (–0.53 to 0.10)	0.08 (–0.27 to 0.43)	0.02 (–0.05 to 0.09)
	Model 3	0 (ref.)	–0.16 (–0.42 to 0.11)	–0.25 (–0.59 to 0.09)	0.10 (–0.28 to 0.48)	0.04 (–0.03 to 0.11)
Change in LA contractile strain, %†	Model 1	0 (ref.)	0.03 (–0.23 to 0.28)	0.01 (–0.30 to 0.33)	0.12 (–0.23 to 0.47)	0.04 (–0.03 to 0.11)
	Model 2	0 (ref.)	0.04 (–0.22 to 0.30)	0.04 (–0.29 to 0.37)	0.18 (–0.19 to 0.55)	0.05 (–0.02 to 0.12)
	Model 3	0 (ref.)	0.14 (–0.14 to 0.42)	0.12 (–0.23 to 0.47)	0.27 (–0.13 to 0.67)	0.05 (–0.03 to 0.12)

Model 1: adjusted for age, sex, education, intervention group, and interaction of all covariates with time. Model 2: adjusted for age, sex, education, intervention group, marital status, smoking, physical activity, height, body mass index, systolic and diastolic blood pressure, diabetes, depression, adherence to the Mediterranean diet, and interaction of all covariates with time, including an interaction term for baseline alcohol consumption and time. Model 3: adjusted for age, sex, education, intervention group, marital status, smoking, physical activity, height, body mass index, systolic and diastolic blood pressure, diabetes, depression, adherence to the Mediterranean diet, interaction of all covariates with time, and differences from baseline to year 5 for the following: smoking, physical activity, body mass index, systolic and diastolic blood pressure, diabetes, depression, and adherence to the Mediterranean diet, including an interaction term for baseline alcohol consumption and time. LA indicates left atrial; LAVi, left atrial volume index; and ref., reference.

*1 drink=14 g of alcohol.

†Association not linear, based on per 1-drink increase.

Table 4. Mixed-Model Estimates of Changes in Alcohol Consumption With Change in LA Measures From Baseline to Year 5

		Decreased consumption (≥1 drinks/day)	No change (–1>drinks/day>1)	Increased consumption (≥1 drinks/day)	Per 1-drink* increase
Change in LAVi, mL/m^2†	Model 1	0.12 (–0.23 to 0.47)	0 (ref.)	0.80 (0.28 to 1.33)	0.19 (0.02 to 0.36)
	Model 2	0.09 (–0.27 to 0.45)	0 (ref.)	0.75 (0.22 to 1.28)	0.15 (–0.02 to 0.33)
	Model 3	0.10 (–0.32 to 0.51)	0 (ref.)	0.71 (0.17 to 1.26)	0.16 (–0.02 to 0.33)
Change in LA reservoir strain, %†	Model 1	–0.02 (–0.35 to 0.31)	0 (ref.)	–0.22 (–0.73 to 0.28)	–0.07 (–0.24 to 0.09)
	Model 2	–0.05 (–0.39 to 0.29)	0 (ref.)	–0.25 (–0.77 to 0.26)	–0.12 (–0.28 to 0.05)
	Model 3	0.12 (–0.28 to 0.52)	0 (ref.)	–0.20 (–0.73 to 0.32)	–0.11 (–0.28 to 0.06)
Change in LA conduit strain, %†	Model 1	0.05 (–0.18 to 0.27)	0 (ref.)	–0.09 (–0.44 to 0.26)	–0.02 (–0.13 to 0.10)
	Model 2	0.04 (–0.19 to 0.26)	0 (ref.)	–0.10 (–0.45 to 0.25)	–0.05 (–0.16 to 0.06)
	Model 3	0.15 (–0.13 to 0.42)	0 (ref.)	–0.09 (–0.45 to 0.27)	–0.06 (–0.18 to 0.06)
Change in LA contractile strain, %†	Model 1	–0.07 (–0.31 to 0.17)	0 (ref.)	–0.14 (–0.50 to 0.23)	–0.06 (–0.18 to 0.05)
	Model 2	–0.09 (–0.33 to 0.15)	0 (ref.)	–0.15 (–0.52 to 0.21)	–0.07 (–0.19 to 0.05)
	Model 3	–0.01 (–0.30 to 0.27)	0 (ref.)	–0.11 (–0.48 to 0.27)	–0.05 (–0.18 to 0.07)

Model 1: adjusted for age, sex, education, intervention group, and interaction of all covariates with time. Model 2: adjusted for age, sex, education, intervention group, marital status, smoking, physical activity, height, body mass index, systolic and diastolic blood pressure, diabetes, depression, adherence to the Mediterranean diet, and interaction of all covariates with time, including an interaction term for baseline alcohol consumption and time. Model 3: adjusted for age, sex, education, intervention group, marital status, smoking, physical activity, height, body mass index, systolic and diastolic blood pressure, diabetes, depression, adherence to the Mediterranean diet, interaction of all covariates with time, including an interaction term for baseline alcohol consumption and time, and differences from baseline to year 5 for the following: smoking, physical activity, body mass index, systolic and diastolic blood pressure, diabetes, depression, and adherence to the Mediterranean diet. LA indicates left atrial; LAVi, left atrial volume index, and ref., reference.

*1 drink=14 g of alcohol.

†Association not linear, based on per 1-drink increase.

study period were associated with increases in LAVi and, to a lesser extent, reductions in LA strain.

Similar findings were present in the community-based Atherosclerosis Risk in Communities study, which reported higher LA size associated with higher alcohol intake in a cross-sectional analysis,[18] and in the Framingham Heart Study, in which higher alcohol intake was associated with higher LA size but not with change in diameter over time.[9] The authors suggested that alcohol may increase LA size up to a certain point, after which the effect plateaus, which may explain the lack of longitudinal associations in this analysis. Furthermore, historical drinking behavior may have some influence on the progression of atrial remodeling and dilation, and as PREDIMED-Plus did not collect data on drinking patterns before the start of the trial, there may be some bias that we cannot account for in this analysis.

Studies conducted in populations with cardiovascular disease have also found associations between higher alcohol consumption and increased LA size or impaired LA function. In the Heart and Soul study, among 601 patients with coronary heart disease, heavy alcohol consumption, based on the Alcohol Use Disorders Identification Test Consumption test to identify alcohol use disorders, was associated with increases in LA volume over a 5-year period.[19] Another study conducted in 160 patients with AF found higher LA volume and impaired LA function in those with higher alcohol consumption.[20]

Patterns of consumption are not typically static; it is important to account for changes in alcohol intake over time. Markers of LA health worsened in PREDIMED-Plus participants who increased their alcohol consumption after initial baseline assessments. While we did not find a reduction in intake to be particularly beneficial, other studies suggest that abstinence may reduce AF burden among frequent drinkers. In an open-label, randomized, controlled trial, Voskoboinik and colleagues reported significant reductions in alcohol intake in patients with symptomatic AF resulted in reductions in AF events and time spent in AF.[21] The availability of randomized controlled trials supporting these associations bolster the results of this present study by bridging the gap between morphological and functional changes in the myocardium and clinical presentation of atrial dysfunction. Unfortunately, there is limited additional evidence evaluating the impact of changes in alcohol consumption on markers of LA structure and function. This information is needed to better understand the role of alcohol on the risk of AF and to expand the findings of Voskoboinik et al to primary prevention settings with an anticipatory perspective.

Alcohol is the most commonly reported trigger for paroxysmal AF[22] and is even thought to be the precipitator of nearly 35% of all new-onset cases of AF.[23] Moreover, phenomena such as *holiday heart syndrome*, an alcohol-induced episode of AF, are common in emergency rooms.[24] Alcohol may exercise

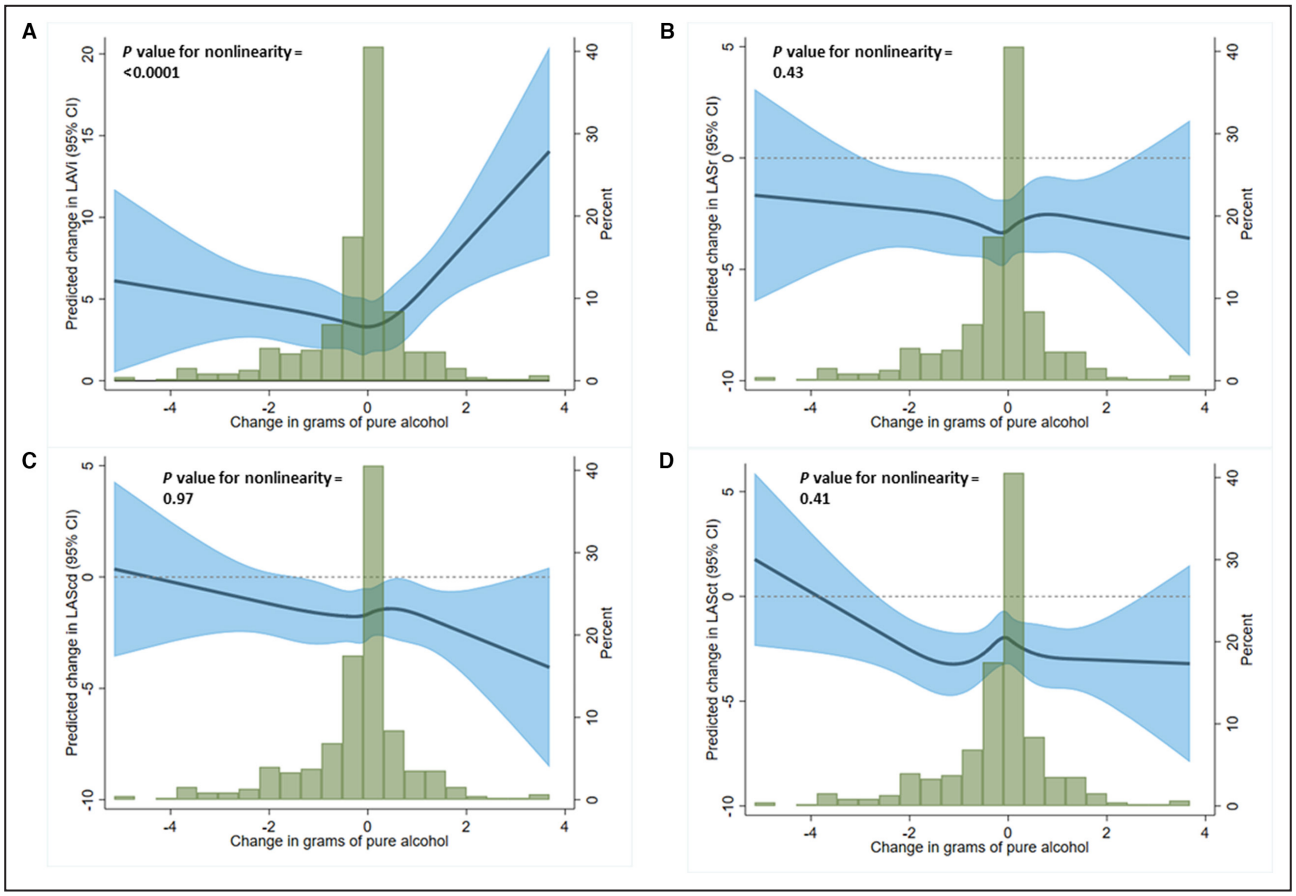

Figure 2. Associations of change in alcohol over 5 years modeled as restricted cubic splines with change in left atrial measures, using the median change in alcohol consumption as the reference point.
A, left atrial volume. **B**, Left atrial reservoir strain. **C**, Left atrial conduit strain. **D**, Left atrial contractile strain. Models adjusted for age, sex, education, and intervention group. LAScd indicates left atrial conduit strain; LASct, left atrial contraction strain; LASr, left atrial reservoir strain; and LAVi, left atrial volume index.

its effects on LA substrate through both direct and indirect methods. Heavy alcohol consumption is an established cause of ventricular enlargement and cardiopathy,[25] which itself may be on the pathway to atrial dysfunction.[26] As the walls of the atria are thinner than the ventricles, the atria may be more susceptible to enlargement and myopathy due to alcohol consumption than the ventricles, resulting in elevated AF risk. Habitual consumption is also associated with common AF risk factors such as hypertension and oxidative stress.[26]

Stratifying our cohort by alcohol type and sex did not appear to impact our original findings. Wine drinking was associated with higher LA volume and lower reservoir and contractile strains at baseline, but not with changes in LA measures by year 5 of the trial. Consumption of beer and spirits did not seem to impact LA measures. Of note, in this older cohort from a Mediterranean country, wine was the main source of alcohol in the diet, with limited variability in the intake of beer or spirits. This lack of variability may explain the observed lack of associations. Wine consumption is part of the MedDiet, but its impact on AF and its related pathways is unclear. On the one hand, wine, particularly red wine, may have some antiarrhythmic benefits by way of the antioxidant resveratrol.[27,28] For every cardioprotective finding, however, there is also evidence of proarrhythmic changes in response to moderate-to-high consumption of alcohol.[26,29] It is important to note, however, that most of these studies to date rarely separate the effects of wine from other alcohol types in the context of AF risk. No clear sex differences were present in this study in the relationship between alcohol and LA measures. Though higher intake was associated with higher volume and lower contractile strains in men and not in women, there was no evidence of statistically significant interactions between sex and alcohol intake.

The main strengths of this analysis include the use of echocardiograms at multiple points within the trial, the use of a central site for reading of echocardiographic studies, the repeated dietary assessments,

the availability of information on multiple potential confounders, and the excellent retention within the study, reducing the risk for informative censoring and subsequent selection bias. It is also important to take note of this analysis's limitations. First, we do not have information on drinking behavior before the trial. Those who are lifelong abstainers may be inherently different from those who abstained later on in life. Second, as alcohol intake in this study is based entirely on self-report, recall errors may be biasing our estimates. Finally, despite common protocols for the echocardiographic studies, within-person and between-person variability in echocardiographic image acquisition may obscure potential associations.

CONCLUSIONS

In this well-characterized cohort of people at high cardiovascular risk, we found evidence of morphological changes and impaired function of the left atrium associated with high or increasing alcohol intake. These results may provide some insight on the underlying mechanisms connecting alcohol and AF, and can contribute in informing recommendations related to alcohol consumption in people at high risk of developing this arrhythmia.

ARTICLE INFORMATION

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Affiliations

Department of Epidemiology, Rollins School of Public Health, Emory University, Atlanta, GA (A.B.A., L.L., A.A.); CIBER Consortium, M.P. Physiopathology of Obesity and Nutrition (CIBERObn), Carlos III Health Institute (ISCIII), Madrid, Spain (E.T.-A., D.R., A.M.A.-G., M.A.M.-G., J.S.-S., M.F.); Navarra's Health Research Institute (IdiSNA), Navarra Institute for Health Research, Pamplona, Spain (E.T.-A., M.A.M.-G., L.T.-S.); Department of Preventive Medicine and Public Health, University of Navarra, Pamplona, Spain (E.T.-A., M.A.M.-G.); Health Research Institute of the Balearic Islands (IdISBa), Palma de Mallorca, Spain (D.R., M.N.M., C.M.-L.); Bioaraba Health Research Institute, Osakidetza Basque Health Service, Araba University Hospital, University of the Basque Country UPV/EHU, Vitoria-Gasteiz, Spain (A.M.A.-G., L.T.-S.); Department of Applied Health Science, Indiana University-Bloomington, School of Public Health, Bloomington, Indiana (I.G.-C.); Human Nutrition Unit, Department of Biochemistry and Biotechnology, Rovira i Virigili University, Reus, Spain (J.S.-S.); Human Nutrition Unit, Pere Virgili Health Research Institute (IISPV), Reus, Spain (J.S.-S.); Cardiovascular Risk and Nutrition Group, Hospital del Mar Medical Research Institute (IMIM), Barcelona, Spain (M.F.); Department of Cardiology, Hospital Universitari Son Espases, Palma, Spain (M.N.M.); Cardiology Department, Hospital de Manacor, Manacor, Spain (C.M.-L.); and Facultad de Medicina, Universitat de les Illes Balears (UIB), Palma, Spain (C. M.-L.).

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Disclosures

None.

Supplemental Material

Tables S1–S6

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