

Alcohol Consumption, Left Atrial Diameter, and Atrial Fibrillation

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Background—Alcohol consumption has been associated with atrial fibrillation (AF) in several epidemiologic studies, but the underlying mechanisms remain unknown. We sought to test the hypothesis that an atrial myopathy, manifested by echocardiographic left atrial enlargement, explains the association between chronic alcohol use and AF.

Methods and Results—We evaluated the relationship between cumulative alcohol consumption and risk of incident AF in 5220 Offspring and Original Framingham Heart Study participants (mean age 56.3 years, 54% women) with echocardiographic left atrial size measurements. The incidence of AF was 8.4 per 1000 person-years, with 1088 incident AF cases occurring over a median 6.0 years (25th–75th percentiles 4.0–8.7 years) of follow-up. After multivariable adjustment for potential confounders, every additional 10 g of alcohol per day (just under 1 drink per day) was associated with a 0.16 mm (95% CI, 0.10–0.21 mm) larger left atrial dimension. Also in multivariable adjusted analysis, every 10 g per day of alcohol consumed was associated with a 5% higher risk of developing new-onset AF (hazard ratio, 1.05; 95% CI, 1.01–1.09). An estimated 24% (95% CI, 8–75) of the association between alcohol and AF risk was explained by left atrial enlargement.

Conclusions—Our study of a large, community-based sample identified alcohol consumption as a predictor of left atrial enlargement and subsequent incident AF. Left atrial enlargement may be an intermediate phenotype along the causal pathway linking long-term alcohol consumption to AF. (*J Am Heart Assoc.* 2016;5:e004060 doi: 10.1161/JAHA.116.004060)

Key Words: alcohol • atrial fibrillation • echocardiography • epidemiology • left atrium

Although alcohol consumption has been associated with atrial fibrillation (AF) in several large epidemiologic studies,^{1–3} the responsible mechanisms remain unknown. Previous electrophysiologic studies have failed to demonstrate an electrical mechanism,^{4–7} suggesting that structural changes in the atrium may be responsible.

Heavy alcohol consumption has long been known to result in ventricular cardiomyopathy.⁸ As the smaller atria are known to be more prone to enlargement and fibrosis than the ventricles,^{9–11} it is possible that more modest amounts of alcohol might be

associated with evidence of atrial myopathy. However, the impact of cumulative alcohol exposure, especially modest alcohol consumption, during adulthood on left atrial structure remains largely undetermined. Furthermore, although an emerging literature provides evidence that alcohol may increase atrial size,¹² studies conducted to date have not taken into account the possible effects of interim AF. As AF itself may lead to left atrial enlargement,^{13,14} it remains unknown whether the alcohol-associated atrial enlargement represents a co-traveler, a subsequent effect of AF, or a key intermediate phenotype along the causal pathway between alcohol exposure and AF.

Using data from the Framingham Heart Study (FHS), we sought to determine whether cumulative alcohol exposure is associated with enlargement of the left atrium in a large ambulatory cohort prior to any ascertainment of AF and to explore the hypothesis that an increase in left atrial size mediates the association between alcohol and risk for incident AF.

Methods

Study Sample

The study sample in the present analysis comprised 5220 participants from Offspring (n=4315) and Original (n=905) Framingham Study cohorts with available echocardiographic

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and clinical data. The Framingham Heart and Offspring Studies, as well as their design and methods, have been described in prior publications.^{9,15} In brief, participants were evaluated by a study physician at the Heart Study facility approximately every 4 to 8 years. At each Heart Study visit, a physician administers a physical examination and obtains a thorough medical history. The standard study examination includes measurements of resting blood pressure. At the same examination, a laboratory evaluation is performed assessing standard risk factors, including fasting blood glucose and lipids. For the analyses examining the relations between alcohol and echocardiographic left atrial dimension (LAD), we focused on Original Cohort attendees at examination cycles 2, 7, 12, 13, 14, 15, 16, and 20 as well as Offspring examination cycles 1 through 8, at which the participants underwent a standardized questionnaire to assess daily alcohol consumption.

Cardiovascular Disease and Risk Factor Definitions

FHS participants prescribed an antihypertensive medication as well as those with either systolic blood pressure ≥ 140 mm Hg or diastolic blood pressure ≥ 90 mm Hg were considered to have hypertension.¹⁶ Body mass index was calculated as weight in kilograms divided by the square of the participant's height in meters (kg/m^2).¹⁶ Treatment with diabetes mellitus medications or a fasting plasma glucose ≥ 126 mg/dL were used to determine the presence of diabetes mellitus.^{17,18} If participants reported smoking ≥ 1 cigarette daily during the year prior to their study examination, they were considered current smokers. If a study physician auscultated a grade 3/6 or higher systolic murmur or any diastolic murmur, participants were deemed to have valvular heart disease. The criteria used by study investigators to define myocardial infarction and heart failure are published.^{9,19,20} In brief, a myocardial infarction was considered present when 2 of 3 following findings were documented in the medical record: (1) symptoms indicative of ischemia; (2) changes in biomarkers of myocardial necrosis; and (3) serial changes in ECGs indicating evolution of infarction. An old myocardial infarction was considered to be present when the ECG showed a stable pattern including either a pathologic Q-wave or loss of precordial R waves. An autopsy report showing an acute, new, or recent infarction of the myocardium was also accepted as evidence of an incident myocardial infarction. A diagnosis of heart failure required that a minimum of 2 major heart failure or 1 major and 2 minor heart failure criteria be present concurrently.²⁰ The presence of other conditions capable of producing the symptoms and signs were considered in evaluating the findings. Study participants provided written informed consent. The

Framingham Original and Offspring study protocols were approved by the Boston University Medical Center Institutional Review Board.

Assessment of Alcohol Consumption

Alcohol consumption was ascertained as part of the standardized general medical history administered to all Framingham Original and Offspring Study participants. Three questions were asked related to alcohol consumption during study examinations by a study physician.¹ These included, "During the past year, how many 12-ounce bottles, cans, or glasses of beer did you consume per week?", "During the past year, how many 4-ounce glasses of wine did you consume per week?", and "During the past year, how many cocktails (eg, drinks containing 1–1.5 ounces of liquor) did you consume per week?"²¹ In this analysis, we transformed responses to the 3 questions above into a total quantity of alcohol consumed per day variable (grams per day).

Echocardiographic Examinations

Each participant completed a maximum of 5 echocardiographic measurements at examinations 2, 4, 5, 6, and 8 (Offspring) or examinations 16 and 20 (Original), yielding a total of 17 659 observations for the prospective analyses. Although the sonographic equipment differed across study examinations, all echocardiograms were performed by experienced technicians and evaluated using a standardized protocol by trained study cardiologists. As is recommended in the American Society of Echocardiography guidelines, LAD was determined from M-mode echocardiographic images using a leading-edge-to-leading-edge method, measuring the maximal distance between the posterior aortic root wall and the posterior LA wall at end-systole. The FHS has reported excellent reproducibility for M-mode-based LAD measures.^{9,20}

Atrial Fibrillation

At each FHS examination, a 12-lead ECG is obtained. In addition, FHS study participants were asked whether or not they have a diagnosis of AF at all study examinations as well as during biennial health updates. Records of all interim hospitalizations were sought for review. If a participant reported any cardiovascular or neurological disease, all inpatient and outpatient medical records were obtained. Multiple sources, including 12-lead ECGs obtained at each FHS examination, as well as ECGs obtained during cardiovascular disease-related hospitalizations and clinician visits, were used to ascertain for AF. In addition, inpatient telemetric data were adjudicated for possible AF. Follow-up for incident

AF ended in 2013. Cases of potential AF underwent adjudication by 2 or more study reviewers (including DDM and EJB).^{18,20} FHS participants were considered to have AF if they had either AF or flutter present on any study or clinically obtained ECG, on a Holter monitor, or if AF was documented in the hospital record by a treating physician.

Statistical Analyses

Normally distributed continuous variables are described as means±SD and compared using a mixed model, while non-normal continuous variables are summarized using quartiles and compared using the Wilcoxon rank sum test. Categorical variables and compared using the χ^2 test and are presented as n (%).

We assessed the effects of alcohol use on AF by LAD by examining the association of alcohol use with LAD, the first link in the proposed pathway, and then determining whether adjustment for the most recent LAD attenuated the association of cumulative alcohol use up to the time of the LAD assessment with subsequent incidence of AF; in this analysis, both cumulative alcohol use and LAD were treated as time-dependent covariates. To be included in the analysis,

participants had to have at least 1 LAD assessment, with alcohol exposure measured to the time of the assessment, as well as subsequent follow-up for AF. A linear mixed model was used to estimate the adjusted association between cumulative alcohol intake, as a time-dependent covariate (TDC), with repeated measures of LAD, accounting for within-individual correlation using random intercepts (Figure 1). Based on prior associations with AF and their associations with LAD in univariate analyses, the linear mixed model was adjusted for age, age², sex, body mass index, systolic blood pressure, antihypertensive treatment, electrocardiographic PR interval, prevalent valvular heart disease or heart failure, and the interaction terms=sex×age², age×valvular heart disease, as well as age×heart failure. In checking the linear mixed model, we assessed normality of the residuals and used likelihood ratio tests to determine the need for more complicated modeling of within-subject correlation. In a second model, we adjusted for age, sex, cohort, body mass index, diabetes mellitus, hypertension, heart failure, heart rate, smoking, and left ventricular ejection fraction.

Nested Cox proportional hazards models were used to estimate the adjusted association of cumulative alcohol use with AF, before and after adjustment for LAD. The TDCs

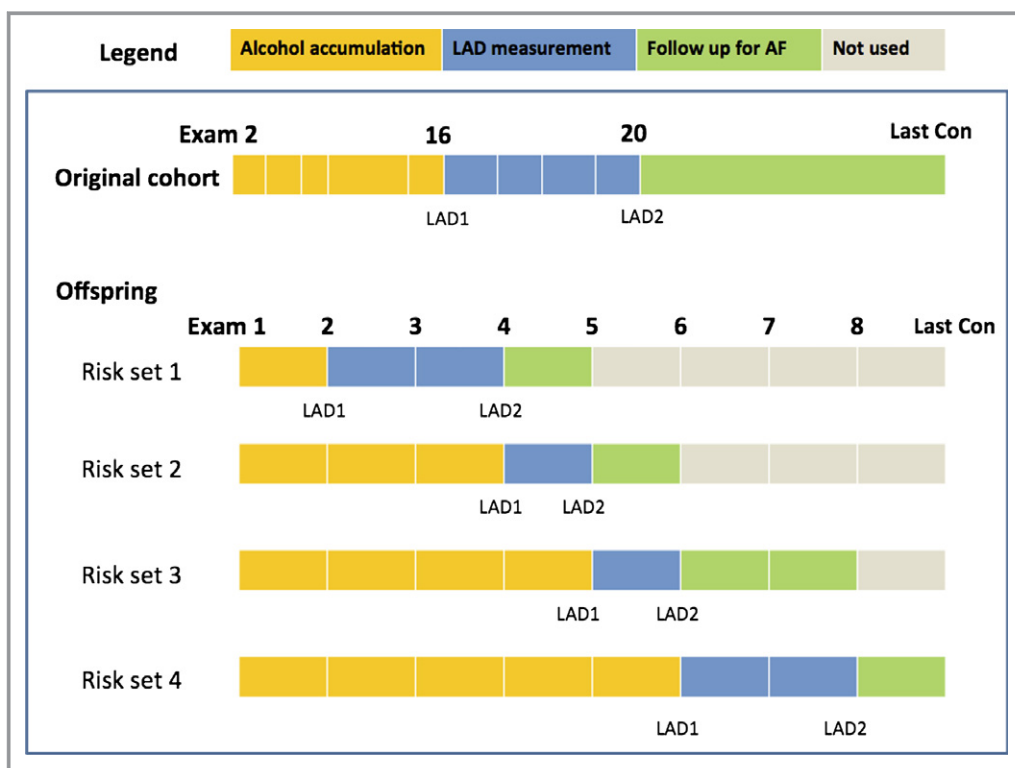


Figure 1. Model 1 analytic design. Illustration of the structure of the first repeated-measure analysis, where the alcohol ascertainment was obtained before the first left atrial diameter measurement (LAD1), the difference in subsequent LAD measurements were considered (LAD2), and incident AF was ascertained after the LAD measurement. These analyses were performed in a repeated fashion within individuals to leverage the longitudinal nature of the study, ongoing assessments, and multiple measures. AF indicates atrial fibrillation; LAD, left atrial diameter; last con, last contact.

capturing alcohol use and LAD were defined to preserve temporal ordering, and thus make causal interpretation more plausible. Specifically, as shown in Figure 2, cumulative alcohol use was assessed in the Original cohort using data from Examinations 2 through 20 and after examination 20; LAD was assessed at Examinations 16 and 20; and then these combinations of TDCs were used to predict incident AF between Examinations 16 and 20, and after Examination 20. Similarly, in the Offspring cohort, alcohol use was successively summarized using data up to and including Examinations 2, 4, 5, 6, and 8; the corresponding TDCs for LAD were assessed at Examinations 2, 4, 5, 6, and 8; and then each combination of TDCs was used to predict incident AF in the intervals between Examinations 2 and 4, 4 and 5, 5 and 6, 6 and 8, and after Examination 8.

Attenuation by LAD was assessed as the percent attenuation of the adjusted regression coefficient for cumulative alcohol consumption after additional adjustment for LAD, with a 95% bootstrap confidence interval (CI). Based on their known association with AF, certain clinical and ECG variables were selected for inclusion in both Cox models: including age, age², sex, body mass index, systolic blood pressure,

antihypertensive treatment, electrocardiographic PR interval, prevalent valvular heart disease or heart failure, as well as interactions between sex and age², age and valvular heart disease, and age and heart failure.²² In a second model, the analysis was adjusted for age, sex, cohort, body mass index, diabetes, hypertension, heart failure, heart rate, smoking, and left ventricular ejection fraction. The proportional hazards assumption was verified using score components.²³

SAS version 9.4 (SAS Institute, Cary, NC) was used for all statistical analyses. Two-tailed $P < 0.05$ were considered statistically significant.

Results

The salient clinical and echocardiographic characteristics of the 5220 participants included in our analysis are shown in Table 1. Our cohort was middle-aged (mean age 56.3 years), over half were women, and most were unaffected by cardiovascular disease. The average alcohol consumption reported by participants was 13.3 ± 16.7 g/day and the mean LAD at study onset was 38.3 ± 5.4 mm. The overall incidence

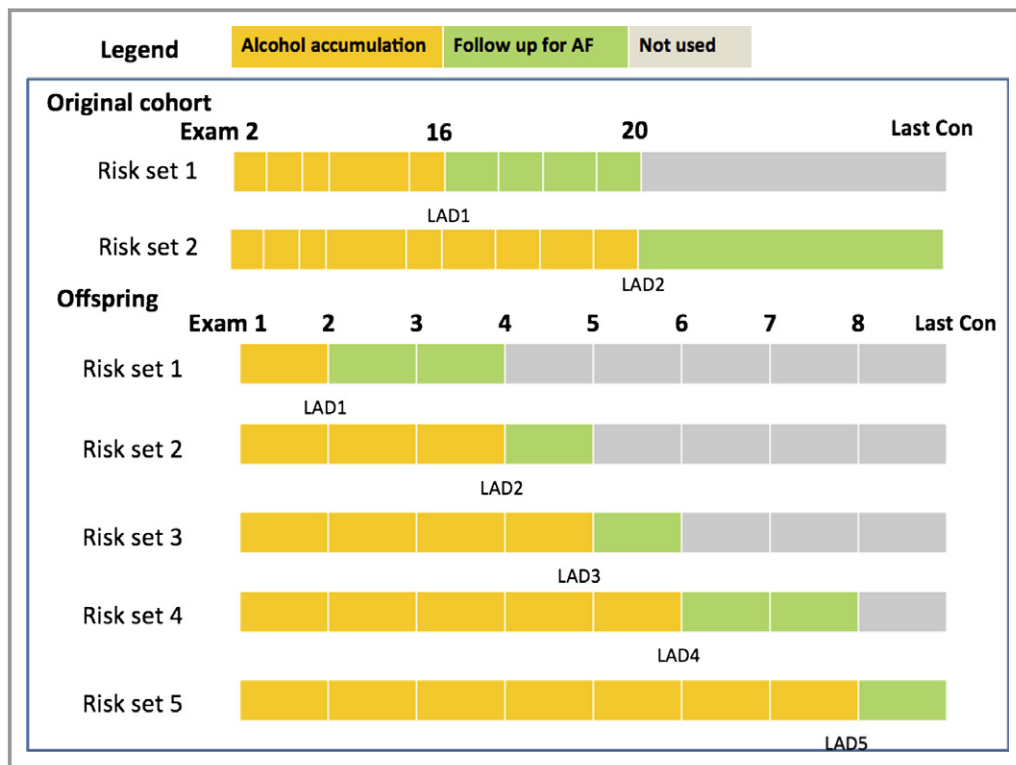


Figure 2. Model 2 analytic design. Illustration of the structure of the second repeated-measure analysis, where the alcohol ascertainment was obtained before the first left atrial diameter measurement (LAD 1), the difference in subsequent LAD measurements were considered (LAD2, LAD3, LAD4, LAD5), and incident AF was ascertained after the LAD measurement. These analyses were performed in a repeated fashion within individuals to leverage the longitudinal nature of the study, ongoing assessments, and multiple measures. AF indicates atrial fibrillation; LAD, left atrial diameter; last con, last contact.

Table 1. Participant Characteristics by Incident AF Status

Variable	No AF* (n=16 571)	Incident AF (n=1088)	P-Values
Age, y	55.5±12.5	68.6±8.6	<0.0001
Men, n (%)	7520 (45)	577 (53)	<0.0001
BMI, kg/m ²	27.0±4.9	28.0±54.9	<0.0001
Average ETOH consumption, in g/day	7.3 [4.0, 16.9]	8.6[3.5, 22.2]	<0.0001
Systolic blood pressure, mm Hg	127±19	138±21	<0.0001
Current smoker	3553 (21)	154 (14)	<0.0001
Prevalent HF, n (%)	67 (0.4)	24 (2.4)	<0.0001
Prevalent valvular heart disease, n (%)	276 (2)	64 (6)	<0.0001
Hypertension	6276 (38)	742 (68)	<0.0001
Diabetes mellitus	1083 (7)	131 (12)	<0.0001
Antihypertensive treatment, n (%)	3456 (23)	492 (49)	<0.0001
Baseline left atrial dimension, mm	38.1±5.3	41.9±6.0	<0.0001
LVDD	48.1±4.7	49.1±5.2	<0.0001
LVFS	0.41±0.12	0.44±0.15	<0.0001
Electrocardiographic PR interval, ms	163±24	172±29	<0.0001
Heart rate	65±12	65±11	0.12

Data are presented as means±SD or number (percentage), except ETOH consumption [interquartile range]. Values reported were measured at baseline of each follow-up window. AF indicates atrial fibrillation; BMI, body mass index; ETOH, alcohol; HF, heart failure; LVDD, left ventricular diastolic dysfunction; LVFS, left ventricular fractional shortening.

*No AF indicates absence of diagnosed AF at baseline or in follow-up. There were 16 571 observations for the 4861 unique participants.

of AF was 8.4 per 1000 person years (based on a total of 1088 incident AF cases out of 17 659 observations) over a median 6.0 (interquartile range 4.0–8.7) years of follow-up. Total alcohol intake and baseline LAD did not vary significantly by cohort.

After multivariable adjustment, every additional 10 g of alcohol consumed per day (just under 1 drink) was associated with a 0.16 mm (95% CI, 0.11–0.22 mm) higher LAD (Table 2). The association between alcohol and LAD did not vary significantly by cohort (*P*=0.13). However, there was no significant association between alcohol and the change in LAD (*P*=0.18) adjusting for the covariates (Table 3). Alcohol consumption was not associated with change in left atrial size over time among men or women (Table 3).

Chronic alcohol consumption was also associated with higher risk for incident AF. In multivariable adjusted analysis, every 10 g per day of alcohol consumed was associated with

Table 2. Effect of Alcohol Consumption on LAD

	Number of Observations	Regression Coefficient (SE) (mm per 10 g/day)	P-Value
Model 1			
Overall group	17 659	0.16 (0.03)	<0.0001
Cohort			
Original	1881	0.12 (0.08)	0.15
Offspring	15 888	0.16 (0.03)	<0.0001
Model 2			
Overall group	17 659	0.16 (0.03)	<0.0001
Cohort			
Original	1881	0.11 (0.09)	0.24
Offspring	15 888	0.18 (0.03)	<0.0001

LAD indicates left atrial dimension; SE, standard error.

Variables included for adjustment in the multivariable model 1: generation, age, age², sex, body mass index, systolic blood pressure, antihypertensive drug treatment, PR interval, valvular heart disease, heart failure, sex×age², age×valvular heart disease, age×heart failure (interaction terms) for pooled analysis. Variables included for adjustment in the multivariable model 2: generation, age, sex, body mass index, diabetes mellitus, hypertension, heart failure, heart rate, current smoking status, and left ventricular ejection fraction for pooled analysis.

a 5% higher risk of developing new-onset AF (hazard ratio, 1.05; 95% CI, 1.01–1.09; Table 4).

Finally, the association between alcohol and AF was substantially attenuated in models adjusting for LAD (Table 4): an estimated 24% (95% CI, 8–75) of the association between alcohol and AF risk was explained by left atrial enlargement.

Discussion

In our cohort study including over 5000 middle-aged and older adults largely free from cardiovascular disease at baseline and

Table 3. Effect of Alcohol Consumption on Change in LAD Over Time

	Number of Observations	Regression Coefficient (SE)* (mm per 10 g/day)	P-Value
Overall group	13 223	−0.08 (0.06)	0.18
Men	6075	−0.09 (0.07)	0.15
Women	7148	−0.02 (0.11)	0.86

BMI indicates body mass index; HF, heart failure; HRX, antihypertensive drug treatment; LAD, left atrial dimension; SBP, systolic blood pressure; VHD, valvular heart disease.

*Mixed linear model was used with LAD variables as outcome, alcohol intake as main predictor, and random effect to account for within-individual correlation. Covariates: generation, age, age², sex, BMI, SBP, HRX, PR, VHD, HF, sex×age², age×VHD, age×HF for pooled analysis; generation, age, age², BMI, SBP, HRX, PR, VHD, HF, age×VHD, age×HF for sex-specific analysis.

Table 4. Relations Between Cumulative Alcohol Consumption and Incident AF Before and After Adjustment for Left Atrial Diameter

Model	Hazard Ratio (95% CI)	P-Value
Before adjustment for LAD	1.05 (1.01–1.09)	0.027
After adjustment for LAD	1.03 (0.99–1.07)	0.13

AF indicates atrial fibrillation; LAD, left atrial dimension.

followed for over 6 years for AF, we observed that heavier self-reported alcohol consumption related to greater left atrial size and higher risk for incident AF. We observed that up to a quarter (and up to 75%) of the association between alcohol and AF was mediated by echocardiographic LAD. The attenuation of the association between alcohol and incident AF after adjustment for LAD is consistent with the hypothesis that LA enlargement is a key intermediate phenotype along the causal pathway to AF.

Principal Findings

Despite the widely held belief by the public that alcohol has a beneficial effect on general heart health, acute alcohol consumption has long been linked to development of AF.²⁴ In the Framingham, Copenhagen, and Women's Health Studies, chronic alcohol consumption, especially 2 or more drinks per day, is associated with up to 30% higher risk for incident AF.^{1–3} Acute alcohol exposure enhances electrophysiologic vulnerability to AF in experimental models,⁷ but our understanding of the mechanisms underlying the observed epidemiological associations between alcohol and AF remains incomplete. The paucity of data relating to the downstream structural and electrophysiological effects of chronic alcohol consumption on the atrium stand in contrast to the abundance of data linking alcohol to ventricular enlargement and systolic dysfunction.²⁵

Understanding the mechanisms underlying the relationships between alcohol and AF is important for several reasons. First, some patients may benefit from moderate consumption of alcohol,^{26–28} and identifying those at risk for cardiovascular-system harm (such as given evidence of LA enlargement) may help to counsel patients regarding their specific risks versus benefits appropriately. Second, as the etiology of AF remains incompletely understood in the majority of patients, identifying mechanisms of known risk factors might help to reveal new therapeutic targets. Third, as alcohol may represent a modifiable risk factor for AF, elucidating the nature by which the substance may enhance AF risk is important.

LA structural remodeling, as assessed by LAD, relates to advancing age, male sex, higher body mass index, and greater

blood pressure, all key risk factors for AF. Exposure to AF risk factors influences tracking of LAD over the adult life course, LA enlargement preceding AF, and higher LAD conferring an increased risk for incident and recurrent AF.^{9,29–32} Chronic alcohol consumption has been associated with ventricular dilation and left ventricular dysfunction.^{1,25,28} Recent studies suggest that atrial remodeling and AF may also result from alcohol exposure.⁸ We sought to better understand the associations between chronic alcohol consumption, atrial remodeling, and incident AF. Atrial remodeling is a process characterized by structural and electrophysiological change. Pathological remodeling facilitates the creation of an atrial substrate that is vulnerable to AF initiation, AF persistence, and AF recurrence.^{9,29–33} LA enlargement, as characterized by echocardiographic LAD, is related to incident AF, heart failure, stroke, and mortality.^{9,29–33} LA enlargement is sometimes seen in association with valvular or ischemic heart disease, and in these settings can reflect atrial volume or pressure overload, or as a consequence of AF.^{13,14,32,34}

The findings of several recent investigations suggest that chronic consumption of alcohol may lead to LA-specific structural and electrophysiological remodeling.^{8,30} In 1 cross-sectional study including over 4000 elderly Atherosclerosis Risk in Community study participants, increasing alcohol intake was associated with larger left ventricular diastolic and systolic diameters as well as larger LA diameter ($P < 0.05$).⁸ We observed a similar association between alcohol consumption and LAD in a larger and younger ambulatory cohort affected by less cardiovascular comorbidity and with modest consumption of alcohol. However, we were not able to detect a statistically significant association between alcohol consumption and change in LAD over serial echocardiograms. One possible explanation for this negative finding is the fact that the effect of chronic alcohol consumption on LA size requires several years or even decades. As such, the first echocardiogram reflects a greater burden of alcohol-related change than is captured by the serial echocardiographic images obtained over a relatively short period of time. Another possible explanation for this finding relates to the fact that alcohol leads to an increase in LAD only up to a point (quantified by the first echo), but with limited or negligible subsequent effect. Lastly, this analysis required that at least 2 LAD measurements be required for inclusion and limited statistical power may have been responsible for our inability to detect significant relations between alcohol consumption and change in LAD over time.

Our study is novel in that it leveraged the serial assessments of LA size and alcohol consumption as part of the FHS to conduct a comprehensive assessment of the relations between fluctuating levels of alcohol consumption and LAD change over time. In another single-center study of 122 patients undergoing pulmonary vein isolation, heavier alcohol

consumption was related to greater atrial scar burden, as measured using low-voltage recordings during electrophysiology study, and AF recurrence postablation. Notably, mediation analyses suggested that the low-voltage area (a surrogate for atrial scar burden) was a mediator of the effect of alcohol consumption on AF recurrence after ablation. The results of our investigation extend and support these findings by suggesting that echocardiographic LAD may also reflect atrial remodeling burden from alcohol consumption and that alcohol-induced pathological atrial remodeling may mediate the relationship between alcohol and new-onset AF in the community.¹⁰

Strengths and Limitations

The strengths of our study include the use of a large, community-based sample with standardized echocardiographic observations and standardized evaluation of alcohol consumption as well as other cardiovascular risk factors. We recognize several limitations to our analyses. First, AF may be asymptomatic and not clinically detected. Although it remains possible that LA enlargement might occur because of undetected AF, rather than directly because of alcohol, occult AF would likely bias our results toward the null hypothesis and would not lead to false-positive associations. Second, the anteroposterior LA dimension provided by M-mode and used for the determination of LAD in our analyses may not reflect true atrial size. Although the LA generally enlarges in a spherical fashion, symmetrical enlargement does not always occur, and thus volumetric assessment of LA size is a more accurate measure of true atrial size. M-mode-based LA assessment is, however, a well-studied and valid measure of LA size,¹⁹ and we were limited by the availability of only M-mode data in the Framingham Study at the earlier examination cycles. Third, participants in the cohort were middle-aged to older adults and largely white, limiting the generalizability of our findings to other age or racial groups.

Conclusions

Given the increasing population burden of AF and the high prevalence of alcohol consumption among Americans, it is important to characterize the relationships between alcohol consumption and AF and to identify important potential intermediate phenotypes, such as increased LAD. Our prospective, community-based investigation identified significant associations between alcohol and AF as well as alcohol and LAD. Furthermore, mediation analyses suggest that a substantial proportion of the association between alcohol and AF is mediated by LAD. These data, although observational, are consistent with the notion that chronic alcohol

consumption, even at moderate levels, can be cardiotoxic and lead to pathological atrial structural change that can, in turn, enhance vulnerability to AF later in life.

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Disclosures

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