Relationship Between Alcohol Consumption and Cardiac Structure and Function in the Elderly

The Atherosclerosis Risk in Communities Study

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Background—Excessive alcohol consumption is associated with cardiomyopathy, but the influence of moderate alcohol use on cardiac structure and function is largely unknown.

Methods and Results—We studied 4466 participants from visit 5 of the Atherosclerosis Risk in Communities (ARIC) study (76±5 years and 60% women) who underwent transthoracic echocardiography, excluding former drinkers and those with significant valvular disease. Participants were classified into 4 categories based on self-reported alcohol intake: nondrinkers, drinkers of ≤7, ≥7 to 14, and ≥14 drinks per week. We related alcohol intake to measures of cardiac structure and function, stratified by sex, and fully adjusted for covariates. In both genders, increasing alcohol intake was associated with larger left ventricular diastolic and systolic diameters and larger left atrial diameter ($P<0.05$). In men, increasing alcohol intake was associated with greater left ventricular mass (8.2±3.8 g per consumption category; $P=0.029$) and higher E/E′ ratio (0.82±0.33 per consumption category; $P=0.014$). In women, increasing alcohol intake was associated with lower left ventricular ejection fraction (−1.9±0.6% per consumption category; $P=0.002$) and a tendency for worse left ventricular global longitudinal strain (0.45±0.25% per consumption category; $P=0.07$).

Conclusions—In an elderly community-based population, increasing alcohol intake is associated with subtle alterations in cardiac structure and function, with women appearing more susceptible than men to the cardiotoxic effects of alcohol. **(*Circ Cardiovasc Imaging*. 2015;8:e002846. DOI: 10.1161/CIRCIMAGING.114.002846.)**

Key Words: alcohol drinking ■ cardiomyopathies ■ echocardiography ■ heart failure ■ population

Excessive alcohol consumption is associated with alcoholic cardiomyopathy, characterized by enlargement of the heart, increased left ventricular (LV) mass, and ventricular dysfunction.[1] Moreover, alcohol intake has been associated with hypertension, which also contributes to alterations in cardiac structure and function.[2] Conversely, numerous studies support a protective association between light to moderate drinking with the risk of coronary artery disease (CAD) and even the risk of heart failure.[3,4] However, the cardiovascular mechanisms of the risks and potential benefits of alcohol are uncertain.[5,6] Furthermore, the variation in the toxic and protective effects of alcohol by sex remains controversial, as women may be more sensitive than men to the toxic effects of alcohol on cardiac function, developing alcoholic cardiomyopathy at a lower total lifetime dose of alcohol compared with men.[7]

See Clinical Perspective

See Editorial by Yoneyama and Lima

Several echocardiographic morphological and functional features are known to contribute to risk stratification for heart failure,[8] but their association with alcohol consumption in the general population, independently of the effects over blood pressure and other factors, is unknown. We assessed the associations between alcohol intake and cardiac structure and function in elderly men and women in the large community-based Atherosclerosis Risk in Communities (ARIC) study.

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Methods

Study Sample

The overall ARIC study is an ongoing, prospective observational study. Detailed study rationale, design, and procedures have been previously published.[9] The original cohort included 15 792 men and women aged 45 to 64 years recruited between 1987 and 1989 (visit 1), selected from 4 communities in the United States: Forsyth County, North Carolina; Jackson, Mississippi; Minneapolis, Minnesota; and Washington County, Maryland. Subsequently, 3 follow-up visits (visit 2–4) occurred at 3-year intervals, with annual telephone interviews conducted between visits. Between 2011 and 2013, 6118 surviving participants performed echocardiography during visit 5, in all 4 ARIC field centers. Institutional review boards from each site approved the study, and informed consent was obtained from all participants.

Our analyses were restricted to the participants who were self-described as black or white (n=6102). We excluded participants without alcohol consumption data (n=149), those classified as former drinkers (n=1459), and those with moderate to severe valvular disease (n=28). A total of 4466 participants, 1781 men and 2685 women, constitute the sample for the present analysis.

Measurements

Alcohol Consumption

Alcohol consumption was ascertained at all visits by means of an interviewer-administered questionnaire. Subjects were asked if they currently drank alcoholic beverages and, if not, whether they had done so in the past. Current drinkers were asked how often they usually drank wine, beer, or liquor per week. In calculating the amount of alcohol consumed (in grams per week), it was assumed that 4 ounces (118 mL) of wine contains 10.8 g, 12 ounces (355 mL) of beer contains 13.2 g, and 1.5 ounces (44 mL) of liquor contains 15.1 g of ethanol. Subsequently, grams of ethanol were converted to drinks per week (14 g of alcohol=1 drink), and participants were classified into 4 categories, as in previous publications,[6] according to their alcohol consumption at visit 5: nondrinkers, drinkers of ≤7, ≥7 to 14, and ≥14 drinks per week. Nondrinking participants at visit 5, who had reported alcohol consumption in visits 1 to 4, were classified as former drinkers and excluded from the analysis. Alcohol consumption measured at visit 5 was used as primary exposure variable in the analysis. In addition, we estimated cumulative average alcohol intake using data acquired from questionnaire responses at all visits, for a mean time exposure of 23.6±0.9 years. The calculation of this variable included the estimation of 4 separate time intervals (visit 1 to visit 2, visit 2 to visit 3, etc.). For each time interval, we estimate the average alcohol consumption by averaging the consumption levels reported at the beginning and end of the interval. We then take a weighted average of the 4 interval estimates, weighting according to the number of days elapsed between the 2 visits. If a participant was missing alcohol consumption for a certain visit, the measurements from the available years were averaged. Cumulative average alcohol intake was also converted to the previously described 4 categories of drinks per week.[6]

Echocardiography Protocol

The echocardiographic imaging and analysis protocol have been previously described in detail.[10] All echocardiograms were performed using dedicated Philips iE33 Ultrasound systems with Vision 2011, using a preprogrammed acquisition protocol. All studies were acquired and stored digitally and transferred from field centers to a secure server at the Corelab, the Echocardiography Reading Center (ERC; Brigham and Women's Hospital, Boston, MA), where echocardiographic measures were performed and over read, using proprietary validated echocardiographic analysis software.

All echocardiograms were obtained in a manner most consistent with good clinical practice, recording ≥3 full cardiac cycles for each view for patients in sinus rhythm and 1 or more 5-second acquisitions per view, for subjects in atrial fibrillation. LV dimensions, wall thickness, anterior–posterior left atrial (LA) dimension, and outflow tract diameter were measured from the parasternal long-axis view according to the recommendations of the American Society of Echocardiography.[11] LV mass was calculated from LV linear dimensions and indexed to body surface area as recommended by American Society of Echocardiography guidelines. LV hypertrophy was defined as LV mass indexed to body surface area (LV mass index) >115 g/m² in men or >95 g/m² in women. Relative wall thickness was calculated from LV end-diastolic dimension and posterior wall thickness. LV volumes were calculated by the modified Simpson method using the apical 4- and 2-chamber views, and LV ejection fraction was derived from volumes in the standard manner. LA volume was measured by the method of disks using apical 4- and 2-chamber views at an end-systolic frame preceding mitral valve opening. Early transmitral velocity (E wave) was measured by pulsed-wave Doppler from the apical 4-chamber view with the sample volume positioned at the tip of the mitral leaflets. Peak lateral and septal mitral annular relaxation velocities (E′) were assessed using tissue Doppler imaging[12] and LV diastolic function classified according to Olmsted criteria.[13] Right ventricular (RV) function was assessed using the tricuspid annular peak systolic velocity measured from the lateral tricuspid annulus, and RV fractional area change was calculated as the percent change in cavity area from end-diastolic to end-systolic tracings of the RV cavity in the apical 4-chamber view. Peak tricuspid regurgitation velocity was measured, and peak RV-to-right atrial systolic gradient was calculated as 4×(peak tricuspid regurgitation velocity).

Deformation analysis was performed using the TomTec Cardiac Performance Analysis package. Analysis was performed on 2-dimensional images acquired at a frame rate of 50 to 80 frames per second. Longitudinal strain was measured by tracing the endocardial borders in the apical 4-chamber and 2-chamber views. Peak longitudinal strain and strain rate were computed automatically, generating regional data from 6 segments and an average value for each view.

Measurement of Other Baseline Covariates

Standardized and validated interviewer-administered questionnaires included the assessment of smoking, current medication, the presence of CAD, or diabetes mellitus. Interviews included the assessment of annual income and educational level, with high education defined as any college or graduate or professional school attendance. Information on demographics, anthropometric measures, and blood pressure was obtained at the time of echocardiography. Established definitions for hypertension, obesity, diabetes mellitus, CAD, and smoking status were used as previously described in the ARIC study.[14] Total cholesterol, high-density lipoprotein cholesterol (HDL), and triglycerides levels were measured in a centralized laboratory, and subsequently, low-density cholesterol was calculated. The assays and their performance have been previously reported.[15] For the purpose of this study, results from visit 5 were considered.[16]

Statistical Methods

The analyses were performed overall and separately for each sex. For the 4 groups (nondrinkers, ≤7, ≥7–14, and ≥14 drinks per week), summary statistics for covariates were calculated as counts and percentages or means and SD for categorical and continuous data, respectively. Comparisons of baseline characteristics between the 4 groups were made using trend tests by regression methods and χ^2 tests for trend for continuous and dichotomous variables, respectively.

Using multivariate linear and logistic models, we examined separately the association of both alcohol intake at visit 5 and cumulative average alcohol intake, with measures of cardiac structure and function, stratified by sex, and adjusted for 3 different models: Model 1, which included age, body mass index, diabetes mellitus, antihypertensive medication, systolic blood pressure, and previously diagnosed myocardial infarction; Model 2, which included Model 1 variables, plus education, income level, and cigarette smoking in all visits; and Model 3, including Model 2 variables with body size represented by body surface area instead of body mass index. The primary analysis variable was the alcohol consumption measured at visit 5, and the main results are presented according to Model 2. The analysis with the cumulative average alcohol consumption was performed as sensitivity analysis. In addition to the test for trend across alcohol consumption categories, we also tested for multivariate linear and curvilinear association between the continuous measure of alcohol consumption at baseline and measures of cardiac measures of cardiac structure and function. In the presence of nonlinear associations, we used a restricted cubic spline model with the number of knots chosen on the basis of maximizing goodness of fit (ie, minimizing Akaike information criterion). Tests for interaction were performed using the likelihood ratio test comparing models with and without interaction terms between either sex or race and the continuous visit 5 drinking status variable(s). Two-sided *P* values <0.05 were considered significant. Analyses were performed using Stata version 13.1 (Stata Corp, College Station, TX).

Results

The final analysis data set included 4466 participants with a mean age of 76±5 years, and ≈54% of subjects reported no alcohol consumption. Overall 2685 (60%) were women and 873 (20%) were black. Table 1 illustrates the characteristics of the study population according to the categories of alcohol intake at visit 5. Nondrinkers were more likely to be women with higher body mass index, and nondrinkers of both sexes were older, had lower education level and lower annual income, and were more likely to be diabetic, to have lower low-density cholesterol and HDL cholesterol, and higher triglyceride/HDL ratio. Drinkers of ≥14 drinks per week of both sexes were more frequently smokers and had higher low-density cholesterol and HDL. The relationship between alcohol consumption and hypertension was U-shaped in both sexes, with hypertension being more frequent among nondrinkers and in those participants drinking ≥14 drinks per week. There was no significant trend in the prevalence of CAD by category of alcohol intake.

Increasing alcohol intake was associated with larger LV diastolic and systolic diameter and larger LA diameter in men and women (Table 2). Among men, increasing alcohol intake was associated with greater LV mass, higher E/E′ ratio and tricuspid annulus peak systolic velocity, and a tendency for larger RV diastolic area. In women, increasing alcohol intake was associated with lower LV ejection fraction and a propensity toward worse peak longitudinal LV strain and increased time to peak longitudinal LV strain (Table 3). In spite of increasing LV end-diastolic diameter, no significant increase in LV volumes was observed in either men or women according to alcohol intake.

The linear association between the continuous measurement of alcohol consumption and LV end-diastolic diameter and LV mass confirmed the results obtained by the multivariate linear model (Figure 1). In addition, we observed a significant reduction in LV relative wall thickness, by increasing alcohol intake and a higher prevalence of LV hypertrophy in men with higher alcohol consumption (Table 2).

We observed a significant interaction between sex and alcohol intake with respect to LV ejection fraction (*P*=0.03) and tricuspid annulus peak systolic velocity (*P*=0.002), in addition to a nominal association in the interaction with respect to peak systolic longitudinal strain (*P*=0.08; Table 3; Figure 2), with women demonstrating worse LV and RV function for any given degree of alcohol consumption, compared with men. We found no significant differences in diastolic function category classification, according to alcohol consumption, but drinkers of ≥14 drinks per week were less likely to have mild diastolic dysfunction and more prone to have moderate-severe (diastolic dysfunction). However, 19% of participants were unclassifiable according to Olmsted criteria.

We observed a significant interaction between race and alcohol intake in men only for LV end-diastolic diameter, with greater increases in LV end-diastolic diameter in black men than in white men, for the same amount of alcohol intake (*P*=0.008; Figure I in the Data Supplement). However, the limited number of black participants, particularly in the highest drinking category, 14 (9.5%) men and 3 (6.4%) women, might have limited the power to estimate potential differences by race.

Discussion

In this study, alcohol intake was independently associated with larger LV diastolic and systolic diameter and larger LA diameter in men and women. Among men, increasing alcohol intake was associated with greater LV mass, higher E/E′ ratio, and higher tricuspid annulus peak systolic velocity. In women, increasing alcohol intake was linearly associated with lower LV ejection fraction, and there was a propensity for worse peak longitudinal LV strain.

Alcohol is a known dose-dependent cardiac toxin, but myocardial damage may be a consequence of direct toxic effects of alcohol or its metabolites by ethanol-induced apoptosis,[17] associated hypertension,[18] coexisting nutritional deficiencies, or, rarely, toxic additives to alcoholic beverages.[19] Alcoholic cardiomyopathy is characterized by enlargement of the heart, increased LV mass, and ventricular dysfunction[1]; besides, total lifetime dose of ethanol correlates inversely with LV ejection fraction and directly with LV mass.[20] Subtle signs of cardiac abnormalities as LV dilatation and impaired LV relaxation have also been reported in chronic asymptomatic heavy drinkers,[21] and previous small studies have described depression of LV contractility by acute alcohol consumption, evaluated by ejection fraction[22] or by global longitudinal strain, which may allow detection of earlier stages of LV dysfunction.[23] Similarly, reversible myocardial injury has been reported after binge drinking in healthy volunteers, with myocardial hyperenhancement demonstrated on MRI.[23] However, in spite of the awareness of alcohol induced LV injury and dysfunction by heavy alcohol intake, associations between alcohol consumption and measures of cardiac structure and function in the general population are mostly unknown.

In this study, of an elderly community-based cohort, we found that alcohol intake was independently associated with larger LA and LV diameters, in both men and women, and with increasing LV mass among men. In patients with CAD, heavier alcohol consumption has been associated with a 5-year increase in LA volume,[24] but the association between LA dimensions and alcohol consumption in the community was generally unknown. LA enlargement is a robust predictor of cardiovascular outcomes,[25] and it has been associated with the incidence and prevalence of heart failure with reduced and preserved LV ejection fraction.[26] Similarly, LV mass is strongly associated with incidence of cardiovascular disease and death.[27] Our results are consistent with those reported with respect to LV mass in the Framingham Study, as alcohol intake was positively associated with LV mass in men but not in women.[28] Moreover, alcohol intake was associated with

Table 1. Participants Characteristics According to Alcohol Consumption* and Sex

No. of Drinks per wk	Nondrinker	0 to 7	7 to 14	≥14	*P* Value
Total participants (n, %)	2402 (53.7)	1467 (32.8)	402 (9.0)	195 (4.4)	...
M	665 (37.3)	707 (39.7)	261 (14.7)	148 (8.3)	...
W	1737 (64.7)	760 (28.3)	141 (5.3)	47 (1.8)	...
Age, y					
M	76.9±5.1	76.2±5.4	75.7±4.6	75.4±4.8	<0.001
W	76.1±5.2	74.9±4.8	75.4±4.8	74.9±4.5	<0.001
White (n, %)					
M	530 (79.7)	628 (88.8)	239 (91.6)	134 (90.5)	<0.001
W	1203 (69.3)	678 (89.2)	137 (97.2)	44 (93.6)	<0.001
BMI, kg/m²					
M	28.8±5.1	28.4±4.3	28.1±4.3	28.2±4.6	0.028
W	29.4±6.4	27.3±5.4	26.2±4.4	27.4±6.5	<0.001
Hypertension (n, %)					
M	560 (84.2)	573 (81.0)	206 (78.9)	128 (86.5)	0.244
W	1497 (86.2)	582 (76.6)	109 (77.3)	41 (87.2)	<0.001
DM (n, %)					
M	257 (38.8)	212 (30.2)	66 (25.5)	47 (31.8)	0.001
W	596 (34.8)	153 (20.3)	22 (15.7)	7 (15.2)	<0.001
CAD (n, %)					
M	67 (10.5)	68 (10.2)	22 (9.2)	12 (8.6)	0.411
W	84 (5.1)	29 (4.1)	7 (5.4)	0 (0.0)	0.204
Current smoker (n, %)					
M	21 (3.2)	33 (4.7)	18 (6.9)	17 (11.5)	<0.001
W	65 (3.7)	56 (7.4)	17 (12.1)	7 (14.9%)	0.246
LDL cholesterol, mg/dL					
M	94.4±32.5	97.3±32.7	98.9±37.9	99.5±32.5	0.026
W	108.6±34.2	112.8±33.2	115.4±33.2	116.1±35.9	<0.001
HDL cholesterol, mg/dL					
M	43.4±9.7	46.2±10.1	50.1±12.7	54.3±15.4	<0.001
W	54.8±12.8	59.8±14.6	67.5±17.9	67.5±13.8	<0.001
Triglycerides, mg/dL					
M	127.6±68.8	123.4±60.5	123.7±74.7	130.4±82.4	0.8755
W	129.0±65.3	124.2±57.3	118.6±56.8	126.4±57.7	0.0354
TG/HDL					
M	3.2±2.1	2.9±1.8	2.7±2.0	2.7±2.4	0.0004
W	2.6±1.7	2.3±1.7	2.0±1.5	2.0±1.0	<0.001
High education level (n, %)					
M	275 (41.4)	430 (60.8)	169 (64.8)	80 (54.1)	<0.001
W	603 (34.7)	396 (52.1)	81 (57.4)	25 (53.2)	<0.001
Income>50 000/y (n, %)					
M	243 (39.1)	404 (59.6)	166 (65.1)	75 (52.8)	<0.001
W	373 (24.0)	338 (49.1)	68 (54.0)	23 (50.0)	<0.001

BMI indicates body mass index; CAD, coronary artery disease; DM, diabetes mellitus; HDL, high-density lipoprotein cholesterol; LDL, low-density lipoprotein cholesterol; M, men; TG, triglyceride; and W, women.

*Categories defined according to alcohol consumption at visit 5. *P* value for trend, considering alcohol consumption at visit 5.

higher E/E′ ratio among men, suggesting increasing LV diastolic pressures.

Men had better measurements of RV systolic function with increasing alcohol intake, in contrast to women. There are limited data on the effects of alcohol on RV function, but it has been reported that low doses of alcohol in normal healthy individuals may lead to dilation of RV end-diastolic diameter and to an acute increase

Table 2. Echocardiographic Morphological Characteristics According to Alcohol Consumption and Sex

No. of Drinks per wk	Nondrinker	0 to 7	7 to 14	≥14	Model 1: Alcohol Consumption Visit 5 Coefficient (SE)	Model 1: P Value	Model 2: Alcohol Consumption Visit 5 Coefficient (SE)	Model 2: P Value	Model 2: Cumulative Average Alcohol Consumption Coefficient (SE)	Model 2 Cumulative: P Value
Total participants (n, %)	2402 (53.7)	1467 (32.8)	402 (9.0)	195 (4.4)	…	…	…	…	…	…
M	665 (37.3)	707 (39.7)	261 (14.7)	148 (8.3)	…	…	…	…	…	…
W	1737 (64.7)	760 (28.3)	141 (5.3)	47 (1.8)	…	…	…	…	…	…
LV end-diastolic diameter, cm										
M	4.6±0.5	4.7±0.5	4.7±0.5	4.7±0.5	0.19 (0.04)	<0.001	0.18 (0.04)	<0.001	.19 (0.04)	<0.001
W	4.2±0.5	4.2±0.4	4.3±0.4	4.3±0.4	0.10 (0.03)	0.004	0.11 (0.04)	0.008	0.15 (0.04)	0.001
LV end-systolic diameter, cm										
M	2.8±0.6	2.9±0.6	2.9±0.5	2.9±0.5	0.12 (0.04)	0.003	0.11 (0.04)	0.014	0.13 (0.04)	0.005
W	2.5±0.4	2.5±0.4	2.6±0.5	2.5±0.5	0.12 (0.03)	0.001	0.14 (0.03)	0.001	0.17 (0.04)	<0.001
LV end-diastolic volume, mL										
M	98.5±26.3	99.4±26.0	100.8±23.8	99.9±23.1	1.8 (1.9)	0.344	0.95 (2.1)	0.654	1.7 (2.1)	0.414
W	70.8±17.7	69.3±15.7	69.0±15.3	68.9±14.8	0.40 (1.4)	0.782	0.37 (1.6)	0.820	0.48 (1.7)	0.782
LV mass, g										
M	170.3±51.4	169.9±44.7	172.5±45.9	175.6±50.1	9.7 (3.5)	0.006	8.2 (3.8)	0.029	9.7 (3.7)	0.010
W	135.4±37.4	128.3±34.4	126.5±30.6	129.3±27.1	−0.07 (2.8)	0.980	0.49 (3.2)	0.877	2.9 (3.3)	0.391
LV mass index, g/m²										
M	85.2±24.5	84.5±20.7	85.3±20.5	86.1±21.2	2.7 (1.7)	0.111	2.5 (1.8)	0.166	3.9 (1.8)	0.033
W	76.7±19.1	74.2±18.1	74.3±17.1	75.1±14.2	−0.61 (1.5)	0.701	0.06 (1.7)	0.969	1.5 (1.8)	0.410
Relative wall thickness, cm										
M	0.43±0.08	0.41±0.07	0.41±0.07	0.42±0.08	−0.01 (0.001)	0.011	−0.01 (0.001)	0.009	−0.01 (0.00)	0.006
W	0.43±0.08	0.42±0.07	0.42±0.05	0.41±0.06	−0.01 (0.001)	0.010	−0.01 (0.001)	0.047	−0.01 (0.00)	0.025
LV hypertrophy (n, %)										
M	68 (10.2)	64 (9.1)	26 (10.0)	20 (13.5)	1.4 (0.39)	0.140	1.5 (0.45)	0.131	1.6 (0.46)	0.090
W	258 (14.9)	78 (10.3)	16 (11.3)	5 (10.6)	0.75 (0.22)	0.347	0.83 (0.27)	0.593	0.95 (0.33)	0.885
LA maximal AP diameter, cm										
M	3.7±0.6	3.8±0.5	3.8±0.5	3.8±0.5	0.17 (0.03)	<0.001	0.16 (0.04)	<0.001	0.18 (0.04)	<0.001
W	3.4±0.5	3.4±0.4	3.4±0.5	3.4±0.5	0.11 (0.04)	0.005	0.12 (0.04)	0.008	0.14 (0.04).	0.002
LA maximal volume, mL										
M	56.2±26.2	54.7±21.3	56.7±21.5	58.1±20.3	3.6 (1.8)	0.043	3.2 (1.9)	0.096	3.3 (1.9)	0.093
W	45.2±15.7	42.6±14.3	42.4±13.7	41.5±11.7	−0.46 (1.2)	0.722	−0.7 (1.4)	0.618	−0.14 (1.5)	0.924
RV end-diastolic area, cm²										
M	22.2±5.4	22.5±5.4	23.5±5.6	23.2±5.5	1.5 (0.45)	0.001	1.1 (0.48)	0.021	0.80 (0.49)	0.100
W	17.8±4.4	17.4±4.0	17.1±3.8	17.2±3.3	0.23 (0.31)	0.545	0.001 (0.40)	0.999	−0.12 (0.46)	0.788

Model 1: adjusted for age, body mass index, diabetes mellitus, previously diagnosed myocardial infarction, antihypertensive treatment and systolic blood pressure. Model 2: adjusted for Model 1+ education and income level and cigarette smoking in all visits. Coefficient (SE) indicates estimated difference per consumption category (SE); LA, left atrial; LV, left ventricle; M, men; RV, right ventricle; and W, women.

in some indices of RV function.[29] Conversely, studies on dogs reported that moderate or high doses of alcohol were associated with RV myocardial dysfunction in a dose-dependent manner.[30]

The sex-related differences in the association between alcohol intake and echocardiography measures of structure and function cannot be explained by differences in age, body mass index or body surface area, current antihypertensive treatment, systolic blood pressure, prevalence of diabetes mellitus or CAD, socioeconomic status, or smoking. They also cannot be plausibly explained by sex differences in alcohol intake reporting, as we observed consistent positive associations between alcohol intake and HDL levels, a biological marker of alcohol consumption,[31] in both men and women. Similarly, the triglyceride/HDL ratio, a predictor of cardiovascular disease and known to be inversely associated with alcohol drinking,[32] decreased with alcohol consumption in both men and women. There are several different mechanisms

Table 3. Echocardiographic Functional Characteristics According to Alcohol Consumption and Sex

No. of Drinks per wk	Nondrinker	0 to 7	7 to 14	≥14	Model 1: Alcohol Consumption Visit 5 Coefficient (SE)	*P* Value	Model 2: Alcohol Consumption Visit 5 Coefficient (SE)	*P* Value	Model 2: Cumulative Average Alcohol Consumption Coefficient (SE)	*P* Value
Total participants (n, %)	2402 (53.7)	1467 (32.8)	402 (9.0)	195 (4.4)	…	…	…	…	…	…
M	665 (37.3)	707 (39.7)	261 (14.7)	148 (8.3)	…	…	…	…	…	…
W	1737 (64.7)	760 (28.3)	141 (5.3)	47 (1.8)	…	…	…	…	…	…
LV ejection fraction, %										
M	63.6±7.1	63.6±7.5	63.1±6.3	64.3±6.5	0.17 (0.55)	0.752	0.11 (0.59)	0.845	−0.13 (0.60)	0.818
W	66.5±5.9	66.2±5.7	65.6±6.9	65.5±6.5	−1.2 (0.54)	0.020	−1.9 (0.62)	0.002	−2.1 (0.66)	0.001
Global long. LV strain, %										
M	−17.3±2.9	−17.5±2.6	−17.4±2.5	−17.4±2.7	−0.005(0.21)	0.808	.001 (0.23)	0.983	.05 (0.23)	0.823
W	−18.3±2.5	−18.6±2.4	−18.1±2.5	−18.1±2.4	0.45 (0.22)	0.044	0.45 (0.25)	0.075	0.42 (0.27)	0.121
SD time to peak longitudinal LV strain, ms										
M	66.9±43.6	66.9±39.0	61.1±32.4	63.1±48.4	−4.2 (3.3)	0.206	−2.4 (3.7)	0.521	−5.4 (3.7)	0.145
W	59.9±33.2	57.6±28.5	52.2±26.8	58.7±25.3	−6.0 (2.9)	0.042	−6.4 (3.3)	0.055	−6.2 (3.5)	0.078
E/A ratio										
M	0.9±0.4	0.9±0.3	0.9±0.3	0.9±0.4	.04 (0.02)	0.100	0.01 (0.02)	0.593	−0.001 (0.02)	0.895
W	0.8±0.3	0.9±0.3	0.9±0.3	0.9±0.3	0.11 (0.02)	<0.001	0.08 (0.02)	0.005	0.06 (0.03)	0.030
E/E′ ratio										
M	9.4±3.8	9.5±3.8	9.7±4.6	10.1±3.7	1.1 (0.30)	<0.001	.82 (0.33)	0.014	.59 (0.33)	0.077
W	10.8±4.1	10.6±4.0	10.3±3.8	11.14±4.0	−0.02 (0.35)	0.948	−0.19 (0.41)	0.643	−0.24 (0.43)	0.577
LV diastolic function classification (n, %)										
M					−0.01 (0.02)	0.508	−0.03 (0.09)	0.704	−0.02 (0.09)	0.816
Unclassified	82 (13.3)	97 (14.8%)	33 (13.7)	20 (14.8)	0.03 (0.02)	0.212	0.02 (0.03)	0.460	0.02 (0.03)	0.389
Normal	202 (32.7)	236 (35.9%)	100 (41.5)	53 (39.3)	0.04 (0.03)	0.212	0.04 (0.04)	0.251	0.01 (0.04)	0.828
Mild	194 (31.4)	181 (27.5%)	51 (21.2)	23 (17.0)	−0.14 (0.03)	<0.001	−0.13 (0.04)	0.001	−0.07 (0.04)	0.054
Moderate-severe	140 (22.7)	143 (21.8%)	57 (23.7)	39 (28.9)	0.65 (0.35)	0.063	0.06 (0.03)	0.114	0.04 (0.03)	0.270
LV diastolic function classification (n, %)										
W					−0.01 (0.10)	0.865	−0.10 (0.12)	0.401	−0.11 (0.12)	0.387
Unclassified	387 (23.0)	145 (19.8%)	32 (23.9)	12 (26.1)	0.02 (0.03)	0.790	0.02 (0.04)	0.528	0.01 (04)	0.664
Normal	371 (22.0)	213 (29.0%)	40 (29.9)	12 (26.1)	0.04 (0.03)	0.274	0.06 (0.04)	0.172	0.08 (0.04)	0.061
Mild	405 (24.0)	139 (18.9%)	22 (16.4)	5 (10.9)	−0.09 (0.03)	0.011	−0.10 (0.04)	0.019	−0.12 (0.04)	0.007
Moderate-severe	521 (30.9)	237 (32.3%)	40 (29.9)	17 (37.0)	0.04 (0.04)	0.303	0.01 (0.04)	0.792	0.01 (0.05)	0.760
RV fractional area change										
M	0.50±0.08	0.50±0.08	0.51±0.07	0.51±0.08	0.01 (0.001)	0.083	0.001 (0.001)	0.382	−0.001 (0.001)	0.935
W	0.54±0.08	0.53±0.08	0.53±0.08	0.53±0.07	−0.01 (0.01)	0.049	−0.00(0.00)	0.275	−0.01 (0.001)	0.240
Tricuspid annulus peak systolic velocity, cm/s										
M	11.3±2.8	11.5±3.1	11.8±3.1	12.3±3.1	0.86 (0.23)	<0.001	0.86 (0.23)	0.001	0.84 (0.26)	0.012
W	11.7±2.9	11.8±2.7	11.5±2.8	11.7±2.9	−0.12 (0.25)	0.618	−0.12 (0.25)	0.719	−0.10 (0.28)	0.969

Model 1: adjusted for age, body mass index, diabetes mellitus, previously diagnosed myocardial infarction, antihypertensive treatment and systolic blood pressure. Model 2: adjusted for Model 1+education and income level and cigarette smoking in all visits. Coefficient (SE) indicates estimated difference per consumption category (SE); LV, left ventricle; M, men; RV, right ventricle; and W, women.

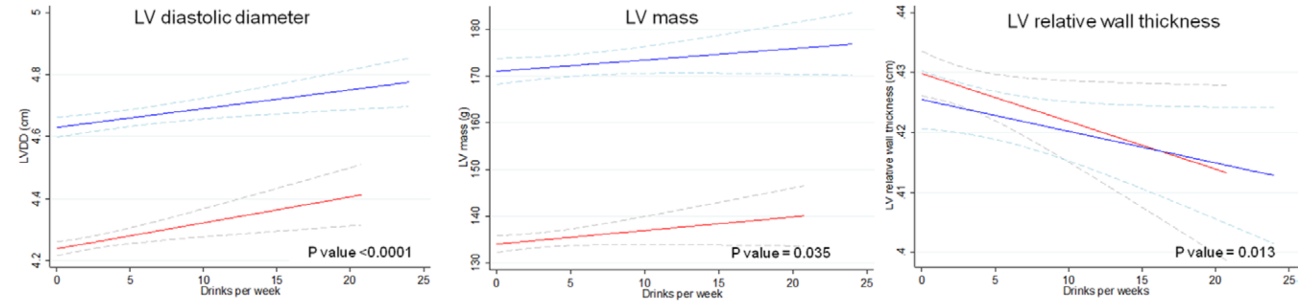

Figure 1. Multivariate analysis of morphological echocardiography characteristics, as a function of alcohol intake, by sex. Multiple linear regression analysis models with 95% confidence intervals indicated by the dashed lines. Models are adjusted for age, body mass index, diabetes mellitus, previously diagnosed myocardial infarction, antihypertensive treatment, systolic blood pressure, education, income level, and cigarette smoking in all visits. *P* values for overall relationship is shown. Blue lines represent men, and red lines represent women. In men and women, left ventricular (LV) end-diastolic diameter (LVDD) and LV mass increase and LV relative wall thickness reduces, by alcohol intake.

by which the effects of alcohol on the heart may differ by sex. Women absorb and metabolize alcohol differently than men,[33] and women seem to be more sensitive than men to the toxic effects of alcohol on cardiac function, developing alcoholic cardiomyopathy with a lower total lifetime dose of alcohol compared with men.[7,34] Consistent with these findings, our study shows associations between alcohol intake and subclinical changes in cardiac structure in both sexes, although only among women, increasing alcohol intake was associated with reduction of LV and RV systolic function. Interestingly, although we observed the classic U-shaped relationship between alcohol consumption and hypertension,[2] there was no threshold for alcohol protection, when associated with measures of cardiac structure and function in this cohort. However, the possibility that the effects of alcohol consumption may be partly mediated by increased blood pressure cannot be ruled out. In addition, alcohol affects sex hormones metabolism,[35] which have been associated with cardiac morphology and function, particularly, higher levels of androgens were associated with greater RV mass and volumes in both sexes. Thus, the part of sex hormones in the sex-related differences in the association between alcohol intake and cardiac structure and function cannot be excluded.[36]

Several limitations should be noted. This is an observational study, and alcohol consumption was self-reported in a questionnaire administered by an interviewer; thus, participants may have under-reported their consumption level. Our population only includes participants aged >65 years, and the number of black participants was too small for interpretation of race-related differences. Therefore, our observations may not be generalizable to other populations. As in any observational study, potential confounding by unmeasured factors can contribute to biased estimates, and the associations observed between alcohol consumption and subclinical changes of cardiac structure and function cannot be assumed to be causal; hence, our results should be interpreted accordingly.

The strengths of this study include its large size, the ability to control for cardiovascular risk factors, CAD, socioeconomic status, and demographic factors. Moreover, we analyzed associations by time updated cumulative average alcohol consumption during 23.6±0.9 years, we excluded former drinkers, minimizing the potential bias because of drinking cessation because of illness, and we were able to analyze sex-specific differences in the association of alcohol intake and measures of cardiac structure and function. In addition, we followed a rigorous echocardiographic protocol using modern echocardiographic techniques.

In summary, we found that increasing alcohol intake in among the elderly is associated with mild alterations in cardiac structure and function. In women, moderate alcohol consumption was associated with modest reduction in systolic

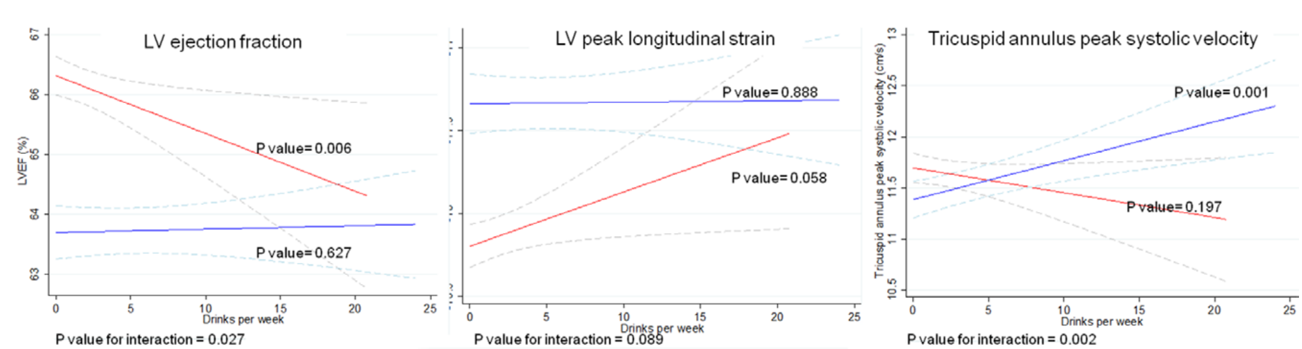

Figure 2. Multivariate analysis of functional echocardiography characteristics, as a function of alcohol intake by sex. Multiple linear regression analysis models with 95% confidence intervals indicated by the dashed lines. Models are adjusted for age, body mass index, diabetes mellitus, previously diagnosed myocardial infarction, antihypertensive treatment, systolic blood pressure, education, income level, and cigarette smoking in all visits. *P* values represented for overall relationship by sex and for interaction between sex and alcohol intake. Blue lines represent men, and red lines represent women. Women present worse left ventricular (LV) and right ventricular (RV) function for any given degree of alcohol consumption, compared with men. LVEF indicates left ventricular ejection fraction.

function, potentially contributing to a higher risk of alcoholic cardiomyopathy, for any given level of alcohol intake.

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Disclosures

None.

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CLINICAL PERSPECTIVE

In this elderly community-based population, increasing alcohol intake was associated with subtle alterations in cardiac structure and function. In women, moderate alcohol consumption was associated with modest reduction in systolic function, potentially contributing to a higher risk of alcoholic cardiomyopathy, for any given level of alcohol intake. There are several different mechanisms by which the effects of alcohol on the heart may differ by sex. Women absorb and metabolize alcohol differently than men, and women seem to be more sensitive than men to the toxic effects of alcohol on cardiac function, developing alcoholic cardiomyopathy with a lower total lifetime dose of alcohol compared with men. Consistent with these findings, our study shows associations between alcohol intake and subclinical changes in cardiac structure in both sexes, although only among women, increasing alcohol intake was associated with mild reduction of ventricular systolic function. In consequence, this study gives strength to the differences in the sensitivity of toxic alcohol effects by sex, which is in agreement with the international recommendations for a lower threshold of alcohol consumption in women compared with men.

Supplemental Material

Supplemental Table 1. Multiple linear regression model results for Echocardiographic Morphological Characteristics According to Alcohol Consumption and Sex

		Alcohol consumption at Visit 5		**Cumulative average alcohol consumption**	
		Coef. (SE)	P Value	Coef. (SE)	P Value
LV end diastolic diameter (cm)	M	.15 (.04)	<0.001	.17 (.04)	<0.001
	W	.10 (.04)	0.015	.13 (.04)	0.003
LV end systolic diameter (cm)	M	.09 (.04)	0.037	.11 (.04)	0.001
	W	.14 (.04)	0.001	.16 (.04)	<0.001
LV end diastolic volume (ml)	M	-.39 (2.0)	0.848	1.04 (2.0)	0.616
	W	.40 (1.5)	0.774	.22 (1.6)	0.895
LV mass (g)	M	4.3 (3.7)	0.255	7.4 (3.7)	0.050
	W	-.55 (3.1)	0.862	1.4 (3.3)	0.666
LV mass index (g/m2)	M	1.9 (1.8)	0.310	3.5 (1.8)	0.061
	W	-.44 (1.7)	0.807	.75 (1.9)	0.690
Relative wall thickness (cm)	M	-.01 (.001)	0.006	-.01 (.001)	0.007
	W	-.01 (.001)	0.051	-.01 (.001)	0.049
LV hypertrophy (*n*, %)	M	1.4 (.41)	0.216	1.5 (.43)	0.136
	W	.80 (.26)	0.507	.85 (.30)	0.659
LA maximal AP diameter (cm)	M	.12 (.04)	0.004	.15 (.04)	<0.001
	W	.10 (.04)	0.023	.11 (.04)	0.015
LA maximal volume (ml)	M	3.6 (1.8)	0.043	2.7 (1.9)	0.158
	W	-.78 (1.4)	0.584	-.54 (1.5)	0.721
RV end diastolic area (cm2)	M	2.1 (1.9)	0.262	.69(.48)	0.150
	W	.23 (.31)	0.545	-.18 (.46)	0.691

Model adjusted for age, body surface area, diabetes, previously diagnosed myocardial infarction, anti-hypertensive treatment, systolic blood pressure, education and income level and cigarette smoking in all visits. Coef. (SE), estimated difference per consumption category (standard error)

Supplemental Table 2. Multiple linear regression model results for Echocardiographic Functional Characteristics According to Alcohol Consumption and Sex

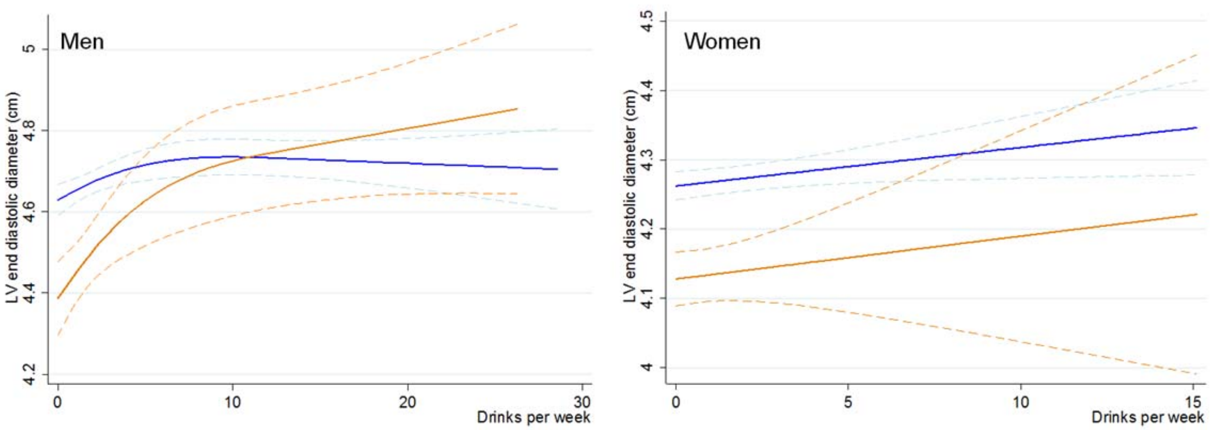
		Alcohol consumption at Visit 5		**Cumulative average alcohol consumption**	
		Coef. (SE)	P Value	Coef. (SE)	P Value
LV ejection fraction (%)	M	.17 (.59)	0.772	-.12 (.60)	0.837
	W	-1.9 (.62)	0.002	-2.0 (.66)	0.002
Global long. LV strain (%)	M	-.03 (.23)	0.878	-.03 (.24)	0.903
	W	.44 (.25)	0.083	.39 (.27)	0.148
SD Time to peak longitudinal LV strain (msec)	M	-2.5 (3.7)	0.499	-5.4 (3.7)	0.145
	W	-6.2 (3.3)	0.062	-5.6 (3.5)	0.114
E/A ratio	M	.02 (.02)	0.531	-.00 (.02)	0.923
	W	.08 (.02)	0.004	.06 (.03)	0.037
E/E' ratio	M	.74 (.33)	0.028	.54 (.33)	0.107
	W	-.02 (.41)	0.547	-.19 (.43)	0.647
LV diastolic function classification (*n*, %)	M	-.01 (.02)	0.508	-.02 (.09)	0.781
Unclassified		.03 (.02)	0.212	.02 (.03)	0.439
Normal		.04 (.03)	0.212	.02 (.04)	0.722
Mild		-.14 (.03)	<0.001	-.07(.04)	0.056
Moderate-severe		.65 (.35)	0.063	.03 (.03)	0.316
LV diastolic function classification	W	-.01 (.10)	0.865	-.01 (.12)	0.351
Unclassified		.02 (.03)	0.790	.02 (.04)	0.623
Normal		.04 (.03)	0.274	.08 (.04)	0.057
Mild		-.09 (.03)	0.011	-.12 (.04)	0.006
Moderate-severe		.04 (.04)	0.303	.01 (.05)	0.786
RV fractional area change	M	.01 (.001)	0.254	.001 (.001)	0.901
	W	-.001 (.01)	0.403	-.001 (.01)	0.395
Tricuspid annulus peak systolic velocity (cm/s)	M	.83 (.26)	0.001	.64 (.25)	0.013
	W	-.09 (.28)	0.741	-.06 (.30)	0.822

Model adjusted for age, body surface area, diabetes, previously diagnosed myocardial infarction, anti-hypertensive treatment, systolic blood pressure, education and income level and cigarette smoking in all visits. Coef. (SE), estimated difference per consumption category (standard error)

Supplementary Figure

Title: Multivariate analysis of left ventricular diastolic diameter, as a function of alcohol intake by race, in men and in women

Caption: Restricted cubic spline model with 95% confidence intervals indicated by the dash lines. Model is adjusted for age, body mass index, diabetes, previously diagnosed myocardial infarction, anti-hypertensive treatment, systolic blood pressure education, income level and cigarette smoking in all visits. P value for interaction of race in men=0.008, in women=0.994. Blue lines represent white race, orange lines represent black race.



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Relationship Between Alcohol Consumption and Cardiac Structure and Function in the Elderly : The Atherosclerosis Risk in Communities Study

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