JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY VOL. 72, NO. 13, 2018

Association Between Alcohol Intake and Cardiac Remodeling

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ABSTRACT

BACKGROUND Alcohol-induced cardiotoxicity is incompletely understood. Specifically, the long-term impact of alcohol use on ventricular remodeling or dysfunction, its modulators, and effect thresholds among young adults remain controversial.

OBJECTIVES The authors sought to evaluate a potential relationship between alcohol intake and cardiac remodeling, assessed by echocardiography, over 20 years of follow-up.

METHODS Among the CARDIA (Coronary Artery Risk Development in Young Adults) study cohort, the authors studied all subjects without baseline heart disorders who provided adequate information on their drinking habits and underwent echocardiographic evaluation at years 5 and 25 of the study. The echocardiographic outcomes were left ventricular (LV) ejection fraction, indexed LV end-diastolic volume and LV mass, and left atrial diameter. Participants were grouped according to their weighted-average weekly drinking habits. An additional analysis used the estimated cumulative alcohol consumption. Regression models and multivariable fractional polynomials were used to evaluate the association between alcohol consumption and the outcomes.

RESULTS Among the 2,368 participants, alcohol consumption was an independent predictor of higher indexed LV mass ($p = 0.014$) and indexed LV end-diastolic volume ($p = 0.037$), regardless of sex. No significant relationship between alcohol intake and LV ejection fraction was found. Drinking predominantly wine was associated with less cardiac remodeling and there was a nonsignificant trend for a harmful effect of binge drinking.

CONCLUSIONS After 20 years of follow-up, alcohol intake was associated with adverse cardiac remodeling, although it was not related with LV systolic dysfunction in this initially healthy young cohort. Our results also suggest that drinking predominantly wine associates with less deleterious findings in cardiac structure. (J Am Coll Cardiol 2018;72:1452–62)

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Manuscript received March 28, 2018; revised manuscript received July 2, 2018, accepted July 3, 2018.

Listen to this manuscript's audio summary by *JACC* Editor-in-Chief Dr. Valentin Fuster.

ISSN 0735-1097/$36.00 https://doi.org/10.1016/j.jacc.2018.07.050

In 2013, 70% of U.S. adults reported drinking alcoholic beverages in the past year, and 7% had an alcohol use disorder (1). Alcohol abuse is a known risk factor for the development of alcoholic cardiomyopathy (ACM) (2,3), which presents as a dilated cardiomyopathy that can lead to heart failure (4,5).

ACM is usually a presumptive diagnosis reserved for patients with a history of "at risk" drinking (for women, >3 drinks on any single day and >7 drinks per week; for men, >4 drinks on any single day and >14 drinks per week, as per the National Institute of Alcohol Abuse and Alcoholism [NIAAA] classification), left ventricular (LV) systolic dysfunction, and increased LV volumes, without other known cause to justify their cardiac impairment (5-7).

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"Idiopathic" nonischemic dilated cardiomyopathy is often diagnosed in patients who also report a history of alcohol intake, albeit generally mild to moderate (7,8). Previous observational studies have shown that approximately one-third of those diagnosed with dilated cardiomyopathy report an excessive alcohol intake (9,10) and that alcohol abstinence can significantly improve both LV function and symptomatic heart failure (11). Furthermore, alcohol may also lead to other cardiac diseases besides LV dysfunction, such as arrhythmias (12) or hypertension (13).

However, the relationship between alcohol intake and cardiac disease does not seem to be linear (14) and, in fact, mild-to-moderate alcohol (up to 1 standardized drink per day for women and up to 2 drinks per day for men) consumption may even be beneficial for coronary artery disease (15) and incident heart failure (16,17).

Previous studies have shown an association between alcohol and subtle echocardiographic changes in cardiac morphology and function, systolic and diastolic (18,19). However, most studies are either cross sectional (19) or performed over a short follow-up period in middle-aged and older individuals (18).

We lack information about the long-term effect of alcohol intake in young adults, and there is still controversy about the impact of other patients' characteristics or the pattern of alcohol intake regarding the threshold level for being injurious. Clarifying these issues related to alcohol's cardiotoxicity could have a significant impact in public health.

The main goal of this study was to assess the potential cardiotoxic role of alcohol in cardiac structure and function over 20 years of follow-up during young adulthood into middle age. We hypothesized that alcohol intake would be associated with LV systolic impairment and dilatation. Furthermore, we explored whether particular population subgroups, specific types of alcoholic beverages, and specific drinking patterns modify such associations.

ABBREVIATIONS AND ACRONYMS

ACM = alcoholic cardiomyopathy

BMI = body mass index

BSA = body surface area

FP = fractional polynomials

LA = left atrial

LV = left ventricular

LVEDV = left ventricular end-diastolic volume

LVEF = left ventricular ejection fraction

NIAAA = National Institute of Alcohol Abuse and Alcoholism

METHODS

STUDY SAMPLE. The CARDIA (Coronary Artery Risk Development in Young Adults) cohort study recruited 5,115 apparently healthy black and white individuals between 18 and 30 years of age, stratified by age, race, sex, and educational level. Enrollment was performed between 1985 and 1986 in 4 North American urban centers (Birmingham, Alabama; Chicago, Illinois; Minneapolis, Minnesota; and Oakland, California). Participants provided written informed consent at each examination, and institutional review boards from each field center and the coordinating center approved the study annually.

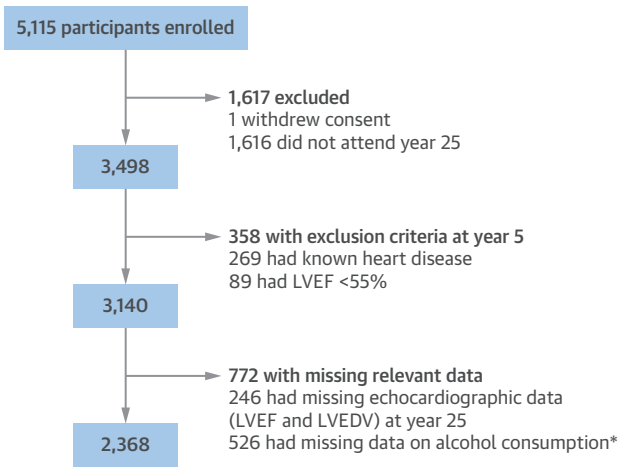
Participants have been followed for >30 years and have undergone a series of questionnaires and examinations at years 0, 2, 5, 7, 10, 15, 20, 25, and 30. Detailed information regarding the design and procedures performed during the study have been published elsewhere (20-22).

We considered year 5 of the CARDIA study as the baseline period of our sample, because it was the first year echocardiographic evaluations were performed. The follow-up period of our study comprised a total of 20 years (i.e., from year 5 until year 25, when a follow-up echocardiogram was obtained).

During this period, 3,498 participants fulfilled attendance criteria. Participants who, at baseline, had either known heart disease (questioned as "has a doctor or a nurse ever said that you have heart problems?") or a left ventricular ejection fraction (LVEF) below 55% were excluded from the analysis (n = 358). Furthermore, we also excluded participants with insufficient information about the echocardiographic outcomes (n = 246) and those who did not provide sufficient information regarding their alcohol consumption habits (i.e., participants who did not respond to the alcohol questionnaires at least at years 5, 15, and 25 of the CARDIA study) (**Figure 1**). Retention rates were 86% at year 5, 74% at year 15, and 72% at year 25; >90% of initial participants have maintained contact over time.

ALCOHOL CONSUMPTION ASSESSMENT. Data regarding alcohol intake were obtained from a questionnaire filled in by the CARDIA study participants at years 5,

FIGURE 1 Flowchart With Exclusion Criteria and Definition of the Study Sample



*Participants who did not respond to the alcohol questionnaires at least at years 5, 15, and 25 of the CARDIA study. LVEDV = left ventricular end-diastolic volume; LVEF = left ventricular ejection fraction.

15, and 25. At each examination, participants were questioned regarding their past drinking habits and, specifically, the number of drinks of wine, beer, and liquor they typically consumed per week.

Using visual aids for estimating a typical drink, the number of drinks of wine, beer, and liquor typically consumed in a week was assessed. The average alcohol consumption per week was calculated assuming that the amount of ethanol in 1 drink of beer, wine, and liquor was 16.7 ml, 17.0 ml, and 19.2 ml, respectively. This total was then divided by 17.24 ml (the amount of ethanol in an average drink, corresponding to 14 g of alcohol) to obtain the number of standardized drinks per week (20,23). This estimation of standard drinks was used to categorize alcohol intake in all the analyses.

We used a modified version of the NIAAA classification (24) to describe alcohol intake, estimating the average consumption of standard drinks per week (self-reported at years 5, 15, and 25), divided into the 5 following groups: alcohol abstainers (no alcohol consumption); participants who consumed on average >0 and <4 standardized drinks per week (very low risk); ≥4 and <7 (low risk); ≥7 and <14 (at risk), and ≥14 (high risk).

We also estimated the cumulative alcohol consumption during the 20 years of follow-up by calculating the product of the average ethanol intake per year (using the reported intake of alcohol per day at year 5 of the study, year 15, and year 25) and the total time interval (20 years). The effect of sex and race on the exposure outcomes was analyzed, which was facilitated by the stratified enrollment of CARDIA.

In order to be able to evaluate potential differences in the cardiotoxic effect of alcohol according to variations in consumption habits, we also extracted information from those 3 questionnaires equally distributed in time regarding the participants' ingestion of particular types of beverages (namely beer, wine, or liquor) and their drinking patterns (specifically evaluating self-reported binge-drinking, defined as the consumption of more 5 or more standardized drinks on the same occasion, at least once within the last 30 days).

ECHOCARDIOGRAPHIC EVALUATION. Our primary endpoint to assess LV systolic function was LVEF. Secondary endpoints were body surface area (BSA)-indexed LV end-diastolic volume (LVEDV) (a marker of LV dilation and ventricular remodeling with a significant prognostic value [25,26]), BSA-indexed LV mass (another marker of ventricular remodeling [25]), and left atrial (LA) diameter (which has been previously associated with adverse cardiovascular events [27]). LVEDV and LVEF measurements were performed by transthoracic echocardiography, using 2-dimensional apical views, whereas M mode was used to assess both BSA-indexed LV mass and LA diameter (the original values were used).

All studies were digitally recorded using an Artida Cardiac Ultrasound Scanner (Toshiba Medical Systems, Otawara, Japan) and assessed by certified analysts at the Johns Hopkins University Echocardiography Reading Center (Baltimore, Maryland), using standard image analysis software (Digisonics, Houston, Texas). These endpoints were assessed at year 25, but we also considered the individual variation (between year 25 and year 5) of the echocardiographic parameters in one of the models.

COVARIATES AND POTENTIAL CONFOUNDERS. Several variables were considered as potentially confounding factors, namely: sex, age, race, hypertension (in the CARDIA questionnaire: "has a doctor or a nurse ever said you have high blood pressure or hypertension?"), dyslipidemia (according to the CARDIA questionnaire: "has a doctor or a nurse ever said you have high blood cholesterol?"), diabetes (self-reported or taking medication), family history of cardiovascular diseases, body mass index (BMI), self-reported tobacco or illicit drug use, educational level (up to high school or above that), physical activity (using a questionnaire about the duration and intensity of self-reported participation in 13 categories of exercise over the previous 12 months [28]), chronic pulmonary disease, obstructive sleep apnea, thyroid

TABLE 1 Sample Characteristics According to Average Alcohol Consumption

		Standard-Drinks per Week					
	Total (N = 2,368)	None (n = 619)	>0 and <4 (n = 934)	≥4 and <7 (n = 303)	≥7 and <14 (n = 320)	≥14 (n = 192)	p Value
Age, yrs	51 (47-53)	50 (47-53)	51 (47-53)	51 (48-53)	51 (48-53)	51 (47-53)	0.171
Sex							
Men	1,051 (44.4)	192 (31.0)	373 (40.0)	146 (48.2)	185 (57.8)	155 (80.7)	<0.001
Race							
White	1,356 (57.3)	258 (42.7)	560 (60.0)	202 (66.7)	218 (68.1)	118 (61.5)	<0.001
Black	1,006 (42.5)	359 (58.0)	371 (39.7)	101 (33.3)	101 (31.6)	74 (38.5)	
Other	6 (0.2)	2 (0.32)	3 (0.32)	0 (0.0)	1 (0.31)	0 (0.0)	
Educational level*							
High school or above	1,593 (67.3)	384 (62.0)	659 (70.6)	221 (72.9)	223 (69.7)	106 (55.2)	<0.001
Below high school	775 (32.7)	235 (38.0)	275 (29.4)	82 (27.1)	97 (30.3)	86 (44.8)	
Physical activity*							
Low	492 (20.9)	149 (24.2)	212 (22.8)	47 (15.6)	53 (16.6)	31 (16.3)	<0.001
Moderate	1,059 (44.9)	302 (49.0)	399 (43.0)	143 (47.4)	144 (45.1)	71 (37.4)	
High	806 (34.2)	166 (26.9)	318 (34.2)	112 (37.1)	122 (38.2)	88 (46.3)	
Body mass index, kg/m^2							
<18.5	17 (0.7)	5 (0.8)	7 (0.8)	1 (0.33)	3 (0.94)	1 (0.52)	<0.001
18.5-25.0	632 (26.7)	122 (19.7)	258 (27.7)	103 (34.0)	94 (29.5)	55 (28.7)	
25.0-30.0	779 (32.9)	164 (26.5)	304 (32.6)	106 (35.0)	127 (39.8)	78 (40.6)	
>30.0	938 (39.6)	328 (53.0)	364 (39.0)	93 (30.7)	95 (29.8)	58 (30.2)	
Relevant medical history							
Smoking†	386 (43.4)	46 (32.2)	116 (36.9)	58 (42.7)	76 (49.0)	90 (64.8)	<0.001
Illicit drug use‡	959 (40.6)	139 (22.5)	349 (37.5)	146 (48.2)	182 (57.1)	143 (75.3)	<0.001
Cerebrovascular disease	41 (1.7)	14 (2.27)	17 (1.82)	3 (0.99)	4 (1.26)	3 (1.56)	0.711
Peripheral arterial disease	28 (1.2)	10 (1.6)	11 (1.2)	2 (0.7)	2 (0.6)	3 (1.6)	0.636
Hypertension	737 (31.2)	229 (37.1)	258 (27.7)	94 (31.1)	94 (29.6)	62 (32.5)	0.003
Diabetes mellitus	220 (9.3)	85 (13.8)	83 (8.9)	17 (5.6)	23 (7.2)	12 (6.3)	<0.001
Dyslipidemia	685 (29.0)	185 (29.9)	262 (28.1)	98 (32.5)	75 (23.6)	65 (34.0)	0.056
Renal disease	144 (6.1)	43 (7.0)	57 (6.1)	18 (6.0)	19 (6.0)	7 (3.7)	0.586
Liver disease	63 (2.7)	15 (2.4)	22 (2.4)	11 (3.6)	7 (2.2)	8 (4.2)	0.478
Thyroid disease	206 (8.7)	72 (11.7)	87 (9.3)	20 (6.6)	19 (6.0)	8 (4.2)	0.002
Obstructive sleep apnea	222 (9.4)	70 (11.3)	85 (9.1)	31 (10.3)	20 (6.3)	16 (8.3)	0.140
Chronic pulmonary disease§	24 (1.0)	5 (0.8)	8 (0.9)	3 (1.0)	5 (1.6)	3 (1.6)	0.653
Other cardiac diseases‖	151 (6.4)	39 (6.3)	61 (6.6)	23 (7.6)	19 (6.0)	9 (4.7)	0.774
Familiar cardiovascular disease	20 (0.9)	9 (1.5)	5 (0.5)	4 (1.3)	2 (0.6)	0 (0.0)	0.180

Values are median (interquartile range) or n (%). Average alcohol intake per week was estimated using the questionnaires at year 5 of the CARDIA study (baseline), year 15 and year 25, as specified in the Methods section. The p value for trend is represented. *All the characteristics were considered if present in any given time over the 20 years of follow-up, except for educational level, physical activity and body mass index, which are relative to baseline only. †Defined as the consumption of cigarettes, cigars, tobacco pipe or smokeless tobacco regularly for at least 3 months. ‡Including cocaine, heroin, amphetamines and methamphetamines (cannabinoids were not taken into account for this parameter). §Specifically asthma, chronic bronchitis or emphysema. ‖Other than dilated cardiomyopathy, specifically ischemic and valvular heart disease.

disease, liver disease, cerebrovascular disease, peripheral artery disease. or renal disease (Table 1). These variables were assessed at year 25, when we analyzed the echocardiographic outcomes, because the questionnaire asked whether the participants ever had one of these diagnoses or characteristics, and we wanted to adjust for them if they were present at baseline or were detected during follow-up; the exceptions were educational level, physical activity, and BMI, which are relative to baseline only. These possible confounders were selected based on clinical relevance and have been described elsewhere (21); the respective questionnaires are available at the CARDIA website. Furthermore, we also accounted for the development of ischemic or valvular heart disease ("other cardiac diseases," defined as the occurrence of myocardial infarction, angina, rheumatic fever, or valvular disease) during the study period as a potential confounder. We also adjusted for baseline echocardiographic values (at year 5).

STATISTICAL ANALYSES. Descriptive statistics and the prevalence of the baseline covariates were determined for the 5 previously mentioned NIAAA alcohol intake groups. The distribution of covariates was compared among the groups using either the

chi-square test or Fisher's exact test (for categorical variables, wherever adequate), analysis of variance (for continuous variables, followed by pairwise comparison with Bonferroni adjustment for multiple comparisons whenever necessary), or Kruskal-Wallis test (for continuous variables without a normal distribution). Categorical variables were expressed as frequencies. Continuous variables were expressed as mean ± SD if normally distributed, or median and interquartile range if not normally distributed. The normality of distribution was investigated using the Kolmogorov-Smirnov test.

In order to assess the relationship between alcohol consumption and LV dysfunction, the various echocardiographic outcome parameters were analyzed using unadjusted and multivariable regression analysis, namely linear regression (considering the outcomes as continuous variables), accounting for the before-mentioned potential confounders in the multivariable models.

In model 1, alcohol consumption was introduced as a categorical variable (i.e., average number of standard drinks per week, distributed into the 5 NIAAA categories). In model 2, alcohol intake was a continuous variable (i.e., estimated cumulative alcohol consumption in liters during the 20 years of follow-up). Covariates used for multivariable analysis were chosen based on unadjusted analysis ($p < 0.10$) and clinical significance.

As a sensitivity analysis, we also performed inverse probability weighted regression adjustment. We compared each category of alcohol intake with abstainers, which was the reference group. To study a possible nonlinear relationship between average alcohol intake and the echocardiographic parameters, we used multivariable fractional polynomials (FP) as a closed test procedure (29) (Model 3).

To assess whether race or sex modified the relationship between cumulative alcohol consumption and our pre-defined outcomes, we analyzed the potential for an interaction between these variables and alcohol consumption.

Finally, subgroup analysis was performed to evaluate the association of specific types of beverages and binge drinking on our main echocardiographic outcomes. A p value below 0.05 was considered statistically significant. The statistical analyses were performed using Stata Software version 13 (Stata Corp, College Station, Texas).

RESULTS

In total, 2,368 participants were included in the analysis (**Figure 1**). Their median age at the end of the study was 51 years of age (interquartile range: 47 to 53 years). In total, 44.4% (n = 1,051) were male and 57.3% (n = 1,356) were Caucasian.

The majority of participants either did not consume alcohol or drank <4 standard drinks per week (**Table 1**). The average daily ethanol intake was 10 ml, and only 8.1% (n = 192) of the participants were "at risk" drinkers, with a weekly alcoholic intake above 14 drinks per week. The estimated mean cumulative alcohol intake was 82 ± 130 l over 20 years (mean of 13 drink-years).

LVEF, END-DIASTOLIC VOLUME AND MASS, AND LA DIAMETER AT THE END OF FOLLOW-UP. The covariates used for adjustment were sex, race, age, educational level, smoking, hypertension, diabetes, BMI, dyslipidemia, illicit drug use, and "other cardiac diseases" (namely, heart attack, angina, mitral valve prolapse, or rheumatic heart disease) at year 25, as well as the echocardiographic values at baseline (year 5). As stated in the Methods section, covariates were chosen based on unadjusted analysis (**Table 1**) and clinical significance (in the case of age and "other cardiac diseases").

We did not find an overall significant association between cumulative alcohol intake and LVEF, even though the first category of alcohol intake had a subtle increase in LVEF, both in conventional and inverse probability weighted adjustment (**Table 2,** Online Table 1). Only 76 participants (3.2%) had LVEF <50% at the end of follow-up, and the relationship between alcohol intake and LVEF as a dichotomous variable was similar to that seen as a continuous variable (not significant overall).

There was a progressive and statistically significant increase in BSA-indexed LVEDV with increasing alcohol intake, which remained statistically significant after adjustment (53.1 ± 10.7 ml/m^2 in non-drinkers vs. 58.8 ± 14.8 ml/m^2 if >14 drinks/week; $p = 0.037$) (**Table 2**). Using inverse probability weighted regression adjustment testing a linear model, this lost significance (Online Table 1). However, using an adjusted analysis with FP, this relationship was also significant, but best defined as nonlinear (model 3, in which age was also included as a nonlinear covariate) (Online Table 2). If we analyzed BSA-indexed LVEDV as a dichotomous variable (considering ≥75 ml/m^2 as abnormal, which is true for both males and females), 131 participants (5.5%) had an increased value at the end of follow-up, and there was a significant association with alcohol intake.

A significant and linear association was found between alcohol intake and BSA-indexed LV mass, which remained after adjustment for covariates

TABLE 2 Echocardiographic Outcomes at Year 25 According to Alcohol Consumption

		Model 1: Standard Drinks per Week Regression Coefficient (95% CI); p Value					
	Total	None (n = 619)	>0 and <4 (n = 934)	≥4 and <7 (n = 303)	≥7 and <14 (n = 320)	≥14 (n = 192)	Model 2: Cumulative Alcohol Intake p Value
LVEF, %	61.6 ± 7.2	61.2 ± 7.4	62.0 ± 6.7	61.4 ± 7.8	61.4 ± 7.2	61.4 ± 7.5	
Unadjusted		Reference	0.81 (0.08 to 1.55); 0.029	0.21 (−0.78 to 1.21); 0.672	0.19 (−0.78 to 1.17); 0.695	0.26 (−0.91 to 1.43); 0.666	0.842
Adjusted		Reference	1.84 (0.08 to 3.60); 0.040	−0.32 (−2.38 to 1.73); 0.758	1.30 (−0.65 to 3.26); 0.192	0.37 (−1.91 to 2.65); 0.752	0.907
BSA-indexed LVEDV, ml/m^2	55.5 ± 12.4	53.1 ± 10.7	55.3 ± 12.2	56.8 ± 13.1	57.0 ± 12.4	58.8 ± 14.8	
Unadjusted		Reference	2.21 (0.96 to 3.45); 0.001	3.68 (2 to 5.37); 0.001	3.92 (2.26 to 5.57); 0.001	5.68 (3.7 to 7.67); 0.001	0.001
Adjusted		Reference	2.94 (0.21 to 5.68); 0.035	4.25 (1.07 to 7.43); 0.009	3.80 (0.76 to 6.84); 0.014	5.69 (2.14 to 9.23); 0.002	0.037
BSA-indexed LV mass, g/m^2	83.6 ± 21.5	81.2 ± 20.9	81.6 ± 20.5	85.8 ± 24.7	87.1 ± 21.5	92.4 ± 19.6	
Unadjusted		Reference	0.43 (−1.83 to 2.71); 0.708	4.59 (1.52 to 7.66); 0.003	5.91 (2.87 to 8.93); 0.001	11.25 (7.55 to 14.94); 0.001	0.001
Adjusted		Reference	0.33 (−4.86 to 5.51); 0.901	4.01 (−2.04 to 10.06); 0.194	6.37 (0.57 to 12.17); 0.031	6.96 (0.19 to 13.73); 0.044	0.014
LA diameter, cm	3.70 ± 0.49	3.67 ± 0.49	3.69 ± 0.49	3.71 ± 0.48	3.70 ± 0.48	3.76 ± 0.47	
Unadjusted		Reference	0.02 (−0.04 to 0.07); 0.562	0.04 (−0.03 to 0.10); 0.311	0.03 (−0.03 to 0.10); 0.335	0.09 (0.01 to 0.17); 0.033	0.062
Adjusted		Reference	0.03 (−0.04 to 0.10); 0.411	0.04 (−0.05 to 0.12); 0.400	−0.01 (−0.09 to 0.08); 0.871	−0.01 (−0.10 to 0.08); 0.877	0.392

Values are mean ± SD unless otherwise indicated. The means for the drinking categories are unadjusted. Adjustment was made for sex, race, age, educational level, smoking, illicit drug use, hypertension, diabetes, body mass index, dyslipidemia, "other cardiac diseases," and for the values of each echocardiographic parameter at baseline (year 5).

BSA = body surface area; CI = confidence interval; LA = left atrial; LV = left ventricular; LVEDV = left ventricular end-diastolic volume; LVEF = left ventricular ejection fraction.

(LV mass of 81.2 ± 20.9 g/m^2 in nondrinkers vs. 92.4 ± 19.6 g/m^2 if >14 drinks/week; p = 0.004) (**Table 2**, Online Table 2).

Finally, there was a significant association of greater LA diameter with greater alcohol consumption in unadjusted analysis. However, this association lost significance in the multivariable analyses.

INDIVIDUAL VARIATION IN LVEF, LVEDV, LV MASS, AND LA DIAMETER DURING FOLLOW-UP. The individual variation (year 25 − year 5) change of each participant, Δ in LVEF, LVEDV, and LV mass was not significantly associated with cumulative alcohol intake in the multiple linear regression analysis (**Table 3**) and using multivariable FP (Online Table 3). There was an association between the variation in LA diameter and alcohol consumption in unadjusted analyses and using inverse probability weighted adjustment (Online Table 4).

EFFECT MODIFICATION OF SEX AND RACE. We did not find a significant difference between women and men or between white and black participants regarding the relationship between cumulative alcohol intake and the echocardiographic parameters using multiple linear regression. Using multivariable FP, there was a nonlinear association between alcohol and LA diameter in women (p = 0.018), not found in men (p = 0.828) (**Central Illustration**, panel A, Online Figure 1). An independent nonlinear association between LA diameter and alcohol was also seen in black participants (p = 0.007), but not in whites (**Central Illustration**, panel B, Online Figure 1).

Regarding the individual variation in echocardiographic parameters, ΔLVEDV in men (p = 0.029) and ΔLA diameter in women (p = 0.007) and in African American participants (p = 0.028) showed an independent linear association with average cumulative alcohol intake.

TYPE OF BEVERAGE. For this analysis, we considered only the predominant beverage (either beer, wine, or liquor—the one with a higher intake in ml of alcohol as assessed by the questionnaires) and excluded the individuals that had never drunk and those who did not show any "type of beverage" preference (n = 1,174). When adjusting for cumulative alcohol intake and covariates that related to the type of predominant beverage taken, drinking wine or liquor was associated with smaller BSA-indexed LVEDV. Drinking predominantly wine was also associated with higher LVEF, lower BSA-indexed LV mass and lower LA diameter than beer or liquor (**Table 4**).

BINGE-DRINKING. In the univariable analysis, binge-drinking was associated with echocardiographic

TABLE 3 Change in Echocardiographic Parameters (Between Year 25 and Year 5) According to Alcohol Consumption

		Model 1: Standard Drinks per Week Regression Coefficient (95% CI); p Value					Model 2: Cumulative Alcohol Intake p Value
	Total	None	>0 and <4	≥4 and <7	≥7 and <14	≥14	
ΔLVEF, % (n = 1,067)	−2.88 ± 15.15	−3.96 ± 26.27	−2.68 ± 8.79	−3.15 ± 7.81	−1.86 ± 8.30	−2.13 ± 7.92	
Unadjusted		Reference	1.28 (−1.10 to 3.65); 0.292	0.81 (−2.46 to 4.08); 0.628	2.10 (−1.08 to 5.27); 0.196	1.82 (−2.0 to 5.66); 0.350	0.309
Adjusted		Reference	0.95 (−1.75 to 3.66); 0.489	−0.72 (−4.01 to 2.57); 0.668	1.64 (−1.52 to 4.78); 0.307	−0.10 (−3.79 to 3.60); 0.959	0.597
ΔLVEDV, ml, (n = 1,073)	−10.2 7 ± 29.54	−8.03 ± 26.90	−11.46 ± 29.34	−11.06 ± 28.68	−11.13 ± 31.09	−13.33 ± 28.42	
Unadjusted		Reference	−3.43 (−7.85 to 0.99); 0.128	−3.03 (−9.11 to 3.04); 0.328	−3.11 (−9.01 to 2.80); 0.303	−5.30 (−12.45 to 1.84); 0.145	0.134
Adjusted		Reference	−2.21 (−11.39 to 6.98); 0.637	0.13 (−11.94 to 6.98); 0.982	1.78 (−8.89 to12.44); 0.743	0.12 (−12.42 to 12.66); 0.985	0.251
ΔLV mass, g, (n = 2,047)	22.18 ± 46.14	24.54 ± 46.27	20.50 ± 44.96	22.15 ± 49.59	21.67 ± 46.73	23.79 ± 45.03	
Unadjusted		Reference	−4.04 (−9.07 to 0.99); 0.116	−2.39 (−9.23 to 4.45); 0.493	−2.87 (−9.55 to 3.81); 0.399	−0.74 (−8.94 to 7.45); 0.858	0.659
Adjusted		Reference	−0.49 (−12.27 to 11.29); 0.935	2.27 (−11.52 to 16.06); 0.746	5.51 (−7.75 to 18.76); 0.415	−0.14 (−15.51 to 15.21); 0.985	0.600
ΔLA diameter, cm, (n = 2,238)	0.18 ± 0.50	0.21 ± 0.50	0.18 ± 0.50	0.17 ± 0.50	0.14 ± 0.45	0.13 ± 0.52	
Unadjusted		Reference	−0.026 (−0.078 to 0.025); 0.318	−0.033 (−0.104 to 0.036); 0.347	−0.069 (−0.138 to −0.001); 0.048	−0.077 (−0.159 to 0.005); 0.066	0.043
Adjusted		Reference	0.029 (−0.040 to 0.099); 0.409	0.036 (−0.047 to 0.119); 0.395	−0.007 (−0.089 to 0.076); 0.873	−0.007 (−0.099 to 0.085); 0.879	0.392

Values are mean ± SD unless otherwise indicated. The means presented for the drinking categories are unadjusted. Adjustment was made for sex, race, age, educational level, smoking, illicit drug use, hypertension, diabetes, body mass index, dyslipidemia, "other cardiac diseases," and for the values of each parameter at baseline (year 5).

Abbreviations as in Table 2.

parameters of cardiac remodeling (higher LVEDV, LV mass, and LA diameter); however, when adjusting for covariates that were associated with binge-drinking habits, only a borderline association with LA diameter was found (Table 5).

DISCUSSION

We intended to study the effects of alcohol intake on cardiac remodeling and function over time in a healthy sample of young adults up to middle age in the CARDIA cohort. In our study, greater alcohol consumption was associated with higher values of indexed LV mass and LVEDV, suggesting that alcohol may cause LV remodeling, which can be detrimental (25,26,30,31).

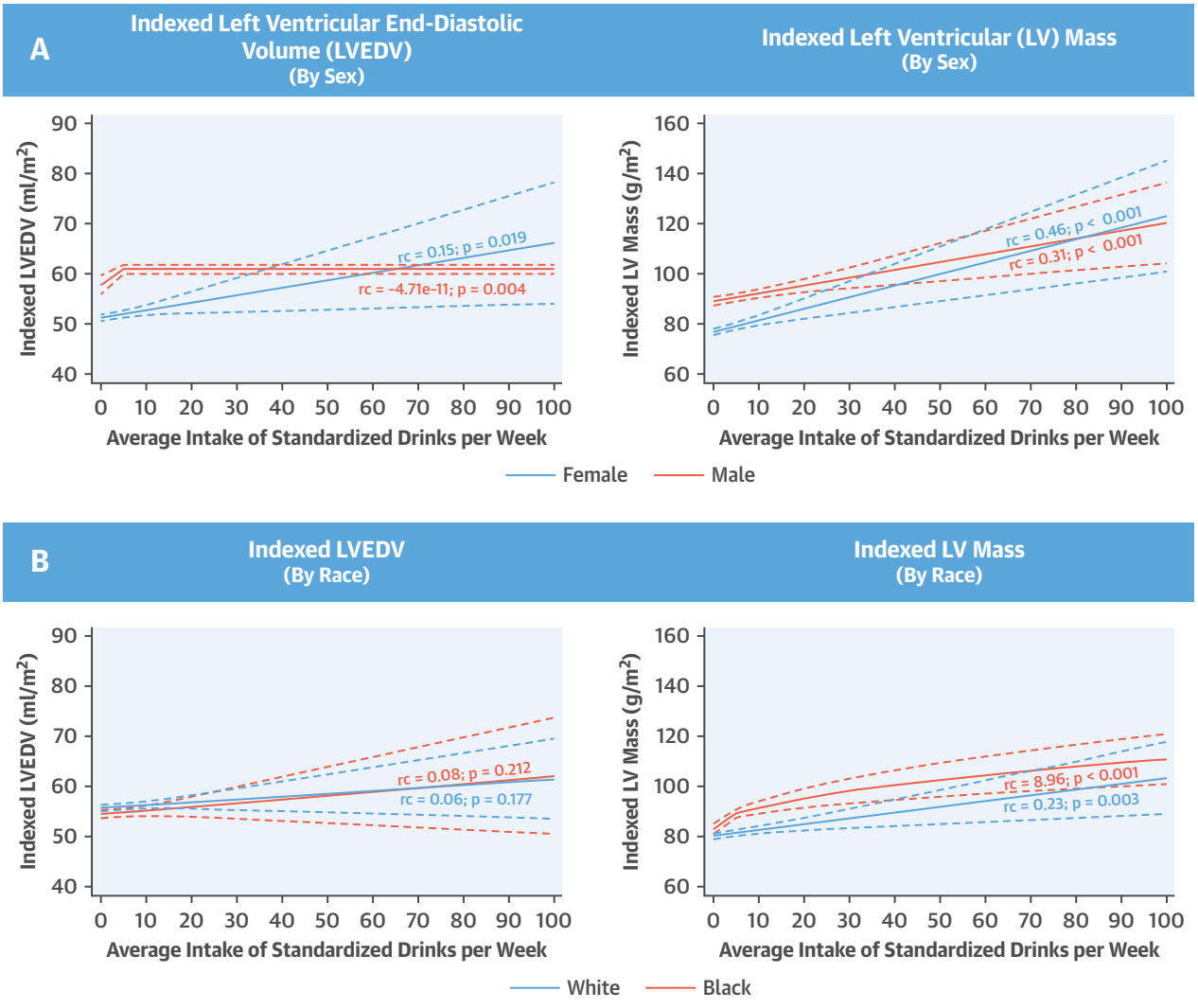
The absolute changes in echocardiographic parameters were small, and overall, the values remained within normal limits. Therefore, our results reinforce the concept that mild alcohol consumption (<7 drinks per week) poses little cardiovascular risk.

The fact that we did not find a significant association between alcohol and the intraindividual variation of the echocardiographic parameters (between year 25 and year 5) is probably due to the fact that we could only calculate the variation in LVED and LVEF in approximately one-half the sample (in 1,073 participants for LVEDV and in 1,067 for LVEF), because the quantification methods were different.

The fact that our sample was relatively young and included few individuals with very high alcohol intake might have contributed to the modest association between alcohol and echocardiographic changes. In our cohort, only 16 patients developed heart failure, and 4 patients had cardiovascular death. Our results also support the idea that the pathogenic role of alcohol in the development of dilated cardiomyopathy may be influenced by other individual factors, for example, genetic predisposition, and may be less easily detected in the general population in the absence of that data.

Another gap in the scientific evidence concerns the existence of a threshold for ethanol cardiotoxicity, whether it is modified by the type of beverage and whether there are specific groups of the population (e.g., in terms of race or sex who may be particularly susceptible to its effects).

CENTRAL ILLUSTRATION **Alcohol Intake and Cardiac Remodeling**



Rodrigues, P. et al. J Am Coll Cardiol. 2018;72(13):1452–62.

Relationship between average alcohol intake and body surface area–indexed left ventricular (LV) end-diastolic volume (LVEDV) and mass, according to sex **(A)** and race **(B)**. In **A**, males are represented in **orange** and females in **blue**. In **B**, black participants are represented in **orange,** and white participants in **blue**. Regression coefficient and p values for each subgroup are shown; 95% confidence intervals are represented by **dashed lines**. Adjustment was made for age, sex, race, educational level, smoking, illicit drug use, hypertension, diabetes, body mass index, dyslipidemia, and "other cardiac diseases" (multivariable regression using fractional polynomials). Alcohol intake was independently associated with higher body surface area–indexed LVEDV and LV mass, in both sexes and races.

Whereas information regarding the cardiac effects of alcohol in different races is scarce, women have shown to be more susceptible to alcohol toxic effects in some studies (32,33). In our cohort, sex or race did not significantly modify the relationship between alcohol intake and echocardiographic parameters of LV systolic function and remodeling. However, the fact that very few women drank heavily may have compromised our ability to detect a difference.

Knowledge regarding the impact of specific types of alcoholic beverages in ventricular function and remodeling was lacking, and the few studies that have addressed this issue before have failed to find any significant differences in association (34,35).

TABLE 4 Impact of the Type of Beverage Preference on Ventricular Remodeling

	Beer (n = 713)	Wine (n = 295)	Liquor (n = 166)
LVEF, %	61.15 ± 7.33	62.61 ± 6.90	62.19 ± 7.19
Unadjusted	Reference	1.45 (0.47 to 2.43); 0.004	1.04 (−0.18 to 2.26); 0.095
Adjusted*	Reference	1.38 (0.38 to 2.39); 0.007	1.08 (−0.15 to 2.31); 0.085
BSA-indexed LVEDV, ml/m^2	58.57 ± 13.32	53.66 ± 11.50	54.70 ± 12.04
Unadjusted	Reference	−4.91 (−6.64 to −3.18); 0.001	−3.87 (−6.03 to −1.72); 0.001
Adjusted*	Reference	−4.90 (−6.64 to −3.16); 0.001	−3.65 (−5.78 to −1.51); 0.001
BSA-indexed LV mass, g/m^2	87.94 ± 23.44	79.86 ± 18.15	85.85 ± 23.25
Unadjusted	Reference	−8.08 (−11.21 to −4.95); 0.001	−2.09 (−6.02 to 1.84); 0.297
Adjusted*	Reference	−5.78 (−8.84 to −2.71); 0.001	− 3.75 (−7.56 to 0.05); 0.053
LA diameter, cm	3.751 ± 0.491	3.616 ± 0.434	3.813 ± 0.495
Unadjusted	Reference	−0.135 (−0.201 to −0.069); 0.001	0.062 (−0.020 to 0.069); 0.140
Adjusted*	Reference	−0.071 (−0.131 to −0.011); 0.019	0.005 (−0.068 to 0.079); 0.888

Values are mean ± SD or regression coefficient (95% CI); p value. The predominant drink at baseline was chosen (the beverage with the intake corresponding to more milliliters of alcohol). *Adjusted for cumulative alcohol intake and the covariates that were associated with a predominant type of drink in univariate analysis (hypertension, race, body mass index, educational level, sleep apnea, and thyroid disease).

Abbreviations as in Table 2.

However, in our study, drinking predominantly wine was associated with less LV and LA dilation and higher LVEF, an interesting finding that warrants further confirmation. Dietary factors can also have a confounding factor that we could not account for.

Binge drinking, a behavior previously correlated primarily with arrhythmias, specifically atrial fibrillation (36), was also associated with adverse cardiac remodeling, but only in the crude analysis. That association lost significance when adjustment was performed, which could be related to confounding but also to the limited number of participants with binge-drinking habits.

STUDY STRENGTHS AND LIMITATIONS. The major strength of the current study was that it analyzed a large race- and sex-balanced sample with a long follow-up. Besides utilizing this large and very complete dataset, we also performed a robust analysis with multiple adjustments for covariates, in order to minimize the likelihood of confounding.

However, we must also highlight the significant limitations of our study and why the study should be interpreted with caution. Firstly, because alcohol intake was assessed using questionnaires, recall bias may have led to an inaccurate estimation. Secondly, in this cohort, alcohol consumption was relatively low, with 78% of the participants drinking only up to 7 standard drinks per week. Because alcohol cardiotoxicity is probably more striking at greater doses (9,10), the low prevalence of at-risk drinkers (>14 drinks per week) in our sample may have limited our power to adequately assess the risks related to heavy alcohol consumption. A selection bias must also be considered, because using participants who attended the study and performed all the required evaluations may have overrepresented certain characteristics of the population. Finally, as with other observational studies, the potential for unmeasured confounding limits our ability to establish a causal relationship. However, because long-term randomized trials assessing the effect of alcohol consumption on LV function would be impractical and unethical, we consider prospective longitudinal studies such as this one to be the most realistic study designs available to assess the cardiac effect of alcohol intake in populations.

The mechanisms behind the relationship between alcohol consumption and cardiac function and structure still need to be better understood. We still cannot predict which patients will develop ACM and,

TABLE 5 Effect of Binge-Drinking on Ventricular Remodeling

	Non-Binge Drinkers (n = 1,449)	Binge Drinkers (n = 300)
LVEF, %	61.83 ± 7.08	61.32 ± 7.32
Unadjusted	Reference	−0.51 (−1.39 to 0.38); 0.263
Adjusted*	Reference	−1.37 (−2.79 to 0.06); 0.060
BSA-indexed LVEDV, ml/m^2	55.81 ± 12.25	58.83 ± 14.89
Unadjusted	Reference	3.01 (1.43 to 4.60); 0.001
Adjusted*	Reference	1.93 (−0.47 to 4.34); 0.114
BSA-indexed LV mass, g/m^2	83.22 ± 21.64	91.32 ± 20.73
Unadjusted	Reference	8.10 (5.20 to 10.99); 0.001
Adjusted*	Reference	1.92 (−2.40 to 6.24); 0.383
LA diameter, cm	3.684 ± 0.491	3.808 ± 0.483
Unadjusted	Reference	0.124 (0.062 to 0.186); 0.001
Adjusted*	Reference	0.085 (0.001 to 0.170); 0.050

Values are mean ± SD or regression coefficient (95% CI); p value. *Adjusted for cumulative alcohol intake and the covariates that were associated with binge drinking in univariable analysis (illicit drug use, smoking, body mass index, educational level and thyroid disease).

Abbreviations as in Table 2.

beyond sex and race, there are probably genetic factors that need to be taken into consideration. Plus, the potential for reversibility has not been adequately studied (5). Further studies of individuals with greater alcohol intake may help us define better prevention strategies to reduce the deleterious effects of alcohol toxicity in populations.

CONCLUSIONS

Greater alcohol intake had an independent adverse association with ventricular structure (greater indexed LV mass and LVEDV) after 20 years of follow-up. This relationship was not significantly modified by sex or race. Moreover, there was also an association between alcohol intake and LA diameter in women and among African American CARDIA participants.

Alcohol consumption was not significantly associated with LV systolic dysfunction measured by LVEF in this cohort of young adults with mild-to-moderate alcohol consumption. There was a nonsignificant trend for a deleterious effect of binge drinking and drinking predominantly wine was associated with less cardiac remodeling.

ACKNOWLEDGMENTS The authors thank Laura Colangelo for her important contribution to the statistical analyses, and all the CARDIA Investigators for making this project possible.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: In most middle-aged Americans, moderate alcohol intake has no major deleterious effects on cardiac structure and function. There is an association between alcohol intake and left ventricular dilatation that could be an early form of dilated cardiomyopathy and that is more pronounced with liquor and beer than with wine consumption and with binge drinking.

TRANSLATIONAL OUTLOOK: Prospective trials of alcohol abstinence in patients with dilated cardiomyopathy are needed to assess the potential reversibility of alcohol toxicity, and long-term follow-up studies of heavy drinkers could clarify modulators of the effect of alcohol on the heart.

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KEY WORDS alcohol, alcoholic cardiomyopathy, cardiac remodeling, heart failure, ventricular dilatation, ventricular function

APPENDIX For details on data availability as well as supplemental tables, please see the online version of this paper.