Am J Cardiovasc Dis 2018;8(5):58-65
www.AJCD.us /ISSN:2160-200X/AJCD0086137

Original Article

Electrocardiographic subclinical myocardial injury and alcohol consumption: a cross-sectional analysis of data from the Third National Health and Nutrition Examination Survey

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Received September 28, 2018; Accepted November 29, 2018; Epub December 15, 2018; Published December 25, 2018

Abstract: Background: Cardiac Infarction/Injury Score (CIIS), an electrocardiographic based scoring system, is a surrogate marker of subclinical myocardial injury (SC-MI) and has shown excellent prognostic value in predicting future cardiovascular mortality. As an association of mild to moderate alcohol consumption with cardiovascular disease (CVD) is conflicting, using an electrocardiographic based scoring system such as CIIS is a simple and cost-effective way to investigate this controversial relationship. Methods: This analysis included 6090 participants (58.42±13.12 years, 54.2% women) free of CVD from the Third National Health and Nutrition Examination Survey (NHANES III). We used multivariable linear regression analysis to examine the cross-sectional association between each alcohol category (non-drinker (reference), 1-6 drinks/week, 7-13 drinks/week, ≥14 drinks/week, and CIIS. SC-MI was defined as CIIS ≥10 units. Results: The prevalence of SC-MI was high among heavy drinkers (≥14 drinks/week) and was lower in participants who were moderate drinkers (7-13 drinks/week). There was a statistically significant and inverse association between moderate alcohol consumption and CIIS (β (95% CI): -0.64 (-1.27, -0.007), P = 0.04) using multivariable linear regression analysis. This inverse association between moderate alcohol consumption and CIIS was more striking among whites compared to non-whites (β (95% CI): -1.06 (-1.93, -0.19) vs. 0.05 (-0.91, 1.00) respectively; interaction *p*-value = 0.08). Also, the association was stronger among women and older participants, however interaction *p*-value did not reach statistical significance. Conclusion: There is an inverse association between moderate alcohol consumption and CIIS in participants without manifestations of CVD. As lower CIIS has been associated with low risk of poor outcomes including CVD mortality, these findings further support the existing evidence of the potential benefits of moderate alcohol consumption on cardiovascular health.

Keywords: Alcohol drinking, CIIS, cardiovascular disease, NHANES, subclinical myocardial injury

Introduction

The relationship between alcohol consumption and cardiovascular disease (CVD) has always been intricate. Alcohol consumption is one of the factors that has both protective and detrimental effects on CVD. Most of the studies to date have consistently shown a J-shaped association of alcohol consumption where light to moderate drinkers have lower CVD events than non-drinkers and heavy drinkers [1]. The exact mechanism of the cardioprotective effect of alcohol is unknown. Alcohol consumption is thought to influence CVD risk predominantly by acting on established CVD risk factors, namely, insulin resistance [2], high-density lipoprotein (HDL) [3, 4] and inflammation [5].

Results of the studies of the association between alcohol consumption and subclinical CVD have been inconsistent. Previous studies focusing on the association of alcohol intake and subclinical atherosclerosis have shown divergent results. Many previous studies have examined the association between alcohol use and coronary artery calcium (CAC) as a surro-

gate marker of subclinical atherosclerosis. These studies have shown a U-shaped association [6], a dose-response association [7], or no association [6-11]. Apart from its effect on atherosclerosis, the relationship between alcohol intake and myocardial injury is unclear and not widely studied. The study ex-amining the association of alcohol consumption with subclinical myocardial damage using high sensitivity cardiac troponin-T (hs-cTnT) showed that moderate drinking was associated with lower concentrations of hs-cTnT [12].

The Cardiac Infarction Injury Score (CIIS) is an electrocardiogram classification system that was developed to identify ischemic heart disease [13]. SC-MI as defined by CIIS ≥10 has shown to be associated with an increased CVD mortality. Using CIIS as a continuous variable, increasing CIIS predicted a higher risk of mortality and lower CIIS predicted a low risk of mortality in the previous studies [14, 15]. To our knowledge, the association between alcohol consumption and CIIS has not been formally examined in a population-based study. In this study, we comprehensively explored the association between alcohol consumption and CIIS using a sample from the Third National Health and Nutrition Examination Survey (NHANES-III) free of CVD.

Methods

Study participants

We analyzed data from the Third National Health and Nutrition Examination Survey (NHANES III), a cross-sectional study conducted between 1988 and 1994 that used a multistage stratified clustered probability design to select a representative sample of the civilian non-institutionalized US population [16]. The NHANES III study was approved by the National Center for Health Statistics (NCHS) Research Ethics Review Board (ERB), and documented consent was obtained from participants. Between 1988 and 1994, initial home interviews were conducted to collect baseline information, including demographics (age, sex, race/ethnicity), medication data (e.g., use of antihypertensive and lipid-lowering medications), past medical history (e.g., history of CVD), and behavioral data (e.g., smoking). Subsequently, participants visited mobile examination centers and gave blood samples to record basic laboratory values for each participant (e.g., total cholesterol, plasma glucose).

Alcohol consumption

In NHANES III, alcohol consumption was assessed by the food frequency questionnaire. Participants reported the number of drinks consumed in the past month for three different types of alcohol: 1) beer; 2) wine; and 3) hard liquor. We defined alcohol consumption as 1) currently drinking (≥1 drink of any type per month) or not currently drinking (<1 per month); 2) the number per week of any type of alcoholic drinks (1-6, 7-13, or ≥14); and 3) the number of beverage-specific drinks per month (1-6, 7-13, or ≥14). The not currently drinking category (<1 drink per month) included past drinkers (subjects consuming at least 12 drinks of any type over a lifetime but not currently drinking alcohol) and lifetime abstainers (subjects consuming <12 drinks in their entire lifetime). Also, the frequency of heavy episodic drinking was assessed during the alcohol and drug component of the examination. Participants were classified as binge drinkers if they had at least five alcoholic drinks in a single day during the past 12 months.

Measurement of cardiac infarction/injury score (CIIS)

Resting 12-lead ECG were obtained with a Marquette MAC 12 system (Marquette Medical Systems, Milwaukee, Wisconsin) during the mobile examination visits by trained technicians. Analysis of ECG was achieved through a computerized automated process and visual inspection by a trained technician located in a centralized core laboratory. The calculation of the cardiac infarction/injury score (CIIS) and methodology have been described previously [13]. Briefly, CIIS is based on a weighted scoring system taking several objective electrocardiographic waveform components related to myocardial injury and ischemia, both discrete and continuous, and generating a risk-stratified scoring system. The score is defined by a combination of 11 discrete and 4 continuous features and provides a simple scoring scheme suitable for both visual and computer classification of a standard 12-lead ECG. By design, CIIS values were multiplied by a factor of 10 in

Table 1. Baseline characteristics of study participants

Characteristics Mean ± SD or n (%)	Non-Drinker N = 3417	Mild alcohol use (0-6 drinks/week) N = 1973	Moderate alcohol use (7-13 drinks/week) N = 545	High alcohol use (≥14 drinks/week) N = 155	*P*-Value†
Age (years)	60.4±13.4	55.1±12.0	57.7±12.6	58.1±12.0	<.0001
Male (%)	1216 (35.5%)	1081 (54.7%)	357 (65.5%)	131 (84.5%)	<.0001
Race					<.0001
Non-Hispanic White	1651 (48.3%)	1003 (50.8%)	327 (60%)	88 (56.7%)	
Non-Hispanic Black	765 (22.3%)	433 (21.9%)	103 (18.9%)	30 (19.3%)	
Mexican American	835 (24.4%)	465 (23.7%)	104 (19.0%)	32 (20.6%)	
Other	166 (4.8%)	72 (3.6%)	11 (2.0%)	5 (3.2%)	
Total Annual Family Income <20,000	1748 (52.1%)	690 (35.5%)	183 (34.0%)	54 (35.2%)	<.0001
Systolic Blood Pressure (mmHg)	132.5±19.9	128.5±17.6	131.2±17.0	133.6±16.5	<.0001
Diastolic Blood Pressure (mmHg)	75.6±10.0	77.0±9.8	77.0±9.9	80.0±9.8	<.0001
Insulin resistance (%)	1418 (41.6%)	704 (35.7%)	207 (38.1%)	69 (44.8%)	0.0002
HDL Cholesterol	50.0±15.1	51.8±16.9	57.9±18.8	59.5±20.8	<.0001
C-reactive protein	0.52±0.81	0.44±0.64	0.42±0.64	0.49±0.75	0.0001
Body mass index (Kg/m^2)	27.9±5.4	27.5±5.2	26.0±4.5	26.5±4.7	<.0001
Smoking (%)					
Current Smoker	607 (17.7%)	530 (26.8%)	195 (35.7%)	61 (39.3%)	<.0001
Former Smoker	984 (28.8%)	679 (34.4%)	210 (38.5%)	66 (42.5%)	<.0001
Never Smoker	1826 (53.4%)	764 (38.7%)	140 (25.6%)	28 (18.0%)	<.0001
Physical Activity (METs per week)*	7.32 (0-27.4)	12.79 (3.2-34.6)	15.11 (3.2-36.2)	13.6 (3.2-34.8)	<.0001
SC-MI (%)	754 (22.0%)	397 (20.1%)	106 (19.4%)	36 (23.2%)	0.23
Cardiac Injury Score	5.40±6.92	4.90±6.60	4.92±6.23	5.44±6.96	0.04

†*p*-value for calculated by ANOVA for continuous and chi^2 for categorical variables. *METs reported as median and IQR. MET, metabolic equivalent; HDL, high-density cholesterol; SC-MI, subclinical myocardial injury. Insulin resistance defined as fasting blood sugar ≥100 mg/dl, or self-reported history of diabetes or taking medications.

NHANES III to avoid using decimal points. We reported CIIS values by dividing by 10. Subclinical myocardial injury (SC-MI) was defined as CIIS values ≥10 points [13, 14].

Measurement of other variables

Age (continuous in years), sex (male and female), race/ethnicity (non-Hispanic white, non-Hispanic black, Mexican American and other), income (<$20,000/year, >$20,000/year), smoking status (never, current, and former), leisure time physical activity (number of times engaged in physical activity in past month), were assessed by interview. Height was measured using a wall-mounted stadiometer, and weight was measured using a Toledo digital scale in minimal clothing. BMI was calculated from height and weight measurements. Waist circumference (WC) was measured at the iliac crest after a normal exhalation of breath. Diabetes was defined as a fasting plasma glucose ≥100 mg/dl, or previous use of diabetes-related medications. Blood pressure (mmHg) was measured three times during the in-home interview and three additional times during the participant's visit to the mobile examination center. Blood samples were collected via venipuncture by a phlebotomist. Samples were analyzed for total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), triglycerides (TG) and glucose, using laboratory procedures as reported by NCHS.

For the purpose of this analysis, we only considered NHANES III participants who underwent an ECG recording (n = 8561). We excluded participants with the history of CVD (myocardial infarction, heart failure, or stroke), or with electrocardiographic evidence of myocardial infarction or any major abnormalities on their electrocardiograms according to the Minnesota Code classification. We also excluded participants with cancer on chemotherapy and missing key covariates. After all exclusions (n = 2391), 6107 participants were included in the analysis.

Statistical analysis

Baseline characteristics were compared across four alcohol categories (Non-drinker, light drinker, moderate drinker, and heavy drinker). Continuous variables were reported as the mean and standard deviation (SD) while cate-

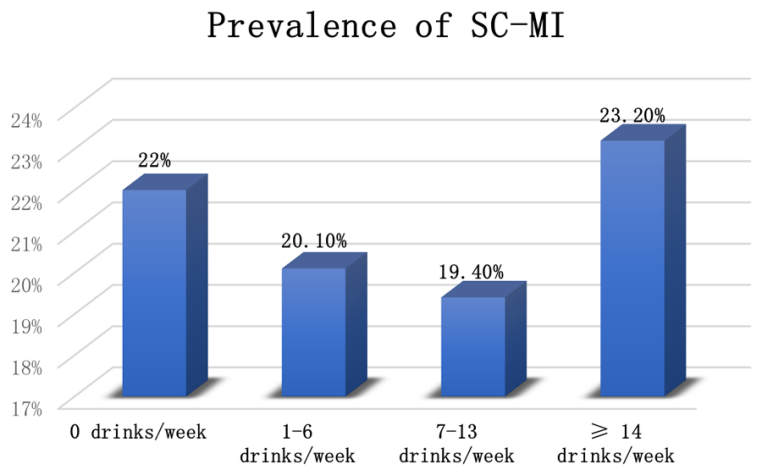

Figure 1. Prevalence of Subclinical Myocardial Injury Across Alcohol categories.

gorical variables were reported as frequency and percentage. Analysis of variance (ANOVA) was used to compare the continuous variables while Chi^2 was used to compare the categorical variables. We performed multivariable linear regression model with each alcohol categories as independent variable and CIIS as the outcome variable to calculate Beta-Coefficient and 95% CI. Model 1 was adjusted for age, sex, race and socioeconomic status and model 2 adjusted for model 1 plus smoking and physical activity, BMI, insulin resistance, hypertension, CRP, and HDL-cholesterol. Using multiple linear regression model, we also calculated least means square (LSMEANS) and standard error (SE) of CIIS across alcohol categories. Models were adjusted similarly as above.

Using multivariable linear regression analysis, we also conducted subgroup analysis stratified by age (using 65 years as a cut point), sex and race (whites vs. non-whites). Models were adjusted for age, sex, race, socioeconomic status, smoking, physical activity, BMI, insulin resistance, hypertension, CRP, and HDL cholesterol.

As an additional analysis, we used multivariable logistic regression analysis to compute odds ratios (OR) and 95% confidence interval (CI) for the cross-sectional association between each alcohol category (light drinkers, moderate drinkers, heavy drinkers, and non-drinkers (reference) and SC-MI. The models were adjusted for confounder as mentioned above.

All statistical analyses were performed using with SAS version 9.4 (SAS Institute Inc, Cary, NC) and *p*-values were considered significant if <0.05.

Results

Our analysis included 6090 participants (58.42±13.12 years, 54.2% women and 50.3% Non-Hispanic Whites). **Table 1** shows the characteristics of participants stratified by alcohol categories. Moderate and heavy drinkers were more likely to be young, male, white, current, and former smokers, high socioeconomic status, elevated SBP, elevated DBP and insulin resistance. Prevalence of SC-MI was 23.2%, 19.4%, 20.1%, and 22% for heavy drinkers, moderate drinkers, light drinkers, and non-drinkers respectively (**Figure 1**).

Using CIIS as continuous variable, in a linear regression model adjusted for demographics, moderate alcohol consumption was associated with lower values of CIIS compared with non-drinker (β (95% CI): -0.56 (-1.18, 0.05), P = 0.07) and this negative association of moderate alcohol consumption with CIIS did not change after adjustment for CVD risk factors and potential mediators (β (95% CI): 0.64 (-1.27, -0.007), P = 0.04). Light and heavy drinking were also associated with lower values of CIIS, but results were not statistically significant in models adjusted for demographics as well as in fully adjusted models (**Table 2**).

Using multiple linear regression analysis, we also calculated least mean square and standard error (SE) of association alcohol categories with CIIS. We found that never drinkers had the higher mean values of CIIS, while moderate drinkers had the lowest mean values of CIIS (**Table 3** and **Figure 2**).

In the subgroup analysis by age, sex, and race, we found heterogeneities in the association between alcohol categories and CIIS. Using linear regression analysis, in a fully adjusted model, females and older participants had lower values of CIIS compared to males, and

Table 2. Multivariable Beta-coefficient and 95% CI of association between alcohol categories and CIIS

Alcohol categories	Model 1		Model 2	
	Beta-Coefficient (95% CI)	*p-value*	*Beta-Coefficient (95% CI)*	*p-value*
0 drinks/week	*Reference*		*Reference*	
1-6 drinks/week	-0.20 (-0.58, 0.18)	0.30	-0.22 (-0.61, 0.17)	0.26
7-13 drinks/week	-0.56 (-1.18, 0.05)	0.07	0.64 (-1.27, -0.007)	0.04
≥14 drinks/week	-0.19 (-1.27, 0.89)	0.72	-0.37 (-1.47, 0.72)	0.50

Beta coefficient and 95% confidence interval calculated from a multivariable linear regression analysis. Model 1 adjusted for age, sex, race, and socioeconomic status. Model 2 adjusted for model 1 plus physical activity, smoking, BMI, HTN, insulin resistance, CRP and HDL. CIIS, cardiac injury score; CRP, C-reactive protein; HDL, high-density lipoprotein; BMI, body mass index. Hypertension defined as systolic blood pressure ≥130 mmHg or diastolic blood pressure ≥85 or taking antihypertensive medications. Insulin resistance defined as fasting blood sugar ≥100 mg/dl, or self-reported history of diabetes or taking medications.

Table 3. Least Mean Square and SE of CIIS across alcohol categories

Alcohol categories	Model 1	Model 2
	Mean ± SE	*Mean ± SE*
0 drinks/week	*5.32±0.11*	*5.34±0.11*
1-6 drinks/week	5.12±0.15	5.12±0.15
7-13 drinks/week	4.75±0.28	4.71±0.29
≥14 drinks/week	5.13±0.53	4.97±0.54

Least mean square and standard error calculated from multiple linear regression analysis. Model 1 adjusted for age, sex, race, and socioeconomic status. Model 2 adjusted for model 1 plus physical activity, smoking, BMI, HTN, insulin resistance, CRP and HDL. CIIS, cardiac injury score; CRP, C-reactive protein; HDL, high-density lipoprotein; BMI, body mass index; SE, standard error.

younger participants in all alcohol categories. However, there was no significant interaction by sex or age. Whites tend to have lower values of CIIS compared to non-whites, especially with moderate alcohol consumption (β (95% CI): -1.06 (-1.93, -0.19) vs. 0.05 (-0.91, 1.00) respectively. The interaction *p*-value was close to the level of significance (P = 0.08) (**Table 4**).

We also calculated OR and 95% CI for SC-MI entered in the models as binary outcome variable defined as CIIS ≥10. There was no significant association between alcohol consumption and SC-MI using logistic regression analysis. However, among alcohol categories, odds of SC-MI was lowest with moderate alcohol consumption (OR (95% CI): 0.79 (0.60-1.04), P = 0.29) (Table S1).

Discussion

In this nationally representative sample of 6090 participants free of CVD at baseline, we found statistically significant cross-sectional associations between moderate alcohol consumption (7-13 drinks/week) and low CIIS. This inverse association between moderate alcohol consumption and CIIS score persisted despite rigorous adjustment for confounders. Although light and heavy drinking were also associated with decreased CIIS score, this association was not statistically significant. Moderate alcohol consumption relative to non-drinkers was associated with lower CIIS score among whites and not among the non-white population. Moreover, the inverse association was much stronger among females and older population (>65 years) compared to men and young (<65 years) respectively.

Most of the previous studies have focused on examining the relationship between alcohol consumption and subclinical atherosclerosis using CAC or carotid intima-media thickness (c-IMT). Vliegenthart et al. [6] found a U-shaped association between alcohol consumption and coronary calcification while Pletcher et al. [7] discovered dose-response relation. A more recent study by Yun et al. [17] found that higher levels of alcohol consumption were associated with an increased risk of coronary calcification in Korean men. But most of the other epidemiological studies have found no association between alcohol use and CAC [8, 9, 11, 18]. The few studies evaluating the effect of alcohol consumption and c-IMT have also provided conflicting results [18-21]. Furthermore, its duplicated an analysis from the Atherosclerosis Risk in Communities (ARIC) study showed that compared to never drinkers, persons who consumed 2-7 drinks per week were less likely to have increased levels of high sensitivity troponin T assays, another measure of SC-MI [12]. To the best of our knowledge, there has not been

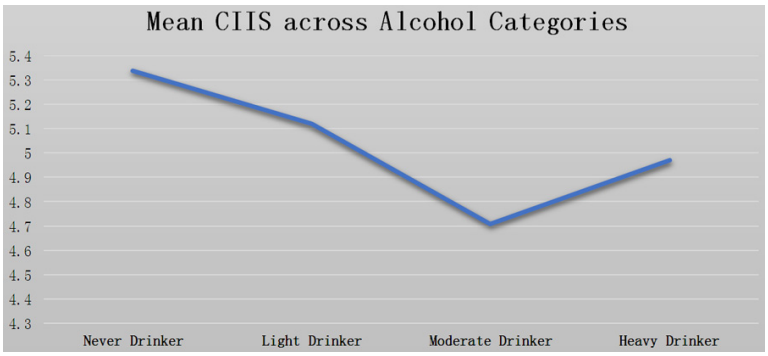

Figure 2. Least Mean Square (LSMEANS) of Cardiac Infarction/Injury Score (CIIS) Across Alcohol Categories after adjustment of all potential confounders.

Table 4. Multivariable beta coefficient and 95% CI for the association between Alcohol categories and CIIS in Subgroups

	Alcohol Categories	Beta-coefficient (95% CI)	Interaction *P*-value
Male	1-6 drinks/week	-0.04 (-0.62, 0.54)	0.68
	7-13 drinks/week	-1.47 (-1.00, 0.70)	
	≥14 drinks/week	-0.02 (-1.29, 1.24)	
Female	1-6 drinks/week	-0.45 (-0.98, 0.07)	
	7-13 drinks/week	-1.35 (-2.35, -0.36)	
	≥14 drinks/week	-1.51 (-4.16, 1.14)	
Whites	1-6 drinks/week	-0.45 (-1.02, 0.13)	0.08
	7-13 drinks/week	-1.06 (-1.93, -0.19)	
	≥14 drinks/week	-1.05 (-2.58, 0.48)	
Non-Whites	1-6 drinks/week	0.07 (-0.46, 0.59)	
	7-13 drinks/week	0.05 (-0.91, 1.00)	
	≥14 drinks/week	0.51 (-1.08, 2.10)	
Age >65 years	1-6 drinks/week	-0.77 (-1.65, 0.11)	0.45
	7-13 drinks/week	-1.47 (-2.76, -0.17)	
	≥14 drinks/week	0.47 (-1.93, 2.86)	
Age ≤65 years	1-6 drinks/week	-0.15 (-0.57, 0.26)	
	7-13 drinks/week	-0.42 (-1.14, 0.30)	
	≥14 drinks/week	-0.74 (-1.95, 0.47)	

Beta coefficient and 95% confidence interval calculated from a multivariable linear regression analysis. Reference group = 0 drinks/week. Model adjusted for Age, Sex, Race, Socioeconomic status, Smoking, Physical Activity, BMI, insulin resistance, Hypertension, high-density cholesterol, CRP. CIIS, cardiac injury score; CRP, C-reactive protein; HDL, high-density lipoprotein; BMI, body mass index. Hypertension defined as systolic blood pressure ≥130 mmHg or diastolic blood pressure ≥85 or taking antihypertensive medications. Insulin resistance defined as fasting blood sugar ≥100 mg/dl, or self-reported history of diabetes or taking medications.

a prior study linking alcohol consumption levels to SC-MI as measured by ECG scoring system such as CIIS in a relatively healthy cohort.

The mechanisms by which alcohol consumption may influence subclinical myocardial injury are not entirely clear. Several proposed mechanisms of alcohol that may explain its cardioprotective effect include increasing high-density lipoprotein (HDL) [3, 4], decreasing c-reactive protein [5], increasing NO release [22], decreasing platelet aggregation [23] and increasing insulin sensitivity [2, 24]. Our finding of moderate alcohol consumption having a protective association with SC-MI is consistent with existing evidence which suggests that moderate alcohol consumption is associated with decreased risk of CVD [1]. Our study showed the stronger inverse relationship between alcohol consumption and CIIS in the older population. As we can see from the potential mechanisms of the cardioprotective effects of alcohol, some effects are mediated through mechanisms that are not reflected by CIIS score. Hence, the protective effect of alcohol may differ in older individuals. Also, the finding of a strong association of alcohol consumption with lower CIIS score among female may suggest a more favorable dietary pattern that might have accentuated the protective effect of alcohol.

A large number of patients with SC-MI will be missed if abnormalities are examined separately. The application of CIIS has been shown to predict CVD and all-cause mortalities among a large group of persons without apparent CVD [14]. The application of CIIS in this study was to find individuals without clinical CVD but who were at an increased risk of CVD and all-cause mortalities. Other electrocardiographic markers which are also associated with increased mortality include QRS duration and minor

Q waves, but they only rely on 1 or 2 data points [25, 26]. In contrast, the application of a scoring system, such as CIIS may be a more sensitive indicator of myocardial injury. It has also been shown that the CIIS improves the accuracy of the standard 12-lead electrocardiogram to identify patients with SC-MI [15].

Our study has several limitations. Alcohol consumption was self-reported, and participants may have underreported heavy consumption. This would most likely have attenuated the associations. Also, there were relatively few heavy drinkers, which limited our ability to explore alcohol associations among this subset. Finally, we adjusted for several confounders, but residual confounding remains a possibility. Our study has many strengths. The strength of our study includes its large sample size, community-based and multiracial population and better generalizability of the US population. Also, we were able to adjust for many potential confounders and mediators including lifestyle variables and CVD risk factors.

In conclusion, moderate alcohol consumption was associated with lower CIIS. As lower CIIS is associated with decreased risk of CVD mortality, it is, therefore plausible that moderate alcohol consumption may be associated with low risk of poor future outcomes. We also observed heterogeneity in association of alcohol consumption with CIIS by age and sex, so these subgroup analyses should be considered exploratory and hypothesis generating. If these associations are causal, further research is needed to understand the mechanisms by which moderate alcohol consumption confers protection in these subgroups.

Disclosure of conflict of interest

None.

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Table S1. Multivariable odds ratio and 95% CI of association between alcohol categories and subclinical myocardial injury

Alcohol Categories	Model 1		Model 2		Model 3	
	Odds Ratio (95% CI)	*p-value*	*Odds Ratio (95% CI)*	*p-value*	*Odds Ratio (95% CI)*	*p-value*
0 drinks/week	*Reference*		*Reference*		*Reference*	
1-6 drinks/week	0.96 (083-1.11)	0.73	0.98 (0.83-1.15)	0.35	0.97 (0.82-1.14)	0.27
7-13 drinks/week	0.83 (0.65-1.04)	0.17	0.82 (0.63-1.07)	0.37	0.79 (0.60-1.04)	0.29
≥14 drinks/week	0.99 (0.67-1.47)	0.72	0.84 (0.54-1.32)	0.67	0.81 (0.51-1.27)	0.59

Model 1 adjusted for age, sex, race and socioeconomic status. Model 2 adjusted for model 1 plus smoking and physical activity, BMI. Model 3 adjusted for model 2 hypertension, insulin resistance, HDL, CRP. CRP, C-reactive protein; HDL, high-density lipoprotein; BMI, body mass index. Hypertension defined as systolic blood pressure ≥130 mmHg or diastolic blood pressure ≥85 or taking antihypertensive medications. Insulin resistance defined as fasting blood sugar ≥100 mg/dl, or self-reported history of diabetes or taking medications.