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Alcohol Consumption and Risk of Coronary Artery Disease (From The Million Veteran Program)

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Abstract

Moderate alcohol consumption has been associated with a lower risk of coronary artery disease (CAD) in the general population, but has not been well studied among U.S. Veterans. We obtained self-reported alcohol consumption from Million Veteran Program participants. Using the electronic health record, CAD events were defined as 1 inpatient or 2 outpatient diagnosis codes for CAD, or 1 code for a coronary procedure. We excluded participants with prevalent CAD (n=69,995) or incomplete alcohol information (n=8,449). We used a Cox Proportional Hazard model to estimate hazard ratios (HR) and 95% confidence intervals (CI) for CAD adjusting for age, sex, body mass index, race, smoking, education, and exercise. Among 156,728 participants, the mean age was 65.3 years (SD=12.1), and 91% were men. There were 6,153 CAD events during a mean follow-up of 2.9 years. Adjusted HRs (95% CI) for CAD were 1.00 (ref), 1.02 (0.92–1.13), 0.83 (0.74–0.93), 0.77 (0.67–0.87), 0.71 (0.62–0.81), 0.62 (0.51–0.76), 0.58 (0.46–0.74), and 0.95 (0.85–1.06) for categories of never, former, current drinkers of ≤0.5 drink/day, >0.5–1 drink/day, >1–2 drinks/day, >2–3 drinks/day, >3–4 drinks/day, and heavy drinkers (>4 drinks/day)/alcohol use disorder, respectively. For a fixed amount of ethanol, intake at ≥3 days/week was associated with lower CAD risk compared to ≤1 day/week. Beverage preference (beer,

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Disclosures

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wine, liquor) did not influence the alcohol-CAD relation. Our data show a lower risk of CAD with light-to-moderate alcohol consumption among U.S. Veterans, and drinking frequency may provide a further reduction in risk.

Keywords

alcohol consumption; epidemiology; coronary artery disease

Cardiovascular disease (CVD) remains the leading cause of death among men and women in the United States and projections of CVD will increase approximately 18% by 2030.[1] Modifiable lifestyle factors such as a healthy diet and exercise have been suggested to lower CVD risk.[2,3] While previous studies have shown that light-to-moderate alcohol consumption is also associated with a lower risk of CVD[4–8] in the general population, there are currently no data available on the relation of moderate alcohol intake with coronary artery disease (CAD) among U.S. Veterans. Few studies have assessed the impact of drinking patterns of moderate amounts of alcohol and beverage preference (beer, wine, or liquor) on CAD risk. Thus, the primary objective of this project was to assess the association between moderate alcohol consumption and incidence of CAD in U.S. Veterans with a focus on drinking patterns and influence of alcoholic beverage preference among light-to-moderate drinkers.

Methods

The Million Veteran Program (MVP) is an ongoing observational cohort study that began in 2011 designed to study genetic and non-genetic determinants of chronic diseases among U.S. Veterans. A detailed description of MVP has been previously published.[9] Each participant provided informed consent, and the Veterans Affairs Central Institutional Review Board approved the study protocol. The current analysis included 235,172 participants who completed a baseline and lifestyle survey. The final sample size consisted of 156,728 U.S. Veterans after exclusion of 69,995 participants with prevalent CAD (defined using ICD-9/10 or CPT code), and 8,449 participants who self-reported current drinking, but did not complete the alcohol questions of the Food Frequency Questionnaire (FFQ).

Alcohol intake was self-reported using the FFQ from the MVP lifestyle survey. Participants were asked to report their average consumption of beer (1 glass, bottle, can), wine (4 oz.), and liquor (1 drink or shot) over the past year. The possible response categories were “Never or less than once per month,” “1–3/month,” “1/week,” “2–4/week,” “5–6/week,” “1/day,” “2–3/day, “4– 5/day,” and “6+/day.” The response categories were converted to reflect drinks of beer, wine, or liquor per day. Total grams (g) of ethanol per day were derived by multiplying the average alcohol content in each beverage by the total number of drinks consumed in a day. We assumed 12 g of ethanol for a 12 oz. beer; 13 g of ethanol for 4 oz. of wine; and 15 g of ethanol for 1.5 oz. of liquor.[10] A standard drink was defined as 12 g of ethanol and moderate drinkers were defined as subjects consuming 1–2 drinks/day for men and 1 drink/day for women.[11] Beverage preference (beer, wine, or liquor) was assigned to the type of a single beverage that provided >50% of total ethanol among light to moderate drinkers; otherwise participants were classified as having no preference. Participants with alcohol use disorder (AUD) were classified if there was any record of ICD-9 diagnosis codes

303.0 or 305.0 or ICD-10 diagnosis codes F10.10, F10.20, F10.21, or F10.229 in the electronic health record. Heavy drinkers were classified if participants reported >48 g/day on the survey. We used total ethanol to create the following exposure categories: never drinkers, former drinkers, current drinkers of ≤6 g/day, >6–12 g/day, >12–24 g/day, >24–36 g/day, >36–48 g/day and heavy drinkers (>48 g/day)/AUD.

For quality control, we selected 1,500 surveys and manually verified accuracy between scanned responses from the data set and reported responses on the survey forms. If multiple responses on the FFQ were checked for the same alcohol question, we took the lower marked answer to be more conservative. If a participant reported drinking one type of beverage on the FFQ but left the other types of alcoholic beverage questions blank, we assumed that they did not consume those types of beverage.

Incident CAD was defined using ICD-9 and ICD-10 diagnosis and procedure codes in the participant's electronic health records. Record of 1 inpatient or 2 outpatient ICD-9 diagnosis code, 410–411.9, 413–414.9 or ICD-10 diagnosis code I20.0- I25.9, or 1 procedure code of ICD-9 procedure code 36.00–36.99 or 0.66, CPT code 33510–33536, 9292x, 9293x, 9294x, 92973, 92974, and 92975 was considered a CAD event.

Self-reported height and weight were used to compute body mass index (BMI). Cigarette smoking, education, exercise frequency, prevalent high cholesterol, hypertension, and diabetes mellitus were also collected from the baseline survey. The patient's electronic health record was used to obtain date of birth and sex if such information was missing from the baseline survey.

Person-time of follow up was computed from the scan date of the lifestyle survey to the date of first occurrence of CAD event, death, or May 31, 2017 as the end of follow-up. A Cox proportional hazard model was used to estimate crude and adjusted hazard ratios and 95% confidence intervals for CAD. We built sequential models based on a priori knowledge of potential confounders. After the crude model, the second model controlled for age and the fully adjusted model adjusted for age (continuous), sex, white race, BMI (continuous), education (high school or less, some college, and college degree or more), exercise frequency (<1 time/wk, 1 time/wk, 2–4 times/wk, and ≥5 times/wk), and smoking (never, former, and current). We examined the shape of the alcohol-CAD relation non-parametrically using restricted cubic splines among current drinkers.[12] For the spline regression, we assigned the median ethanol amount among heavy drinkers (62.5 g) to those with AUD. We used never drinkers as the reference group and placed knots at 12, 24, and 36 g/day. Proportional hazards assumptions were tested and were met (all $p>0.05$). All analyses were completed using SAS version 9.4 and SAS Enterprise Guide version 7.1.

Results

The mean age was 65.3 ± 12.1 years and 91% of subjects were men (Table 1). A total of 6,153 incident CAD events occurred during an average follow-up time of 2.9 years. In the multivariable adjusted Cox regression model, we observed a U-shaped relation between alcohol consumption and incident CAD (Table 2). Using restricted cubic splines, we showed

a non-linear relation between alcohol intake and CAD risk among never and current drinkers (Figure 1, p for non-linearity <0.001). We observed similar findings when stratified by sex (p interaction of sex and alcohol drinker =0.51, Figure 2) and by race (p interaction of race and alcohol drinker=0.17, Figure 2). In a sensitivity analysis using light drinkers (≤6 g/day) as the reference group, we observed a 15% lower risk of CAD among those who consume >12–24g/day (supplemental Table 1). We conducted another sensitivity analysis to verify never drinker status using the Alcohol Use Disorders Identification Test (AUDIT-C) responses from the participant's electronic health record closest to the lifestyle survey date. Among 11,907 self-reported never drinkers, 10,832 had an AUDIT-C available and 10,045 (92.7%) were concordant with the self-reported never drinker status. After removing those with discordant AUDIT-C responses, adjusted HR (95%CI) were similar to the results in the primary analysis (data not shown).

In the analysis examining alcohol drinking pattern among light to moderate drinkers, we found evidence in support of lower risk of CAD with high frequency of intake when the amount of ethanol was fixed. For a fixed amount of ethanol, we observed a further reduction in risk if alcohol was consumed ≥4 days/week compared to never drinkers (Table 3). Lastly, beverage preference did not influence the alcohol-CAD relation (Table 4).

Discussion

Our study found a lower risk of CAD with light-to-moderate alcohol consumption. Furthermore, for a fixed amount of ethanol of up to 48 g, the number of days per week that alcohol was consumed was inversely associated with CAD risk. Alcohol preference (beer, wine, liquor) did not influence the observed alcohol-CAD relation among light to moderate drinkers. Our findings among U.S. Veterans are consistent with other large cohort studies that found a reduction in CAD risk with light-to-moderate alcohol consumption[13–16] and also suggest that frequency of consumption is important in reducing CAD risk.

Previous studies suggest that for a given amount of ethanol, higher frequency of drinking per week (that is spreading alcohol intake ≥3 days/week) may provide a greater benefit for CAD risk than irregular or binge drinking.[17,18] Findings from the Nurses' Health Study and the Health Professionals Follow-Up Study were also consistent with beneficial effects of drinking frequency for a fixed amount of alcohol.[19,20] Our data also suggests that heavy drinking or alcohol use disorder is associated with a higher risk of CAD compared to light drinkers. Studies have shown that the benefit of moderate alcohol consumption can be reversed if consumed in heavy episodic amounts or when binge drinking.[21]

Data in the literature have been inconsistent on the role of beverage type, specifically, whether wine has an advantage over beer or spirits on CAD risk. "The French Paradox" refers to the lower incidence of CAD in France compared to other developed nations, despite consumption of a diet higher in saturated fat; it has been hypothesized that higher consumption of red wine in France might explain the French paradox.[22] The Cardiovascular Health Study reported similar HRs (95% CI) for intake of wine [0.70 (0.44–1.11)], beer [0.71 (0.43–1.19)], and liquor [0.89(0.61–1.30)] and CAD risk when participants drank ≥7 drinks per week. Furthermore, a systematic review of 25 studies did not find a consistent

pattern of a specific beverage type and a lower risk of CAD.[23] Thus, the observed lower risk of CAD may be from ethanol and not from non-ethanol components of alcoholic beverages, such as polyphenols found in red wine.

Several biologic mechanisms have been proposed to explain the causal association between ethanol and CAD risk. Alcohol has been shown to raise high-density lipoprotein cholesterol and apolipoprotein A-I, which are inversely associated with the risk of CAD, and lower the concentration of fibrinogen.[24,25] Ethanol can also affect levels of endothelial cell activity, prevent platelet aggregation and reactivity.[26] Alcohol consumption may also influence atherosclerotic plaque composition and provide stabilizing benefits.[27] Furthermore, there are consistent findings that moderate alcohol consumption improves insulin sensitivity and lowers the risk of Type 2 Diabetes, a risk factor of CAD.[28]

There are limitations to our study. Alcohol consumption was collected through self-report and misclassification of alcohol could have biased our results. There was a small proportion of participants with an AUD diagnosis in each self-reported alcohol consumption category (3% among never drinkers), suggesting underreporting of actual drinking habits. Such misclassification would have resulted in an underestimation of the true effect of light-to-moderate consumption if heavy drinking is associated with a higher CAD risk. Additionally, we removed never drinkers with discordant AUDIT-C responses in our sensitivity analysis, and consumption of light to moderate amounts was still associated with a lower risk of CAD compared to never drinkers. We excluded participants who self-reported as a current drinker, but did not complete the FFQ which was needed to compute total grams of ethanol. If those excluded were different from people included with respect to alcohol consumption and CAD, selection bias would have been introduced in our results. However, when all current drinkers were combined and compared to never drinkers, the HR (95%CI) for CAD was 0.79 (0.72–0.87) (data not shown). Our inability to update alcohol intake over time in this cohort could have led to further misclassification of exposure. Additionally, our follow-up time was short (<5 years), thereby limiting adequate lag time to alcohol exposure and assessment of long-term effects. However, it is reasonable to assume that people tend to maintain their lifestyle habits including drinking patterns over time in the absence of major new diseases.[29] We did not have information to distinguish between fatal and non-fatal CAD events in our analyses. However, studies have reported a lower risk of both fatal and non-fatal CAD with moderate alcohol intake.[7] Our population was predominantly men and white; nonetheless, we had enough data to show similar alcohol-CAD relation in women and African-Americans, albeit with limited precision. Despite these limitations, our study has numerous strengths including a large sample size to examine drinking patterns, adequate number of CAD events for sub-analyses, ability to control for several confounding factors, robustness of our data to sensitivity analyses, and access to the electronic health record.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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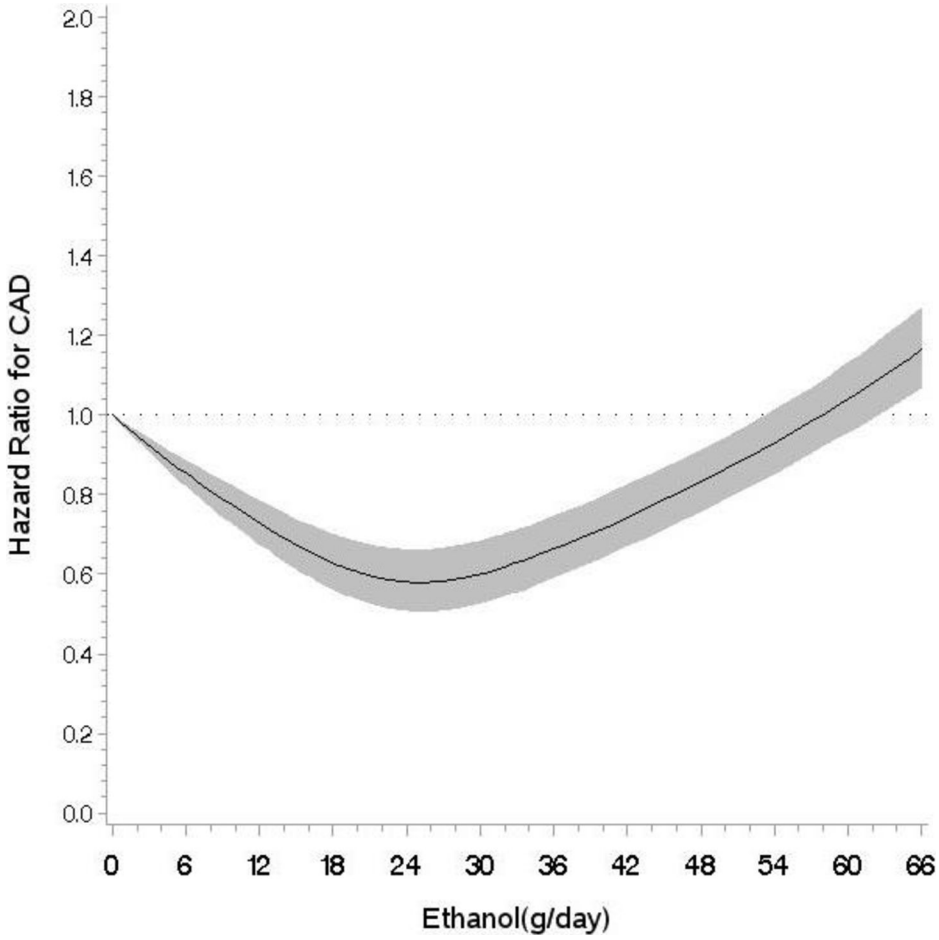

Figure 1.

Spline regression of ethanol (g/day) intake and hazard ratios (95%CI) for coronary artery disease, adjusted for age, body mass index, sex, education, exercise, white race. Knots are placed at 12, 24, and 36 grams/day.

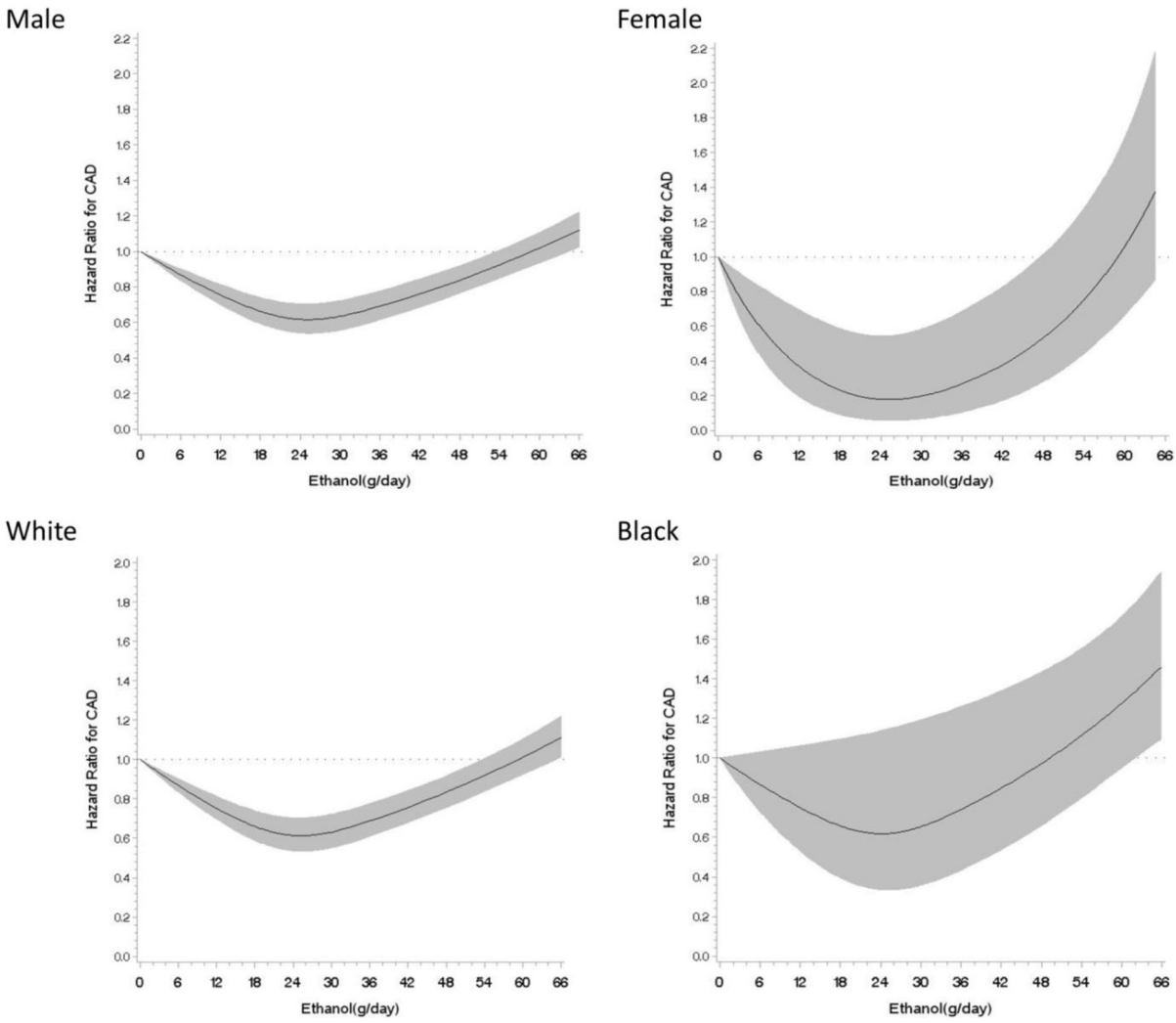

Figure 2.

Spline regression of ethanol (g/day) intake and hazard ratios (95%CI) for coronary artery disease stratified by sex and stratified by white and black race, adjusted for age, body mass index, white race, and education. Knots are placed at 12, 24, and 36 grams/day for both stratified spline regressions.

Table 1.

Characteristics of 156,728 Million Veteran Program participants by alcohol consumption

Characteristic	Never drinkers	Former drinkers	Current drinker of ≤6 g/day	>6–12 g/day	>12–24 g/day	>24–36 g/day	>36–48 g/day	AUD & heavy drinker
	(n=11,871)	(n=48,132)	(n=31,668)	(n=14,820)	(n=12,559)	(n=4,633)	(n=3,005)	(n=30,040)
Age (years)	67.2 ± 12.5	65.9 ± 11.4	63.0 ± 13.0	64.9 ± 12.3	67.3 ± 12.8	67.3 ± 11.0	68.5 ± 10.8	61.1 ± 10.7
Body mass index (kg/m^2)	28.9 ± 5.9	29.4 ± 5.9	29.2 ± 5.3	28.4 ± 4.8	27.9 ± 4.6	27.4 ± 4.5	27.9 ± 4.5	28.4 ± 5.4
Men	86%	91%	87%	93%	94%	95%	97%	93%
White	81%	84%	86%	89%	92%	94%	94%	78%
Black	14%	13%	10%	8%	6%	4%	5%	18%
American Indian	3%	4%	3%	3%	2%	2%	2%	4%
Asian	2%	1%	1%	1%	1%	0.5%	0.4%	0.8%
Pacific Islander	0.2%	0.2%	0.2%	0.2%	0.1%	0.0%	0.1%	0.2%
Other	3%	3%	3%	2%	1%	2%	1%	4%
Education								
≤High school	27%	31%	19%	18%	13%	19%	14%	31%
Some college	36%	42%	40%	39%	32%	35%	34%	45%
≥College degree	37%	27%	41%	43%	55%	46%	52%	24%
Hypertension	57%	60%	52%	52%	53%	56%	62%	59%
Diabetes mellitus	27%	29%	19%	15%	13%	12%	14%	18%
“High” cholesterol	49%	54%	51%	51%	51%	53%	55%	48%
Exercise Frequency (times/wk)								
<1	42%	45%	37%	31%	29%	32%	34%	47%
1	13%	13%	14%	15%	14%	13%	13%	14%
2–4	28%	27%	35%	38%	40%	36%	36%	26%
≥5	17%	15%	14%	16%	17%	19%	17%	14%
Smoker								
Never	68%	25%	38%	31%	29%	22%	20%	16%
Former	27%	64%	54%	61%	65%	69%	73%	57%
Current	4%	11%	8%	8%	6%	9%	7%	27%

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* Data presented as mean ± standard deviation or percentage.

† Missing data on body mass index (n=4,706), race (n=453), education (n=2,048), exercise (n=2,292)

Table 2.

Incidence rate and hazard ratios (95% CI) for coronary artery disease by alcohol consumption

Alcohol Consumption	CAD Events	Crude Incidence Rate per 1,000 person-years	Crude Hazard Ratio and 95% CI	Adjusted Hazard Ratio[1] and 95% CI
Never drinkers	509	14.5	1.00 (ref)	1.00 (ref)
Former drinkers	2,325	16.6	1.14 (1.04–1.26)	1.02 (0.92–1.13)
Alcohol Consumption (g/day)				
≤6	1,051	11.6	0.79 (0.71–0.88)	0.83 (0.74–0.93)
>6–12	480	11.4	0.78 (0.69–0.88)	0.77 (0.67–0.87)
>12–24	497	13.6	0.74 (0.65–0.85)	0.71 (0.62–0.81)
>24–36	130	9.8	0.67 (0.55–0.81)	0.62 (0.51–0.76)
>36–48	84	9.6	0.66 (0.53–0.83)	0.58 (0.46–0.74)
AUD/heavy drinkers	1,252	14.0	0.96 (0.87–1.06)	0.95 (0.85–1.06)
P for trend			<0.001	0.002

[1] Adjusted for age (continuous), sex, body mass index (continuous), smoking, exercise, education, white race

Table 3.

Adjusted hazard ratios (95% CI) by alcohol drinking pattern and fixed total ethanol consumption

Ethanol Consumed (g)	Number of Days/week Alcohol Consumed				
	0	≤1	2–3	4–5	6–7
0	1.00 (ref)				
>0–6		0.84 (0.74–0.94)	0.82 (0.67–1.01)	0.68 (0.41–1.14)	0.72 (0.34–1.52)
>6–12		0.86 (0.72–1.02)	0.76 (0.6–0.90)	0.74 (0.56–0.96)	0.45 (0.27–0.73)
>12–24		0.74 (0.55–0.98)	0.69 (0.56–0.85)	0.67 (0.54–0.83)	0.72 (0.58–0.90)
>24–48		0.72 (0.40–1.31)	0.64 (0.45–0.90)	0.59 (0.45–0.78)	0.59 (0.47–0.74)

*Adjusted for age (continuous), sex, body mass index (continuous), smoking, exercise, education, white race

Table 4.

Incidence rate and hazard ratios (95% CI) for coronary artery disease by beverage preference among light and moderate drinkers

Preferred Alcoholic beverage	CAD Events	Crude Incidence Rate per 1,000 person-years	Crude Hazard Ratio and 95% CI	Adjusted Hazard Ratio[1] and 95% CI
Never drinker	532	15.2	1.00 (ref)	1.00 (ref)
No preference	323	10.9	0.72 (0.63–0.83)	0.76 (0.65–0.89)
Preferred beer	653	11.3	0.74 (0.66–0.83)	0.74 (0.65–0.84)
Preferred wine	678	11.7	0.78 (0.70–0.88)	0.83 (0.73–0.94)
Preferred spirits	567	12.2	0.81 (0.72–0.91)	0.76 (0.67–0.87)

[1] Adjusted for age (continuous), sex, body mass index (continuous), smoking, exercise, education, white race