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Association of alcohol consumption and aortic calcification in healthy men aged 40–49 years for the ERA JUMP Study

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AUTHORS CONTRIBUTIONS

HM designed the research question, analyzed, and interpreted the data, drafted the manuscript. K Masaki, BW, K Miura, AF, TH, TO, HU, RE, and EB-M collected the data and critically reviewed the manuscript for important intellectual content. AV, VA, JC, CS, JG, and SS critically reviewed the manuscript for important intellectual content. LK designed the research question, collected the data, and critically reviewed the manuscript for important intellectual content. AS designed the research question, analyzed, and interpreted the data, drafted the manuscript, critically reviewed the manuscript for important intellectual content, provided administrative and material support. HM and AS have full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Conflict of Interest

The authors declared they do not have anything to disclose regarding conflict of interest with respect to this manuscript.

We wish to confirm that there are no known conflicts of interest associated with this publication and there has been no significant financial support for this work that could have influenced its outcome.

We confirm that the manuscript has been read and approved by all named authors and that there are no other persons who satisfied the criteria for authorship but are not listed. We further confirm that the order of authors listed in the manuscript has been approved by all of us. We confirm that we have given due consideration to the protection of intellectual property associated with this work and that there are no impediments to publication, including the timing of publication, with respect to intellectual property. In so doing we confirm that we have followed the regulations of our institutions concerning intellectual property.

We understand that the Corresponding Author (Dr. Hemant Mahajan, email: hdm12@pitt.edu) is the sole contact for the Editorial process (including Editorial Manager and direct communications with the office). He is responsible for communicating with the other authors about progress, submissions of revisions and final approval of proofs. We confirm that we have provided a current, correct email address which is accessible by the Corresponding Author and which has been configured to accept email from.

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Abstract

Background and aims—Several studies have reported a significant inverse association of light to moderate alcohol consumption with coronary heart disease (CHD). However, studies assessing the relationship between alcohol consumption and atherosclerosis have reported inconsistent results. The current study was conducted to determine the relationship between alcohol consumption and aortic calcification.

Methods—We addressed the research question using data from the population-based ERA-JUMP Study, comprising of 1006 healthy men aged 40-49 years, without clinical cardiovascular diseases, from four race/ethnicities: 301 Whites, 103 African American, 292 Japanese American, and 310 Japanese in Japan. Aortic calcification was assessed by electron-beam computed tomography and quantified using the Agatston method. Alcohol consumption was categorized into four groups: 0 (non-drinkers), ≤1 (light drinkers), >1 to ≤3 (moderate drinkers) and >3 drinks per day (heavy drinkers) (1 drink=12.5 grams of ethanol). Tobit conditional regression and ordinal logistic regression were used to investigate the association of alcohol consumption with aortic calcification after adjusting for cardiovascular risk factors and potential confounders.

Results—The study participants consisted of 25.6% nondrinkers, 35.3% light drinkers, 23.5% moderate drinkers, and 15.6% heavy drinkers. Heavy drinkers [Tobit ratio (95% CI) = 2.34 (1.10, 4.97); odds ratio (95% CI) = 1.67 (1.11, 2.52)] had significantly higher expected aortic calcification score compared to nondrinkers, after adjusting for socio-demographic and confounding variables. There was no significant interaction between alcohol consumption and race/ethnicity on aortic calcification.

Conclusions—Our findings suggest that heavy alcohol consumption may be an independent risk factor for atherosclerosis.

Keywords

Alcohol; Aorta; Atherosclerosis; Calcification; Men

INTRODUCTION

Although a J-shaped association has been very well established between alcohol consumption and coronary heart disease (CHD)[1], with light to moderate drinkers showing a reduced risk compared to both heavy drinkers and nondrinkers, the underlying pathophysiological mechanisms remain to be elucidated. Plausible mechanisms for the protective effect of moderate alcohol consumption on CHD include: increase in high-density lipoprotein cholesterol (HDL-C), lower inflammation, anticoagulant effect (inhibition of the fibrinolytic system), improved endothelial function, and a reduced risk of type 2 diabetes mellitus[2–5]. Studies assessing the relationship between alcohol use and atherosclerosis (the major underlying cause of CHD[6]) reported conflicting results: no significant association[7, 8],

a U or J-shaped association[9–12], and a dose-response association[13–15]. The reason for these inconsistent results is not clear. To investigate the relationship between alcohol and atherosclerosis may help clarify the mechanisms underlying the association between alcohol and CHD.

Aortic calcification, a reliable and validated biomarker of atherosclerosis, is independently associated with cardiovascular morbidity and mortality[16, 17] and has a high specificity for detection of severe coronary atherosclerosis[18]. Aortic calcification is a less commonly used measure of atherosclerosis compared to coronary artery calcification (CAC) which is a well-established biomarker of coronary atherosclerosis. Some studies have reported that aortic calcification may be a better measure of atherosclerosis than CAC because it is more prevalent, has an earlier onset[19], has a better association with cardiovascular risk factors[16, 20, 21], and seems to add prognostic information of atherosclerotic burden beyond CAC[16, 20]. However, unlike CAC, studies examining the relationship between alcohol consumption and aortic calcification are scarce[10, 13, 19]. Moreover, the available results are inconsistent partly because of variability in studied populations, aortic segment examined, imaging modalities, and scoring method used, which avert an unbiased comparison across different populations[13, 19, 22].

Our objective is to determine the relationship between alcohol consumption and aortic calcification measured in asymptomatic men aged 40-49 years, using data from the ERA-JUMP Study (the Electron Beam Computed Tomography (**E**BCT), **r**isk factor **a**ssessment among **J**apanese and the United States (**U**S) **m**en in the **p**ost-World-War-II birth cohort). Based on our previous finding of a J-shaped association between alcohol consumption and CAC among Japanese in Japan[23], as well as following the notion of a J-shaped association between alcohol consumption and CHD, we hypothesized that light to moderate alcohol consumption would have an inverse association, and heavy alcohol consumption would have a positive association with aortic calcification. To our knowledge, this is the first population-based study exploring the association of alcohol consumption and aortic calcification among asymptomatic middle-aged men across different races/ethnicities, from various countries, in a standardized manner.

MATERIALS AND METHODS

Study population

The details of the study protocol have been described previously[24]. Briefly, during 2002–2006, a population-based sample of 1033 men aged 40–49 years, with no clinical cardiovascular diseases (CVD) or other severe illnesses, was obtained from 3 centers: 310 White and 107 Black from Pittsburgh, Pennsylvania, US; 303 Japanese American from Honolulu, Hawaii, US; and 313 Japanese from Kusatsu City, Shiga, Japan[24, 25]. The study protocol followed ‘the 1975 Declaration of Helsinki ethical guidelines’. The Institutional Review Boards of University of Pittsburgh, Pittsburgh, US; Kuakini Medical Center, Honolulu, Hawaii, US; Shiga University of Medical Science, Otsu, Japan approved the study. Written informed consent was obtained from all participants. We excluded participants with missing data for aortic calcification (n=27). Our final sample size was

1006, with 301 US White, 103 US Black, 292 Japanese American, and 310 Japanese in Japan.

Risk factor assessment

All participants underwent a physical examination, completed a lifestyle questionnaire, and a laboratory, as described previously[24, 25]. Data collection procedures were standardized across all centers. Body weight and height were measured while the participant was wearing light clothing without shoes. Body Mass Index (BMI) was calculated as weight (kg) divided by the square of the height (m^2). Blood pressure and heart rate were measured after the participant emptied his bladder and sat quietly for 5 min. Blood pressure was measured twice on the right arm with an automated sphygmomanometer (BP-8800, Colin Medical Technology, Komaki, Japan) using an appropriately sized cuff; average of the two measurements was used. Hypertension was defined as systolic blood pressure ≥140 mmHg and/or diastolic blood pressure ≥90 mmHg or use of antihypertensive medications[26]. Participants were considered smokers if they reported current use of cigarettes or had stopped smoking within the past 30 days. Pack-years of smoking were calculated as years of smoking multiplied by the number of cigarettes per day divided by 20. Use of medications (antihypertensive, antidiabetic, and lipid-lowering) was reported as 'yes/no'. Meat intake was defined as individuals who ate beef, pork, or sausage ≥2 times per week. Physical activity related to the current job was self-reported and categorized into sedentary, light, medium, and heavy physical activity[27].

Venipuncture was performed early in the clinic visit after a 12-h fast. Blood samples were stored at −70°C and shipped on dry ice from all the centers to the University of Pittsburgh. Serum lipids were determined using the protocol standardized by the Centers for Disease Control and Prevention, including total cholesterol, HDL-C, and triglycerides[28]. Low-density lipoprotein cholesterol (LDL-C) was estimated by the Friedewald equation[29]. When the value of triglycerides exceeded 4.52 mmol/l (400 mg/dl), LDL-C was measured directly using an automated spectrophotometric assay [LDL Direct Liquid Select (Equal Diagnostics, Exton US)]. Serum glucose was determined by using hexokinase-glucose-6-phosphate-dehydrogenase enzymatic assay. Diabetes was defined as individuals with fasting glucose ≥7.0 mmol/l or use of medications for diabetes[30]. C-reactive protein (CRP) was determined using a calorimetric-competitive-enzyme-linked-immuno-sorbent assay, and fibrinogen was determined using an automated-clot-rate assay (Diagnostica Stago, Parsippany, U.S.)

Alcohol consumption assessment

The drinking habits of each subject were assessed by a validated self-administered questionnaire[31]. Alcohol consumption was assessed by asking whether the participant drank beer, wine, liquor, sake (Japanese rice wine), or other alcoholic beverages. Alcoholic status of the study participants was decided as never drinker (lifetime abstainers), former drinkers, and current drinkers. Among current drinkers, alcohol consumption per day was estimated assuming that the concentration of alcohol was 5% for beer, 12% for wine, 40% for liquor, and 16% for sake. Current alcohol drinkers were further categorized into three groups: 'light drinkers' (≤1 drink), 'moderate drinkers' (>1 to ≤3 drinks), and 'heavy drinkers' (>3 drinks) per day, with one drink, equaled to 12.5 grams of alcohol[32] [which is approximately

equivalent to 350 ml (12 oz) of regular beer, 150 ml (one glass) of wine, 45 ml of distilled spirits, and 110 ml of sake]. Former alcohol drinkers were combined with never drinkers (lifetime abstainers) and were together considered as 'nondrinkers.'

Aortic calcification assessment

EBCT was performed using a GE-Imatron C150 Electron Beam Tomography scanner (GE Medical Systems, South San Francisco, US) at the three center sites, using standardized methods as described previously[33, 34]. The scanner was set to acquire 6 mm images from the aortic arch to the iliac bifurcation to evaluate aortic calcification. Technicians regularly calibrated scanners following a standardized protocol. All scan data were saved to optical disc. Readings of the scans were done centrally in the Cardiovascular Institute, University of Pittsburgh, using a DICOM (Digital Imaging and Communications in Medicine) workstation and software by AccuImage (AccuImage Diagnostic Cooperation, San Francisco, US). The software program implemented the widely accepted Agatston scoring method[35]. One trained radiology technician evaluated the readings. The reader was blinded to each participant's characteristics and the study centers. The intra-reader reproducibility of non-zero Agatston Aortic Calcification Score (AoCaS) had an intra-class correlation of 0.98.

Statistical analysis

Distributions of triglycerides, years of education, and pack-years of smoking were highly skewed and therefore log transformed. Continuous variables with approximately normal distributions (age, BMI, LDL-C, and HDL-C) were standardized. Across the different categories of alcohol consumption and AoCaS: (i) age and race/ethnicity adjusted BMI, LDL-C, and HDL-C were expressed as means ± standard error (SE), (ii) age and race/ethnicity adjusted triglycerides, number of education years, and pack-years of smoking were expressed as a median and interquartile range, (iii) age and race/ethnicity adjusted categorical variables were expressed in percentages. A *p*-value for trend across the different categories of alcohol consumption and AoCaS was determined either using linear regression when a response variable is continuous, or using quartile regression when a response variable is skewed, continuous or logistic regression when a response variable is categorical.

We used Tobit conditional regression and ordinal logistic regression to model the association of alcohol consumption and aortic calcification adjusting for potential confounders and intermediary variables. We considered Tobit conditional regression because it is suited to the uncommon distribution of AoCaS data (right sided skewness and many participants with zero scores)[36, 37]. For Tobit conditional regression, outcome variable aortic calcification was log transformed after addition of one [ln (AoCaS + 1)]. "Tobit conditional regression is a combination of two regression approaches: a logistic regression of the presence of aortic calcification (AoCaS = 0 vs. AoCaS >0) and a linear regression of log-transformed aortic calcification when AoCaS >0[38]. The combination of two regression approaches provides a single point estimate for the relationship of predictors with aortic calcification. Secondarily, we also performed the ordinal logistic regression to assess the likelihood of study participants being in a higher category of AoCaS. Four AoCaS categories used were: 0, 1-99, 100-299 and ≥300. Model I was adjusted for sociodemographic variables (age, race/ethnicity, and years of education); Model II was further adjusted for potential confounders

(pack-years of smoking, BMI, diabetes, lipid-lowering medications, physical activity related to current job, meat intake, LDL-C, and CRP); Model III was additionally adjusted for intermediary variables (hypertension, HDL-C, triglycerides, and fibrinogen) in the relation between alcohol consumption and atherosclerosis/CHD. In Model III, we tested the interaction between race/ethnicity and alcohol consumption on aortic calcification. To minimize the possibility of residual confounding, the inclusion of variables in regression models was based on the published literature on alcohol and atherosclerosis/CHD. In Tobit regression, as well as in ordinal regression, a *p*-value for linear and quadratic trend across different categories of alcohol consumption was calculated using contrast.

We also conducted the race/ethnicity stratified analysis because including the term 'race' in a multivariable model may not have provided adequate adjustment for race/ethnicity differences. In addition, the inclusion of former drinkers and lifelong abstainers into the nondrinker group could have substantially increased the adverse effect of alcohol consumption among nondrinkers, we repeated the analysis by excluding former drinkers from the non-drinker category.

All *p*-values were two-tailed and a *p*-value <0.05 was considered as significant. SAS version 9.4 (SAS Institute, Cary, North Carolina) and STATA version 14.0 (StataCorp LP, College Station, TX, US) were used for all statistical analyses.

RESULTS

Overall as well as by race/ethnicity, baseline characteristics are presented in Table 1. We included 1006 study participants in our final analyses. The mean (SD) age of the study participants was 45.3 (2.8) years. Study participants consisted of 25.6% nondrinkers [16.5% never drinkers + 9.1% former drinkers], 35.3% light drinkers, 23.5% moderate drinkers, and 15.6% heavy drinkers. Overall, 56.9% study participants had AoCaS >0.

Table 2 describes the age and race/ethnicity adjusted demographic and clinical characteristics of participants across the alcohol consumption categories. Compared to nondrinkers, alcohol consumers had a lower age, BMI, anti-lipid medication use, rate of diabetes, CRP, and fibrinogen; and a higher AoCaS, HDL-C, and pack-years of smoking.

As shown in Table 3, except for HDL-C, compared to the no AoCaS category, participants with AoCaS >0 had a higher age and race/ethnicity adjusted BMI, pack-years of smoking, LDL-C, triglycerides, rate of diabetes, rate of hypertension, lipid-lowering medication use, CRP, and fibrinogen.

The Tobit regression analysis showed that in Model II, heavy drinkers had a significantly higher expected AoCaS [TR (95% CI) = 2.34 (1.10, 4.97)] compared to nondrinkers. In Model II, moderate drinkers appeared to have an inverse association with aortic calcification [TR (95% CI) = 0.86 (0.45, 1.66)], but this association was statistically nonsignificant. In Model III, with further adjustment for potential mediators in the relationship between alcohol and atherosclerosis/CHD, a significant association of heavy drinking with aortic calcification attenuated and became nonsignificant [TR (95% CI) = 1.90 (0.84, 4.28)].

Results of the ordinal regression analysis were very similar to the Tobit regression analysis (Table 5). In Model II, heavy drinkers had significantly higher odds of being in a higher category of AoCaS [OR (95% CI) = 1.67 (1.11, 2.52)]. In Model III, with further adjustment for potential mediators, a significant association of heavy drinking with aortic calcification attenuated and became nonsignificant [OR (95% CI) = 1.54 (0.99, 2.40)]. In Tobit regression, as well as in ordinal regression, in Model III, attenuation in significance was mainly due to adjustment for hypertension and HDL-C. When we repeated the analysis by excluding hypertensive patients (n=257) from the main analysis (n=1006), there was no significant association between heavy alcohol consumption and aortic calcification after adjusting for sociodemographic variables and potential confounders [Model II: TR (95% CI) = 2.37 (0.88, 6.35), OR (95% CI) = 1.05 (0.58, 1.89)] (data not shown).

In Tobit regression, as well as in ordinal regression, there was no significant interaction between alcohol consumption and race/ethnicity on aortic calcification. In a race/ethnicity stratified analysis, either in Model II or Model III, none of the alcohol consumption categories were significantly associated with aortic calcification (Table 4 and 5). After excluding former drinkers from the nondrinker category (reference category = never drinker), heavy drinkers [TR (95% CI) = 2.68 (1.15, 6.24); OR (95% CI) =1.80 (1.15, 2.81)] had a significantly higher expected AoCaS compared to never drinkers, after adjusting for socio-demographic and confounding variables (Supplementary Table 2 and 3).

DISCUSSION

In this community-based sample of asymptomatic middle-aged men (the US White, US Black, Japanese American, and Japanese in Japan), heavy alcohol consumption was significantly associated with higher AoCaS independent of potential confounders. The available literature describes various patterns of association between alcohol consumption and atherosclerosis: no significant association[7, 8], a U or J-shaped association[9–12], and a dose-response association[13–15]. Our results are consistent with results from several other studies, which have reported harmful effects of heavy drinking on atherosclerosis, with no beneficial effect of light to moderate drinking[10, 14, 22]. McClelland et al. in the Multi-Ethnic Study of Atherosclerosis, among White, African American, Hispanic, or Chinese men and women aged 45-84 years, from six different US communities, reported the significant positive association of alcohol consumption (≥2 drinks/day) with both baseline CAC and CAC progression[22]. Similarly, Tanaka et al.[14], in the Circulatory Risk in Communities Study of men aged 30-79 years, reported a significant positive association of heavy alcohol consumption with endothelial dysfunction, which is hypothesized to contribute to the development of atherosclerosis and CHD[39]. Jiang et al., in a population-based cohort study with men and women aged 50-85 years, showed a significant association between heavy alcohol consumption and the presence and severity of aortic arch calcification in men. There was no beneficial effect of moderate drinking in total alcohol or any types of alcoholic beverages on aortic arch calcification[13]. Pletcher and colleagues, in the CARDIA Study among US White middle-aged men and women aged 33-45 years, found a direct association between higher levels of alcohol consumption and CAC[15].

Our study findings imply that heavy alcohol consumption (>37.5 grams of alcohol/day) may have a detrimental effect on atherosclerosis indicated by aortic calcification among healthy middle-aged men. Although not tested in this study, the positive relationship between heavy alcohol consumption and aortic calcification could be explained by the deleterious effect of heavy alcohol consumption on endothelial function, platelet aggregation, the activation of the clotting cascade, and the promotion of LDL oxidation by acetaldehyde[14, 40]. Several lines of evidence suggest that endothelial dysfunction is the initial step of atherosclerosis development[41]. Heavy alcohol consumption reduces nitric oxide (NO) production by reducing endothelial NO synthase activity, increases endothelial permeability to lipoproteins and other plasma components, and causes inflammatory/oxidative injury to the endothelium[42]. In response to the altered endothelial functions following various humoral and hemodynamic insults, as a part of the reparative mechanism, the systemic vasculature can respond by depositing calcium at the site of injury[43,44].

In our study, light to moderate alcohol consumption was nonsignificantly associated with AoCaS. In contrast to our results, several studies have reported either a J-shaped association[10–12] with light to moderate alcohol consumption showing a protective effect on atherosclerosis or no significant association[7, 8, 45] between alcohol consumption and atherosclerosis. Mukamal and colleagues, in the Cardiovascular Health Study, among men and women aged ≥65 years, and free of clinical CVD, found that alcohol consumption of 1-6 drinks/week had 0.07±0.04 mm significantly lower composite carotid intima-media thickness (CIMT) than abstainers. This relationship was consistent across men and women and internal and common carotid artery[10]. Vliegenthart et al., in the Rotterdam Coronary Calcification Study of men and women aged ≥55 years, reported a J-shaped association between alcohol consumption and CAC, with light and moderate drinkers having significantly lower odds of extensive CAC compared to non-drinkers[11]. Ellison et al., in the NHLBI Family Heart Study of men and women, with an average age of 55 years, reported no association between alcohol consumption and CAC[7]. Yang et al., in the South Bay Heart Watch Study[45] of men and women aged ≥45 years, and intermediate risk for CHD, reported no association between alcohol drinking and CAC. A J-shaped association in the Rotterdam Study or a null association in the NHLBI Family Heart Study and the South Bay Heart Watch study could be because of ‘abstainer error’ (classifying people who had reduced or stopped drinking as lifetime abstainers). The potential for abstainer error is very high in all three studies because of inclusion of former drinkers, who might have stopped drinking because of age, ill health, or drugs that may interact with alcohol (‘Sick Quitters’), in the never drinker group. The inclusion of former drinkers and lifelong abstainers into the nondrinker group could have substantially increased the risk of CAC among nondrinkers. In our study, the potential for abstainer error is very minimal because it is unlikely that healthy middle-aged men would stop drinking because of ill-health. In addition, results were unchanged in a sensitivity analysis excluding former drinkers from the nondrinker category.

Our study has several limitations. First, we did not examine the relation of different drinking patterns (regular *vs.* episodic) and various types of alcohol beverages. Several lines of evidence suggest that binge drinking (episodic drinking of ≥5 drinks on any given occasion) is associated with atherosclerosis, and cardiovascular morbidity and mortality[15, 46, 47]. Second, alcohol consumption was assessed using self-administered standardized

questionnaires, and we expect that participants might have underreported their alcohol consumption to avoid social embarrassment[48]. Under-reported alcohol consumption would most likely have attenuated the strength of the association between alcohol and aortic calcification. Third, we mainly examined healthy men aged 40-49 years in Japan and the US; therefore, the results of the study cannot be generalized to females, other populations, or age groups. Fourth, although we have controlled for a variety of sociodemographic and clinical characteristics, the possibility of residual confounding cannot be excluded. However, any remaining potential confounder would need to be strongly associated with both alcohol consumption and atherosclerosis and not related to other covariates included in regression models. Fifth, we cannot establish any causality between alcohol consumption and aortic calcification based on our cross-sectional analyses.

The strengths of the current study include (i) the community-based nature of the study design, with participants from four different races/ethnicities from various countries; (ii) all variable measurements standardized across all centers; (iii) a considerable proportion of daily drinkers and subjects with aortic calcification to evaluate their association; (iv) use of EBCT to detect aortic calcification, which allowed detailed examination of subclinical disease in arterial beds, with accurate visualization of small calcific deposits in the arteries compared to X-ray; and (v) availability of data on several potential confounders and intermediary variables in the relationship between alcohol consumption and atherosclerosis/CHD.

Our study findings have public health and clinical significance. All over the world, alcohol is one of the most commonly used recreational substances. Evidence concerning alcohol consumption and atherosclerosis is limited. Nevertheless, available evidence suggests the detrimental effect of heavy alcohol consumption on atherosclerosis, measured by CAC[15] or aortic calcification[13] or CIMT[10]. Heavy alcohol consumption is associated with a risk of developing communicable diseases, non-communicable diseases, mental and behavioral disorders[49]. Evidence generated from this study further adds to the evidence on the serious health hazards of heavy alcohol consumption among healthy middle-aged men. Although results generated from a cross-sectional study like ours should be extrapolated to clinical care with caution, our study does support the 2015-2020 US dietary guidelines for Americans[50], which recommends ‘if alcohol is consumed, it should be consumed in moderation—up to two drinks per day for men.’ Mechanistically, the nonsignificant association of light to moderate alcohol consumption with aortic calcification may imply that a major part of the cardiovascular benefits of light to moderate alcohol consumption is mediated through mechanisms other than the deposition of calcium in an arterial wall. These mechanisms may include the favorable effect of moderate alcohol consumption within the coagulation system or on the endothelial function or an antioxidant effect or increase resistance of myocyte to ischemic injury[2–5].

Conclusions

Our study showed a null association of light to moderate drinking and a positive association of heavy alcohol consumption with aortic calcification. Thus, heavy alcohol consumption may be an independent risk factor for atherosclerosis and light to moderate alcohol

consumption may decrease cardiovascular risk through mechanisms other than those associated with the reduced deposition of calcium in the atherosclerotic lesions. Prospective data are needed to further clarify the association between alcohol consumption and incidence and the progression of atherosclerosis.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Highlights

- Alcohol consumption has a J-shaped association with CHD
- Studies reported a conflicting relationship between alcohol consumption and atherosclerosis
- We cross-sectionally examined the relationship between alcohol consumption and aortic calcification
- Heavy alcohol consumption was positively associated with aortic calcification
- Decreased CHD risk in light to moderate alcohol consumption may occur through mechanisms other than the reduced deposition of calcium in atherosclerotic lesions

Table 1

Descriptive characteristics of study participants for the ERA-JUMP Study, 2002–2006.

Race/Ethnicity	Overall	US White	US Black	Japanese in Japan	Japanese American
Total number (%)	1006 (100)	301 (29.9)	103 (10.2)	310 (30.8)	292 (29.0)
Age[a], years	45.3 (2.8)	45.0 (2.8)	45.0 (2. 8)	45.1 (2. 8)	46.1 (2.8)
BMI[a], kg/m^2	26.8 (4.6)	27.8 (4.2)	29.7 (5.8)	23.7 (3.1)	27.9 (4.3)
Pack-years of smoking[b]	0.0 (0.0, 15.0)	0.0 (0.0, 1.5)	0.0 (0.0, 9.5)	18.9 (3.3, 29.0)	0.0 (0.0, 3.6)
LDL-C[a], mg/dl	129.5 (35.5)	134.9 (33.6)	128.1 (42.0)	132.3 (36.0)	121.4 (33.0)
HDL-C[a], mg/dl	51.0 (13.5)	47.8 (12.8)	51.4 (16.0)	54.1 (13.7)	50.8 (12.3)
Triglycerides[b], mg/dl	133.0 (95.0 188.0)	128.0 (93.0, 186.0)	108.0 (78.0, 166.0)	137.0 (104.0, 182.0)	141.5 (93.0, 225.5)
Hypertension[c]	257 (25.6)	44 (14.6)	33 (32.0)	83 (26.8)	97 (33.2)
Diabetes[c]	77 (7.7)	10 (3.3)	9 (8.8)	19 (6.1)	39 (13.4)
Anti-lipid med[c]	124 (12.3)	36 (12.0)	9 (8.7)	11 (3.6)	68 (23.3)
Meat intake[c]	761 (75.7)	232 (77.1)	75 (72.8)	207 (66.8)	247 (84.6)
Years of education[b]	16.0 (14.0, 16.0)	16.0 (16.0, 18.0)	14.0 (12. 0, 16.0)	16.0 (12.0, 16.0)	16.0 (14.0, 16.0)
CRP, mg/dl[b]	0.68 (0.29, 1.37)	0.94 (0.51, 1.82)	1.46 (0.90, 3.11)	0.32 (0.15, 0.68)	0.66 (0.33, 1.32)
Fibrinogen[a], mg/dl	289.7 (74.4)	291.0 (70.2)	314.2 (73.7)	255.8 (65.8)	315.9 (73.4)
AoCaS[b]	4.9 (0.0, 50.0)	9.0 (0.0, 45.0)	14.0 (0.0, 46.0)	0.0 (0.0, 41.0)	5.0 (0.0, 77.0)
Alcohol intake[b], gm/day	7.4 (0.0, 25.9)	4.6 (1.0, 16.1)	3.1 (0.0, 24.7)	16.5 (2.5, 42.4)	1.0 (0.0, 25.9)

AoCaS, aortic calcification score; BMI, body mass index; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; CRP, C-reactive protein.

[a]Continuous normally distributed variables expressed as mean (standard deviation).

[b]Continuous non-normally distributed variables expressed as median (inter-quartile range).

[c]Categorical variables expressed as numbers (%).

SI conversion factors: to convert LDL-C and HDL-C to mmol/L, multiply values by 0.0259. To convert triglycerides to mmol/L, multiply values by 0.01129. To convert fibrinogen to μmol/L, multiply values by 0.0294. To convert CRP to nmol/L, multiply values by 9.524.

Table 2

Demographic and clinical characteristics by alcohol consumption categories for the ERA-JUMP Study, 2002–2006 (n = 1006)

Alcohol categories	Non-drinker	Light drinker	Moderate drinker	Heavy drinker	*p*-trend[d]
Total number (%)	258 (25.6)	355 (35.3)	236 (23.5)	157 (15.6)	–
Age[a], years	45.7 (0.2)	45.1 (0.2)	45.1 (0.2)	45.6 (0.2)	0.61/0.01
BMI[a], kg/m^2	28.3 (0.4)	27.9 (0.3)	27.4 (0.3)	27.6 (0.4)	0.07/0.30
Pack – years of smoking[b]	0.0 (0.0, 3.1)	0.0 (0.0, 3.1)	0.0 (0.0, 3.1)	3.8 (0.0, 11.1)	0.01/0.01
LDL-C[a], mg/dl	134.2 (3.0)	134.8 (2.3)	137.8 (2.9)	124.8 (3.7)	0.03/0.01
HDL-C[a], mg/dl	44.0 (1.1)	46.9 (0.8)	51.5 (1.0)	57.7 (1.3)	0.01/0.06
Triglycerides[b], mg/dl	132.8 (90.1, 189.3)	129.3 (91.4, 186.3)	117.8 (93.5, 168.5)	123.8 (98.1, 201.5)	0.14/0.39
Hypertension[c]	42 (16.4)	44 (12.3)	34 (14.4)	60 (38.1)	0.01/0.01
Diabetes[c]	15 (5.7)	10 (2.6)	7 (3.0)	6 (3.5)	0.21/0.07
Anti-lipid med[c]	31 (14.9)	34 (12.2)	17 (9.2)	17 (13.5)	0.52/0.14
Meat intake[c],	187 (72.7)	269 (75.8)	195 (81.7)	130 (82.9)	0.01/0.63
Years of education[b]	16.0 (16.0, 18.0)	16.0 (16.0, 18.0)	16.0 (16.0, 18.0)	16.0 (16.0, 18.0)	1.00/1.00
CRP[b], mg/dl	1.04 (0.59, 1.84)	0.93 (0.51, 1.87)	0.82 (0.50, 1.62)	0.86 (0.50, 1.93)	0.02/0.23
Fibrinogen[a], mg/dl	301.6 (6.0)	291.2 (4.7)	285.3 (5.8)	292.1 (7.4)	0.13/0.07
AoCaS[b]	0.8 (0.0, 9.9)	0.6 (0.0, 11.3)	0.4 (0.0, 11.0)	0.7 (0.0, 16.0)	0.84/0.51

AoCaS, aortic calcification score; BMI, body mass index; LDL-C low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; CRP, C-reactive protein.

Values for all variables except age were adjusted for ‘age’ and ‘race/ethnicity’: value of age was fixed at 45.3 years and race was fixed as ‘US White’.

[a]Continuous normally distributed variables were expressed as mean (standard error).

[b]Continuous non-normally distributed variables were expressed as median (inter-quartile range);

[c]Categorical variables were expressed as numbers (%).

[d]*p*-trend shows *p*-values for linear and quadratic trend across the alcohol consumption categories.

SI conversion factors: To convert LDL-C and HDL-C to mmol/L, multiply values by 0.0259. To convert triglycerides to mmol/L, multiply values by 0.01129. To convert fibrinogen to μmol/L, multiply values by 0.0294. To convert CRP to nmol/L, multiply values by 9.524.

Table 3

Demographic and clinical characteristics by aortic calcification score categories for the ERA-JUMP Study, 2002–2006 (n = 1006).

AoCaS categories	AoCaS=0	AoCaS 1-99	AoCaS 100-299	AoCaS ≥300	*p*-trend[d]
Total number (%)	434 (43.1)	372 (37.0)	91 (9.1)	109 (10.8)	–
Age[a], years	44.9 (0.1)	45.4 (0.2)	46.2 (0.3)	46.3 (0.3)	0.01/0.27
BMI[a], kg/m^2	26.2 (0.3)	28.8 (0.3)	28.9 (0.5)	27.4 (0.4)	0.01/0.01
Pack-years of smoking[b]	0.0 (0.0, 0.9)	0.0 (0.0, 1.2)	0.0 (0.0, 13.6)	11 (0.0, 19.7)	0.01/0.01
Alcohol[b], gm/day	5.0 (1.0, 15.9)	3.7 (1.0, 13.6)	3.4 (1.0, 11.5)	22.9 (2.1, 35.0)	0.01/0.01
LDL-C[a], mg/dl	130.5 (2.6)	137.8 (2.3)	131.8 (4.1)	137.9 (3.8)	0.18/0.83
HDL-C[a], mg/dl	50.3 (1.0)	46.4 (0.9)	46.0 (1.5)	49.6 (1.4)	0.62/0.01
Triglycerides[b], mg/dl	115.1 (80.7, 156.8)	130.1 (95.7, 185.5)	149.4 (104.7, 209.0)	134.3 (94.7, 239.0)	0.01/0.03
Hypertension[c]	43 (9.9)	60 (16.1)	19 (20.7)	18 (16.0)	0.01/0.02
Diabetes[c]	10 (2.3)	11 (2.9)	7 (7.3)	6 (5.3)	0.01/0.25
Anti-lipid med[c]	39 (9.0)	40 (10.8)	24 (26.1)	16 (14.3)	0.01/0.03
Meat intake[c]	325 (74.9)	290 (78.0)	74 (80.6)	83 (75.9)	0.70/0.25
Years of education[b]	17.0 (16.0, 18.0)	17.0 (16.0, 18.0)	16.0 (16.0, 18.0)	16.0 (16.0, 18.0)	0.01/1.00
CRP[b], mg/dl	0.81 (0.42, 1.60)	1.04 (0.55, 1.84)	0.99 (0.53, 2.17)	1.03 (0.49, 1.94)	0.04/0.17
Fibrinogen[a], mg/dl	284.7 (5.2)	293.0 (4.8)	300.4 (8.1)	299.1 (7.6)	0.04/0.40

AoCaS, aortic calcification score; BMI, body mass index; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; CRP, C-reactive protein.

Values for all variables except age were adjusted for ‘age’ and ‘race/ethnicity’: Value of age was fixed at 45.3 years and race was fixed as ‘US White’.

[a]Continuous normally distributed variables were expressed as mean (standard error).

[b]Continuous non-normally distributed variables were expressed as median (inter-quartile range).

[c]Categorical variables were expressed as numbers (%).

[d]*p*-trend shows *p*-values for linear and quadratic trends across the aortic calcification score categories.

SI conversion factors: To convert LDL-C and HDL-C to mmol/L, multiply values by 0.0259. To convert triglycerides to mmol/L, multiply values by 0.01129. To convert fibrinogen to μmol/L, multiply values by 0.0294. To convert CRP to nmol/L, multiply values by 9.524.

Table 4

Tobit conditional regression describing the association between alcohol consumption and aortic calcification score for the ERA-JUMP Study, 2002-2006

Alcohol categories	Non-drinkers	Light drinkers	Moderate drinkers	Heavy drinkers	–
All participants (n = 1006)					
n (%)	258 (25.6)	355 (35.3)	236 (23.5)	157 (15.6)	–
Mean AoCaS	81.2	107.7	112.5	283.7	–
	TR	**TR (95% CI)**	**TR (95% CI)**	**TR (95% CI)**	***p*-trend**[a]
Unadjusted	1.00	0.92 (0.49, 1.75)	0.48 (0.24, 0.98)	1.15 (0.52, 2.55)	0.85/0.07
Model I	1.00	1.09 (0.58, 2.05)	0.67 (0.33, 1.33)	2.63 (1.19, 5.81)	0.06/0.02
Model II	1.00	1.25 (0.69, 2.27)	0.86 (0.45, 1.66)	2.34 (1.10, 4.97)	0.06/0.13
Model III	1.00	1.23 (0.67, 2.23)	0.82 (0.42, 1.60)	1.90 (0.84, 4.28)	0.22/0.22
Race/ethnicity stratified analysis					
US White (n = 301)					
n (%)	57 (18.9)	162 (53.8)	71 (23.6)	11 (3.7)	–
Mean AoCaS	66.7	105.7	90.7	381.0	–
	TR	**TR (95% CI)**	**TR (95% CI)**	**TR (95% CI)**	***p*-trend**[a]
Model II	1.00	1.43 (0.61, 3.34)	1.25 (0.46, 3.37)	1.34 (0.20, 9.11)	0.85/0.77
Model III	1.00	1.41 (0.60, 3.34)	1.35 (0.48, 3.75)	1.89 (0.26, 13.59)	0.61/0.98
Japanese in Japan (n = 310)					
n (%)	53 (17.1)	82 (26.5)	81 (26.1)	94 (30.3)	–
Mean AoCaS	121.0	76.5	67.7	251.3	–
	TR	**TR (95% CI)**	**TR (95% CI)**	**TR (95% CI)**	***p*-trend**[a]
Model II	1.00	1.13 (0.15, 8.27)	0.78 (0.11, 5.83)	2.68 (0.39, 18.36)	0.42/0.31

Alcohol categories	**Non-drinkers**	**Light drinkers**	**Moderate drinkers**	**Heavy drinkers**	**–**
Model III	1.00	0.85 (0.11, 6.34)	0.79 (0.10, 6.04)	1.54 (0.20, 11.95)	0.67/0.42
Japanese American (n = 292)					
n (%)	113 (38.7)	75 (25.7)	59 (20.2)	45 (15.4)	–
Mean AoCaS	82.1	157.8	224.9	232.5	–
	TR	**TR (95% CI)**	**TR (95% CI)**	**TR (95% CI)**	***p*-trend**[a]
Model II	1.00	1.25 (0.46, 3.38)	0.86 (0.30, 2.52)	2.02 (0.59, 6.07)	0.36/0.53
Model III	1.00	1.33 (0.50, 3.59)	0.95 (0.33, 2.77)	1.60 (0.41, 5.17)	0.59/0.84

TR, Tobit ratio; CI, confidence interval; AoCaS, aortic calcification score.

Model I: alcohol consumption, age, race, years of education.

Model II: Model I + pack-years of smoking, BMI, diabetes, anti-lipid medication, job physical activity, meat intake, LDL-C, and CRP.

Model III: Model II + HDL-C, triglycerides, hypertension, fibrinogen.

[a] *p-trend* shows *p*-values for linear and quadratic trends across the alcohol consumption categories calculated using contrast.

Table 5

Ordinal logistic regression describing the association between alcohol consumption and aortic calcification score for the ERA-JUMP Study, 2002–2006.

Alcohol categories	Non-drinkers	Light drinkers	Moderate drinkers	Heavy drinkers	–
All Participants (n = 1006)					
n (%)	258 (25.6)	355 (35.3)	236 (23.5)	157 (15.6)	–
Mean AoCaS	81.2	107.7	112.5	283.7	–
	OR	**OR (95% CI)**	**OR (95% CI)**	**OR (95% CI)**	***p*-trend**[a]
Unadjusted	1.00	0.92 (0.68, 1.23)	0.68 (0.49, 0.94)	1.05 (0.73, 1.52)	0.15/0.30
Model I	1.00	1.02 (0.74, 1.39)	0.79 (0.56, 1.12)	1.67 (1.13, 2.47)	0.19/0.31
Model II	1.00	1.10 (0.79, 1.52)	0.86 (0.60, 1.23)	1.67 (1.11, 2.52)	0.48/0.32
Model III	1.00	1.07 (0.77, 1.50)	0.83 (0.58, 1.21)	1.54 (0.99, 2.40)	0.47/0.55
Race/ethnicity stratified analyses					
US White (n = 301)					
n (%)	57 (18.9)	162 (53.8)	71 (23.6)	11 (3.7)	–
Mean AoCaS	66.7	105.7	90.7	381.0	–
	OR	**OR (95% CI)**	**OR (95% CI)**	**OR (95% CI)**	***p*-trend**[a]
Model II	1.00	1.26 (0.69, 2.31)	1.10 (0.55, 2.23)	1.30 (0.35, 4.84)	0.65/0.85
Model III	1.00	1.21 (0.65, 2.25)	1.10 (0.53, 2.29)	1.62 (0.42, 6.35)	0.87/0.61
Japanese in Japan (n = 310)					
n (%)	53 (17.1)	82 (26.5)	81 (26.1)	94 (30.3)	–
Mean AoCaS	121.0	76.5	67.7	251.3	
	OR	**OR (95% CI)**	**OR (95% CI)**	**OR (95% CI)**	***p*-trend**[a]
Model II	1.00	1.02 (0.46, 2.25)	0.96 (0.44, 2.12)	1.68 (0.79, 3.55)	0.69/0.39

Alcohol categories	Non-drinkers	Light drinkers	Moderate drinkers	Heavy drinkers	–
Model III	1.00	0.89 (0.39, 2.01)	1.00 (0.44, 2.27)	1.40 (0.62, 3.14)	0.60/0.43
Japanese American (n = 292)					
n (%)	113 (38.7)	75 (25.7)	59 (20.2)	45 (15.4)	
Mean AoCaS	82.1	157.8	224.9	232.5	–
	OR	**OR (95% CI)**	**OR (95% CI)**	**OR (95% CI)**	***p*-trend[a]**
Model II	1.00	1.16 (0.66, 2.05)	0.78 (0.42, 1.44)	1.47 (0.75, 2.87)	0.83/0.97
Model III	1.00	1.21 (0.68, 2.17)	0.81 (0.43, 1.53)	1.38 (0.66, 2.91)	0.96/0.88

OR, odds ratio; CI, confidence interval; AoCaS, aortic calcification score.

Model I: alcohol consumption, age, race, years of education.

Model II: Model I + pack-years of smoking, BMI, diabetes, anti-lipid medication, job physical activity, meat intake, LDL-C, and CRP.

Model III: Model II + HDL-C, triglycerides, hypertension, and fibrinogen.

[a] *p-trend* shows *p*-values for linear and quadratic trends across the alcohol consumption categories calculated using contrast.