ORIGINAL INVESTIGATION

Alcohol Consumption and Coronary Calcification in a General Population

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Background: A U- or J-shaped association exists between alcohol consumption and coronary heart disease. One of the proposed mechanisms for this association involves atherogenesis, but there are no data on the association between alcohol consumption and coronary atherosclerosis in asymptomatic subjects. Coronary calcification, a measure of coronary atherosclerosis, allows for the study of the association.

Methods: This cross-sectional study was performed using data from the population-based Rotterdam Coronary Calcification Study. Data on alcohol consumption were available for 1795 individuals without coronary heart disease. Mean ± SD age of the participants was 71 ± 5.7 years. Coronary calcification was detected on electron beam computed tomographic scans and quantified as a calcium score by the Agatston method. Extensive coronary calcification was defined as a calcium score above 400.

Results: In this population, 15.8% of individuals consumed no alcohol; 46.5% consumed 1 alcoholic drink or less per day; 16.9% consumed 1 to 2 drinks per day; and 20.9% consumed more than 2 drinks per day. A U-shaped association was found between alcohol consumption and coronary calcification. Compared with nondrinkers, the odds ratio of extensive coronary calcification was 0.60 (95% confidence interval [CI], 0.44-0.82) for those who consumed 1 drink or less daily; 0.51 (95% CI, 0.35-0.76) for those who consumed 1 to 2 drinks daily; and 0.90 (95% CI, 0.62-1.29) for those who consumed more than 2 drinks. The association remained after multivariate adjustment.

Conclusions: The consumption of 2 alcoholic drinks or fewer per day was inversely associated with extensive coronary calcification. The risk of extensive coronary calcification was 50% lower in individuals who consumed 1 to 2 alcoholic drinks per day than in nondrinkers.

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A U- OR J-SHAPED ASSOCIATION exists between alcohol consumption and coronary morbidity and mortality, and light to moderate drinkers face a lower risk than nondrinkers or heavy drinkers.[1-3] The underlying mechanism of the reduced risk associated with moderate levels of alcohol is not well understood. One potential mechanism is the effect of alcohol on atherogenesis.[3,4] The association between alcohol and coronary atherosclerosis has been investigated by assessing the severity of angiographically determined coronary artery disease.[5,6] However, studies involving invasive coronary angiography can only be conducted in symptomatic subjects suspected of having coronary artery disease. Whether alcohol consumption is associated with coronary atherosclerosis in asymptomatic subjects is unknown.

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The development of electron beam computed tomography (EBCT) enables noninvasive measurement of coronary calcification, which, because it is part of the atherosclerotic process and therefore of the plaque burden,[7] can be used as a measure of coronary atherosclerosis. The risk of coronary heart disease increases with the amount of coronary calcification,[8,9] but how alcohol consumption affects coronary atherosclerosis, as reflected by the amount of coronary calcification, has not been established. One study that compared the amount of coronary calcification of drinkers and nondrinkers found no difference.[10] However, in that study, information on alcohol consumption was limited to a dichotomous variable (daily consumption of at least 1 drink vs no consumption at all).

The Rotterdam Coronary Calcification Study is a prospective population-based study of older adults with detailed data on alcohol consumption. We studied the consumption of different types of alcohol in relation to coronary calcification in 1795 subjects without coronary heart disease at baseline.

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METHODS

STUDY POPULATION

The Rotterdam Coronary Calcification Study was designed to study the determinants and consequences of coronary calcification detected by EBCT. The study was embedded in the Rotterdam Study, a prospective, population-based study of 7983 individuals 55 years and older that began in 1990. The rationale and design of the Rotterdam Study have been described elsewhere.[11] From 1997 onward, individuals 85 years or younger were invited to participate in the Rotterdam Coronary Calcification Study and undergo an EBCT scan. Residents of nursing homes did not visit the research center and thus were not recruited for the study. Scans were obtained for 2063 (61%) of the 3370 eligible individuals. However, owing to several causes, eg, metal clips from cardiac surgery, registration errors, and errors pertaining to electrocardiography or image acquisition, data could not be reconstructed or analyzed for 50 of these. Thus, data were available for 2013 individuals. All other information was obtained from examinations conducted for the Rotterdam Study. These examinations included an extensive interview on the participants' lifestyle, medical history, and medication use; a physical examination; and blood pressure, electrocardiography, and laboratory measurements. The interview included questions concerning the number of hours participants spent weekly performing different activities. An estimate of their level of exercise was obtained by adding the number of hours per week that they reported for specified activities (sporting, gardening, or heavy housekeeping activities). The method used for risk factor assessment has been previously described in detail.[12] The median time interval between examinations at the Rotterdam Study center and EBCT scans was 50 days. The medical ethics committee of Erasmus University, Rotterdam approved the study, and all participants gave informed consent. History of coronary heart disease was considered positive when myocardial infarction, coronary artery bypass graft, or percutaneous transluminal coronary angiography was reported and confirmed by physicians' records. Individuals in whom coronary heart disease was present at the time of scanning (n=218) were excluded from the current investigation.

ALCOHOL INTAKE

Alcohol consumption was assessed as part of the interview. The dietary interviews were performed using a computer program that verified all data simultaneously. Participants reported the number of alcoholic beverages that they consumed on a weekly basis in each of 4 categories: beer, wine, moderately strong alcoholic beverages such as port wine or sherry, and liquor. A drink was defined as 250 mL of beer (containing 12.5 mL of alcohol), 100 mL of wine (12 mL of alcohol), 75 mL of a moderately strong, sherry-type beverage (12 mL of alcohol), or 35 mL of liquor (12.3 mL of alcohol). Nondrinkers were asked whether they had been alcohol consumers in the past. By adding the number of drinks of specific alcoholic beverages consumed per week, the total daily consumption of alcohol in drinks per day was calculated. Since most of the moderately strong alcoholic drinks were wine types of beverages, this category was combined with the wine category in the analyses. Alcohol consumption was divided into 4 levels of daily consumption: 0 drinks (nondrinking), 1 drink or fewer, 1 to 2 drinks, and more than 2 drinks.

CORONARY CALCIFICATION

We assessed coronary calcifications in the epicardial coronary arteries detected on EBCT scanning. Imaging was performed with a C-150 Imatron scanner (GE-Imatron, South San Francisco, Calif). All scans were performed with the same scanner by trained technicians. Before the participants were scanned, they performed breath-holding exercises. From the root of the aorta through the heart, 38 images were obtained with a scanning time of 100 milliseconds and a slice thickness of 3 mm. We acquired images at 80% of the cardiac cycle using electrocardiogram triggering during a single breath-holding period. Scan readers, who were blinded to the clinical data of the participants, performed quantification of coronary calcifications using AccuImage software (AccuImage Diagnostics Corporation, South San Francisco). This software displays all pixels with a density greater than 130 Hounsfield units (HU). A calcification was defined as a minimum of 2 adjacent pixels (area=0.65 mm^2) with a density greater than 130 HUs. Calcium scores were calculated by the Agatston et al method.[13] In this scoring method, the area (in square millimeters) of individual calcific lesions is multiplied by a factor based on the maximum density of the lesion. This factor ranges from 1 to 4 in the following manner: 1=130 to 199 HU; 2=200 to 299 HU; 3=300 to 399 HU; and 4=400 HU or greater. The total calcium score is the sum of the scores for all individual lesions. Extensive coronary calcification was defined as a calcium score of 400 or above, in concordance with the Rumberger et al[14]calcium score categorization. A calcium score of 400 is associated with at least 1 significant stenosis by coronary angiography[15] and with flow abnormalities on stress myocardial perfusion tomography.[16]

STATISTICAL ANALYSIS

Levels of potential confounders were compared between categories of alcohol consumption using a general linear model. In this model, age and sex were included as covariates. Logistic regression analysis adjusted for age and sex was used to calculate odds ratios (ORs) of extensive coronary calcification in categories of alcohol consumption, using nondrinkers as the reference category. The logistic regression analysis was repeated with additional adjustment for cardiovascular risk factors (total cholesterol, high-density lipoprotein cholesterol, body mass index, diabetes mellitus, smoking status, level of exercise, and educational level). The logistic models were also used after exclusion of former drinkers and by sex. The logistic models were repeated for each category of alcoholic beverage, with additional adjustment for total alcohol consumption. All measures of association are presented with 95% confidence intervals (CIs). The software package SPSS for Windows, version 11.0, (SPSS Inc, Chicago, Ill) was used for data analysis.

RESULTS

CHARACTERISTICS OF THE STUDY POPULATION

Table 1 shows the characteristics of this study population of asymptomatic older adults. Its mean±SD age was 70.6±5.6 years, and it comprised more women than men (57.5% vs 42.5%). In this population, 15.8% of individuals consumed no alcohol; 46.5% consumed up to 1 alcoholic drink per day; 16.9% consumed 1 to 2 drinks per day; and 20.9% consumed more than 2 drinks per day. Only 10.9% of the population consumed more than 3 drinks per day. The proportion of men increased with increasing alcohol consumption. In the nondrinking group, three quarters of the individuals were women whereas in the group who drank more than 2 drinks per day, two thirds of the individuals were men. Increasing

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Table 1. Baseline Characteristics of 1795 Study Participants Without Coronary Heart Disease by Alcohol Consumption Category*

Characteristic	Alcohol Consumption, No. of Drinks/d			
	0 (n = 283)	≤1 (n = 834)	1-2 (n = 303)	>2 (n = 375)
Men, %	26.1	33.1	53.8	66.4†
Age, y	71.3 ± 5.5	70.7 ± 5.6	70.9 ± 5.6	69.6 ± 5.4
Systolic BP, mm Hg	145 ± 21	143 ± 21	143 ± 21	144 ± 20
Diastolic BP, mm Hg	76 ± 12	76 ± 11	77 ± 10	76 ± 11
Total cholesterol, mg/dL (mmol/L)	225 ± 36 (5.8 ± 0.9)	225 ± 36 (5.8 ± 0.9)	230 ± 38 (5.9 ± 1.0)	232 ± 36 (6.0 ± 0.9)†
HDL cholesterol, mg/dL (mmol/L)	49 ± 14 (1.3 ± 0.4)	53 ± 14 (1.4 ± 0.4)	55 ± 16 (1.4 ± 0.4)	59 ± 16 (1.5 ± 0.4)†
Body mass index‡	27.5 ± 4.8	27.0 ± 4.0	26.7 ± 3.5	27.0 ± 3.5
Diabetes mellitus, %	16.0	12.5	8.6	11.1†
Smoker status, %				
Current	14.1	14.0	14.9	24.5
Former	42.4	46.9	65.7	60.8
Never	43.5	39.1	19.5	14.7†
Tertiles of exercise, %				
Low	18.8	50.2	14.7	16.4
Moderate	12.1	49.1	17.6	21.2
High	15.5	40.5	18.8	25.2†
Educational level, %				
Low	38.5	28.8	23.8	18.4
Intermediate	54.4	57.9	61.7	61.3
High	7.1	13.3	14.5	20.3†
Calcium score§	121 (9-500)	76 (7-339)	90 (11-346)	164 (23-640)
Extensive coronary calcification‖	30.0	21.7	23.1	34.4†

Abbreviations: BP, blood pressure; HDL, high-density lipoprotein.
*Values are given as mean ± SD unless otherwise indicated.
†$P<.05$ using the χ^2 test (for percentages) or analysis of variance (for means).
‡Calculated as weight in kilograms divided by the square of height in meters.
§Calcium score values are expressed as median (interquartile range) because of its skewed distribution.
‖Extensive calcification was defined as a calcium score greater than 400.

levels of alcohol consumption were associated with statistically significant differences in total and high-density lipoprotein (HDL) cholesterol levels, presence of diabetes mellitus, smoking status, level of exercise, and educational level. Of the participants who did not drink alcohol at the time of scanning, 38.2% (n=108) had consumed alcohol in the past. Of the former drinkers, 4.0% reported a daily consumption of more than 3 alcoholic drinks in the past. The distribution of consumption of different alcoholic beverages is shown in the **Figure**. While beer and liquor were consumed by a minority of the population (29.3% and 35.4%, respectively), almost three quarters drank wine or sherry types of beverages (73.3%). Of these individuals, 18.9% consumed at least 1 drink per day. Corresponding percentages for beer and liquor were 5.0% and 10.9%, respectively. The distribution of the calcium score was highly skewed, with a median of 97 and an interquartile range of 10 to 430. Extensive coronary calcification was present in 25.9% of the study population. The percentage of participants with extensive coronary calcification was similar among those who consumed 2 to 3 drinks daily and those who consumed more than 3 drinks (data not shown).

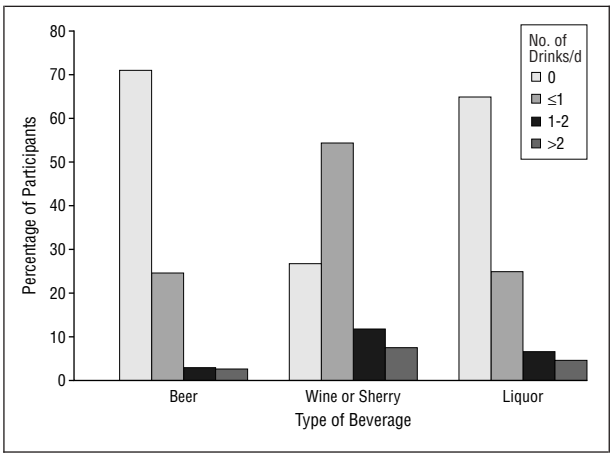

Figure. Consumption of 3 types of alcoholic beverages in 1795 study participants without coronary heart disease.

ALCOHOL AND CORONARY CALCIFICATION

Table 2 presents ORs of extensive coronary calcification for levels of alcohol consumption after adjustment for age and sex and after multivariate adjustment. There was a U-shaped association between alcohol consumption and coronary calcification. The risk of extensive coronary calcification was reduced by 10% to 49% for alcohol drinkers compared with nondrinkers. The inverse association was statistically significant for daily consumption of up to 2 alcoholic drinks. Consuming more than 2 drinks per day was associated with a significantly higher risk of a high calcium score in comparison with consuming up to 1 or 1 to 2 drinks per day. In a multivariate model additionally adjusted for total cholesterol, HDL-cholesterol, body mass index, diabetes mellitus, smoking, level of exercise, and educational level, similar results were found (Table 2). Exclusion of

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Table 2. Risk of Extensive Coronary Calcification According to Level of Alcohol Consumption Among 1795 Study Participants Without Coronary Heart Disease*

Daily Alcohol Consumption, No. of Drinks†	Extensive Coronary Calcification, No. of Participants		Age- and Sex-Adjusted OR (95% CI)	Multivariate OR (95% CI)‡
	Present	Absent		
0	85	198	1.00 (Reference)	1.00 (Reference)
<1	181	653	0.60 (0.44-0.82)§	0.53 (0.38-0.76)§
1-2	70	233	0.51 (0.35-0.76)§	0.43 (0.28-0.67)§
>2	129	246	0.90 (0.62-1.29)	0.72 (0.48-1.09)

Abbreviations: CI, confidence interval; OR, odds ratio.
*Extensive calcification was defined as a calcium score greater than 400.
†A drink was defined as 250 mL of beer (containing 12.5 mL of alcohol); 100 mL of wine (12 mL of alcohol); 75 mL of moderately strong sherry types of beverages (12 mL of alcohol); or 35 mL of liquor (12.3 mL of alcohol).
‡Multivariate analysis was additionally adjusted for total and high-density lipoprotein cholesterol levels, body mass index, presence of diabetes mellitus, smoking status, level of exercise, and educational level. Because of missing data for some variables, multivariate analyses only included 1728 participants.
§$P<.01$.

Table 3. Risk of Extensive Coronary Calcification by Level of Consumption of Different Types of Alcoholic Beverages Among 1795 Study Participants Without Coronary Heart Disease*

Daily Alcohol Consumption†	Extensive Coronary Calcification, No. of Participants		OR With Model 1 (95% CI)‡	OR With Model 2 (95% CI)§
	Present	Absent		
Beer, No. of drinks				
0	302	967	1.00 (Reference)	1.00 (Reference)
<1	129	307	0.76 (0.57-1.01)	0.80 (0.59-1.09)
1-2	19	30	1.11 (0.58-2.11)	0.99 (0.50-1.98)
>2	15	26	0.96 (0.45-2.04)	0.77 (0.34-1.74)
Wine, No. of drinks‖				
0	159	321	1.00 (Reference)	1.00 (Reference)
<1	229	746	0.71 (0.55-0.91)¶	0.66 (0.50-0.88)¶
1-2	38	169	0.50 (0.32-0.77)¶	0.53 (0.33-0.84)¶
>2	39	94	0.90 (0.55-1.49)	0.92 (0.54-1.58)
Liquor, No. of drinks				
0	265	894	1.00 (Reference)	1.00 (Reference)
<1	116	325	0.68 (0.51-0.92)#	0.64 (0.47-0.88)¶
1-2	53	60	1.59 (1.02-2.50)#	1.51 (0.92-2.46)
>2	31	51	0.93 (0.53-1.63)	0.77 (0.42-1.42)

Abbreviations: CI, confidence interval; OR, odds ratio.
*Extensive calcification is defined as a calcium score greater than 400.
†A drink was defined as 250 mL of beer (containing 12.5 mL of alcohol); 100 mL of wine (12 mL of alcohol); 75 mL of moderately strong sherry types of beverages (12 mL of alcohol); or 35 mL of liquor (12.3 mL of alcohol).
‡Model 1 was adjusted for age, sex, and total alcohol consumption.
§Model 2 was additionally adjusted for total and high-density lipoprotein cholesterol levels, body mass index, presence of diabetes mellitus, smoking status, level of exercise, and educational level. Because of missing data for some variables, multivariate analyses only included 1728 participants.
‖The wine category included both wine and sherry types of beverages.
¶$P<.01$.
#$P<.05$.

former drinkers resulted in comparable risk estimates: age- and sex-adjusted ORs were 0.70 (95% CI, 0.47-1.03) for consumption of 1 drink or fewer per day, 0.60 (95% CI, 0.38-0.95) for 1 to 2 drinks per day, and 1.04 (95% CI, 0.68-1.61) for more than 2 drinks per day compared with nondrinkers. Stratification by sex resulted in similar ORs for men and women (data not shown).

The odds of extensive coronary calcification associated with the use of separate types of alcoholic beverages was computed and adjusted for age, sex, and total alcohol consumption (**Table 3**). Daily consumption of up to 1 drink of any type of alcoholic beverages was inversely associated with extensive coronary calcification. The strongest inverse association, an OR of 0.50 (0.32-0.77), was found for a daily consumption of 1 to 2 drinks of port wine or sherry types of beverages. The associations remained after multivariate adjustment.

COMMENT

To our knowledge, this is the first study assessing the effect of alcohol consumption on coronary atherosclerosis in a general population of asymptomatic subjects. In 1795 subjects, a strong inverse association was found between daily alcohol consumption of 2 drinks or fewer and coronary ath-

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erosclerosis, as measured by coronary calcification. The largest risk reduction of extensive coronary calcification, 50%, was found in subjects consuming 1 to 2 alcoholic drinks per day. The associations remained after multivariate adjustment.

Some methodological issues concerning this study need attention. First, we used coronary calcification, a measure of coronary atherosclerosis,[7] as the outcome. Because most individuals with coronary calcification are asymptomatic, changes in drinking habits elicited by clinical symptoms were not likely to affect the associations. Second, with increasing age, most drinkers reduce their level of alcohol consumption.[17] In this population of asymptomatic older adults, less than a quarter of individuals consumed more than 2 alcoholic drinks per day. Current levels of alcohol consumption may not reflect the possibly higher level of consumption during earlier decades. If a moderate consumption of alcoholic beverages has a protective effect on atherosclerosis and if previously heavy drinkers report moderate alcohol use, the effect of moderate alcohol consumption may have appeared less protective. Similarly, if previously light to moderate drinkers report abstaining from alcohol, the protective effect of moderate alcohol consumption may be underestimated. Because of the limited range of alcohol consumption in the study population, we could not examine the relation between heavy drinking and coronary calcification. Third, nondrinkers may not be the most appropriate reference category, since this category consists of lifelong abstainers and former drinkers.[18] Lifelong abstainers could have an adverse risk profile whereas former drinkers may have stopped drinking because of ill health, particularly ischemic heart disease. Thus, nondrinkers as the reference category has been suggested to exaggerate the apparent benefits of light to moderate alcohol consumption.[18] However, bias in the category of nondrinkers probably did not play a considerable role in our study: of the 15.8% of individuals who did not drink alcohol at the time of scanning, 38.2% were former drinkers. Most lifelong nondrinkers (73.0%) were women, for whom abstaining from alcohol is common. Of the former drinkers, only 4% had been moderate or heavy drinkers in the past, and individuals with a history of coronary heart disease were excluded from our study. Fourth, self-reported drinking habits may result in underreporting of alcohol consumption, especially in heavy drinkers.[19] Underreporting the level of consumption tends to weaken the associations found. Bias by differential misreporting of alcohol consumption by sex is possible. However, because analyses were adjusted for sex, we do not expect this bias to fully explain our findings. Finally, drinking patterns may influence the association between alcohol intake and coronary heart disease.[20,21] Regularity in alcohol drinking was not ascertained.

Alcohol consumption is associated with the occurrence of coronary heart disease.[1-3] One of the possible mechanisms is the effect of alcohol on coronary atherosclerosis.[3,4] Light to moderate alcohol consumption is inversely associated with extracoronary measures of atherosclerosis such as peripheral arterial disease[22,23] and carotid plaque.[4,24] However, there are no population-based data on the effect of alcohol consumption on atherosclerosis in the coronary arteries. To our knowledge, this is the first population-based study in asymptomatic individuals on the association between levels of alcohol consumption and coronary atherosclerosis, as measured by coronary calcification. In one study of 1196 individuals at high risk, the amount of coronary calcification was not found to differ between drinkers and nondrinkers.[10] The association between levels of alcohol consumption and coronary calcification was not investigated in that study, but it has been previously addressed by assessing the severity of coronary artery disease determined angiographically.[5,6] Those who consumed alcoholic beverages showed a lower risk of severe coronary stenosis than those who did not, but no dose-response effect was found. Since these studies were based on the results of invasive coronary angiography, only symptomatic individuals suspected of having coronary artery disease were involved. Symptoms of coronary artery disease may have caused changes in alcohol consumption leading to spurious associations. In addition, coronary calcification has a closer association with coronary atherosclerotic plaque burden than with the level of stenosis.[25]

Even after statistical adjustment, smoking can have a confounding effect on the association between alcohol consumption and measures of atherosclerosis.[23] In our study, the percentage of individuals who had never smoked decreased significantly with increasing alcohol consumption. When we repeated the analyses for "current or former smokers" and "never smokers" separately, an inverse relationship between alcohol consumption and coronary calcification was present for lower levels of alcohol consumption in both groups, with similar ORs (data not shown). With a daily alcohol consumption of more than 2 drinks, the inverse association was present among "never smokers" (OR, 0.40 [95% CI, 0.16-1.04] but not for current or former smokers (OR, 0.98 [95% CI, 0.64-1.51]) Several mechanisms have been proposed to explain how alcohol consumption affects atherogenesis. Part of the protective effect is mediated by an elevation of the levels of serum HDL-cholesterol.[26] Alcohol consumption influences hemostasis[27] and levels of adhesion molecules[28] and enhances insulin sensitivity.[29] Our results showed a significant inverse association between alcohol consumption and coronary calcification, even after adjustment for blood lipid values. This is suggestive of an effect of alcohol on atherosclerosis apart from its effect on blood lipid levels. Since the amount of coronary calcification is strongly associated with the risk of coronary heart disease,[8,9] our finding of a 50% reduction in extensive coronary calcification associated with moderate alcohol consumption suggests that moderate alcohol consumption may be a significant contributor to the prevention of coronary heart disease.

Whether specific alcoholic beverages are equivalent in their ability to protect from coronary heart disease is a matter of debate. Some studies have suggested that wine consumption provides a more protective effect than beer or liquor.[30,31] The hypothesis that wine contains additional beneficial substances is supported by several clinical and experimental studies.[32-35] A recent meta-analysis concluded that both beer and wine drinkers faced a lower risk of cardiovascular disease, but an inverse dose-response effect was only found for light to moderate consumption of wine.[36] The authors warned to interpret the finding for beer consumption with caution. Others have suggested that some components of wine offer additional cardiovascular ben-

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efits and pointed to possible differences in risk factors, diet, or drinking pattern among consumers of different categories of alcoholic beverages.[33,37] Evidence exists that wine drinkers are more likely to consume alcohol during a meal, and generally have a healthier lifestyle. In our study, a daily consumption of up to 1 drink of beer, wine, or liquor showed a similar reduction in the risk of a high calcium score, whereas a daily consumption of 1 to 2 drinks of wine or sherry type of beverage seemed to reduce the risk the most. However, this finding should be interpreted with caution, as the number of participants who consumed a high quantity of beer was very small, and the apparently stronger protective effect of wine consumption may be confounded by life style and drinking pattern. Larger studies with a larger range of consumption levels of the different types of alcoholic beverages are needed to verify our findings.

In conclusion, this is the first population-based study of asymptomatic subjects on the effect of alcohol consumption on coronary atherosclerosis, as measured by coronary calcification. The association between alcohol consumption and coronary calcification was U-shaped. Although possible misreporting of alcohol consumption calls for some caution in interpreting the results, our findings suggest that an alcohol consumption of 2 drinks or fewer per day has a strong inverse association with the amount of coronary calcification. The risk of extensive coronary calcification was 50% lower for subjects who consumed 1 to 2 drinks of alcohol per day than for nondrinkers.

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