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Alcohol Intake and Cardiovascular Disease Risk: Cheers, Tears, or Both?

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Cardiovascular diseases (CVD) are among the leading causes of shorter life expectancy and loss of quality of life worldwide. Thus, any influence of diet or life habits on the cardiovascular system may have important implications for public health. Epidemiological studies have shown that moderate alcohol consumption is associated with a lower risk of coronary heart disease (CHD). Moreover, high alcohol intake implies an increased risk for numerous health outcomes. To fully understand the relation between light-to-moderate drinking and CVD, the role of drinking patterns, beverage types, and genetic variations influencing alcohol metabolism should be further examined. The aim of this review article is to present current knowledge with respect to the effect of alcohol intake on CVD risk.

Keywords alcohol, cardiovascular disease, polyphenols, antioxidants

Introduction

During the last 30 years a considerable number of medical articles investigating the potential role of alcohol intake against coronary heart disease (CHD) have been published. The status of alcohol in all of these publications has been discussed as either a risk factor for CHD or as a cardioprotective one. The association of heavy alcohol consumption with a large number of health risks is well known. Nevertheless, moderate alcohol intake is associated with lower risk of cardiovascular diseases (CVD), with the lowest mortality occurring in those who consume 1 or 2 drinks per day. People with no alcohol consumption have higher total mortality than those who drink 1 to 2 drinks per day.[1] Conversely, mortality due to several other diseases increases as the number of drinks consumed per day increases.[2–6] Alcohol has had a long and complicated role in human society and health. Excessive alcohol consumption causes enormous morbidity and mortality worldwide, but the health effects of alcohol use within recommended guidelines are diverse and complex.[7] The effect of alcohol intake on CVD remains controversial because the biological mechanisms underlying the effect are not clear and not all individuals gain benefit from moderate alcohol consumption. Although many studies have dealt with the question of whether various types of alcoholic beverages (vodka, beer, red or white wine, liquor) might offer a greater protection, red wine has been suggested as a cardioprotective alcoholic beverage. Red wine's additional health benefits, due to its polyphenolic compounds content (antioxidants), has been tracked among moderate drinkers compared to abstainers or heavy

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drinkers. Numerous observational studies have consistently demonstrated a reduction of CHD with moderate consumption of alcohol.[8–11]

Additionally, there are many epidemiological studies that have demonstrated either a U- or a J-shaped relation between alcohol consumption and a variety of adverse health outcomes such as CHD, hypertension, heart failure, ischemic stroke, and all-cause mortality. Light to moderate drinkers have less risk than abstainers, and heavy drinkers are at the highest risk.[12–17] These epidemiological studies support the hypothesis of increased risk among heavy alcohol drinkers and indicate a lower risk among lighter drinkers. Specifically, high alcohol intake implies an increased risk of a large number of health outcomes, such as dementia, breast cancer, colorectal cancer, cirrhosis, upper digestive tract cancer, and alcohol dependency. On the other hand, alcohol has been studied for its beneficial effects, especially with regard to prevention of thrombosis.[18] In a recent review, Klatsky stated that light-to-moderate alcohol consumption is related to lower risks of coronary artery disease (CAD), ischemic stroke, and CAD-related heart failure.[5]

Some authors have suggested that nonethanol ingredients of alcoholic beverages might be responsible for the beneficial effects on CHD risk, especially in the case of wine.[19] However, in several studies, a reduced risk of CHD has been reported for moderate consumption of either wine or beer.[20] The epidemiological evidence regarding the cardioprotective effect of ethanol intake and other compounds mainly found in red wine arises from ecological, case control, and cohort studies. Thus, the aim of this review article is to present current knowledge with respect to the effect of alcohol intake on CVD risk.

Selection of Studies

Original research studies that were published in English between 2000 and 2009 were selected through a computer-assisted literature search (i.e., Pubmed, http://www.ncbi.nlm.nih.gov/pubmed/, and Scopus, http://www.scopus.com). Computer searches used combinations of key words relating to disease (heart failure, CHD, CVD, stroke, myocardial infraction [MI]) and alcohol intake. In addition, the reference lists of the articles retrieved directed the search to relevant articles that were not found through the search procedure. The following information was presented according to a fixed protocol: design of study (prospective cohort, cross-sectional, intervention studies), sample size, mean age and sex of participants, follow-up duration, and degree of adjustment for potential confounders. Thus, 14 studies were selected to be presented in the form of a table, from which 8 were prospective, 4 were case control, and 2 were intervention studies. Finally, 60 articles were selected to be discussed in this review, according to the criteria mentioned previously (Table 1).

Prospective Studies Evaluating the Relationship between Alcohol Intake and CVD Risk Factors

Results from prospective studies evaluating the risk factors for developing any kind of CVD revealed that alcohol consumption was related to incidence of CVD disease.

In a cohort study by Moraes *et al.*, 1091 individuals were interviewed at home, regarding various sociodemographic characteristics, dietary habits, lifestyle factors (i.e., physical activity, smoking, alcohol intake), and prevalence of chronic diseases diagnosed by a physician, such as CVD or diabetes. Results of this study showed a slight association between alcoholic beverage consumption and incidence of CVD (hazard ratio [HR] = 1.001, 95% confidence interval [CI] = 1.00–1.003).[21] The same effect of alcohol on the incidence of CHD was found in a study conducted by Fuchs *et al.*[22] among black men, whereas

Table 1
Summary of the selected studies according to publication year, design, region, sample characteristics, and assay methods used

Region and follow-up duration	Objective	Sample size; mean age and gender; alcohol intake	Assay methods	Main finding	Ref.
Prospective/cohort studies					
Cross-sectional, population-based, multistage probability sampling, Brazil, 1995–2003	To present risk factors for CVD in Brazil	1091 Individuals, 45% male, 42.8 ± 16.9	The average daily alcohol intake was calculated taking into account the concentration of ethanol in the beverages	Slight association between alcoholic beverage consumption and incidence of CVD	(21)
Atherosclerosis Risk in Communities Study cohort, United States, 1987–1998	To evaluate the relation between consumption of alcoholic beverages and incidence of CHD in white and African American participants	14,506 (92% Participation rate) persons with information on incident CHD	Alcohol consumption was ascertained at baseline by means of an interviewer-administered dietary questionnaire. Former drinkers were asked to give the number of drinks of hard liquor, bottles of beer, and glasses of wine that they used to drink per week. In calculating the amount of ethanol consumed (in g/week), it was assumed that 4 ounces (118 mL) of wine contains 10.8 g of ethanol, 12 ounces (355 mL) of beer contains 13.2 g, and 1.5 ounces (44 mL) of liquor contains 15.1 g	Positive association betewn alcoholic beverage consumption and incidence of CHD between black men and inverse association between white men	(22)

Longitudinal study, the HALE project, 11 European countries, 1988–2000	To investigate the single and combined effect of Mediterranean diet, being physically active, moderate alcohol use, and nonsmoking on all-cause and cause-specific mortality in European elderly individuals	1507 Apparently healthy men and 832 women, 70–90 years		Moderate alcohol consumption was associated with lower mortality rates from all causes	(23)
British Regional Heart Study, Britain, 1978/1980–1998/2000	To examine associations between alcohol intake and the 20-year risk of CHD, stroke, and all-cause mortality	6544 Middle-aged males	Alcohol intake, ascertained from questions inquiring about frequency, quantity, and type of alcoholic beverage consumed	U-shaped relations between baseline alcohol intake and both CVD and all-cause mortality	(24)
Prospective cohort study, China, 1991–2000	To examine the relation between alcohol consumption and risk for stroke	64,338 Men, aged $\geq$ 40 years who were free of stroke at baseline	Alcohol use was assessed by interviewer-administered questionnaire with six questions regarding regularity, frequency, amount, and type of alcoholic drinks consumed. Information was collected on consumption of liquor, beer, wine, and rice wine; 12.5 g of pure alcohol was considered as one standard drink	Heavy alcohol drinking increased the risk for stroke	(25)
Health Professionals Follow-Up Study, United States, 1986–2002	To investigate whether alcohol whether consumption is inversely associated with CVD	11,711 Men with hypertension, 40–75 years	Questionnaire; alcohol consumption and dietary variables were updated every 4 years; beer and liquor consumption into four categories (none, 0.1–9.9 g/d, 10.0–29.9 g/d, and 30 g/d), white and red wine intake into three categories (none, 0.1–14.9 g/d, and 15 g/d)	A dose-dependent inverse association between alcohol consumption and risk for MI has been revealed	(26)

(*Continued*)

Table 1
(Continued)

Region and follow-up duration	Objective	Sample size; mean age and gender; alcohol intake	Assay methods	Main finding	Ref.
Cardiovascular Health Study, four communities in Pennsylvania, Maryland, North Carolina, and California, 1989/1990; 1992/1993	To evaluate the relation of alcohol intake to lower-extremity arterial disease	5888 Men and women, ≥ 65 years	Participants reported their usual frequency of consumption of beer, wine, and liquor and the usual number of 12-ounce (355-mL) cans or bottles of beer, 6-ounce (177-mL) glasses of wine, and shots of liquor that they drank on each occasion	Alcohol consumption of 1–13 drinks per week in older adults may be associated with lower risk of lower-extremity arterial disease	(27)
Case control studies					
Matched (by age [5 years], sex, and area of residence), incident case control study, Central Valley of Costa Rica, 1994–2004	To determine whether alcohol intake and drinking patterns are associated with plasma lipids and the risk of MI	Analysis of amount and type of alcohol consumed, total of 4180 subjects (2090 cases, 2090 controls). Analyses of patterns of alcohol intake, 3864 subjects. Analyses that used the number of drinking days had 3298 subjects	Frequency of intake of the five commonly consumed alcoholic beverages: beer, rum, whiskey, vodka, and wine. We estimated the amount of alcohol consumed per day by multiplying the number of servings per day by the amount of alcohol per serving, which was 12.8 g for beer, 14 g for liquor, and 11 g for wine. We estimated the number of drinks per day by dividing the total amount of alcohol consumed per day by 14, the amount of absolute alcohol in a standard drink	The lowest risk of MI was observed for those who drank on average three drinks/week compared with lifelong abstainers	(30)

Population-based case control study, 1996–2001	To examine the association between alcohol volume and various drinking patterns and nonfatal MI	320 Incident MI cases, 1565 controls, women, 35–69 years	Volume and drinking patterns for the 12–24 months prior to interview (controls) or MI (cases) were assessed in detail	A reduced likelihood of MI was observed between current drinkers compared to lifelong abstainers	(31)
A matched case control (1:5) analysis, March 2002–June 2006	To examine particular lifestyle factors in relation to the risk of myocardial infarction, hemorrhagic stroke, and ischemic stroke in this population of Chinese men	518 Myocardial infarction 64.7 ± 8.0 years, 333 hemorrhagic stroke 62.3 ± 8.8 years, and 1927 ischemic stroke cases 65.9 ± 7.5 years; 2590 controls 64.5 ± 8.2 years, 1665 controls 62.2 ± 8.8 and 9635 controls 65.9 ± 7.5 years, respectively, for cases; males	Alcohol consumption was divided into two categories (ever or never) based on whether a subject had ever consumed alcohol at least three times a week for more than 6 months	Inverse association of alcohol consumption with MI and positive association with hemorrhagic and ischemic stroke	(32)
A population-based case control study, Porto-Portugal, 1999–2003	To estimate the population attributable fractions of established risk factors for nonfatal acute myocardial infarction	1489 Men: 638 cases (270 ≤ 45 years; 368 > 45 years) and 851 controls (289 ≤ 45 years; 562 > 45 years). Cases survived beyond the 4th day after a first diagnosis of an acute MI	Dietary intake during the previous year was estimated using a validated 82-item semi-quantitative food frequency questionnaire. Different classes of alcohol consumption were defined using cut points of 30.0 g a day (g/day) and 60.0 g/day (excessive alcoholic habits)	Positive association between alcohol consumption and acute MI in both alcohol abstainers and heavy drinkers	(33)

(*Continued*)

Table 1
(Continued)

Region and follow-up duration	Objective	Sample size; mean age and gender; alcohol intake	Assay methods	Main finding	Ref.
Intervention studies					
Dietary intervention, crossover study with three 8-week treatment periods	To establish the effect of moderate alcohol consumption on blood lipid risk factors for CVD in postmenopausal women	51 Postmenopausal women, 60 years (49–79)	During each period, postmenopausal women consumed a controlled diet and were provided a beverage each day that contained 0, 15, or 30 g alcohol (95% ethanol). Each subject completed each of the three periods, and the sequence of alcohol treatment for each subject was randomly assigned before the study started. Before each treatment period, there was a 2- to 5-week period during which the subjects could not consume alcohol but had no other restrictions on food intake. The subjects were instructed to consume their beverage (alcohol or control) with the evening snack food (provided as part of the controlled diet) over a 1- to 2-hour period before going to bed and after completing activities requiring substantial manual dexterity, including driving	Significant increase in plasma HDL and apolipoprotein A-I levels and a decrease in apolipoprotein B levels was observed after 30 g/day ethanol intake	(34)

After a 2-week run-in period during which subjects abstained from alcohol, they were randomized using a random number table in combination with a block assignment schedule into a four-period open-label crossover study	To determine whether red wine may improve vascular function and have less of an impact on BP because of its high content of antioxidant polyphenolic compounds	The four interventions included abstention from all alcohol and grape products (control period), 375 mL red wine (13% alcohol/vol, 2023 mg/L polyphenols), 375 mL of the same red wine that had been dealcoholized using spinning cone column technology (0% alcohol/vol, 2094 mg/L polyphenols), and 3 × 375 mL cans bitter beer (4.6% alcohol/vol) each day for 4 weeks. Red wine was made with grapes destemmed before crushing and grape juice was kept in contact with grape skins for 6 days. Throughout the 18-week study, subjects were asked to maintain their usual food intake, restrict their tea intake (≤2 cups/d), avoid any antioxidant supplementation or over-the-counter medication, and not consume alcoholic beverages other than those provided	Results showed that the systolic and diastolic BP were not different between control–abstinence and dealcoholized red wine	(35)

an inverse association among white men was revealed (HR = 1.13, 95% CI = 1.01–1.28; HR = 0.88, 95% CI = 0.79–0.99, respectively). In the same study, the hazard ratios for incident CHD among current drinkers by predominant type of beverage consumed (beer, wine, liquor, no preference) were also assessed. The hazard ratios showed an inverse association for all beverage types for white women and a positive association in black men but were statistically significant only for liquor in black men. In white men, the association was positive for beer and wine and inverse for liquor and no preference (not statistically significant).[22]

Results from three samples of the MONICA study, which aimed to assess the relationship between alcohol consumption (beer, wine, other spirits) and systemic markers of inflammation in three European countries, showed that moderate consumption of either wine or beer is associated with lower levels of systemic inflammatory markers in three different European areas, suggesting that ethanol itself might be largely responsible for the potential anti-inflammatory effects of these beverages.[8]

Most of the studies investigate how dietary habits and lifestyle factors are associated with all-cause mortality or CHD or CVD alone. The HALE project aimed to investigate the single and combined effect of a Mediterranean diet, being physically active, moderate alcohol use, and nonsmoking on all-cause and cause-specific mortality in European elderly individuals. Results regarding alcohol intake showed that moderate alcohol consumption had a protective effect, because it was associated with lower mortality rates from all causes (HR = 0.78, 95% CI = 0.67–0.91). In addition, moderate alcohol intake was inversely associated with CHD (HR = 0.60, 95% CI = 0.40–0.88) and CVD (HR = 0.74, 95% CI = 0.59–0.93; HRs controlled for age, sex, years of education, body mass index, study, and other factors).[23]

Emberson and his colleagues[24] sought to evaluate the impact of variation in alcohol intake over time on estimated risk relations in a sample of 6544 middle-aged British men with no previous CVD, which was followed for cardiovascular events and all-cause mortality over 20 years, from 1978/1980 to 1998/2000. This study displayed the U-shaped relations between baseline alcohol intake and CVD and all-cause mortality as well, with light drinkers having the lowest risks and nondrinkers and heavy drinkers having similarly high risks. Moreover, regular heavy drinkers had a 74% higher risk of a major coronary event, a 133% higher risk of stroke, and a 127% higher risk of all-cause mortality than did occasional drinkers (these estimates were 8, 54, and 44% before adjustment for intake variation; HR = 1.74, 95% CI = 1.31–2.33; HR = 2.33, 95% CI = 1.46–3.71; HR = 2.27, 95% CI = 1.84–2.81, respectively).[24]

In a most recent prospective cohort study among 64,338 Chinese men aged ≥ 40 years, free of stroke, Bazzano *et al.*[25] suggested that heavy alcohol drinking may increase the risk for stroke in Chinese men. After adjustment for age, body mass index, lifestyle factors (i.e., physical activity, cigarette smoking), geographic characteristics (i.e., degree of urbanization [urban vs rural], geographic variation [north vs. south]), educational status, and history of diabetes, compared with nondrinkers, relative risk (95% confidence interval) of incident stroke was 0.92 (0.80–1.06) for participants consuming 1 to 6 drinks/week, 1.02 (0.93–1.13) for those consuming 7 to 20 drinks/week, 1.22 (1.07–1.38) for those consuming 21 to 34 drinks/week, and 1.22 (1.08 –1.37) for those consuming 35 or more drinks per week. The results do not seem to differ when adjustment was additionally performed for systolic blood pressure (BP).[25] During the same period (i.e., 2007), Beulens and colleagues[26] sought to assess whether alcohol consumption is inversely associated with CVD in terms of incident cases of nonfatal MI, fatal CHD, and stroke among men with hypertension. The researchers observed an approximately dose-dependent inverse

association between alcohol consumption and risk for MI in models adjusted for age and smoking, multivariate models (adjusted for age, smoking, body mass index, physical activity, diabetes, hypercholesterolemia, family history of MI, aspirin use, lipid-lowering therapy, energy intake, and energy-adjusted quintiles of saturated fat, *trans* fatty acids, sodium, potassium, magnesium, folate, vitamin E, *n-3* fatty acids, and dietary fiber), and fatal and nonfatal end points. More specifically, participants with prevalent and incident hypertension who consume $\geq$ 50 g alcohol per day had 60% less risk of developing MI (HR = 0.41, 95% CI = 0.22–0.77). The results were similar for fatal and nonfatal end points (i.e., HR = 0.42, 95% CI = 0.17–1.04; HR = 0.37, 95% CI = 0.14–0.97, respectively). Britton *et al.*[27] have also demonstrated the inverse relation between moderate alcohol consumption and CHD among 5164 hypertensive men participating in the Physicians' Health Study who were apparently healthy and free of CHD at baseline. Compared to subjects consuming less than 1 drink per week, hazard ratios for MI were 1.05 (95% CI = 0.85–1.28), 0.78 (95% CI = 0.64–0.97), and 0.57 (95% CI = 0.35–0.95) for alcohol consumption of 1–4, 5–7, and $\geq$ 8 drinks per week adjusted for age, body mass index, smoking, exercise, diabetes, multivitamin supplements use, vegetable intake, breakfast cereal intake, and cholesterol levels (p for trend $<$ 0.0022).[26]

Finally, Mukamal *et al.*,[28] in a part of the Cardiovascular Health Study, examined the association of alcohol intake and lower-extremity arterial disease among 5635 participants who reported the consumption of beer, wine, and spirits yearly. Results of this study revealed that alcohol consumption of 1–13 drinks per week in older adults may be associated with lower risk of lower-extremity arterial disease. More specifically, compared with abstention, the multivariable-adjusted (i.e., adjusted for age, sex, race, smoking, education, income, marital status, physical activity, depressive symptoms, body mass index, diabetes, and cardio- and cerebrovascular disease) hazard ratios for annually updated intake were 1.10 (95% CI = 0.71–1.71) for $<$1 alcoholic drink per week, 0.56 (95% CI = 0.33–0.95) for 1–13 drinks per week, and 1.02 (95% CI = 0.53–1.97) for $\geq$14 drinks per week (p for quadratic trend $<$ 0.04) (Table 2).[28]

Case Control Studies Evaluating the Relationship between Alcohol Intake and CVD Risk Factors

Results from case control studies are in line with those from the prospective studies, all indicating alcohol intake as a significant predictor of coronary events, whereas low-to-moderate alcohol intake seems to be associated with a lower risk of MI. The case control studies that are presented in this section were conducted to determine the effect of alcohol intake on heart failure.

In a case control study (the CARDIO 2000) conducted in Greece by Panagiotakos *et al.*,[29] the authors aimed to assess coronary risk based on established and emerging lifestyle risk factors such as smoking habit, physical activity, alcohol consumption, and depression in a Mediterranean population. In this study, 1322 individuals were participating. Among cases, 535 male and 126 female were patients with a first event of an acute coronary syndrome, and 661 controls matched by sex, age, and region were entered into the study. A J-shaped association was found between alcohol intake and coronary risk, though the effect of depression on coronary risk differs according to gender (+15% in males vs. 32% in females), that interacts with retirement, current smoking, physical inactivity, alcohol consumption, and social status, increasing the risk from 15 to 189%.[29] In addition, Pitsavos *et al.*,[15] in the second part of CARDIO 2000, showed a J-shaped association

Table 2
Effect size measures and confounding factors used in the studies presented in this review

Outcome/endpoint/ case/intervention	Categories	Effect sizes (OR = odds ratio; HR = hazard ratio)	95% Confidence interval	Confounding factors	Ref.
Prospective/cohort studies					
Incident CVD	Alcohol intake (g/d)	1.001	1.000–1.003	Adjusted for age, gender, body mass index, alcohol consumption, smoking, and systolic and diastolic BP	(21)
Incident CHD	White men, current drinkers (g/week)			Adjusted for age, cigarette-years of smoking, body mass index, LDL cholesterol level, waist : hip ratio, educational level, income, sport index, diabetes mellitus, systolic BP, use of antihypertensive medication, and HDL cholesterol level	(22)
	1 to <70	1.05	0.70–1.58		
	70 to <140	0.81	0.50–1.32		
	140 to <210	0.81	0.45–1.44		
	≥210	0.69	0.40–1.18		
	Black men, current drinkers (g/week)				
	1 to <70	1.80	0.86–3.76		
	70 to <140	1.13	0.45–2.84		
	140 to <210	2.67	1.12–6.34		
	≥210	1.10	0.40–2.98		
Death cause: CHD	Moderate alcohol drinking	0.60	0.40–0.88	HRs controlled for age, sex, years of education, body mass index, study	(23)
Death cause: CVD	Moderate alcohol drinking	0.74	0.59–0.93		
Death cause: All-cause	Moderate alcohol drinking	0.78	0.67–0.91		

Major CHD	None	0.91	0.72–1.15	(24)
	Occasional (1–2 times/month)	1		
	Light (1–2 drinks/day)	0.74	0.63–0.87	
	Moderate (3–6 drinks/day)	1.01	0.84–1.21	
	Heavy (>6 drinks/day)	1.74	1.31–2.33	
Stroke	None	1.08	0.73–1.60	
	Occasional (1–2 times/month)	1		
	Light (1–2 drinks/day)	0.93	0.71–1.22	
	Moderate (3–6 drinks/day)	1.45	1.08–1.96	
	Heavy (>6 drinks/day)	2.33	1.46–3.71	
All-cause mortality	None	0.93	0.77–1.12	
	Occasional (1–2 times/month)	1		
	Light (1–2 drinks/day)	0.82	0.72–0.93	
	Moderate (3–6 drinks/day)	1.32	1.15–1.52	
	Heavy (>6 drinks/day)	2.27	1.84–2.81	

(*Continued*)

Table 2
(Continued)

Outcome/endpoint/ case/intervention	Categories	Effect sizes (OR = odds ratio; HR = hazard ratio)	95% Confidence interval	Confounding factors	Ref.
Stroke incidence	Nondrinkers	1		Stratified by province and adjusted for age, body mass index, physical activity, urban rural residence, northern or southern China, cigarette smoking, diabetes, and education for average systolic BP from three measures at baseline	(25)
	1–6 Drinks/week	0.94	0.77–1.16		
	7–20 Drinks/week	0.87	0.76–1.01		
	21–34 Drinks/week	0.86	0.72–1.04		
	>35 Drinks/week	0.99	0.82–1.18		
Ischemic stroke	Nondrinkers	1			
	1–6 Drinks/week	0.76	0.54–1.05		
	7–20 Drinks/week	1.06	0.86–1.29		
	21–34 Drinks/week	0.85	0.64–1.13		
	>35 Drinks/week	1.19	0.95–1.50		
Hemorrhagic stroke	Nondrinkers	1			
	1–6 Drinks/week	0.93	0.76–1.14		
	7–20 Drinks/week	0.93	0.80–1.07		
	21–34 Drinks/week	1.03	0.86–1.25		
	>35 Drinks/week	1.13	0.97–1.33		
Total MI	None	1		Adjusted for age; smoking; body mass index; physical activity; diabetes; hypercholesterolemia; family history of MI; aspirin use; lipid-lowering therapy; energy intake; and energy-adjusted quintiles of saturated fat, *trans* fatty acids, sodium, potassium, magnesium, folate, vitamin E, omega-3 fatty acids, and dietary fiber	(26)
	0.1–4.9	1.09	0.86–1.37		
	5.0–9.9	0.81	0.60–1.08		
	10.0–14.9	0.68	0.51–0.91		
	15.0–29.9	0.72	0.54–0.97		
	30.0–49.9	0.67	0.48–0.94		
	>50.0	0.41	0.22–0.77		

Fatal CHD	None	1			
	0.1–4.9	0.92	0.63–1.34		
	5.0–9.9	0.85	0.55–1.33		
	10.0–14.9	0.45	0.28–0.74		
	15.0–29.9	0.79	0.50–1.25		
	30.0–49.9	0.59	0.34–1.01		
	>50.0	0.42	0.17–1.04		
Nonfatal MI	None	1			
	0.1–4.9	1.25	0.92–1.69		
	5.0–9.9	0.80	0.54–1.20		
	10.0–14.9	0.86	0.59–1.26		
	15.0–29.9	0.69	0.46–1.03		
	30.0–49.9	0.76	0.49–1.18		
	>50.0	0.37	0.14–0.97		
Hospitalization for lower-extremity arterial disease	Nondrinker	1		Adjusted for age, sex, race, smoking (current, former, and pack-years), education, income, marital status, physical activity, depressive symptoms, body mass index, diabetes, and cardio- and cerebrovascular disease	(28)
	Former drinker	1.21	0.80–1.82		
	<1 drink/week	1.10	0.71–1.71		
	1–6 drinks/week	0.55	0.30–1.02		
	7–13 drinks/week	0.58	0.25–1.35		
	≥14 drinks/week	1.02	0.53–1.97		

(*Continued*)

Table 2
(Continued)

Outcome/endpoint/ case/intervention	Categories	Effect sizes (OR = odds ratio; HR = hazard ratio)	95% Confidence interval	Confounding factors	Ref.
Case control studies					
First nonfatal acute MI	Past drinkers	0.81	0.64–1.03	Adjusted for smoking, history of diabetes, history of hypertension, abdominal obesity, physical activity, income, intake of total energy, dietary fiber, saturated fat, *trans* fat, polyunsaturated fat, and intake of folate	(30)
	≤4.9 g/d	0.77	0.61–0.97		
	5.0–9.9 g/d	0.44	0.31–0.61		
	10.0–14.9 g/d	0.61	0.43–0.86		
	15.0–29.9 g/d	0.70	0.48–1.02		
	≥30 g/d	0.58	0.40–0.84		
	Lifelong abstainers	1			(31)
	Current drinkers (2.3 ± 2.2 drinks/ drinking day)	0.67	0.43–1.03		
	Wine drinkers	0.56	0.33–0.96		
	Consumers of mixed beverage types	0.56	0.31–1.01		
MI	Never	1		Adjusted for family history of CHD and/or stroke and annual personal income. All of the lifestyle factors of interest were also included in the same model for mutual adjustment. Body mass index at age 20 was additionally adjusted for when analyzing the effect of weight change	(32)
	Ever	0.63	0.50–0.80		
Hemorrhagic stroke	Never	1			
	Ever	1.2	0.92–1.57		
Ischemic stroke	Never	1			
	Ever	1.04	0.93–1.17		

Acute MI	≤45 Years			Adjusted for age, education, family history of infarction, waist-to-hip ratio, smoking, total energy intake and leisure-time physical activity, hypertension, dyslipidemia, and diabetes	(33)
	0 (g/day)	2.21	1.10–4.45		
	0.1–30.0 (g/day)	1			
	30.1–60.0 (g/day)	1.83	1.01–3.28		
	>60.0 (g/day)	2.17	1.11–4.25		
	>45 Years				
	0 (g/day)	1.3	0.75–2.25		
	0.1–30.0 (g/day)	1.23	0.84–1.80		
	30.1–60.0 (g/day)	1			
	>60.0 (g/day)	2.23	1.40–3.55		
Intervention studies					
Plasma lipid and lipoprotein concentrations					(34)
	Alcohol intake (g/d)		SEE		
Triacylglycerol (mmol/L)	0	1.43	0.071		
	15	1.34			
	30	1.28			
Total cholesterol (mmol/L)	0	5.49	0.06		
	15	5.38			
	30	5.35			
HDL cholesterol (mmol/L)	0	1.4	0.023		
	15	1.43			
	30	1.48			
LDL cholesterol (mmol/L)	0	3.45	0.053		
	15	3.34			
	30	3.29			

(*Continued*)

Table 2
(Continued)

Outcome/endpoint/ case/intervention	Categories	Effect sizes (OR = odds ratio; HR = hazard ratio)	95% Confidence interval	Confounding factors	Ref.
Apolipoprotein A-I (g/L)	0	1.80	0.022		
	15	1.80			
	30	1.85			
Apolipoprotein A-II (g/L)	0	0.342	0.006		
	15	0.344			
	30	0.351			
Apolipoprotein B (g/L)	0	0.947	0.0119		
	15	0.935			
	30	0.917			
Vascular function		Mean	Standard error/95% CI	P	(35)
FMD	Abstinence/control	6.09	0.43	0.29	
Dealcoholized red wine	5.71	0.52			
Red wine	6.5	0.63			
	Beer	6.38	0.66		
GTNMD	Abstinence/control	20.1	1.0	0.23	
	Dealcoholized red wine	20.6	1.2		
	Red wine	21.2	1.3		
	Beer	21.2	1.1		

Endothelin-1	Abstinence/control	14.5	11.2–18.9	0.21
	Dealcoholized red wine	14.7	12.0–18.2	
	Red wine	18.0	14.3–22.8	
	Beer	16.0	12.9–19.9	
Systolic BP	Abstinence/control	122.8	0.48	0.0047
	Dealcoholized red wine	123.5	0.48	
	Red wine	125.0	0.48	
	Beer	124.5	0.48	
Diastolic BP	Abstinence/control	77.0	0.38	NS
	Dealcoholized red wine	77.1	0.38	
	Red wine	77.9	0.38	
	Beer	77.7	0.38	
Heart rate	Abstinence control	64.7	0.46	<0.0001
	Dealcoholized red wine	64.4	0.46	
	Red wine	66.9	0.46	
	Beer	67.2	0.46	

between alcohol intake and the risk of acute coronary syndrome (ACS) by examining 216 hospitalized diabetic patients with a first event of an ACS and 196 frequency-matched (age–sex) diabetic controls without any clinical evidence of CHD. Findings suggest that low alcohol consumption (<12 g/day) was associated with a 47% (odds ratio [OR] = 0.53, 95% CI = 0.28–0.97) reduction of the prevalence of ACS, whereas a higher intake (12–24 and >24 g/day) increased the prevalence by 2.7-fold (OR = 2.72, 95% CI = 1.39–5.38) and 5.4-fold (OR = 5.44, 95% CI = 1.21–24.55), respectively.[15]

Another case control study carried out in Costa Rica, 2090 cases of a first nonfatal acute MI and 2090 population-based controls matched by age, sex, and residence aimed to determine whether alcohol intake and drinking patterns were associated with plasma lipids and the risk of MI in a population with a low intake of wine. Results of this study showed that the lowest risk of MI (OR = 0.44; 95% CI = 0.31–0.61) was observed for those who drank on average three drinks/week (compared with lifelong abstainers), adjusted for several confounders (i.e., smoking, history of diabetes, history of hypertension, abdominal obesity, physical activity, income, intake of total energy, dietary fibre, saturated fat, *trans* fat, and polyunsaturated fat). With respect to the frequency of consumption, researchers have reported that the risk of MI among daily drinkers (OR = 0.64, 95% CI = 0.41–1.01) was not significantly different (p = 0.23) from that of weekend drinkers (OR = 0.76; 95% CI = 0.59–0.98) regardless of the amount consumed (additionally adjusted for folate and total alcohol intake).[30]

So far, the majority of studies have been focused on men. However, evidence continues to emerge indicating the pattern of alcohol consumption as important implications for CVD risk in both genders. Dorn *et al.*[31] aimed to examine the association between volume of alcohol intake and various drinking patterns and nonfatal MI in women aged 35–69 years. A reduced likelihood of MI (OR = 0.67, 95% CI = 0.43–1.03) was observed between current drinkers compared to lifelong abstainers. Furthermore, volume drinks/drinking day and frequency were associated inversely with MI risk (p for trend < 0.001). Wine drinkers (OR = 0.56, 95% CI = 0.33–0.96) and consumers of mixed beverage types (OR = 0.56, 95% CI = 0.31–1.01) had lower odds of MI compared to abstainers. Among current drinkers, for alcohol volume and most patterns, similar but somewhat weaker associations were noted than when abstainers were the reference.[31]

All of the above-mentioned studies were mostly conducted in Caucasians. Wen *et al.*[32] performed a matched case control (1 case to 5 controls) analysis in Chinese people, including 518 MI, 333 hemorrhagic stroke, and 1927 ischemic stroke cases. The aim of this study was to evaluate the associations of selected lifestyle factors (i.e., alcohol, tea, and ginseng consumption; physical activity during adolescence; and weight change from age 20 to 40) with MI and stroke. Results regarding alcohol consumption revealed an inverse association with MI (OR = 0.63, 95% CI = 0.50–0.80). On the other hand, alcohol consumption showed positive associations with hemorrhagic and ischemic stroke (OR = 1.20, 95% CI = 0.92–1.57; OR = 1.04, 95% CI = 0.93–1.17, respectively).[32]

Finally, in a study by Oliveira *et al.*[33] among participants aged ≤ 45 years, alcohol abstainers showed similar a effect in acute MI with those characterised by excessive alcohol habits (>60 g/day) (i.e., OR = 2.21, 95% CI = 1.10–4.45, vs. OR = 2.17, 95% CI = 1.11–4.25) compared to those of light alcohol intake (0.1–30 g/day). This pattern seems to differ among participants over 45 years old, where abstainers have 30% more odds to develop acute MI (OR = 1.30, 95% CI = 0.75–2.25) and excessive alcohol drinkers have increased prevalence by 2.2-fold (OR = 2.23, 95% CI = 1.40–3.55) (Table 2).[33]

Intervention Studies Evaluating the Relationship between Alcohol Intake and CVD Risk Factors

Intervention studies regarding alcohol intake are sensitive to apply due to bioethics. However, two studies (one among women and one among men) were conducted to assess the effect of alcohol intake within a controlled diet scheme in CVD. Baer *et al.*[34] sought to examine the effect of alcohol consumption in CVD among postmenopausal women on blood lipids profile. Postmenopausal women were classified into three groups that consumed 0 drinks/day (controls), 1 drink/day (15 g ethanol/day), and 2 drinks/day (30 g ethanol/day) for 8 weeks as part of a controlled diet in a randomized crossover design. Compared with concentrations after the control diet, plasma low-density lipoprotein (LDL) cholesterol decreased from 3.45 to 3.34 mmol/L ($p = 0.04$) and triacylglycerols from 1.43 to 1.34 mmol/L ($p = 0.05$) after 15 g ethanol/day. Compared with concentrations after the control diet, plasma high-density lipoprotein (HDL) cholesterol increased from 1.40 to 1.43 mmol/L after 15 g ethanol/day ($p > 0.05$) but increased to 1.48 mmol/L after 30 g ethanol/day ($p = 0.02$). Apolipoprotein A-I increased significantly and apolipoprotein B decreased significantly after 30 g ethanol/day relative to their concentrations after the control diet.[34]

A study by Zielkens *et al.*[35] was planned to investigate the controversial issue of the effect of specific alcoholic beverages. More specificically, this study aimed to determine whether red wine may improve vascular function due to its high content of antioxidant polyphenolic compounds, by including four interventions: (1) abstention from all alcohol and grape products (control period); (2) 375 mL red wine (13% alcohol/vol, 2023 mg/L polyphenols); (3) 375 mL of the same red wine, which was dealcoholized (0% alcohol/vol, 2094 mg/L polyphenols); and (4) 3 × 375-mL cans of beer (4.6% alcohol vol/vol) each day for 4 weeks. The variation in BP was measured. Results showed that the systolic and diastolic BP were not different between control–abstinence and dealcoholized red wine. However, compared with control–abstinence, both red wine and beer increased awake systolic BP (2.9 and 1.9 mmHg, respectively; $p < 0.05$) (Table 2).[35]

Potential Pathophysiological Mechanisms

Most world populations consume alcoholic beverages. Because alcohol may have both protective and harmful effects on cardiovascular health, identification of the biochemical mechanisms that could explain such paradoxical effects is necessary. The vascular endothelium is the target of important mediating pathways of differential ethanol concentrations, such as oxidative stress, lipoproteins, and insulin resistance. The endothelium is sensitive to changes in blood flow, BP, inflammatory signs, and circulating hormones, with a capacity to integrate hemodynamic and humoral signs and to modulate the vasomotor tone according to the local tissue metabolic needs. Endothelial dysfunction precedes the formation of atheromatic plaque and has a predictive value for the development of CVD.[36,37]

Harmful effects of alcohol on the cardiovascular system include congestive cardiomyopathy, systemic hypertension, and cerebral vascular incidents.[1] Compromised heart function is regularly seen in patients with chronic alcohol ingestion and is often marked as cardiomegaly, reduced myocardial contractility, myocardial fibrosis, enhanced risk of stroke and hypertension, and disruptions in the myofibrillary structure. A number of mechanisms including oxidative damage, deposition of triacyloglycerols, altered fatty acid extraction, decreased myofilament $Ca^{(2+)}$ sensitivity, and impaired protein synthesis

have been proposed for the development of alcoholic cardiomyopathy. Several alcohol metabolites have been identified as specific toxins of myocardial tissue, including acetaldehyde and fatty acid ethyl esters. Acetaldehyde directly impairs cardiac contractile function, disrupts cardiac excitation–contraction coupling, and promotes oxidative damage and lipid peroxidation.[38,39]

The protective effects of alcohol against CHD include the stimulation of HDL-mediated processes such as reverse cholesterol transport and antioxidative effects. An important property of HDL is its capacity to take up excess cholesterol from peripheral cells and transport it to the liver for excretion and degradation to bile acids. In addition, a range of mechanisms, such as effects on LDL, haemostasis, and endothelium-dependent functioning of the vascular wall (vasodilation), enhance the protective role of moderate alcohol consumption. A number of other mechanisms have been proposed, including the effects of alcohol on blood clotting and nonalcoholic components of alcoholic beverages, particularly in red wine and dark beer, which may have antioxidant properties due to their polyphenolic content. Certain polyphenols, including flavonoids, which are important component of red wine, have been shown to possess antioxidant and health beneficial properties. This antioxidant capacity may explain why red wine may have more pronounced cardioprotective effects than other alcoholic beverages. In a recent review, Lotito and Frei[40] investigated the relation between flavonoid-rich foods and plasma antioxidant capacity and reported increased plasma antioxidant capacity levels due to wine and beer consumption.[40] The protective effect of red wine is strengthened by its content in antioxidants and not due to its content in ethanol, even though low ethanol intake has the ability to increase antioxidant capacity and improve insulin resistance and thus result in prevention of subsequent hypertensive and atherosclerotic consequences.[41–43]

There is genetic and phenotypic heterogeneity in alcohol response, and despite the apparent beneficial biochemical effects of low doses of ethanol, there is not enough clinical and epidemiological evidence to allow the recommendation of alcohol consumption for abstemious individuals. The findings highlight several of the pathways involved in alcohol response and consumption, such as reward, behavioural dyscontrol, and vulnerability to stress, and demonstrate a role for these pathways during the early stages of alcohol exposure in adolescence, especially in terms of behavioural, neurobiological, and psychological changes that occur during adolescence. Genetic variants that alter functioning of the serotonin, endogenous opioid, and corticotrophin-releasing hormone systems are shown to influence these changes and in some cases interacting with early experience to indicate gene by environment interactions.[44]

Discussion

Identifying genes that may influence alcohol behaviour has been impeded by genetic heterogeneity and the inability to control environmental factors and psychological assessments and questionnaires to quantify alcohol-related phenotypes. It is therefore difficult to design large-scale experiments in humans to verify a causal roles for genes. However, studies in ethnically defined populations have implicated alleles of alcohol dehydrogenase, aldehyde dehydrogenase, the GABAA receptor complex, and the serotonin 1B receptor as contributing to variation in alcohol sensitivity.[45] Furthermore, alcohol-induced endothelial damage or protection may be related to the synthesis or action of several markers (such as nitric oxide, cortisol, endothelin-1, adhesion molecules, tumor necrosis factor alpha, interleukin-6, C-reactive protein, and haemostatic factors), whose expression was found consistent with the J-shaped curve between alcohol consumption and cardiovascular

health.[37] Considering the potential for addiction in alcoholic beverage consumption and other negative consequences of alcohol, it would be worthwhile to identify substances able to mimic the beneficial effects of low doses of ethanol without its adverse effects.[46,47]

Alcohol Drinking and CVD

A protective alcohol-CVD hypothesis is supported by plausible biological mechanisms attributable to ethyl alcohol. Possible nonalcoholic beneficial components in wine (especially red types) could explain the extra protection of wine, but a healthier pattern of drinking or more favourable risk traits in wine drinkers may also be involved. Advice regarding alcohol drinking for health needs to be individualized according to specific risks and benefits. Controversy remains as to whether the alcohol or polyphenols contribute more to the health benefits of regular/moderate wine consumption. The overall effect of wine consumption on health depends upon the total amount consumed, the style, and possibly the pattern of consumption. The apparent effect of wine consumption may be modified by the non-wine diet composition of the consumer in that alcohol may comprise the primary component in consumers with high fruit, vegetable, and whole grain intakes, and the benefits from polyphenols may become significant in diets where wine is the primary dietary source of phytochemicals.[48,49]

On the basis of clinical and experimental data, the favourable effect of moderate intake of alcohol arises from its action on lipids profile, haemostatic parameters, and lowering of inflammation markers. Established effects include increased high-density lipoprotein cholesterol and antithrombotic activity, providing plausible mechanisms for the observed association of moderate drinking with lower risk of CHD but higher risk of hemorrhagic stroke.[50] Red wine has been proposed to provide greater cardiovascular benefit than alcohol alone due to its content of additional constituents (i.e., polyphenols). Studies have demonstrated that polyphenols might reduce atherosclerosis by inhibiting lipoprotein oxidation and thrombosis independent of alcohol. It is the antioxidant and chemopreventive properties of polyphenols and their probable role in the prevention of various diseases associated with oxidative stress (i.e., cancer, cardiovascular, and neurodegenerative diseases) that have assisted in the recognition of the beneficial effect of red wine.[51]

Wine or Alcohol Drinking Regarding Cardiac Health

Although the "French paradox" confirms the favourable effect of modest alcohol consumption on cardiovascular risk, as observed in many epidemiological studies, the superiority of wine over other alcoholic drinks is debatable. Many studies show that wine drinkers tend to have a healthier lifestyle profile than consumers of beer and/or other spirits. In contrast to moderate drinking, there is quite some evidence that incidental heavy or binge drinking is associated with an increased cardiovascular risk. However, van de Wiel and de Lange[4] suggested that protection or harm is related to the quantity of alcohol that we consume rather than the content of the bottle. In addition, binge drinking (defined as consumption of three or more alcoholic drinks within 1 to 2 hours) has deleterious health effects, whereas light-to-moderate alcohol consumption spread over several days of the week appears to yield most of the beneficial health effects.[52] Nevertheless, many confounding factors such as lifestyle, diet, age, race, ethnic background, and education should be taken into account in order to provide further evidence regarding the role of quantity, type, and frequency of alcohol intake in inflammatory biomarkers.[53,54]

Britton and McKee support the role of the alcohol consumption pattern in the recognized beneficial effect of ethanol, rather than the amount of alcohol consumed.[55] Moreover, important cultural differences between countries seem to influence this pattern. For instance, in Mediterranean countries alcohol is consumed as wine with meals, whereas in Northern countries binge drinking is much more frequent. Binge drinking indicates risk behaviour compared to drinking wine at meals and, along with other differences in nutritional habits between these countries, may also be just a proxy to explain the differences in the incident rates of CVD.[56] Nevertheless, further research is warranted, with the hope that careful evaluation of the dose-related effects of alcohol and alcoholic beverages on endothelial function in both conduit and resistance vessels may provide further insight into the balance of cardiovascular risks and benefits anticipated from the regular consumption of alcohol.[57–59]

Conclusion

Alcohol's effects on the cardiovascular system can be beneficial or deleterious, depending on quantity, quality, drinking pattern, and the consumer. Beneficial effects of moderate alcohol drinking include increase in high-density lipoproteins and decreased platelet aggregation and plasma fibrinogen levels. These protective effects are attributed, in part, to phenolic secondary metabolites. Regarding the comparison between drinking wine and other alcoholic beverages in terms of cardiovascular health, the antagonists of inflammatory phospholipid mediators contained in wine (red or white) and the role of antioxidants in reducing LDL oxidation enhance the beneficial effect of wine on the progress of atherogenesis.[60,61] In contrast, the harmful effects of excessive drinking may induce hypertension and hypercoagulability and reduce cerebral blood flow. Although clinical trials or interventional studies are limited due to ethical issues and prospective studies are required to evaluate causality regarding the effect of alcohol as well as the type of alcohol consumed on cardiovascular system, it should be noted that there is no reason to recommend alcohol use to those who do not drink. However, practices to direct heavy drinkers toward becoming low or moderate drinkers are emerging.

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References

1. Seiler, C. Alcohol, the heart and cardiovascular system. Therapeutische Umschau **2000**, *57*(4), 200–204.
2. Gutjahr, E.; Gmel, G. Association of alcohol consumption to mortality and person-years of life lost in Switzerland—measuring the impact of some methodological options. European Journal of Epidemiology **2005**, *20*(1), 37–47.
3. Rehm, J.; Room, R.; Taylor, B. Method for moderation, measuring lifetime risk of alcohol-attributable mortality as a basis for drinking guidelines. International Journal of Methods in Psychiatric Research **2008**, *17*(3), 141–151.
4. van de Wiel, A.; de Lange, D.W. Cardiovascular risk is more related to drinking pattern than to the type of alcoholic drinks. Netherlands Journal of Medicine **2008**, *66*(11), 467–473.

5. Klatsky, A.L. Alcohol and cardiovascular diseases. Expert Review of Cardiovascular Therapy **2009**, *7*(5), 499–506.
6. Halme, J.T.; Seppä, K.; Alho, H.; Poikolainen, K.; Pirkola, S.; Aalto, M. Alcohol consumption and all-cause mortality among elderly in Finland. Drug and Alcohol Dependence **2010**, *106*(2–3), 212–218.
7. Papadakis, J.A.; Ganotakis, E.S.; Mikhailidis, D.P. Beneficial effect of moderate alcohol consumption on vascular disease: myth or reality? Journal of the Royal Society for the Promotion of Health **2000** *120*(1), 11–15.
8. Imhof, A.; Woodward, M.; Doering, A.; Helbecque, N.; Loewel, H.; Amouyel, P.; Lowe, G.D.; Koenig, W. Overall alcohol intake, beer, wine, and systemic markers of inflammation in western Europe, results from three MONICA samples (Augsburg, Glasgow, Lille). European Heart Journal **2004**, *25*(23), 2092–2100.
9. Athyros, V.G.; Liberopoulos, E.N.; Mikhailidis, D.P.; Papageorgiou, A.A.; Ganotakis, E.S.; Tziomalos, K.; Kakafika, A.I.; Karagiannis, A.; Lambropoulos, S.; Elisaf, M. Association of drinking pattern and alcohol beverage type with the prevalence of metabolic syndrome, diabetes, coronary heart disease, stroke, and peripheral arterial disease in a Mediterranean cohort. Angiology **2007**, *58*(6), 689–697.
10. Rajdl, D.; Racek, J.; Trefil, L.; Siala K. Effect of white wine consumption on oxidative stress markers and homocysteine levels. Physiology Research **2007**, *56*(2), 203–312.
11. de Lorgeril, M.; Salen, P.; Martin, J.L.; Boucher, F.; de Leiris, J. Interactions of wine drinking with omega-3 fatty acids in patients with coronary heart disease, a fish-like effect of moderate wine drinking. American Heart Journal **2008**, *155*(1), 175–181.
12. Sacco, R.L.; Elkind, M.; Boden-Albala, B.; Lin, I.F.; Kargman, D.E.; Hauser, W.A.; Shea, S.; Paik, M.C. The protective effect of moderate alcohol consumption on ischemic stroke. JAMA **1999**, *281*(1), 53–60.
13. Bell, R.A.; Mayer-Davis, E.J.; Martin, M.A.; D'Agostino, R.B., Jr.; Haffner, S.M. Associations between alcohol consumption and insulin sensitivity and cardiovascular disease risk factors, the Insulin Resistance and Atherosclerosis Study. Diabetes Care **2000**, *23*(11), 1630–1636.
14. Sieri, S.; Agudo, A.; Kesse, E.; Klipstein-Grobusch, K.; San-José, B.; Welch, A.A.; Krogh, V.; EPIC Working Group on Dietary Patterns. Alcohol consumption in EPIC cohorts from ten European countries. IARC Scientific Publications **2002**, *156*, 173–176.
15. Pitsavos, C.; Makrilakis, K.; Panagiotakos, D.B.; Chrysohoou, C.; Ioannidis, I.; Dimosthenopoulos, C.; Stefanadis, C.; Katsilambros, N. The J-shape effect of alcohol intake on the risk of developing acute coronary syndromes in diabetic subjects, the CARDIO2000 II Study. Diabetic Medicine **2005**, *22*(3), 243–248.
16. Bagnardi, V.; Zatonski, W.; Scotti, L.; La Vecchia, C.; Corrao, G. Does drinking pattern modify the effect of alcohol on the risk of coronary heart disease? Evidence from a meta-analysis. Journal of Epidemiology & Community Health **2008**, *62*(7), 615–619.
17. Niccoli, G.; Bacà, M.; Cosentino, N.; Fabretti, A.; Crea, F. Association between ethanol intake and ischemic heart disease. Recenti Progressi in Medicina **2008**, *99*(11), 565–571.
18. Grønbaek, M. The positive and negative health effects of alcohol and the public health implications. Journal of Internal Medicine **2009**, *265*(4), 407–420.
19. Bell, J.R.; Donovan, J.L.; Wong, R.; Waterhouse, A.L.; German, J.B.; Walzem, R.L.; Kasim-Karakas, S.E. (+)-Catechin in human plasma after ingestion of a single serving of reconstituted red wine. American Journal of Clinical Nutrition **2000**, *71*(1), 103–108.
20. Rimm, E.B.; Stampfer, M.J. Wine, beer, and spirits, are they really horses of a different color? Circulation **2002**, *105*(24), 2806–2807.
21. Moraes, R.S.; Fuch, F.D.; Beltrami-Moreira, L.; Wiehe, M.; Pereira, G.M.; Fuchs, S.C. Risk factors for cardiovascular disease in a Brazilian population-based cohort study. International Journal of Cardiology **2003**, *90*(2–3), 205–211.
22. Fuchs, F.D.; Chambless, L.E.; Folsom, A.R.; Eigenbrodt, M.L.; Duncan, B.B.; Gilbert, A.; Szklo, M. Association between alcoholic beverage consumption and incidence of coronary heart disease in whites and blacks: the Atherosclerosis Risk in Communities Study. American Journal of Epidemiology **2004**, *160*(5), 466–474.

23. Knoops, K.T.B.; de Groot, L.C.P.G.M.; Kromhout, D.; Perrin, A.E.; Moreiras-Varela, O.; Menotti, A.; van Staveren, W.A. Mediterranean diet, lifestyle factors, and 10-year mortality in elderly European men and women, the HALE Project. JAMA **2004**, *292*(12), 1433–1439.
24. Emberson, J.R.; Shaper, A.G.; Wannamethee, S.G.; Morris, R.W.; Whincup, P.H. Alcohol intake in middle age and risk of cardiovascular disease and mortality, accounting for intake variation over time. American Journal of Epidemiology **2005**, *161*(9), 856–863.
25. Bazzano, L.A.; Gu, D.; Reynolds, K.; Wu, X.; Chen, C.S.; Duan, X.; Chen, J.; Wildman, R.P.; Klag, M.J.; He, J. Alcohol consumption and risk for stroke among Chinese men. Annals of Neurology **2007**, *62*(6), 569–578.
26. Beulens, J.W.; Rimm, E.B.; Ascherio, A.; Spiegelman, D.; Hendriks, H.F.; Mukamal, K.J. Alcohol consumption and risk for coronary heart disease among men with hypertension. Annals of Internal Medicine **2007**, *146*(1), 10–19.
27. Britton, K.A.; Gaziano, J.M.; Sesso, H.D.; Djoussé, L. Relation of alcohol consumption and coronary heart disease in hypertensive male physicians (from the Physician's Health Study), American Journal of Cardiology **2009**, *104*(7), 932–935.
28. Mukamal, K.J.; Kennedy, M.; Cushman, M.; Kuller, L.H.; Newman, A.B.; Polak, J.; Criqui, M.H.; Siscovick, D.S. Alcohol consumption and lower extremity arterial disease among older adults. The Cardiovascular Health Study. American Journal of Epidemiology **2008**, *167*(1), 34–41.
29. Panagiotakos, D.B.; Pitsavos, C.; Chrysohoou, C.; Stefanadis, C.; Toutouzas, P. Risk stratification of coronary heart disease through established and emerging lifestyle factors in a Mediterranean population, CARDIO2000 Epidemiological Study. Journal of Cardiovascular Risk **2001**, *8*(6), 329–335.
30. Kabagambe, E.K.; Baylin, A.; Ruiz-Narvaez, E.; Rimm, E.B.; Campos, H. Alcohol intake, drinking patterns, and risk of nonfatal acute myocardial infarction in Costa Rica. American Journal of Clinical Nutrition **2005**, *82*(6), 1336–1345.
31. Dorn, J.M.; Hovey, K.; Williams, B.A.; Freudenheim, J.L.; Russell, M.; Nochajski, T.H.; Trevisan, M. Alcohol drinking pattern and non-fatal myocardial infarction in women. Addiction **2007**, *102*(5), 730–739.
32. Wen, W.; Xiang, Y.B.; Zheng, W.; Xu, W.H.; Yang, G.; Li, H.; Shu, X.O. The association of alcohol, tea, and other modifiable lifestyle factors with myocardial infarction and stroke in Chinese men. CVD Prevention and Control **2003**, *3*(3), 133–140.
33. Oliveira, A.; Barros, H.; Azevedo, A.; Bastos, J.; Lopes, C. Impact of risk factors for non-fatal acute myocardial infarction. European Journal of Epidemiology **2009**, *24*(8), 425–432.
34. Baer, D.J.; Judd, J.T.; Clevidence, B.A.; Muesing, R.A.; Campbell, W.S.; Brown, E.D.; Taylor, P.R. Moderate alcohol consumption lowers risk factors for cardiovascular disease in postmenopausal women fed a controlled diet. American Journal of Clinical Nutrition **2002**, *75*(3), 593–599.
35. Zilkens, R.R.; Burke, V.; Hodgson, J.M.; Barden, A.; Beilin, L.J.; Puddey, I.B. Red wine and beer elevate blood pressure in normotensive men. Hypertension **2005**, *45*(5), 874–879.
36. Puddey, I.B.; Zilkens, R.R.; Croft, K.D.; Beilin, L.J. Alcohol and endothelial function, a brief review. Clinical and Experimental Pharmacology and Physiology **2001**, *28*(12), 1020–1024.
37. Bau, P.F.D.; Bau, C.H.D.; Rosito, G.A.; Manfroi, W.C.; Fuchs, F.D. Alcohol consumption, cardiovascular health and endothelial function markers. Alcohol **2007**, *41*(7), 479–488.
38. Ren, J.; Wold, L.E. Mechanisms of alcoholic heart disease. Therapeutic Advances in Cardiovascular Disease **2008**, *2*(6), 497–506.
39. Covas, M.I.; Gambert, P.; Fitó, M.; de la Torre R. Wine and oxidative stress, up-to-date evidence of the effects of moderate wine consumption on oxidative damage in humans. Atherosclerosis **2010**, *208*(2), 297–304.
40. Lotito, S.B.; Frei, B. Consumption of flavonoid-rich foods and increased plasma antioxidant capacity in humans, cause, consequence, or epiphenomenon? Free Radical Biology and Medicine **2006**, *41*(12), 1727–1746.

41. Whitehead, T.P.; Robinson, D.; Allaway, S.; Syms, J.; Hale, A. Effect of red wine ingestion on the antioxidant capacity of serum. Clinical Chemistry **1995**, *41*(1), 32–35.
42. Serafini, M.; Maiani, G.; Ferro-Luzzi, A. Alcohol-free red wine enhances plasma antioxidant capacity in humans. Journal of Nutrition **1998**, *128*(6), 1003–1007.
43. Crozier, A.; Jaganath, I.B.; Clifford, M.N. Dietary phenolics, chemistry, bioavailability and effects on health. Natural Product Reports **2009**, *26*(8), 1001–1043.
44. Schwandt, M.L.; Lindell, S.G.; Chen, S.; Higley, J.D.; Suomi, S.J.; Heilig, M.; Barr, C.S. Alcohol response and consumption in adolescent rhesus macaques: life history and genetic influences. Alcohol **2010**, *44*(1), 67–80.
45. Morozova, T.V.; Anholt, R.R.H.; Mackay, T.F.C. Phenotypic and transcriptional response to selection for alcohol sensitivity in *Drosophila melanogaster*. Genome Biology **2007**, *8*(10), R231, 8–15, doi:10.1186/gb–2007–8–10–r231.
46. Foppa, M.; Fuchs, F.D.; Duncan, B.B. Alcohol and atherosclerosis. Arquivos Brasileiros de Cardiologia **2001**, *76*(2), 171–176.
47. Saremi, A.; Rohit, A. The cardiovascular implications of alcohol and red wine. American Journal of Therapeutics **2008**, *15*(3), 265–277.
48. Walzem, R.L. Wine and health, state of proofs and research needs. Inflammopharmacology **2008**, *16*(6), 265–271.
49. Di Castelnuovo, A.; Costanzo, S.; di Giuseppe, R.; de Gaetano, G.; Iacoviello, L. Alcohol consumption and cardiovascular risk, mechanisms of action and epidemiologic perspectives. Future Cardiology **2009**, *5*(5), 467–477.
50. Mukamal, K.J.; Rimm, E.B. Alcohol consumption, risks and benefits. Current Atherosclerosis Reports **2008**, *10*(6), 536–543.
51. Liu, Z.; Hu, M. Natural polyphenol disposition via coupled metabolic pathways. Expert Opinion on Drug Metabolism and Toxicology **2007**, *3*(3), 389–406.
52. Djoussé, L.; Gaziano, J.M. Alcohol consumption and heart failure, a systematic review. Current Atherosclerosis Reports **2008**, *10*(2), 117–120.
53. Galimanis, A.; Mono, M.L.; Arnold, M.; Nedeltchev, K.; Mattle, H.P. Lifestyle and stroke risk, a review. Current Opinion in Neurology **2009**, *22*(1), 60–68.
54. Mente, A.; de Koning, L.; Shannon, H.S.; Anand, S.S. A systematic review of the evidence supporting a causal link between dietary factors and coronary heart disease. Archives of Internal Medicine **2009**, *169*(7), 659–669.
55. Britton, A.; McKee, M. The relation between alcohol and cardiovascular disease in Eastern Europe, explaining the paradox. Journal of Epidemiology & Community Health **2000**, *54*(5), 328–332.
56. Fuchs, F.D.; Chambless, L.E. Is the cardioprotective effect of alcohol real? Alcohol **2007**, *41*(6), 399–402.
57. van Tola, A.; Hendriksb, H.F.J. Moderate alcohol consumption, effects on lipids and cardiovascular disease risk. Current Opinion in Lipidology **2001**, *12*(1), 19–23.
58. Karatzi, K.; Papamichael, C.; Aznaouridis, K.; Karatzis, E.; Lekakis, J.; Matsouka, C.; Boskou, G.; Chiou, A.; Sitara, M.; Feliou, G.; Kontoyiannis, D.; Zampelas, A.; Mavrikakis, M. Constituents of red wine other than alcohol improve endothelial function in patients with coronary artery disease. Coronary Artery Disease **2008**, *15*(8), 485–490.
59. Vasdev, S.; Gill, V.; Singal, P.K. Beneficial effect of low ethanol intake on the cardiovascular system, possible biochemical mechanisms. Vascular Health and Risk Management **2006**, *2*(3), 263–276.
60. Fragopoulou, E.; Antonopoulou, S.; Nomikos, T.; Demopoulos, C.A. Structure elucidation of phenolic compounds from red/white wine with antiatherogenic properties. Biochemica et Biophysica Acta. **2003**, *1632*(1–3), 90–99.
61. Fragopoulou, E.; Nomikos, T.; Karantonis, H.C.; Apostolakis, C.; Pliakis, E.; Samiotaki, M.; Panayotou, G.; Antonopoulou, S. Biological activity of acetylated phenolic compounds. Journal of Agricultural and Food Chemistry **2007**, *55*(1), 80–89.