Wine and Cardiovascular Health

A Comprehensive Review

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ABSTRACT: Alcoholic beverages have been consumed for thousands of years, attracting great human interest for social, personal, and religious occasions. In addition, they have long been debated to confer cardioprotective benefits. The French Paradox is an observation of a low prevalence of ischemic heart disease, with high intakes of saturated fat, a phenomenon accredited to the consumption of red wine. Although many epidemiological investigations have supported this view, others have attributed it to beer or spirits, with many suggesting that the drink type is not important. Although excessive consumption of alcoholic beverages is commonly regarded to be detrimental to cardiovascular health, there is a debate as to whether light-to-moderate intake is cardioprotective. Although there is extensive epidemiological support for this drinking pattern, a consensus has not been reached. On the basis of published work, we describe the composition of wine and the effects of constituent polyphenols on chronic cardiovascular diseases.

Alcoholic beverages have been consumed for thousands of years, predating biblical times and spanning as far back as early human emergence. Before there was wine, beer, or spirits, primates lived on a diet predominantly consisting of fruits and vegetables, with water serving as the main fluid for survival. Until proper methods of water delivery and decontamination were conceived, our ancestors relied on fresh water from streams, rivers, and precipitation, but fermented fruits including berries and even mead could have been regularly consumed in the form of drinks. Following the Neolithic era ≈10 000 BC, cultivation and maintenance of crops allowed for the production of the earliest forms of what we now consider wine and beer; however, alcohol was almost certainly consumed much earlier. Fruits, grains, and even honey were fermented to produce alcoholic beverages, and alcohol became a staple of consumption to our hunter-gatherer predecessors.[1]

There is no doubt that wine and alcohol have attracted great human interest for recreational and personal use.[1] The culture of drinking has only grown since its initiation, and fermented products including fruits and grains have been used to produce alcoholic beverages. In addition, scientific intrigue has also grown extensively for alcohol since the 20th century, as epidemiological evidence amassing large prospective, cross-cultural studies emerged in support for the hypothesis of a negative correlation with moderate consumption of alcohol and ischemic heart disease (IHD).[2] Such correlation has also been reported individually for red wine.[3] Although evidence of these cardiovascular benefits is inconsistent and heavily debated by physicians and scientists alike,[4] epidemiological studies have strongly

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supported this view being specific to wine,[5] especially red wine. More specifically, some postulate that red wine's bioactive constituents, polyphenols, impart cardioprotective effects.[6] Others argue that there may be an equilibrium between alcohol and wine polyphenols, which in concert would be accountable for the cardioprotective benefits in the human body.[7]

The French Paradox is a term derived from the observation of a decreased incidence of IHD despite a high intake of saturated fat.[8] This is linked to France and led scientists to attribute this phenomenon to the high consumption of wine.[8] The French Paradox started extensive research into wine and led to the identification of many compounds, namely polyphenols, that are thought to be the basis of wine's apparent cardioprotective potential. Red wine, among other constituents, is also included in the Mediterranean diet, and this diet has been labeled as beneficial by scientific advisory committees.[9]

Although excessive or binge drinking of alcoholic beverages is regarded to be detrimental to cardiovascular and general health, light-to-moderate intake of regular amounts is recommended in the literature.[10] Adverse effects of acute and chronic alcohol consumption are dependent on the doses of intake; however, differing opinions exist regarding red wine's potential as a therapeutic agent, regardless of the pattern of drinking.[11] From a public health perspective, alcohol consumption is regarded as a risk factor for chronic diseases, and globally it contributes to an increase in disease burden.[12] Although these detrimental risks are present and may outweigh the benefits of alcohol consumption, wine and alcohol will continue to be ever-present in our society.

With a popular drink like wine surrounded by such scientific intrigue, it is desirable to provide a comprehensive account, from a cardiovascular point of view, of its anatomy, mechanisms of actions, and risks and benefits of consumption. Most reviews and meta-analyses to date have focused on the individual characteristics of wine, but a much more inclusive review of the literature on wine and its comparisons with other alcoholic beverages is needed. This review aims to investigate wine and its cardioprotective potential, highlight the importance of individual components of wine and their interactions with the cardiovascular system at large, and present up-to-date epidemiological and experimental evidence of wine's impact on chronic cardiovascular diseases. We also address the debate around the light-to-moderate intake of consumption, variable definitions of drinking, and current recommendations for consumption.

DEFINITIONS OF CONSUMPTION

What Constitutes a Standard Drink?

Alcoholic intake, if not monitored, can contribute to various adverse conditions that affect day-to-day life.[13] Hence, governments and international institutions have defined a unit called a "standard drink."[14] Epidemiological and experimental studies take advantage of this metric to quantify consumption and assess population risk. Therefore, a standard drink size has become an important, but often publicly misunderstood metric, for population-based studies assessing phenomena related to the intake of alcohol. Quite apparent from the literature is the definition of a standard drink, which varies across country borders and across the scientific literature.[15]

A standard drink, or a unit of alcohol in the United Kingdom, is a national concept that is expressed in amounts of pure ethanol.[16] To the general public, it is presented in amounts of beer, wine, or spirits, because they are the most commonly consumed beverages.[16] The units of alcohol in a beverage can vary depending on the source, but most common ones include standard drink, grams, milliliters, ounces, and alcoholic concentration by volume.[17]

The guidelines from the World Health Organization (WHO) on standard drink assume 1 standard drink to be 10 g of pure ethanol, with recommendations of not exceeding 2 standard drinks per day, with at least 2 nondrinking days during the week.[18] This definition is not widely adopted across country borders and carries great country-to-country variation. Kalinowski and Humphreys[14] systematically gathered international guidelines on standard drink definitions. Their methods of analysis and most important findings are summarized in Table 1. They identified 75 governments that did not adopt such a definition. Their analysis included 37 countries that did adopt the WHO standard drink measure but cited large variability between countries, ranging from 8 to 20 g. The authors further reported the 10-g WHO guideline to be the modal definition between countries, with variations ranging from 10 g/d to 56 g/d for low-risk alcohol consumption. The standard drink is defined in terms of pure ethanol. Red wine, beer, and spirits are all composed of some percentage of pure ethanol. The WHO guidelines present a guide on calculating the alcoholic content of a beverage.[18] The method of calculation, variables, and values are presented in Table 2. The alcoholic content within a drink depends on 2 variables: size of beverage and percent strength of pure ethanol.[18] These variables vary across countries, cultures, and even vendors, but this guideline presents the most common scenario as a tool for drinkers to calculate the amount of pure ethanol in a drink.

A quantitative measure of a standard drink is essential; however, given the mathematical nature, the general public has difficulty comprehending it and would rather prefer a more qualitative, day-to-day metric to regulate their consumption. The WHO guidelines define a standard drink in terms of glasses of wine, beer,

Table 1. Most Important Methods and Findings of Governmental Standard Drink Definitions and Low-Risk Consumption

	Outcomes	Comments
Data collection period	May to August 2015	–
Mode of data collection	Government health nutrition websites Health ministries FAO ISPOR Personal communications with country-specific experts Personal contacts	Most data accumulation through Internet searches. Personal communication with country-specific experts was through email.
Analysis of countries	37 countries included 4 countries (Lesotho, Israel, Norway, Netherlands) did not create standard drink definitions and low-risk guidelines Unable to locate definitions from 15 countries	The starting point of analysis was the list of WHO countries. Authors also included countries not on the list.
Guidelines across countries	Standard drink definition WHO=10 g Modal standard drink size=10 g Low-risk consumption Men: 10–56 g/d Women: 10–42 g/d	Low-risk consumption guidelines were variable across countries, and the range was presented in the analysis.
Guidelines discrepancies	Some countries defined standard drinks exactly, whereas others gave approximations and ranges. Variable guidelines for low-risk consumption across countries. Wide national variability across nations. Discrepancies within a country: Austria: Domestic standard drink size of 20 g, but health ministry documents suggest a size of 8 g. Malaysia and Malta: Standard drink definitions available but no low-risk consumption guidelines. Japan: Low-risk consumption guidelines available but no defined standard drink.	–
Limitations	Some data collected from personal accounts.	–

FAO indicates Food and Agriculture Organization of the United Nations; ISPOR, International Society for Pharmacoeconomics and Outcomes Research; and WHO, World Health Organization.

Adapted from Kalinowski and Hymphreys[14] with permission of the publisher. Copyright © 2016, John Wiley & Sons.

liquor, and shots of spirits (Table 3). They claim that these amounts roughly equal 1 standard drink.

Light, Moderate, and Excessive Consumption

Voskoboinik and coauthors[19] define light alcohol consumption as <7 standard drinks (std) per week, moderate as 7–21 std/wk, and excessive as >21 std/wk. This translates to <1 std/d for light consumption, 1–3 std/d for moderate, and >3 std/d for excessive consumption, where 1 standard drink is defined as 12 g of pure ethanol.

IMPORTANCE OF WINE AS A BIOLOGICAL BEVERAGE

The molecular properties of wine and their interactions with the human body were extensively researched after a negative correlation for IHD was reported with alcohol consumption. Since then, researchers have focused on pinpointing how this beverage imparted cardioprotection against chronic cardiovascular diseases. After fermentation, wine still possesses a mixture of compounds known as polyphenols that, besides ethanol, have emerged as key players in explaining red wine's antioxidant, anti-inflammatory, and cytoprotective properties.[20]

Why Red Wine? The Hypothesis

St Leger and colleagues[3] reported a negative correlation between alcohol consumption and IHD deaths, and attributed this observation predominantly to wine. Renaud and de Lorgeril[8] subsequently described what they called the French Paradox, referring to the indirect observation that the French population consumed red wine with their diet, which was mostly high in saturated fat, so this correlation between wine and cardiovascular mortality was attributed to the consumption of red wine.[21] Since then, numerous studies have come out in favor of wine and alcohol conferring cardiovascular benefits, but with one important caveat: most of these investigations, although involving large sample sizes with cross-cultural and geographical comparisons, were epidemiological. Scientists have thus questioned these results, but intrigue still surrounds the community. Several explanations for the French Paradox have been postulated,[21] with epidemiologists presenting strong correlations in favor of wine (both

Table 2. The World Health Organization's Guidelines on Alcohol Content Calculation of a Beverage

Type of Beverage	Approximate Size of Beverage, mL*	Strength, % Pure Ethanol†	Conversion Factor‡	Formula for Standard Drink
Wine	140	10.5–18.9	0.79	Standard drink=beverage size × strength × conversion factor
Beer	330	2–5	0.79	
Spirits	40	24.3–90	0.79	

*Beverage containers vary in size but are approximately in this range.
†The common strengths of beverage as described from the WHO report.
‡Conversion factor allows for a conversion of volume (of ethanol) to grams (of ethanol).
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white and red), with other scientific literature criticizing these observations.

Red Wine Composition

Wine is an alcoholic beverage of complex composition that is obtained through the fermentation of grape must, and thus the quality and variety of grapes used in the vinification process have an impact on the composition of wine.[22] Red wine is composed of >500 compounds, with the most important constituents being water, alcohol (ethanol), and polyphenols.[23] They can be divided into 2 primary groups: the flavonoids and nonflavonoids. The general composition of wine can be viewed in Figure 1. Flavonoids have been known to provide taste and color to wine while being important for health, while resveratrol (nonflavonoid) is debated to contribute to the potential bioactive properties of wine. Polyphenols amount to only a fraction of wine's total content, but are of particular interest in cardiology for their potential biological and cardioprotective properties.

Red Wine Versus White Wine

Red wine is known to be 10-fold higher in polyphenolic content than white wine, and this variability arises because of red wine's grape must fermentation.[22] This is why white wine is given much less importance than red wine in the literature. In addition, apart from the varying sugar content, polyphenols are the only major component different between red and white wines. There are few studies directly comparing the effects of the 2 drinks; therefore, conclusive evidence regarding the comparison of the 2 wines is poor. Because the polyphenolic ratio in red and white wines differs significantly, white wines' protective mechanisms may be different from red wines'. Bertelli[24] postulates that relatively unknown active compounds identified in white wines, namely tyrosols, caffeic acid, and shikimic acids, might explain the biological basis of white wine's cardioprotective effects.

BIOACTIVE COMPONENTS OF RED WINE

Bioavailability of Polyphenols

The biological properties of polyphenols are only utilizable if they are bioavailable, which is dictated primarily by their chemical structure. Most polyphenols cannot be absorbed in their native form and are chemically modified after ingestion. Post–wine consumption, polyphenols are structurally modified and metabolized fairly quickly; thus, a component of the biological activity from wine is derived from metabolized polyphenols.[25] The bioavailability of wine polyphenols is low; however, there is consistent evidence that bioavailable concentrations after acute and chronic consumption of wine are able to exert beneficial biological effects in vivo.[24]

Flavonoids

Flavonoids are plant-based antioxidants that are included in the family of polyphenols. They are found primarily in vegetables, fruits, and beverages such as tea and wine.[26] Flavonoids can be synthesized only by plants and have been investigated for their protective abilities against chronic cardiac diseases (Figure 2). In the previous few decades, flavonoids have received much attention after epidemiological investigations specifically discovered that dietary flavonoids were inversely associated with IHD mortality.[27] Flavonoids from red wine have been credited to inhibit low-den-

Table 3. The World Health Organization's Estimates of a Standard Drink for Conventional Alcoholic Beverages

Type of Beverage	Standard Drink Equivalent	Quantitative Metric
Wine	1 glass of wine; 1 small glass of sherry	140 mL (12% strength); 90 mL (18% strength)
Beer	1 can of beer	330 mL (5% strength)
Spirits	1 shot of whisky, gin, vodka; 1 small glass of liquor	40 mL (40% strength); 70 mL (25% strength)

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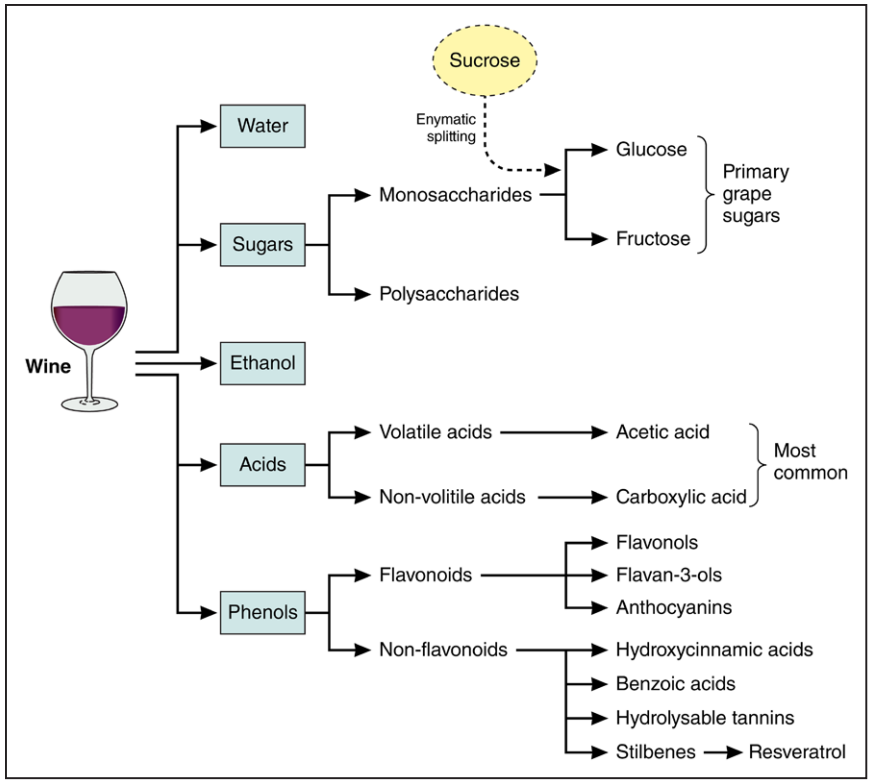

Figure 1. Overview of the chemical components of wine.

sity lipoprotein (LDL) oxidation[28] and prevent endothelial dysfunction,[29] which is postulated to increase atherosclerosis development.[30] Hence, flavonoids have antiatherosclerotic properties that are particularly apparent when wine is studied devoid of ethanol, as dealcoholized wine (see Dealcoholized Red Wine: Cardioprotection of Wine Polyphenols Beyond Ethanol). Of the flavonoids, quercetin is known to be a potent antioxidant because it has been shown to have a negative correlation with cardiovascular mortality.[29] In a dietary investigation of >1000 participants, high quercetin intakes were associated with lower IHD mortality (relative risk [RR], 0.79; 95% confidence interval [CI], 0.63–0.99; *P*=0.02) and lung cancer incidence (RR, 0.42; 95% CI, 0.25–0.72; *P*=0.001).[31]

Quercetin

Quercetin, a plant polyphenol from the flavonoid group, has amassed much scientific intrigue. It is an important dietary flavonoid that is prominent in red wine and the Mediterranean diet.[32] Of the flavonoid group, it is the most abundant dietary flavonoid that has been investigated for its antihypertensive, anti-inflammatory, acute platelet thrombogenesis, and protective capabilities against IHDs.[33]

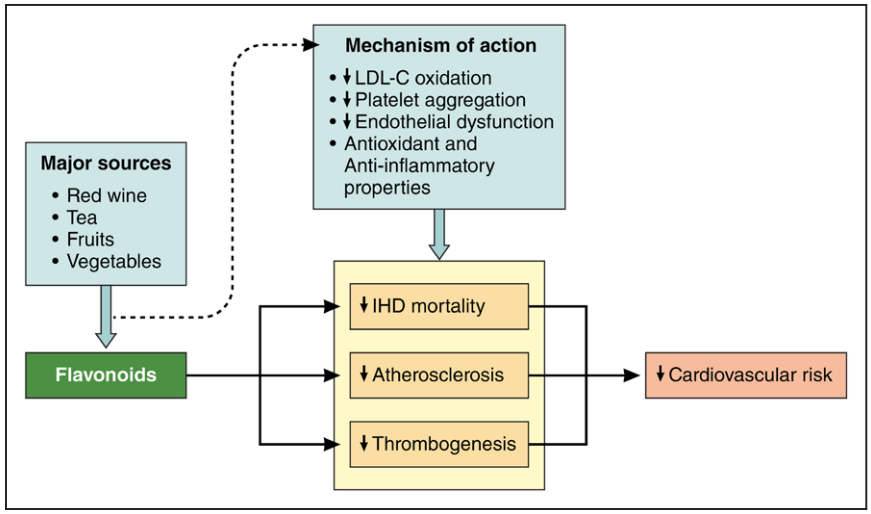

Figure 2. The cardioprotective effects and implicated mechanisms of flavonoids in cardiovascular risk reduction.
IHD indicates ischemic heart disease; and LDL-C, low-density lipoprotein cholesterol.

Quercetin is found as a conjugated derivative in plasma, and those metabolites subsequently exert physiological effects.[34] Quercetin is known to be an effective free radical scavenger that prevents LDL oxidation in humans.[35] It causes endothelium-dependent vasodilation of vascular smooth muscles and inhibits platelet aggregation, which can subsequently contribute to atherosclerosis.[29] In apolipoprotein E gene–deficient mice, Loke and colleagues[36] studied quercetin and other dietary flavonoids' capabilities to reduce atherosclerotic lesions. This group demonstrated that quercetin attenuated lesions by inhibiting inflammation, improving nitric oxide (NO) bioavailability, and inducing heme oxygenase-1, which all seemed to have been protective. In human subjects, however, contradictory results have come to light, showing that dietary quercetin did not change biomarkers of inflammation.[37] To elucidate causation, further dose-response, randomized, and placebo-controlled studies are needed.

In dogs with experimental myocardial infarction, quercetin intervention led to an improvement in left ventricular contractile function.[38] Similarly, quercetin has further been documented to protect the myocardial tissue against reperfusion injury and global ischemia.[39]

Resveratrol

Resveratrol is a nonflavonoid stilbene derivative produced by plants that is prominently present in red wine and grapes.[40] Resveratrol from red wine is postulated to be an important contributor in explaining the French Paradox. The increased publicity of resveratrol's bioactive potential and treatment of chronic disorders such as cardiovascular diseases and cancer has engaged public interest in resveratrol supplements.[41]

A number of preclinical and clinical studies have demonstrated a very low oral bioavailability for resveratrol[42]; however, Goldberg and coworkers[43] demonstrated that resveratrol and other polyphenols reached peak concentrations 30 minutes postprandial, with the absorption of transresveratrol being 20-fold more efficient than the flavonoid catechin.[44] However, broadly speaking for all polyphenols, the bioavailability is enough to exert antioxidant effects. A wealth of data has been collected on resveratrol and its effects on hypertension, atherosclerosis, stroke, myocardial infarction, and heart failure.[45] In general, beneficial effects of the administration of resveratrol as a supplement have been reported for the aforementioned diseases and may be one of the reasons why this compound is being heavily advertised as a cardioprotective supplement.

PUTATIVE MECHANISMS OF ACTION

According to reports, the exact mechanisms of action that underlie cardioprotection for red wine have not yet been causally interpreted; however, in vitro, in vivo, and human epidemiological studies have shown cardiovascular benefits of drinking red wine, and have postulated interesting explanations for cardioprotection. A summary of the biological events and triggering chemicals is presented in Figure 3.

Protective Mechanisms: Red Wine Polyphenols and Ethanol

Red wine polyphenols reduce platelet aggregation[46] and improve fibrinolysis.[47] The endothelium controls NO release, which subsequently regulates vascular tone, relaxes vascular smooth muscle cells, and inhibits platelet aggregation.[48] Moderate wine consumption increases NO production,[49] which induces vasodilation.[29] Endothelial dysfunction reduces NO bioavailability that is associated with cardiovascular diseases including atherosclerosis, thrombosis, and hypertension.[48] In regard to hypertension, alcohol consumption in moderation is linked to a reduction in systolic and diastolic blood pressure.[50]

Polyphenols are strong antioxidants that improve the lipid profile by reducing the susceptibility of LDL to oxidation.[28] Conversely, the intake of red wine increases blood high-density lipoprotein (HDL) levels and triglycerides.[51] A meta-analysis of 42 human studies[52] found that an experimental dose of 30 g ethanol/d increases concentrations of HDL cholesterol (3.99 mg/dL; 95% CI, 3.25–4.73), triglycerides (5.69 mg/dL; 95% CI, 2.49–8.89), and apolipoprotein AI (8.82 mg/dL; 95% CI, 7.79–9.86), a main protein in HDL cholesterol. Case presentations have supported the hypothesis of HDL cholesterol and apolipoprotein AI deficiencies playing a significant role in an increased risk of atherosclerosis.[53]

Alcohol intake at regular intervals is observed to be beneficial for diabetes mellitus. Light-to-moderate consumption enhances insulin sensitivity by increasing insulin-mediated glucose uptake.[54] Increased insulin sensitivity is proposed to be associated with greater HDL cholesterol and apolipoprotein AI levels[55] and possibly contributes to a decreased incidence of IHD.[56]

Pathophysiological Mechanisms: Alcohol and Atrial Fibrillation

Atrial fibrillation (AF) is the most common arrhythmia encountered in clinical practice.[57] Consumption of alcohol may trigger AF, and sustained consumption may cause atrial electric remodeling.[19] Voskoboinik and coworkers[19] reviewed alcohol's effects on AF and concluded that its consumption was a risk factor for AF, causing increased recurrence and higher rates of paroxysmal and persistent AF. They further commented that the cardioprotective benefits of alcohol on IHD do not apply to AF. In a UK cohort (N=703 777), moderate-to-

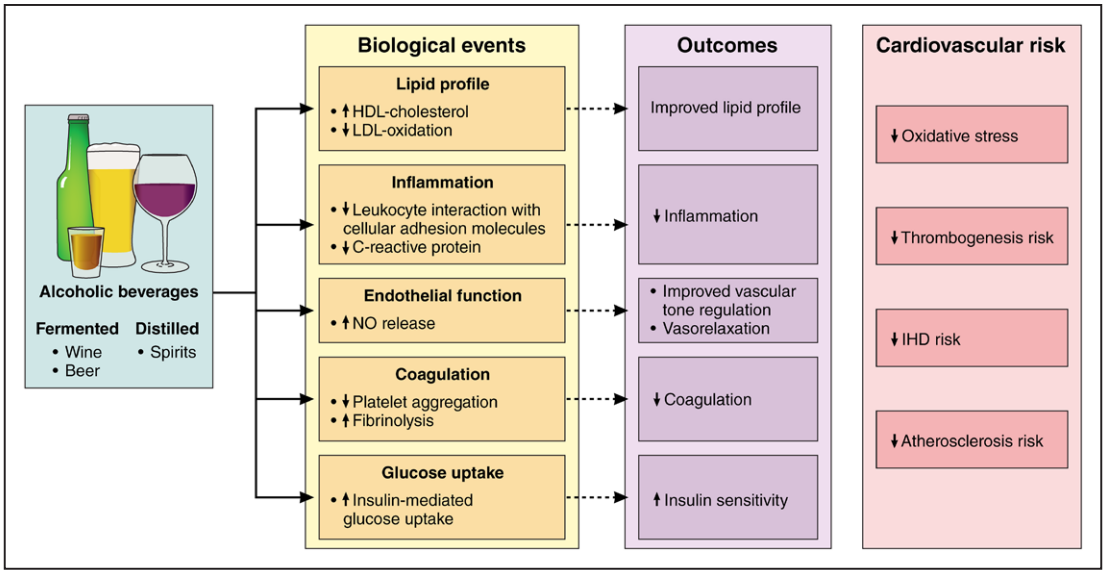

Figure 3. Schematic representation of the biological mechanisms of alcohol intake.
HDL indicates high-density lipoprotein; IHD, ischemic heart disease; LDL, low-density lipoprotein; and NO, nitric oxide.

high consumption of alcohol was identified as an independent risk factor for progression of paroxysmal AF to persistent AF (odds ratio, 2.7; 95% CI, 1.2–6.0).[58] In 115 patients with a recorded idiopathic AF episode, patients who experienced recurrence (n=32) had a significantly higher incidence of consuming alcohol regularly (P=0.014).[59] Alcohol's effects on cardiac conduction have also been investigated. In a pilot study of 14 patients with a reported heart disease, acute excessive alcohol intake slowed intra-atrial conduction and shortened ventricular myocardial refractory periods.[60] As for interatrial conduction, which is usually measured by the P-wave duration and has been found to be a predictor of AF;[61] a study showed that average P-wave duration was significantly affected after alcohol intake in normal healthy subjects (107±9 versus 125±11; P<0.05).[62] However, the duration was more altered after alcohol consumption for patients with a documented history of paroxysmal AF than in control subjects (125±11 versus 158±29; P<0.05).

THE FRENCH PARADOX AND BEYOND

Renaud and de Lorgeril[8] first coined the term French Paradox in 1992, an observation of low IHD and associated mortality despite the high intake of saturated fat in southern France. The authors attributed the cardioprotective effects of this phenomenon to the moderate consumption of alcoholic beverages, especially red wine, which was highly consumed in the area. Although Renaud and de Lorgeril strengthened their association between wine consumption and IHD by controlling for dairy fat intake,[63] other authors have argued that there were characteristics and confounding variables not controlled for in their analysis (drinking patterns, lifestyle characteristics, dietary intake, human behavior) which may have led to such a correlation.[64]

Role of Wine Versus Other Alcoholic Beverages on IHD and Total Mortality

A J- or U-shaped relationship between alcohol consumption and total mortality has been well documented,[65] with the first incidence being reported as a U-shaped curve between IHD mortality for heavy male smokers and nonsmokers in the Framingham Heart Study.[66] Since then, several investigators have focused on exploring the effects of specific alcoholic beverages on IHD. An L-shaped relation between cardiovascular mortality and alcohol intake has been shown,[67] implying that a low dose of alcohol intake can have protective effects that do not decrease with elevated intakes. Many studies have reported inverse associations between specific types of alcoholic drinks and IHD. No consistent pattern of a specific type of alcoholic drink (wine, beer, or spirits) reducing the risk of IHD has been confirmed, rather a strong epidemiological accord that all alcoholic drinks are linked with a reduction in risk from IHD, if not consumed in excessive amounts, or binged on. Rimm and colleagues[64] conducted a systematic review assessing the risk of specific alcoholic drinks on IHD. Focusing on ecological, case-controlled, and cohort studies, they identified 4 investigations that reported an inverse association between wine intake and IHD and mortality,[68–71] 4 that correlated beer intake and coronary events,[68,72–74] and 3 with an emphasis on a correlation for spirits.[2,74,75] A summary of selected major clinical studies reporting the associations between IHD and alcohol consumption, including wine, is presented in Table 4. The 3 largest prospective studies mentioned

Table 4. Major Studies Examining the Relationship Between Alcohol Consumption of Wine, Beer, and Spirits

Studies	Sample Size, n	Setting	Study Design	Follow-up	Age Range, y	Alcoholic Drinks Assessed	Incidences, n	Significant Findings Related to IHD and Mortality
Keil et al[67]	2084 (1071 men; 1013 women)	Augsburg, Germany	Population-based prospective cohort	8 y	45–64	Wine, beer, and spirits Results in favor of beer	All-cause mortality: 141 (96 men; 45 women) IHD-associated mortality: 62 men	In men, RR for IHD in drinkers vs nondrinkers was 0.51 (95% CI, 0.27–0.95) Report a cardioprotective effect from IHD in a predominantly beer-drinking population (starts with 0.1–0.99 g/d alcohol intake, and effect did not decrease with higher intake)
Grønbæk et al[68]	24 525 (13 064 men; 11 459 women)	Copenhagen, Denmark	Population-based prospective cohort	257 859 person-years	20–98	Wine, beer, and spirits Results in favor of wine	Total mortality: 4833 IHD-associated mortality: 1075	Wine drinkers had lower mortality from IHD than nonwine drinkers (P=0.007). At all levels of intake of alcohol, wine drinkers were at a significantly lower risk for all-cause mortality than nonwine drinkers (P<0.001).
Stampfer et al[69]	87 526 women	United States (11 states)	Population-based prospective cohort	334 382 person-years	34–59	Wine, beer, and spirits	200 IHD incidences (164 nonfatal MI, 36 deaths) 66 ischemic strokes 28 subarachnoid hemorrhages	Women who consumed 5–14 g alcohol/d had a RR of 0.6 (95% CI, 0.4–0.9); 15–24 g/d RR 0.6 (95% CI, 0.3–1.1); ≥25g/d RR 0.4 (95% CI, 0.2–0.8). Report that for middle-aged women, moderate alcohol consumption decreased the risk of IHD.
Levantesi et al[70]	11 248 (9601 men; 1647 women)	Italy	Results from a multicenter open-label study	37 021 person-years	Cohort not controlled for age	Wine Results in favor of wine	889 IHD incidences 169 strokes 264 sudden cardiac death	Moderate intake of wine was associated with a significant reduction of cardiovascular events including cardiovascular death, nonfatal MI, or nonfatal strokes: HR, 0.87 (95% CI, 0.76–0.99). Risk of cardiovascular events was significantly reduced by 13% with wine consumption up to 0.5 L/d (defined as moderate consumption).
Yano et al[72]	7705 men	Hawaii	Prospective cohort	8 y	Cohort not controlled for age	Wine, beer, and spirits Results in favor of beer	294 IHD incidences IHD-associated mortality: 43 136 nonfatal MI 27 ACI 88 angina pectoris	Significant negative association between moderate alcohol consumption (defined as ≤60 mL/d), mainly from beer, and IHD and nonfatal MI risk.

(*Continued*)

Table 4. Continued

Studies	Sample Size, n	Setting	Study Design	Follow-up	Age Range, y	Alcoholic Drinks Assessed	Incidences, n	Significant Findings Related to IHD and Mortality
Salonen et al[75]	4063 men	Eastern Finland	Prospective cohort	7 y	30–59	Beer and spirits Results in favor of spirits	209 acute MI 31 liver cirrhosis or acute pancreatitis 223 all-cause deaths	Spirits use at least once per week or more was associated with a significant reduction in acute MI risk: RR, 0.3 (95% CI, 0.1–0.7). Consumption of beer did not have a significant relationship with acute MI risk.
Rimm et al[2]	51 529 men	United States	Prospective cohort	72 290 person-years	40–75	Wine, beer, and spirits Results in favor of wine	350 coronary events (164 nonfatal MI, 50 coronary deaths, 12 sudden deaths) 136 CABG or PTCA procedures	Significant inverse relation between alcohol consumption and total coronary events (P=0.0001). Inverse correlation between IHD and alcohol consumption (P=0.0005).

ACI indicates acute coronary insufficiency; CABG, coronary artery bypass graft; CI, confidence interval; HR, hazard ratio; IHD, ischemic heart disease; MI, myocardial infarction; PTCA, percutaneous transluminal coronary angiography; and RR, relative risk.

(N=87 526 women; 81 825 men and women; 51 529 men),[2,69,71] where the absolute consumption of wine, beer, and spirits would be the greatest, found that the risk of IHD was lower with all 3 types of drinks, with no particular drink emerging as a clear winner.[64]

A prospective observational study by Klatsky and Armstrong[71] found that individuals who preferred wine were at a lower risk of death from IHD, after comparisons with spirits drinkers as a reference group (RR, 0.7; 95% CI, 0.5–0.9). To support their findings, this group reported an inverse association between IHD risk and frequency of wine consumption, but they were not able to confidently conclude that wine confers a greater protective advantage because of user differences and the inability to control for all potentially confounding variables. A Danish cohort study[68] assessing the population for all 3 types of alcoholic drinks in a homogeneous setting, where not 1 alcoholic drink predominated, found a significant decrease in mortality, from IHD and all causes, among wine drinkers, at all levels of alcoholic intake. Conversely, light alcohol drinkers who avoided wine had a relatively higher risk of death from IHD than drinkers who consumed wine (RR, 0.76; CI, 0.63–0.92 versus RR, 0.58; CI, 0.47–0.72). Additional evidence of the cardioprotective effects of wine from IHD is provided by the results of the GISSI (Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto miocardico)-Prevenzione trial,[70] which found that moderate wine consumption (≤0.5 L/d) was associated with a significant reduction in the risk of cardiovascular events.

Examining the association between beer and IHD, the Honolulu Heart Study, a prospective epidemiological investigation,[72] found a significant negative correlation between moderate alcohol consumption of beer and death from IHD during a 6-year follow-up period. Such association for wine was not found, but beer was the predominantly consumed drink in the population. Further support for beer is provided by the MONICA (Monitoring Trends and Determinants of Cardiovascular Diseases) Augsburg cohort study,[67] in which a protective effect from light-to-moderate drinking of alcohol was observed in a predominantly beer-drinking population. Risk reduction from IHD was close to 50%, and the L-shaped relationship was also confirmed.[67] For spirits, Salonen et al[75] reported that consumption at least once a week was associated with a reduced risk of acute myocardial infarction among IHD-free men aged 30 to 59 (RR, 0.5; 95% CI, 0.3–0.9). Furthermore, in a study by Rimm et al,[2] in which spirits were the most commonly consumed drink, found that they were also the most cardioprotective by having a significant inverse association between consumption and risk of IHD (P=0.0004).

The Debate Around Light-to-Moderate Intake of Wine and Other Alcoholic Beverages

Although an inverse relationship between alcohol consumption and risk of IHD has been extensively documented in studies using an epidemiological design, there is a debate regarding which of the 3 drinks provides better cardiovascular benefits, or on a broader scale, if alcohol itself can provide protective benefits. One side of the argument is presented by Rehm et al,[12] who argue that alcohol consumption contributes to

the global chronic disease burden, and further evidence suggests that high doses of alcohol consumption confer a disadvantage to the heart, especially with an increased risk of arrhythmia, sudden cardiac death, alcoholic cardiomyopathy, and hypertension, among others.[76] The other side of the argument is presented in the literature on light-to-moderate alcohol consumption, which is in favor of a reduction in IHD and total mortality.[3] Yano et al[72] were successful in showing a strong negative correlation between moderate alcohol consumption and incidence of IHD for all 3 beverages, supporting the idea of the protective benefit of moderate alcohol consumption. The findings of moderate alcohol consumption were further supported by clinical angiography studies[77] that show a reduction in atherosclerosis and average IHD.

As for wine, Grønbæk[68] showed that, in a Danish cohort, IHD mortality decreased across levels of stable drinking, and that wine (8–21 drinks/wk) conferred a greater protective effect than the intake of light-to-moderate beer or spirits. In Oakland and San Francisco populations, it was shown that light drinkers were at low risk of IHD, with the greatest reduction observed in older populations.[78] The investigators further showed that wine preference and its consumption were associated with a significant reduction in cardiovascular death (RR, 0.7; 95% CI, 0.6–0.9; *P*=0.01), with no such correlation observed for beer or spirits.

Significant inverse associations were reported for the 3 alcoholic beverages, especially wine, albeit with limitations, because of their epidemiological and clinical study design. There were populations in whom consumption of a single type of drink prevailed over another, and in most cases, that drink conferred the greater effect. Drinking patterns, lifestyle characteristics, dietary intake, and risk factors varied in the populations studied; hence, these could be potential confounding variables for such associations.[64] There are methodological inconsistencies present among all studies, and they make it difficult to draw causal interpretations regarding a specific type of alcoholic drink providing cardioprotective effects, but rather support the finding that alcohol intake of all beverages as a whole is linked with a reduction in risk from IHD, if not consumed excessively or binged on. Considering the aforementioned limitations and methodological inconsistencies present in observational and epidemiological studies, one should be cautious when providing general recommendations to the public. Is it time to change our approach to find the answer? Some have suggested doing prospectively controlled, double-blinded randomized clinical trials,[15] but the ethical dilemma of pursuing such an endeavor still needs to be debated within the scientific community. For now, we shall rely on the evidence at present to make an informed decision.

Acute, Sustained, or No Consumption: Which Is Better?

Most epidemiological and population-based literature surrounding alcoholic beverages considers their sustained consumption to be cardioprotective for IHD-associated mortality.[79] Acute and sustained excessive consumption in the form of binge drinking is associated with arrhythmias (holiday heart syndrome), transient ischemic attack, and sudden cardiac death.[76] Hence, regulation of dosage is a very important consideration among drinkers. Red wine polyphenols in an acute setting postprandial, however, have been shown to exert antioxidant and anti-inflammatory effects. Covas et al[25] reviewed randomized controlled human studies on the effects of sustained wine usage on oxidation. They reported contradictory studies[80,81] for an increase in plasma antioxidant activity after sustained wine consumption in healthy participants. It must be noted that these studies used parallel and crossover study designs with small sample sizes (n=78 and 40, respectively). The participants were also not followed up throughout their lifetimes, all possible reasons for the reported contradiction.

Is one worse off consuming no wine or any alcoholic drink? From a public health perspective, no, because dependence on alcohol only adds to the growing cohort of alcohol use disorders.[13] There are studies, however, that have presented compelling evidence for abstinence from alcohol being a risk factor for myocardial infarction[82] and type 2 diabetes mellitus.[83]

DEALCOHOLIZED RED WINE: CARDIOPROTECTION OF WINE POLYPHENOLS BEYOND ETHANOL

It is common to dealcoholize wine, and special attention is paid during the manufacturing process to ensure no loss of polyphenols. With such a drink, effects of polyphenols can be studied in isolation. Oxidative modifications in LDL are thought to be an initiator for the development of atherosclerosis, whereas polyphenols are thought to prevent this oxidative stress and enhance plasma antioxidant capability by being present.[84] Inhibition of LDL oxidation is one of the proposed mechanisms by which polyphenols delay the onset of atherosclerosis and reduce cardiovascular risk. Furthermore, red wine and components catechins and anthocyanins inhibited in vitro LDL oxidation, whereas ethanol and dealcoholized red wine did not affect measured oxidation levels.[84] These observations were also present in wine with ethanol; here, we confirm the same results in dealcoholized red wine. To evaluate the effects of wine polyphenols and their antioxidant potential, Serafini et al[85] conducted a human pilot study of patients with IHD and showed that ingestion of dealcoholized red but not

white wine at 1-week intervals greatly increased in vitro plasma antioxidant capacity, with this effect being credited to red wine polyphenols, which are found in much greater concentrations in red wine than in white.[85] An investigation by Stein et al[86] reported that ingestion of purple grape juice (devoid of ethanol) was associated with improved endothelial function via a reduction in susceptibility of LDL-cholesterol to oxidation in 15 adults with IHD.

Red wine polyphenols have also been hypothesized to exert positive effects on flow-mediated vasodilation, which is known to be endothelium-dependent. In the Stein et al[86] cohort, grape juice was also associated with improved flow-mediated vasodilation of the brachial artery, which would in turn improve endothelial function. Treatment of human umbilical vein endothelial cells with dealcoholized red wine led to a 3.0-fold increase in NO release, and a 2.0-fold increase in human endothelial NO synthase, an enzyme isoform that synthesizes NO.[87] In addition, dealcoholized red wine polyphenol extract has been found to almost completely reverse the prothrombotic effects of a 2% cholesterol-rich diet by a NO-dependent mechanism.[88] Red wine polyphenols have displayed potent antioxidant properties in vivo for arterial stiffness. Dealcoholized red wine has been acutely demonstrated to reduce arterial stiffness 60 minutes postprandial intake in patients with coronary artery disease, with this reduction attributed to red wine antioxidants.[89]

ALCOHOL AND CARDIOPROTECTION: IMPLICATIONS FOR CAUSALITY FROM OBSERVATIONAL EVIDENCE

Much of the evidence regarding alcohol consumption and its beneficial effects on the cardiovascular system derives from observational data. Epidemiological studies have been integral to this discussion, with multiple cohorts with cross-cultural and geographical comparisons reaching similar conclusions. That being said, can one infer causality from epidemiological investigations using an observational-based approach, in which subject bias is inherent with self-reported data?

To determine causation, randomized controlled trials have long been considered the gold standard. However, epidemiological, public health, and clinical research are sometimes barred by ethical concerns, where, for instance, an experimental treatment such as alcohol being investigated for a therapeutic cause may leave participants in harm's way.[90] Nonetheless, several methods have been developed to make causal inferences from epidemiological research, starting with the seminal set of criteria proposed by Austin Hill, to distinguish causal and correlational associations.[91] Since then, other methods have been developed. Some common ones used today include instrumental variables regression analysis, difference in differences, and regression discontinuity designs.[90] These methods seek to use a randomized approach, assigning variables to observational data and using mathematical models to associate the effects of a treatment with measured health outcomes. Evaluating for causal inferences in epidemiology is a growing interest, and it is worthwhile to stress that, in cases where longitudinal epidemiological evidence overwhelmingly points in one direction, when a large number of studies are arriving at similar conclusions, when many proposed mechanisms of action are biologically sound and understandable, and when the aforementioned statistical approaches also associate the treatment positively to the health outcome, one can begin to suggest causal links.

Decades of longitudinal data have shown an improvement in cardiovascular risk factors with low-to-moderate alcohol and wine consumption. Very recently, studies based on Mendelian randomization approaches, an instrumental variables analysis using genetic variants as instruments for analysis, have questioned the cardiovascular benefits of alcohol consumption.[92] In the context of alcohol, Mendelian randomization studies seek to provide evidence of causal relationships and provide a magnitude of the risk associated with lifelong alcohol use by comparing genotypes of interest.[92] Two large European studies (N=261 991; 54 604) using a Mendelian randomization approach to explore causal effects of long-term alcohol consumption on IHD and cardiovascular risk factors (body mass index, blood pressure, interleukin, and lipid levels) by assessing variants of the alcohol dehydrogenase (ADH1B and ADHIC) gene reported adverse effects of alcohol consumption on the cardiovascular risk profile and an increased risk of IHD.[93,94] Further evidence by Yun et al[95] reports detrimental effects of alcohol consumption on coronary calcification in the Korean population. These studies stand in contrast to the epidemiological investigations.

PUBLIC HEALTH PERSPECTIVES

Because alcohol is a ubiquitous part of culture, its ever-increasing consumption today because of industrialization and globalization also increases the adverse effects associated with its intake.[13] Alcohol consumption in excessive amounts can lead to social and personal ramifications not only for individuals, but also for the population as a whole.[96] Intoxication still remains a major factor in adverse events such as car crashes and domestic violence, both of which are major problems for public health.[97,98] Rehm et al[13] explain how some diseases are causally linked to alcohol and would not exist if alcohol was not a contributor to our day-to-day lives. These include alcoholic liver disease, alcohol use disorder, and pancreatitis induced by alcohol. Further

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analysis by this group on alcohol-associated detriments finds that in 2004, 3.8% of global mortality was alcohol-associated, greater for men (6.3%) than for women (1.1%). They report the cause of these deaths to be from injury, cancer, liver cirrhosis, and cardiovascular diseases. Surprisingly, the authors find that almost all preventable deaths were from the cardiovascular category. However, this does not take away from the fact that, on average, alcohol is detrimentally linked to many diseases and increases the global disease burden.[13]

RECOMMENDATIONS FOR WINE CONSUMPTION

The most comprehensive manual for healthcare professionals is the WHO guide for hazardous and harmful drinking.[18] It provides healthcare professionals a day-to-day guide on dealing with patients who are more inclined to abuse alcohol. Important sections include concepts and terms related to the use and abuse of alcohol, intervention guidelines, 4 zones of risk management, definition of a standard drink, and guidelines for low-risk alcohol consumption. The 2015 to 2020 Dietary Guidelines for Americans[10] recommend a moderate consumption of alcohol (≤2 std/d men; ≤1 std/d women; 1 standard drink=14 g of pure ethanol). Excessive consumption (≥5 std/d men; ≥4 std/d women) and binge drinking (≥5 std/d men; ≥4 std/d women within 2 hours) are discouraged. High-risk individuals (alcoholics, pregnant or breastfeeding women, individuals on prescribed medications) are advised not to consume alcohol. The American Heart Association advisories[99,100] conclude that a moderate intake of alcohol (1–2 drinks/d) is associated with a reduction in IHD risk with no clear consensus of wine conferring greater benefits than alcoholic beverages. For women, however, suggested consumption was of no more than 1 drink/d.[99] To substantially reduce cardiovascular disease risk, their recommendation is to focus on a consumption of a healthy diet.[100]

Conclusions

Despite a lack of consensus on a specific type of beverage being beneficial to the heart, mounting evidence suggests that ethanol and polyphenols within wine can synergistically confer benefits against chronic cardiovascular diseases, mostly IHD. The polyphenols in red wine can be divided into 2 important groups, flavonoids and nonflavonoids, that together can decrease platelet aggregation, improve fibrinolysis, increase HDL cholesterol, and promote NO release.

Discrepancies remain for the definition of a standard drink, with the WHO definition of 10 g not adopted internationally. A light-to-moderate intake is considered cardioprotective by epidemiological and experimental investigations after observations of an inverse correlation for IHD.

DISCLOSURES

None.

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FOOTNOTES

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REFERENCES

1. Phillips R. *Alcohol: A History*. Chapel Hill, NC: UNC Press Books; 2014.
2. Rimm EB, Giovannucci EL, Willett WC, Colditz GA, Ascherio A, Rosner B, Stampfer MJ. Prospective study of alcohol consumption and risk of coronary disease in men. *Lancet Lond Engl*. 1991;338:464–468. doi: 10.1016/0140-6736(91)90542-W.
3. St Leger AS, Cochrane AL, Moore F. Factors associated with cardiac mortality in developed countries with particular reference to the consumption of wine. *Lancet*. 1979;1:1017–1020. doi:10.1016/S0140-6736(79)92765-X.
4. Criqui MH, Ringel BL. Does diet or alcohol explain the French paradox? *Lancet*. 1994;344:1719–1723. doi:10.1016/S0140-6736(94)92883-5.
5. Grønbaek M, Deis A, Sørensen TI, Becker U, Schnohr P, Jensen G. Mortality associated with moderate intakes of wine, beer, or spirits. *BMJ*. 1995;310:1165–1169. doi: 10.1136/bmj.310.6988.1165.
6. Pignatelli P, Ghiselli A, Buchetti B, Carnevale R, Natella F, Germanò G, Fimognari F, Di Santo S, Lenti L, Violi F. Polyphenols synergistically inhibit oxidative stress in subjects given red and white wine. *Atherosclerosis*. 2006;188:77–83. doi: 10.1016/j.atherosclerosis.2005.10.025.
7. Iriti M, Varoni EM. Cardioprotective effects of moderate red wine consumption: polyphenols vs. ethanol. *J Appl Biomed*. 2014;12:193–202. doi:10.1016/j.jab.2014.09.003.
8. Renaud S, de Lorgeril M. Wine, alcohol, platelets, and the French paradox for coronary heart disease. *Lancet*. 1992;339:1523–1526. doi:10.1016/0140-6736(92)91277-F.
9. Kris-Etherton P, Eckel RH, Howard BV, Jeor SS, Bazzarre TL. Lyon Diet Heart Study. *Circulation*. 2001;103:1823–1825. doi:10.1161/01.CIR.103.13.1823.
10. US Department of Health and Human Services. *Dietary Guidelines for Americans 2015–2020*. New York, NY: Skyhorse Publishing Inc; 2017.
11. Soobrattee MA, Neergheen VS, Luximon-Ramma A, Aruoma OI, Bahorun T. Phenolics as potential antioxidant therapeutic agents: mechanism and actions. *Mutat Res*. 2005;579:200–213. doi: 10.1016/j.mrfmmm.2005.03.023.
12. Rehm J, Room R, Monteiro M, Gmel G, Graham K, Rehn N, Sempos CT, Jernigan D. Alcohol as a risk factor for global burden of disease. *Eur Addict Res*. 2003;9:157–164. doi: 10.1159/000072222.
13. Rehm J, Mathers C, Popova S, Thavorncharoensap M, Teerawattananon Y, Patra J. Global burden of disease and injury and economic cost attributable to alcohol use and alcohol-use disorders. *Lancet*. 2009;373:2223–2233. doi: 10.1016/S0140-6736(09)60746-7.
14. Kalinowski A, Humphreys K. Governmental standard drink definitions and low-risk alcohol consumption guidelines in 37 countries. *Addiction*. 2016;111:1293–1298. doi: 10.1111/add.13341.
15. Kloner RA, Rezkalla SH. To drink or not to drink? That is the question. *Circulation*. 2007;116:1306–1317. doi: 10.1161/CIRCULATIONAHA.106.678375.
16. Mongan D, Long J. Standard drink measures throughout Europe; peoples' understanding of standard drinks and their use in drinking guidelines, alcohol surveys and labelling. Dublin, Ireland: Health Research Board; 2015.

17. Kerr WC, Stockwell T. Understanding standard drinks and drinking guidelines. *Drug Alcohol Rev*. 2012;31:200–205. doi: 10.1111/j.1465-3362.2011.00374.x.
18. Babor TF, Higgins-Biddle JC. *Brief Intervention for Hazardous and Harmful Drinking: A Manual for Use in Primary Care*. Geneva, Switzerland: World Health Organization; 2001. http://apps.who.int/iris/bitstream/10665/67210/1/WHO_MSD_MSB_01.6b.pdf. Accessed April 6, 2017.
19. Voskoboinik A, Prabhu S, Ling LH, Kalman JM, Kistler PM. Alcohol and atrial fibrillation: a sobering review. *J Am Coll Cardiol*. 2016;68:2567–2576. doi: 10.1016/j.jacc.2016.08.074.
20. Brown L, Kroon PA, Das DK, Das S, Tosaki A, Chan V, Singer MV, Feick P. The biological responses to resveratrol and other polyphenols from alcoholic beverages. *Alcohol Clin Exp Res*. 2009;33:1513–1523. doi: 10.1111/j.1530-0277.2009.00989.x.
21. Ferrières J. The French paradox: lessons for other countries. *Heart*. 2004;90:107–111. doi: 10.1136/heart.90.1.107.
22. Markoski MM, Garavaglia J, Oliveira A, Olivaes J, Marcadenti A. Molecular properties of red wine compounds and cardiometabolic benefits. *Nutr Metab Insights*. 2016;9:51–57. doi: 10.4137/NMI.S32909.
23. Stockley C, Teissedre PL, Boban M, Di Lorenzo C, Restani P. Bioavailability of wine-derived phenolic compounds in humans: a review. *Food Funct*. 2012;3:995–1007. doi: 10.1039/c2fo10208k.
24. Bertelli AA. Wine, research and cardiovascular disease: instructions for use. *Atherosclerosis*. 2007;195:242–247. doi: 10.1016/j.atherosclerosis.2007.04.006.
25. Covas MI, 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;208:297–304. doi: 10.1016/j.atherosclerosis.2009.06.031.
26. McCullough ML, Peterson JJ, Patel R, Jacques PF, Shah R, Dwyer JT. Flavonoid intake and cardiovascular disease mortality in a prospective cohort of US adults. *Am J Clin Nutr*. 2012;95:454–464. doi: 10.3945/ajcn.111.016634.
27. Hertog MG, Feskens EJ, Hollman PC, Katan MB, Kromhout D. Dietary antioxidant flavonoids and risk of coronary heart disease: the Zutphen Elderly Study. *Lancet*. 1993;342:1007–1011. doi:10.1016/0140-6736(93)92876-U.
28. Nigdikar SV, Williams NR, Griffin BA, Howard AN. Consumption of red wine polyphenols reduces the susceptibility of low-density lipoproteins to oxidation in vivo. *Am J Clin Nutr*. 1998;68:258–265.
29. Perez-Vizcaino F, Duarte J, Andriantsitohaina R. Endothelial function and cardiovascular disease: effects of quercetin and wine polyphenols. *Free Radic Res*. 2006;40:1054–1065. doi: 10.1080/10715760600823128.
30. Mano T, Masuyama T, Yamamoto K, Naito J, Kondo H, Nagano R, Tanouchi J, Hori M, Inoue M, Kamada T. Endothelial dysfunction in the early stage of atherosclerosis precedes appearance of intimal lesions assessable with intravascular ultrasound. *Am Heart J*. 1996;131:231–238. doi: 10.1016/S0002-8703(96)90346-4.
31. Knekt P, Kumpulainen J, Järvinen R, Rissanen H, Heliövaara M, Reunanen A, Hakulinen T, Aromaa A. Flavonoid intake and risk of chronic diseases. *Am J Clin Nutr*. 2002;76:560–568.
32. Ferro-Luzzi A, Branca F. Mediterranean diet, Italian-style: prototype of a healthy diet. *Am J Clin Nutr*. 1995;61(6 suppl):1338S–1345S.
33. Mohamed Saleem TS. Red wine: a drink to your heart. *J Cardiovasc Dis Res*. 2010;1:171–176. doi: 10.4103/0975-3583.74259.
34. Manach C, Morand C, Crespy V, Demigné C, Texier O, Régérat F, Rémésy C. Quercetin is recovered in human plasma as conjugated derivatives which retain antioxidant properties. *FEBS Lett*. 1998;426:331–336. doi:10.1016/S0014-5793(98)00367-6.
35. Hollman PC, vd Gaag M, Mengelers MJ, van Trijp JM, de Vries JH, Katan MB. Absorption and disposition kinetics of the dietary antioxidant quercetin in man. *Free Radic Biol Med*. 1996;21:703–707. doi:10.1016/0891-5849(96)00129-3.
36. Loke WM, Proudfoot JM, Hodgson JM, McKinley AJ, Hime N, Magat M, Stocker R, Croft KD. Specific dietary polyphenols attenuate atherosclerosis in apolipoprotein E-knockout mice by alleviating inflammation and endothelial dysfunction. *Arterioscler Thromb Vasc Biol*. 2010;30:749–757. doi: 10.1161/ATVBAHA.109.199687.
37. Bae SC, Jung WJ, Lee EJ, Yu R, Sung MK. Effects of antioxidant supplements intervention on the level of plasma inflammatory molecules and disease severity of rheumatoid arthritis patients. *J Am Coll Nutr*. 2009;28:56–62.
38. Kolchin IuN, Maksiutina NP, Balanda PP, Luĭk AI, Bulakh VN, Moĭbenko AA. [The cardioprotective action of quercetin in experimental occlusion and reperfusion of the coronary artery in dogs]. *Farmakol Toksikol*. 1991;54:20–23.
39. Ikizler M, Erkasap N, Dernek S, Kural T, Kaygisiz Z. Dietary polyphenol quercetin protects rat hearts during reperfusion: enhanced antioxidant capacity with chronic treatment. *Anadolu Kardiyol Derg*. 2007;7:404–410.
40. Bonnefont-Rousselot D. Resveratrol and cardiovascular diseases. *Nutrients*. 2016;8. doi:10.3390/nu8050250.
41. Smoliga JM, Baur JA, Hausenblas HA. Resveratrol and health—a comprehensive review of human clinical trials. *Mol Nutr Food Res*. 2011;55:1129–1141. doi: 10.1002/mnfr.201100143.
42. Walle T, Hsieh F, DeLegge MH, Oatis JE Jr, Walle UK. High absorption but very low bioavailability of oral resveratrol in humans. *Drug Metab Dispos*. 2004;32:1377–1382. doi: 10.1124/dmd.104.000885.
43. Goldberg DM, Yan J, Soleas GJ. Absorption of three wine-related polyphenols in three different matrices by healthy subjects. *Clin Biochem*. 2003;36:79–87. doi:10.1016/S0009-9120(02)00397-1.
44. Soleas GJ, Yan J, Goldberg DM. Ultrasensitive assay for three polyphenols (catechin, quercetin and resveratrol) and their conjugates in biological fluids utilizing gas chromatography with mass selective detection. *J Chromatogr B Biomed Sci Appl*. 2001;757:161–172. doi:10.1016/S0378-4347(01)00142-6.
45. Zordoky BN, Robertson IM, Dyck JR. Preclinical and clinical evidence for the role of resveratrol in the treatment of cardiovascular diseases. *Biochim Biophys Acta*. 2015;1852:1155–1177. doi: 10.1016/j.bbadis.2014.10.016.
46. Ruf JC, Berger JL, Renaud S. Platelet rebound effect of alcohol withdrawal and wine drinking in rats. Relation to tannins and lipid peroxidation. *Arterioscler Thromb Vasc Biol*. 1995;15:140–144.
47. Pikaar NA, Wedel M, van der Beek EJ, van Dokkum W, Kempen HJ, Kluft C, Ockhuizen T, Hermus RJ. Effects of moderate alcohol consumption on platelet aggregation, fibrinolysis, and blood lipids. *Metabolism*. 1987;36:538–543. doi:10.1016/0026-0495(87)90163-6.
48. Virdis A, Ghiadoni L, Taddei S. Human endothelial dysfunction: EDCFs. *Pflugers Arch*. 2010;459:1015–1023. doi: 10.1007/s00424-009-0783-7.
49. Gresele P, Pignatelli P, Guglielmini G, Carnevale R, Mezzasoma AM, Ghiselli A, Momi S, Violi F. Resveratrol, at concentrations attainable with moderate wine consumption, stimulates human platelet nitric oxide production. *J Nutr*. 2008;138:1602–1608.
50. Gillman MW, Cook NR, Evans DA, Rosner B, Hennekens CH. Relationship of alcohol intake with blood pressure in young adults. *Hypertension*. 1995;25:1106–1110. doi:10.1161/01.HYP.25.5.1106.
51. Araya J, Rodrigo R, Orellana M, Rivera G. Red wine raises plasma HDL and preserves long-chain polyunsaturated fatty acids in rat kidney and erythrocytes. *Br J Nutr*. 2001;86:189–195. doi:10.1079/BJN2001369.
52. Rimm EB, Williams P, Fosher K, Criqui M, Stampfer MJ. Moderate alcohol intake and lower risk of coronary heart disease: meta-analysis of effects on lipids and haemostatic factors. *BMJ*. 1999;319:1523–1528. doi:10.1136/bmj.319.7224.1523.
53. Norum RA, Lakier JB, Goldstein S, Angel A, Goldberg RB, Block WD, Noffze DK, Dolphin PJ, Edelglass J, Bogorad DD, Alaupovic P. Familial deficiency of apolipoproteins A-I and C-III and precocious coronary-artery disease. *N Engl J Med*. 1982;306:1513–1519. doi: 10.1056/NEJM198206243062503.
54. Facchini F, Chen YD, Reaven GM. Light-to-moderate alcohol intake is associated with enhanced insulin sensitivity. *Diabetes Care*. 1994;17:115–119. doi:10.2337/diacare.17.2.115.
55. Kiechl S, Willeit J, Poewe W, Egger G, Oberhollenzer F, Muggeo M, Bonora E. Insulin sensitivity and regular alcohol consumption: large, prospective, cross sectional population study (Bruneck study). *BMJ*. 1996;313:1040–1044. doi:10.1136/bmj.313.7064.1040.
56. Lazarus R, Sparrow D, Weiss ST. Alcohol intake and insulin levels. The Normative Aging Study. *Am J Epidemiol*. 1997;145:909–916. doi:10.1093/oxfordjournals.aje.a009050.
57. Gul EE, Pal R, Caldwell J, Boles U, Hopman W, Glover B, Michael KA, Redfearn D, Simpson C, Abdollah H, Baranchuk A. Interatrial block and interatrial septal thickness in patients with paroxysmal atrial fibrillation undergoing catheter ablation: long-term follow-up study. *Ann Noninvasive Electrocardiol*. 2016;22. doi:10.1111/anec.12428.
58. Ruigómez A, Johansson S, Wallander MA, García Rodríguez LA. Predictors and prognosis of paroxysmal atrial fibrillation in general practice in the UK. *BMC Cardiovasc Disord*. 2005;5:20. doi: 10.1186/1471-2261-5-20.
59. Planas F, Romero-Menor C, Vázquez-Oliva G, Poblet T, Navarro-López F; en representación de los investigadores del Estudio FAP de los hospitales comarcales y centros extrahospitalarios de Cataluña. [Natural history of and risk factors for idiopathic atrial fibrillation recurrence (FAP Registry)]. *Rev Esp Cardiol*. 2006;59:1106–1112.

60. Gould L, Reddy CV, Becker W, Oh KC, Kim SG. Electrophysiologic properties of alcohol in man. *J Electrocardiol*. 1978;11:219–226. doi:10.1016/S0022-0736(78)80120-4.
61. Alexander B, MacHaalany J, Lam B, van Rooy H, Haseeb S, Kuchtaruk A, Glover B, Bayés de Luna A, Baranchuk A. Comparison of the extent of coronary artery disease in patients with versus without interatrial block and implications for new-onset atrial fibrillation. *Am J Cardiol*. 2017;119:1162–1165. doi: 10.1016/j.amjcard.2016.12.032.
62. Steinbigler P, Haberl R, König B, Steinbeck G. P-wave signal averaging identifies patients prone to alcohol-induced paroxysmal atrial fibrillation. *Am J Cardiol*. 2003;91:491–494. doi:10.1016/S0002-9149(02)03258-7.
63. Gurr MI. Wine and coronary heart disease. *Lancet*. 1992;340:313. doi:10.1016/0140-6736(92)92410-H.
64. Rimm EB, Klatsky A, Grobbee D, Stampfer MJ. Review of moderate alcohol consumption and reduced risk of coronary heart disease: is the effect due to beer, wine, or spirits. *BMJ*. 1996;312:731–736. doi:10.1136/bmj.312.7033.731.
65. Di Castelnuovo A, Costanzo S, Bagnardi V, Donati MB, Iacoviello L, de Gaetano G. Alcohol dosing and total mortality in men and women: an updated meta-analysis of 34 prospective studies. *Arch Intern Med*. 2006;166:2437–2445. doi: 10.1001/archinte.166.22.2437.
66. Friedman LA, Kimball AW. Coronary heart disease mortality and alcohol consumption in Framingham. *Am J Epidemiol*. 1986;124:481–489.
67. Keil U, Chambless LE, Döring A, Filipiak B, Stieber J. The relation of alcohol intake to coronary heart disease and all-cause mortality in a beer-drinking population. *Epidemiology*. 1997;8:150–156.
68. Grønbæk M. Type of alcohol consumed and mortality from all causes, coronary heart disease, and cancer. *Ann Intern Med*. 2000;133:411. doi:10.7326/0003-4819-133-6-200009190-00008.
69. Stampfer MJ, Colditz GA, Willett WC, Speizer FE, Hennekens CH. A prospective study of moderate alcohol consumption and the risk of coronary disease and stroke in women. *N Engl J Med*. 1988;319:267–273. doi: 10.1056/NEJM198808043190503.
70. Levantesi G, Marfisi R, Mozaffarian D, Franzosi MG, Maggioni A, Nicolosi GL, Schweiger C, Silletta M, Tavazzi L, Tognoni G, Marchioli R. Wine consumption and risk of cardiovascular events after myocardial infarction: results from the GISSI-Prevenzione trial. *Int J Cardiol*. 2013;163:282–287. doi: 10.1016/j.ijcard.2011.06.053.
71. Klatsky AL, Armstrong MA. Alcoholic beverage choice and risk of coronary artery disease mortality: do red wine drinkers fare best? *Am J Cardiol*. 1993;71:467–469. doi:10.1016/0002-9149(93)90460-T.
72. Yano K, Rhoads GG, Kagan A. Coffee, alcohol and risk of coronary heart disease among Japanese men living in Hawaii. *N Engl J Med*. 1977;297:405–409. doi: 10.1056/NEJM197708252970801.
73. Kittner SJ, Garcia-Palmieri MR, Costas R Jr, Cruz-Vidal M, Abbott RD, Havlik RJ. Alcohol and coronary heart disease in Puerto Rico. *Am J Epidemiol*. 1983;117:538–550.
74. Klatsky AL, Armstrong MA, Friedman GD. Risk of cardiovascular mortality in alcohol drinkers, ex-drinkers and nondrinkers. *Am J Cardiol*. 1990;66:1237–1242. doi: 10.1016/0002-9149(90)91107-H.
75. Salonen JT, Puska P, Nissinen A. Intake of spirits and beer and risk of myocardial infarction and death—a longitudinal study in Eastern Finland. *J Chronic Dis*. 1983;36:533–543. doi: 10.1016/0021-9681(83)90131-5.
76. Fernández-Solà J. Cardiovascular risks and benefits of moderate and heavy alcohol consumption. *Nat Rev Cardiol*. 2015;12:576–587. doi: 10.1038/nrcardio.2015.91.
77. Ducimetiere P, Guize L, Marciniak A, Milon H, Richard J, Rufat P. Arteriographically documented coronary artery disease and alcohol consumption in French men. The CORALI Study. *Eur Heart J*. 1993;14:727–733. doi:10.1093/eurheartj/14.6.727.
78. Klatsky AL, Armstrong MA, Friedman GD. Alcohol and mortality. *Ann Intern Med*. 1992;117:646–654.
79. Mukamal KJ, Jensen MK, Grønbaek M, Stampfer MJ, Manson JE, Pischon T, Rimm EB. Drinking frequency, mediating biomarkers, and risk of myocardial infarction in women and men. *Circulation*. 2005;112:1406–1413. doi: 10.1161/CIRCULATIONAHA.105.537704.
80. Arendt BM, Ellinger S, Kekic K, Geus L, Fimmers R, Spengler U, Müller WU, Goerlich R. Single and repeated moderate consumption of native or dealcoholized red wine show different effects on antioxidant parameters in blood and DNA strand breaks in peripheral leukocytes in healthy volunteers: a randomized controlled trial (ISRCTN68505294). *Nutr J*. 2005;4:33. doi: 10.1186/1475-2891-4-33.
81. Micallef M, Lexis L, Lewandowski P. Red wine consumption increases antioxidant status and decreases oxidative stress in the circulation of both young and old humans. *Nutr J*. 2007;6:27. doi: 10.1186/1475-2891-6-27.
82. Yusuf S, Hawken S, Ounpuu S, Dans T, Avezum A, Lanas F, McQueen M, Budaj A, Pais P, Varigos J, Lisheng L; INTERHEART Study Investigators. Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries (the INTERHEART study): case-control study. *Lancet*. 2004;364:937–952. doi: 10.1016/S0140-6736(04)17018-9.
83. Hu FB, Manson JE, Stampfer MJ, Colditz G, Liu S, Solomon CG, Willett WC. Diet, lifestyle, and the risk of type 2 diabetes mellitus in women. *N Engl J Med*. 2001;345:790–797. doi: 10.1056/NEJMoa010492.
84. Kerry NL, Abbey M. Red wine and fractionated phenolic compounds prepared from red wine inhibit low density lipoprotein oxidation *in vitro*. *Atherosclerosis*. 1997;135:93–102. doi:10.1016/S0021-9150(97)00156-1.
85. Serafini M, Maiani G, Ferro-Luzzi A. Alcohol-free red wine enhances plasma antioxidant capacity in humans. *J Nutr*. 1998;128:1003–1007.
86. Stein JH, Keevil JG, Wiebe DA, Aeschlimann S, Folts JD. Purple grape juice improves endothelial function and reduces the susceptibility of LDL cholesterol to oxidation in patients with coronary artery disease. *Circulation*. 1999;100:1050–1055. doi: 10.1161/01.CIR.100.10.1050.
87. Leikert JF, Räthel TR, Wohlfart P, Cheynier V, Vollmar AM, Dirsch VM. Red wine polyphenols enhance endothelial nitric oxide synthase expression and subsequent nitric oxide release from endothelial cells. *Circulation*. 2002;106:1614–1617. doi:10.1161/01.CIR.0000034445.31543.43.
88. De Curtis A, Murzilli S, Di Castelnuovo A, Rotilio D, Donati MB, De Gaetano G, Iacoviello L. Alcohol-free red wine prevents arterial thrombosis in dietary-induced hypercholesterolemic rats: experimental support for the 'French paradox.' *J Thromb Haemost*. 2005;3:346–350. doi: 10.1111/j.1538-7836.2005.01126.x.
89. Karatzi KN, Papamichael CM, Karatzis EN, Papaioannou TG, Aznaouridis KA, Katsichti PP, Stamatelopoulos KS, Zampelas A, Lekakis JP, Mavrikakis ME. Red wine acutely induces favorable effects on wave reflections and central pressures in coronary artery disease patients. *Am J Hypertens*. 2005;18(9 pt 1):1161–1167. doi: 10.1016/j.amjhyper.2005.03.744.
90. Listl S, Jürges H, Watt RG. Causal inference from observational data. *Community Dent Oral Epidemiol*. 2016;44:409–415. doi: 10.1111/cdoe.12231.
91. Kundi M. Causality and the interpretation of epidemiologic evidence. *Environ Health Perspect*. 2006;114:969–974. doi:10.1289/ehp.8297.
92. Zuccolo L, Holmes MV. Commentary: Mendelian randomization-inspired causal inference in the absence of genetic data. *Int J Epidemiol*. 2016. doi:10.1093/ije/dyw327.
93. Holmes MV, Dale CE, Zuccolo L, Silverwood RJ, Guo Y, Ye Z, Prieto-Merino D, Dehghan A, Trompet S, Wong A, Cavadino A, Drogan D, Padmanabhan S, Li S, Yesupriya A, Leusink M, Sundstrom J, Hubacek JA, Pikhart H, Swerdlow DI, Panayiotou AG, Borinskaya SA, Finan C, Shah S, Kuchenbaecker KB, Shah T, Engmann J, Folkersen L, Eriksson P, Ricceri F, Melander O, Sacerdote C, Gamble DM, Rayaprolu S, Ross OA, McLachlan S, Vikhireva O, Sluijs I, Scott RA, Adamkova V, Flicker L, Bockxmeer FM, Power C, Marques-Vidal P, Meade T, Marmot MG, Ferro JM, Paulos-Pinheiro S, Humphries SE, Talmud PJ, Mateo Leach I, Verweij N, Linneberg A, Skaaby T, Doevendans PA, Cramer MJ, van der Harst P, Klungel OH, Dowling NF, Dominiczak AF, Kumari M, Nicolaides AN, Weikert C, Boeing H, Ebrahim S, Gaunt TR, Price JF, Lannfelt L, Peasey A, Kubinova R, Pajak A, Malyutina S, Voevoda MI, Tamosiunas A, Maitland-van der Zee AH, Norman PE, Hankey GJ, Bergmann MM, Hofman A, Franco OH, Cooper J, Palmen J, Spiering W, de Jong PA, Kuh D, Hardy R, Uitterlinden AG, Ikram MA, Ford I, Hyppönen E, Almeida OP, Wareham NJ, Khaw KT, Hamsten A, Husemoen LL, Tjønneland A, Tolstrup JS, Rimm E, Beulens JW, Verschuren WM, Onland-Moret NC, Hofker MH, Wannamethee SG, Whincup PH, Morris R, Vicente AM, Watkins H, Farrall M, Jukema JW, Meschia J, Cupples LA, Sharp SJ, Fornage M, Kooperberg C, LaCroix AZ, Dai JY, Lanktree MB, Siscovick DS, Jorgenson E, Spring B, Coresh J, Li YR, Buxbaum SG, Schreiner PJ, Ellison RC, Tsai MY, Patel SR, Redline S, Johnson AD, Hoogeveen RC, Hakonarson H, Rotter JI, Boerwinkle E, de Bakker PI, Kivimaki M, Asselbergs FW, Sattar N, Lawlor DA, Whittaker J, Davey Smith G, Mukamal K, Psaty BM, Wilson JG, Lange LA, Hamidovic A, Hingorani AD, Nordestgaard BG, Bobak M, Leon DA, Langenberg C, Palmer TM, Reiner AP, Keating BJ, Dudbridge F, Casas JP; InterAct Consortium. Association between alcohol and cardiovascular disease: Mendelian randomisation analysis based on individual participant data. *BMJ*. 2014;349:g4164. doi:10.1136/bmj.g4164.
94. Lawlor DA, Nordestgaard BG, Benn M, Zuccolo L, Tybjaerg-Hansen A, Davey Smith G. Exploring causal associations between alcohol and coronary heart disease risk factors: findings from a Mendelian randomization study in the Copenhagen General Population Study. *Eur Heart J*. 2013;34:2519–2528. doi: 10.1093/eurheartj/eht081.

95. Yun KE, Chang Y, Yun S, Davey Smith G, Ryu S, Cho S, Chung EC, Shin H, Khang Y. Alcohol and coronary artery calcification: an investigation using alcohol flushing as an instrumental variable. *Int J Epidemiol*. 2017;46:950–962. doi:10.1093/ije/dyw237.
96. World Health Organization. *The World Health Report 2002: Reducing Risks, Promoting Healthy Life.* Geneva, Switzerland: World Health Organization; 2002. https://books.google.ca/books?hl=en&lr=&id=epuQi1PtY_cC&oi=fnd&pg=PR9&dq=WHO.+The+world+health+report+2002:+reducing+risks,+promoting+healthy+life.+Geneva:+World+Health+Organization,+2002&ots=N2N6cWGgQl&sig=QPEs4uSwlfVCtNTaPopkSzxLISw. Accessed May 7, 2017.
97. Shults RA, Elder RW, Sleet DA, Nichols JL, Alao MO, Carande-Kulis VG, Zaza S, Sosin DM, Thompson RS; Task Force on Community Preventive Services. Reviews of evidence regarding interventions to reduce alcohol-impaired driving. *Am J Prev Med*. 2001;21(4 suppl):66–88. doi:10.1016/S0749-3797(01)00381-6.
98. Foran HM, O'Leary KD. Alcohol and intimate partner violence: a meta-analytic review. *Clin Psychol Rev*. 2008;28:1222–1234. doi: 10.1016/j.cpr.2008.05.001.
99. Goldberg IJ, Mosca L, Piano MR, Fisher EA. Wine and your heart. *Circulation*. 2001;103:472–475. doi:10.1161/01.CIR.103.3.472.
100. Lichtenstein AH, Appel LJ, Brands M, Carnethon M, Daniels S, Franch HA, Franklin B, Kris-Etherton P, Harris WS, Howard B, Karanja N, Lefevre M, Rudel L, Sacks F, Horn LV, Winston M, Wylie-Rosett J. Diet and Lifestyle Recommendations Revision 2006. *Circulation*. 2006;114:82–96. doi:10.1161/CIRCULATIONAHA.106.176158.

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