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REVIEW

# Cardiovascular risk is more related to drinking pattern than to the type of alcoholic drinks

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## ABSTRACT

**Many observational studies have shown an association between moderate alcohol consumption and a lower risk for cardiovascular morbidity and mortality. Some of these studies, whether or not inspired by the French paradox, suggest a more favourable effect of wine than of other alcoholic drinks. Certain polyphenols including the flavonoids, more abundant in red than in white wine, are held responsible for this 'bonus' effect. However, this conclusion seems premature, since no significant bioactive effect of wine polyphenols has been shown in humans so far. Furthermore, wine drinking proves to be associated with a healthier lifestyle profile than consumption of beer and liquor, and this may have a substantial influence on the outcome of studies.**

**In contrast to moderate drinking, incidental heavy or binge drinking is associated with an increased cardiovascular risk by influences both on the electrical conduction system of the heart and the process of atherothrombosis. Although only prospective randomised intervention trials including a sufficient number of people will give definite answers, the chances are small that they will ever be performed given the ethical and practical objections of such studies. Available data so far justify the conclusion with regard to cardiovascular risk that the pattern of drinking is of more importance than the content of the bottle.**

## KEYWORDS

Alcohol, binge drinking, cardiovascular risk, ethanol, wine

## INTRODUCTION

Health aspects of alcohol have been debated for centuries. Alcoholic drinks have been used as restoratives, stimulants, appetizers, and even as analgesics for many of the body's aches. But alcohol consumption has also proven to be associated with liver disease, cardiomyopathy, trauma and injuries, the Wernicke-Korsakov syndrome and some forms of cancer.

In ancient and medieval times, wine and beer were part of everyday diet, because many places on earth lacked reliable sources of drinking water. Nowadays, they are mostly regarded as regular staples of modern day living and their consumption parallels the increase in welfare. During the last two decades the popularity of alcoholic drinks, especially wine, has received an extra boost because of an assumed beneficial effect on the cardiovascular system. This was first observed in observational studies comparing countries with regard to wine consumption and cardiac mortality.[1] Despite a high intake of saturated fats, a significant lower mortality rate of coronary heart disease was observed in France compared with other Northern European countries, a phenomenon which became known as the French paradox.[2] This paradox was initially explained by ingredients of the Mediterranean diet, which resulted in much attention to the potential favourable effect of wine, especially in the lay press. Most physicians and medical organisations, however, stayed critical and reserved towards the promotion of wine drinking, being aware of the other and darker side of the Janus head. Furthermore, later analyses and studies threw doubt on the superiority of red wine over other alcoholic drinks. This review focuses on the pitfalls of the studies analysing the relationship between wine drinking and cardiovascular risk. It concludes that the pattern of drinking may be more important than the content of the bottle.

## THE FRENCH PARADOX, WINE AND POLYPHENOLS

From its very first description in medical literature, the 'French paradox' has been a matter of dispute. In 1992 Renaud and De Lorgeril observed a lower mortality rate of coronary heart disease in France in comparison with other Northern European countries and especially the United Kingdom, despite a similar or even higher intake of saturated fats.[2] The authors explained the paradox primarily by the characteristics of the 'Mediterranean diet', with an abundance of vegetables, fruits, olive oil, and especially red wine.

At that time there were already indications of a U-shaped relationship between alcohol consumption and mortality risk with the lowest risk in moderate drinkers.[1,3,4] But the French paradox hinted on the idea that red wines with their relatively high concentrations of flavonoids had more to offer than other alcoholic drinks.

Although our knowledge of the chemical composition of grapes has advanced greatly in the last 40 years, much still remains a mystery. The number of compounds identified in wine has increased dramatically since the development and combination of high-pressure liquid chromatography, infrared spectroscopy and mass spectrometry.[5] More than 500 compounds have been recognised in wine thus far, of which 160 are esters. The concentrations of the majority range between $10^{-1}$ and $10^{-6}$ mg/l. At these levels the individual compounds play very little or no role in the human taste perception, but collectively they may be very important. The most predominant chemical constituents of wine and grapes are water, followed by alcohol, sugars, polysaccharides, and acids. Phenols are a large and complex group of compounds of particular importance for the characteristics and quality of wines. They may come from the fruit (skins and seeds) and vine stems, production by yeast metabolism, or extraction from wood cooperage. Their concentration in white wines is much lower than in red wines. Chemically, phenols are cyclic benzene compounds possessing one or more hydroxyl groups associated directly with the benzene structure. Flavonoids are characterised as molecules possessing two phenols joined by a pyran (oxygen containing) carbon ring structure. The concentration of phenols in wines increases during skin fermentation and subsequently begins to fall as phenols bond and precipitate with proteins and yeast hulls (cell remnants). During maturation, the phenols continue to decrease, and ageing has a further effect on their reduction.

Polyphenols are not exclusive for wines but are widely present in trees, plants and vegetables, such as in tea, cacao and onions.[6-8] In nature, they exhibit a wide range of biological effects as antioxidants, antimicrobials, and modulators of various enzyme systems.[6-8] This remarkable spectrum of biochemical and cellular functions certainly holds promise and some of these effects have been shown in *in vitro* and *ex vivo* models. However, not enough is known yet about their absorption, bioavailability and bioactivity to conclude that they are indeed operative in the wine-consuming human being.

## ALCOHOL AND CARDIOVASCULAR PROTECTION

Through the last two decades of the last century, a rather consistent body of epidemiological data has accumulated pointing to a 20 to 40% reduced incidence of morbidity and mortality from coronary heart disease among those who consume alcohol in moderation by comparison with abstainers.[9-20] Although alcohol consumption increases the risk of various cancers, hypertension, liver disease, unintentional injuries, and violence, the relationship between alcohol intake and all-cause mortality is U-shaped, with nondrinkers and heavier drinkers having higher risks than light and moderate drinkers.[21-27] Furthermore favourable effects have also been shown in other atherothrombosis-related disorders such as cerebrovascular accidents and some forms of dementia.[28,29] This risk reduction by alcohol can partly be explained by an increase in high-density lipoprotein cholesterol (HDL-c), but is also related to levels of fibrinogen and $HbA_{1c}$.[30] This association of alcohol with HDL-c levels seems related to cholesteryl ester transfer protein (CETP) polymorphism.[31] Various studies now focus on the effects of alcohol on other parts of the atherothrombotic process such as platelet function, coagulation, fibrinolysis, inflammation, oxidative stress, and gene expression.

There are, however, some serious pitfalls with observational studies. These studies might reveal a certain association between alcohol consumption and a decreased mortality, but they do not necessarily prove cause and effect. Observational studies have difficulty in allocating subjects to the intervention and control groups, as those subjects are not randomised. It is possible to correct for known confounders; however, unknown confounders or unmeasured variables still influence outcome. For instance, in the Copenhagen study with 24,000 participants, the consumers of red wine appeared to have a relative risk for cardiovascular diseases of 0.66 (95% confidence interval 0.55 to 0.77) compared with non-drinkers.[32] However, wine drinking was significantly associated with a higher IQ, a higher parental education level and a higher socioeconomic status. Therefore, wine drinking might just be an innocent bystander in the cascade that leads to cardiovascular disease or just an indication of a healthier lifestyle that might have been cardioprotective.[33] In other population studies a specific wine-related effect might be masked by

the fact that many alcohol consumers drink all types of alcohol (also beer and spirit) not allowing any conclusion on a wine effect.

To prove cause and effect, randomised and blinded trials are needed. But with alcohol such trials are hardly feasible for ethical and practical reasons. Alcohol is a potentially hazardous substance with severe side effects, danger of addiction and misuse. Secondly, consuming alcohol does not go unnoticed, making blinding of the subjects very difficult. Furthermore the follow-up should be very long, since it takes many years for atherothrombotic disorders to develop, and the number of individuals needed to follow would be substantial.

Trials that have been performed so far on human volunteers or patients, therefore, focused on surrogate endpoints for cardiovascular diseases needing less time and a limited number of individuals. Recently, two small randomised trials, both with 24 healthy volunteers, showed that alcohol consumption increased blood pressure slightly, but statistically significantly without a change in flow-mediated dilatation after only four weeks.[34,35] In 20 other healthy volunteers, red wine consumption improved antioxidant status and reduced LDL oxidation after two weeks.[36] An increase in HDL cholesterol content after four weeks was observed in another 69 volunteers.[37] Beneficial effects of alcohol consumption on lipids and cholesterol had already been shown in small randomised trials with cross-over design after three weeks.[38-41] In a study focusing on the early steps in reverse cholesterol transport no significant difference in HDL lipids could be observed between beer, wine and spirits indicating the effects only to be related to the alcohol component.[42] Only few randomised trials have involved patients with established coronary artery disease. In these patients consumption of wine did improve flow-mediated dilatation after 360 minutes of ingestion.[43] In short, randomised trials have been performed, but are often of short duration (up to four weeks) and have included few subjects (mostly 20 to 30 healthy, young volunteers). However, a longer follow-up was performed by Mezzano *et al.*, who studied the effects of the Mediterranean diet and the supplementary effects of red wine in cross-over design in 21 volunteers for 90 days and they did not find any effect on lipids or *ex vivo* platelet aggregation.[44,45]

## WINE OR BEER

Several population-based studies and meta-analyses have reported the beverage-specific risk estimates for cardiovascular disease for wine and beer. They report a strong and statistically significant benefit for both beer and wine at levels of moderate consumption (defined as up to 150 ml of red wine and up to 20 grams of alcohol daily), but they find a stronger inverse association for wine (32% risk reduction) than for beer (22%).[15] Other reviews, however, found the benefits of wine to be about the same as those of beer or spirits, and state that it is unlikely that any one beverage is substantially more beneficial. It is therefore helpful to examine their results in more detail and to explore the importance of potential biases that may have influenced the findings.

The ethanol content in a serving of wine is similar to that in a serving of beer, and results from metabolic studies suggest that the effects of these beverages on lipid and haemostatic factors are similar.[46] Thus, if this apparent difference in beverage-specific relative risks is true, then components in wine other than alcohol must confer substantial additional benefit. As mentioned, several antioxidants and other compounds have been identified in red wine, but the incremental benefits of these compounds on biomarkers predictive of coronary heart disease have not been established yet.

An alternative explanation might be that beer and wine have the same physiological effect, but differences in the risk factor patterns among beer and wine drinkers might create the appearance of a difference in coronary heart disease risk.[47,48] A meta-analysis by Di Castelnuovo *et al.*[15] is instructive for further examination of these results because it outlines the important influences of individual study characteristics. Although the authors reported little difference between prospective and retrospective studies when they excluded the studies that did not simultaneously adjust for different types of alcoholic beverages (the most unbiased method to control for confounding), there was no longer a difference in the relative risk of cardiovascular disease between wine drinkers (25%) and beer drinkers (23%) compared with abstainers. These differences may be due to chance, but they do illustrate how susceptible results from meta-analyses are to a few biased studies. An additional pitfall of meta-analyses is that important covariates may not be treated equally across studies. Therefore, pooling relative risks from studies that do not equally account for other risk factors, such as smoking or dietary pattern, can exaggerate or mask differences.

This becomes especially difficult for alcoholic beverage consumption because the direction of potentially important confounders, such as a healthy diet, can be completely opposite as a result of the cultural norms of the population under study. For example, in the aforementioned Danish study, fruit and vegetable consumption was strongly associated with wine intake,[47] whereas in a French EPIC study[49] drinkers of wine consumed less fruits and vegetables. Even within the same country, the direction of confounding can differ. Contrary to the results from the EPIC study, in a separate population from France, wine consumption was associated with a better lifestyle; after controlling for diet and social class, the differential beneficial effects of wine over beer were eliminated.[50]

In other populations another type of alcohol may be the predominant drink related to a healthier lifestyle, thus showing the beneficial effect for that type of alcohol.[51]
In general, studies typically found that wine drinkers tend to have a healthier lifestyle profile than beer drinkers. Without careful control for such confounders across all studies, it is not possible to interpret the biases that may occur by pooling such estimates. The growing number of studies in recent years addressing drinking patterns and preferences should provide better insight into the importance of specific alcoholic beverages.[31,48,52-57] Regardless of the population or the distribution of beverage consumption, residual confounding by diet, physical activity, behavioural characteristics, or even psychological parameters[55] needs to be carefully addressed.

## DRINKING PATTERN AND CARDIOVASCULAR DISEASE

Although light-to-moderate alcohol consumption appears to have a U-shaped relationship to cardiovascular disease and especially coronary artery disease, 'binge drinking' seems to put consumers at an increased risk for cardiovascular diseases.[58] A report by Knupfer[59] suggested that the pattern of daily light drinking is, in fact, not at all common. This study indicated that most light drinkers do not drink daily and most daily drinkers are not light drinkers; that is, consumers of two standard drinks per day.
At the other end of the spectrum, the use of the term 'binge drinking' is similarly confusing. It may refer to heavy drinking on a single occasion or drinking heavily and continuously over a number of days or weeks, abstaining and then repeating the cycle. A quantitative definition for binge drinking has been reported in studies from the United States as the consumption of five or more drinks per occasion for men and four or more for women, with one drink being equivalent to 360 ml of beer, 120 ml of wine or one shot (37 ml) of hard liquor.[60,61] In Australian studies, however, binge drinking has been referred to as consuming five or more alcoholic drinks in a row, or even more loosely as consuming large amounts of alcohol on three or four days of the week.[61] The lack of consistent quantitative measures describing binge drinking may contribute to the difficulty in identifying and classifying the type of drinking patterns that dictate alcohol and cardiovascular disease relationships and may account in part for differences in reported findings between studies of alcohol intake and its impact on various cardiovascular outcomes.
McElduff and Dobson found that binge drinkers (in this instance defined as women who consumed five or more drinks on an occasion, or men who consumed nine or more drinks on an occasion) had higher risks for major coronary events than abstainers, even when the overall volume of drinking was low.[63] More recent prospective studies also concluded that heavy drinking episodes increase the risk of coronary heart disease even in light-to-moderate drinkers.[53,64,65] This pattern effect persists after controlling average volume of drinking. Heavier alcohol consumption has detrimental effects on blood pressure and coronary heart disease.[66,67] In the prospective, observational CARDIA study, over 3000 participants between the age of 30 and 45 were followed for 15 years. In this American study population, heavier drinking was associated with a higher incidence of coronary calcifications (again, a surrogate endpoint) after adjustments for potential confounders and intermediary factors.[58] In this study not only high levels of alcohol consumption but also binge drinking was associated with atherosclerosis of the coronary arteries. This association is consistent with previous studies of binge drinking and coronary heart disease events, most of which found higher rates of events among persons who binge.[53,68] So, binge drinking seems to be associated with coronary heart disease by its influence on atherosclerosis, and dysregulation of inflammatory cytokines associated with the hangover after a binge has been suggested to be a possible mechanism.[69,70]
This influence on atherosclerosis also becomes apparent in a study that showed that men with a heavy, acute style of alcohol consumption had a significantly greater four-year progression of carotid atherosclerosis than men with a more evenly distributed drinking pattern.[69] The positive relationship between heavy doses per sitting and carotid atherosclerosis progression was observed for use of both beer and spirits, after adjustment for the total average level of alcohol use. The magnitude of these relationships was largely unaffected by adjustment for baseline atherosclerosis, known risk factors, and medications. The findings were consistent across different measures of atherosclerosis progression, with heavy acute drinking showing progression of maximum and mean intima-media thickness of the carotid artery and increased plaque height. The observed relationships remained, and appeared to be even stronger, in the analysis of the subgroup that was initially free of the diagnosis or signs of prevalent ischaemic heart disease.
Binge drinking has other detrimental cardiovascular effects. In addition to its effect on coronary heart disease, an irregular pattern of heavy drinking appears to have a relationship with other types of cardiovascular death, such as stroke or sudden cardiac death.[71,72] This relationship is consistent with the increased thrombosis[73] and lowered threshold for ventricular fibrillation that occur after heavy drinking.[74,75] Irregular heavy drinkers seem predisposed to structural (i.e., histological) changes in the heart muscle and the adjacent impulse-conducting system, which decreases the threshold for ventricular fibrillation.[76]

Additionally, heavy drinking has been shown to increase low-density lipoproteins, which have been linked to negative cardiovascular outcomes.[46]

In summary, a pattern of irregular heavy drinking is mainly associated with physiological mechanisms that increase the risk of sudden cardiac death and other cardiovascular outcomes, whereas regular low-to-moderate alcohol consumption might be associated with physiological mechanisms linked to favourable cardiac outcomes.[75,77] However, epidemiological studies that have focused on individuals and the consequences of drinking (e.g. cohort and case-control studies) are still scarce, and some of them have found heavy-drinking occasions to have no detrimental effects on morbidity.[66,78]

## BINGE DRINKING AND CONFOUNDERS

Even in studies where a drinking pattern has been evaluated carefully, it should be taken into account that there are several potential confounding lifestyle and demographic factors associated with both drinking pattern behaviour and cardiovascular risk that need to be considered. A pattern of binge drinking behaviour may be linked to other 'risk' behaviour with cardiovascular implications, including tobacco smoking or even illicit drug use.[79]

Age, a major atherosclerosis risk factor, has a significant bearing on alcohol drinking patterns. Alvarez and colleagues[80] reported a higher weekend alcohol intake by Spaniards aged 14 to 29 years, while those aged 30 to 59 years had a more regular but higher intake during the rest of the week. Among Australian males aged 18 to 64 years, most drank at responsible levels with the largest proportion (over 90%) of responsible drinking being in those aged 65 years or over. However, males aged 18 to 24 years made up the greatest percentage (14.8%) of those drinking at harmful levels. This is similar to findings in the United States, where frequent heavy drinking comprised 27% of 18- to 29-year-old men, while only a smaller (4%) proportion was found in those 65 years and over.[81]

Gender, another major risk factor for atherosclerosis, is also associated with differences in alcohol drinking patterns. Studies show consistently higher rates of binge drinking among men than women. However, some of these studies used the same definition of binge drinking for both men and women, without accounting for gender differences in the metabolism of ethanol or body mass. The pattern of alcohol consumption varies according to social groups.[80,82] Those who are single, separated or divorced, or living in a shared accommodation, drink more frequently and are more likely to be heavy drinkers (defined as consuming >80 g of alcohol/day, approximately six standard drinks) than those who are married.[83] Those who are unemployed have a higher alcohol intake and a higher frequency of alcohol use than those who studied, worked, performed homemaker duties or were retired.[80] Ragland *et al.*[82] showed that even in high-stress occupations, being married was associated with lower alcohol consumption, possibly protecting against occupational factors that influence alcohol consumption. Alvarez and colleagues[80] found that individuals with a low academic level, which included those with no schooling or who received primary or secondary schooling, drank less frequently but in higher quantities.

Alcoholic beverage preference is also associated with alcohol drinking patterns and represents another potential confounder of interpretation of alcohol and cardiovascular disease relationships.[19] A Spanish study[83] found that in regular drinkers, those aged <39 years, predominantly consumed beer and spirits while those aged ≥40 years favoured wine. Another Spanish study showed that people who consume one type of beverage often drink in low-to-moderate amounts, unlike people drinking all three beverages (beer, wine and spirits), who showed the highest percentage of a heavy drinking pattern.[84] In a Danish study moderate wine drinkers appeared to be at lower risk of becoming heavy and excessive drinkers favouring the health effect of wine over the other types of alcohol.[85] On the other hand, in Australia, young binge-drinking men were almost exclusively beer drinkers while women consumed a much wider variety of beverages including beer, wine and spirits.

## CONCLUSIONS

The French paradox illustrates the relationship between lifestyle and cardiovascular risk. It is, however, doubtful whether this paradox still exists for the current French population. According to the 'time-lag hypothesis' modern France does not differ from the rest of the world with regard to the incidence of cardiovascular disorders.[86] The mortality rates in the 1980s, on which the paradox was based, reflect the lifestyle of France in the 1950s and 60s rather than in the 1980s, since it takes decades for atherosclerosis to develop. In the view of the supporters of the paradox the consumption of wine plays a pivotal role influencing the atherothrombotic process. Although it confirms the favourable effect of modest alcohol consumption on cardiovascular risk 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 liquor. A large survey in the United States even demonstrated that some or all of the apparent protective effects of moderate alcohol consumption on cardiovascular diseases may be due to residual or unmeasured confounding.[87] Without adequate control for such confounders conclusions are premature

and not justified. The exact clinical significance of other constituents in wine, such as the polyphenols, is not elaborated yet.

In contrast to moderate drinking, there is quite some evidence that incidental heavy or binge drinking is associated with an increased cardiovascular risk. However, for both spectra of consumption only randomised intervention trials with many participants, a long follow-up, and solid study end points might unravel the mysteries of alcohol. Because of ethical and practical objections it is unlikely that such a study will ever be performed. Nevertheless, the message at this stage seems clear: protection or harm is more related to the quantity of alcohol that we consume than to the content of the bottle.

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