

## Is it merely a myth that alcoholic beverages such as red wine can be cardioprotective?

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### Abstract

It has been suggested that although the negative impact of alcohol consumption varies from person to person, on a global level the adverse effect of alcohol on cardiovascular disease outweighs any protective effect by between two- and three-fold. This is inaccurate. There is a proven positive relationship between alcohol consumption and cardiovascular disease that is acknowledged by the World Health Organisation. For example, moderate alcohol consumption reduces the risk of cardiovascular disease by approximately 25%, such that alcohol consumption per se accounts for -4.7% of the total cardiovascular disease burden in Australia. Correspondingly, cardiovascular disease accounted for 34% of the total number of deaths in Australia in 2008, and 18% of the overall burden of disease in Australia in 2003, with coronary heart disease and stroke contributing over 80% of this burden. Australia is not substantially different from other developed countries having similar demographics to, and the same leading causes of burden as, other high-income developed countries. This article examines the suggestions and evidence surrounding the relationship between light-to-moderate alcohol consumption and benefits to human health.

### Introduction

It is well documented and cannot be disputed that the immoderate use of an alcoholic beverage such as wine, i.e. above the (Australian) National Health and Medical Research Council's (2009) recommendations of not more than two standard drinks per day for both men and women (20 g alcohol per day), is associated adverse health effects.<sup>1</sup> These can be short-term effects as accidents, drowning and suicides generally associated binge drinking patterns, i.e. a large amount consumed in a small period of time; or long-term effects associated with continuous heavier consumption, over many years, such as alcohol-related cardiovascular disease, certain cancers, liver cirrhosis and pancreatitis.

It is also well documented in peer-reviewed published data over more than three decades that light-to-moderate alcohol consumption, i.e. approximately corresponding to the recommended level of not more than two standard drinks per day for both men and women, is associated with a reduced risk of developing and dying from cardiovascular diseases, certain cancers, diabetes, and cognitive function disorders such as dementia.<sup>2-9</sup>

This equates to a reduced risk of dying from all or any causes, and is in comparison to abstainers and heavy consumers. These relationships have best been described as j-shaped and most relevant for individuals aged over 40–45 years, i.e. in particular for those who are at greater risk of cardiovascular disease.<sup>10–13</sup> The risk of adverse health effects increases, however, when alcohol consumption increases from light-to-moderate to heavy.<sup>14–18</sup> A meta-analysis by Klutzy and Udaltsova<sup>19</sup> suggests that the benefit extends to approximately four standard drinks per day (40 g alcohol per day), as does that of Mukamal et al.<sup>20</sup> and Doll et al.<sup>21</sup>

### Contested?

A paper by Jackson et al.<sup>22</sup> and subsequent papers by Fillmore et al.<sup>23,24</sup> suggested that 'this view is contested', and argued that 'any coronary protection from light to moderate drinking will be very small and unlikely to outweigh the harms'.

The meta-analysis by Fillmore et al.<sup>23</sup> of 54 previously published epidemiological studies on all-cause mortality and 35 on coronary heart disease mortality has suggested, however, that confounding has led to bias in the majority of studies showing less cardiovascular disease among light-to-moderate drinkers, and consequently that the cardioprotection afforded by alcoholic beverages may have been overestimated. For example, studies may have misclassified ex drinkers, who are a higher risk of coronary heart disease, in the abstainer category, thereby inflating the mortality in abstainers compared with moderate drinkers. They also suggested that calculations of mortality from heavier drinking may also be overestimated. Indeed, while they conceded that 'alcohol [among other substances, lifestyles and behaviours] conveys benefit to the heart' they also concluded that 'the actual outcomes in human populations for cardiac benefit have been exaggerated'. In addition, in further communications from Fillmore et al.,<sup>24</sup> they suggested that if there is a protective effect of light-to-moderate alcohol consumption against the incidence of coronary heart disease or any other diseases, we currently do not know enough to recommend regular alcohol consumption for health reasons, and, from 2006, this should be taken into account in both policy and clinical practice.

### Evidence?

Evidence, i.e. sound scientific data over more than three decades, suggests, however, that moderate alcohol

consumers are at considerably lower risk of cardiovascular disease, and newer studies also indicate that they are at lower risk of other diseases of ageing.<sup>19,25,26</sup> Analysis of 84 longitudinal cohort studies of cardiovascular disease comparing alcohol consumers with abstainers, for example, showed that the pooled adjusted relative risks for alcohol consumers relative to abstainers in random-effects models for the outcomes of interest were: '0.75 (95% confidence interval 0.70 to 0.80) for cardiovascular disease mortality (21 studies), 0.71 (0.66 to 0.77) for incident coronary heart disease (29 studies), 0.75 (0.68 to 0.81) for coronary heart disease mortality (31 studies), 0.98 (0.91 to 1.06) for incident stroke (17 studies), and 1.06 (0.91 to 1.23) for stroke mortality (10 studies).'<sup>27</sup> (If the relative risk was 1.0, the risk would be the same for alcohol consumers and abstainers.) This analysis also showed that alcohol consumption at 2.5–14.9g per day was consistently associated with a 14–25% reduction in the risk of all outcomes assessed compared with abstaining from alcohol. Consistent with a j-shaped relationship, risk increased with increased consumption, but differed for different cardiovascular disease outcomes. The cardioprotective association with alcohol was consistently observed in diverse patient populations and in both men and women, and was apparent when controlling for known confounders such as cigarette smoking, diet and exercise.

Klatsky and Udaltsova<sup>19</sup> reworked previously published data<sup>28,29</sup> to address the purported confounding and potential overestimation of a health benefit from moderate alcohol consumption claimed by Fillmore et al.,<sup>23,24</sup> and showed a shallower but still significant j-shaped relationship between alcohol consumption and all-cause mortality risk. The data were of 21,535 deaths through to 2002, where the follow-up included 2,618,523 person-years of observation with a mean follow-up of 20.6 years. Their reanalysis reconfirmed the relationship previously published with an increased risk for individuals consuming more than three (14 g) drinks per day and a reduced risk at three or fewer drinks (14 g) per day, almost always due to a reduced risk of death from cardiovascular disease. Former consumers were observed to be at increased risk of death from non-cardiovascular disease and occasional consumers were observed to have a risk similar to lifelong abstainers.

Most recently, Fuller<sup>26</sup> aimed to determine the extent to which the 'confounding and bias' in early epidemiological studies led to potentially erroneous conclusions about the inverse association between moderate alcohol consumption and cardiovascular disease. The analysis was based on prospective data for more than 124 000 persons interviewed in the US National Health Interview Surveys of 1997 – 2000 and was designed to avoid the 'errors' of some earlier studies including those identified by Fillmore et al.<sup>23</sup> The results support the significant majority of prospective studies and indicate that moderate alcohol consumers have

a lower risk of cardiovascular diseases and all-cause mortality. Fuller<sup>26</sup> contends that these results lend credence to the argument that the inverse association between moderate alcohol consumption and mortality is causal.

There are also other relatively recent studies where neither type of 'error' studied by Fillmore et al.<sup>23</sup> was present. For example, a study by Mukamal et al.<sup>20</sup> on a large group of older adults which separated lifetime abstainers from former drinkers, and occasional drinkers from regular light drinkers, demonstrated reductions in the risk of a variety of cardiovascular outcomes from moderate consumption, as did Di Castelnuovo et al.<sup>30</sup> In another study on older people by Tolvanen et al.,<sup>31</sup> where ex drinkers were separated from lifetime abstainers, total mortality was highest in the ex drinkers and lifetime abstainers, and 30 – 40% lower in current consumers. In addition, another study by Klatsky et al.<sup>32</sup> which identified lifetime abstainers and separated occasional drinkers from regular light drinkers showed that consumption of one to two drinks per day was associated with 40% less risk of heart failure associated with coronary artery disease. Further, another study by Holahan et al.,<sup>33</sup> which assessed total mortality in 1,824 middle- aged and older people followed for 20 years, even controlling for a wide range of traditional and non-traditional confounding factors associated with abstinence, including those identified by Fillmore et al.,<sup>23</sup> ex drinkers and lifetime abstainers and heavy drinkers (>42 g alcohol per day) continued to show increased mortality risks of 51% and 45%, respectively, compared to moderate drinkers (14 to <42 g alcohol per day).

Eight commentaries were subsequently published in the February 2007 edition of the journal *Addiction Research and Theory* following a panel discussion at the Symposium on Moderate Alcohol Consumption: Health Risks and Benefit on 17–18 May 2006.<sup>25,34,35</sup> One of the salient points to come out of the commentaries, as well as from the May 2007 edition of the *Annals of Epidemiology*, is that there is evidence for plausible biological mechanisms for protection against coronary heart disease by moderate alcohol consumption which adds credence to a causal hypothesis. These mechanisms include effects via high-density lipoprotein cholesterol, improved haemostatic factors, improved endothelial function, and a lower risk of diabetes mellitus, and are primarily imparted by the alcohol component common to all alcoholic beverages.<sup>36 – 39</sup> These were well summarised by Brien et al.,<sup>40</sup> who stated: 'Favourable changes in several cardiovascular biomarkers (higher levels of high density lipoprotein cholesterol and adiponectin, and lower concentration of fibrinogen) provide indirect pathophysiological support for a protective effect of moderate alcohol use on coronary heart disease.'

## Further Evidence?

An earlier meta-analysis of 42 experimental studies, which examined the effects of alcohol consumption on cardiovascular biomarkers, attributed the cardioprotective effect of light-to-moderate alcohol consumption: 60% to effects on high-density lipoprotein, 20–30% to fibrinogen, 5–10% to insulin and 0 – 5% to other haemostatic factors.<sup>14</sup> The meta-analysis also estimated that 30 g alcohol per day would increase the plasma concentration of high-density lipoprotein by approximately 4 mg dL<sup>-1</sup>, which would be associated with a 17% reduction in risk of coronary heart disease. It would also decrease the plasma concentration of fibrinogen by approximately 0.075g L<sup>-1</sup>, which would be associated with a 12.5% reduction in risk of coronary heart disease.<sup>41</sup> This translated into an overall 24.7% reduction in the risk of coronary heart disease from the consumption of 30g alcohol per day. Klatsky and Udaltsova<sup>19</sup> further translated this into a 10% reduction in risk of all-cause mortality. Interestingly, in their reply to the eight commentaries on this point, Fillmore et al.<sup>24</sup> do not dispute the evidence for plausible biological mechanisms and merely suggest that ‘the lot falls to epidemiology to establish whether human populations will benefit greatly from the use of alcohol and if they should be advised to use the substance for medicinal purposes’.

## Amount Or Pattern Of Alcohol Consumption?

Essentially all epidemiological studies that have considered patterns of alcohol consumption have shown that regular moderate consumption is allied to a lower risk of diseases rather than occasional consumption,<sup>42–46</sup> while episodic heavy consumption, considered as binge drinking, negates any beneficial health effect.<sup>47–51</sup> For example, from the 2003 and 2005 studies by Mukamal et al.,<sup>44,52</sup> men who consumed light-to-moderate amounts of alcohol at 3–4 or 5–7 days per week had decreased risks of myocardial infarction and ischaemic stroke compared with men who consumed alcohol less than once per week. This is a similar observation to that of Tolstrup et al.,<sup>53</sup> where for the same average consumption of alcohol an infrequent intake implied a higher risk of mortality than a frequent one, and also to that of Baglietto et al.,<sup>54</sup> who investigated associations between average volume of alcohol consumption, beverage type and consumption pattern, and all-cause mortality. After adjustment for total amount of alcohol consumed, the number of drinking days was inversely associated with the risk of dying in men, confirming previous observations about the effect of average volume of alcohol and beverage type and suggest that consumption pattern is an independent risk factor for all-cause mortality. The beneficial health effects of alcohol may thus be limited or linked to certain patterns of consumption,<sup>55,56</sup> as are the harmful effects. Even Shaper,<sup>57</sup> on whose 1988 hypothesis the Fillmore et al.<sup>23</sup> meta-analysis is based,

concludes in his commentary that ‘there is no evidence that light drinking, one to two per day for men and one for women, has any untoward effects and most would accept that this level of alcohol intake provides both individual and social pleasure’.

Similarly, the World Health Organisation’s Global Status Report on Alcohol<sup>58</sup> recognises that both the amount and pattern of alcohol consumption influence the potential health benefits of alcohol consumption and includes the following statement: ‘The relationship between alcohol consumption and cardiovascular diseases is complex. Light to moderate drinking can have a beneficial impact on morbidity and mortality for ischaemic heart disease and ischaemic stroke. However, the beneficial cardioprotective effect of drinking disappears with heavy drinking occasions. Roerecke and Rehm (2010)<sup>59</sup> have shown, based on meta-analyses, that, on average, light to moderate drinkers experienced no protective effect if they reported at least one heavy drinking occasion per month. Moreover, alcohol consumption has detrimental effects on hypertension, cardiac dysrhythmias and haemorrhagic stroke, regardless of the drinking pattern.’<sup>60</sup>

## Is Wine Different?

Diet is also a significant source of variation in cardiovascular risk and is accordingly a risk factor that can be readily modified to reduce cardiovascular risk, as well as the impact of other important cardiovascular risk factors.<sup>61–65</sup> From a 30-year follow-up study in seven countries, the risk of cardiovascular disease was at least two- to three-fold lower in countries consuming a Mediterranean-style diet compared to that in northern Europe and the USA, where the diet was generally higher in fat.<sup>66</sup> The core components of a Mediterranean-style diet include the high consumption of cereals, fruits, legumes, vegetables and wine, which typically contain a high concentration of phenolic compounds, and have previously been associated with a reduced risk of cardiovascular disease.<sup>67–69</sup> For example, subjects placed on a Mediterranean-style diet for 46 months had a 50–70% lower risk of recurrent cardiovascular disease, compared to control subjects on a higher-fat diet.<sup>68</sup> Furthermore, 55% of patients with metabolic syndrome (high blood pressure, a high cholesterol concentration and a high body mass index) who followed a Mediterranean diet for 2 years were symptomless and had a reduced risk of cardiovascular disease at follow-up compared with only 14% of patients in the control group.<sup>70</sup>

Epidemiological or population studies have indicated that consumers of wine have a reduced risk of cardiovascular disease and all-cause mortality,<sup>71–74</sup> similar but additive to that for consumers of a traditional Mediterranean diet. The studies do not differentiate between wine styles and types. This is exemplified in an epidemiological study assessing the geographical distribution of cardiovascular disease in Spain, one of the 18 Mediterranean countries. A higher rate of

cardiovascular disease was observed in those Spanish regions with the lowest per capita wine consumption, despite having, overall, a Mediterranean-style diet. The rate of cardiovascular disease was, however, still less than that of countries consuming a higher fat and lower phenolic compound diet.<sup>75</sup>

The components of wine that might confer a reduced risk of cardiovascular disease, by enhancing endothelial function and exerting anti-inflammatory and anti-atherosclerotic effects, are represented by the phenolic compounds. These compounds, also present in the fruit and vegetable components of a Mediterranean-style diet, have been associated with a reduced risk of cardiovascular disease.<sup>69</sup> There are approximately 10 classes of phenolic compounds in grapes, which are pulp, seed and skin derived. Their amount in grapes and wine is dependent upon a complex interaction of viticultural and oenological variables.<sup>76</sup> Catechin, quercetin and resveratrol represent some of the primary phenolic compounds in both red and white wine.<sup>77</sup> Several test tube (in vitro) and animal studies have demonstrated that catechin, quercetin and resveratrol, administered either as single or multiple doses, exert significant beneficial effects on established biological markers of cardiovascular disease risk such as endothelial function<sup>78–83</sup> and blood pressure,<sup>84–87</sup> as well as more broadly on blood clotting and flow factors.<sup>88,89</sup>

### Proposed Mechanisms

The potential biological mechanisms for the cardioprotection appear to be misunderstood by the popular press, which continuously cites that antioxidation is solely responsible for the cardioprotection of wine-derived phenolic compounds and hence wine. The data actually suggest that phenolic compounds, while antioxidative in the test tube, are not so in vivo, leading to suggestions that wine is not a different type of alcoholic beverage or does not confer additional protection against cardiovascular disease.

Antioxidation is not the primary mechanism associated with preventing cardiovascular disease, and it is not the primary cardioprotective mechanism associated with light-to-moderate wine consumption.

Cardiovascular disease involves a complex interplay between multiple altered cellular and molecular functions in heart muscle (such as cardiomyocytes), blood vessels (such as endothelial cells), vascular smooth muscle cells, blood cells (such as platelets and monocytes) and plasma components (such as lipoproteins, and blood clotting and blood flow factors) as well as gene function.<sup>90</sup>

Accordingly, there are multiple biological mechanisms involved in reducing the risk of cardiovascular disease, including haemostatic effects on a blood pressure and blood flow, anti-inflammatory effects and enhanced

endothelial function, i.e. the ability of the artery wall to expand and contract, thus providing a protective effect during the early phases of atherosclerosis.<sup>70,91–93</sup>

The lining of the artery wall (endothelium) plays a crucial role in regulating blood flow and the supply of oxygen to organs and tissues through the production of nitric oxide.<sup>94</sup> Nitric oxide regulates arterial tone, i.e. how much the arteries resist being stretched, and exerts significant anti-inflammatory and anti-atherosclerotic effects.<sup>94</sup> Endothelial dysfunction, which is the inability of the lining of the artery wall to expand and contract, has been shown to be an independent predictor of cardiovascular disease even after adjusting for traditional risk factors such as hypertension and hypercholesterolaemia, which are characterized by an impairment of endothelium-dependent vasodilatation.<sup>95</sup> Therefore, improving haemostatic effects, anti-inflammatory effects and endothelial function by means of drug and non-drug therapies such as moderate wine consumption with food might represent an important therapeutic target.<sup>95,96</sup>

### Conclusions that can be drawn

In addition to reducing the risk of cardiovascular disease and certain cancers, for example, light-to-moderate alcohol consumption reduces the risk of dying from all or any causes (all-cause mortality). A recent study of 16,958 US individuals followed for 18 years by the US Centers for Disease Control and Prevention (CDC) examined the relationship between four low-risk behaviours and mortality. 'Moderate consumption of alcohol' was considered as one of 'four healthy lifestyle behaviours that exert a powerful and beneficial effect on mortality.'<sup>97</sup> Moderate or low-risk alcohol consumption was defined as less than or equal to 2 drinks per day but more than 0 for men and less than or equal to 1 drink per day but more than 0 for women. The other low-risk behaviours were non smoking, eating a healthy diet and physical activity. These CDC study authors stated that: 'The number of low-risk behaviours was inversely related to the risk for mortality. Compared with participants who had no low-risk behaviours, which included abstinence from alcohol as well as excessive alcohol consumption, those who had all four experienced significantly reduced all-cause mortality, mortality from malignant neoplasms [cancers], major cardiovascular disease, and other causes'; i.e. the men and women were 63% less likely to die, 66% less likely to die from a malignant neoplasms, 65% less likely to die from major cardiovascular disease and 57% less likely to die from other causes. Considering the potential dangers of excessive drinking, these CDC study authors also conducted sensitivity analyses omitting moderate alcohol use; the mortality risk for those who also consumed alcohol was significantly lower than for those having only the three other behaviours. Chiuve et al.<sup>98</sup>

also included light-to-moderate alcohol consumption (5 – 10 g per day) as one of five low-risk behaviours associated with a reduced risk of coronary heart disease irrespective of concurrent medication for hypertension or hypercholesterolaemia. These behaviours were based on the Healthy Eating Index (HEI), created by the US Department of Agriculture to assess how well the US population met dietary recommendations based on the Food Guide Pyramid and the Dietary Guidelines for Americans. The HEI defined moderate alcohol consumption of 1.5–2.5 drinks per day as ideal servings for men and 0.5–1.5 drinks per day as ideal for women on the basis of the lower risk of cardiovascular disease associated with moderate alcohol consumption.<sup>99</sup>

A similar, little-publicised Australian study of 7,989 individuals aged 65–83 years followed for 5 years showed consistent results with this CDC study.<sup>100</sup> The eight selected low-risk behaviours included having no more than two alcoholic (total 20 g alcohol) drinks per day. Individuals with five or more of the selected low-risk behaviours had a lower risk of death from any cause within 5 years compared with those having less than five. More importantly, the study showed that while most individuals already have some healthy habits, almost all could make changes to their diet and lifestyle to improve their health. The study did not suggest abstinence from alcohol, and avoidance of heavier alcohol consumption is also inferred.

In addition, Lee et al.<sup>101</sup> showed that although light-to-moderate drinkers may have better risk factor profiles than non-drinkers, including higher socioeconomic status and fewer functional limitations (such as activities of daily living, instrumental activities of daily living and mobility), which explain some of the survival advantage associated with alcohol consumption, light- to-moderate drinkers still maintain their survival advantage even after adjustment for these factors.

Further, Sun et al.<sup>46</sup> recently showed that, in addition to lower mortality, women moderate alcohol consumers surviving to age 70 years and older generally had less disability and disease, and more signs of 'successful ageing'. For 'regular' light-to-moderate alcohol consumers (on 5–7 days per week), there was an approximately 50% greater chance of such successful ageing compared with non-drinkers.

## Epilogue

Population ageing is occurring on a global scale, with faster ageing projected for the coming decades than has occurred in the past. Globally, the population aged 60 years and over is projected to nearly triple by 2050, while the population aged 80 years and over is projected to experience a more than five-fold increase. In Australia, between now and 2050 the number of older individuals (65–84 years) is expected to more than double; and very old individuals (85 and over)

are expected to more than quadruple from 0.4 million people today to 1.8 million in 2050 ([www.treasury.gov.au/igr/igr2010](http://www.treasury.gov.au/igr/igr2010)). Increased numbers of older individuals may have implications for associated expenditure on income support, housing and health services, although a healthy, independent older population can also form a valued social resource, for example in providing care for others, sharing skills and knowledge and engaging in volunteer activities. Consequently, simple dietary measures such as moderate alcohol and wine consumption to supplement a healthy exercise and nutrition routine, or as an adjunct to prescription medicines when appropriate, may thus be needed to maintain an ageing population.

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