

Moderate alcohol consumption and cardiovascular risk reduction: open issues

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Abstract

Background: The inverse relationship between low to moderate alcohol consumption and several favorable health outcomes has been well established in many epidemiological studies and meta-analyses. However, several questions still remain controversial.

Aims: To discuss a number of open questions relating to the healthy effect of a moderate intake of alcohol (especially wine) on cardiovascular disease and total mortality. This will be based on findings from the literature, with a particular emphasis on meta-analyses.

Results and Conclusion: The role of different alcoholic beverages, age and sex, confounding, former drinkers and study design has been discussed.

Whether wine is better than beer or spirits, though suggestive, remains to be established.

Cardiovascular morbidity and total mortality is significantly reduced both in men and women who are regular drinkers of low amounts of alcohol; however, the predicted protection in women disappears at lower doses than in men.

The primary protection of alcohol decreases after adjustment for known variables, thus confirming the importance of confounding in assessing drinking effects, but it remains significant and of undoubted public health value.

As the cardiovascular protection by moderate alcohol consumption might have been unduly overestimated by inclusion in control groups of former drinkers, we compared studies that used as a reference group the category of no alcohol intake and/or formally excluded former drinkers with studies which did not: the protection was indeed somewhat lower in the former than in the latter studies, but was still statistically significant.

We conclude that the dose-response relationship between alcohol intake and cardiovascular risk or total mortality, consistently described by J-shaped curves, can be reasonably attributed to a combination of both real beneficial (at lower doses) and harmful (at higher doses) effects of alcohol or wine consumption.

Key words: alcohol, wine, cardiovascular disease, all-cause mortality, meta-analysis

Introduction

The protective effect of moderate alcohol consumption in coronary heart disease (CHD) and cerebrovascular disease has been consistently shown in many epidemiological studies and confirmed in meta-analyses. [1-9] Several non-vascular or non primarily vascular diseases are also known to be less frequent in moderate drinkers than in non drinkers. These include diabetes, [10,11] osteoporosis, [12] gall bladder disease [13] and other pathological conditions. [4] Finally, total mortality rates were also reduced in moderate drinkers. [6,14-18] However, excess of drinking is definitely harmful. [14,19]

Anti-atherogenic alterations in plasma lipoproteins, which are particularly increased in high density lipoprotein (HDL) cholesterol, are considered as the most plausible mechanism of

the protective effect of alcohol consumption on CHD. Other potential mechanisms contributing to the cardio-protective effect of moderate alcohol consumption include anti-thrombotic down-regulation of blood platelet function, as well as of the coagulation factors with concomitant fibrinolysis activation. [20]

However, several questions still remain controversial. In particular, we will discuss a number of open questions concerning the role of different alcoholic beverages, age and sex, confounding, former drinkers and study design.

Alcohol: wine, beer or spirit?

The influence of separate wine, beer, and spirit intake on health outcomes has been examined in various conditions but with somewhat different results.



Cardiovascular Disease

Many epidemiological studies have explored the hypothesis that consuming alcohol in the form of wine might confer significant protection against CHD above that expected from its alcohol content. Wine might indeed conceivably show additional non-ethanol related beneficial effects. In fact, while the mechanisms underlying the effects of alcohol have been essentially limited to lipid metabolism and the haemostatic system, those related to wine consumption have been extended to specific antioxidant and vaso-relaxant properties of its polyphenolic constituents. [21,22] In spite of a large number of experimental studies that confirm this hypothesis, epidemiological evidence of a greater effect of wine has not been definitely established. A meta-analysis from our group [6] tested such a hypothesis. The main outcome measure was wine or beer consumption versus the relative risk of morbidity and mortality from vascular disease. From 13 studies (209 418 subjects) only reporting relative risk of moderate (1-2 drinks a day) versus no wine consumption, the overall relative risk was 0.68 (95%CI: 0.59-0.77; Figure 1). In addition, there was strong evidence from 10 studies (involving 176,042 persons) to support a J-shaped relationship between different amounts of wine intake and vascular risk. A statistically significant inverse association was found up to a daily intake of 150 ml of wine. On the other hand, the overall relative risk of moderate beer consumption, measured in 15 studies (involving 208,036 persons), was 0.78 (95%CI: 0.70-0.86). More

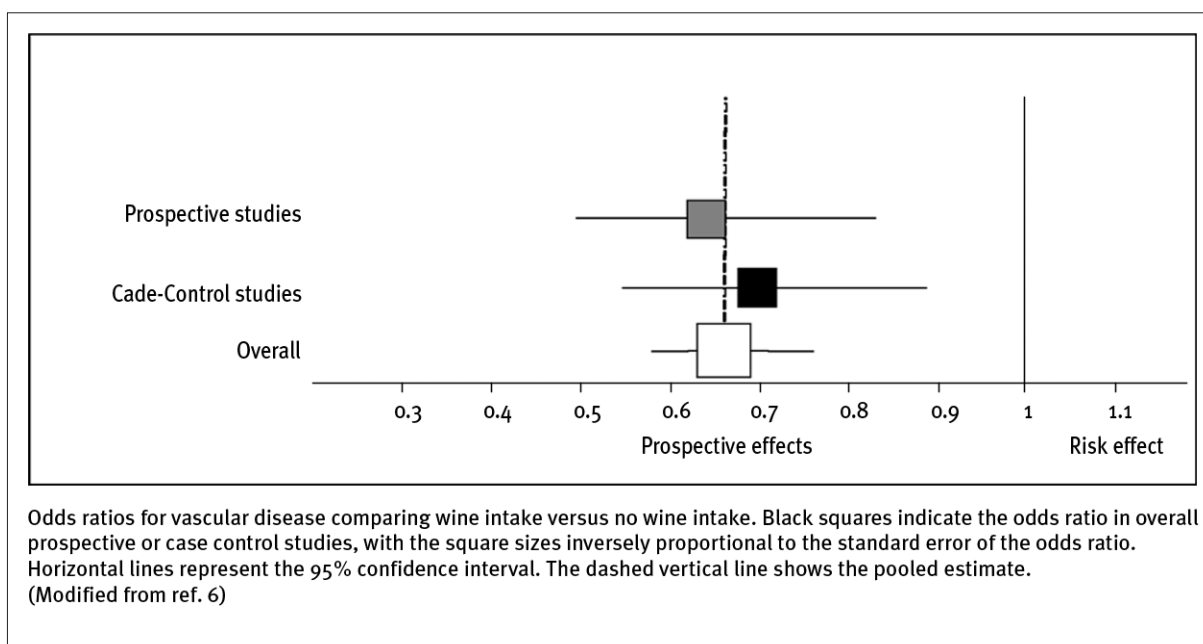
importantly, no significant relationship between different amounts of beer intake and vascular risk was found after performing a meta-analysis of 7 studies involving 136,382 persons.

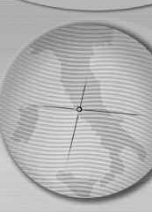
Total Mortality

Epidemiological studies have shown that light and moderate wine drinking, in contrast with beer or spirit drinking, was associated with a dose-dependent decrease in *all-cause* mortality rates, attributable to a decrease in mortality not only from cardiovascular and cerebrovascular disease but also from other causes. A moderate intake of alcohol from beer was also associated with a lower risk of cardiovascular mortality, but did not reduce death from cancer. *All-cause* mortality was unchanged. [17] This finding suggests that wine might contain one or several substances that add to the beneficial effect of alcohol intake (e.g., both *in vitro* and *in vivo* resveratrol from grapes inhibits initiation, promotion, and progression of cancer). [23] Intake of beer and spirits was even reportedly associated with a dose-dependent increase in risk for death from cancer. [24]

Whether wine is better than beer or spirits remains however to be definitely established. Future studies addressing this issue should be of large sample size and carefully designed, because differences between beverages, if any, are expected to be limited and might reflect differences in the risk factor patterns among categories of drinkers rather than a true difference in CHD risk and total mortality.

Figure 1.





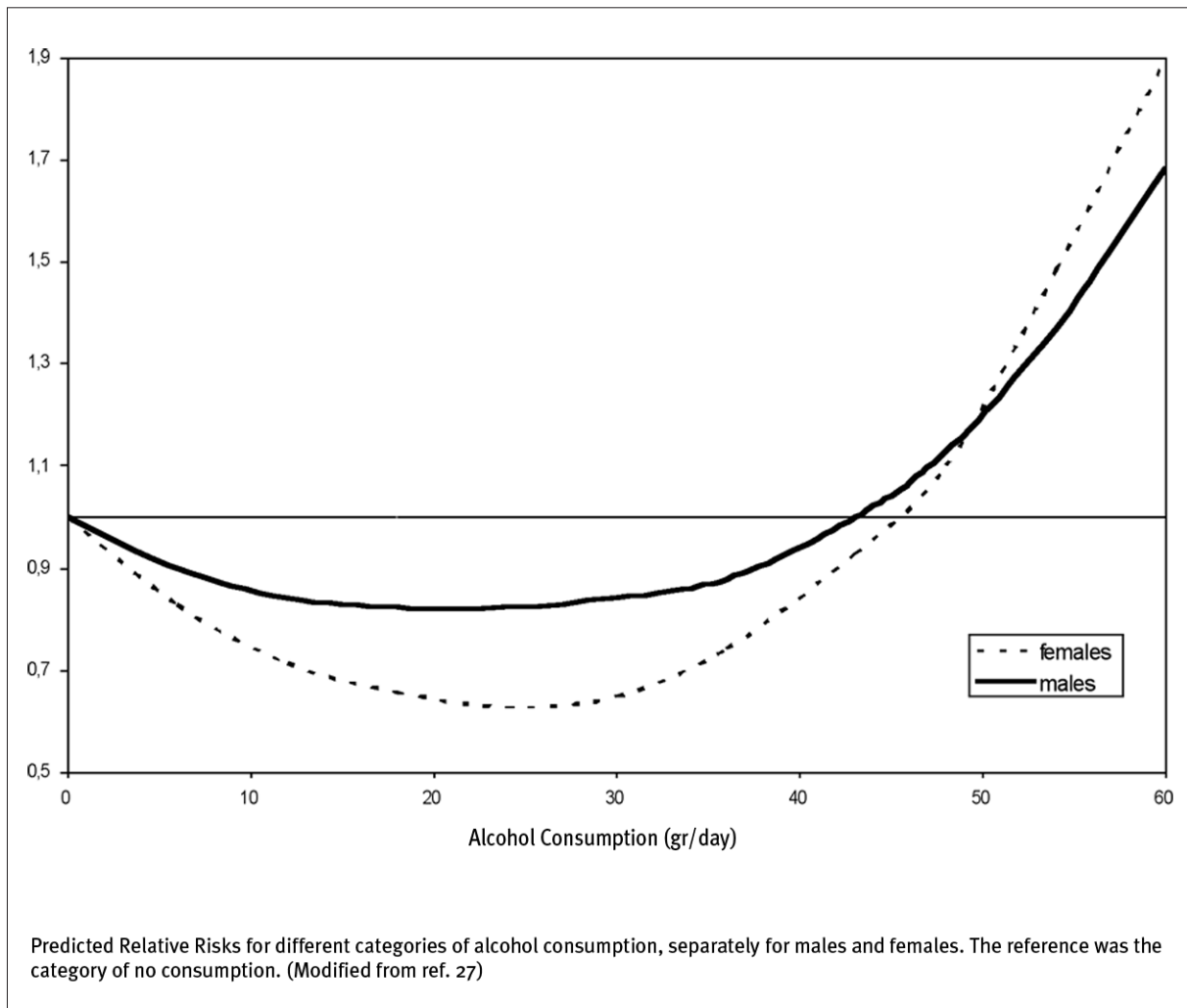
Are the effects of alcohol different in males and females?

Cardiovascular Disease

A possible gender difference in the protective effect of alcohol on vascular risk might exist and explain apparently controversial results in different epidemiological studies. In a report [25] on mortality and alcohol consumption in a large cohort in the USA (128 934 adults, 16 431 deaths in 20 years of follow up), the protective effect of moderate alcohol intake against cardiovascular deaths was essentially restricted to women (20% reduced risk *versus* a non significant 10% reduction in men). On the contrary, a meta-analysis of Corrao *et al.* [26] found a lower protective effect of alcohol consumption against coronary artery disease risk in women. We performed a meta-analysis of studies reporting "trend" (dose-response) effect of alcohol intake on vascular risk, separately for males and females. [27] To allow

meaningful comparisons between sexes, only studies that separately analyzed males and females, recruited from the same population, and that used the same categories of alcohol consumption for both sexes were selected, in all 12 such studies were identified (altogether 184 791 persons were enrolled). Half were case-control and half were follow up studies. The end-points were cerebrovascular disease, coronary heart disease and peripheral arterial disease. "Dose-response" curves (relative risks at different amounts of alcohol intake) for each study were used to construct an average "trend" curve, for both men and women. The predicted dose-response models were very similar for both sexes. A maximum reduction (RR=0.80; 95%CI: 0.57-1.12 in males and RR=0.66; 95%CI: 0.39-1.12 in females; Figure 2) was predicted in both groups at 18-24 grams of ethanol *per day*, but statistical significance was only reached up to the amount of 12 grams of ethanol *per day*. At 12 grams of ethanol *per day* the relative risk was

Figure 2.





0.83 (95%CI: 0.69-0.99) in males and 0.72 (95%CI: 0.54-0.96) in females.

The apparent greater effect of alcohol in women may be explained by several factors, such as increased HDL cholesterol levels or a better endothelial protective effects, or decreased insulin resistance; it is also known that equivalent alcohol doses result in higher blood levels of alcohol in women because the average size of a women is smaller, they have a higher proportion of body fat, as well as reduced gastric metabolism of ethanol. [28] One should also consider that men binge drink more frequently than women. As a different gender-related protective role of alcohol was observed in our meta-analysis on wine consumption, [6] and in the study of Klatsky *et al.* [25] in which women were more likely to drink wine, we cannot exclude that sex-related differences might be linked not only to alcohol, but also to additional properties of specific wine components. [21,22]

Total mortality

In a recently completed meta-analysis including 34 prospective studies, [29] we pooled findings from about one million subjects and 100,000 deaths from any cause. The expected J-shaped relationship between total mortality and increasing amounts of alcohol consumed, showed that low to moderate consumption of alcohol (≤ 1 drink/day in females and ≤ 2 drink/day in males) significantly reduces total mortality, while higher doses increase it. Our meta-analysis provides a definite confirmation of previous results, [30-32] in a set of data including 10

studies published after the year 2000 that could not be considered in less recent meta-analyses. Data were analysed using a recently proposed approach, [32] and special attention was given to differences between gender and to the possible effect of confounding. The predictive dose-response models were very similar for both sexes when the intake of alcohol was light, but they did differ with heavier intake (Table 1).

To better compare the effect of alcohol in males and females, a subsequent analysis was restricted to 13 studies that analysed males and females, *recruited from the same population*, separately. Our results indicate that total mortality is reduced in both men and women; however, the predicted protection in women disappears earlier than in men (Figure 3), which is in keeping with previous findings. [31] It means that women are more exposed to all causes of death at moderate to high level of alcohol consumption than men, probably due - as mentioned above - to different metabolism of alcohol and/or increasing risk of various cancers (e.g., breast cancer). [33] Women are known to metabolize ethanol differently, resulting in higher blood ethanol levels for a given intake. [34] They have a lower gastric alcohol dehydrogenase activity, and consequently a higher amount of alcohol reaches the liver directly, increasing the risk of liver disease.

The influence of age

A small number of prospective studies explored the influence of age on the relationship between

Table 1. A meta-analysis of 34 studies: general characteristics and main results

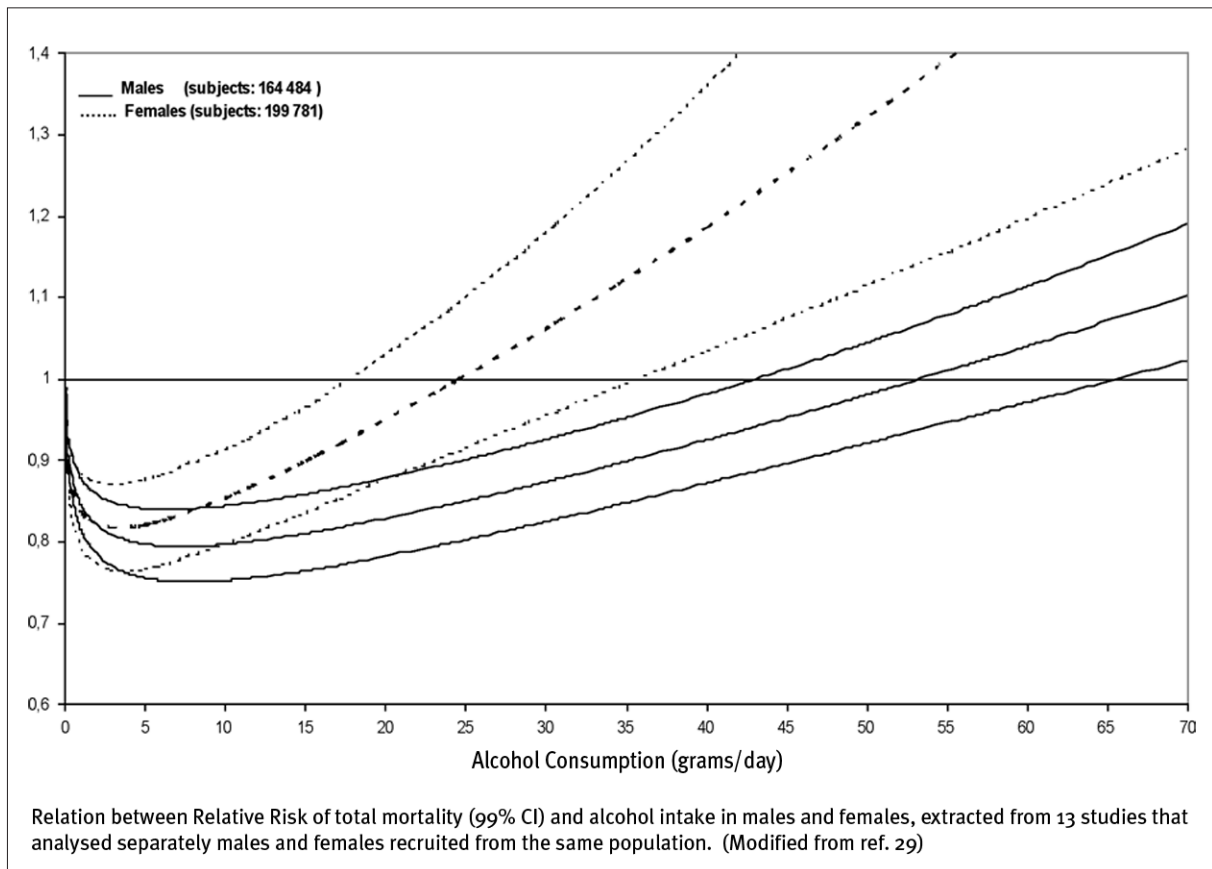
Subgroup	Number of subjects	Number of deaths	Maximum protection			Reversion Point*		P for difference
			%	99% CI	gr/day	gr/day		
All	1015835	94533	19	17-20 [†]	6	42	-	
Level of adjustment								
Not adjusted	107653	7592	36	21-40	10	68		
Adjusted (at least for age)	908182	86941	17	15-18	6	37	<0.0001 ^a	
Adjusted for social status too	414680	29560	18	15-21	9	46	<0.0001 ^b	
Adjusted for social status	126712	7916	18	12-24	6	30	0.0252 ^c	
Sex[†]								
Females	285490	13448	18	13-22	5	18		
Males	622692	73493	17	15-19	6	38		
Type of reference group[†]								
With small and/or former drinkers	247 194	23 937	23	20-26	8	52		
Without small and/or former drinkers	660 988	63 004	16	14-18	5	30	<0.0001	

*The reversion point is defined as the dose of alcohol at which the protection against total mortality is no longer statistically significant at 99% confidence level. [†]95% confidence interval. [†]In 29 adjusted studies.

^aP for the comparison: adjusted vs not adjusted; ^bP for the comparison: adjusted for social status vs adjusted except for social status; ^cP for the comparison: adjusted for social status and dietary factors vs adjusted for social status but not for dietary factors.

(Modified from ref. 29)

Figure 3.



alcohol consumption and mortality. While in a cohort of young men, [35] no J-shaped curve was able to describe the association between alcohol and mortality, the J-shaped was confirmed in elderly cohorts.

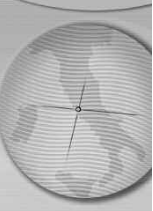
In a study performed by Goldberg *et al.* [36], relating to the effects of alcohol in middle-aged and elderly men, trends for a beneficial effect of very light drinking on total cardiovascular and cancer mortality were apparent in both groups, with the exception of deaths due to stroke in the elderly.

As causes of death have different incidences for different age categories (e.g., cardiovascular deaths in young cohorts are lower than in the elderly) the effect of alcohol on health and disease may differ in different life periods.

The effect of confounding

A recent comment in *The Lancet* [37] has made the provocative statement that any coronary protection from moderate alcohol drinking is very small and unlikely to outweigh the known harms, mainly because of uncontrolled confounding by associated lifestyle factors. Quoting data obtained in the USA, [38] Jackson *et al.* [37] argue that drinkers have many healthier characteristics than

non drinkers and thus have lower ischemic heart disease risk. While a similar observation was previously made in Denmark, it could not be confirmed in Italy, suggesting that association of moderate drinking with “protective” lifestyles does not necessarily occur in countries, where alcohol is a traditional beverage uniformly consumed across socio-economic status or education. [27,29,39] Moderate alcohol intake decreases the risk of cardiovascular disease, but the other side of the coin shows an increased risk of certain cancers, cirrhosis and death for accidents with increasing alcohol consumption. [33] Uncontrolled confounding, if present, could not substantially change the scenario; in our meta-analysis, [29] for example, 29 studies (908 182 subjects and 86 941 deaths) showed adjusted relative risks at least for age; among them, 15 were adjusted for social status too, and 6 for social status and dietary markers. Table 1 shows relative risks of total mortality for different levels of adjustment. P for difference was highly significant ($P < 0.0001$), showing that part of heterogeneity is attributable to adjustment. While the protection decreased in adjusted studies (the maximum protection fell from 36% to 17%, Table 1), it remained substantial and statistically significant.



Moreover, as the observed difference between the five not adjusted and the 29 adjusted studies could not be only due to the level of adjustment - these results coming from different studies - we compared adjusted or not unadjusted data from the same studies. Therefore, when adjusted and unadjusted data from the same studies were compared, the effect due to known confounders (age, smoking, social status, dietary factors) resulted in the reduction of the maximum protection from 19% to 16%; for analogy, even in the pessimistic hypothesis that residual confounding would have a similar strength as the known one in lowering the protection, one can assume that the "real" (maximum) protection against total mortality associated with low consumption of alcohol would be largely higher than 10%.

Although the protection of alcohol or wine decreases when data are adjusted, thus confirming the importance of confounding in assessing drinking effects, it would nevertheless remain in a range of undoubted public health value.

The influence of study design

A recent meta-analysis of 54 studies [40] on moderate alcohol and total mortality investigated the extent to which the inclusion of abstainers in control group affect the results. Most of the prospective studies - these Authors argue - included as abstainers people who had reduced or stopped drinking owing to ageing or illness. The analysis of the studies judged to be error-free did not show any significant cardiovascular and total mortality protection, suggesting that the cardiovascular protection by moderate alcohol consumption may have been unduly overestimated.

However, in our meta-analysis on alcohol dosing and total mortality, [29] we tested the same hypothesis by comparing studies that used as reference group the category of no alcohol intake and/or excluded former drinkers with studies which, in contrast, included in the reference group occasional or former drinkers or people reporting low alcohol intake: the protection was indeed lower in the first studies, but remained statistically significant (Table 1).

Alcohol consumption and stroke

The relationship between alcohol consumption and stroke risk is controversial. Epidemiological studies and meta-analysis report a dose-dependent protective effect of alcohol (described by the classic J-shaped curve) on the risk of ischemic stroke owing to the anti-thrombotic effect of

moderate alcohol consumption. [9] Otherwise, the same anti-thrombotic action may be associated with an increase in hemorrhagic stroke, although epidemiologic evidence is not clear. A meta-analysis of Corrao *et al.* [33] shows there was evidence of a not significant threshold beneficial effect against both ischemic and hemorrhagic stroke (53 and 28 g/day, respectively).

Reynolds *et al.* [9] affirms that heavy alcohol consumption increases the relative risk of stroke while light or moderate consumption may be protective against total and ischemic stroke.

Nonetheless, Mazzaglia *et al.* [41] conclude that there is insufficient evidence that high-to-moderate alcohol or wine intake have beneficial effects on stroke, and the risk of stroke in binge drinkers is reportedly higher than in regular drinkers.

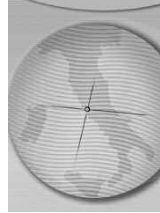
It is necessary to better investigate the effects of alcohol consumption on cerebrovascular disease. Prevention of the risk of stroke in heavy and irregular alcohol drinkers should be the first health step.

Alcohol consumption in the secondary prevention of cardiovascular disease

The beneficial effect of moderate alcohol consumption on cardiovascular risk was mainly studied in healthy cohorts. Few studies show controversial data on the impact of moderate alcohol consumption in patients with previous cardiovascular disease.

Mukamal *et al.* [5] studied the effect of prior alcohol consumption on long-term mortality among early survivors of acute myocardial infarction and concluded that a moderate alcohol consumption in the year prior to myocardial infarction was associated with reduced mortality during follow-up. Muntwyler *et al.* [42] observed that men with myocardial infarction who consumed small to moderate amounts of alcohol had a lower total mortality, and de Lorgeril *et al.* [43] confirmed that moderate alcohol consumption was associated with a significant reduction in the risk of cardiovascular complications. In contrast, a study of Shaper [44] *et al.* showed that regular light alcohol consumption (1-14 drinks *per week*) in men with established coronary heart disease was not associated with any significant benefit or deleterious effect for coronary or cardiovascular disease or all-cause mortality while higher levels of intake (> 3 drinks *per day*) were associated with increased mortality in men with previous myocardial infarction.

Further studies on secondary prevention of cardiovascular disease by moderate wine or alcohol intake are obviously needed.



Conclusion

In conclusion, a review of the most recent literature confirms that light-to-moderate alcohol consumption is protective for cardiovascular morbidity and total mortality, both in males and females. In contrast, both heavy and binge drinkers have higher vascular and mortality risks than regular and moderate drinkers.

The influence of the type of alcohol consumption on health outcomes has been examined under various conditions; however, whether wine possesses some additional beneficial properties in respect to other alcoholic beverages, although highly suggestive, still remains to be definitely established.

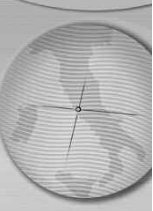
Some currently controversial questions such as possible differential protection by alcohol and wine of men and women, methodological limitations of observational study design or the role of uncontrolled confounding have been discussed on the basis of recent extensive meta-analyses. It is concluded that the dose-response relationship between alcohol intake and mortality, invariably described by J-shaped curves, can be reasonably attributed to a variable combination of both real beneficial (at lower doses) and harmful (at higher doses) effects of alcohol or wine consumption.

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