



VIEWPOINT

Moderate alcohol consumption and lower total mortality risk: Justified doubts or established facts?



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Abstract For almost a century, the scientific community is aware of the J-shaped curve between alcohol consumption and all-cause mortality. Moderate drinkers seem to live longer than both abstainers and heavy drinkers. These epidemiological observations regarding moderate alcohol consumption and beneficial health effects have been incessantly scrutinised for confounding and bias. This viewpoint discusses previous and recent criticisms regarding the J-shaped curve between alcohol consumption and total mortality risk. The controversies regarding the J-shaped curve between alcohol consumption and mortality are ongoing, as well as the debate among scientists in this area of research, resulting in conflicting messages in media and in different alcohol guidelines. Although it appears quite difficult to come up with a position statement only based on the currently available scientific data, it is imperative to fairly inform the public, without creating confusion and, worst case, disbelief in science.

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Almost a century ago, a population study based in Baltimore found that moderate alcohol drinkers live apparently longer than both abstainers and heavy drinkers [1]. Since then, numerous other studies have shown a J-shaped

relationship between alcohol consumption and all-cause mortality risk [2–4].

Overall, studies on alcohol consumption and mortality show that the lowest mortality risk occurs with consumption of around 10 g of alcohol per day, with about 15% lower risk as compared to abstainers (Fig. 1). Additionally, the usual pattern of alcohol drinking may also be important: the most favourable to health is to consume alcohol in moderation and regularly, possibly during meals, avoiding binge and heavy drinking [5,6]. The effect of drinking patterns was particularly evident in the recent Wood et al. paper [7], in which people reporting binge drinking or concentrating the weekly alcohol intake in two

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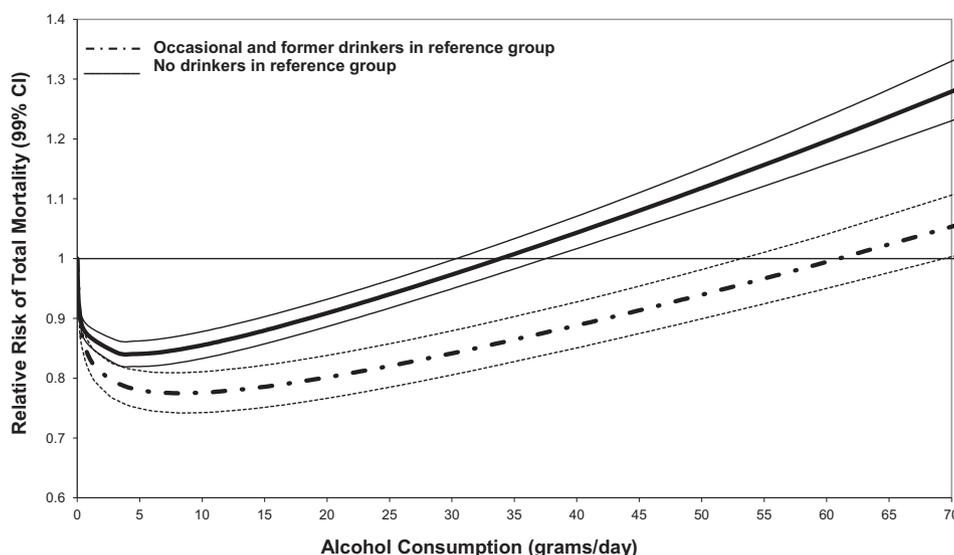


Figure 1 Relative risk of all-cause mortality and alcohol consumption. Reprinted with permission from Di Castelnuovo et al. [2].

or less drinking occasions, showed deleterious effects on all-cause mortality as compared with moderate and regular drinkers, even if the total alcohol intake in the week was similar.

However, people who do not drink alcoholic beverages should not be encouraged to start drinking (even in moderation) for health reasons only [2]. Alcohol consumption in some cases leads to excessive use and addiction, which are harmful to health. The excess mortality associated with heavy alcohol intake is multifactorial but includes increased risk of certain cancers, liver disease, and accidents [6].

According to some studies, moderate alcohol intake is one of the most relevant components of the Mediterranean diet explaining its favourable health effects [8–10].

These epidemiological observations regarding moderate alcohol consumption and beneficial health effects have been incessantly scrutinised for confounding and bias. This viewpoint discusses previous and recent criticisms regarding the J-shaped curve between alcohol consumption and all-cause mortality risk.

Is the association of alcohol in moderation with mortality invalidated by confounding factors or selection bias?

In 1988, the sick quitter theory was introduced, casting doubts on the existence of the J-shaped curve [11]. This theory postulated that abstainers include people who quit their alcohol consumption because of health problems, leading to poor health profile of abstainers. Scientists then began to collect more precise data on previous drinking to better control for drinking pattern (previous intake, regular versus binge drinking). In almost every well-conceived and controlled study, a J-shaped curve for mortality among moderate drinkers remained, even when ex-drinkers were not included in the referent group or after controlling for

former problem drinking (Fig. 1) [2,12–15]. Even in most recent studies, moderate drinkers had a lower mortality risk compared with life-long abstainers [16,17].

Another concern often raised is the possibility that moderate drinkers have lifestyle characteristics that could explain their longer survival over non-drinkers [18]. Most epidemiologic studies have adjusted for factors like smoking status, physical activity, body mass index, indicators of social status and so on. After these adjustments, however, there is still a lower risk of mortality [2,10,19,20].

Related to the discussion of lifestyle characteristics is the possibility that healthier, more resilient drinkers or less risky drinkers would tend to be over represented in study cohorts compared to the general population [21]. This might theoretically result in overestimation of the potential benefits of low-volume average consumption among study cohorts relative to what would be experienced among low-volume average consumption among drinkers in ‘real world’ scenarios. However, such a possibility has not been confirmed so far.

Concerns regarding modalities of alcohol consumption data acquisition have also been raised. Some scientists suggested that lifetime alcohol consumption should be the preferred measure of interest. The reason for this is that alcohol consumption may vary over time [22]. Therefore, the association between alcohol and mortality might be underestimated or overestimated when only baseline consumption is considered. However, studies that have estimated lifetime alcohol consumption also showed similar J-shaped relationships with all-cause mortality risk [23,24].

Large studies of alcohol consumption usually rely on self-reporting, which can lead to the possibility of misclassification of exposure. There is a large consensus that underreporting of alcohol consumption by heavier drinkers is frequent [25,26]. This would mean that including “real” heavier drinkers in “apparently” lower intake categories will falsely lower the threshold of

apparent harm, while the beneficial effect on mortality risk could not be limited to light drinkers. This problem was explored in a study of underreporting in the relationship between moderate drinking and hypertension [27]. Consumers of one to two drinks a day in that study included a disproportionate number of likely under-reporters, based on reported heavier alcohol intake at another time, high liver enzymes or having an alcohol-related diagnosis. Suspected under-reporters had a higher prevalence of hypertension compared to more reliable moderate drinkers. A similar finding has been observed in a study on moderate alcohol intake and cancer [28]. There was an elevated risk of any cancer in the likely under-reporters, whereas there was no apparent risk for the more likely “true” moderate drinkers.

On the basis of this observation, Klatsky et al. suggest that at present, a possible increased cancer risk at moderate intake should enter into individual estimation of the overall risk-benefit equation for alcohol drinking [29].

Current methodological criticisms

Despite the fact that especially more recent studies have been conducted taking into account the confounding factors and the selection biases discussed above, other studies concluded that low-volume alcohol consumption would not have any mortality benefit compared with lifetime abstinence or occasional drinking [7,30–33]. If so, the J-shaped curve would be based on misleading references resulting in outdated advice and wishful thinking [34]. However, these recent studies exhibit drawbacks and limitations that make their findings and conclusions rather weak.

The study by Knott et al., [30] which stratified individuals by age, sex, and alcohol intake into small groups, was grossly underpowered for that type of analysis [35] which makes it impossible to draw any firm conclusion. Nonetheless, the observed data were strikingly compatible with the 10–20% protection that has been previously suggested [36,37].

Goulden [31] failed to consider the effects of under-reporting of alcohol consumption when choosing the referent group. In addition, he over-corrected for confounding by adjusting for factors that have been shown to be in the causal path between alcohol and the risk of disease and mortality [37]. Interestingly, the exhibited trends are still consistent with the previously reported J-shaped relationship between light-to-moderate alcohol consumption and mortality [38].

Stockwell et al. [32] excluded many well-done studies in their meta-analysis, leading to a small number of studies from which conclusions could be based [39]. Their method of meta-analysis was however suggested to be invalid [40].

In the study, already mentioned, by Wood et al. [7] the non-drinkers were eliminated from the analysis with the obvious consequence of completely eliminating the left rising arm of the J-curve [41]. And finally, there are several caveats in the recently published global burden of diseases

by alcohol use [33]. Calculations are based on mainly ecological data and predominantly mathematical models. Combining of data from widely divergent Countries with marginal controlling for confounding, may conceal significant effects of social and cultural factors. A major caveat is that total mortality as an outcome measure is missing, which makes that the conclusion “no level of alcohol consumption improves health” cannot be firmly drawn [42]. It has however been recently noted that the risk relationship between alcohol consumption and disease occurrence may differ depending on whether the outcome used is mortality or morbidity: more studies using morbidity or cause specific disease outcomes as end-points would be required for a more comprehensive estimation of the total burden of alcohol related harm [43]. In our view, however, total mortality remains a most useful and easy to measure unbiased endpoint in alcohol and health issues [42].

The J-shaped relationship between alcohol consumption and all-cause mortality is the combined result from truly dozens of epidemiological studies. The challenge with these studies is that residual or unmeasured confounding and bias can never be completely excluded [2]. There is no doubt that confounding and bias in research are important issues, but they should be equally applied to all studies. Data on alcohol-related harms derive from the same studies as data on benefits, yet concerns about confounders and bias are rarely raised when harms are in question. Or according to Roerecke and Rehm: ‘We sense a desire by some in the field to apply tough standards on protective effects and more lenient standards on other effects’ [44].

Mendelian randomization

Recently several studies have been published using Mendelian randomization as new approach to investigate the association between alcohol consumption and health, specifically cardiovascular disease [45,46].

On the basis of a Mendelian randomization study (261,991 participants of European ancestry from 56 studies) Holmes et al. [45] concluded that loss-of-function mutations in gene for alcohol dehydrogenase (ADH1B-rs1229984), associated with reduction of alcohol consumption even for light to moderate drinkers, is beneficial for cardiovascular health. However, the genetic variant itself, and not the reduced alcohol intake, seems to protect against cardiovascular disease among abstainers, e.g. due to lower blood pressure and lower inflammation markers.

A recent study on 161,498 Chinese participants (of which 66,378 male), genotyped for two genetic variants common in east Asian populations (ADH1B-rs1229984 and ALDH2-rs671), concluded that genetic predisposition to consume alcohol increases the risk of stroke in men, reporting an increase of 38% for alcohol intake per 280 g alcohol per week [46]. The genetic epidemiological analyses identified no clear net association with acute myocardial infarction and total coronary heart disease. The external validity for this study is not satisfactory: the

results from a study population which preferred consuming liquors (the Chinese male participants reported to drink mainly strong (46.8%) and weak (22.8%) spirits) and without collecting information on drinking patterns (Chinese men are more habitual binge drinkers), cannot be extended to make predictions about populations with a regular and light to moderate consumption of beer and wine, preferably with meals.

Moreover, the studied polymorphisms are associated, in the different China regions considered, with extremely different absolute alcohol intakes. This suggests that the effect of the different social, environmental and lifestyle conditions of the various regions may overcome that attributable to the studied polymorphisms, greatly limiting the value of this Mendelian randomization study.

The Mendelian randomization approach applied to alcohol epidemiology is questionable for two main reasons. Indeed, when the genetic regulation of a phenotype is strong, stable over time and marginally influenced by non-genetic (environmental) factors, the Mendelian randomization approach is more appropriate. But in the case of alcohol, Mendelian randomization investigates the association between a “genetic predisposition” to consume alcohol (at any dose) and the outcome. The polymorphisms that “regulate” its consumption actually have limited impact on the phenotype, which is on the contrary largely influenced by environmental/cultural factors.

Second, the crucial issue is whether drinking in moderation, say a drink a day, is better for the health than not drinking at all. From a Mendelian randomization perspective, this would require a targeted genetic analysis comparing light-drinkers vs abstainers, which has not been carried out so far, to the best of our knowledge. If we compare (any daily dose) drinkers vs non-drinkers, it may well happen that identified-by-polymorphisms drinkers (without any reliable distinction on consumption levels) are at higher outcome risk in comparison with identified-by-polymorphisms non-drinkers [46].

Conclusions

It is, of course, imperative to train a continuous critical eye on scientific data and challenge them over and over again. After all, in observational studies, cause and effect are hard to establish— although some findings may be more reliable than others because they have plausible and relevant biological underpinnings. The lower mortality risk among moderate drinkers is thought to be mainly explained by its effects on several cardio-protective pathways. Numerous experimental studies have shown beneficial changes in high-density lipoprotein cholesterol, clotting factors, endothelial function, insulin sensitivity, and inflammation [47,48]. All these findings support biological plausibility of beneficial effects of moderate alcohol consumption as shown in observational studies. Nevertheless, as summarized here, the controversies regarding the J-shaped curve are ongoing.

In addition to what is discussed in this viewpoint, one should not forget that consumption of alcohol is a complex behaviour that has social, political, religious implications

and determinants. Thus, the final interpretation of the findings remains open to the perspective of the scientist who evaluates the evidence.

Finally, it is often suggested that the increasing involvement of industry in scientific research may affect the objectivity of independent scientists and the integrity of science [49,50]. Taken all together, this results in conflicting messages in media and also in differences in alcohol guidelines [51,52], creating confusion and, worst case, disbelief in science among the public at large.

New strategies/methodologies should be proposed to help further independent investigations of the complex relationship between alcohol in moderation, disease burden and mortality. Observational epidemiology has a lesser, but still important, place in the hierarchy of methods to establish causal relationships in medicine. However, more definitive and solid answers to the controversies around the health benefits of moderate alcohol consumption will be provided by large, controlled and long term intervention trials [53].

Author contributions

All authors equally contributed to the manuscript.

Conflicts of interest

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G.d.G. is a member of the International Scientific Forum on Alcohol Research, an independent organization of scientists that prepares critiques of emerging research reports on alcohol and health. The members of the Forum donate their time and effort in the review of papers and receive no financial support. The Forum itself receives no support from any organization or company in the alcoholic beverage industry. G.d.G. was also a consultant to the Web Newsletter of Assobirra, the Italian Association of the Beer and Malt Industries and is a corresponding member of the non-profit Accademia Italiana della Vite e del Vino.

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