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Alcohol Intake Revisited: Risks and Benefits

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Abstract The relationship between alcohol consumption and health outcomes has a long history and has generated much research. Heavy drinking is detrimental to health; however, there is considerable and convincing evidence from both short-term biochemical experimental studies and observational studies of a beneficial association with certain health outcomes related to atherosclerotic processes. This beneficial association is most important for an average alcohol intake of one to two drinks per day. Important factors in determining the magnitude or direction of effects have been identified. Most criticisms based on methodological issues have been dismissed in recent years from an epidemiological point of view. However, important questions remain about the circumstances of such a beneficial association. The net effect of alcohol consumption on health outcomes is detrimental overall, owing to the negative effect of cancers, infectious disease, gastrointestinal diseases, alcohol-use disorders and injuries.

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Introduction

Owing to the prevalent use of alcohol in many countries and its association with many diseases, the role of alcohol consumption has received much attention in the last three decades. The overall effect on health caused by alcohol consumption worldwide is clearly negative. Recent estimates put alcohol among the top contributors to the global burden of disease, with an estimated net effect of 3.8 % of all deaths and 4.6 % of all disability-adjusted life years being attributable to alcohol [1]. Although the effect of alcohol on most diseases, such as many cancers, liver cirrhosis, injuries and accidents, is detrimental, much interest among both scientists and the public has been generated by the findings of favourable effects on diseases in which atherosclerotic processes are the main mechanism of disease progression [2•]. Studies showing a potential beneficial effect from 'moderate' alcohol intake date back almost a century [3]. These effects, mainly on ischaemic heart disease, ischaemic stroke and diabetes, have been found in both short-term experiments and most epidemiological studies.

In this review we build on an earlier review in this journal [4] and focus mostly on recent advances in the understanding of the role of alcohol consumption derived from systematic investigations of the vast epidemiological literature. Although the negative influence of alcohol on short-term outcomes such as intentional and unintentional injuries has been indisputably demonstrated, data on the effects on chronic diseases developing over many years, in particular potential beneficial effects, are subject to criticism because of limitations of epidemiological investigations. In light of a lack of long-term trials,

however, much of the evidence comes from epidemiological studies examining the association of alcohol intake and most disease outcomes. However, the relationship between alcohol intake and favourable disease outcomes is complex and cannot be accurately described in terms of drinking versus non-drinking. The large number of systematic investigations in this vast epidemiological literature in the last 5–10 years gives us the opportunity to summarize current knowledge of the risks and benefits associated with alcohol consumption, highlighting the complexity of the overall association of alcohol and health outcomes. We will pay special attention to potential benefits of alcohol consumption derived from epidemiological evidence.

Alcohol and Cardiovascular Diseases

Support for a causal beneficial association of low-level alcohol intake with ischaemic disease outcomes comes from short-term experimental studies. The meta-analysis by Rimm et al. [5] was recently updated by Brien et al. [6•]. Both analyses showed significant and substantial increases in the levels of biomarkers, supporting a beneficial association of alcohol consumption with atherosclerotic risk factors (for a detailed review of the underlying processes, see [4, 7]). Most importantly, a favourable effect on high-density lipoprotein, apolipoprotein A1, adiponectin and fibrinogen levels was found in the most recent meta-analysis [6•]. Before we analyse the epidemiological evidence in detail, several dimensions of alcohol intake need to be distinguished to understand the benefit–risk relationship. Several factors influencing the association of alcohol consumption with cardiovascular diseases have been consistently identified in meta-analyses. Among them are sex, drinking pattern (irregular heavy drinking as compared with steady non-heavy drinking) and disease end point (mortality versus morbidity). In this review we define low average alcohol intake as a maximum of two drinks per day for men and a maximum of one drink per day for women (one drink is equivalent to about 12 g of pure alcohol), consistent with low-risk drinking guidelines [8, 9]. For cardiovascular diseases, heart disease, ischaemic stroke and, to a lesser degree, diabetes are the main health outcomes that have been shown to have a beneficial association with low alcohol intake in epidemiological studies.

Because average alcohol consumption has been the focus of research to date, we will summarize the evidence using this conceptualization of exposure first. Every meta-analysis, starting with the work of English et al. [10], has found a beneficial association, at least for low levels of average alcohol intake [11–13, 14•], commonly described as a J-curve. The two most recent meta-analyses both confirmed findings of a beneficial effect on heart disease. Ronksley et al. [11] showed that drinking versus non-drinking was beneficial for heart disease, with relative risks (RRs) for heart disease mortality between 0.70 and 0.80 depending on the average drinking level and adjustment used. Roerecke and Rehm [14•] in their meta-analysis of 44 epidemiological studies showed that the J-curve was confirmed when high-quality epidemiological studies with detailed exposure measurement were stratified by sex and heart disease end point while separating former drinkers and occasional drinkers (maximum of one drink per week). The beneficial association for an average intake of one drink per day was stronger in women, but the upturn of the curve into a detrimental association was at substantially lower levels of average intake than for men. The effect of average alcohol consumption (maximum of two drinks per day for men and maximum of one drink per day for women) on morbidity compared with mortality seemed to be stronger in both sexes: RRs (all compared with life-long abstainers) for mortality were between 0.86 and 0.89 in men and 0.84 and 1.03 in women; RRs for morbidity were between 0.75 and 0.77 in men and 0.54 and 0.61 in women. In men no detrimental effect was estimated up to 72 g of pure alcohol average consumption per day (about six drinks with 12 g of pure alcohol per drink), at which level of intake the analysis ended [14•]. Higher intake is scarce in typical cohort studies [15]. In each stratum, there was little if any additional benefit of an average intake higher than two drinks per day for men and one drink per day for women [14•]. The stronger beneficial association for morbidity outcomes has been shown in prior epidemiological studies. A former-drinker effect (sick-quitter) is a long-standing criticism of earlier individual studies and meta-analyses. Although the effect is significant and substantial depending on the drinking culture across countries, it is not strong enough to explain the beneficial association [11, 14•].

It has been suggested that components in wine other than ethanol are responsible for the beneficial association. A recent meta-analysis does not support this hypothesis. Costanzo et al. [16] pooled observational studies separately for wine, beer and spirits. When fatal and non-fatal cardiovascular events (including stroke) were combined, the risk curves were practically identical for wine and beer. The curves were L-shaped for fatal and non-fatal events combined; when only fatal events were considered, the curves were J-shaped. Although spirits did not show statistically significant associations, an inverse relationship emerged. However, pure spirit intake is relatively rare, and the pattern of consumption (which is mostly via heavy drinking occasions) might play a role.

Costanzo et al. [17] reported results from a meta-analysis of alcohol consumption and mortality in patients with cardiovascular diseases. Maximum beneficial associations with cardiovascular disease mortality as the outcome were between 5 and 13 g of pure alcohol per day on average (maximum of one drink) depending on the sex, the type of the cardiovascular event and the reference group. For all-cause mortality the maximum beneficial association was estimated to occur between 2.5 and 12 g of pure alcohol per day (maximum of one drink). All curves were J-shaped [17].

Important points to consider when looking at the epidemiological evidence are the inclusion of former drinkers in the reference group and the effect of age. Typically, former drinkers are not included in an analysis of current drinking in current epidemiological practice (if such information is available). The association of former drinkers (without taking into account former drinking behaviour) and heart disease is detrimental, with no evidence for a beneficial association. For ischaemic heart disease mortality, a 54 % increased risk compared with life-long abstainers in men and a 25 % increased risk compared with life-long abstainers in women were reported in a recent meta-analysis including 38 epidemiological studies [18]. Ischaemic heart disease morbidity in former drinkers was not statistically significantly associated with an increase in risk in either sex. It is evident from the epidemiological literature on alcohol consumption that people in all drinking groups (including abstainers) can change their consumption considerably over their lifetime [19–21]. Thus, former and current drinking behaviour (both in frequency and in volume) in all participants in cohort studies should be assessed and analysed. It is currently unclear what, if any, influence alcohol consumption over the lifetime (other than crude assessment of former drinking status) has on heart disease risk.

Most epidemiological studies have conceptualized alcohol intake as average daily alcohol consumption; however, this may or may not reflect actual drinking behaviour because both weekend heavy drinking and steadily drinking small amounts daily can result in the same average daily consumption. There is accumulating evidence that the pattern of consumption has a substantial influence on the risk–benefit relationship for heart disease. A recent meta-analysis found an increased risk for drinkers with heavy episodic drinking (HED; five drinks or more per episode) compared with drinkers without HED [18]. The risk was increased by 45 % [95 % confidence interval (CI), 27-72 %]; former drinkers and abstainers were excluded from this analysis, and many primary studies included in the meta-analysis were adjusted for either education or social class, and smoking status [18]. Another meta-analysis found that there was no increased or decreased risk for drinkers with HED compared with abstainers [22]. Two recent individual studies have shown a twofold risk increase for HED compared with no HED [23, 24]. There are plausible biochemical mechanisms supporting no beneficial association with heavy drinking episodes [25, 26], but the evidence base is not as plentiful as it is for non-heavy-drinking episodes. Evidence for an influence of the drinking pattern is particularly important for average alcohol intake of one to two drinks per day. However, it is difficult to distinguish the number of heavy drinking episodes from the number of drinking days in this range of average alcohol consumption. Heavy drinking episodes may substantially increase the risk of cardiovascular disease mortality in people with hypertension [27]. Therefore, there is considerable and consistent evidence for a beneficial association of low levels of average alcohol intake (one to two drinks on average) with heart health, and no evidence for a beneficial association of HED with heart health.

Alcohol and Cerebrovascular Diseases

The two main types of stroke, ischaemic and haemorrhagic, have different underlying mechanisms and consequently different relationships with alcohol consumption. Ischaemic stroke and ischaemic heart disease have similar causes, with blockage of arteries in the brain being the main cause. Similarly, the drinking pattern should have the same impact on ischaemic stroke as it has on ischaemic heart disease, but epidemiological evidence is scarce [28]. For ischaemic stroke, the most recent meta-analysis, using data from 26 studies, reported pooled risks separated by sex and end point [29]. For a maximum alcohol consumption of one drink on average per day, similar risks for morbidity and mortality were found in men (mortality RR 0.86, morbidity RR 0.87) and women (mortality RR 0.66, morbidity RR 0.82). No beneficial associations or mostly detrimental associations were found for three or more drinks on average per day. A Finnish study reported a risk of ischaemic stroke of 1.56 (95 % CI, 1.06-2.31) for drinkers whose pattern included heavy drinking episodes compared with those whose pattern did not [30]. No beneficial association with total stroke was found in a Korean study examining binge drinking and cardiovascular diseases [27]. Thus, there is considerable and consistent evidence for a beneficial association of a low level of average alcohol intake with ischaemic stroke. Even though there is a lack of evidence, as this relationship has not been tested, we believe that there is no beneficial association of heavy drinking episodes with ischaemic stroke for the same reasons as mentioned for ischaemic heart disease.

For haemorrhagic stroke, alcohol consumption has not been found to have any beneficial effects on either subtype of haemorrhagic stroke, intracerebral and subarachnoid haemorrhage, both caused by ruptures of blood vessels in the brain. To the contrary, the risk is elevated for all consumption levels. On the basis of the most recent meta-analysis, the risk increases rapidly with increasing average alcohol consumption in women (in particular for haemorrhagic stroke mortality), in whom a twofold risk of haemorrhagic stroke is observed for an average intake of 48 g of pure alcohol (about four drinks) per day. In men, a twofold risk was estimated for an average intake of about 90 g of pure alcohol (about seven drinks) per day [29]. Thus, there is considerable and consistent evidence for a detrimental association of any alcohol consumption and haemorrhagic stroke, and no evidence for a beneficial association.

Alcohol and Diabetes

Both observational studies [31, 32] and randomized trials [33, 34] support a beneficial association of low levels of alcohol intake with type 2 diabetes through an increase in insulin sensitivity. Other plausible mechanisms include anti-inflammatory effects of alcohol consumption [35, 36], and a decrease in triglyceride concentrations [33]. For a more detailed review, see [37]. As with ischaemic heart disease, most epidemiological studies found a J-shaped curve for type 2 diabetes [38]. Maximum benefit was estimated to occur for about two drinks per day (22 g/day for men and 25 g/day for women). Risk reduction at those drinking levels was about 40 % (95 % CI, 31-48 %) in women and 13 % (95 % CI, 0-24 %) in men. Consumption of four or more drinks per day on average showed about the same risk as for life-long abstainers [38]. Therefore, both experimental and epidemiological evidence for a beneficial association is accumulating, although the evidence base is not as large as it is for cardiovascular diseases. A potential confounding effect with body mass index should be pointed out; a large population-based study in the USA found that moderate drinkers were more likely to have a lower body mass index than non-drinkers [39].

Alcohol and Cancer

In the early twentieth century, Lamy [40] observed that patients with cancer mainly of the oesophagus were more likely to be alcoholics. The accumulation of research on the relationship between ethanol and cancers led the International Agency for Research on Cancer in the 1980s to conclude that there is sufficient evidence to indicate that consumption of alcoholic beverages is carcinogenic to humans [41]. More recently, the group of cancers which is seen as causally impacted by alcohol consumption was revised and enlarged to include oral cavity, pharyngeal, laryngeal, oesophageal, liver, colorectal and female breast cancers [42••]. A 2010 International Agency for Research on Cancer monograph [42••] gives a good overview of the underlying literature, with more up-to-date systematic reviews and meta-analyses on alcohol consumption in the following contributions: [43] for colorectal cancer, [44] for oesophageal squamous cell carcinoma, [45] for laryngeal cancer and [46, 47] for oral and pharyngeal cancers.

In general, the relationships between the level of alcohol consumption and risk of the above-specified cancers is continuous and almost linear [2•, 48], i.e. the more alcohol is consumed, the higher the risk of cancer incidence and mortality. There is no apparent threshold, and pooled analyses of studies have shown that even one drink of alcohol per day on average can significantly increase the risk of cancer [49].

Ethanol clearly is the most problematic causal ingredient in alcoholic beverages causing cancer [50]. One of the major mechanisms for its impact is via acetaldehyde, which is part of the alcohol metabolism in the human body [42••]. Acetaldehyde may also be part of alcoholic beverages, increasing the risk of cancer [51].

The development of cancer takes time, and thus reduction or cessation of drinking reduces the risk of cancer only after years, and it may take almost two decades after cessation before the risk is back to the level of that of life-long abstainers [52, 53].

Overall, the impact of alcohol on the risk of cancer is a considerable public health threat [1]. For instance, in Europe, a recent cohort study with more than 300,000 participants found that among men and women, 10 % (95 % CI, 7-13 %) and 3 % (95 % CI, 1-5 %) of the incidence of total cancer was attributable to former and current alcohol consumption [54•]. Of course, the attributable fractions are larger for alcohol-attributable cancers. We conclude that there is clear and substantial evidence for a detrimental association of any alcohol consumption and several cancer sites.

Alcohol and Infectious Diseases

Even though heavy consumption of spirits has been identified as a main cause of tuberculosis in the eighteenth century [55], the causality of the relationship between alcohol and infectious diseases has long been disputed. Newer research into the effects of alcohol on the immune system [56–58], as well as epidemiological work controlling the effects of potential confounders, especially tobacco smoking, have established alcohol as a causal factor for tuberculosis [59, 60], HIV/AIDS [61, 62] and other sexually transmitted diseases and pneumonia [63]. The most debated of these relationships was between alcohol consumption and sexually transmitted diseases, especially HIV/AIDS, as it was hard to exclude the impact of third variables such as risk seeking which could impact on both risky drinking and risky sexual behaviour [61]. However, a recent meta-analysis was done on experimental control of alcohol and intention to engage in risky sexual behaviour [62], which can be taken as a valid proxy variable for actual behaviour [64–66]. The results clearly show that an increased level of alcohol intake led to diminished control and greater likelihood to engage in unprotected sex.

The relationship between alcohol consumption and infections is clearly more pronounced at higher levels of consumption, and a minimal threshold of consumption cannot be excluded (for risk curves and further argumentation, see [63, 67, 68]). Such a threshold would also be in line with the research on the impact of alcohol consumption on the immune system (see above and [69]).

Alcohol and Other Health Outcomes

The relationship between alcohol and various gastrointestinal disease categories is so strong that the International Classification of Diseases [70] has established several disease categories which include "alcohol" or "alcoholic" in their name:

- K29.2: alcoholic gastritis
- K70: alcoholic liver disease
- K85.2: alcohol-induced acute pancreatitis
- K86.0: alcohol-induced chronic pancreatitis

The relationship between consumption and these gastrointestinal disease categories is exponential, i.e. there is relatively small risk at moderate levels of drinking, with a accelerating pattern of increase of risk with increasing levels of overall consumption [71, 72].

Obviously, alcohol-use disorders are wholly attributable to alcohol consumption, and the risk relationship is increases exponentially [73, 74]. It should also be noted that injuries make up a large fraction of the detrimental effects of alcohol consumption on health [1].

Conclusions

Overall, even though alcohol has many more detrimental effects on health than benefits, the beneficial effects have been in the focus of the media in many high-income countries. These beneficial effects, mainly comprising the protective effect of light to moderate drinking on ischaemic heart disease, have been corroborated in many studies, and many different explanations and critical points based on methodological problems in epidemiology have been investigated [11, 14•, 17, 18]; for a review of other issues, see [75]. The overall conclusion of these analyses was that a beneficial association exists, and evidence against a beneficial association has to be regarded as weak. A beneficial association is also supported by a vast amount of epidemiological evidence which rivals the amount of evidence for any other risk factor for heart disease. Biologically plausible mechanisms have been confirmed in systematic investigations of short-term experimental studies. However, there are still important research questions to be answered, such as the effect of alcohol consumption over the lifetime and potential interaction with other risk factors for heart disease.

In terms of a summary indicator of risks and benefits, often all-cause mortality is used. The most recent meta-analysis of epidemiological studies supports a beneficial association of low to moderate alcohol consumption with all-cause mortality [76]. Pooled results showed a J-curve with maximum benefit for less than one drink per day on average, mainly reflecting the effect of alcohol consumption on ischaemic disease. Neither adjustment for social status nor adjustment for dietary factors changed the curve in a substantial way. All adjusted curves showed an RR between 0.80 and 0.90 compared with abstainers [76].

However, these numbers are misleading. They are based on cohort studies mainly selected for their ease of follow-up and with people with lifestyles and causes of death different from those of the general population. Alcohol-attributable causes of death specifically related to low socioeconomic status such as injury, liver cirrhosis and infectious diseases are underrepresented in such cohorts; they are even underrepresented in so-called representative general population cohorts, as these do not include many vulnerable populations such as the homeless and those in institutions [77]. To obtain a summary of the effect of alcohol in any given region or country, it is thus necessary to disaggregate the effects and apply them to the real pattern of mortality in each region or country [78, 79]. On the basis of such considerations, at most one drink per day for women and two drinks per day for men seem to result in a low risk level in most countries.

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- •• Of outstanding importance

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