EVIDENCE ABOUT HEALTH EFFECTS OF "MODERATE" ALCOHOL CONSUMPTION:

REASONS FOR SCEPTICISM AND PUBLIC HEALTH IMPLICATIONS

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EXECUTIVE SUMMARY

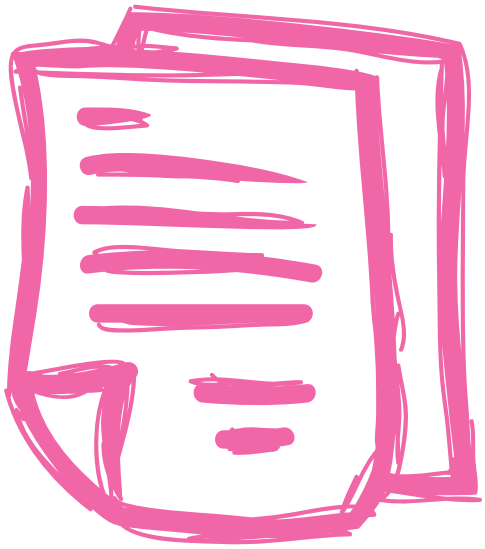
This report summarizes and examines the scientific evidence regarding the health effects of "moderate" (i.e., low-dose) alcohol consumption, and discusses the implications of this research for clinical practice, low-risk drinking guidelines, and alcohol policy development.

The existing evidence finding cardiovascular benefits from low-dose alcohol consumption is weak, and emerging evidence suggests that these protective effects are spurious (i.e., do not exist, or are harmful). The view that alcohol confers health benefits is therefore even less of a valid counter-argument against the adoption of effective alcohol control policies (e.g., those which reduce alcohol's availability and affordability).

- Although alcohol consumption is a leading cause of preventable death and social problems worldwide, previous studies often find an association between low-dose consumption and a reduced risk of cardiovascular (CVD) disease. Despite shortcomings in the science, this information has been promoted extensively, used to argue against the adoption of policies to reduce excessive drinking and led some doctors to advise patients to drink for better health.
- However, there have been no "randomised" studies of low-dose alcohol consumption and any disease or death outcomes to confirm findings from non-randomised studies. Randomised studies are the gold standard used to determine the safety and effectiveness of medical drugs. There are more than 10 recent examples in which conclusions from observational studies were contradicted later by randomised studies (e.g. hormone replacement therapy for the reduction of heart disease in women).
- Laboratory studies have indicated that low-dose alcohol consumption reduces some biological markers of heart disease. However, more recent and sophisticated studies have refuted some markers as causal factors of CVD mortality (e.g., HDL cholesterol). Further, low-dose alcohol consumption is associated with physiological effects that should increase CVD mortality, such as increased blood pressure.
- There are many methodological problems with non-randomised (i.e., observational) studies. Most important among these are confounding and misclassification. Non-drinkers and moderate drinkers differ in many ways besides alcohol consumption. The majority of observational studies classify people as abstainers who have cut down or quit drinking, many of whom have health problems. This makes moderate drinkers appear to be healthier than they really are.
- The observation of apparent health benefits from moderate drinking has also been made for a number of health conditions for which there is no plausible physiological basis (e.g., liver cirrhosis, improved childhood development, cancers, hip fractures, deafness and the common cold), suggesting that protective associations with other conditions may not exist.
- A large international genetic (Mendelian) randomisation study found that having a genetic disposition that causes less drinking is associated with a significantly reduced risk of coronary disease, even among those who consume modest amounts of alcohol.
- Studies of populations that have experienced reductions in total alcohol consumption do not find any evidence of increased rates of cardiovascular disease.
- Even assuming cardiovascular benefits from moderate drinking are real, the WHO estimates are that alcohol causes far more death and disability than it prevents. Further, if real, the optimal mortality benefits apply at very low levels (maximally half a drink per day for women, and less than one drink per day for men) and increase thereafter.
- Physician advice to patients and low-risk drinking guidelines should focus on reducing consumption to safer levels among current drinkers, and should discourage drinking initiation or increased consumption on the basis of health-related considerations
- From the public health perspective, governments should adopt and strengthen effective alcohol control policies to reduce alcohol-related deaths, social problems and economic costs. The growing scientific scepticism regarding evidence about the health effects of low-dose alcohol consumption should further enhance their rationale for doing so.

SECTION 1. INTRODUCTION: "MODERATE" (LOW-DOSE) ALCOHOL CONSUMPTION

Is alcohol good for health? Over the past 40 years a growing list of epidemiological studies suggest that when drunk in "moderation" alcohol is associated with a reduced risk of death from all causes and, in particular, a significantly reduced risk of cardiovascular disease (CVD) [1] and diabetes.[2] On the other hand, a longstanding and much larger literature has made it clear that heavy drinking causes a multitude of medical harms.[3, 4] The list of alcohol related medical conditions has grown over the years and now includes more than 60 major types of health condition, reflecting that the toxicity of alcohol affects all tissues and organs of the human body. Globally, about 3.3 million deaths or 5.9% of all deaths were estimated to be caused by alcohol in 2012. This figure is a net figure estimated after the assumed beneficial effects of low-dose alcohol consumption have been taken into account.



Although alcohol has toxic and carcinogenic properties, this does not necessarily preclude the possibility of health benefits in low doses, as is the case with a large number of pharmaceuticals. A number of mechanisms whereby alcohol could exert a beneficial effect have been proposed, including its effect on blood lipids and blood clotting. An important observation, however, is that the literature on beneficial effects primarily addresses chronic disease while the literature on alcohol's detrimental effects to a large extent involve acute effects such as accidents and violence. Even low doses of alcohol consumption increases the risk for acute harm, e.g. from traffic injuries. Of the traffic deaths in Sweden, 21% are caused by drivers under the influence of alcohol.[5] Low-dose alcohol also increases the risk for several chronic conditions like cancer and hypertension.

Nevertheless, the notion of beneficial effects from low-dose or "moderate" drinking has had a huge impact in the alcohol field, with implications for medical practitioners as well as for policy makers. Almost every time a new study suggesting health benefits has been published, these results have been given good coverage in the media and this appears to have shaped attitudes in the general population regarding the potential risks versus benefits from drinking alcohol. For many practitioners, the message from researchers about positive health effects has caused uncertainty about what advice is appropriate to provide to patients. Even if most practitioners recognize the hazards related to alcohol, they may be hesitant to convey a message that is too restrictive as this might deny their patients a positive health effect. In some cases moderate drinking may be recommended by physicians, even for abstainers.

For policy makers, the question arises as to how to regulate a dangerous commodity where research also suggests positive health effects when this commodity is used in moderation. The message from the alcohol industry is clear: alcohol policies should focus on the minority in the population with problem drinking, offering these individuals treatment, and leave the rest, the majority who are moderate drinkers, alone. This conflicts with the conclusions from alcohol policy research, where policies that reduce total consumption through restrictions on the economic and physical availability have been shown to be more effective in reducing alcohol problems. A challenge to researchers and policy makers alike is the fact that in reality low-dose alcohol consumption does not exist in isolation. There is a strong link between the prevalence of moderate drinking and excessive drinking, where an increase in the former is followed by the latter. Low-dose consumption is not something that we can "choose" as a preferred drinking option for populations, and among developed countries a substantial fraction of drinkers consume alcohol in ways that clearly increase the risk of health and social consequences for themselves and others.

The notion of beneficial effects on CVD mortality from moderate drinking therefore is crucial. One important question is whether the conclusions about these effects from the published literature are in fact correct. Over the past decade a number of doubts have been raised regarding the methodology underlying the studies informing this evidence base, which is comprised entirely of non-randomised studies. It is increasingly being understood that a large part of the beneficial effect of alcohol found in many studies is likely due to a number of methodological limitations, which are discussed below. It is also likely that moderate alcohol use is an indicator of positive health and social well-being. The studies that find beneficial effects all involve asking people questions about their drinking patterns which are then matched with their personal health outcomes. Even if large in number, such studies (often called observational studies) all share the methodological weaknesses that are inherent in this type of research, chief among these is a lack of randomisation of exposure. Critically, there are no experimental studies in which participants are randomly assigned to groups where alcohol is consumed or not consumed

(the control group). Such experimental studies, i.e., randomised controlled studies, are normally required in medicine as a basis for testing an intervention such as a pharmaceutical drug.

SECTION 2. HARMS FROM ALCOHOL CONSUMPTION

Alcohol is a toxic substance with psychoactive properties and the capability to cause dependence among users along with a variety of other health conditions. As a result, globally, about 3.3 million net deaths were estimated to be caused by alcohol in 2012 (this estimate took into account the assumed beneficial effect of low-dose alcohol consumption).[6] The estimated burden of alcohol-related death, disease and disability has increased in the last decades in WHO sponsored international studies. In 2010, out of more than 60 risk factors, alcohol was ranked as the fifth leading cause of death and disability globally, up from eighth place in 1990.[7]

For people aged 15–49 years, alcohol is the leading health-related risk factor worldwide, followed by tobacco smoking, high blood pressure and high body-mass index.[8] This is greater than, for example, the proportion of deaths from HIV/AIDS (2.8%), violence (0.9%) or tuberculosis (1.7%). Not all of the conditions linked to alcohol are included in these estimates.[9] The estimated negative effect on the global burden of disease from alcohol is more than 30 times as large as the beneficial effect.[10]

The proportion of alcohol-attributable burden of disease is highest in the WHO European Region (12.8 %). In high-income countries within Europe, such as Sweden, there is a much higher alcohol-attributable disease burden compared to alcohol-attributable deaths because of the disabling impact of alcohol use disorders.[11]

2.1. Harms from Chronic Health Conditions

Alcohol produces a large chronic disease burden as a necessary cause of a large number of specific conditions such as alcoholic liver cirrhosis and fetal alcohol syndrome. In addition it is a contributing causal factor in a large number of other disease conditions, such as cancers, cardiovascular disease, and infectious disease.[12]

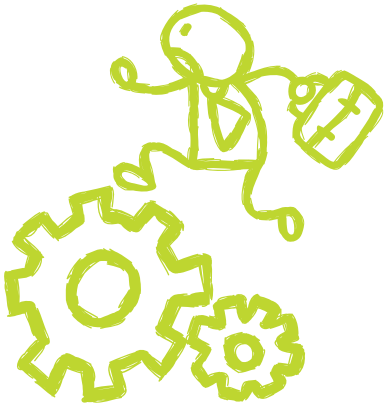
Alcohol has been classified as carcinogenic to humans since 1988 by the WHO International Agency for Research on Cancer, IARC.[13] In 2007 two new reviews on alcohol and cancer were published, one by IARC and one by the World Cancer Research Fund / American Institute for Cancer Research. Both reviews concluded that alcohol not only caused malignant tumours of the oral cavity, pharynx, larynx, oesophagus and liver, conditions that were linked to alcohol already in the 1988 report, but that alcohol also was a cause for colorectal and female breast cancer.[14, 15] As breast cancer and colorectal cancer are two of the most common cancers worldwide, the proportion of cancers attributable to alcohol consumption became higher than previously estimated.

The cancer risk from alcohol increases with the amount of ethanol drunk, in the absence of any threshold below which no effect is evident.[16, 17] For example, the relative risk of breast cancer is estimated to increase with increasing alcohol intake by about 10% per 10 g per day.[18] Among other disease categories, alcohol is directly responsible for between 4% and 25% of the disease burden related to specific cancers worldwide. Alcohol consumption also contributes to about 10% of the disease burden due to tuberculosis, epilepsy, haemorrhagic stroke and hypertensive heart disease in the world.

For the majority of diseases linked to alcohol the risk increases with increasing consumption without a threshold under which there is no increased risk.[19] A meta-analysis from 2004 [20] concluded e.g. that the risk of hypertension increased by 43 per cent for a consumption of two standard drinks per day. For the same level of consumption the risk for haemorrhagic stroke increased 19 per cent, and the risk for liver cirrhosis was almost three times greater, compared to non-drinkers.

2.2 Harms from Acute Health Conditions

The effects of alcohol consumption are not only confined to chronic diseases arising from long-term exposure but also increase the risk for acute conditions which typically occur from acute intoxication with alcohol. Alcohol is a psychoactive substance which produces specific in-the-moment impairment for hand-eye coordination, depth perception, general judgment, and reflex response. As a result, alcohol is involved in a number of acute harms even at low dosage which require specific skills and responses including operating automobiles, boats, machinery, and other complex tasks. A recent German experiment found that low-dose alcohol had a greater impairment on attention performance for adolescents compared to adults on the same test.[21] These results suggest that low-dose drinking by youth can result in more impairment in complex tasks like driving or operating machinery than for adults. A significant number of personal injuries and violent events are associated with

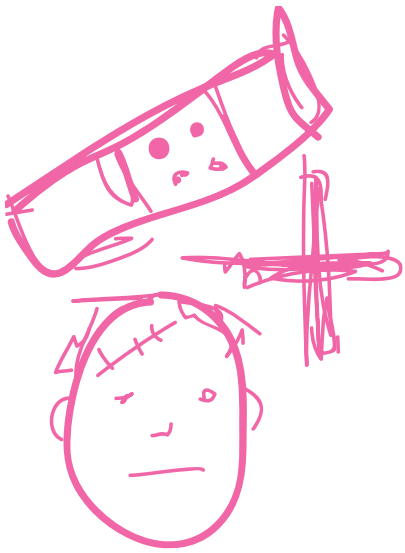


alcohol impairment. The impairment of the drinker also has serious social and economic consequences for individuals other than the drinker, e.g. assaults, traffic crashes, property damage, domestic violence, and child neglect or abuse.

That drinking to intoxication increases risks for injuries is well-known, however, low-dose consumption also increases the risk for several types of injuries. In Sweden, like most developed countries in which driving is a major mode of travel, alcohol-impaired drivers cause a substantial number of traffic deaths.[22] Experiments with alcohol consumption in connection with driving have shown that a BAC of 0.03% significantly increases stop distance and the ability to avoid obstacles.[23] A review in 2004 of studies from the past fifty years came to the conclusion that there is no evidence of a threshold below which impairment do not occur and that significant impairment occurs at very low BAC, below 0.02 %.[24]

Low-dose alcohol consumption also increases the risk for injuries other than those that are traffic-related. A study from a Swiss hospital emergency department of all types of injuries found that of alcohol related injuries, acute low-dose consumption (one unit or fewer of alcohol for women and two units or fewer for men) was related to 50 per cent of transport injuries, 44 per cent of falls, 50 per cent of exposure to forces and other events and 24 per cent of injuries from interpersonal violence. As percentage of all injuries, low-dose alcohol consumption was related to 21.5 per cent of transport injuries, 22 per cent of falls, 21 per cent of exposure to forces and other events and 16 per cent of injuries from interpersonal violence.[25] A recent Norwegian study, found that, the risk of an alcohol-related injury increases linearly with frequency of binge drinking.[26]

While alcohol has been often linked to interpersonal violence in naturalistic observational studies, there are recent laboratory experiments which suggest a linear dose-response relationship up to a high dose of 1.0g/kg relationship between alcohol and aggression.[27]



SECTION 3. REASONS FOR SCEPTICISM ABOUT THE EFFECTS OF LOW-DOSE ALCOHOL

3.1. Limitations of existing observational studies, lack of randomised trials

Most of the studies that provide evidence for health benefits associated with moderate drinking involve the observation of a group of individuals followed up over a number of years. There are no control groups as in an experimental study rather, people are compared according to various behaviours such as their diet, substance use and exercise habits and/or on the basis of characteristics such as gender, socio-economic status and ethnicity. Such "observational studies" on their own can identify associations between potential risk factors and disease outcomes over time but are not generally sufficient to prove causation. Thus, in studies of alcohol consumption and disease, observed associations can be caused by a variety of other lifestyle, psychosocial, genetic and physiological factors each of which may be independently associated with alcohol consumption in the population being studied. The strongest scientific evidence for causal relationships is generally accepted to be from randomised controlled trials (RCT), where potential confounding factors can be reduced by randomising participant exposure to a potential factor like drinking alcohol at a particular level and then comparing them to a control group who are not exposed to that factor.

In alcohol research, however, there has not been any RCT involving alcohol that assesses a morbidity or mortality outcome/endpoint. One reason for this lack of RCTs is that there are substantial practical and possibly even ethical problems with randomising individuals to drink or not drink over a period of many years. Regardless, this represents a major limitation in the evidence base about the effects of low-dose alcohol consumption. Other sources of evidence for the existence of causal relationships will be discussed here including: (i) the use of laboratory experiments to identify the impacts of low-doses of alcohol on biological markers known to be risk factors for disease; (ii) the study of the impact of random genetic variations in the population; and, (iii) the impact on disease outcomes of population level changes in exposure to alcohol consumption.

Although many observational studies have found a J-shaped curve in which people with low average alcohol consumption have lower mortality from all causes than people who do not drink at all, it is important to remember that even a large number of consis-

tent observational studies showing similar outcomes can be consistently wrong. Indeed, findings from even well done observational studies with plausible biologic hypotheses may differ from those of randomised controlled trials, and these differences are believed to be partly due to residual or unmeasured confounding.[28]

OBSERVED HEALTH BENEFITS CONTRADICTED BY CONTROLLED STUDIES

Hypothesis	Observational	Randomised controlled trials
Beta carotene protective for cancer and CVD	Yes	No
Vitamin E protective for dementia and CVD	Yes	No
Hormone replacement therapy protective for coronary heart disease	Yes	No
Bisphosphonates protective for post menopausal breast cancer	Yes	No
Omega 3 fatty acids protective for diabetes	Yes	No

Considering the much wider literature on the interpretation of observational studies examining the psychosocial and behavioural risk factors for diseases, it is most often found that frequently observed associations are confirmed in randomised controlled trials.[29] However, this is not always the case and some notable exceptions have been recorded in which multiple observational studies appear to have been biased to produce misleading conclusions. For example, many observational studies suggested that increased beta carotene intake might be associated with reductions in CVD and cancer, that hormone replacement therapy and vitamin E supplementation were associated with reductions in CVD and dementia, and that Chlamydia infection was associated with atherosclerotic heart disease. However, beta-carotene, vitamin E, hormone replacement therapy, and antimicrobial treatment for Chlamydia were found to be ineffective when subjected to randomised trials.[30, 31, 32, 33, 34] Hormone replacement therapy offers a particularly striking example, since multiple well-done observational studies by eminent epidemiologists suggested 40% reductions in coronary heart disease, and no effect was found when RCTs were conducted.

Recently statins, which have been used in medicines to lower cholesterol levels used to prevent cardiovascular disease, have been added to this list. Observational data have shown statins to have a beneficial effect on acute respiratory distress syndrome and chronic obstructive pulmonary disease but this has now been disproved in randomised controlled trials.[35] Another recent example is the use of bisphosphonates associated with a substantially decreased risk of breast cancer found in several observational studies. In the RCTs, contrary results were found, showing 3 to 4 years of bisphosphonate treatment did not decrease the risk of invasive postmenopausal breast cancer.[36]

While it may be challenging to conduct population level trials in which individuals are randomised into drinking alcohol or abstaining over long periods, two other main approaches have been employed to investigate whether the observed health benefits are causally related to moderate alcohol consumption. One has been to conduct laboratory experiments over relatively short time periods in which individuals are randomised to receive measured doses of alcohol or to abstain under controlled conditions. Biological measures believed to be indicative of cardiac health and functioning have been used as the main outcome measures. Another more recent approach is known as Mendelian randomisation in which the observed effects of genetic variations between individuals can be considered equivalent to a randomised controlled trial. In the field of alcohol and health studies, this has become possible through the identification of a genetic variation thought to be uniquely associated with abstinence or greatly reduced alcohol consumption. The results of these studies will be summarised below along with a number of other methodological concerns which need to be considered when interpreting the large and apparently compelling literature of studies connecting improved health outcomes with moderate or low volume alcohol consumption.

Confounding

Confounding (i.e., when a factor that is associated with both the exposure and the outcome, but when the factor is not in the causal pathway between them) is an important threat to validity for observational studies that can lead to erroneous associations between an exposure (i.e., low-dose alcohol intake) and disease outcomes (e.g., cardiovascular disease). If the health of moderate drinkers is to be compared to that of non-drinkers in order to determine the effect of alcohol, a meaningful comparison would require that the two groups be generally similar in most respects other than alcohol consumption. However, evidence demonstrates that confounding is a serious problem in studies of alcohol consumption and cardiovascular disease conducted among Western populations. Specifically, studies from Europe and North America find that among non-drinkers most traditional cardiovascular risk factors are more prevalent and intense among non-drinkers compared to those who drink moderately, particularly those who drink small amounts frequently.[37, 38, 39, 40, 41, 42] Assuming that the differential distribution of many of these factors is not the result of alcohol consumption (or lack thereof), these risk factors represent poten-

tial confounders that could make low-dose alcohol consumption appear to be protective for cardiovascular disease.

While most analyses try to adjust for these differences, studies do not always collect information about relevant potential confounders, including "traditional" cardiac risk factors.[43] However, even in well-controlled studies, the disproportionate number and intensity of risk factors associated with non-drinking status means that the threat of residual confounding is high (i.e. confounding that persists even after attempts to control for it in analyses) and likely to bias studies in favour of moderate drinkers such that they appear in better health. Furthermore, those with more risk factors have more possible combinations of risk factors that could be synergistic in terms of risk. To the extent that synergistic risk (i.e., independent additional risk beyond the sum of independent risks) is not captured in observational studies, this would again bias studies in favour of moderate drinkers. Finally, because coronary heart disease risk factors tend to cluster in certain individuals and populations, it is plausible that unknown or unmeasured confounders may be more prevalent among non-drinkers than those with low average alcohol consumption, which could again favour apparent reduced risk among moderate drinkers.

In addition to the distribution of traditional cardiac risk factors, low-dose alcohol consumption appears to be a marker of "non-traditional" socio-economic factors such as affluence, leisure, education, mental health, and dentition.[44, 45] These non-traditional risk factors are major determinants of mortality, and few of these factors are plausibly caused by alcohol consumption itself.[46] Since there is no likely causal relationship between, for example, drinking alcohol and having previously achieved higher educational attainment, it seems likely that moderate drinking is merely a reflection or result of prosperity and wellness, rather than its genesis. This makes non-traditional risk factors a rich source of confounding that could distort the apparent relationship between alcohol consumption and health outcomes. Unfortunately, few surveys that include alcohol consumption also include questions about many of these non-traditional risk factors, which make it difficult or impossible to account for them statistically.

Findings from Sweden are consistent with the notion that non-drinkers have more risk factors and worse health at baseline. A study of Swedish women found that abstainers and occasional drinkers had lower levels of education, more use of psychotropic drugs, and were more likely to receive a disability pension.[47] In terms of mortality, non-drinkers had a significantly increased risk for death compared to moderate drinkers, but after accounting for household composition, level of education, employment, social network, smoking, regular medical control for a physical or mental disease, hypertension and diabetes, nondrinking was no longer a risk factor for death. The authors concluded that this underlines the importance of including health status at base-line when prospectively studying the association between alcohol use and mortality, otherwise moderate alcohol consumption may appear more beneficial than is the case.[48]

Among Swedish abstainers, two groups can be distinguished: those who abstain for reasons of principle (e.g., religion, healthy lifestyle, social solidarity, etc.) and those whose abstinence is related to economic hardship, social isolation or health.[49] A Swedish conscripts study found that nondrinking conscripts deviated from moderate drinkers on a number of psychosocial measures. The study population consisted of young men, mostly aged 18 to 19 years. Abstainers compared with moderate drinkers had lower emotional control, felt more insecure in the company of others, reported being less popular in school, had fewer friends, and were more anxious. U-shaped curves were produced when indicators of poor sociability were depicted in relation to level of alcohol consumption. Abstainers also had more psychopathology than moderate consumers.[50]

Because of the heterogeneity of non-drinkers, it may be most relevant to examine the risk of death among those who abstain for religious or family reasons rather than for reasons related to poor health or economic deprivation. A U.S. national survey of more than 40 000 adults aged 21 years or greater obtained reasons for not drinking among abstainers. People stating that the main reason for not drinking was "have responsibility to my family", "religious or moral reasons" or "don't socialize very much" had an equal risk of death as current drinkers with a consumption of less than one drink per day. People stating reasons as "do not like alcohol", "am an alcoholic", "thought I might become an alcoholic", "medical or health reasons" and "costs too much" had a higher risk of death.[51, 52]

Corroborating concerns about confounding, there are several diseases for which low-dose consumption has an implausible protective association for which convincing biological mechanisms have not been proposed. These include protective effects of low-dose alcohol for deafness, hip fracture, asthma, the common cold, and overweight.[53] Moderate consumers of alcohol have even been shown to have lower risks for conditions like alcoholic liver cirrhosis[54] and cancer[55] than non-drinkers, despite the fact that alcohol is a leading cause of cirrhosis and that alcohol is recognized as a human carcinogen.

Another study on self-reported health of adults and children living in the same family in a national representative US sample from 2008 to 2010 has highlighted the importance of residual confounding as a major source of misleading results. The study found that family members including children who co-habited with light to moderate drinkers but who were not necessarily themselves drinkers had better health than abstainers.[56] This 'shared' protection is unlikely to be due to physiologic effects from alcohol, particularly in relation to those under 18 years (most of whom would have been non-drinkers). Rather, the finding is more likely to be explained by shared socioeconomic and lifestyle characteristics.

Furthermore, several studies have found that offspring of mothers who consumed small amounts of ethanol during pregnancy have better developmental outcomes compared with offspring of mothers who abstained from drinking during pregnancy. This is likely a result of residual confounding remaining after attempts to control for the markedly privileged socio-economic status of low-volume drinking mothers, particularly since ethanol is the world's leading fetal neurotoxin.[57]

That people in southern France seem to have lower rates of heart disease in spite of eating food rich in fat and drinking alcohol, mainly wine, has been called 'the French paradox' - a well-publicized phenomenon. However, in a recent study randomised with respect to the Mediterranean diet but not in relation to alcohol consumption found that those consuming the Mediterranean diet had a lower risk of cardiovascular mortality. This shows that the apparent cardiovascular benefit asserted by the 'French paradox' can be explained by diet, irrespective of alcohol consumption.[58] Another explanation of a large part of this seeming paradox may be the coding practices of French doctors, who have been shown to overuse non-specific codes for cardiovascular disease referred to as 'garbage codes', which has the effect of artificially lowering the reported prevalence of ischaemic heart disease per se.[59]

Misclassification of drinkers and abstainers

In the classic studies, the relationship between drinking level and risk of disease or death is described as a J shaped curve, where "moderate" drinkers are observed to have a lower risk than people classified as

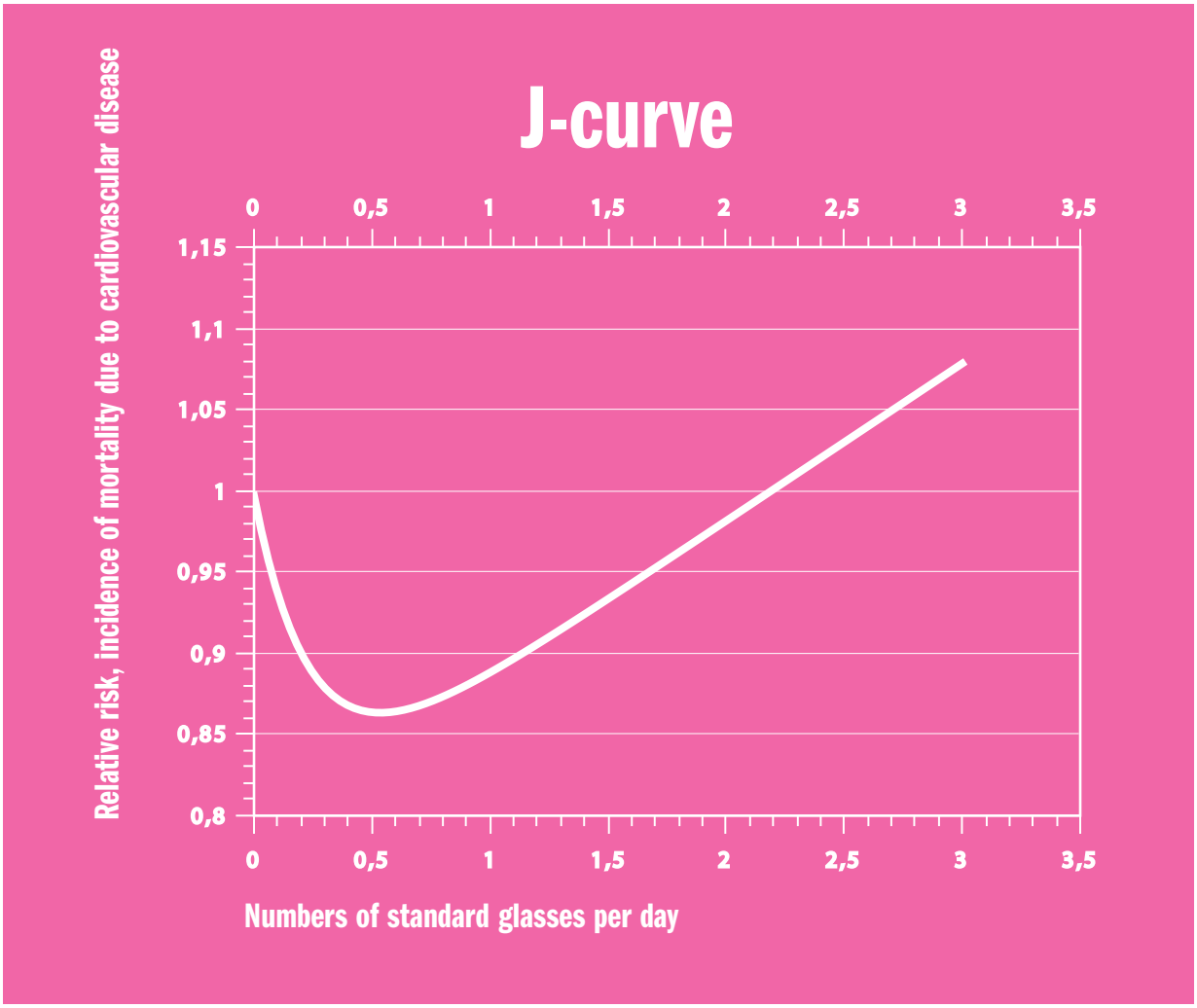


Figure 1. A hypothetical example of a J-curve. The risk for abstainers is set at 1, and falls for low-dose consumers, rising in conjunction with increased consumption.

"abstainers" but those drinking at heavier levels have higher risk than abstainers.

Numerous problems can arise in these studies, however, in relation to how accurately different studies classify who is an abstainer and who is a moderate drinker. Failure to make this classification accurately can lead to biased comparisons between these two groups. Mostly, such biases cause the people identified as moderate drinkers to appear healthy in comparison with those classified as abstainers. The best-known example of this is sometimes referred to as the "sick quitter effect" whereby former drinkers are mixed in with lifetime abstainers. Because people who give up alcohol have significantly worse health profiles, this procedure contaminates the abstainer reference group and makes the moderate drinkers "look good" by comparison.

There are several other examples of drinker misclassification errors which can bias this literature. In many developed countries it has been observed that as people age and become increasingly frail they also tend to either completely abstain from drinking or cut right down and become occasional drinkers. The common practice of combining these near abstainers into the abstainer reference group could therefore also create bias by making this reference group less healthy and hence moderate drinkers appear more healthy by comparison. A well-known review of this literature by Fillmore et al (2006) [60] attempted to identify all the studies which contained either former or occasional drink bias i.e., the abstainer reference group included former and/or occasional drinkers. They reported that among the relatively few (seven) studies which did not contain such bias there was no longer evidence of reduced mortality risk among moderate drinkers.

It is important to stress that misclassification errors are the rule rather than the exception among studies of the relationship between alcohol consumption and health. Specifically in relation to the literature on cardio-protection and moderate drinking, Stockwell and colleagues (2012) [61] examined the 84 studies used by Ronksley et al (2011) [62] in their influential meta-analysis with a view to identifying how many contained serious methodological problems including misclassification evidence. As illustrated in Figure 2 below, after eliminating studies that were duplicates, that did not control for basic lifestyle confounding factors such as smoking and that did not adequately measure both quantity and frequency of alcohol consumption, only 49 studies remained. Among these 49, 32 contained former drinker bias and a further seven contained occasional drinker bias i.e. former and/or occasional drinkers were included in the reference group of "abstainers". A further eight studies contained "reverse occasional drinker bias" whereby occasional drinkers were grouped with moderate drinkers which is also capable of biasing comparisons with abstainers. The two remaining relatively error-free studies produced inconsistent findings in relation to the presence of cardio protection.

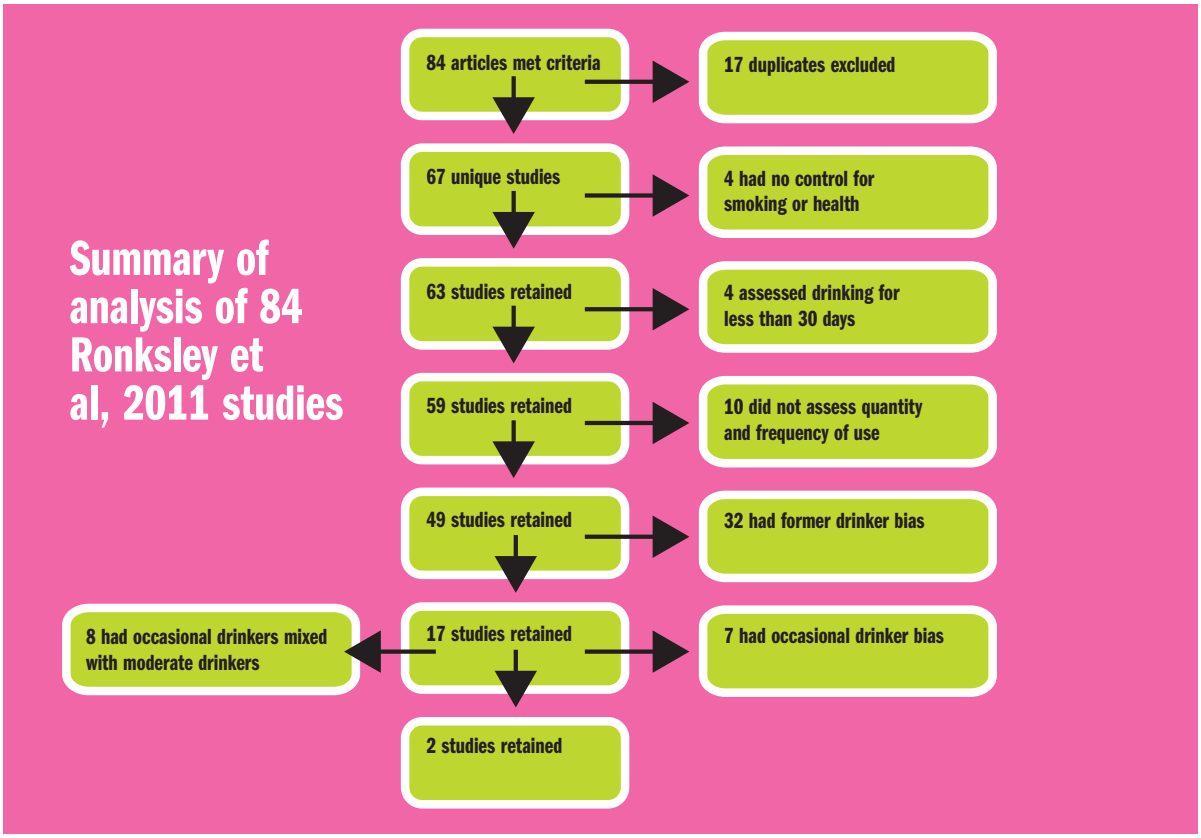


Figure 2. From Stockwell et.al. (2012), How good is the science. BMJ 2012, 344:e2276, reference 61.

Another perspective on the "sick quitter effect" or former drinker bias, is that it is insufficient to separate out these former drinkers into their own group and report mortality outcomes for them separately from people who continue to drink. Over the course of these long-term observational studies, arguably this just result in weeding out sick people with poor outcomes from different groups of drinkers including those classified as "moderate". Liang and Chikritzhs (2013) [63] pursued this idea and investigated what happens to the J shaped curve when former drinkers are classified into different groups of current drinkers. Since past drinking status of former drinkers is rarely known or recorded in cohort studies, Liang and Chikritzhs obtained an estimate of this by using multiple imputations, a common strategy used for dealing with missing values. They demonstrated that when former drinkers were placed back into drinker groups, evidence of health protection at light and moderate levels was substantially diminished.

Liang and Chikritzhs (2013) [64] argue that this reallocation of former drinkers is necessary and is akin to the problem of dealing with missing cases in randomised clinical trials. If either the treated or untreated individuals in such studies are more likely missing at follow-up this will create bias. An "intention-to-treat" approach is recommended to deal with this problem so that missing cases are included in the final analysis, both of the treated and untreated groups. It is suggested that to be analogous with a clinical trial approach and to avoid bias, data on former drinkers should be replaced back into a drinking category which best describes their past level and pattern of alcohol exposure. This methodological problem has also been recognised in tobacco research where it has been emphasized that ex-smokers and current smokers should be combined in analyses rather than being treated as two distinct groups.[65]

Epidemiological studies rely heavily on accurate participant recall, that is, an individual's ability to faithfully report the quantity and frequency of their own drinking. Unfortunately, recall bias, whereby people (invariably) underestimate their drinking, is well documented in relation to self-reported alcohol consumption.[66] This is a particular problem for studies of alcohol and chronic disease as it undermines the ability of researchers to correctly classify drinkers and non-drinkers. A study based on the 1958 British Birth Cohort provides a striking example of the extent of recall bias in relation to alcohol exposure. Caldwell et al. reviewed respondent's own reports of their current alcohol use (e.g. non-drinker, occasional drinker, drinks on most days) at ages 16, 23, 33, 42 and 45 years. Remarkably, some 60% of 45 year old respondents who self-identified as 'never' drinkers had actually reported drinking alcohol at any one of the previous follow-up surveys -- almost a quarter had previously reported drinking at least once a week. Moreover, almost 60% of 45 year olds who self-reported as lifetime 'occasional only' drinkers had previously reported drinking at least once a week.[67]

Although misclassification is an important type of selection bias, there are other types of selection bias that confront studies of alcohol consumption. After one begins drinking one might become a moderate drinker, quit drinking, become a heavy drinker, or die prior to the study's inception. In observational studies, these last three possibilities are not taken into account. Quitters have been discussed previously, but even if former drinkers are correctly classified as such, removing them from the analysis biases results in favour of moderate drinkers because former drinkers are generally unhealthy, regardless of whether they stopped due to the effects of alcohol or for other reasons. However, from an intention-to-treat perspective, their poor outcomes should rightly accrue to drinkers. In addition, heavy drinkers are ignored since they do not meet inclusion criteria as moderate drinkers. Not including those who already died also biases results in favour of drinking, assuming that deaths at young ages among drinkers are more likely to be from alcohol than they are to be from not drinking among non-drinkers. This is likely the case, since alcohol consumption is a leading cause of death among young and middle aged persons, and because protective effects of alcohol are not observed in young age groups.

Publication bias

Another concern with this literature is that bias may be present in terms of which types of studies are more likely to get published. It is known to be harder to publish studies with no significant results and studies finding that alcohol in moderation is good for you may be more likely to be published. It has also been suggested that wealthy commercial groups with an interest in the sale of alcoholic beverages are more likely to fund researchers with a track record of using methods which detect health benefits from drinking. Evidence to support this concern was reported in one of the major early reviews of this literature by Corrao and colleagues.[68] They concluded that among smaller studies, estimates of mortality risk among moderate drinkers were skewed significantly downwards away from mean values.

3.2. Contradictory lines of evidence from epidemiological studies

Increases in aggregate per capita alcohol consumption are not associated with reduced CVD

Aggregate-level studies can eliminate bias in individual-level studies, and it is important to weigh together evidence from various sources of data: clinical, observational as well as aggregate data, rather than to rely on one kind of data only. For example, if there is a substantial cardioprotective effect of low-dose drinking, mortality rates would be expected to respond to changes in aggregate consumption. If there is no aggregate-level effect on cardiovascular disease of changes in drinking, the explanation could very well be that the cardioprotective effect is the result of confounding in individual-level studies or that it is too small to be of much interest from the point of view of public health.[69]

It is well established from international studies that changes in per capita alcohol consumption are significantly and positively correlated with corresponding changes in rates of alcohol-related diseases. One study of 14 European countries spanning over 45 years of data found that this held for a number of specific outcomes such as liver cirrhosis and injury rates as well as for total alcohol-related mortality.[70, 71, 72, 73] However, no relationship was found between per capita alcohol consumption and rates of cardiovascular mortality.[74] A similar study on Canadian data from 1950 to 1998 reported an increase of IHD mortality of one per cent for a 1-litre increase in per capita consumption, but the estimates did not reach statistical significance. The study concludes that an increase in overall alcohol consumption is more likely to cause an increase in IHD mortality than to lower the number of IHD deaths.[75] A study on data from US states from 1950 to 2002 found a similar effect on total consumption of alcohol, i.e. an increase of one per cent IHD mortality per litre of alcohol.[76] A study of Norwegian time series data from 1955 to 1977 reported a protective effect of alcohol bordering on statistical significance between per capita alcohol consumption and ischaemic heart disease mortality only in the age group 60-74 years.[77] This effect was only apparent the same year as per capita consumption changed. A study from Hong Kong in connection with a decrease of excise taxes on beer and wine by fifty per cent in March 2007, reported that ischaemic heart disease mortality increased by 18% for elderly men and 15% for elderly women. Alcohol duty on beer and wine was eliminated one year later, in March 2008, but this was not found to have impacted the CVD death rates.[78]

Several aggregate population level studies have reported an increase in total mortality related to an increase in alcohol consumption. In a study of 25 European countries between 1982 and 1990, an increase in consumption of one litre of pure alcohol increased total mortality by 1.3 per cent.[79] A study of European countries demonstrated that mortality significantly increased with increasing consumption in eight out of 14 countries. The effect on mortality tended to be stronger in low-consumption countries (3% per litre) than in medium- and high-consumption countries (1%). In no country were increases in consumption significantly associated with decreased mortality.[80] A similar effect was found for Canada where for every one litre increase in per capita consumption there was a 1.7 per cent increase in total mortality.[81]

While measures of per capita alcohol consumption of the population do not discriminate between light, moderate or heavy drinking, some authors have suggested that there may be cardiac benefits for heavy as well as moderate drinking.[82, 83] If this was the case, arguably increases in per capita alcohol consumption should result in reductions in cardiovascular disease but this has been shown not to occur. These findings weaken the argument that alcohol exposure is causally related to reduced risk of mortality.

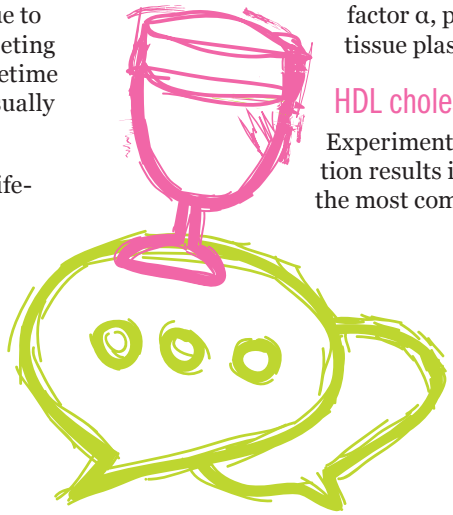
No CVD benefit from low-dose consumption among non-white and non-Western Cultures

Several studies report no reduced risk for heart disease or mortality for non-white or non-western cultures. In a study by Flavio Fuchs the risk for coronary heart disease increased linearly for black American men but decreased for white male consumers of low doses.[84] A study on different ethnic American groups found a reduced risk for mortality only in whites but not in blacks or Hispanic.[85] Similarly in studies on Chinese or Indian alcohol consumption, cardiovascular disease is reported to increase already at low-dose consumption of 1-6 drinks per week.[86, 87, 88] This raises the question whether not alcohol consumption, and especially moderate consumption, is a sign of healthy living, rather than the cause of reduced risk, a connection that is present in some cultures but not in others. This is in agreement with the positive effects of fish oil consumption and other dietary elements on mortality and cardiovascular disease seen in large observational studies, an effect not easily repeated in randomised controlled trials.[89]

Importance of assessing cohorts over the life course, ideally soon after drinking initiation

Another line of concern has emerged from a recent and thorough investigation of a large cohort (n=400,000+) from the European Prospective Investigation into Cancer (EPIC) reported by Bergmann et al.[90] This study recognized the fact that over the life course individuals have competing risks of death from different causes. Earlier in life there is a greater risk of death from injuries while death from cardiovascular disease tends to occur much later in life. By only examining risk of death from one particular outcome at a time and ignoring these competing risks, biased results may emerge. If drinkers are more likely to die from alcohol-related causes earlier in life it may give the appearance that risk of death from a different cause such as coronary heart disease later in life is produced for surviving

drinkers. This problem is exacerbated based on the length of time that elapses between the age of drinking initiation and the time in which a study group or cohort is identified, or by having study populations that are relatively older in age. After conducting their competing risk analysis the authors of the study concluded: "The apparent health benefit of low to moderate alcohol-use found in observational studies could therefore in large part be due to various selection biases and competing risks, which are related to both lifetime alcohol-use and risk of disease, usually occurring later in life."



In a US study the relationship of life-course drinking patterns to diabetes, heart problems, and hypertension among those 40 and older in the 2005 was assessed. Normally, studies only take into account current drinking as reported by those who participate. The study did not find evidence of a protective effect of life-time moderate drinking on heart problems or hypertension, nor did it find evidence of increased risk for heart problems among lifetime heavy drinkers. The results did confirm previous findings of a protective effect of lifetime moderate drinking on diabetes risk.[91]

Contradicting examples exist also for diabetes. A study on a national representative sample of adolescents in the USA reported that adolescents with a frequent heavy alcohol use (consuming an average of 5+ drinks on 3 or more days/week) was 12 times more likely to develop diabetes than abstainers.[92] In a review of seven cohort studies on Japanese, alcohol consumption, even at low doses were linked to an increased risk of diabetes. The effect was larger for men with a relative low BMI (BMI <= 22). For higher BMI the results varied. Some of the studies reported a lower risk for diabetes and some a higher risk.[93]

3.3. Some biological mechanisms supporting the plausibility of cardiovascular protection are now in question, or are inconsistent with epidemiologic studies

Biological mechanisms that can be the cause of a correlation found in observational studies strengthen the plausibility that an observed correlation is causal, e.g. the correlation between low-dose alcohol consumption and coronary heart disease. Such mechanisms have been found and a review and meta-analysis of 44 RCT laboratory studies found that moderate alcohol consumption had favourable effects on levels of the good cholesterol high density lipoprotein (HDL) cholesterol, apolipoprotein A1, adiponectin, and fibrinogen. The study concluded that the results strengthened the case for a causal link between alcohol intake and reduced risk of coronary heart disease. The analysis found that alcohol consumption did not affect a number of other factors also associated with risk of coronary heart disease, as total cholesterol, low density lipoprotein (LDL) cholesterol, triglycerides, Lp(a) lipoprotein, C reactive protein, interleukin 6, tumour necrosis factor α, plasminogen activator inhibitor 1 and tissue plasminogen activator antigens.[94]

HDL cholesterol

Experimental studies show that alcohol consumption results in increases in HDL, and this has been the most compelling source of biologic plausibility for how alcohol might reduce CVD. However, the cardioprotective effect of HDL has recently come into question. First, a meta-analysis of studies on the use of statins and other lipid-lowering drugs, has shown that these medicines have no independent effect on CVD mortality after controlling for their effects on the "bad cholesterol" (i.e., LDL cholesterol).[95] Second, pharmaceutical drugs that raise HDL levels have not resulted in decreases in CVD mortality.[96] And third, Mendelian randomisation, in this case focusing on a genetic effect that raises HDL in the blood, study results have also shown no effect of higher HDL levels for reducing the risk for myocardial infarction.[97]

Coronary calcification, carotid intima-media thickness

Serum biomarkers such as HDL are thought to work through improvements in vascular health. However, histologic markers of vascular health are a more proximate indication of vascular health than serum biomarkers, and alcohol consumption is associated with worse vascular health by these measures. For example, coronary calcification was measured over 15 years in a sample of 3,037 U.S. participants aged 33–45 years. It was found that coronary calcification was associated with increased rates of atherosclerosis at all levels of consumption. Among those consuming less than 7 drinks per week the risk was increased by 10 % compared with abstainers, was 50% higher among those drinking on average 7 to 14 drinks per week and 100% higher for those drinking more than 14 drinks per week. Among binge drinkers the risk was also doubled. The lowest proportion of participants with coronary calcification was found among lifetime abstainers.[98] Similarly, a study on Finnish data on carotid intima–media thickness (IMT), a marker of subclinical atherosclerosis, in young, healthy adults found a direct positive relationship between alcohol consumption and carotid intima–media thickness, with a significant increase starting from consumption of less than two drinks per day compared to non-drinkers.[99]

Brain atrophy, cognition

A number of epidemiological studies find that low-dose alcohol consumption is associated with better cognition. However, a study on middle-aged US men found that each additional drink per week was associated with increased brain atrophy as measured by MRI imaging.[100] In addition, two recent Mendelian randomisation studies found no association between alcohol use and improved cognitive ability.[101, 102] Collectively, these findings further strengthen the notion that the observed apparently beneficial effects on cardiovascular health among low and moderate drinkers may actually reflect good cognitive health, rather than cause good cognitive health.

Blood pressure, hypertension

Although a number of epidemiologic studies find a linear relationship between alcohol consumption and blood pressure and hypertension,[103] others find a J-shaped curve in which low-dose alcohol consumption is associated with lower blood pressure.[104, 105, 106] However, in a meta-analysis of Mendelian randomisation studies of a gene related to reduced alcohol consumption, alcohol consumption increased blood pressure and the risk of hypertension among men, even at moderate levels of consumption. The researchers were also able to estimate that for men, the lifetime effect of drinking 1 g of alcohol a day (1/12 standard drink in Sweden) increased systolic blood pressure by 0.24 mmHg. No association was found in females, for whom drinking levels were low in the studies.[107]

3.4. New genetic evidence: Mendelian randomisation study suggests CVD harm, not benefit, from alcohol consumption, even at low doses

In the absence of clinical RCTs, genetic (Mendelian) randomisation studies are perhaps the strongest available study design to assess the effects of alcohol consumption, particularly for chronic disease-related outcomes. The distribution of genetic variants is usually random in a population, and can therefore minimize the leading sources of bias encountered in observational studies. Furthermore, because genes are present from birth, they can better capture the effects of lifetime exposures to a particular factor.

Although this type of study has been used to assess the relationship of alcohol consumption with health-related conditions and risk factors (e.g., blood pressure, HDL, cognition), it is only very recently (July, 2014) that this study design has been applied to cardiovascular mortality.[108] This is important since CVD is the driver behind the possible mortality benefit among those who consume modest amounts of alcohol.

REASONS FOR SCEPTICISM ABOUT EFFECTS OF LOW-DOSE ALCOHOL CONSUMPTION

- Benefits have not been confirmed in controlled studies
- Other observed health benefits have not been confirmed by RCTs
- Biological mechanisms for health benefits recently disconfirmed
- Evidence for adverse physiological effects of low-dose alcohol
- “Moderate” drinkers have generally healthier lifestyles than abstainers
- Many studies systematically exclude unhealthy drinkers
- Most studies misclassify unhealthy ex-drinkers as abstainers
- Unlikely health benefits observed e.g. liver cirrhosis, cancer, deafness
- Benefits usually observed only in Caucasian populations
- Genetic disposition to drink less provides reduced coronary risk
- Studies showing benefits are more likely to be published
- Reduced population drinking is not associated with increased CVD

Individuals with genetic variants of alcohol metabolism genes that are associated with less alcohol consumption were compared to individuals without this variant. If the protective effect of alcohol consumption on CVD mortality were real, one would expect the group carrying the genetic variant to have a higher risk of cardiovascular mortality because of their lower alcohol consumption. However, this study of more than 260 000 individuals showed that individuals with a genetic predisposition to consume less alcohol had lower, not higher, mortality rates from coronary heart disease. This effect was observed among those within low and moderate drinking categories. Furthermore, the fact that the genetic variant was not significantly associated with CVD mortality among non-drinkers is evidence that this genetic variant does not affect CVD except through its effects on alcohol consumption. In addition, there was no association of the gene with type 2 diabetes or coagulation markers.

SECTION 4. SUMMARY, IMPLICATIONS FOR PUBLIC HEALTH

This report is primarily a summary and critique of the methodology and evidence in scientific research on the effects of low-dose alcohol consumption. To date, all studies of the relationship between alcohol consumption and morbidity and mortality outcomes have been observational by nature (i.e. mainly non-randomised cohort and case-control studies). While there are many epidemiological studies of this nature, they all suffer from the same fundamental weaknesses that are inherent in observational research illustrating that a substantial body of observational studies can be consistently wrong.

In general, the chief threats to validity for observational studies are confounding and selection bias, and recent evidence demonstrates that observational studies about effects of low-dose alcohol from developed countries are plagued by both. These methodological problems are clearly apparent in a number of studies where protective effects from low-dose alcohol are found despite the absence of any biologically plausible mechanism, including deafness, hip fracture, the common cold, and alcoholic liver cirrhosis.

Fundamentally, observed associations can be caused by a variety of other lifestyle factors as well as socio-economic and psychosocial factors which may be independently associated with alcohol consumption in the population being studied. These background factors can to some extent be controlled through statistical methods, but the extent to which this has been done varies considerably. Furthermore, there are many factors that are only partially understood, and, most likely, many factors that are unknown.

The reported beneficial effects of alcohol are largely the result of comparisons with abstainers. It has become increasingly clear however that many abstainers are at higher risk for ill health in ways unrelated to their non-consumption of alcohol.

Another major source of methodological uncertainty in observational research is the misclassification of research subjects. Numerous problems can arise in these studies in relation to how accurately different studies classify who is an abstainer and who is a moderate drinker. Failure to make this classification accurately can lead to biased comparisons between these two groups. Mostly, such biases cause the people identified as moderate drinkers to appear healthy in comparison with those classified as abstainers. The best-known example of this is sometimes referred to as the “sick quitter effect” whereby former drinkers are mixed in with lifetime abstainers. Because people who give up alcohol tend to have significantly worse health profiles, this procedure contaminates the abstainer reference group and makes the moderate drinkers “look good” by comparison. Furthermore, it is insufficient to separate out former drinkers into their own group and report mortality outcomes for them separately from people who continue to drink. Over the course of long-term observational studies, this arguably results in weeding out sick people with poor outcomes from different groups of drinkers including those classified as “moderate”. To avoid spurious conclusions, reallocation of former drinkers may be necessary and is akin to the problem of dealing with missing cases in randomised clinical trials.

Correlations between alcohol and health outcomes found in observational studies also require plausible biological mechanisms to be considered causal. Such mechanisms have been identified and include favourable effects of moderate alcohol consumption on some blood biomarkers such as high density lipoprotein (HDL) cholesterol. A number of RCTs, summarized in a review and meta-analysis have supported this effect. However, the cardioprotective effect of HDL has recently come into question so that the alcohol-induced increase of HDL should also be questioned. Recent research on atherosclerosis demonstrates that alcohol consumption is only positively associated with coronary calcification and increased carotid artery thickness. The lowest risk of coronary calcification was found among lifetime abstainers.

In the medical literature, many observed associations are confirmed in subsequent randomised controlled trials. However, this is not always the case, and some notable exceptions have been recorded in which multiple observational studies were subsequently refuted by RCTs. Notable examples described in this report include beta carotene intake for the reductions in CVD and cancer, and hormone replacement therapy for the reduction of CVD, among other examples. However, both beta-carotene and hormone replacement therapy, were found to be ineffective when subjected

to randomised trials. These are strong arguments for performing randomised controlled studies, where both known and unknown background variables can be controlled through randomisation, but so far no RCTs have been performed in this area. This scientific standard is warranted particularly for an agent that is a leading cause of death, disability and social problems.

The initiation of alcohol consumption should not be recommended for reasons of health.

The protective effect of moderate drinking is not commonly found in different ethnic groups, eg black American men, Chinese and Indian populations. This adds to doubts about the cardioprotective role of alcohol, as opposed to other lifestyle factors and cultural differences.

Aggregate level research from many countries involving whole populations finds that changes in per capita alcohol consumption are significantly and positively correlated with corresponding changes in rates of alcohol-related diseases. However, no relationships have been found between per capita alcohol consumption and rates of cardiovascular mortality. This is yet another indication that the cardioprotective effect may be confounded in individual-level studies.

In the absence of randomised controlled trials on alcohol and mortality, Mendelian randomisation studies which utilize genetic variants that affect alcohol consumption in individuals have emerged as a good alternative to randomised clinical trials. A recent meta-analysis found that those with a genetic predisposition to consume less alcohol had lower, not higher, odds of dying from coronary heart disease, including among those with moderate alcohol consumption. This is a powerful piece of evidence suggesting that concerns with observational epidemiologic studies of the health effects of low-dose alcohol on cardiovascular health are justified.

4.1 Implications of weak evidence for health benefits: Why it matters

Our conclusion is that the evidence of protective effects for low-dose alcohol consumption is surprisingly weak, and does not warrant the far reaching conclusions that have been drawn from it. This report should be considered in the context of the fact that alcohol consumption in general is a major negative health determinant in terms of mortality, morbidity and social problems. Furthermore, alcohol results in far more adverse health impacts than it prevents, even assuming some cardiovascular benefit for low-dose consumption. With new research being reported over the last decades, estimates of the total disease burden caused by alcohol has increased considerably. New disease categories have been added, where the role of alcohol had not been recognized earlier. This particularly applies to cancer, where alcohol now is recognized as a major carcinogenic agent.

For clinicians: drinking guidelines, whether drinking should be recommended

While it is possible that low-dose alcohol consumption may be beneficial for some health outcomes including cardiovascular disease, the current evidence in support of this is weak. However, the appeal of purported health benefits, and of alcohol in particular, clearly has resulted in a lower than usual scientific standard when evaluating evidence for clinical intervention. No randomised controlled studies have been undertaken in contrast to what is required for most medical procedures or pharmaceutical products. Furthermore, the many side effects of alcohol, if viewed as a pharmaceutical, would prohibit its use, even in very moderate doses.

Strong alcohol control policies targeting price and availability should not be undermined by claims of beneficial effects of low-dose alcohol consumption.

Given the lack of evidence from randomised trials and considering the many negative consequences of alcohol consumption, public health recommendations should remain focused on: 1) reducing excessive drinking among those who already drink, and 2) discouraging initiation of alcohol consumption or more frequent drinking on the basis of health and safety considerations.

Implications for policy

The purported beneficial effects of low-dose alcohol consumption have been used as an argument against the implementation of effective population-level policies. Given the strong possibility that there are actually no cardio-protective effects and given the negative effects of alcohol, there are no reasons to oppose effective policies to reduce alcohol-related harm, e.g. raising alcohol prices and restricting the physical availability of alcohol.

However, even if there were cardio-protective effects, there are still compelling reason to adopt public popu-

lation-based polices to reduce alcohol consumption. First, alcohol consumption results in far more adverse health impacts than it is thought to prevent. Second, the evidence of negative effects of excessive alcohol consumption is more robust than for effects of low-dose consumption for the following reasons: 1) alcohol is a predominant risk factor or has 100% attribution in many conditions; 2) These associations have large effect sizes; and 3) many conditions have short latency periods between the exposure to alcohol and the adverse outcomes. Third, current meta-analyses of all-cause mortality suggest that the lowest risk for death is associated with very low levels of consumption (approximately half a drink a day for women and less than one per day for men). Therefore, population-wide reductions in consumption through the implementing effective alcohol policies would not only reduce the death and disability from excessive drinking, but could increase the number of persons to whom any benefits of moderate consumption might accrue.

The disease burden of alcohol is enormous. Over the centuries nations have struggled with the challenge to control and reduce the costs from alcohol to individuals and society. There are clearly opposing forces in this struggle. On the one hand are commercial forces that gain profit from increased consumption of alcohol and on the other hand are health and safety interests that seek to reduce the harm from alcohol through reduced drinking.

A message that moderate drinking is good for health has been used to undermine efforts to achieve effective alcohol policies on the national level. This message also sometimes confuses medical practitioners as to appropriate advice regarding alcohol consumption. The grounds for challenging the protective effects of moderate drinking have increased. This report attempts to summarise the scientific evidence concerning this issue. It concludes that the evidence for the beneficial health effects of moderate drinking in many respects is quite weak and should not compromise society's response to the problems caused by alcohol.

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